

MODULATORS OF ALPHA7 NICOTINIC ACETYLCHOLINE RECEPTORS AND THERAPEUTIC USES THEREOF

The present invention relates to compounds with $\alpha 7$ nicotinic acetylcholine receptor ($\alpha 7$ nAChR) agonistic activity, processes for their preparation, pharmaceutical compositions containing the same and the use thereof for the treatment of neurological and psychiatric diseases.

5 **Background of the invention**

A number of recent observations point to a potential neuroprotective effect of nicotine in a variety of neurodegeneration models in animals and in cultured cells, involving excitotoxic insults (1-5), trophic deprivation (6), ischemia (7), trauma (8), A β -mediated neuronal death (9-11) and protein-
10 aggregation mediated neuronal degeneration (9;12). In many instances where nicotine displays a neuroprotective effect, a direct involvement of receptors comprising the $\alpha 7$ subtype has been invoked (7;11;13-16) suggesting that activation of $\alpha 7$ subtype-containing nicotinic acetylcholine receptors may be instrumental in mediating the neuroprotective effects of nicotine. The available
15 data suggest that the $\alpha 7$ nicotinic acetylcholine receptor represents a valid molecular target for the development of agonists/positive modulators active as neuroprotective molecules. Indeed, $\alpha 7$ nicotinic receptor agonists have already been identified and evaluated as possible leads for the development of neuroprotective drugs (18-22). Involvement of $\alpha 7$ nicotinic acetylcholine
20 receptor in inflammatory processes has also recently been described (23). Thus, the development of novel modulators of this receptor should lead to novel treatments of neurological, psychiatric and inflammatory diseases.

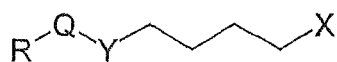
Summary of the invention

The invention provides compounds acting as full or partial agonists at

the $\alpha 7$ nicotinic acetylcholine receptor ($\alpha 7$ nAChR), pharmaceutical compositions containing the same compounds and the use thereof for the treatment of diseases that may benefit from the activation of the alpha 7 nicotinic acetylcholine receptor such as neurological and psychiatric disorders, in particular Alzheimer's disease and schizophrenia.

Description of the invention

In a first aspect, the invention provides a compound of formula I



(I)

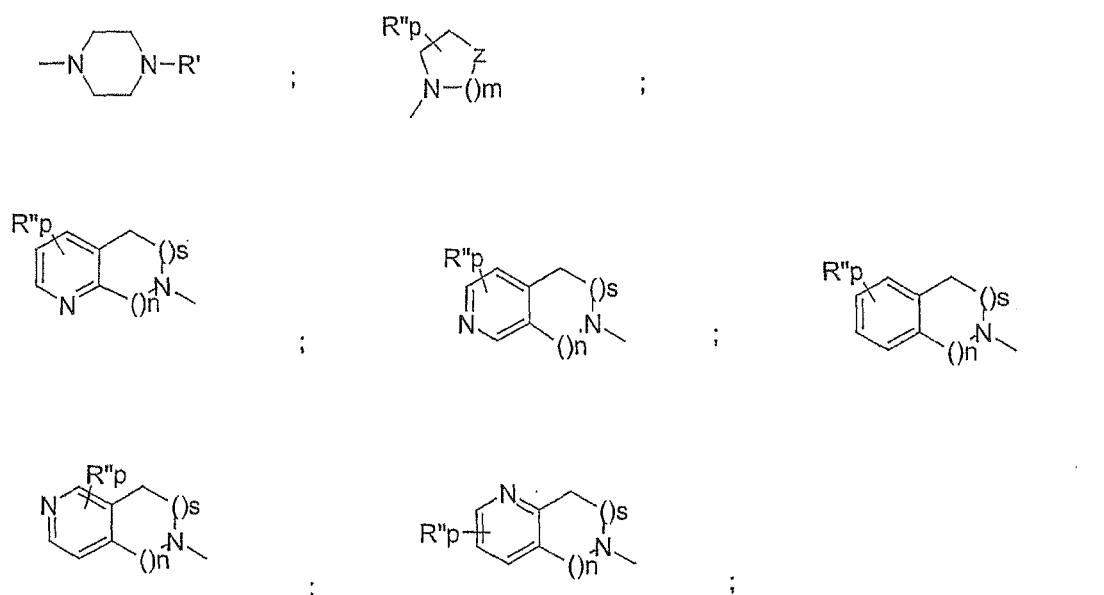
wherein:

Y is a group $-\text{CONH}-$; $-\text{NHCONH}-$; $-\text{NHCO}-$; $-\text{SO}_2\text{NH}-$; $-\text{NHSO}_2-$; $-\text{NHSO}_2\text{NH}-$; $-\text{OCONH}$; $-\text{NHCOO}-$

Q is a 5 to 10-membered aromatic or heteroaromatic ring

R is hydrogen; halogen; linear, branched or cyclic (C_1 - C_6) alkyl, haloalkyl, alkoxy or acyl; hydroxy; cyano; nitro; mono- or di- (C_1 - C_6) alkylamino, acylamino or alkylaminocarbonyl; carbamoyl; (C_6 - C_{10}) aryl- or (C_1 - C_6) alkylsulphonylamino; (C_6 - C_{10}) aryl- or (C_1 - C_6) alkylsulphamoyl; a 5 to 10-membered aromatic or heteroaromatic ring optionally substituted with: halogen; linear, branched or cyclic (C_1 - C_3) alkyl, haloalkyl, alkoxy or acyl; hydroxy; cyano; nitro; amino; mono- or di- (C_1 - C_6) alkylamino, acylamino or alkylaminocarbonyl groups; carbamoyl; (C_6 - C_{10}) aryl- or (C_1 - C_6) alkylsulphonylamino; (C_6 - C_{10}) aryl- or (C_1 - C_6) alkylsulphamoyl;

X is a group of formula



wherein

R' represents (C₁-C₆) acyl; linear, branched or cyclic (C₁-C₆) alkyl; a
 5 -(CH₂)_j-R''' group, wherein j = 0,1 and R''' is a 5 to 10-membered aromatic or
 heteroaromatic ring optionally substituted with: halogen; hydroxy; cyano;
 nitro; (C₁-C₆) alkyl, haloalkyl, alkoxy, acyl, acylamino groups;

Z is CH₂, N or O

m is an integer from 1 to 4

10 n is 0 or 1;

s is 1 or 2;

p is 0, 1 or 2;

R'', independently from one another for p = 2, represents hydrogen;
 halogen; hydroxy; cyano; nitro; linear, branched or cyclic (C₁-C₆) alkyl,
 15 haloalkyl, alkoxy, acyl; a -(CH₂)_j-R''' group, wherein n and R''' are as above
 defined; carbamoyl; (C₆-C₁₀) aryl- or (C₁-C₃) alkylsulphonylamino; (C₆-C₁₀)
 aryl- or (C₁-C₃) alkylsulphamoyl; mono- or di-[linear, branched or cyclic
 (C₁-C₆) alkyl]aminocarbonyl;

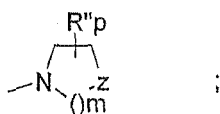
A first group (Ia) of preferred compounds of formula I are those in
 20 which:

Y is -CONH-; -NHCO-; -NHCONH-

Q is a 5 to 10-membered aromatic or heteroaromatic ring;

R is selected from the group consisting of hydrogen; halogen; linear, branched or cyclic (C_1 - C_6) alkyl, alkoxy or alkylamino; trihaloalkyl; phenyl; naphthyl; pyridyl; pyrimidinyl; quinolinyl; isoquinolinyl; indolyl; thienyl; benzothienyl; furanyl; benzofuranyl; imidazolyl; benzoimidazolyl; pyrrolyl; optionally substituted as indicated above for the compounds of formula (I);

X is a group



10 Z is CH_2 , N or O

m is an integer from 1 to 4

p is 0, 1 or 2

R'', independently from one another for $p = 2$, is selected from the group consisting of hydrogen; mono- or di-[linear, branched or cyclic (C_1 - C_6) alkyl]aminocarbonyl; linear, branched or cyclic (C_1 - C_6) alkyl, alkoxy, acyl;

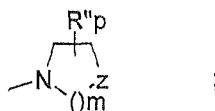
Particularly preferred compounds Ia are those where

Y is -CONH(Q)-;

Q is a 5 to 10-membered aromatic or heteroaromatic ring

R is selected from the group consisting of phenyl; naphthyl; pyridyl; pyrimidinyl; quinolinyl; isoquinolinyl; indolyl; thienyl; benzothienyl; furanyl; benzofuranyl; imidazolyl; benzoimidazolyl; pyrrolyl; optionally substituted as indicated above for the compounds of formula (I);

X is a group



25 where

Z is CH_2 , N or O

m is an integer from 1 to 4

p is 0, 1 or 2

R'', independently of one another for p = 2, is selected from the group consisting of hydrogen; mono- or di-[linear, branched or cyclic (C₁-C₆) alkyl]aminocarbonyl; linear, branched or cyclic (C₁-C₆) alkyl, alkoxy, acyl;

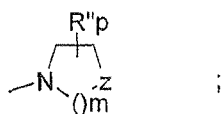
Another group of particularly preferred compounds Ia are those where

Y is -NHCONH(Q)-;

Q is a 5 to 10-membered aromatic or heteroaromatic ring

R is selected from the group consisting of halogen; linear, branched or cyclic (C₁-C₆) alkyl, alkoxy or alkylamino; haloalkyl; phenyl; naphthyl; pyridyl; pyrimidinyl; quinolinyl; isoquinolinyl; indolyl; thienyl; benzothienyl; furanyl; benzofuranyl; imidazolyl; benzoimidazolyl; pyrrolyl; optionally substituted as indicated above for the compounds of formula (I);

X is a group



Z is CH₂, N or O

m is an integer from 1 to 4

p is 0, 1 or 2

R'', independently from one another for p = 2, is selected from the group consisting of hydrogen; mono- or di-[linear, branched or cyclic (C₁-C₆) alkyl]aminocarbonyl; linear, branched or cyclic (C₁-C₆) alkyl, alkoxy, acyl;

Another group of particularly preferred compounds Ia are those where

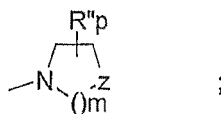
Y = -NHCO(Q)-;

Q is phenyl

R is selected from the group consisting of phenyl; naphthyl; pyridyl; pyrimidinyl; quinolinyl; isoquinolinyl; indolyl; thienyl; benzothienyl; furanyl; benzofuranyl; imidazolyl; benzoimidazolyl; pyrrolyl; optionally substituted as

indicated above for the compounds of formula (I);

X is a group



where

5 Z is CH₂, N or O

m is an integer from 1 to 4

p is 0, 1 or 2

R'', independently of one another for p = 2, is selected from the group consisting of hydrogen; mono- or di-[linear, branched or cyclic (C₁-C₆) alkyl]aminocarbonyl; linear, branched or cyclic (C₁-C₆) alkyl, alkoxy, acyl;

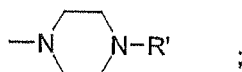
A further group (Ib) of preferred compounds of formula (I) are those in which

Y is -CONH(Q)

Q is phenyl, indolyl

15 R is selected from the group consisting of halogen; phenyl; naphthyl; pyridyl; quinoliny; isoquinoliny; indolyl; thienyl; benzothienyl; furanyl; benzofuranyl; imidazolyl; benzoimidazolyl; pyrrolyl; optionally substituted as indicated above for the compounds of formula (I);

X is a group



20

where R' is a 5-10-membered aromatic or heteroaromatic ring optionally substituted with halogen or (C₁-C₆) alkoxy groups;

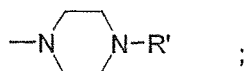
A further group (Ic) of preferred compounds of formula (I) are those in which

25 Y is -NHCONH(Q)

Q is phenyl, indolyl

R is selected from the group consisting of halogen; phenyl; naphthyl; pyridyl; quinolinyl; isoquinolinyl; indolyl; thienyl; benzothienyl; furanyl; benzofuranyl; imidazolyl; benzoimidazolyl; pyrrolyl; optionally substituted as indicated above for the compounds of formula (I);

5 X is a group



where R' is a 6-membered aromatic or heteroaromatic ring optionally substituted with halogen or (C₁-C₆) alkoxy groups;

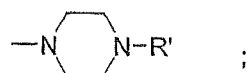
10 Another group (Id) of preferred compounds of formula I are those in which

Y is -NHCO(Q);

Q is phenyl, pyridyl

R is selected from the group consisting of phenyl; naphthyl; pyridyl; 15 quinolinyl; pyrimidinyl; isoquinolinyl; indolyl; thienyl; benzothienyl; furanyl; benzofuranyl; imidazolyl; benzoimidazolyl; pyrrolyl; optionally substituted as indicated above for the compounds of formula (I);

X is a group



20 where R' is a phenyl ring optionally substituted with halogen or (C₁-C₆) alkoxy groups;

Particularly preferred are the compounds (Id) wherein

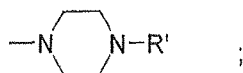
Y is -NHCO(Q);

Q is phenyl

25 R is selected from the group consisting of phenyl; pyridyl; indolyl; pyrimidinyl; optionally substituted with: halogen; linear, branched or cyclic (C₁-C₃) alkyl, alkoxy or acyl; cyano; (C₁-C₆) alkylamino; acylamino;

alkylaminocarbonyl groups; carbamoyl;

X is a group



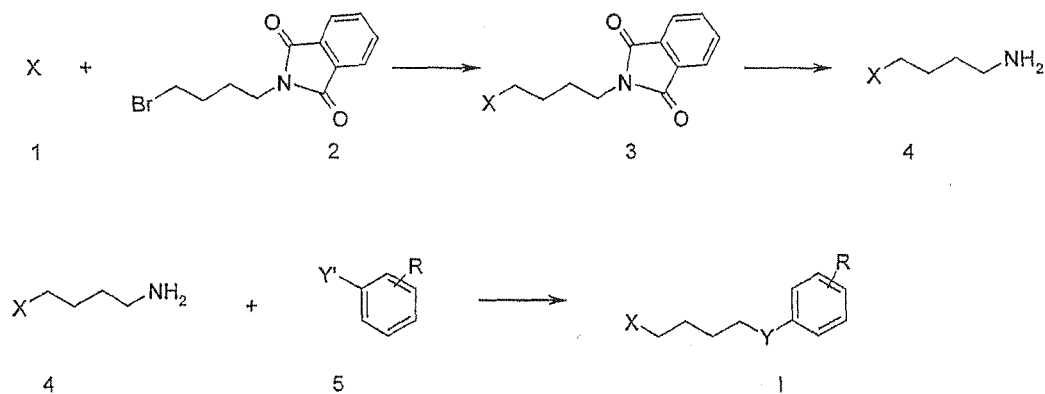
where R' is a phenyl ring optionally substituted with halogen or (C₁-C₆)

5 alkoxy groups

The compounds of the invention can be in the form of free bases or acid addition salts, preferably salts with pharmaceutically acceptable acids. The invention also includes separated isomers and diastereomers of compounds I, or mixtures thereof (e.g. racemic mixtures).

10 The compounds of Formula (I) can be prepared through a number of synthetic routes amongst which the ones illustrated in Schemes 1, 2, and 3 (see also for reference *Bioorg. Med. Chem. Lett.* **1995**, 5 (3), 219-222).

a) Scheme 1:



Y' = activated acid, isocyanate

Y = -NHCO-, -HNCONH-

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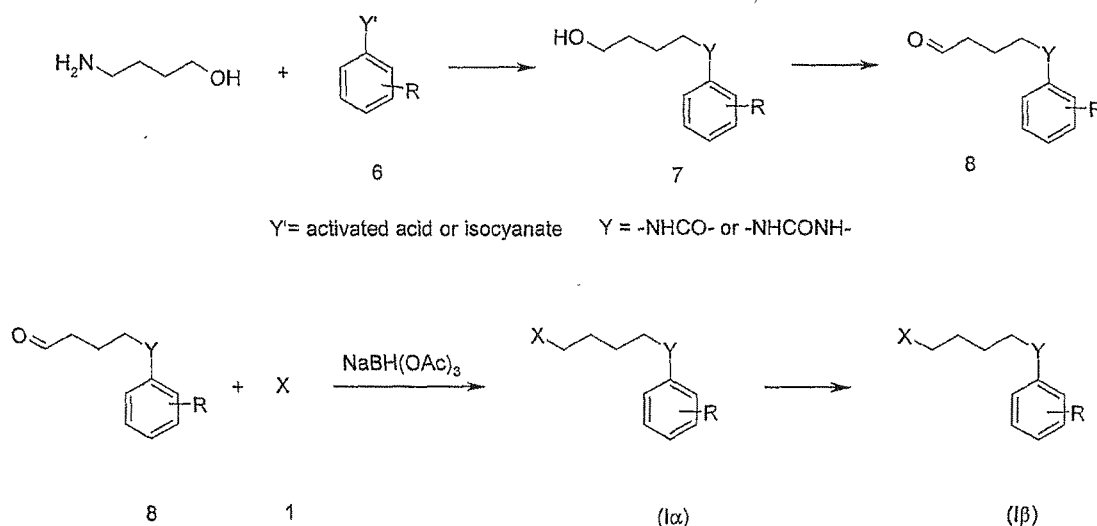
According to Scheme 1, a suitably activated butylphthalimide (compound 2) is reacted with an amine (compound 1) in an organic solvent in the presence of a base. For example, a mixture of 1 (or its hydrochloride salt) and 2 are refluxed in methylethyl ketone in the presence of alkaline carbonate until the reaction is complete, then the reaction mixture is cooled, the insoluble materials removed by filtration, the filtrate washed with CHCl₃, and

20

the filtrate and washings concentrated to dryness.

In the following step, the N-(4-aminobutyl)phthalimide 3 is converted into a (4-aminobutyl)amine 4, for example by refluxing a mixture of 3 and hydrazine hydrate in ethanol. Then 4 is reacted with an activated species 5 such as for example (but not limited to) an acid chloride or an isocyanate in an organic solvent in the presence of a base. For example, to a mixture of 4 and 5 in CH₂Cl₂ triethylamine and a catalytic amount of DMAP are added, to give compounds I. Alternatively, a mixture of 4, 5, a carbodiimide or carbonyldiimidazole and DMAP are reacted to yield compounds I.

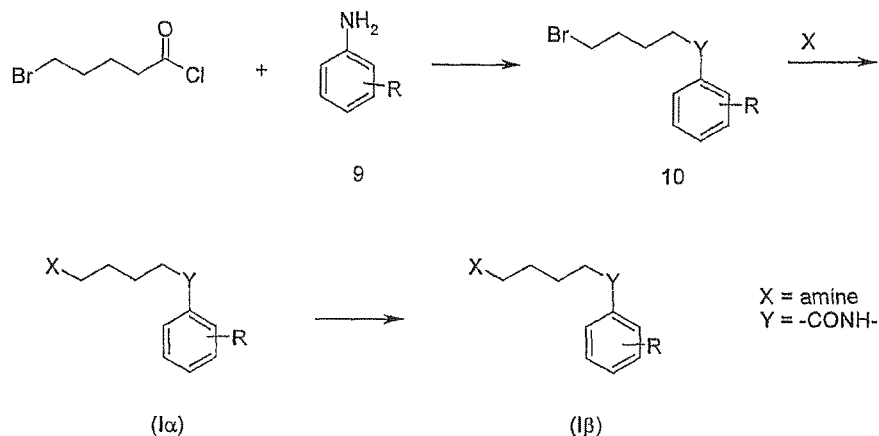
10 b) Scheme 2:



According to Scheme 2, aminobutanol is reacted with an activated acid species or an isocyanate - for example (but not limited to) a substituted acid chloride 6 in the presence of a base - in an organic solvent like dichloromethane until the reaction is complete. The alcohol 7 thus obtained is then oxidised under standard conditions (for example Swern oxidation) and aldehyde 8 is then reacted with the suitably substituted amine 1 under standard conditions - for example with sodium triacetoxyborohydride - to afford compound Ia. In the case of R being a halogen, Ia can be further processed - for example via a cross-coupling reaction with a boronic acid - to yield

compound I β .

c) Scheme 3:



5 According to Scheme 3, 5-bromopentanoyl chloride is reacted with an (hetero)aromatic amine 9 in the presence of an organic base to afford a 5-bromopentanoic acid amide 10. This species is reacted with an amine 1 to displace the halogen and furnish compounds I α . In the case of R being a halogen, I α can be further processed – for example via a cross-coupling
 10 reaction with a boronic acid - to yield compounds I β .

The compounds of formula I, their optical isomers or diastereomers can be purified or separated according to well-known procedures, including but not limited to chromatography with chiral matrix and fractional crystallisation.

The pharmacological activity of a representative group of compounds of
 15 formula I was demonstrated in an *in vitro* assay utilising cells stably transfected with the alpha 7 nicotinic acetylcholine receptor and cells expressing the alpha 1 and alpha 3 nicotinic acetylcholine receptors and 5HT3 receptor as controls for selectivity. Neuroprotection of these compounds was demonstrated in a cell-based excitotoxicity assay utilising primary neuronal
 20 cell cultures.

According to a further aspect, the invention is therefore directed to a method of treating neurological and psychiatric disorders, which comprises

administering to a subject, preferably a human subject in need thereof, an effective amount of a compound of formula I. Neurological and psychiatric disorders that may benefit from the treatment with the invention compounds include but are not limited to senile dementia, attention deficit disorders, 5 Alzheimer's disease and schizophrenia. In general, the compounds of formula I can be used for treating any disease condition, disorder or dysfunction that may benefit from the activation of the alpha 7 nicotinic acetylcholine receptor, including but not limited to Parkinson's disease, Huntington's chorea, amyotrophic lateral sclerosis, multiple sclerosis, epilepsy, memory or learning 10 deficit, panic disorders, cognitive disorders, depression, sepsis, arthritis, immunological and inflammatory disorders.

The dosage of the compounds for use in therapy may vary depending upon, for example, the administration route, the nature and severity of the disease. In general, an acceptable pharmacological effect in humans may be 15 obtained with daily dosages ranging from 0.01 to 200 mg/kg.

In yet a further aspect, the invention refers to a pharmaceutical composition containing one or more compounds of formula I, in association with pharmaceutically acceptable carriers and excipients. The pharmaceutical compositions can be in the form of solid, semi-solid or liquid preparations, 20 preferably in form of solutions, suspensions, powders, granules, tablets, capsules, syrups, suppositories, aerosols or controlled delivery systems. The compositions can be administered by a variety of routes, including oral, transdermal, subcutaneous, intravenous, intramuscular, rectal and intranasal, and are preferably formulated in unit dosage form, each dosage containing 25 from about 1 to about 1000 mg, preferably from 1 to 600 mg of the active ingredient. The compounds of the invention can be in the form of free bases or as acid addition salts, preferably salts with pharmaceutically acceptable acids.

The invention also includes separated isomers and diastereomers of compounds I, or mixtures thereof (e.g. racemic mixtures). The principles and methods for the preparation of pharmaceutical compositions are described for example in Remington's Pharmaceutical Science, Mack Publishing Company,
5 Easton (PA).

Description of the Figures

Figure 1

Effect of compound from Example 64 on NMDA-induced toxicity in rat cortical neurons. Rat cortical neurons were pre-treated with the compound at
10 the indicated concentrations 24 h before addition of NMDA and toxicity determined by lactate dehydrogenase (LDH) measurements after 24 h. Data of all experiments are normalised to 100% NMDA toxicity. Statistical analysis:

* $p < 0.05$ vs NMDA treatment; One-Way ANOVA and Tukey post test values were normalised to the level of NMDA (=100%).

15 *Figure 2*

Effect of sub-chronic treatment of compound from Example 1 or nicotine on number of ChAT-positive neurons in the nucleus basalis of quisqualic acid injected animals. Compounds were administered 24 h and 1 h before quisqualic acid injection and for 7 days after lesioning. Doses: compound 3 mg/kg i.p.
20 daily or nicotine 0.3 mg/kg i.p. daily. The doses were selected on the basis of literature data and comparable effects in behavioral studies. Number of neurons is expressed as % changes vs non-injected hemisphere. Statistical analysis: ANOVA and Fisher Post-Hoc test: $F(3,21) = 13.00$ $P < 0.001$ * $P < 0.05$ vs quisqualic acid injected rats # $P < 0.05$ vs nicotine treated rats.

25 *Figure 3*

Figure 3a - Results of passive avoidance test

Effect of acute administration of compound from Example 1 on

scopolamine-induced amnesia in young rats in passive avoidance test and reversion by the selective alpha-7 antagonist MLA. Amnesia was induced by scopolamine 0.5 mg/kg i.p. 20 min before training trial and the compound (3 mg/kg i.p.) was injected 5 min after scopolamine. MLA (5 mg/kg i.p.) was administered 10 min before scopolamine and compound administration. Results are presented as retest latencies 24 h after the training trial.

Statistical analysis: ANOVA and Tukey Post-Hoc test: * $P < 0.05$ vs saline and scopolamine-treated rats # $P < 0.05$ vs saline treated rats.

Figure 3b - Results of object recognition test

Effect of acute administration of compound from Example 1 on scopolamine-induced amnesia in young rats.. Amnesia was induced by scopolamine 0.2 mg/kg i.p. 20 min before training trial and the compound (3 mg/kg i.p.) was injected 5 min after scopolamine. Results are presented as discrimination index calculated on the exploration time of new (N) and familiar (F) objects during the test trial performed after 2 h from the training trial as follow: Discrimination index: $N-F/N+F$. Statistical analysis: ANOVA and Tukey Post-Hoc test: * $P < 0.05$ scopolamine-treated rats.

Experimental Procedures - Synthesis of compounds

General

Unless otherwise specified all nuclear magnetic resonance spectra were recorded using a Bruker AC200 (200 MHz) or a Varian Mercury Plus 400 Mhzspectrometer equipped with a PFG ATB Broadband probe.

HPLC-MS analyses were performed with an Agilent 1100 instrument, using a Zorbax Eclipse XDB-C8 4.6 x 150 mm; a Zorbax CN 4.6 x 150 mm column or a Zorbax Extend C18 2.1 x 50 mm column, coupled to an atmospheric API-ES MS for the 2.5 minutes method. The 5 and 10 minute methods were run using a waters 2795 separation module equipped with a

Waters Micromass ZQ (ES ionisation) and Waters PDA 2996, using a Waters XTerra MS C18 3.5 μ m 2.1 x 50 mm column.

Preparative HPLC was run using a Waters 2767 system with a binary Gradient Module Waters 2525 pump and coupled to a Waters Micromass ZQ
5 (ES) or Waters 2487 DAD, using a Supelco Discovery HS C18 5.0 μ m 10 x 21.2 mm column

Gradients were run using 0.1% formic acid/water and 0.1% formic acid/acetonitrile with gradient 5/95 to 95/5 in the run time indicated.

All column chromatography was performed following the method of
10 Still, C.; J. Org Chem 43, 2923 (1978). All TLC analyses were performed on silica gel (Merck 60 F254) and spots revealed by UV visualisation at 254 nm and KmnO₄ or ninhydrin stain.

All microwave reactions were performed in a CEM Discover oven.

N-(4-(Arylpiperazin-1-yl)-butyl)phthalimides

15 The compounds were prepared following the general procedure outlined in Nishikawa, Y.; et al; *Chem. Pharm. Bull.*, 1989, 37 (1), 100-105.

A mixture of N-(4-bromobutyl)-phthalimide (0.00135 mol), 1-(aryl)-piperazine hydrochloride (0.00135 mol), K₂CO₃ (0.00270 mol), NaI (0.00186 mol) and methylethyl ketone (7 mL) was refluxed for 20 h with
20 stirring. After the mixture was cooled, the insoluble materials were removed by filtration and washed with CHCl₃. The filtrate and the washings were concentrated to dryness in vacuo.

The residue was subjected to chromatography on silica gel using CHCl₃/MeOH 95/5 as eluent.

25 *4-[4-(Arylpiperazin-1-yl)]-butylamines*

A solution of N-(4-(Arylpiperazin-1-yl)-butyl)phthalimides (0.236 mmol) and hydrazine hydrate (0.478 mmol) in ethanol (2 mL) was

refluxed for 2 h with stirring. After the solution had cooled, the insoluble materials were removed by filtration and washed with EtOH. The filtrate and the washings were concentrated to dryness in vacuo. The residue was taken up with CHCl₃. The CHCl₃ layer was washed with water, dried and concentrated
5 to give the title amine.

4-[4-(2-Methoxy-phenyl)-piperazin-1-yl]-butylamine

a) Following the general procedure, 2-methoxyphenyl-piperazine (3.4 mL, 17.7 mmol) is added to a suspension of N-(4-bromobutyl)phthalimide (5 g, 17.7 mmol), sodium iodide (1.33 g, 8.85 mmol)
10 and potassium carbonate (3.67 g, 26.6 mmol) in 2-butanone (70 mL). The resulting suspension is stirred for 18 h at 100°C, before LC-MS check. The reaction is filtered and the solvent removed by vacuum distillation; the resulting oil is dissolved in 5% MeOH in dichloromethane, washed with water and sat. NaCl, dried over Na₂SO₄. The solvent is removed under reduced
15 pressure to yield the desired product as a thick yellow oil. The residue is extracted into ethyl acetate and washed with water and then saturated brine and dried over sodium sulphate. The solvent is removed under reduced pressure to afford 5.01 g of 2-{4-[4-(2-methoxy-phenyl)-piperazin-1-yl]-butyl}-isoindole-1,3-dione used without further purification in step b) below
20 (72%).

2-{4-[4-(2-Methoxy-phenyl)-piperazin-1-yl]-butyl}-isoindole-1,3-dione (5.01 g, 12.7 mmol) is dissolved in abs. EtOH (60 mL) and hydrazine monohydrate (2.54 mL, 26 mmol) is added dropwise. The reaction is heated at 100°C for 1 h; the reaction is filtered, concentrated at reduced pressure and
25 transformed into its hydrochloride salt. The salt is dissolved in 15% NaOH and extracted into ethyl acetate to yield 2.04 g of 4-[4-(2-Methoxy-phenyl)-piperazin-1-yl]-butylamine as waxy solid (7.8 mmol, 61%).

$C_{15}H_{25}N_3O$ Mass (calculated) [263.39]; (found) $[M+H+] = 264.39$

LC Rt = 0.45, 92% (5 min method)

NMR (400 MHz, $CDCl_3$): 1.48 (2H, m); 1.57 (2H, m); 2.42 (2H, m);
2.65 (4H, bs); 2.72 (2H, m); 3.1 (4H, bs); 3.86 (3H, s); 6.85 (1H, d); 6.97 (3H,
5 m).

4-[4-(2,4-Difluoro-phenyl)-piperazin-1-yl]-butylamine

To a solution of N-(4-bromobutyl)phthalimide (5 g, 17.73 mmol) and 1-(2,4-difluoro-phenyl)-piperazine (17.73 mmol) in 2-butanone (100 mL), potassium carbonate (26.6 mmol) and potassium iodide (13.3 mmol) were
10 added. The resulting mixture was heated at 90°C overnight. After cooling the solution was filtered and evaporated to dryness. The residue was dissolved in dichloromethane (100 mL) and washed with water. The organic phase was dried over sodium sulphate and evaporated. This material was dissolved in ethanol (100 mL) and hydrazine (2 eq) was added. The solution was refluxed
15 for 4 hours when a thick precipitate formed. Conc. HCl (5 mL) was then added and the mixture heated for a further hour. After cooling the solvent was evaporated and the residue dissolved in 2M HCl (100 mL). This solution was filtered and the aqueous filtrate evaporated again to dryness. The resulting residue was taken in isopropanol (30 mL) and filtered to give the
20 hydrochloride salt of the required product. The salt was converted in the free amine by dissolution in NaOH (15% w/w) and extraction with dichloromethane. (2.6 g, 54%).

1H -NMR ($CDCl_3$) δ 1.3 (br s, 2H), 1.46-1.58 (m, 4H), 2.41 (t, 2H), 2.62 (s, 4H), 2.73 (t, 2H), 3.05 (br s, 4H), 6.77-6.83 (m, 2H), 6.87-6.94 (m, 1H)

25 (M+1) e/z 270

4-Morpholin-4-yl-butylamine

a) Following the general procedure, morpholine (1.7 mL, 20 mmol) is

added to a suspension of N-(4-bromobutyl)phthalimide (5.36 g, 20 mmol), sodium iodide (1.5 g, 10 mmol) and potassium carbonate (5.53 g, 40 mmol) in 2-butanone (80 mL). The resulting suspension is stirred for 18 h at 100°C, before LC-MS check. The reaction is filtered and the solvent removed by vacuum distillation; the resulting oil is dissolved in 5% MeOH in dichloromethane, washed with water and sat. NaCl, dried over Na₂SO₄. The solvent is removed under reduced pressure to yield the desired product as a thick yellow oil. The residue was extracted into ethyl acetate and washed with water and then saturated brine and dried over sodium sulphate. The solvent was removed under reduced pressure to afford 5.7 g of 2-(4-Morpholin-4-yl-butyl)-isoindole-1,3-dione used without further purification in step b) below.

$C_{16}H_{20}N_2O_3$ Mass (calculated) [288.35]; (found) [M+H⁺] = 289.36

Lc Rt = 0.83, 95% (3 min method)

b) 4-Morpholin-4-yl-butyl-isoindole-1,3-dione (5.69 g, 19 mmol) is dissolved in abs. EtOH (95 mL) and hydrazine monohydrate (3.8 mL, 80 mmol) is added dropwise. The reaction is heated at 100°C for 1 h; LC-MS show the reaction to be complete. The reaction is filtered, concentrated at reduced pressure and taken up with toluene and dichloromethane to remove excess phthalhydrazide; the crude amine is purified by SCX column, eluting with MeOH:dichloromethane 1:1 followed by 2 M NH₃ in MeOH, to afford 1.46 g (9.2 mmol, 48%).

$C_8H_{18}N_2O$ Mass (calculated) [158.25]; (found) [M+H⁺] = 159.27

LC Rt = 0.29, 96% (3 min method)

NMR (400 MHz, CD₃OD): 1.51 (4H, m); 2.36 (2H, m); 2.46 (4H, s); 2.64 (2H, m); 3.68 (4H, m).

¹H-NMR (CDCl₃) δ 1.26 (br s, 2H), 1.44-1.57 (m, 4H), 2.35 (t, 2H), 2.44 (br s, 4H), 2.71 (t, 2H), 3.72 (m, 4H)

4-(4-Methyl-piperazin-1-yl)-butylamine

Prepared in analogous manner as 4-[4-(2,4-difluoro-phenyl)-piperazin-1-yl]-butylamine and obtained in yield = 25%.

¹H-NMR (dmso-d₆ + D₂O) δ 1.53-1.61 (m, 2H), 1.66-1.74 (m, 2H),
5 2.80 (t, 2H), 2.85 (s, 3H), 3.17 (m, 2H), 3.38 (br s, 4H), 3.67 (br s, 4H); (M+1)
e/z 172.

4-Piperidin-1-yl-butylamine

a) Following the general procedure, N-(4-bromobutyl)phthalimide
(5.96 g, 20 mmol) was added to a suspension of piperidine (1.98 mL,
10 20 mmol), sodium iodide (1.5 g, 10 mmol) and potassium carbonate (4.15 g,
21 mmol) in 2-butanone (100 mL). The resulting suspension was stirred for
18 h at 85°C. The reaction was filtered and the solvent removed by vacuum
distillation; the resulting oil was washed with water and recovered with
dichloromethane. The solvent was removed under reduced pressure to afford
15 3.7 g of desired product as a white solid (yield: 65%).

C₁₇H₂₂N₂O₂ Mass (calculated) [286.38]; (found) [M+H+] = 287

Lc Rt = 0.97, 95% (5 min method)

NMR (400 MHz, CDCl₃) 1.41 (2H, m), 1.49-1.59 (6H, m), 1.65-1.72 (2H,
m), 2.15-2.35 (6H, m), 3.69-3.73 (6H, m), 7.69-7.74 (2H, m), 7.80-7.85 (2H, m).

20 b) 2-(4-Piperidin-1-yl-butyl)-isoindole-1,3-dione (3.7 g, 13 mmol) was
dissolved in EtOH (50 mL) and hydrazine monohydrate (1.26 mL, 26 mmol)
was added dropwise. The mixture was heated at 80°C for 4 h. The reaction
was filtered, concentrated at reduced pressure and taken up with toluene and
dichloromethane to remove excess phthalhydrazide by filtration; the crude
25 amine was purified by SCX column, eluting with MeOH:dichloromethane 1:1
followed by 2 M NH₃ in MeOH, to afford g (410 mg, 35%).

C₉H₂₀N₂ Mass (calculated) [156.27]; (found) [M+H+] = 157

LC Rt = 0.31 (5 min method)

NMR (400 MHz, CD₃OD): 1.45-1.62 (10 H, m), 2.30-2.43 (10 H, m), 2.64-2.67 (2H, m).

1-(4-Amino-butyl)-piperidine-3-carboxylic acid diethylamide

5 a) Following the general procedure, commercially available N,N-diethylnipecotamide (3.4 g, 40 mmol) was weighed, placed in a flask and dissolved in 150 mL 2-butanone. To this N-(4-bromobutyl)phthalimide (11.3 g, 40 mmol), NaI (3 g, 20 mmol) and K₂CO₃ (8.28 g, 60 mmol) were added. The resulting mixture was heated at 85°C for 20 hours. The solution
10 was dried under vacuum and the crude solution was washed twice with water and dichloromethane. The organic layer was purified by flash chromatography using dichloromethane/MeOH 96/4.

C₂₂H₃₁N₃O₃ Mass (calculated) [385.50]; (found) [M+H⁺] = 386

LC Rt = 2.63, 94% (10 min method)

15 NMR (400 MHz, CDCl₃): 1.08-1.12 (2H, m), 1.14-1.21 (2H, m), 1.52-1.76 (8H, m), 2.1 (1H, m), 2.23 (1 H, m), 2.44 (1H, m), 2.79 (1H, m), 2.94 (2H, m), 3.29-3.35 (4H, m), 3.69-3.73 (2H, m), 7.71-7.82 (2H, m), 7.82-7.86 (2H, m).

b) The phthalimide was deprotected using the general method described for the previous examples to obtain the desired product in 38% yield.

20 C₁₄H₂₉N₃O Mass (calculated) [255.23]; (found) [M+H⁺] = 256

LC Rt = 0.35 (10 min method)

NMR (400 MHz, CDCl₃): 1.09 (3H, m); 1.21 (3H, m); 1.50-1.60 (1H, m); 1.62-1.84 (6H, m), 2.13-2.19 (1H, m); 2.35-2.40 (1H, m); 2.46-2.50 (2H, m); 2.79-3.02 (5H, m); 3.27-3.47 (4H, m); 5.20-5.31 (3H, m).

25 *General Procedure for the synthesis of biaryl carboxylic acids*

Prepared according to the procedure outlined in Gong, Y. and Pauls, H. W. Synlett, 2000, 6, 829-831.

A catalytic amount of $\text{Pd}(\text{PPh}_3)_4$ was added to a degassed solution of 4-carboxyphenylboronic acid (0.001 mol) and aryl bromide (0.001 mol) in 0.4 M sodium carbonate solution (5 mL) and acetonitrile (5 mL).

The mixture was heated at 90°C under N_2 for 15-20 h. The hot suspension was filtered. The filtrate was concentrated to about a half the original volume and then washed with CH_2Cl_2 . The aqueous layer was acidified with conc. HCl and the resulting precipitate was collected.

2'-Amino-biphenyl-4-carboxylic acid

Yield: 80%

$^1\text{H-NMR}$ (CD_3OD) δ (ppm): 8.10 (d, 1H); 7.50 (d, 2H); 6.94 (m, 4H)

Mass (ES) m/z %: 214 ($M+1$, 100%).

4-(Pyridin-2-yl)-benzoic acid

Yield: 70%;

$^1\text{H-NMR}$ (CD_3OD) δ (ppm): 8.63 (d, 1H); 8.05 (m, 4H); 7.90 (m, 2H); 7.51 (m, 1H).

Mass (ES) m/z %: 200 ($M+1$, 100%).

4-(1-Oxy-pyridin-2-yl)-benzoic acid

Mass (ES) m/z %: 216 ($M+1$, 100%).

2'-Methylbiphenyl-4-carboxylic acid

Prepared with a modification of the procedure outlined in Leadbeater, N. E.; Marco, M; *Org. Lett.* **2002**, 4 917) 2973-2976:

In a 10 mL glass tube were placed 4-carboxyphenyl boronic acid (166 mg, 1.0 mmol), 2-bromotoluene (120 μL , 1.0 mmol), Na_2CO_3 (315 mg, 3 mmol), $\text{Pd}(\text{OAc})_2$ (1 mg, 0.004 mmol), 2 mL of water and a magnetic stirbar. The vessel was sealed with a septum and placed into the microwave cavity. Microwave irradiation (maximum emitted power 200W) was used to increase the temperature to 150°C; the reaction mixture was then kept at this

temperature for 5 min.

The mixture was allowed to cool to room temperature, and the reaction mixture was filtered washing with little CHCl_3 . The aqueous layer was acidified, and the precipitate collected. The product was purified by chromatography on silica gel using Petroleum Ether/AcOEt 50/50 as eluent to give 67.8 mg of **12**, yield 32%.

$^1\text{H-NMR}$ (CD_3OD) δ (ppm): 8.05 (m, 2H, arom); 7.41 (m, 2H, arom); 7.21 (m, 4H, arom); 2.22 (s, 3H, C- CH_3).

Mass (ES) m/z %: 424 (2M, 100%).

10 *2'-Nitrobiphenyl-4-carboxylic acid*

To a stirred solution of 2'-aminobiphenyl-4-carboxylic acid (213 mg, 0.001 mol) in hexane/water/acetone (6.7:5:1, 6 mL), were added at 0°C NaHCO_3 (400 mg) and Oxone (1.050 g). After 20 min a second portion of NaHCO_3 (400 mg) and Oxone® (1050 mg) was added and, after 20 min, a final portion of NaHCO_3 (400 mg) and Oxone® (1050 mg) was added. After 6 h the suspension was diluted with water and the organic layer was extracted with CH_2Cl_2 . The combined organic layers were evaporated to give 2'-nitro-biphenyl-4-carboxylic acid (138.5 mg, 0.00057 mol), yield 57%.

$^1\text{H-NMR}$ (CD_3OD) δ (ppm): 7.80 (m, 8H)

20 Mass (ES neg) m/z %: 242 (M-1, 100%); 226 (M-1-16, 70%)

2'-Methoxy-biphenyl-4-carboxylic acid

To a solution of 4-carboxyphenylboronic acid (3.32 g, 20 mmol), Fibrecat®1007 (2 g) and potassium carbonate (3.03 g, 22 mmol) in ethanol/water (20 mL/20 mL), 1-bromo-2-methoxy-benzene was added (4.11 g, 22 mmol). The reaction mixture was heated to reflux for 3 hours. After cooling, was filtered and the solution evaporated under reduced pressure. The residue was suspended in aq. citric acid (10% w/v), filtered and

washed with water and diethyl ether. The resulting solid was dried under vacuum to yield the title compound (4.02 g, 88%).

$^1\text{H-NMR}$ (dmso- d_6) δ 3.79 (s, 3H), 7.08 (m, 1H), 7.34 (m, 1H), 7.58 (d, 1H), 7.96 (d, 1H)

5 *2'-Chloro-biphenyl-4-carboxylic acid*

A mixture of 4-carboxyphenylboronic acid (3.32 g, 20 mmol), Fibrecat®1007 (1 g), potassium carbonate (3.03 g, 22 mmol) and 1-bromo-2-chloro-benzene (4.2 g, 22 mmol) were exposed to microwave irradiation in a CEM Discovery Microwave for 15 minutes up to the maximum temperature of
10 120°C. After cooling, the mixture was filtered and the solution evaporated under reduced pressure. The residue was suspended in 1M HCl solution, filtered and washed with water and diethyl ether. The resulting solid was dried under vacuum to yield the title compound (4.0 g, 86%).

$^1\text{H-NMR}$ (dmso- d_6) δ 7.38-7.45 (m, 3H), 7.50-7.59 (m, 3H), 7.98-8.02
15 (m, 2H); (M+1) e/z 233

2',4'-Difluoro-biphenyl-4-carboxylic acid

Prepared as outlined for 2'-chloro-biphenyl-4-carboxylic acid and obtained in yield = 49%.

$^1\text{H-NMR}$ (dmso- d_6) δ 7.24 (m, 1H), 7.42 (m, 1H), 7.62-7.60 (m, 3H),
20 8.04 (d, 2H); (M+1) e/z 235

2'-Carbamoyl-biphenyl-4-carboxylic acid

Prepared as outlined for 2'-chloro-biphenyl-4-carboxylic acid and obtained in yield = 29%.

$^1\text{H-NMR}$ (dmso- d_6) δ 7.33 (s, 1H), 7.40-7.52 (m, 6H), 7.70 (s, 1H),
25 7.95 (d, 2H); (M+1) e/z 242

2-Methyl-biphenyl-4-carboxylic acid

Prepared as outlined for 2'-chloro-biphenyl-4-carboxylic acid and

obtained in yield = 59%.

$^1\text{H-NMR}$ (dmso-d₆) δ 2.29 (s, 3H), 7.31-7.50 (m, 6H), 7.83 (dd, 1H), 7.89 (s, 1H); (M+1) e/z 213

6-Phenyl-nicotinic acid

5 Prepared as outlined for 2'-chloro-biphenyl-4-carboxylic acid

$^1\text{H-NMR}$ (dmso-d₆) δ 7.47-7.55 (m, 3H), 8.1 (d, 1H), 8.11-8.16 (m, 2H), 8.32 (dd, 1H), 9.13 (s, 1H), 13.39 (br s, 1H); (M+1) e/z 200

4-(5-oxo-4,5-dihydro-[1,2,4]oxadiazol-3-yl)-benzoic acid

a) 4-(N-hydroxycarbamimidoyl)-benzoic acid methyl ester

10 A mixture of 4-cyano-benzoic acid methyl ester (16.5 g, 102 mmol), hydroxylamine hydrochloride (102 mmol), NaHCO₃ (110 mmol) in methanol (200 mL) was stirred for 30 minutes at room temperature and heated to the reflux for a further 3 hours. After cooling, water (400 mL) was added, the precipitate collected by filtration, washed and dried in a vacuum oven at 50°C
15 for 8 hours to give the title compound as a white solid (16,5 g, 83%).

(M+1) e/z 195

b) 4-(5-Oxo-4,5-dihydro-[1,2,4]oxadiazol-3-yl)-benzoic acid

To a solution of 4-(N-hydroxycarbamimidoyl)-benzoic acid methyl ester (5.7 g, 29.4 mmol) in dioxane (30 mL) was added CDI (1.2 eq). The
20 reaction mixture was heated to 110°C for 30 minutes. After cooling the solvent was evaporated, the residue suspended in water and the pH adjusted to pH=2 with aq. HCl (3M). The precipitate was collected by filtration washed with water, suspended in aqueous solution of NaOH (30 mL, 10% w/w) and methanol (50 mL) and left stirring at room temperature overnight. After
25 evaporation of the solvents, the residue was taken in water (30 mL), pH adjusted to pH=2 adding aq. HCl (3M). The precipitate was collected by filtration, washed with water and dried under vacuum to yield the title

compound as a white solid (4.1 g, 68%).

¹H-NMR (dms_o-d₆) δ 2.29 (s, 3H), 7.31-7.50 (m, 6H), 7.83 (dd, 1H), 7.89 (s, 1H); (M+1) *e/z* 213

4-(3-Methyl-[1,2,4]oxadiazol-5-yl)-benzoic acid

5 *a) N-(4-Methoxycarbonylbenzoyl)oxy)acetamidine*

To a solution of terephthalic acid monomethyl ester (5 g, 27.7 mmol) in dichloromethane (40 mL), CDI (27.7 mmol) was added. After 10 minutes stirring, N-hydroxy-acetamidine (27.7 mmol) was added and the resulting mixture stirred at room temperature for 3 hours. The solution was filtered and
10 evaporated under reduced pressure to yield the title compound as a white solid (4.9 g, 75%).

(M+1) *e/z* 237

b) 4-(3-Methyl-[1,2,4]oxadiazol-5-yl)-benzoic acid

A mixture of N-(4-methoxycarbonylbenzoyl)oxy)acetamidine (4.9 g, 20.7 mmol) and sodium acetate (20.7 mmol) in methanol (70 mL) and water
15 (20 mL) was heated to 90°C for 8 hours. After cooling a solid crystallised out of solution. The solid was filtered out, suspended in aq. NaOH solution (10% w/w, 30 mL) and methanol (30 mL) and left stirring at room temperature overnight. The solution was then evaporated under reduced pressure, the pH
20 adjusted to pH=3 adding aq. HCl (6M). A precipitated formed, which was collected by filtration, washed with water, diethyl ether and dried under vacuum to yield the title compound as a white solid (2.5 g, 44%).

¹H-NMR (dms_o-d₆) δ 2.44 (s, 3H), 8.17 (m, 4H); (M+1) *e/z* 205

4-(1H-Tetrazol-5-yl)-benzoic acid

25 A mixture of 4-cyano-benzoic acid methyl ester (4.02 g, 25 mmol), sodium azide (32.5 mmol) and triethylamine hydrochloride (32.5 mmol) in toluene (40 mL) is heated at 97°C for 7 hours. After cooling the solution,

water (100 mL) was added. The aqueous phase was separated and to this solution HCl conc (7 g) was added. A precipitate formed which was isolated by filtration and washed with water. The obtained solid was suspended in aq. NaOH solution (20 mL, 10% w/w) and methanol (20 mL) and left stirring at room temperature for 2 hours. The solvent was then evaporated, water was added to the residue and the pH acidified with HCl (6M). A white precipitate formed which was isolated by filtration, washed with water and dried under vacuum to give the title compound (4.5 g, 95%).

$^1\text{H-NMR}$ (dmso-d₆) δ 8.09-8.17 (m, 4H); (M+1) m/z 191

10 *4-(5-Methyl-[1,2,4]oxadiazol-3-yl)-benzoic acid*

To a solution of 4-(N-hydroxycarbamimidoyl)-benzoic acid methyl ester (3.88 g, 20 mmol) in dichloromethane (20 mL), acetic anhydride (40 mmol) was added. The mixture was left stirring at room temperature overnight. After 16 hours the solvent was evaporated, pyridine (30 mL) was added and the reaction mixture heated at 95°C for 2 days. After cooling the solution a solid crystallised out of solution. To this solution, water (20 mL) was added and after 2 hours stirring at room temperature it was filtered and the solid collected. The solid was suspended in aq. NaOH (30 mL, 10% w/w) and methanol (50 mL) and left stirring at room temperature overnight. After evaporation of the solvents, the residue was taken in water (30 mL), pH adjusted to pH=2 adding aq. HCl (3M). A precipitate formed which was collected by filtration, washed with water and dried under vacuum to yield the title compound as a white solid (3.8 g, 93%). (M+1) m/z 205.

General Procedure for the synthesis of biaryl-carboxylic acid chlorides

25 The biarylcarboxylic acids (0.00057 mol) were treated with 5 mL of SOCl₂ for 5 h under reflux. The excess of SOCl₂ was removed by distillation and the crude acid chloride was used in the next reaction without further

purification.

General Procedure for acid - amine coupling method using acid chlorides

A mixture of (4-aryl-piperazin-1-yl)-alkylamine (0.3 mmol),
5 biarylcarboxylic acid chloride (0.3 mmol), triethylamine (0.56 mmol) and a catalytic amount of DMAP in CH_2Cl_2 was stirred at 0°C for 10 min then at room temperature for 4 h.

The CH_2Cl_2 layer was washed with water, dried and concentrated. The residue purified by chromatography on silica gel with $\text{CHCl}_3/\text{MeOH}$ 95/5 as
10 eluent to give the title compound.

General Procedure for acid - amine coupling method using carbodiimide

A solution of (4-aryl-piperazin-1-yl)-alkylamine (0.00014 mol) in 5 mL of dry CH_2Cl_2 was cooled to 0°C . The carboxylic acid (0.0002 mol),
15 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) (0.0002 mol) and a catalytic amount of DMAP were added and the reaction mixture was stirred at room temperature for 16 h.

The CH_2Cl_2 layer was then washed with water, dried and concentrated in vacuo and the residue purified by chromatography eluting with a gradient
20 $\text{CHCl}_3/\text{MeOH}$ 99:1 to 95:5.

General Procedure for acid - amine coupling method using N,N'-carbonyldiimidazole (CDI)

To the preweighed acid (0.55 mmol), dimethylformamide was added (2 mL) to dissolve, followed by N,N'-carbonyldiimidazole (CDI) (0.55 mmol).
25 The solution was then left for 60 minutes before adding the amine (0.6 mmol) and the reaction was stirred for a further 16 hours. The solvent was removed under reduced pressure and the crude mixture was treated with 5% MeOH in

dichloromethane (2 mL) and washed with 10% sodium hydroxide solution (2 mL). This mixture was passed through a column packed with 5 grams of diatomaceous earth and the eluting the product with dichloromethane. The collected organic layer, containing the desired compound, was further purified
5 using flash chromatography eluting with 10% MeOH in dichloromethane. Fractions containing the product were combined and the solvent removed under reduced pressure.

For less reactive carboxylic acids, activation was accomplished by heating the reaction at 60°C for 2 h before adding the amine (1 eq)
10 (1M solution in dimethylformamide) to the reaction mixture upon cooling; the reaction is then shaken at room temperature for 18-24 h.

Alternatively, to a solution of carboxylic acid (0.3 mmol) and CDI (0.3 mmol) in acetonitrile (3 mL), the amine (0.3 mmol) was added after 10 minutes. The reaction mixture was exposed to microwave irradiation for
15 10 minutes at 100°C. After cooling the reaction mixture was absorbed on a SCX cartridge, eluted with dichloromethane, methanol and methanol/ammonia solution. After evaporation, the residue was purified by silica column eluting with a gradient ethyl acetate/cyclohexane (1:1)→ethyl acetate→ethyl acetate/methanol (9:1). The fractions containing the product
20 were combined and the solvent evaporated.

General Procedure for coupling of 4-oxo-butyl-benzamides via reductive alkylation

a) 4-bromo-N-(4-hydroxybutyl)benzamide

A solution of 4-aminobutan-1-ol (20.71 g, 232 mmol) in
25 dichloromethane (50 mL) was added to a stirring solution of 4-bromobenzoyl chloride (51 g, 232 mmol) in dichloromethane (250 mL). Diisopropylethylamine (40.4 mL, 232 mmol) was added and the colourless

solution was stirred at room temperature. LC/MS indicated completion of the reaction after 50 mins. The solution was transferred to a separating funnel and washed with water. A white solid precipitated out which was filtered off and washed with dichloromethane to afford pure product. The filtrate was treated
5 with H₂O which gave rise to further precipitate. The organic layer was washed with 1M HCl and NaHCO₃ (sat), dried over MgSO₄, filtered and concentrated in-vacuo to afford a further batch of product (total yield 57.99 g).

MS (ES) m/z 272/274 (Br)

b) 4-Bromo-N-(4-oxobutyl)-benzamide

10 A solution of oxalyl chloride (4.15 mL, 47.6 mmol) in dichloromethane (200 mL) was stirred under a N₂ flow at -60 °C. DMSO (6.76 mL, 95.2 mmol) was added cautiously ensuring that the temperature remained below -50°C. After 15 mins a solution of 4-bromo-N-(4-hydroxybutyl)benzamide (10 g, 36.6 mmol) in a mixture of dichloromethane (20 mL), THF (40 mL) and
15 DMSO (5 mL) was added. After 30 mins the temperature had risen to -50°C. After 1 h triethylamine (1.637 g, 16.18 mmol) was added. The mixture was allowed to warm to room temperature and stirred overnight. LC/MS indicated completion of the reaction. H₂O (200 mL) was added to the reaction mixture. The organic layer was washed with 1M HCl, NaHCO₃ (sat) and brine, dried
20 over MgSO₄, filtered and concentrated in-vacuo to afford an orange oil (9.93 g).

MS (ES) m/z 270/272 (Br); 252/254 (Br)

a) 3-Bromo-N-(4-hydroxybutyl)benzamide

A solution of 4-aminobutan-1-ol (20.3 g, 228 mmol) in dichloromethane
25 (50 mL) was added to a stirring solution of 3-bromobenzoyl chloride (50 g, 228 mmol) in dichloromethane (250 mL). DIPEA (39.6 mL, 228 mmol) was added and the colourless solution was stirred at room temperature. LC/MS

indicated completion of the reaction after 50 mins. The solution was transferred to a separating funnel and washed with water. A white solid precipitated out which was filtered off and washed with dichloromethane to afford pure product. The filtrate was treated with H₂O which gave rise to
5 further precipitate. The organic layer was washed with 1M HCl and NaHCO₃ (sat), dried over MgSO₄, filtered and concentrated in-vacuo to afford a further batch of product (total yield 46.82 g, 76%, 97% pure by LC/MS).

Rt = 1.09; MS (ES) m/z 272/274 (Br)

b) 3-Bromo-N-(4-oxo-butyl)-benzamide

10 A solution of oxalyl chloride (20.85 mL, 239 mmol) in dichloromethane (900 mL) was stirred under a N₂ flow at -60°C. DMSO (33.9 mL, 478 mmol) was added cautiously ensuring that the temperature remained below -50°C. After 15 mins a solution of 3-bromo-N-(4-hydroxybutyl)benzamide 1 (50 g, 184 mmol) in a mixture of dichloromethane (100 mL), THF (400 mL) and
15 DMSO (50 mL) was added. After 30 mins the temperature had risen to -50°C. After 1 h triethylamine (96.7 g, 956 mmol) was added. The mixture was allowed to warm to room temperature and stirred overnight. LC/MS indicated completion of the reaction. H₂O (1 L) was added to the reaction mixture. The organic layer was washed with 1M HCl, NaHCO₃ (sat) and brine, dried over
20 MgSO₄, filtered and concentrated in-vacuo to afford an orange oil (9.93 g, >100%, 97% pure by LC/MS).

Rt = 1.18; MS (ES) m/z 252/254, 270/272 (Br)

Reductive alkylation on N-(4-oxo-butyl)benzamides

To the preweighed amine (1 equivalent), the aldehyde was added
25 dissolved in anhydrous dichloromethane (1.2 eq, dichloromethane). The solution was left to mix for 90 minutes before addition of sodium triacetoxyborohydride (1.5 equivalents). The reaction was left to mix for a

further 16 hours. The crude reaction was then washed with saturated NaHCO_3 (2 mL solution/reaction) and the organic layer extracted. The dichloromethane crude solution was passed through an SCX column, eluting the desired product in 20% ammonia in methanol. Fractions containing the compound were
5 combined and the product purified further using HPLC prep.

General Procedure for Suzuki coupling of N-(4-amino)butyl-3- or 4-bromobenzamides - exemplified in detail for N-(4-(4-acetylpiperazin-1-yl)butyl)-4-bromobenzamide and 2-ethylphenylboronic acid

N-(4-(4-acetylpiperazin-1-yl)butyl)-4-bromobenzamide (86 mg,
10 0.225 mmol) was dissolved in DME:EtOH 1:1 (20 mL) and added to a microwave tube containing 2-ethylphenylboronic acid (34 mg, 0.225 mmol). 1M Na_2CO_3 in H_2O was added (300 μl , 0.3 mmol) followed by $\text{Pd}(\text{PPh}_3)_4$ (26 mg, 0.0225 mmol). The tube was capped, shaken by hand and loaded into the microwave for 10 mins at 150 °C. The reaction was filtered through celite
15 and washed with MeOH. The filtrate was concentrated in-vacuo and purified by reverse phase preparative HPLC. The product was taken on directly to form the HCl salt: 200 μl 1.25 M HCl in MeOH and 800 μl dichloromethane were added to the title compound and the solution was shaken and concentrated in-vacuo to afford the hydrochloride salt (38.7 mg).

20 MS (ES) m/z 408

General procedures for 5-alkylaminopentanoic acid arylamides preparation from 5-bromopentanoyl chloride

In dichloromethane at 0°C-room temperature: A solution of aromatic amine (1 eq) and triethylamine (1 eq) in dichloromethane (0.2 mmol/mL) is
25 cooled at 0°C under nitrogen atmosphere. 5-Bromopentanoyl chloride (1 eq) in dichloromethane (0.3 mmol/mL) is slowly added and the mixture stirred at room temperature for 1.5 hr. The amine (5 eq) and triethylamine (1 eq) are

added at once and the reaction is stirred at room temperature for 40 hrs. The organic solution is then washed with brine, dried and the solvent removed. The product are crystallised by hexane: diethylether 1:1 or purified by flash chromatography.

5 *Modified room temperature conditions for array synthesis:* To a solution of aniline (1 eq) and triethylamine (1 eq) in dichloromethane (2 mL) at room temperature was slowly added 5-bromo-pentanoyl chloride (1 eq) and the mixture stirred for 1.5 hr. The solution was added to a previously prepared vial containing the amine (5 eq) and triethylamine (1 eq) and the reactions
10 were shaken at room temperature for 40 hrs. The organic solution was washed with brine, dried and the solvent removed. The products were purified by flash chromatography or by preparative HPLC.

In dichloroethane/dimethylformamide at 55°C: A substituted aromatic amine (1 eq) and triethylamine (1 eq) are weighed in a glass vial and
15 1,2-dichloroethane is added to give a 1.2 M solution; 5-bromovaleryl chloride (0.95 eq) is then added dropwise as a solution in dimethylformamide (1.2 M) and the reaction is shaken at room temperature for 1 h 30 min. The amine (3 eq) and triethylamine (1 eq) are then added as a solution in DCE (amine concentration 1.8 M) and the reaction mixture shaken at 55°C for 4 h. After
20 this period, the reaction mixture is cooled and partitioned between water and dichloromethane; the organic layer is washed with sat. NaCl and dried over Na₂SO₄. The crude amides obtained after solvent evaporation at reduced pressure are purified by preparative HPLC.

5-(4-Methyl-piperazin-1-yl)-pentanoic acid (4-bromo-phenyl)-amide

25 Prepared according the general procedure in dichloromethane at room temperature to give 3.7 g (70%) of the title compound.

 C₁₆H₂₄N₃OBr Mass (calculated) [354.29]; found [M+H⁺] = 354/356

(Br),

Lc Rt = 0.58, 93%

NMR (400 MHz, DMSO): 1.43 (2H, m); 1.55 (2H, m); 2.23 (3H, s);
2.27-2.50 (12H, m); 7.44 (2H, d, J= 9 Hz); 7.55 (2H, d, J= 9 Hz); 10.05 (1H,
5 s).

General Suzuki cross-coupling procedure for the synthesis of arylamides

To a degassed mixture of 5-alkylamino-pentanoic acid bromoaryl-amide
(0.1 g, 1 eq) and a substituted benzenboronic acid (1.1 eq) in
10 acetonitrile/sodium carbonate 0.4 M solution 1/1 (4 mL) a catalytic amount of
Pd[(PPh₃)]₄ (5 mmol %) was added. The reaction mixture was heated at 90°C
for 20 minutes under microwave irradiation (150 Watt) and then again other
20 minutes. The organic layer was separated and purified by SCX column.
The solvent was removed under reduced pressure to afford the corresponding
15 product.

General procedure for urea synthesis from isocyanates

To a cooled 0.2 M solution of amine (1 eq) in dichloromethane, 1 eq of
bromophenylisocyanate was added. The mixture was left stirring at 0°C and it
was stopped when a white solid was formed (1 h), after ca. 1 hour. The
20 product was recovered by filtration as a white solid which was used without
further purification.

General Suzuki cross- coupling procedure for the synthesis of ureas

Microwave irradiation

To a degassed 0.067 M solution of bromide (1 eq, prepared following
25 the procedure for ureas described above) in acetonitrile/water (1/1), the
appropriate boronic acid (1 eq) and Na₂CO₃ (3eq) were added followed by
Pd[(PPh₃)]₄ (10% mol). The solution was irradiated under microwave

conditions, using the following parameters: power = 200 watt; ramp time = 1 min; hold time = 20 min; temp = 90°C; pressure = 200 psi. The acetonitrile layer was separated and the crude mixture was purified using a SCX column washing with dichloromethane/MeOH followed by MeOH and then
5 NH₃/MeOH to elute the product. The fractions containing the desired product were combined and dried under reduced pressure.

Thermal heating

The urea was weighted (1 eq, prepared following the procedure for ureas described above), placed in a 2-neck flask and dissolved in a degassed
10 solution of acetonitrile/water (4/1, 0.04 M). To this solution boronic acid (1.1 eq), Na₂CO₃ (3 eq) and Pd[(PPh₃)]₄ (10% mmol) were added. The mixture was heated at 80°C and stirred for 20 hours. The solution was filtered on Celite layer and purified using SCX or preparative HPLC.

Example 1

15 *N*-{4-[4-(2,4-Dimethoxy-phenyl)-piperazin-1-yl]-butyl}-4-(pyridin-2-yl)-benzamide

a) 1-(2,4-dimethoxy-phenyl)-piperazine hydrochloride

Prepared with a modification of Pascal, J. C.; et al. *Eur. J. Med. Chem.*, 1990, 25, 291-293: a solution of 1.48 g (0.0097 mol) of 2,4-dimethoxyaniline,
20 1.89 g (0.0160 mol) of bis-2-chloroethylamine hydrochloride and 2.00 g of K₂CO₃ in 25 mL of 1-butanol was refluxed for 24 h then filtered hot.

The solvent was removed under reduced pressure and the residue triturated with acetone. The resulting powder was filtered and dried to give 1.25 g of the title compound.

25 ¹H-NMR (DMSO-d₆) δ (ppm): 9.21 (br s, 1H); 6.82 (d, 1H); 6.52 (s, 1H); 6.42 (d, 1H); 3.74 (s, 3H); 3.68 (s, 3H); 3.12 (s, 4H); 3.07 (s, 4H).

b) 2-{4-[4-(2,4-Dimethoxy-phenyl)-piperazin-1-yl]-butyl}-isoindole-1,3-

dione

Prepared following the general procedure outlined in Nishikawa, Y.; et al; *Chem. Pharm. Bull.*, 1989, 37 (1), 100-105.

A mixture of *N*-(4-bromobutyl)phthalimide (0.00135 mol), 1-(2',4'-
5 dimethoxyphenyl)-piperazine hydrochloride (0.00135 mol), K_2CO_3 (0.00270 mol), NaI (0.00186 mol) and methylethyl ketone (7 mL) was refluxed for 20 h with stirring. After the mixture had cooled, the insoluble materials were removed by filtration and washed with $CHCl_3$. The filtrate and the washings were concentrated to dryness in vacuo.

10 The residue was purified by chromatography on silica gel with $CHCl_3$ /MeOH 95/5 as eluent. Yield: 68%.

1H -NMR ($CDCl_3$) δ (ppm): 7.73 (m, 4H); 6.82 (d, 1H); 6.40 (m, 2H); 3.79 (s, 3H), 3.73 (s, 3H), 3.65 (m, 2H); 2.98 (m, 4H); 2.61 (m, 4H); 2.41 (t, 2H); 1.66 (m, 4H).

15 *c) 4-[4-(2,4-Dimethoxy-phenyl)-piperazin-1-yl]-butylamine*

A solution of 2-{4-[4-(2,4-dimethoxy-phenyl)-piperazin-1-yl]-butyl}-
-isoindole-1,3-dione (0.000236 mol) and hydrazine hydrate (0.000478 mol) in ethanol (2 mL) was refluxed for 2 h with stirring. After the solution had cooled, any insoluble materials were removed by filtration and washed with
20 EtOH. The filtrate and the washings were concentrated in vacuo to dryness. The residue was taken up with $CHCl_3$. The $CHCl_3$ layer was washed with water, dried and concentrated to give the title amine. Yield: 50%.

1H -NMR ($CDCl_3$) δ (ppm): 6.85 (d, 1H); 6.41 (m, 2H); 3.81 (s, 3H); 3.75 (s, 3H); 3.01 (m, 4H); 2.63 (m, 4H); 2.40 (t, 2H); 1.35 (m, 6H).

25 *d) N-{4-[4-(2,4-Dimethoxy-phenyl)-piperazin-1-yl]-butyl}-4-(pyridin-2-yl)-benzamide*

Prepared by reaction with 4-(pyridin-2-yl)-benzoic acid according to the

general procedure (acid chloride method).

Yield: 35%.

Mp 154.5-156°C (free base); 212-216°C (HCl salt)

¹H-NMR (CDCl₃) δ (ppm): 8.66 (d, 1H); 8.02 (d, 2H); 7.85 (d, 2H);
5 7.75 (m, 2H); 7.23 (m, 1H); 6.96 (br s, 1H); 6.76 (d, 1H); 6.42 (d, 1H); 6.36
(dd, 1H); 3.78 (s, 3H); 3.72 (s, 3H); 3.47 (m, 2H); 2.97 (m, 4H); 2.65 (m, 4H);
2.47 (t, 2H); 1.70 (m, 4H)

Mass (ES) m/z %: 475 (M+1, 100%); 497 (M+Na, 19%)

HPLC: column Zorbax C8 MeOH 80% / H₂O 20%, 1.0 mL/min;

10 Rt 6.54; area = 99%

Example 2

Biphenyl-4-carboxylic acid {4-[4-(2,4-dimethoxy-phenyl)-piperazin-1-yl]-butyl}-amide

Prepared from 4-[4-(2,4-dimethoxy-phenyl)-piperazin-1-yl]-butylamine
15 and 4-biphenylcarboxylic acid following the general procedure (acid chloride method).

Yield: 35%

¹H-NMR (CDCl₃) δ (ppm): 7.82 (d, 2H); 7.5-7.6 (m, 4H); 7.48-7.5 (m,
3H); 6.89 (br s, 1H); 6.77 (d, 1H); 6.45 (d, 1H); 6.34 (dd, 1H); 3.80 (s, 3H); 3.73
20 (s, 3H); 3.49 (m, 2H); 2.96 (m, 4H); 2.64 (m, 4H); 2.45 (t, 2H); 1.68 (m, 4H).

Mass (ES) m/z %: 474 (M+1, 100%); 496 (M+Na, 6%).

HPLC: column: Zorbax CN AcCN 40%/H₂O (CF₃COOH pH = 2,3)
60%, 0.8 mL/min; Rt = 5.396; Area 98%

Example 3

25 *2'-Nitro-biphenyl-4-carboxylic acid {4-[4-(2,4-dimethoxy-phenyl)-piperazin-1-yl]-butyl}-amide*

Prepared from 4-[4-(2,4-dimethoxy-phenyl)-piperazin-1-yl]-butylamine

and 2'-nitrobiphenyl-4-carboxylic acid following the general procedure (acid chloride method).

Yield: 17%

¹H-NMR (CDCl₃) δ (ppm): 7.7-7.9 (m, 3H); 7.45-7.55 (m, 2H); 7.3-7.4
5 (m, 3H); 6.84 (br s, 1H); 6.80 (d, 1H); 6.44 (d, 1H); 6.37 (dd, 1H); 3.80 (s, 3H); 3.74 (s, 3H); 3.49 (m, 2H); 2.97 (m, 4H); 2.63 (m, 4H); 2.46 (t, 2H); 1.68 (m, 4H)

Mass (ES) m/z %: 519 (M+1, 100%); 541 (M+Na, 11%)

HPLC: column Zorbax CN MeOH 50% / H₂O (CF₃COOH pH = 2) 50%,
10 0.4 mL/min; Rt = 17.209; Area 88%

Example 4

2'-Fluoro-biphenyl-4-carboxylic acid {4-[4-(2,4-dimethoxy-phenyl)-piperazin-1-yl]-butyl}-amide

Prepared from 4-[4-(2,4-dimethoxy-phenyl)-piperazin-1-yl]-butylamine
15 and 2'-fluorobiphenyl-4-carboxylic acid following the general procedure (acid chloride method).

Yield: 20%

Mp = 124-125.5°C

R_t (CHCl₃/MeOH 95/5) 0.21

20 ¹H-NMR (CDCl₃) δ (ppm): 7.81 (d, 2H); 7.56 (d, 2H); 7.1-7.4 (m, 4H); 6.99 (s br, 1H); 6.76 (d, 1H); 6.43 (d, 1H); 6.33 (dd, 1H); 3.78 (s, 3H); 3.71 (s, 3H); 3.46 (m, 2H); 2.94 (m, 4H); 2.60 (m, 4H); 2.44 (t, 2H); 1.66 (m, 4H)

Mass (ES) m/z %: 492 (M+1, 100%);

HPLC: column Zorbax CN AcCN 50% / H₂O (CF₃COOH pH = 2,3)
25 50%, 0.4 mL/min; Rt = 13.525; Area 96%

Example 5

2'-Methyl-biphenyl-4-carboxylic acid {4-[4-(2,4-dimethoxy-phenyl)-

piperazin-1-yl]-butyl}-amide

Prepared from 4-[4-(2,4-dimethoxy-phenyl)-piperazin-1-yl]-butylamine and 2'-methylbiphenyl-4-carboxylic acid following the general procedure (acid chloride method).

5 Yield: 21%

¹H-NMR (CDCl₃) δ (ppm): 7.80 (d, 2H); 7.35 (d, 2H); 7.2-7.4 (m, 4H); 6.88 (br s, 1H); 6.79 (d, 1H); 6.46 (d, 1H); 6.36 (m, 1H); 3.82 (s, 3H); 3.76 (s, 3H); 3.50 (m, 2H); 2.98 (m, 4H); 2.66 (m, 4H); 2.47 (m, 2H); 2.25 (s, 3H); 1.70 (m, 4H)

10 Mass (ES) m/z %: 488 (M+1, 100%)

HPLC: column Zorbax C8 AcCN 40%/H₂O (CF₃COOH pH = 2,3) 60%, 1.0 mL/min; Rt = 11.748; Area 96%

Example 6

N-{4-[4-(2-Methoxy-phenyl)-piperazin-1-yl]-butyl}-4-(pyridin-2-yl)-
15 benzamide

a) 2-{4-[4-(2-Methoxy-phenyl)-piperazin-1-yl]-butyl}-isoindole-1,3-dione

Prepared according to the general procedure

Yield: 80%

20 ¹H-NMR (CDCl₃) δ (ppm): 7.72 (m, 4H); 6.89 (m, 4H); 3.81 (s, 3H); 3.69 (t, 2H); 3.15 (m, 4H); 2.60 (4H, m); 2.40 (t, 2H); 1.66 (m, 4H).

b) 4-[4-(2-Methoxy-phenyl)-piperazin-1-yl]-butylamine

Prepared according to the general procedure

Yield: 53%

25 ¹H-NMR (CD₃OD) δ (ppm): 6.90 (m, 4H); 3.83 (s, 3H); 3.05 (m, 4H); 2.79 (t, 2H); 2.66 (4H, m); 2.43 (m, 2H); 1.60 (m, 4H).

Mass (ES) m/z %: 264 (M+1, 100%).

c) *N*-{4-[4-(2-Methoxy-phenyl)-piperazin-1-yl]-butyl}-4-(pyridin-2-yl)-benzamide

Prepared by reaction with 4-(pyridin-2-yl)-benzoic acid according to the general procedure - carbodiimide method.

5 Yield: 41%

Mp = 152.3-154.6°C

R_t (CHCl₃/MeOH 95/5) = 0.15

¹H-NMR (CDCl₃) δ (ppm): 8.66 (d, 1H); 8.00 (d, 2H); 7.84 (d, 2H); 7.70 (m, 2H); 7.21 (m, 1H); 6.8-7.0 (m, 5H); 3.80 (s, 3H); 3.44 (m, 2H); 3.03
10 (m, 4H); 2.62 (m, 4H); 2.43 (m, 2H); 1.65 (m, 4H).

Mass (ES) m/z %: 445 (M+1, 100%); 467 (M+Na, 78%).

HPLC: column Zorbax C8 MeOH 80%/H₂O 20%, 0.8 mL/min; R_t = 4.72; area: 99.9%.

Example 7

15 *1H-Indole-6-carboxylic acid* {4-[4-(2,4-difluoro-phenyl)-piperazin-1-yl]-butyl}-amide

Following the general procedure, 6-indolecarboxylic acid (44 mg, 0.27 mmol) is dissolved in dimethylformamide (1 mL) and 1,1'-carbonyldiimidazole (44 mg, 0.27 mmol) is added. 4-[4-(2,4-Difluoro-phenyl)-piperazin-1-yl]-butylamine (73 mg, 0.27 mmol) dissolved in
20 dimethylformamide (0.25 mL) is then added and the mixture is allowed to react for 18 h. Work-up followed by preparative HPLC affords the title compound (51 mg, 41%, > 95% pure) as formate salt.

C₂₃H₂₆F₂N₄O Mass (calculated) [412.49]; (found) [M+H⁺] = 413

25 LC R_t = 3.02, 100% (10 min method)

NMR (400 MHz, CDCl₃): 1.51 (4H, m); 2.34 (2H, t); 2.47 (4H, bs); 2.93 (4H, bs); 3.26 (2H, m); 6.49 (1H, s); 6.95-7.01 (2H, m); 7.12-7.17 (1H,

m); 7.40 (2H, m); 7.6 (1H, dd, J=8.4, 1.2), 8.09 (1H, s); 8.17 (1H, HCOOH,s); 8.26 (1H, t); 11.27 (1H, s).

Example 8

N-(4-Azepan-1-yl-butyl)-4-pyridin-2-yl-benzamide

5 *a) N-(4-Hydroxy-butyl)-4-pyridin-2-yl-benzamide*

CDI (4.07 g, 25 mmol) was added to a solution of 4-pyridin-2-yl-benzoic acid (5.0 g, 25 mmol) in dichloromethane and the reaction mixture stirred for 4 hours. 4-aminobutanol (3.0 mL, 30 mmol) was added and the reaction mixture stirred for 4 hours after which the solution was washed with a
10 saturated solution of Na₂CO₃. The organic layer was separated, dried over MgSO₄, filtered and the solvent removed under reduced pressure. The product was purified by column chromatography (dichloromethane, dichloromethane/MeOH 1%) to give 2.4 g of the title alcohol.

LC Rt = 0.98 min (5 min run)

15 (M+1=271)

¹H NMR (400 MHz, DMSO): 8.71-8.66 (1H,m), 8.53-8.46 (1H, m), 8.78 (2H,d, 8.1 Hz), 8.12 (1H, d, 8.3 Hz), 7.94 (2H, d, 8.1 Hz), 7.92-7.83 (1H, m), 7.46-7.36 (1H, m), 4.38 (1H, t, 6.6 Hz), 3.42 (2H, dd, 6.6 Hz, 12.0 Hz), 3.35-3.25 (2H, m), 1.60-1.42 (4H,m).

20 *b) N-(4-Oxo-butyl)-4-pyridin-2-yl-benzamide*

A solution of oxalyl chloride (42 µL, 0.48 mmol) in dichloromethane (5 mL) was stirred under N₂ at -60°C. DMSO (34 µL, 0.48 mmol) was added followed after 15 mins by a solution of alcohol (100 mg, 0.37 mmol) in dichloromethane (100 mL). After 2 h triethylamine (106 µl, 0.74 mmol) was
25 added. The mixture was then allowed to warm to room temperature and stirred overnight. LC/MS indicated completion of the reaction. The organic layer was washed with a saturated solution of NH₄Cl, dried over MgSO₄, filtered and

concentrated under reduced pressure to give 100 mg of a white powder (92% pure by LC/MS $R_t = 0.98$, $M+1 = 269$) which was used in the next step without further purification.

c) N-(4-Azepan-1-yl-butyl)-4-pyridin-2-yl-benzamide

5 Azepane (50 μ l, 0.45 mmol) was weighed into a clean glass vial. To this, the crude *N*-(4-oxo-butyl)-4-pyridin-2-yl-benzamide (100 mg, 0.37 mmol) was added, dissolved in 2 mL of anhydrous dichloromethane. The reaction was left to mix for 90 minutes before addition of sodium triacetoxyborohydride (118 mg, 0.56 mmol), after which it was stirred for
10 16 hours at room temperature before washing the crude reaction with saturated NaHCO_3 (2 mL solution) and extracting the organic layer. The dichloromethane crude solution was passed through an SCX column, eluting the desired product in 20% ammonia in methanol. Fractions containing the compound were combined and the product purified further using HPLC prep
15 to yield *N*-(4-Azepan-1-yl-butyl)-4-pyridin-2-yl-benzamide as the formate salt (47 mg, 36% yield).

^1H NMR (CDCl_3) 8.08 (m, 4H), 7.77 (m, 3H), 7.27 (m, 1H), 3.54 (m, 2H), 3.10 (m, 6H), 1.89 (m, 6H), 1.73 (m, 6H)

Example 9

20 *5-Piperidin-1-yl-pentanoic acid (3-chloro-phenyl)-amide*

Following the general procedure in dichloroethane/dimethylformamide at 55°C, 3-chloroaniline (76 mg, 0.6 mmol) and triethylamine (60 mg, 0.6 mmol) are dissolved in dimethylformamide (0.5 mL) and 5-bromovaleryl chloride (113 mg, 0.57 mmol) in dimethylformamide (0.5 mL) is added
25 dropwise. After 1h 30 min, piperidine (153 mg, 1.8 mmol) and triethylamine (60 mg, 0.6 mmol) in dimethylformamide (0.5 mL) and the reaction mixture heated at +55°C for 4 h. Work-up followed by preparative HPLC affords the

title compound (118 mg, 67%) as a white solid as formate salt.

$C_{16}H_{23}N_2O$ Mass (calculated) [294.82]; (found) $[M+H]^+ = 295$

LC Rt = 1.78, 100% (10 min method)

NMR (400 MHz, dms α -d $_6$): 1.48 (2H, m); 1.52 (6H, m); 2.31 (2H, t);
5 2.48 (6H, m); 7.05 (1H, dd, J=8, 1.2); 7.30 (1H, m); 7.41 (1H, dd, J=8.4, 0.8);
7.80 (1H, s); 8.21 (1H, HCOOH, s); 10.1 (1H, bs).

Example 10

5-morpholin-4-yl-pentanoic acid (4-bromo-phenyl)-amide

Prepared according the general procedure in dichloromethane at room
10 temperature to give 6.4 g (93%) of the title compound.

$C_{15}H_{21}N_2O_2Br$ Mass (calculated) [341.24]; found $[M+H]^+ = 341/343$
(Br)

Lc Rt = 2.30, 100%

NMR (400 MHz, DMSO): 1.44 (2H, m); 1.57 (2H, m); 2.29 (8H, m),
15 3.54 (4H, m), 7.44 (2H, d, J=7 Hz), 7.54 (2H, d, J=7 Hz).

Example 11

5-Piperidin-1-yl-pentanoic acid (3-bromo-phenyl)-amide

Prepared according the general procedure in dichloromethane at room
temperature to give 1.7 g (33%) of the title compound.

20 $C_{16}H_{23}N_2OBr$ Mass (calculated) [339.28]; found $[M+H]^+ = 339/341$
(Br),

Lc Rt = 1.86, 98%

NMR (400 MHz, DMSO): 1.51-1.64 (10H, m); 2.34 (2H, m); 2.23 (2H,
m); 2.76 (4H, m); 2.97 (2H, m); 7.12-7.264 (2H, m); 7.48 (2H, br d, J= 8 Hz);
25 7.97 (1H, s).

Example 12

5-Morpholin-4-yl-pentanoic acid (2'-trifluoromethyl-biphenyl-4-yl)-

amide

Prepared according the general procedure in dichloromethane at room temperature followed by Suzuki coupling to give 0.1 g (92%) of the title compound.

5 $C_{22}H_{25}N_2O_2F_3$ Mass (calculated) [406.44]; (found) $[M+H+] = 407$

Lc Rt = 3.36, 98%

NMR (400 MHz, DMSO): 1.45 (2H, m); 1.6 (2H, m); 2.3 (8H, m); 3.55 (4H, m); 7.21 (2H, d, $J=8.4$ Hz); 7.36 (1H, d, $J=7.3$ Hz); 7.56 (1H, m); 7.63 (2H, d, $J=8.4$ Hz); 7.68 (1H, m); 7.79 (1H, d, $J=7.7$ Hz)

10 *Example 13*

4'-[5-(4-Methyl-piperazin-1-yl)-pentanoylamino]-biphenyl-3-carboxylic acid amide

Prepared according the general procedure in dichloromethane at room temperature followed by Suzuki coupling to give 0.07 g (63%) of the title
15 compound.

$C_{23}H_{30}N_4O_2$ Mass (calculated) [394.51]; (found) $[M+H+] = 395$

Lc Rt = 1.06, 100%

NMR (400 MHz, DMSO): 1.43 (2H, m); 1.58 (2H, m); 2.10 (3H, s);
2.12-2.44 (12H, m); 7.40 (1H, s); 7.49 (1H, m); 7.68 (4H, m); 7.78 (2H, m);
20 8.06 (1H, s); 8.11 (1H, s); 9.97 (1H, s).

Example 14

5-(4-Acetyl-piperazin-1-yl)-pentanoic acid (2'-methoxy-biphenyl-4-yl)-amide

Prepared according the general procedure in dichloromethane at room
25 temperature followed by Suzuki coupling to give 46 mg (51%) of the title compound.

$C_{24}H_{31}N_3O_3$ Mass (calculated) [409.53]*; (found) $[M+H+] = 410$

LC Rt = 2.21, 100% (10 min method)

NMR (400 MHz, CD₃OD): 1.62 (2H, m); 1.74(2H, m); 2.07 (3H, s); 2.41-2.49 (8H, m); 3.53 (2H, m); 3.58 (2H, m); 3.78 (3H, s); 6.98 (1H, m); 7.04 (1H, d, J=8); 7.27 (2H, m); 7.43 (2H, d, J= 8.8); 7.56 (2H, d, J=8.8)

5 *Example 15*

4-Acetyl-1-[4-(2',3'-difluoro-biphenyl-4-ylcarbamoyl)-butyl]-[1,4]diazepan-1-ium formate

Prepared according the general procedure in dichloromethane at room temperature followed by Suzuki coupling to give 0.04 g (37%) of the title
10 compound.

C₂₄H₂₉N₃O₂F₂ HCO₂H Mass (calculated) [429.51/46.01]; (found) [M+H+] = 430.28

Lc Rt = 2.98, 100%

NMR (400 MHz, DMSO): 1.44 (2H, m); 1.58 (2H, m); 1.66 (1H, m);
15 1.75 (1H, m); 1.96 (3H, s), 2.32 (2H, m); 2.42 (2H, m); 2.52 (3H, m); 2.62 (1H, m); 3.54 (4H, m), 7.24-7.42 (3H, m); 7.5 (2H, d, J=9 Hz); 7.7 (2H, d, J=9 Hz); 8.16 (1H, s); 10.03 (1H, s)

Example 16

5-Piperidin-1-yl-pentanoic acid (3'-hydroxy-biphenyl-3-yl)-amide

20 Prepared according the general procedure in dichloromethane at room temperature followed by Suzuki coupling to give 0.06 g (58%) of the title compound.

C₂₂H₂₈N₂O₂ Mass (calculated) [352.47]; (found) [M+H+] = 353.32

Lc Rt = 1.90, 99%

25 NMR (400 MHz, DMSO): 1.34 (2H, m); 1.40-1.47 (6H, m); 1.57 (2H, m); 2.19-2.33 (8H, m); 6.73 (1H, d, J= 8 Hz); 6.95 (1H, s); 6.99 (1H, d, J= 7 Hz); 7.23 (2H, m); 7.32 (1H, m); 7.51 (1H, d, J= 9 Hz); 7.87 (1H, s); 9.56

(1H, br s); 9.94 (1H, s).

Example 17

1-(2'-Chloro-biphenyl-4-yl)-3-(4-morpholin-4-yl-butyl)-urea

1-(4-Bromo-phenyl)-3-(4-morpholin-4-yl-butyl)-urea was weighed
5 (0.8 g, 0.22 mmol), placed in 2 necks flask and dissolved in a degassed
solution of acetonitrile (4 mL) and water (1 mL). 2-Chloro-phenylboronic acid
(0.33 g, 0.24 mmol) and Na₂CO₃ (0.65 g, 0.6 mmol) and a catalytic amount of
Pd[(PPh₃)]₄ werer then added in sequence and the mixture was heated at 80°C
and stirred for 20 hours. The solution was filtered on Celite layer and purified
10 using preparative HPLC.

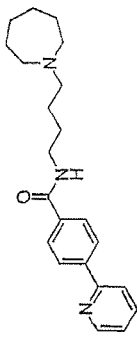
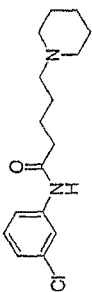
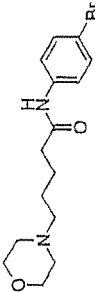
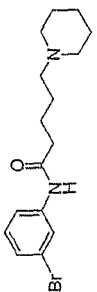
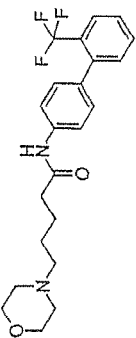
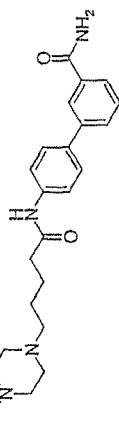
C₂₁H₂₆N₃O₂ Mass (calculated) [387.91]; (found) [M+H+] = 388

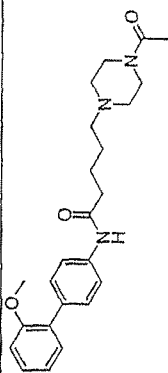
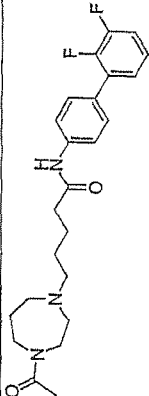
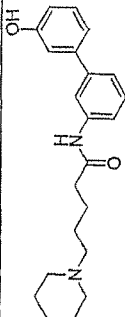
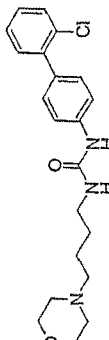
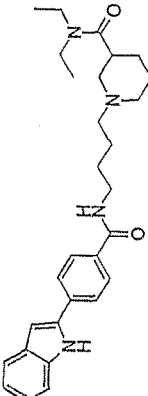
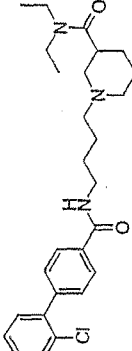
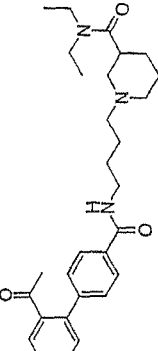
Lc Rt: 3.20 (96%)

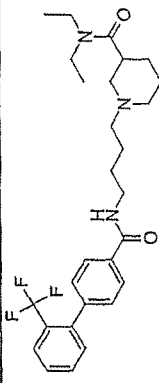
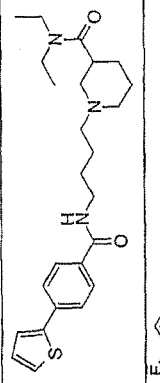
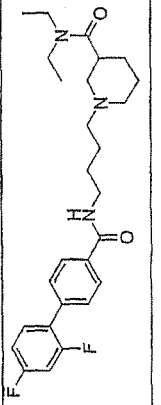
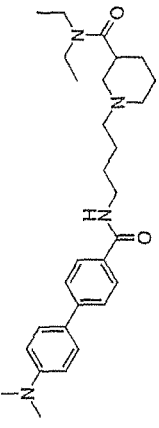
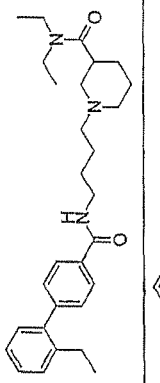
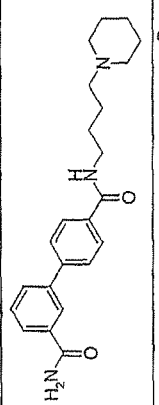
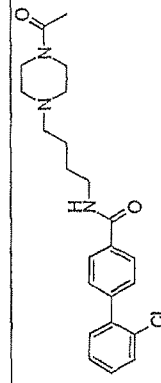
NMR (400 MHz, MeOH): 1.56-1.58 (2H, m), 1.71 (2H, m), 2.94-2.98
(2H, m), 3.06-3.22 (4H, m), 3.22-3.25 (2H, m), 3.8 (4H, m), 7.24-7.29 (5H,
15 m), 7.37-7.42 (3H, m), 8.31 (1H, s)

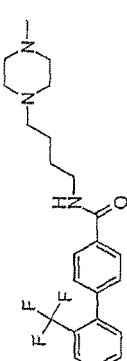
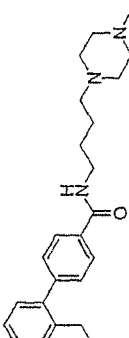
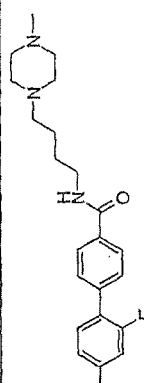
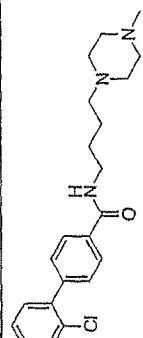
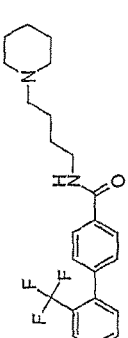
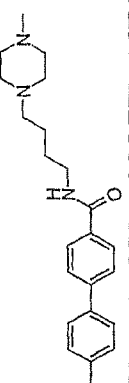
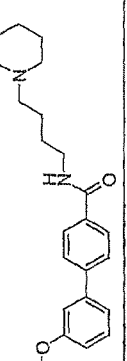
Table 1 - Examples 18-254

Table 1 shows a selection of the compounds synthesised, which were
prepared according to the method indicated in the last column of the table and
discussed in detail in the Experimental Procedures with the synthesis of
20 *Examples 1-17*. When the compound is indicated as the HCl salt, the salt was
formed by dissolution of the free base in methanol and addition of 1 eq 1M
HCl in ether followed by evaporation of the solvents. When the compound is
indicated as HCOOH (formic acid) salt, the compound was purified by
preparative HPLC.

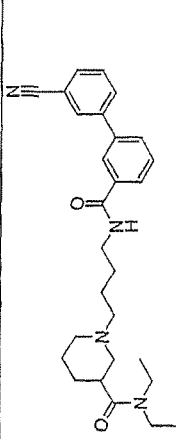
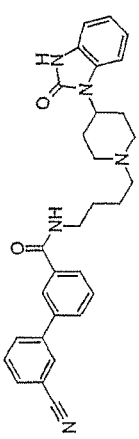
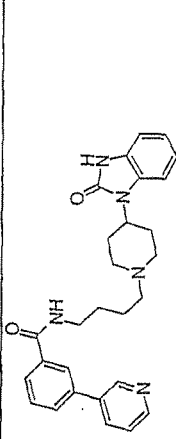
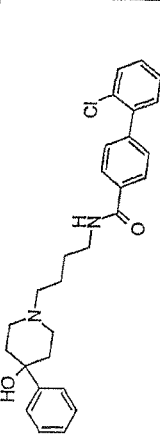
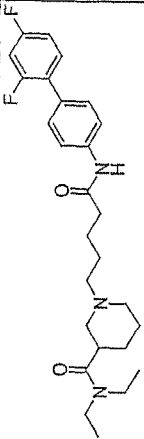
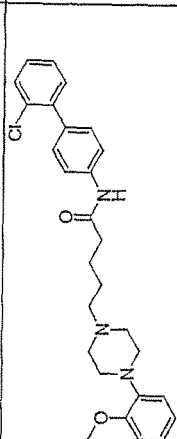
Example	Structure	Salt	Parent Formula	Parent MW	Mass found	LC purity %	LC Rt	LC method (min)	Synthetic Method
8		HCOOH	C ₂₂ H ₂₉ N ₃ O	351.49	352	100	1.79	10	acid-amine coupling with CDI, room temp.
9		HCOOH	C ₁₆ H ₂₃ N ₂ OCl	294.82	295	100	1.78	10	from 5-bromopentanoyl chloride in DCM/DMF, 55C
10			C ₁₅ H ₂₁ N ₂ O ₂ Br	341.24	341, 343	100	2.3	10	from 5-bromopentanoyl chloride, 0C-rt
11		HCOOH	C ₁₆ H ₂₃ N ₂ O ₂ Br	339.27	339, 341	100	1.96	10	from 5-bromopentanoyl chloride in DCM/DMF, 55C
12			C ₂₂ H ₂₅ N ₂ O ₂ F ₃	406.44	407	98	3.36	10	from 5-bromopentanoyl chloride 0C-rt, followed by Suzuki coupling
13			C ₂₃ H ₃₀ N ₄ O ₂	394.51	395	100	1.06	10	from 5-bromopentanoyl chloride 0C-rt, followed by Suzuki coupling

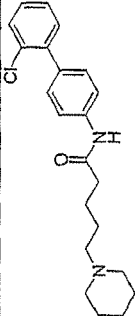
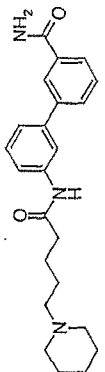
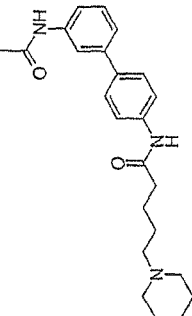
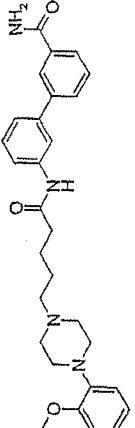
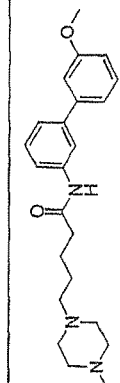
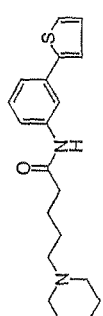
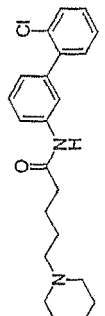
14			C24H31N3O3	409.52	410	100	2.21	10	from 5-bromopentanoyl chloride 0C-rt, followed by Suzuki coupling
15		HCOOH	C24H29N3O2F2	429.50	430	100	2.98	10	from 5-bromopentanoyl chloride 0C-rt, followed by Suzuki coupling
16			C22H28N2O2	352.47	353	99	1.9	10	from 5-bromopentanoyl chloride 0C-rt, followed by Suzuki coupling
17		HCOOH	C21H26N3O2Cl	387.90	388	98	3.2	10	urea synthesis followed by Suzuki under thermal heating
18		HCl	C29H38N4O2	474.64	475	98	1.35	2.5	reductive alkylation on N-(4-oxo-butyl)bromobenzamide followed by Suzuki coupling
19		HCl	C27H36N3O2Cl	470.05	470	97	1.34	2.5	reductive alkylation on N-(4-oxo-butyl)bromobenzamide followed by Suzuki coupling
20		HCl	C29H39N3O3	477.64	478	94	1.18	2.5	reductive alkylation on N-(4-oxo-butyl)bromobenzamide followed by Suzuki coupling

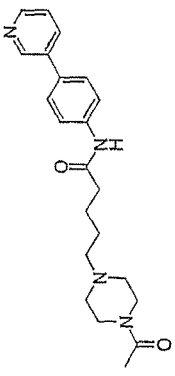
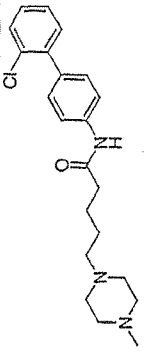
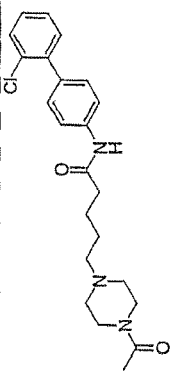
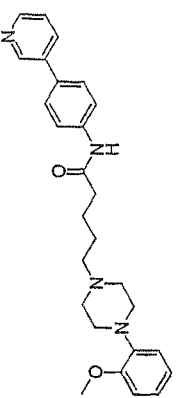
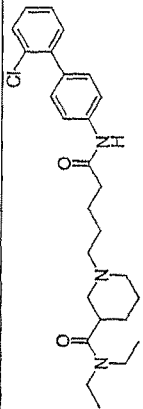
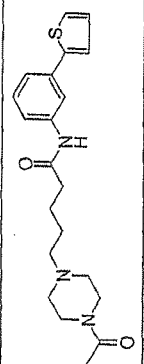
21		HCl	C28H36N3O2F3	503.60	504	99	1.42	2.5	reductive alkylation on N-(4-oxo-butyl)bromobenzamide followed by Suzuki coupling
22		HCl	C25H35N3O2S	441.63	442	100	1.29	2.5	reductive alkylation on N-(4-oxo-butyl)bromobenzamide followed by Suzuki coupling
23		HCl	C27H35N3O2F2	471.58	472	98	1.37	2.5	reductive alkylation on N-(4-oxo-butyl)bromobenzamide followed by Suzuki coupling
24		HCl	C29H42N4O2	478.67	479	96	1.37	2.5	reductive alkylation on N-(4-oxo-butyl)bromobenzamide followed by Suzuki coupling
25		HCl	C29H41N3O2	463.65	464	100	1.46	2.5	reductive alkylation on N-(4-oxo-butyl)bromobenzamide followed by Suzuki coupling
26		HCl	C23H29N3O2	379.50	380	100	1.12	2.5	reductive alkylation on N-(4-oxo-butyl)bromobenzamide followed by Suzuki coupling
27		HCl	C23H28ClN3O2	414.00	414, 416	100	1.17	2.5	reductive alkylation on N-(4-oxo-butyl)bromobenzamide followed by Suzuki coupling

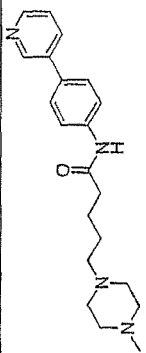
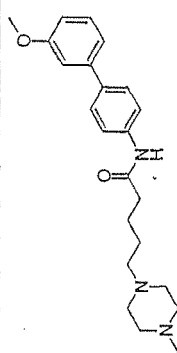
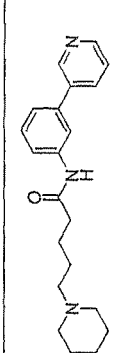
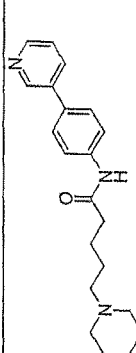
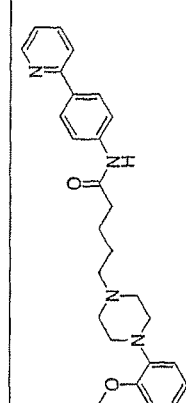
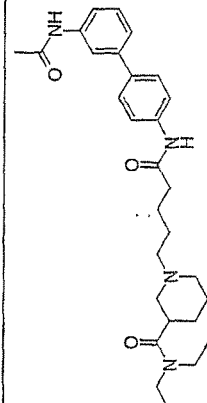
28		HCl	C23H28N3OF3	419.48	420	100	1.22	2.5	reductive alkylation on N-(4-oxo-butyl)benzamide followed by Suzuki coupling
29		HCl	C24H33N3O	379.54	380	100	1.29	2.5	reductive alkylation on N-(4-oxo-butyl)benzamide followed by Suzuki coupling
30		HCl	C22H27N3OF2	387.47	388	100	1.16	2.5	reductive alkylation on N-(4-oxo-butyl)benzamide followed by Suzuki coupling
31		HCl	C22H28N3OCl	385.93	386	100	1.2	2.5	reductive alkylation on N-(4-oxo-butyl)benzamide followed by Suzuki coupling
32		HCl	C23H27N2OF3	404.47	405	92	1.65	2.5	reductive alkylation on N-(4-oxo-butyl)benzamide followed by Suzuki coupling
33		HCl	C22H28N3OCl	385.93	386	100	1.25	2.5	reductive alkylation on N-(4-oxo-butyl)benzamide followed by Suzuki coupling
34		HCl	C23H30N2O2	366.50	367	100	1.55	2.5	reductive alkylation on N-(4-oxo-butyl)benzamide followed by Suzuki coupling

35		HCl	C23H27N3O2F2	415.48	416	100	1.15	2.5	reductive alkylation on N-(4-oxo-butyl)benzamide followed by Suzuki coupling
36			C23H27N3O	361.48	362	100	2.69	10	acid-amine coupling with CDI, room temp.
37		HCl	C24H32N2O	364.52	365	100	1.75	2.5	reductive alkylation on N-(4-oxo-butyl)benzamide followed by Suzuki coupling
38		HCl	C28H31F2N3O2	479.60	480	97	1.55	2.5	reductive alkylation on N-(4-oxo-butyl)benzamide followed by Suzuki coupling
39		HCl	C28H32ClN3O2	478.00	478, 480	95	1.55	2.5	reductive alkylation on N-(4-oxo-butyl)benzamide followed by Suzuki coupling
40		HCl	C22H26N2OF2	372.45	373	98	1.63	2.5	reductive alkylation on N-(4-oxo-butyl)benzamide followed by Suzuki coupling
41		HCl	C31H35N5O3	525.64	526	100	1.16	2.5	reductive alkylation on N-(4-oxo-butyl)benzamide followed by Suzuki coupling

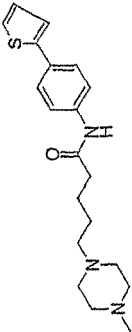
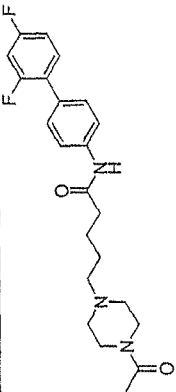
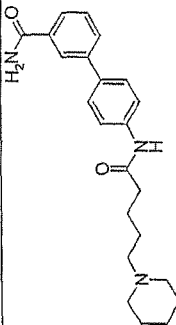
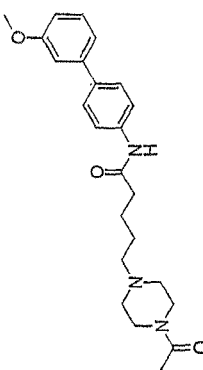
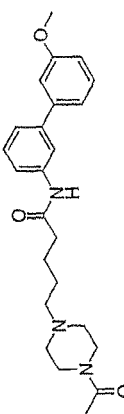
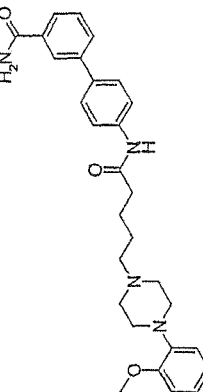
42		HCl	C ₂₈ H ₃₁ N ₅ O ₂	460.61	461	100	1.24	2.5	reductive alkylation on N-(4-oxo-butyl)bromobenzamide followed by Suzuki coupling
43		HCl	C ₃₀ H ₃₁ N ₅ O ₂	493.60	494	100	1.33	2.5	reductive alkylation on N-(4-oxo-butyl)bromobenzamide followed by Suzuki coupling
44		HCl	C ₂₈ H ₃₁ N ₅ O ₂	469.58	470	100	1.09	2.5	reductive alkylation on N-(4-oxo-butyl)bromobenzamide followed by Suzuki coupling
45		HCl	C ₂₈ H ₃₁ N ₅ O ₂ Cl	463.01	462, 464	91	1.1	2.5	reductive alkylation on N-(4-oxo-butyl)bromobenzamide followed by Suzuki coupling
46		HCl	C ₂₇ H ₃₅ N ₃ O ₂ F ₂	471.58	472	91	1.45	2.5	from 5-bromopentanoyl chloride 0C-rt, followed by Suzuki coupling
47		HCl	C ₂₈ H ₃₂ N ₃ O ₂ Cl	478.03	478	98	1.63	2.5	from 5-bromopentanoyl chloride 0C-rt, followed by Suzuki coupling

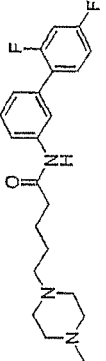
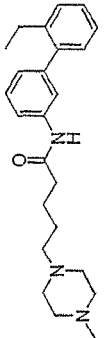
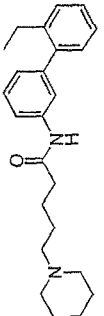
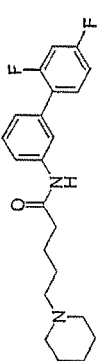
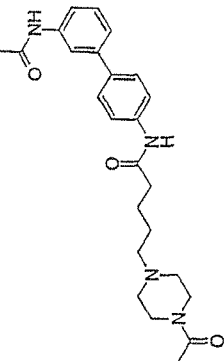
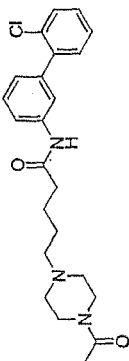
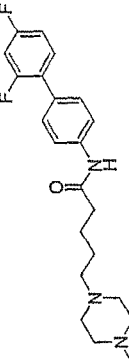
48		HCl	C22H27N2OCl	370.92	370, 372	100	1.8	2.5	from 5-bromopentanoyl chloride 0C-rt, followed by Suzuki coupling
49		HCl	C23H29N3O2	379.50	380	100	1.21	2.5	from 5-bromopentanoyl chloride 0C-rt, followed by Suzuki coupling
50		HCl	C24H31N3O2	393.52	394	92	2.63	10	from 5-bromopentanoyl chloride 0C-rt, followed by Suzuki coupling
51		HCl	C29H34N4O3	486.61	487	96	1.23	2.5	from 5-bromopentanoyl chloride 0C-rt, followed by Suzuki coupling
52		HCl	C23H31N3O2	381.51	382	100	1.25	2.5	from 5-bromopentanoyl chloride 0C-rt, followed by Suzuki coupling
53		HCl	C20H26N2OS	342.50	343	100	1.68	2.5	from 5-bromopentanoyl chloride 0C-rt, followed by Suzuki coupling
54		HCl	C22H27N2OCl	370.92	370, 372	100	1.79	2.5	from 5-bromopentanoyl chloride 0C-rt, followed by Suzuki coupling

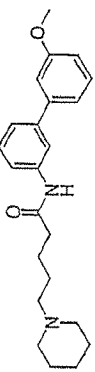
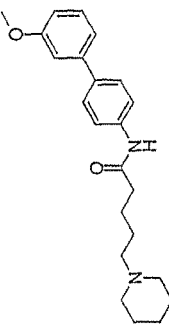
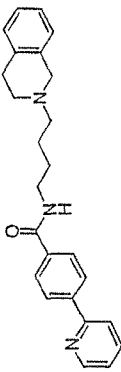
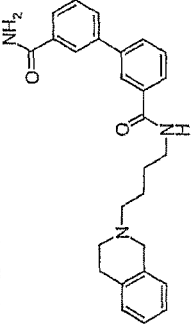
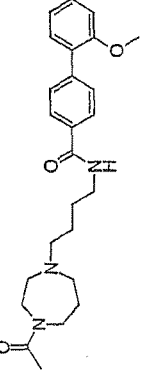
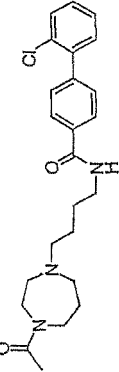
55		HCl	C22H28N4O2	380.48	381	93	0.87	2.5	from 5-bromopentanoyl chloride 0C-rt, followed by Suzuki coupling
56		HCl	C22H28N3OCl	385.93	385, 387	100	1.29	2.5	from 5-bromopentanoyl chloride 0C-rt, followed by Suzuki coupling
57		HCl	C23H28N3O2Cl	413.94	413, 415	97	1.24	2.5	from 5-bromopentanoyl chloride 0C-rt, followed by Suzuki coupling
58		HCl	C27H32N4O2	444.57	445	99	1.23	2.5	from 5-bromopentanoyl chloride 0C-rt, followed by Suzuki coupling
59		HCl	C27H36N3O2Cl	470.05	469, 471	94	1.47	2.5	from 5-bromopentanoyl chloride 0C-rt, followed by Suzuki coupling
60		HCl	C21H27N3O2S	385.52	386	91	1.15	2.5	from 5-bromopentanoyl chloride 0C-rt, followed by Suzuki coupling

61		HCl	C21H28N4O	352.47	353	100	0.92	2.5	from 5-bromopentanoyl chloride 0C-rt, followed by Suzuki coupling
62		HCl	C23H31N3O2	381.51	382	93	1.21	2.5	from 5-bromopentanoyl chloride 0C-rt, followed by Suzuki coupling
63		HCl	C21H27N3O	337.46	338	100	1.3	2.5	from 5-bromopentanoyl chloride 0C-rt, followed by Suzuki coupling
64		HCl	C21H27N3O	337.46	338	99	0.65	10	from 5-bromopentanoyl chloride 0C-rt, followed by Suzuki coupling
65		HCl	C27H32N4O2	444.57	445	96	1.31	2.5	from 5-bromopentanoyl chloride 0C-rt, followed by Suzuki coupling
66		HCl	C29H40N4O3	492.65	493	100	1.11	2.5	from 5-bromopentanoyl chloride 0C-rt, followed by Suzuki coupling

[illegible]

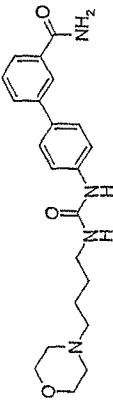
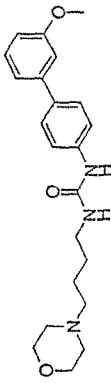
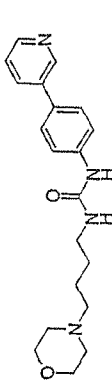
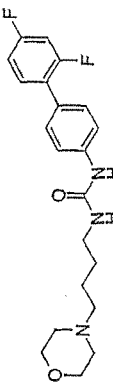
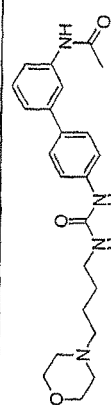
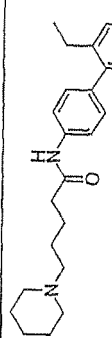
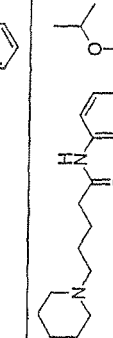
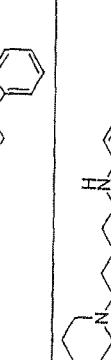
74		HCl	C20H27N3OS	357.51	358	95		1.19	2.5	from 5-bromopentanoyl chloride 0C-rt, followed by Suzuki coupling
75		HCl	C23H27N3O2F2	415.48	416	98		1.22	2.5	from 5-bromopentanoyl chloride 0C-rt, followed by Suzuki coupling
76		HCl	C23H29N3O2	379.50	380	99		2.41	10	from 5-bromopentanoyl chloride 0C-rt, followed by Suzuki coupling
77		HCl	C24H31N3O3	409.52	410	94		1.18	2.5	from 5-bromopentanoyl chloride 0C-rt, followed by Suzuki coupling
78		HCl	C24H31N3O3	409.52	410	92		1.19	2.5	from 5-bromopentanoyl chloride 0C-rt, followed by Suzuki coupling
79		HCl	C29H34N4O3	486.61	487	96		1.19	2.5	from 5-bromopentanoyl chloride 0C-rt, followed by Suzuki coupling

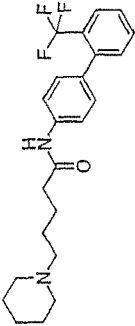
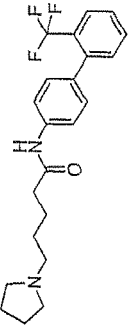
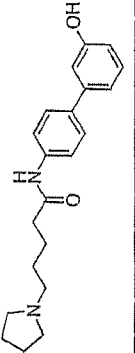
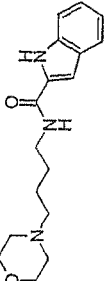
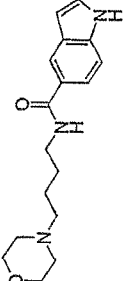
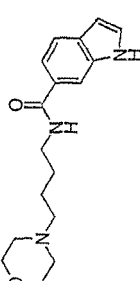
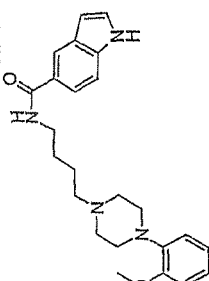
80		HCl	C22H27N3OF2	387.47	388	93		1.22	2.5	from 5-bromopentanoyl chloride 0C-rt, followed by Suzuki coupling
81		HCl	C24H33N3O	379.54	380	91		1.4	2.5	from 5-bromopentanoyl chloride 0C-rt, followed by Suzuki coupling
82		HCl	C24H32N2O	364.52	365	100		1.9	2.5	from 5-bromopentanoyl chloride 0C-rt, followed by Suzuki coupling
83		HCl	C22H26N2OF2	372.45	373	100		1.73	2.5	from 5-bromopentanoyl chloride 0C-rt, followed by Suzuki coupling
84		HCl	C25H32N4O3	436.55	437	92		0.98	2.5	from 5-bromopentanoyl chloride 0C-rt, followed by Suzuki coupling
85		HCl	C23H28N3O2Cl	413.94	413, 415	98		1.27	2.5	from 5-bromopentanoyl chloride 0C-rt, followed by Suzuki coupling
86		HCl	C22H27N3OF2	387.47	388	100		1.24	2.5	from 5-bromopentanoyl chloride 0C-rt, followed by Suzuki coupling

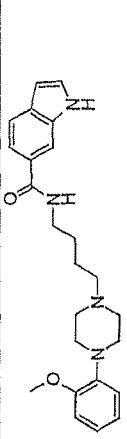
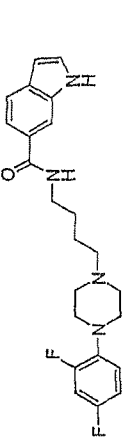
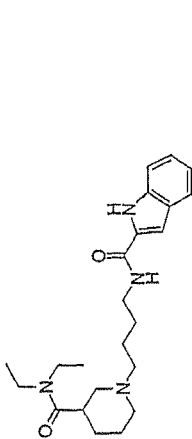
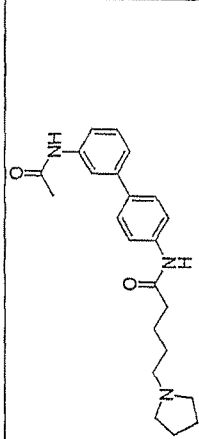
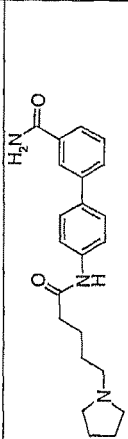
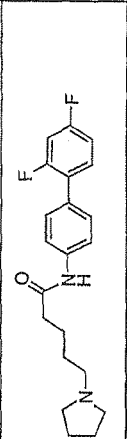
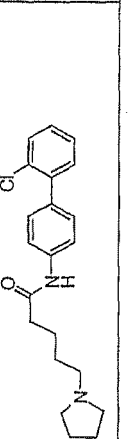
87		HCl	C23H30N2O2	366.50	367	100	1.69	2.5	from 5-bromopentanoyl chloride 0C-rt, followed by Suzuki coupling
88			C23H30N2O2	366.50	367	99	2.42	10	from 5-bromopentanoyl chloride 0C-rt, followed by Suzuki coupling
89		HCOOH	C25H27N3O	385.50	386	94	2.06	10	acid-amine coupling with CDI, room temp.
90		HCl	C27H29N3O2	427.54	428, 485	100	1.29	2.5	reductive alkylation on N-(4-oxo-butyl)bromobenzamide followed by Suzuki coupling
91		HCl	C25H33N3O3	423.55	424	100	1.17	2.5	reductive alkylation on N-(4-oxo-butyl)bromobenzamide followed by Suzuki coupling
92		HCl	C24H30N3O2Cl	427.97	428, 430	95	1.24	2.5	reductive alkylation on N-(4-oxo-butyl)bromobenzamide followed by Suzuki coupling

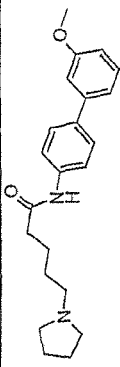
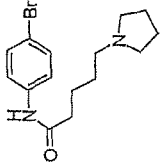
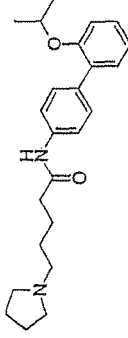
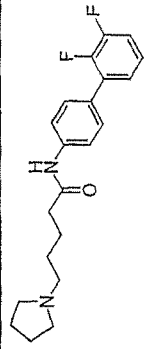
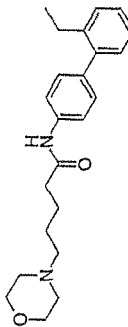
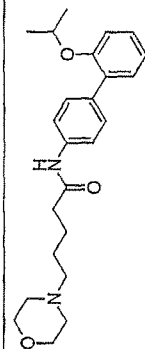
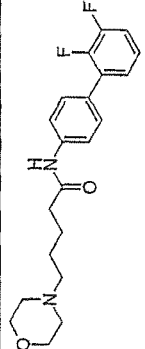
93			C28H34N4O3	474.59	475	98	3.7	10	acid-amine coupling with CDI, room temp.
94			C29H34N3O3Cl	508.05	508	98	4.31	10	acid-amine coupling with CDI, room temp.
95			C16H23N2OBr	339.27	339, 341	99	2.74	10	from 5-bromopentanoyl chloride, 0°C-rt
96		HCOOH	C25H32N4O3	436.55	437	100	2.74	10	acid-amine coupling with CDI, 60°C
97		HCOOH	C25H32N4O3	436.55	437	100	2.86	10	acid-amine coupling with CDI, 60°C
98			C15H22N3O2Br	356.26	356/358	100	1.54	10	urea synthesis
99			C27H33N5O2	459.58	460	95	1.21	10	urea synthesis followed by cross-coupling in microwave

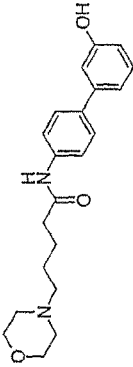
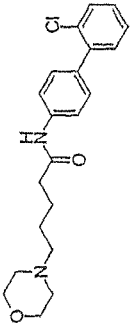
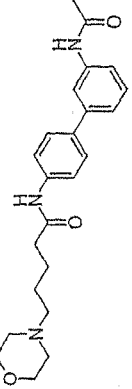
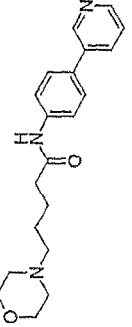
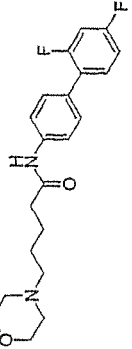
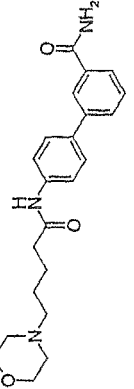
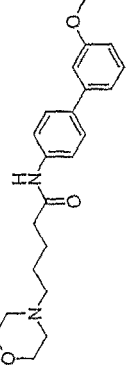
100			C29H36N4O3	488.62	489	97	2.69	10	urea synthesis followed by cross-coupling in microwave
101			C21H27N3O	337.46	338	100	2.25	10	reductive alkylation of 4-oxobutylbenzamide
102			C16H24N3OBr	354.29	356	100	1.73	10	urea synthesis
103		HCl	C30H37N5O3	515.65	516	100	2.22	10	urea synthesis followed by cross-coupling in microwave
104		HCOOH	C28H33N4O2Cl	493.04	493	93	3.77	10	urea synthesis followed by cross-coupling in microwave
105			C26H29N5O2F2	465.54	466	100	2.39	10	urea synthesis followed by cross-coupling in microwave
106		HCOOH	C28H35N5O3	489.61	490	92	2.3	10	urea synthesis followed by Suzuki under thermal heating

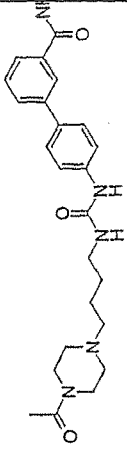
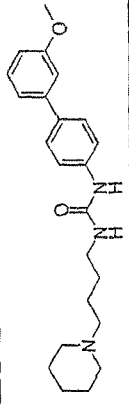
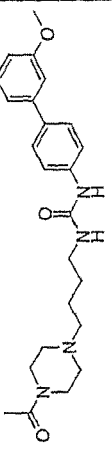
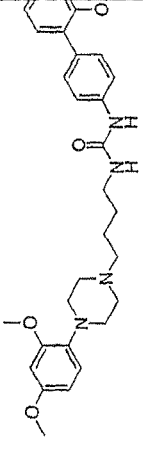
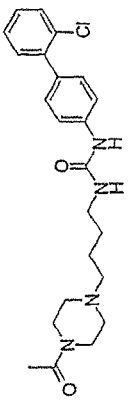
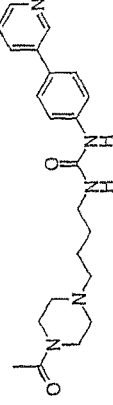
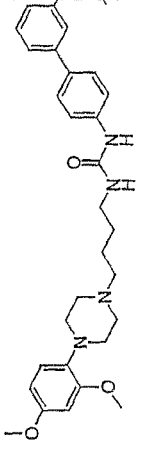
107		C22H28N4O3	396.48	397	92	2.27	10	urea synthesis followed by cross-coupling in microwave
108		C22H29N3O3	383.48	384	98	3.01	10	urea synthesis followed by cross-coupling in microwave
109		C20H26N4O2	354.45	355	100	0.58	10	urea synthesis followed by cross-coupling in microwave
110		C21H25N3O2F2	389.44	390	100	3.15	10	urea synthesis followed by cross-coupling in microwave
111		C23H30N4O3	410.51	411	90	2.5	10	urea synthesis followed by cross-coupling in microwave
112		C24H32N2O	364.52	365	100	3.63	10	from 5-bromopentanoyl chloride 0C-rt, followed by Suzuki coupling
113		C25H34N2O2	394.55	395	100	3.64	10	from 5-bromopentanoyl chloride 0C-rt, followed by Suzuki coupling
114		C22H28N2O2	352.47	353.39	98	2.7	10	from 5-bromopentanoyl chloride 0C-rt, followed by Suzuki coupling

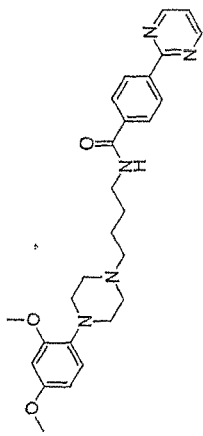
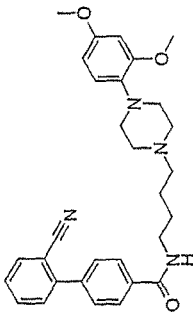
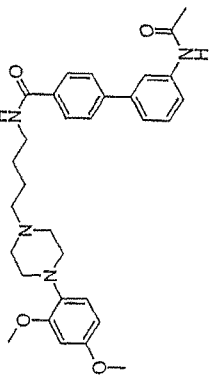
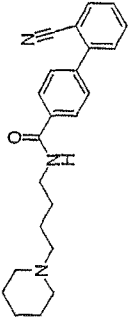
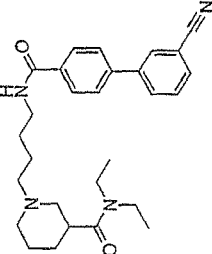
115				C ₂₃ H ₂₇ N ₂ O ₃ F ₃	404.47	405	98	3.54	10	from 5-bromopentanoyl chloride 0C-rt, followed by Suzuki coupling
116				C ₂₂ H ₂₅ N ₂ O ₃ F ₃	390.44	391	98	3.48	10	from 5-bromopentanoyl chloride 0C-rt, followed by Suzuki coupling
117				C ₂₁ H ₂₆ N ₂ O ₂	338.44	339.35	100	2.65	10	from 5-bromopentanoyl chloride 0C-rt, followed by Suzuki coupling
118		HCOOH		C ₁₇ H ₂₃ N ₃ O ₂	301.38	302	98	2.37	10	acid-amine coupling with CDI, 60°C
119				C ₁₇ H ₂₃ N ₃ O ₂	301.38	302	99	2.00/2.07	10	acid-amine coupling with CDI, 60°C
120		HCOOH		C ₁₇ H ₂₃ N ₃ O ₂	301.38	302	100	1.79	10	acid-amine coupling with CDI, 60°C
121		HCOOH		C ₂₄ H ₃₀ N ₄ O ₂	406.52	407	100	2.90	10	acid-amine coupling with CDI, 60°C

122			C24H30N4O2	406.52	407	95	2.76	10	acid-amine coupling with CDI, 60°C
123		HCOOH	C23H26N4OF2	412.48	413	100	2.89	10	acid-amine coupling with CDI, 60°C
124		HCOOH	C23H34N4O2	398.54	399	100	2.89	10	acid-amine coupling with CDI, 60°C
125			C23H29N3O2	379.50	380	99	1.61	10	from 5-bromopentanoyl chloride 0C-rt, followed by Suzuki coupling
126			C22H27N3O2	365.47	366	99	1.37	10	from 5-bromopentanoyl chloride 0C-rt, followed by Suzuki coupling
127			C21H24N2OF2	358.42	359	97	2.41	10	from 5-bromopentanoyl chloride 0C-rt, followed by Suzuki coupling
128			C21H25N2OCl	356.89	357	95	2.49	10	from 5-bromopentanoyl chloride 0C-rt, followed by Suzuki coupling

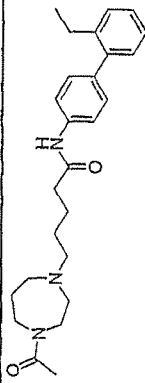
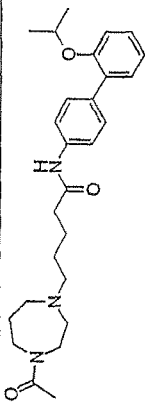
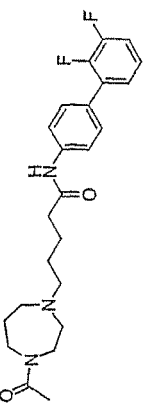
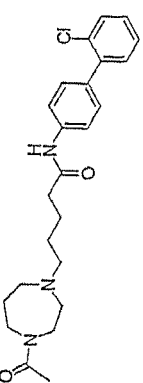
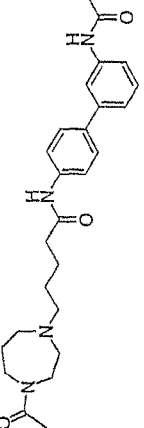
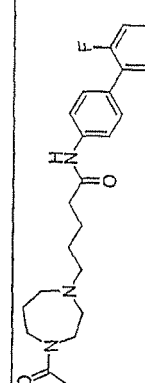
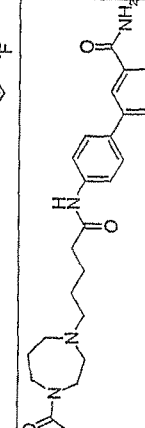
129			C22H28N2O2	352.47	353	98		2.25	10	from 5-bromopentanoyl chloride 0C-rt, followed by Suzuki coupling
130			C15H21N2OBr	325.24	325, 327	99		1.71	10	from 5-bromopentanoyl chloride, 0C-rt
131			C24H32N2O2	380.52	381	98		3.45	10	from 5-bromopentanoyl chloride 0C-rt, followed by Suzuki coupling
132			C21H24N2OF2	358.42	359	100		3.19	10	from 5-bromopentanoyl chloride 0C-rt, followed by Suzuki coupling
133			C23H30N2O2	366.50	367	99		3.39	10	from 5-bromopentanoyl chloride 0C-rt, followed by Suzuki coupling
134			C24H32N2O3	396.52	397	99		3.44	10	from 5-bromopentanoyl chloride 0C-rt, followed by Suzuki coupling
135			C21H24N2OF2	374.42	375	95		3.19	10	from 5-bromopentanoyl chloride 0C-rt, followed by Suzuki coupling

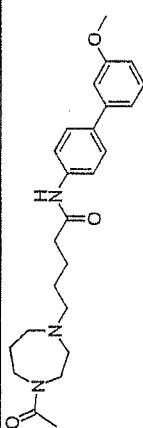
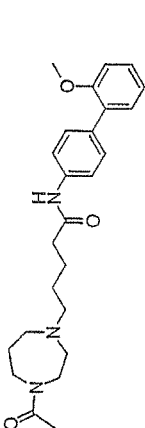
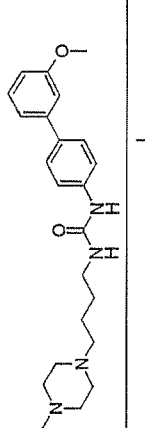
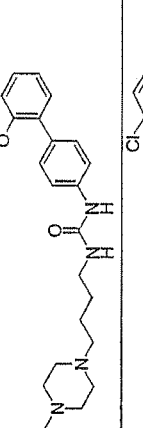
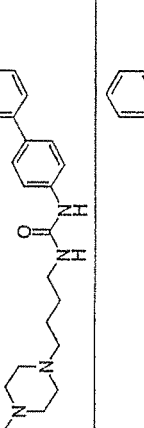
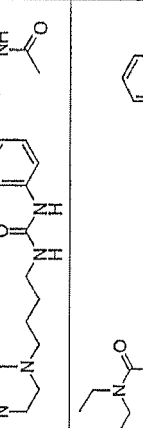
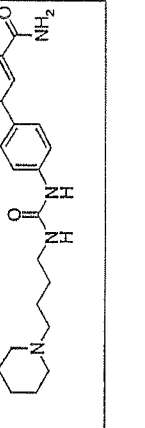
136				C21H26N2O3	354.44	355.34	99	2.48	10	from 5-bromopentanoyl chloride 0C-rt, followed by Suzuki coupling
137				C21H25N2O2Cl	372.89	373	96	3.2	10	from 5-bromopentanoyl chloride 0C-rt, followed by Suzuki coupling
138				C23H29N3O3	395.49	396	97	2.49	10	from 5-bromopentanoyl chloride 0C-rt, followed by Suzuki coupling
139				C20H25N3O2	339.43	340	99	double peak 0.57- 1.19	10	from 5-bromopentanoyl chloride 0C-rt, followed by Suzuki coupling
140				C21H24N2O2F2	374.42	375	97	3.14	10	from 5-bromopentanoyl chloride 0C-rt, followed by Suzuki coupling
141				C22H27N3O3	381.47	382	95	2.29	10	from 5-bromopentanoyl chloride 0C-rt, followed by Suzuki coupling
142				C22H28N2O3	368.47	369	100	3.05	10	from 5-bromopentanoyl chloride 0C-rt, followed by Suzuki coupling

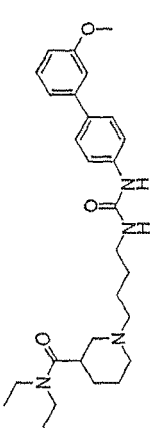
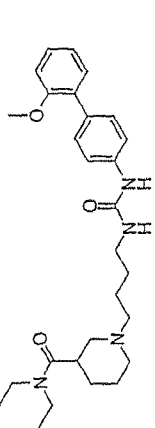
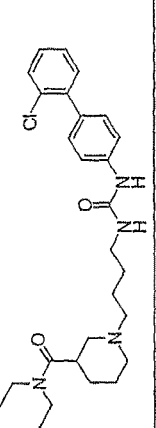
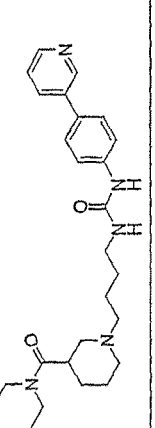
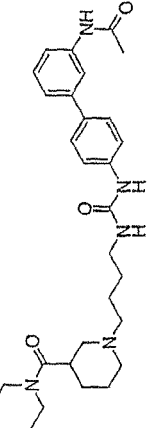
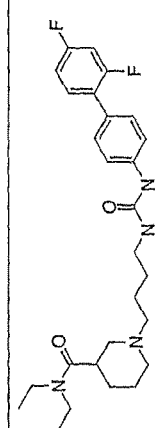
143			C24H31N5O3	437.53	438	100	1.95	10	urea synthesis followed by cross-coupling in microwave
144			C23H31N3O2	381.51	382	96	2.99	10	urea synthesis followed by cross-coupling in microwave
145		HCOOH	C24H32N4O3	424.54	425	92	2.7	10	urea synthesis followed by cross-coupling in microwave
146			C30H38N4O4	518.65	519	94	3.33	10	urea synthesis followed by cross-coupling in microwave
147			C23H29N4O2Cl	428.95	429	100	2.97	10	urea synthesis followed by cross-coupling in microwave
148		HCl	C22H29N5O2	395.50	396	95	0.52	10	urea synthesis followed by cross-coupling in microwave
149		HCl	C31H39N5O4	545.67	546	96	2.87	10	urea synthesis followed by cross-coupling in microwave

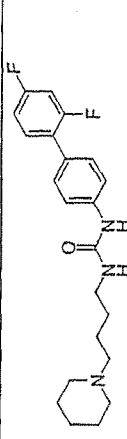
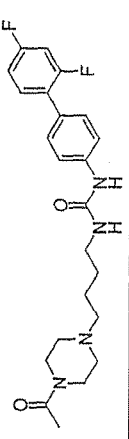
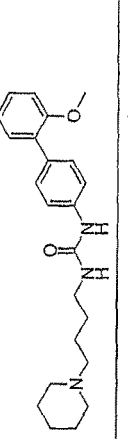
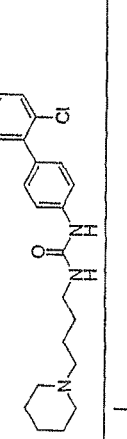
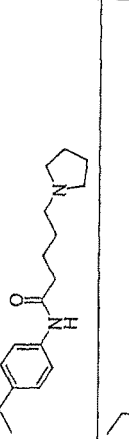
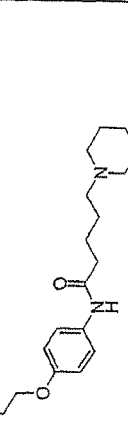
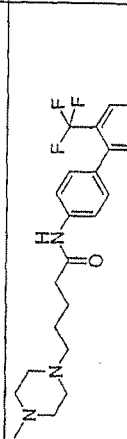
158		C27H33N5O3	475.58	476	96	2.51	10	acid-amine coupling with CDI, room temp.
159		C30H34N4O3	498.62	499	100	3.18	10	acid-amine coupling with CDI, room temp.
160		C31H38N4O4	530.66	531, 266	100	2.81	10	acid-amine coupling with CDI, room temp.
161		C23H27N3O	361.48	362	100	2.66	10	acid-amine coupling with CDI, room temp.
162		C28H36N4O2	460.61	461	100	2.84	10	acid-amine coupling with CDI, room temp.

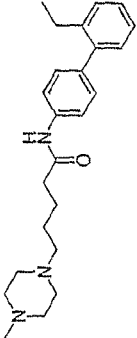
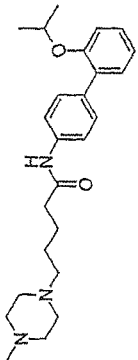
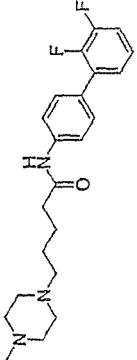
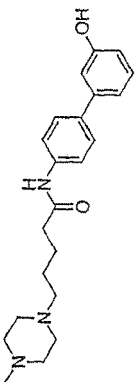
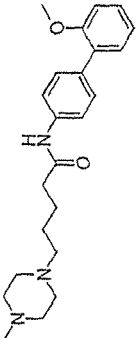
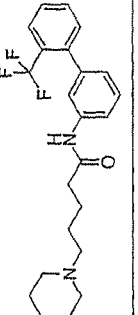
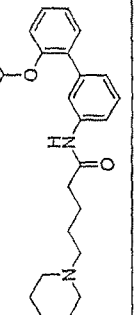
163				C28H36N4O2	460.61	461	100	2.88	10	acid-amine coupling with CDI, room temp.
164				C29H40N4O3	492.65	493	100	2.58	10	acid-amine coupling with CDI, room temp.
165				C24H28N4O2	404.50	405	99	2.35	10	acid-amine coupling with CDI, room temp.
166		HCOOH		C23H30N2O	350.50	351	98	3.25	10	from 5-bromopentanoyl chloride 0C-rt, followed by Suzuki coupling
167		HCOOH		C22H28N2O3	368.47	369	94	3.01	10	from 5-bromopentanoyl chloride 0C-rt, followed by Suzuki coupling
168		HCOOH		C25H30N3O2F3	461.52	462.3	100	3.07	10	from 5-bromopentanoyl chloride 0C-rt, followed by Suzuki coupling

169		HCOOH	C26H35N3O2	421.58	422.33	100		3.23	10	from 5-bromopentanoyl chloride 0C-rt, followed by Suzuki coupling
170		HCOOH	C27H37N3O3	451.60	452.35	100		3.14	10	from 5-bromopentanoyl chloride 0C-rt, followed by Suzuki coupling
171		HCOOH	C24H31N3O3	409.52	410.31	96		2.19	10	from 5-bromopentanoyl chloride 0C-rt, followed by Suzuki coupling
172		HCOOH	C24H30N3O2Cl	427.97	428.25	95		2.98	10	from 5-bromopentanoyl chloride 0C-rt, followed by Suzuki coupling
173		HCOOH	C26H34N4O3	450.57	451.31	99		2.2	10	from 5-bromopentanoyl chloride 0C-rt, followed by Suzuki coupling
174		HCOOH	C24H29N3O2F2	429.50	430.3	100		2.89	10	from 5-bromopentanoyl chloride 0C-rt, followed by Suzuki coupling
175		HCOOH	C25H32N4O3	436.55	437.32	100		2	10	from 5-bromopentanoyl chloride 0C-rt, followed by Suzuki coupling

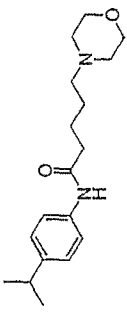
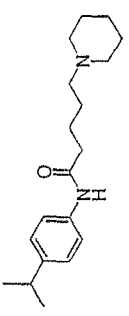
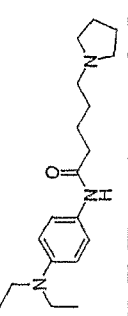
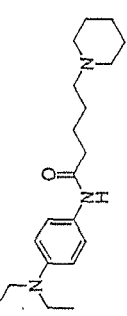
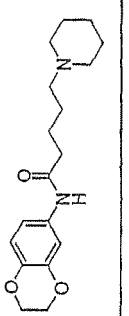
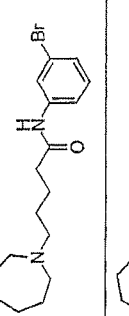
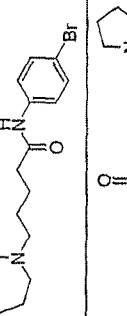
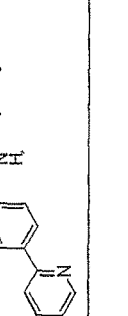
176		HCOOH	C25H33N3O3	423.55	424.37	99	2.77	10	from 5-bromopentanoyl chloride 0C-rt, followed by Suzuki coupling
177		HCOOH	C25H33N3O3	423.55	424.33	100	2.85	10	from 5-bromopentanoyl chloride 0C-rt, followed by Suzuki coupling
178			C23H32N4O2	396.53	397	93	2.4	10	urea synthesis followed by cross-coupling in microwave
179		HCOOH	C23H32N4O2	396.53	397	100	2.39	10	urea synthesis followed by cross-coupling in microwave
180		HCOOH	C22H29N4OCl	400.94	401	99	2.54	10	urea synthesis followed by cross-coupling in microwave
181			C24H33N5O2	423.55	424	100	1.85	10	urea synthesis followed by cross-coupling in microwave
182		HCOOH	C28H39N5O3	493.64	494	100	2.39	10	urea synthesis followed by cross-coupling in microwave

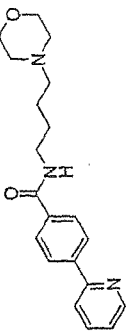
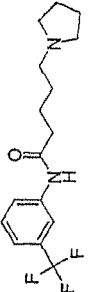
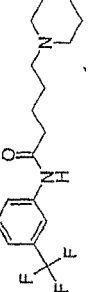
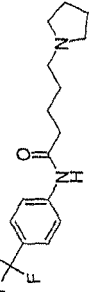
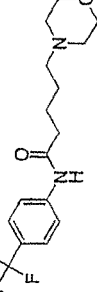
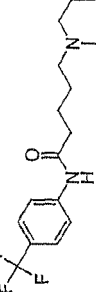
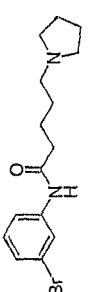
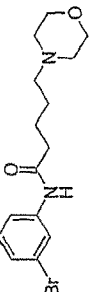
183		HCOOH	C ₂₈ H ₄₀ N ₄ O ₃	480.64	481	96	3.05	10	urea synthesis followed by cross-coupling in microwave
184			C ₂₈ H ₄₀ N ₄ O ₃	480.64	481	91	3.19	10	urea synthesis followed by cross-coupling in microwave
185			C ₂₇ H ₃₇ N ₄ O ₂ Cl	485.06	485	96	3.38	10	urea synthesis followed by cross-coupling in microwave
186		HCOOH	C ₂₆ H ₃₇ N ₅ O ₂	451.60	452	100	1.64	10	urea synthesis followed by cross-coupling in microwave
187			C ₂₉ H ₄₁ N ₅ O ₃	507.67	508	97	2.64	10	urea synthesis followed by cross-coupling in microwave
188			C ₂₇ H ₃₆ N ₄ O ₂ F ₂	486.60	487	95	3.4	10	urea synthesis followed by cross-coupling in microwave

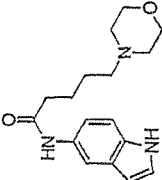
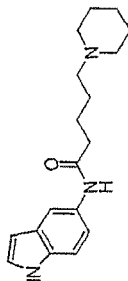
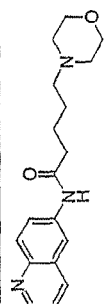
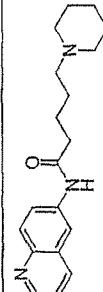
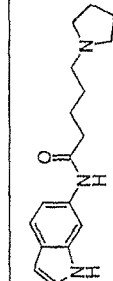
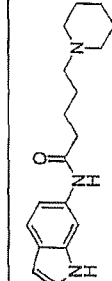
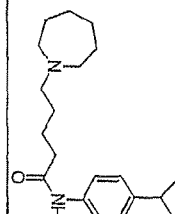
189			C ₂₂ H ₂₇ N ₃ O ₂ F ₂	387.47	388	96		3.08	10	urea synthesis followed by cross-coupling in microwave
190			C ₂₃ H ₂₈ N ₄ O ₂ F ₂	430.49	431	97		2.89	10	urea synthesis followed by cross-coupling in microwave
191		HCOOH	C ₂₃ H ₃₁ N ₃ O ₂	381.51	382	98		2.9	10	urea synthesis followed by cross-coupling in microwave
192		HCOOH	C ₂₂ H ₂₈ N ₃ OCl	385.93	386	99		3.08	10	urea synthesis followed by cross-coupling in microwave
193			C ₁₈ H ₂₈ N ₂ O	288.43	289	100		2.10	10	from 5-bromopentanoyl chloride in DCM/DMF, 55°C
194			C ₂₀ H ₃₂ N ₂ O ₂	332.48	333	100		2.35	10	from 5-bromopentanoyl chloride in DCM/DMF, 55°C
195		HCOOH	C ₂₃ H ₂₈ N ₃ O ₂ F ₃	419.48	420	100		2.13	10	from 5-bromopentanoyl chloride 0°C-rt, followed by Suzuki coupling

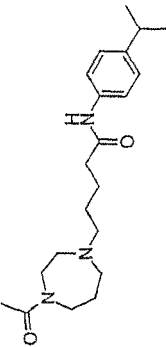
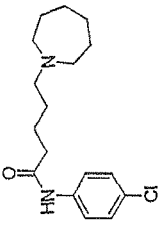
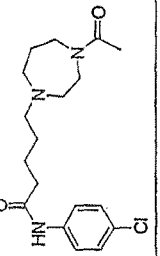
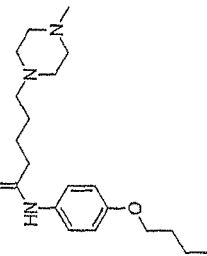
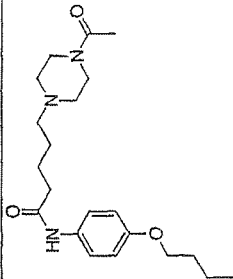
196		HCOOH	C24H33N3O	379.54	380	100	2.2	10	from 5-bromopentanoyl chloride 0C-rt, followed by Suzuki coupling
197		HCOOH	C25H35N3O2	409.56	410	100	2.18	10	from 5-bromopentanoyl chloride 0C-rt, followed by Suzuki coupling
198		HCOOH	C22H27N3OF2	387.47	388	100	1.95	10	from 5-bromopentanoyl chloride 0C-rt, followed by Suzuki coupling
199			C22H29N3O2	367.48 468	369.32	100	1.29	10	from 5-bromopentanoyl chloride 0C-rt, followed by Suzuki coupling
200			C23H31N3O2	381.51	382	100	1.83	10	from 5-bromopentanoyl chloride 0C-rt, followed by Suzuki coupling
201			C23H27N2OF3	404.47	405	97	2.69	10	from 5-bromopentanoyl chloride 0C-rt, followed by Suzuki coupling
202			C25H34N2O2	394.55	395	97	2.75	10	from 5-bromopentanoyl chloride 0C-rt, followed by Suzuki coupling

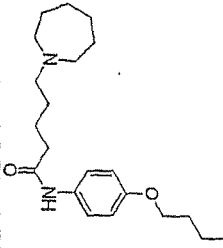
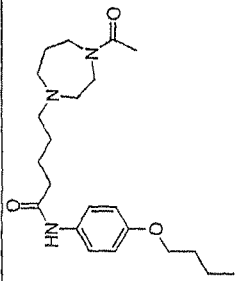
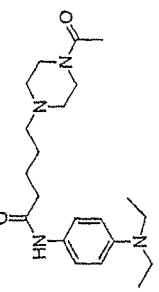
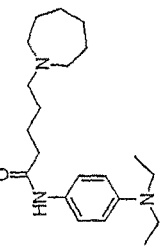
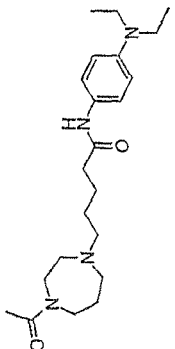
203			C22H26N2OF2	372.45	373	100	2.49	10	from 5-bromopentanoyl chloride 0C-rt, followed by Suzuki coupling
204		HCOOH	C23H30N2O2	366.50	367	100	2.35	10	from 5-bromopentanoyl chloride 0C-rt, followed by Suzuki coupling
205			C15H21N2OCl	280.79	281	100	1.67	10	from 5-bromopentanoyl chloride in DCM/DMF, 55C
206			C16H23N2OCl	294.82	295	100	1.78	10	from 5-bromopentanoyl chloride in DCM/DMF, 55C
207			C19H30N2O2	318.45	319	100	2.24	10	from 5-bromopentanoyl chloride in DCM/DMF, 55C
208			C19H30N2O3	334.45	335	100	2.18	10	from 5-bromopentanoyl chloride in DCM/DMF, 55C
209			C17H26N2O2	290.40	291	100	1.27	10	from 5-bromopentanoyl chloride in DCM/DMF, 55C

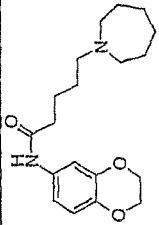
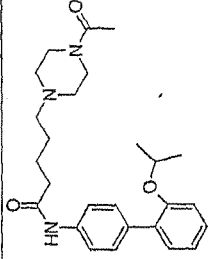
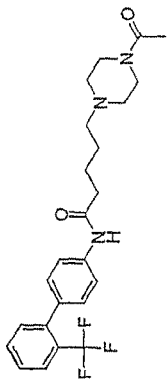
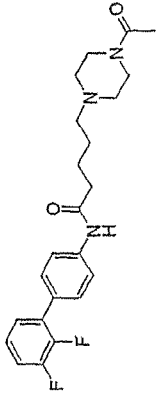
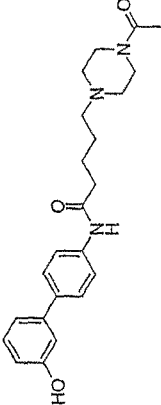
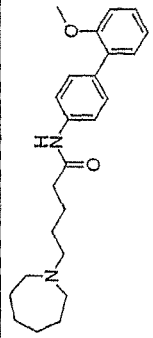
210		HCOOH	C ₁₈ H ₂₈ N ₂ O ₂	304.43	305	100	1.99	10	from 5-bromopentanoyl chloride in DCM/DMF, 55C
211		HCOOH	C ₁₉ H ₃₀ N ₂ O	302.45	303	100	2.24	10	from 5-bromopentanoyl chloride in DCM/DMF, 55C
212		HCOOH	C ₁₉ H ₃₁ N ₃ O	317.47	318	100	0.38	10	from 5-bromopentanoyl chloride in DCM/DMF, 55C
213		HCOOH	C ₂₀ H ₃₃ N ₃ O	331.50	332	100	0.40	10	from 5-bromopentanoyl chloride in DCM/DMF, 55C
214		HCOOH	C ₁₈ H ₂₆ N ₂ O ₃	318.41	319	100	1.24	10	from 5-bromopentanoyl chloride in DCM/DMF, 55C
215			C ₁₇ H ₂₅ N ₂ OBr	353.30	353, 355	100	1.97	10	from 5-bromopentanoyl chloride - array conditions
216			C ₁₇ H ₂₅ N ₂ OBr	353.30	353, 355	100	1.95	10	from 5-bromopentanoyl chloride - array conditions
217		HCOOH	C ₂₀ H ₂₅ N ₃ O	323.43	324	100	0.85	10	reductive alkylation of 4-oxobutylbenzamide

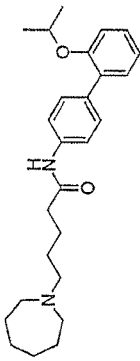
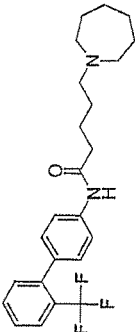
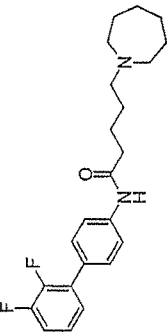
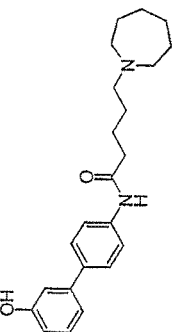
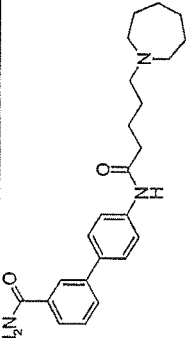
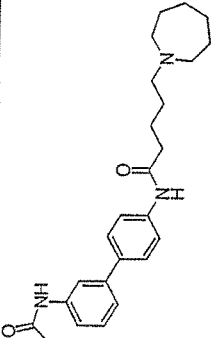
218		HCOOH	C ₂₀ H ₂₅ N ₃ O ₂	339.43	340	100	0.79	10	reductive alkylation of 4-oxobutylbenzamide
219		HCOOH	C ₁₆ H ₂₁ N ₂ O _F ₃	314.35	315	100	2.10	10	from 5-bromopentanoyl chloride in DCM/DMF, 55°C
220		HCOOH	C ₁₇ H ₂₃ N ₂ O _F ₃	328.37	329	100	1.98	10	from 5-bromopentanoyl chloride in DCM/DMF, 55°C
221		HCOOH	C ₁₆ H ₂₁ N ₂ O _F ₃	314.35	315	100	2.18	10	from 5-bromopentanoyl chloride in DCM/DMF, 55°C
222		HCOOH	C ₁₆ H ₂₁ N ₂ O ₂ F ₃	330.35	331	100	2.05	10	from 5-bromopentanoyl chloride in DCM/DMF, 55°C
223		HCOOH	C ₁₇ H ₂₃ N ₂ O _F ₃	328.37	329	100	2.09	10	from 5-bromopentanoyl chloride in DCM/DMF, 55°C
224		HCOOH	C ₁₅ H ₂₁ N ₂ O ₂ Br	325.24	325, 327	100	1.83	10	from 5-bromopentanoyl chloride in DCM/DMF, 55°C
225		HCOOH	C ₁₅ H ₂₁ N ₂ O ₂ Br	341.24	341, 343	100	1.63	10	from 5-bromopentanoyl chloride in DCM/DMF, 55°C

226		HCOOH	C17H23N3O2	301.38	302	100	double peak 0.42/0.69	10	from 5-bromopentanoyl chloride in DCM/DMF, 55C
227		HCOOH	C18H25N3O	299.41	300	95	1.14	10	from 5-bromopentanoyl chloride in DCM/DMF, 55C
228		HCOOH	C18H23N3O2	313.39	315	100	0.36	10	from 5-bromopentanoyl chloride in DCM/DMF, 55C
229		HCOOH	C19H25N3O	311.42	312	100	0.38	10	from 5-bromopentanoyl chloride in DCM/DMF, 55C
230		HCOOH	C17H23N3O	285.38	286	97	0.94	10	from 5-bromopentanoyl chloride in DCM/DMF, 55C
231		HCOOH	C18H25N3O	299.41	300	97	1.17	10	from 5-bromopentanoyl chloride in DCM/DMF, 55C
232		HCOOH	C20H32N2O	316.48	317	100	2.26	10	from 5-bromopentanoyl chloride in DCM/DMF, 55C

233		HCOOH	C ₂₁ H ₃₃ N ₃ O ₂	359.51	360.44	100	1.82	10	from 5-bromopentanoyl chloride - array conditions
234		HCOOH	C ₁₇ H ₂₅ N ₂ OCl	308.85	309	100	1.81	10	from 5-bromopentanoyl chloride in DCM/DMF, 55C
235		HCOOH	C ₁₈ H ₂₆ N ₃ O ₂ Cl	351.87	352.32	100	1.28	10	from 5-bromopentanoyl chloride - array conditions
236		HCOOH	C ₂₀ H ₃₃ N ₃ O ₂	347.50	348	100	1.44	10	from 5-bromopentanoyl chloride in DCM/DMF, 55C
237		HCOOH	C ₂₁ H ₃₃ N ₃ O ₃	375.51	376	100	2.02	10	from 5-bromopentanoyl chloride in DCM/DMF, 55C

238		HCOOH	C21H34N2O2	346.51	347	95	2.30	10	from 5-bromopentanoyl chloride in DCM/DMF, 55°C
239		HCOOH	C21H34N4O2	374.52	375.43	100	0.29	10	from 5-bromopentanoyl chloride - array conditions
240		HCOOH	C21H34N4O2	374.52	375	100	0.29	10	from 5-bromopentanoyl chloride in DCM/DMF, 55°C
241		HCOOH	C21H35N3O	345.52	346	100	0.32	10	from 5-bromopentanoyl chloride in DCM/DMF, 55°C
242		HCOOH	C22H36N4O2	388.55	389.41	100	0.30	10	from 5-bromopentanoyl chloride - array conditions

243		HCOOH	C19H28N2O3	332.44	333	100	1.34	10	from 5-bromopentanoyl chloride in DCM/DMF, 55°C
244			C26H35N3O3	437.57	438	96	2.55	10	from 5-bromopentanoyl chloride 0°C-rt, followed by Suzuki coupling
245			C24H28N3O2F3	447.49	448	98	2.49	10	from 5-bromopentanoyl chloride 0°C-rt, followed by Suzuki coupling
246			C23H27N3O2F2	415.48	416	100	2.33	10	from 5-bromopentanoyl chloride 0°C-rt, followed by Suzuki coupling
247			C23H29N3O3	395.49	396.40	100	1.70	10	from 5-bromopentanoyl chloride 0°C-rt, followed by Suzuki coupling
248		HCOOH	C24H32N2O2	380.52	381	100	2.54	10	from 5-bromopentanoyl chloride 0°C-rt, followed by Suzuki coupling

249		HCOOH	C ₂₆ H ₃₆ N ₂ O ₂	408.58	409	100	2.93	10	from 5-bromopentanoyl chloride 0C-rt, followed by Suzuki coupling
250		HCOOH	C ₂₄ H ₂₉ N ₂ O ₂ F ₃	418.50	419	100	2.91	10	from 5-bromopentanoyl chloride 0C-rt, followed by Suzuki coupling
251		HCOOH	C ₂₃ H ₂₈ N ₂ O ₂ F ₂	386.48	387	100	2.74	10	from 5-bromopentanoyl chloride 0C-rt, followed by Suzuki coupling
252			C ₂₃ H ₃₀ N ₂ O ₂	366.50	367.42	100	2.05	10	from 5-bromopentanoyl chloride 0C-rt, followed by Suzuki coupling
253		HCOOH	C ₂₄ H ₃₁ N ₃ O ₂	393.52	394	100	1.77	10	from 5-bromopentanoyl chloride 0C-rt, followed by Suzuki coupling
254		HCOOH	C ₂₅ H ₃₃ N ₃ O ₂	407.55	408	100	2	10	from 5-bromopentanoyl chloride 0C-rt, followed by Suzuki coupling

Biological activity

Cloning of alpha7 nicotinic acetylcholine receptor and generation of stable recombinant alpha7 nAChR expressing cell lines

Full length cDNAs encoding the alpha7 nicotinic acetylcholine receptor were cloned from a rat brain cDNA library using standard molecular biology techniques. Rat GH4C1 cells were then transfected with the rat receptor, cloned and analyzed for functional alpha7 nicotinic receptor expression employing a FLIPR assay to measure changes in intracellular calcium concentrations. Cell clones showing the highest calcium-mediated fluorescence signals upon agonist (nicotine) application were further subcloned and subsequently stained with Texas red-labelled α -bungarotoxin (BgTX) to analyse the level and homogeneity of alpha7 nicotinic acetylcholine receptor expression using confocal microscopy. Three cell lines were then expanded and one characterised pharmacologically (see Table 2 below) prior to its subsequent use for compound screening.

Table 2 - Pharmacological characterisation of alpha7 nAChR stably expressed in GH4C1 cells using the functional FLIPR assay

Compound	EC ₅₀ [microM]
Acetylcholine	3.05 $\pm$ 0.08 (n=4)
Choline	24.22 $\pm$ 8.30 (n=2)
Cytisine	1.21 $\pm$ 0.13 (n=5)
DMPP	0.98 $\pm$ 0.47 (n=6)
Epibatidine	0.012 $\pm$ 0.002 (n=7)
Nicotine	1.03 $\pm$ 0.26 (n=22)

Development of a functional FLIPR assay for primary screening

A robust functional FLIPR assay ($Z' = 0.68$) employing the stable

recombinant GH4C1 cell line was developed to screen the alpha7 nicotinic acetylcholine receptor. The FLIPR system allows the measurements of real time Ca^{2+} -concentration changes in living cells using a Ca^{2+} sensitive fluorescence dye (such as Fluo4). This instrument enables the screening for agonists and antagonists for alpha 7 nAChR channels stably expressed in GH4C1 cells.

Cell culture

GH4C1 cells stably transfected with rat- alpha7-nAChR (see above) were used. These cells are poorly adherent and therefore pretreatment of flasks and plates with poly-D-lysine was carried out. Cells are grown in 150 cm^2 T-flasks, filled with 30ml of medium at 37°C and 5% CO_2 .

Data analysis

EC_{50} and IC_{50} values were calculated using the IDBS *XLfit4.1* software package employing a sigmoidal concentration-response (variable slope) equation:

$$Y = \text{Bottom} + ((\text{Top}-\text{Bottom}) / (1 + ((\text{EC}_{50}/X)^{\text{HillSlope}})))$$

Assay validation

The functional FLIPR assay was validated with the alpha7 nAChR agonists nicotine, cytosine, DMPP, epibatidine, choline and acetylcholine. Concentration-response curves were obtained in the concentration range from 0.001 to 30 microM. The resulting EC_{50} values are listed in Table 2 and the obtained rank order of agonists is in agreement with published data (Quirk et al., 1997).

The assay was further validated with the specific alpha7 nAChR antagonist MLA (methyllycaconitine), which was used in the concentration range between 1microM to 0.01 nM, together with a competing nicotine concentration of 10 microM. The IC_{50} value was calculated as 1.31 ± 0.43 nM in nine independent experiments.

Development of functional FLIPR assays for selectivity testing

Functional FLIPR assays were developed in order to test the selectivity of compounds against the $\alpha 1$ (muscular) and $\alpha 3$ (ganglionic) nACh receptors and the structurally related 5-HT₃ receptor. For determination of activity at $\alpha 1$ receptors natively expressed in the rhabdomyosarcoma derived TE 671 cell line an assay employing membrane potential sensitive dyes was used, whereas $\alpha 3$ selectivity was determined by a calcium-monitoring assays using the native SH-SY5Y cell line. In order to test selectivity against the 5-HT₃ receptor, a recombinant cell line was constructed expressing the human 5-HT_{3A} receptor in HEK 293 cells and a calcium-monitoring FLIPR assay employed.

Screening of compounds

The compounds were tested using the functional FLIPR primary screening assay employing the stable recombinant GH4C1 cell line expressing the $\alpha 7$ nAChR. Hits identified were validated further by generation of concentration-response curves. The potency of compounds from *Examples 1-254* as measured in the functional FLIPR screening assay was found to range between 10 nM and 30 μ M, with the majority showing a potency ranging between 10 nM and 10 μ M.

The best exemplified compounds were also demonstrated to be selective against the $\alpha 1$ nACh, $\alpha 3$ nACh and 5HT₃ receptors.

Cell based assay of neuroprotection

Neuroprotective activity of selected compounds was analyzed in an established cell-based assay of excitotoxicity induced by NMDA in mixed primary rat cortical neurons as described previously (Stevens et al, 2003). In brief, test compounds were added 24 h before NMDA application. Incubation with NMDA lasted 10 min or 24 h and cell mortality was assessed 24 h after application of the excitotoxic stimulus (see *Figure 1*). Selected compounds (at

concentrations ranging from 0.1 to 10 microM) reduced mortality on average by 50% and in some experiments a maximum of 80% neuroprotection was observed.

In vivo neuroprotection assay

- 5 Neuroprotective activity of compounds was analyzed in an *in vivo* animal model of cholinergic degeneration induced by quisqualic acid injection in the nucleus basalis of rats. Subchronic treatment i.p. daily, for 7 days, with the compound at a dose of 3 mg/kg resulted in 60% reduction in the degeneration of cholinergic neurons as demonstrated by determination of the number of
- 10 ChAT-positive neurons (a representative result is shown in *Figure 2*).

Cognitive behaviour

- Cognitive behaviour was studied for selected compounds from example using the passive avoidance (PA) and object recognition (ORT) tests in order to test the capability to reverse scopolamine-induced amnesia in rats. The
- 15 compounds showed mild to good cognitive improvement of short term-working and episodic memory by inducing significant reversion of scopolamine-induced amnesia in one or both tests (a representative result is shown in *Figure 3*).

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CLAIMS

1. A compound of general formula (I):



wherein:

Y is a group $-\text{CONH}(\text{Q})-$ or $-\text{NHCONH}(\text{Q})-$;

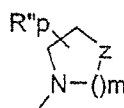
Q is a 5 to 10-membered aromatic or heteroaromatic ring;

10 R is hydrogen; halogen; linear, branched or cyclic (C_1 - C_6) alkyl, haloalkyl, alkoxy or acyl; hydroxy; cyano; nitro; mono- or di- (C_1 - C_6) alkylamino, acylamino or alkylaminocarbonyl; carbamoyl; (C_6 - C_{10}) aryl- or (C_1 - C_6) alkylsulphonylamino; (C_6 - C_{10}) aryl- or (C_1 - C_6) alkylsulphamoyl; a 5 to 10-membered aromatic or heteroaromatic ring optionally substituted with:

15 halogen; linear, branched or cyclic (C_1 - C_3) alkyl, haloalkyl, alkoxy or acyl; hydroxy; cyano; nitro; amino; mono- or di- (C_1 - C_6) alkylamino, acylamino or alkylaminocarbonyl groups; carbamoyl; (C_6 - C_{10}) aryl- or (C_1 - C_6) alkylsulphonylamino; (C_6 - C_{10}) aryl- or (C_1 - C_6) alkylsulphamoyl;

X is a group

20



wherein

Z is CH_2 , N or O;

m is an integer from 1 to 4;

25 p is 0, 1 or 2;

R'' , independently from one another for $p = 2$, is selected from the group consisting of hydrogen; mono- or di-[linear, branched or cyclic (C_1 - C_6) alkyl]aminocarbonyl; linear, branched or cyclic (C_1 - C_6) alkyl, alkoxy, acyl;

salts, isomers, diastereomers or racemic mixtures thereof,

with the exception of the following compounds:

N-[4-(Dimethylamino)phenyl]-1-piperidinepentanamide

N-(4-Acetylphenyl)-1-piperidinepentanamide

5 N-(4-Methoxyphenyl)-1-piperidinepentanamide

N-(4-Nitrophenyl)-1-piperidinepentanamide

N-Phenyl-1-piperidinepentanamide

N-(4-Methylphenyl)-1-piperidinepentanamide

N-(4-Chlorophenyl)-1-piperidinepentanamide.

10 2. A compound according to claim 1 wherein:

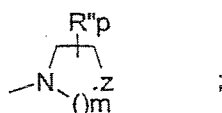
Y is -CONH(Q)-;

Q is a 5 to 10-membered aromatic or heteroaromatic ring;

R is selected from the group consisting of phenyl; naphthyl; pyridyl; pyrimidinyl; quinolinyl; isoquinolinyl; indolyl; thienyl; benzothienyl; furanyl;

15 benzofuranyl; imidazolyl; benzoimidazolyl; pyrrolyl; optionally substituted as indicated in claim 1;

X is a group



where

20 Z is CH₂, N or O

m is an integer from 1 to 4

p is 0, 1 or 2

R'', independently from one another when p = 2, is selected from the group consisting of hydrogen; mono- or di-[linear, branched or cyclic (C₁-C₆)

25 alkyl]aminocarbonyl; linear, branched or cyclic (C₁-C₆) alkyl, alkoxy, acyl;

3. A compound according to claim 1

wherein

Y is -NHCONH(Q)-;

Q is a 5 to 10-membered aromatic or heteroaromatic ring;

R is selected from the group consisting of halogen; linear, branched or cyclic (C₁-C₆) alkyl, alkoxy or alkylamino; haloalkyl; phenyl; naphthyl; pyridyl; pyrimidinyl; quinolinyl; isoquinolinyl; indolyl; thienyl; benzothienyl; furanyl; benzofuranyl; imidazolyl; benzoimidazolyl; pyrrolyl; optionally substituted as indicated in claim 1;

X is a group



Z is CH₂, N or O

m is an integer from 1 to 4

15 p is 0, 1 or 2

R'', independently from one another when p = 2, is selected from the group consisting of hydrogen; mono- or di-[linear, branched or cyclic (C₁-C₆) alkyl]aminocarbonyl; linear, branched or cyclic (C₁-C₆) alkyl, alkoxy, acyl.

4. A pharmaceutical composition containing a compound according to claims 1-3, in combination with a pharmaceutically acceptable carrier or excipient.

5. The use of a compound according to claims 1-3, for the preparation of a medicament for the treatment of neurological, psychiatric, cognitive, immunological and inflammatory disorders.

25 6. The use according to claim 5, for the treatment of Alzheimer's disease.

7. Use of a compound according to claims 1-3 in the manufacture of a medicament for the prevention or treatment of diseases, conditions or dysfunctions involving the alpha 7 nAChR.

8. The use according to claim 7, wherein the disease, condition or dysfunction involving the alpha 7 nAChR is a neurodegenerative disease.
9. The use according to claim 8, wherein the neurodegenerative disease is Alzheimer's disease or schizophrenia.