(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
15 June 2006 (15.06.2006)

PCT

(10) International Publication Number
WO 2006/061377 A1

(51) International Patent Classification:
A61K 31/423 (2006.01) *C07D 413/12* (2006.01)
C07D 263/58 (2006.01) *A61P 25/00* (2006.01)

(21) International Application Number:
PCT/EP2005/056506

(22) International Filing Date:
6 December 2005 (06.12.2005)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/634,074 8 December 2004 (08.12.2004) US
04106394.2 8 December 2004 (08.12.2004) EP

(71) Applicant *(for all designated States except US)*: **SOLVAY PHARMACEUTICALS B.V.** [NL/NL]; C.J. Van Houtenlaan 36, NL-1381 CP Weesp (NL).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **FEENSTRA, Roelof, W.** [NL/NL]; c/o Solvay Pharmaceuticals B.V., IPSI Department C.J. van Houtenlaan 36, NL-1381 CP Weesp (NL). **STOIT, Axel** [NL/NL]; c/o Solvay Pharmaceuticals B.V., IPSI Department C.J. van Houtenlaan 36, NL-1381 CP Weesp (NL). **TERPSTRA, Jan-Willem** [NL/NL]; c/o Solvay Pharmaceuticals B.V., IPSI Department C.J. van Houtenlaan 36, NL-1381 CP Weesp (NL). **PRAS-RAVES, Maria, L.** [NL/NL]; c/o Solvay Pharmaceuticals B.V., IPSI Department C.J. van Houtenlaan 36, NL-1381 CP Weesp (NL). **MCCREARY, Andrew, C.** [GB/NL]; c/o Solvay Pharmaceuticals B.V., IPSI Department C.J. van Houtenlaan 36, NL-1381 CP Weesp (NL). **VAN VLIET, Bernard, J.** [NL/NL]; c/o Solvay Pharmaceuticals B.V., IPSI Department C.J. van Houtenlaan 36, NL-1381 CP Weesp (NL). **HESSELINK, Mayke, B.** [NL/NL]; c/o Solvay Pharmaceuticals B.V., IPSI Department C.J. van Houtenlaan 36, NL-1381 CP Weesp (NL). **KRUSE, Cornelis, G.** [NL/NL]; c/o Solvay Pharmaceuticals B.V., IPSI Department C.J. van Houtenlaan 36, NL-1381 CP Weesp (NL). **VAN SCHARRENBURG, Gustaaf, J., M.** [NL/NL]; c/o Solvay Pharmaceuticals B.V., IPSI Department C.J. van Houtenlaan 36, NL-1381 CP Weesp (NL).

(74) Agent: **VERHAGE, Marinus**; Octrooibureau Zoan B.V., P.O. Box 140, NL-1380 AC Weesp (NL).

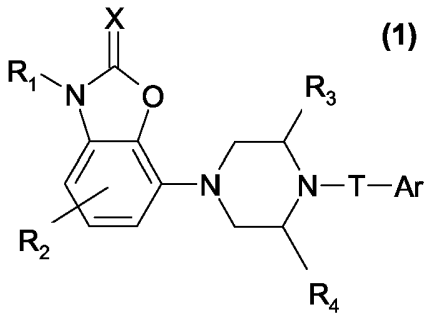
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: PHENYLPIPERAZINE DERIVATIVES WITH A COMBINATION OF PARTIAL DOPAMINE-D2 RECEPTOR AGONISM AND SEROTONIN REUPTAKE INHIBITION



(1)

(57) Abstract: The invention relates to a group of novel phenylpiperazine derivatives with a dual mode of action: serotonin reuptake inhibition and partial agonism on dopamine -D_2 receptors. The invention also relates to the use of a compound disclosed herein for the manufacture of a medicament giving a beneficial effect. The compounds have the general formula (1):wherein the symbols have the meanings given in the specification. and tautomers, stereoisomers and N -oxides thereof, as well as pharmacologically acceptable salts, hydrates and solvates of said compounds of formula (1) and its tautomers, stereoisomers and N -oxides.

WO 2006/061377 A1

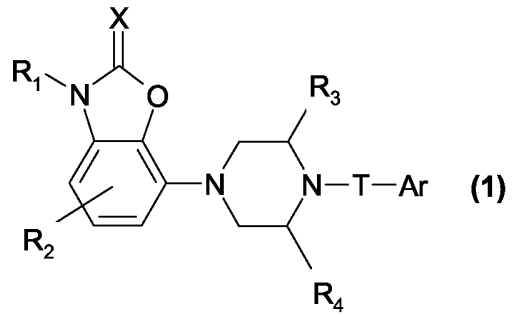
PHENYLPIPERAZINE DERIVATIVES WITH A COMBINATION OF PARTIAL DOPAMINE-D_2 RECEPTOR AGONISM AND SEROTONIN REUPTAKE INHIBITION

The present invention relates to a group of novel phenylpiperazine derivatives with a dual mode of action: serotonin reuptake inhibition and partial agonism on dopamine-D_2 receptors. The invention also relates to the use of a compound disclosed herein for the manufacture of a medicament giving a beneficial effect. A beneficial effect is disclosed herein or apparent to a person skilled in the art from the specification and general knowledge in the art. The invention also relates to the use of a compound of the invention for the manufacture of a medicament for treating or preventing a disease or condition. More particularly, the invention relates to a new use for the treatment of a disease or condition disclosed herein or apparent to a person skilled in the art from the specification and general knowledge in the art. In embodiments of the invention specific compounds disclosed herein are used for the manufacture of a medicament useful in the treatment of disorders in which dopamine-D_2 receptors and serotonin reuptake sites are involved, or that can be treated via manipulation of those targets.

Compounds with a dual action as dopamine-D_2 antagonists and serotonin reuptake inhibitors are known from WO 00/023441, WO 00/069424 and WO 01/014330. This combination of activities is useful for the treatment of schizophrenia and other psychotic disorders: it enables a more complete treatment of all disease symptoms (e.g. positive symptoms and negative symptoms).

The goal of the present invention was to provide further compounds with a dual action as partial dopamine-D_2 antagonists and serotonin reuptake inhibitors.

The invention relates to a group of novel compounds of the formula (1):

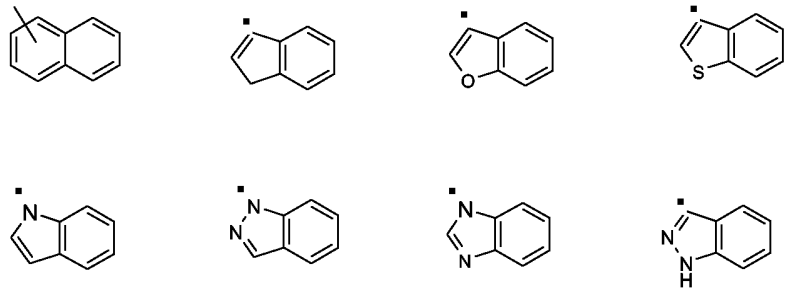


(1)

wherein: X = S or O,
R_1 is H, $(C_1\text{-}C_6)$alkyl, CF_3, CH_2CF_3, OH or O-$(C_1\text{-}C_6)$alkyl
R_2 is H, $(C_1\text{-}C_6)$alkyl, halogen or cyano
R_3 is H or $(C_1\text{-}C_6)$alkyl
R_4 is H, $(C_1\text{-}C_6)$alkyl, optionally substituted with a halogen atom

T is a saturated or unsaturated carbon chain of 2-7 atoms, wherein one carbon atom may be replaced with a nitrogen atom, optionally substituted with an $(C_1\text{-}C_3)$alkyl, CF_3 or CH_2CF_3 group, an oxygen atom or a sulphur atom, which chain is optionally substituted with one or more substituents selected from the group consisting of $(C_1\text{-}C_3)$alkyl, $(C_1\text{-}C_3)$alkoxy, halogen, cyano, trifluoromethyl, OCF_3, SCF_3, $OCHF_2$ and nitro,

Ar is selected from the groups:



which Ar group is optionally further substituted with one or more substituents selected from the group consisting of $(C_1\text{-}C_3)$alkyl, $(C_1\text{-}C_3)$alkoxy, halogen, cyano, trifluoromethyl, OCF_3, SCF_3, $OCHF_2$ and nitro,

and in which Ar groups that contain a five-membered ring, the double bond in the five-membered ring may be saturated,

and tautomers, stereoisomers and N-oxides thereof, as well as pharmacologically acceptable salts, hydrates and solvates of said compounds of formula (1) and its tautomers, stereoisomers and N-oxides.

In the groups 'Ar', the dot represents the attachement point of group 'T'.

In the description of the substituents the abbreviation 'alkyl(C_{1-3})' means 'methyl, ethyl, n-propyl or isopropyl'.

Prodrugs of the compounds mentioned above are in the scope of the present invention. Prodrugs are therapeutic agents which are inactive per se but are transformed into one or more active metabolites. Prodrugs are bioreversible derivatives of drug molecules used to overcome some barriers to the utility of the parent drug molecule. These barriers include, but are not limited to, solubility, permeability, stability, presystemic metabolism and targeting limitations (Medicinal Chemistry: Principles and Practice, 1994, Ed.: F. D. King, p. 215; J. Stella, "*Prodrugs as therapeutics*", Expert Opin. Ther. Patents, 14(3), 277-280, 2004; P. Ettmayer et al., "*Lessons learned from marketed and investigational prodrugs*", J.Med.Chem., 47, 2393-2404, 2004). Pro-drugs, i.e. compounds which when administered to humans by any known route, are metabolised to compounds having formula (1), belong to the invention. In particular this relates to compounds with primary or secondary amino or hydroxy groups. Such compounds can be reacted with organic acids to yield compounds having formula (1) wherein an additional group is present which is easily removed after administration, for instance, but not limited to amidine, enamine, a Mannich base, a hydroxyl-methylene derivative, an O-(acyloxy-methylene carbamate) derivative, carbamate, ester, amide or enaminone.

N-oxides of the compounds mentioned above are in the scope of the present invention. Tertiary amines may or may not give rise to N-oxide metabolites. The extend to what N-oxidation takes place varies from trace amounts to a near quantitative conversion. N-oxides may be more active than their corresponding tertiary amines or less active. Whilst N-oxides are easily reduced to their corresponding tertiary amines by chemical means, in the human body this happens to varying degrees. Some N-oxides undergo nearly quantitative reductive conversion to the corresponding tertiary amines, in other cases the conversion is a mere trace reaction or even completely absent. (M.H. Bickel: "*The pharmacology and Biochemistry of N-oxides*", Pharmaco-logical Reviews, 21(4), 325 – 355, 1969).

It has been found that the compounds according to the invention show high affinity for both the dopamine D_2 receptor and the serotonin reuptake site. The compounds show activity at dopamine D_2 receptors with varying degree of agonism. All of the

compounds show activity as inhibitors of serotonin reuptake, as they potentiate 5-HTP induced behaviour in mice (B.L. Jacobs., '*An animal behaviour model for studying central serotonergic synapses*', Life Sci., 1976, 19(6), 777-785).

In contrast to the use of full dopamine-D_2 receptor agonists or antagonists, the use of partial dopamine-D_2 receptor agonists offers a dynamic medication that self-adjusts on a moment–to–moment basis to the endogenous state of the patient. Thus, it provides the desired flexible modulation of the dopamine system and avoidance of the many adverse effects caused either by treatment using full dopamine-D_2 receptor agonists like bromocriptine (hallucinations, nausea, vomiting, dyskinesia, orthostatic hypotension, somnolescence) or full dopamine-D_2 receptor antagonists like haloperidol (emotional blunting, dysphoria, tardive dyskinesia). Because of these many adverse effects, full agonists and antagonists have found only very limited use in the therapy of depressive and anxiety disorders. Partial dopamine-D_2 receptor agonists not only show a flexible modulation and a favourable side-effect profile, they also have a pronounced anxiolytic profile in relevant animal models (Drugs of the Future 2001, 26(2): 128-132).

Partial dopamine-D_2 receptor agonists, according to the present invention, are compounds that - when tested in a concentration response range – achieve activation in the functional cAMP cell based assay (as described below). Partial dopamine-D_2 receptor agonists will act as an agonist in cases when the endogenous synaptic tone of dopamine is low, or in the the presence of a full dopamine-D_2 receptor antagonist, and will act as an antagonist in cases when the endogenous synaptic tone of dopamine is high, or in the presence of a full dopamine D_2 receptor agonist. Like full agonists, partial dopamine-D_2 receptor agonists in general are active in sensitized systems. They induce contralateral turning in rats with unilateral 6-hydroxy-dopamine (6-OHDA) lesions in the substantia nigra pars compacta. In MPTP-treated common marmosets they produce potent and long-lasting reversal of motor symptoms (Drugs of the Future 2001, 26(2): 128-132). In contrast to full agonists, however, partial dopamine-D_2 agonists are substantially less active in non-sensitized systems: they hardly reverse reserpine induced hypolocomotion in rats.

For the treatment of CNS disorders involving an overactive dopaminergic system a pharmaceutical preparation combining partial dopamine-D_2 receptor agonistic activity having low intrinsic functional activity with serotonin reuptake inhibitory activity is recommended. In case of a disorder involving dopamine

insufficiency a pharmaceutical preparation combining partial dopamine -D_2 receptor agonistic activity with high intrinsic functional activity and serotonin reuptake activity according to the invention has considerable advantages.

Disorders characterized by dynamic fluctuations in dopamine neurotransmission like bipolar depression and addiction will profit in particular from the flexible adjustment of the dopamine system by the partial dopamine -D_2 receptor agonists in the pharmaceutical preparation. Combining this "dopaminergic neurotransmission stabilizing" activity with serotonin reuptake inhibito ry activity will enhance antidepressive and anxiolytic efficacy. The compounds can be used for the treatment of affections or diseases of the central nervous system caused by disturbances in the dopaminergic and serotonergic systems, for example: aggression, anxiety disorders, autism, vertigo, depression, disturbances of cognition or memory, Parkinson's disease, and in particular schizophrenia and other psychotic disorders.

Pharmaceutically acceptable salts may be obtained using standard procedures well known in the art, for example by mixing a compound of the present invention with a suitable acid, for instance an inorganic acid such as hydrochloric acid, or with an organic acid.

PHARMACEUTICAL PREPARATIONS

The compounds of the invention can be brought into forms suitable for administration by means of usual processes using auxillary substances such as liquid or solid carrier material. The pharmaceutical compositions of the invention may be administered enterally, orally, parenterally (intramuscularly or intravenously), rectally or locally (topically). They can be administered in the form of solutions, powders, tablets, capsules (including microcapsules), ointments (creams or gel) or suppositories. Suitable excipients for such formulations are the pharmaceutically customary liquid or solid fillers and extenders, solvents, emulsifiers, lubricants, flavorings, colorings and/or buffer substances. Frequently used auxillary substances which may be mentioned are magnesium carbonate, titanium dioxide, lactose, mannitol and other sugars, talc, lactoprotein, gelatin, starch, cellulose and its derivatives, animal and vegetable oils such as fish liver oil, sunflower, groundnut or sesame oil, polyethylene glycol and solvents such as, for example, sterile water and mono- or polyhydric alcohols such as glycerol.

Compounds of the present invention are generally administered as pharmaceutical compositions which are important and novel embodiments of the invention because of the presence of the compounds, more particularly specific compounds disclosed herein. Types of pharmaceutical compositions that may be used include but are not limited to tablets, chewable tablets, capsules, solutions, parenteral solutions, suppositories, suspensions, and other types disclosed herein or apparent to a person skilled in the art from the specification and general knowledge in the art. In embodiments of the invention, a pharmaceutical pack or kit is provided comprising one or more containers filled with one or more of the ingredients of a pharmaceutical composition of the invention. Associated with such container(s) can be various written materials such as instructions for use, or a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals products, which notice reflects approval by the agency of manufacture, use, or sale for human or veterinary administration.

PHARMACOLOGICAL METHODS

***In vitro* affinity for dopamine-D_2 receptors**

Affinity of the compounds for dopamine-D_2 receptors was determined using the receptor binding assay described by I. Creese, R. Schneider and S.H. Snyder: "[^{3}H]-Spiroperidol labels dopamine receptors in rat pituitary and brain", Eur.J.Pharmacol., 46, 377 - 381, 1977.

***In vitro* affinity for serotonin reuptake sites**

Affinity of the compounds for serotonin reuptake sites was determined using the receptor binding assay described by E. Habert *et al.*,: "Characterisation of [^{3}H]-paroxetine binding to rat cortical membranes", Eur.J.Pharmacol., 118, 107 –114, 1985.

Inhibition of forskolin-induced [^{3}H]-cAMP accumulation

The *in vitro* functional activity at dopamine-D_2 receptors, including the intrinsic activity (ε) of the compounds of the invention was measured by their ability to inhibit forskolin-induced [^{3}H]-cAMP accumulation.

Human dopamine $D_{2,L}$ receptors were cloned in fibroblast cell line CHO -K1 cells and obtained from Dr. Grandy, Vollum Institute, Portland, Oregon, USA. CHO cells were grown in a Dulbecco's modified Eagle's medium (DMEM) culture medium, supplemented with 10% heat-inactivated fetal calf serum, 2 mM glutamine, 1 mM pyruvate, 5000 units/ml penicillin, 5000 μg/ml streptomycin and 200 μg/ml G-418 at 37 ^{0}C in 93% air/7% CO_2. For incubation with test compounds, confluent cultures grown in 24 wells plates were used. Each condition or substance was routinely tested in quadruplicate. Cells were loaded with 1 μCi [^{3}H]-adenine in 0.5 ml medium/well. After 2 hours, cultures were washed with 0.5 ml PBS containing 1 mM of the phosphodiesterase inhibitor isobutylmethylxanthine (IBMX) and incubated for 20 min with 0.5 ml PBS containing 1 mM IBMX and forskolin with or without test compound. After aspiration the reaction was stopped with 1 ml trichloroacetic acid 5% (w/v). The [^{3}H]-ATP and [^{3}H]-cAMP formed in the cellular extract were assayed as described by Solomon Y, Landos C, Rodbell M, 1974, A highly selective adenylyl cyclase assay, Anal Biochem 58:541-548 and Weiss S, Sebben M, Bockaert JJ, 1985, Corticotropin-peptide regulation of intracellular cyclic AMP productio n in cortical neurons in primary culture, J Neurochem 45:869-874. 0.8 ml Extract was passed over Dowex (50WX-4 200-400 mesh) and aluminumoxide columns, eluted with water and 0.1M imidazole (pH=7.5). Eluates were mixed with 7 ml Insta -gel and radioactivity was counted with a liquid scintillation counter. The conversion of [^{3}H]-ATP into [^{3}H]-cAMP was expressed as the ratio in percentage radioactivity in the cAMP fraction as compared to combined radioactivity in both cAMP and ATP fractions, and basal activity was subtracted to correct for spontaneous activity.

Test compounds were obtained as 10 mM stock solutions in 100% DMSO, and diluted in PBS/IBMX to final concentrations. Typically, compounds were used in concentrations that ranged from 10^{-10}M to 10^{-5}M. From quadruplicate data counts, the mean was taken as an estimate for drug-induced, receptor-mediated effects at specified second messenger accumulation, expressed as percentage of control values (forskolin-stimulated cAMP accumulation, subtracted by basal ac tivity). By

using the non-linear curve-fitting program INPLOT or the Excel-add-in XL-Fit, mean values were plotted against drug concentration (in molar) and a sigmoid curve (four-parameter logistic curve) was constructed. The maximal forskolin-induced stimulated conversion is taken as maximum value and the maximal inhibition (usually at drug concentrations 10^{-6} M or 10^{-5} M) as minimum and these values were fixed during the fitting process. Thus, concentrations of the compound, causing 50% of the maximally obtained inhibition of forskolin-induced cAMP accumulation (EC_{50}), are averaged over several experiments and presented as mean pEC_{50} ± SEM. Antagonist potency is assessed by co-incubating cells with a fixed agonist concentration and specified antagonist concentrations. Curve fitting procedures are identical to those used for estimating EC_{50} values. Thus IC_{50} values, i.e. the concentration that is able to achieve 50% of maximal antagonism that can be achieved by this compound. IC_{50} values are corrected using a Cheng-Prussoff equation, correcting it for agonist concentration and EC_{50} values that is obtained in the same experiment. Thus, K_b = IC_{50} / (1+ [agonist]/EC_{50}, agonist).The corresponding pA_2 value is –log (K_b). Concentration-response curve fitting allows estimation of pEC_{50} values and of maximal achievable effect (intrinsic activity or efficacy (ε). A full receptor agonist has ε = 1, a full receptor antagonist has ε = 0, and a partial receptor agonist has an intermediate intrinsic activity.

DOSAGES

The affinity of the compounds of the invention for dopamine-D_2 receptors and serotonine reuptake sites was determined as described above. From the binding affinity measured for a given compound of formula (1), one can estimate a theoretical lowest effective dose. At a concentration of the compound equal to twice the measured K_i-value, 100% of the receptors likely will be occupied by the compound. Converting that concentration to mg of compound per kg of patient yields a theoretical lowest effective dose, assuming ideal bioavailability. Pharmacokinetic, pharmacodynamic, and other considerations may alter the dose actually administered to a higher or lower value. The dosage expediently administered is 0.001 – 1000 mg/kg, preferably 0.1-100 mg/kg of patient's bodyweight.

TREATMENT

The term 'treatment' as used herein refers to any treatment of a mammalian, preferably human condition or disease, and includes: (1) preventing the disease or condition from occurring in a subject which may be predisposed to the disease but has not yet been diagnosed as having it, (2) inhibiting the disease or condition, i.e., arresting its development, (3) relieving the disease or condition, i.e., causing regression of the condition, or (4) relieving the conditions caused by the disease, i.e., stopping the symptoms of the disease.

MATERIALS AND METHODS

^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance DRX600 instrument (600 MHz), Varian UN400 instrument (400 MHz) or on a Varian VXR200 instrument (200 MHz) using DMSO-D_6 or $CDCl_3$ as solvents with tetramethylsilane as an internal standard. Chemical shifts are given in ppm (δ scale) downfield from tetramethylsilane. Peakshapes in the NMR spectra are indicated with the symbols 'q' (quartet), 'dq' (double quartet), 't' (triplet), 'dt' (double triplet), 'd' (doublet), 'dd' (double doublet), 's' (singlet), 'bs' (broad singlet) and 'm' (multiplet). Flash chromatography was performed using silica gel 60 (0.040 -0.063 mm, Merck). Column chromatography was performed using silica gel 60 (0.063 -0.200 mm, Merck). Mass spectra were recorded on a Micromass QTOF -2 instrument with MassLynx application software for acquisition and reconstruction of the data. Exact mass measurement was done of the quasimolecular ion $[M+H]^+$. Melting points were recorded on a Büchi B-545 melting point apparatus. Yields refer to isolated pure products.

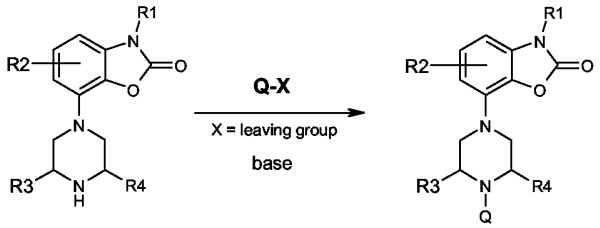
The preparation of the compounds having formula (I) will now be described in more detail in the following Examples.

EXAMPLES

The H-atom of the N-H moiety of amines **I**-H to **X**-H can be replaced by **Q** in two different chemical ways, A and B, eventually leading to the compounds of the invention which are listed in table 1 (*see below*).

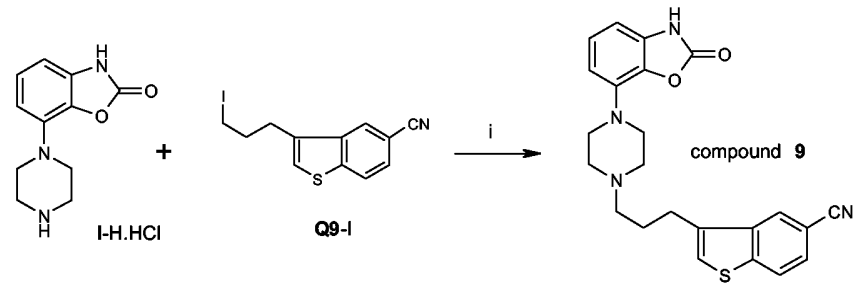
Method A:

The compounds were prepared via the synthesis depicted in scheme A1: an amine (from fig. 1) was reacted with **Q**-X (X = leaving group like *e.g.* Cl, Br, I) in *e.g.* acetonitrile or butyronitrile with Et(*i*-Pr)$_2$N acting as a base, in some cases KI (or NaI) was added. Et$_3$N can be used instead of Et(*i*-Pr)$_2$N.



scheme A1

Example 1:



scheme A2

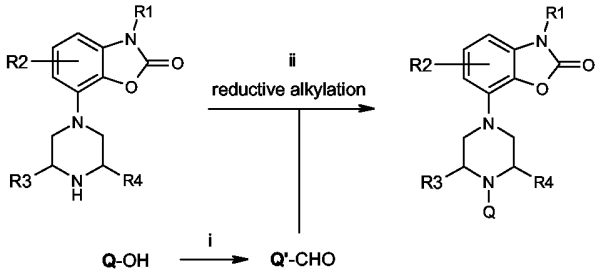
Scheme A2, step i:

To a suspension of 0.6 g (2.35 mmol) of the piperazine hydrochloride **I**-H.HCl in 100 ml of acetonitril were added 0.77 g (2.35 mmol) of the iodide, 0.71 g (4.7 mmol) of NaI and 1.39 ml (8 mmol) of DIPEA. The mixture was refluxed for 20 hours and concentrated *in vacuo*. The residue was taken up in CH_2Cl_2 and the resulting mixture washed with water. The organic layer was dried on Na_2SO_4. The drying agent was removed by filtration and the solvent by concentration *in vacuo*.

The residue was purified by flash column chromatography (SiO_2, eluent CH_2Cl_2/MeOH/NH_4OH 960/37.5/2.5). The product containg fractions were concentrated *in vacuo* leaving a residue which was stirred in diisopropylether. The solid material was collected by filtration, yielding 0.79 g (81 %) of compound **9**. M.p.: 228-230 °C.

Method B:

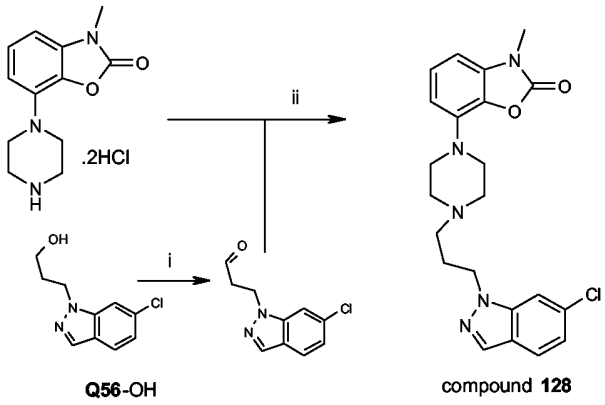
The compounds were prepared via the synthesis depicted in scheme B1: an amine (from fig. 1) was alkylated by means of a reductive alkylation. **Q**-OH was oxidized to the corresponding aldehyde **Q'**-CHO after which reductive alkylation was performed. THF and DCE are suitable solvents for this type of reaction.



scheme B1

Example 2:

The Swern oxidation was carried out according to literature: Anthony J. Mancuso, Daniel Swern; *Synthesis*, (1981) 165-184.



scheme B2

Scheme B2, step i:

A solution of oxalyl chloride (0.45 ml, 5.2 mmol) in 15 ml DCM is placed in a three-necked round bottom flask equipped with a thermometer and two pressure-equalizing dropping funnels respectively containing dimethyl sulfoxide (0.74 ml, 10.4 mmol) in 3 ml DCM, and the 3-(6-chloro-indazo-1-yl)-propanol **Q56**-OH (1.0 g, 4.7 mmmol) in 5 ml DCM under an N_2 atmosphere. The dimethyl sulfoxide is added to the stirred oxalyl chloride solution at -50°C to -60°C. The reaction mixture is stirred for 2 minutes and the alcohol is added within 5 minutes ; stirring is continued for an additional 15 minutes. Triethylamine (3.3 ml, 23.73 mmol) is added and the reaction

mixture is stirred for 15 minutes and then allowed to warm to room temperature. Water is added and the aqueous layer is re-extracted with additional DCM. The organic layer is washed with 0.3 N HCl, water, 5% $NaHCO_3$, saturated NaCl solution and dried with Na_2SO_4. The filtered solution is evaporated yielding the corresponding aldehyde.

Scheme B2, step ii:

The crude product containing the aldehyde (from step i) is added to a stirred solution of 3-methyl-7-piperazin-1-yl-3H-benzooxazole-2-one.2HCl (**V**.2HCl) (0.57 g, 2.44 mmol) and tri-ethyl amine (0.76 ml, 5.38 mmol) in 100 ml DCE. The reaction mixture is stirred for 1 hour and $NaBH(OAc)_3$ (0.83 g, 3.91 mmol) is added. The mixture is stirred for an additional 8 hours. Water was added and the resulting fraction extracted with DCM (3 times). The combined organic layers were evaporated. The crude product was purified by flash chromatography on silica (eluent: 1.5% MeOH in DCM → 2% MeOH in DCM) to afford **128** as a crystalline solid in a 58% yield. Melting point: 118-120 °C.

Table 1: examples of compounds of the invention.

Structures of the phenylpiperazine part of the compounds of formula (1), herein termed 'amines', and groups 'Q' are given below. In the column 'method', the general method (A or B) is given, and in case of method A, the next column gives the leaving group.

Comp. nr.	amine	Q	meth.	L-group	salt	melting r. °C
1	I	1	A	I	free base	194-196.5
2	I	2	A	I	free base	168-170
3	I	3	A	I	free base	206.5-207.5
4	I	4	A	I	free base	173.5-175
5	I	5	A	I	free base	173-176
6	I	6	A	I	free base	180-182
7	I	7	A	I	free base	211-213
8	I	8	A	I	free base	193-195
9	I	9	A	I	free base	228-230
10	I	10	A	I	free base	186-188
11	I	11	A	I	free base	176-178
12	I	12	A	I	free base	212-214
13	I	13	A	I	free base	183-184
14	I	14	A	I	HCl	225-227
15	I	15	A	I	HCl	255-260
16	I	16	A	I	free base	143-145
17	I	17	A	I	free base	152-157
18	I	18	A	I	free base	157-159
19	I	19	A	I	HCl	179-181
20	I	20	A	I	free base	174.5-177
21	I	21	A	Cl	free base	180-183

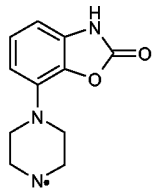
22	**I**	**22**	A	I	free base	206-208
23	**I**	**23**	A	I	free base	202-204
24	**I**	**25**	A	I	free base	154-156
25	**I**	**29**	A	I	free base	amorph
26	**I**	**30**	A	I	free base	177-179
27	**I**	**31**	A	I	free base	153-156
28	**I**	**32**	A	I	free base	174-177
29	**I**	**33**	A	Br	free base	187-190
30	**I**	**34**	A	Br	free base	190-192
31	**I**	**35**	A	Br	free base	174-177
32	**I**	**36**	A	Br	free base	198-200
33	**I**	**37**	A	Br	free base	194-195
34	**I**	**38**	A	Br	free base	137-138
35	**I**	**39**	A	Br	free base	136-138
36	**I**	**40**	A	Cl	free base	121-123
37	**I**	**41**	A	Br	free base	133-135
38	**I**	**42**	A	Br	free base	135-137
39	**I**	**43**	A	Cl	free base	111-112
40	**I**	**44**	B		free base	200-202
41	**I**	**45**	A	Br	free base	197-199
42	**I**	**46**	A	Cl	free base	162-164
43	**I**	**47**	A	Br	free base	204-206
44	**I**	**48**	A	Cl	free base	162-164
45	**I**	**49**	A	Br	free base	188-189
46	**I**	**50**	A	Cl	free base	146-149
47	**I**	**51**	A	Cl	free base	109-113
48	**I**	**52**	A	Br	free base	75-105 amorph
49	**I**	**53**	A	Br	free base	209-210
50	**I**	**54**	B		free base	201-203
51	**I**	**55**	B		free base	161-162
52	**I**	**56**	B		free base	203-204
53	**I**	**57**	B		free base	83-86
54	**I**	**58**	B		free base	172-174
55	**I**	**59**	B		free base	134-137
56	**I**	**60**	A	Br	free base	214-6
57	**I**	**61**	A	I	HCl	214-6
58	**I**	**62**	A	I	HCl	275-7 (d)
59	**I**	**63**	A	I	free base	NMR**
60	**I**	**64**	A	Cl	free base	234-6
61	**II**	**3**	A	I	free base	187-189
62	**II**	**5**	A	I	free base	157-159
63	**II**	**6**	A	I	free base	154-156
64	**II**	**8**	A	I	free base	190-192
65	**II**	**9**	A	I	free base	234-236
66	**II**	**11**	A	I	free base	176-178
67	**II**	**13**	A	I	free base	236-239
68	**II**	**15**	A	I	free base	156-158
69	**II**	**16**	A	I	HCl	256-260
70	**II**	**17**	A	I	HCl	244-246
71	**II**	**26**	A	I	HCl	232-5 (d)
72	**II**	**29**	A	I	free base	157-158
73	**II**	**31**	A	I	free base	190-1
74	**II**	**32**	A	I	free base	168-170
75	**II**	**35**	A	Br	free base	170-173
76	**II**	**36**	A	Br	free base	193-196
77	**II**	**45**	A	Br	free base	166-169
78	**II**	**47**	A	Br	free base	108-113
79	**II**	**49**	A	Br	free base	168-170
80	**II**	**50**	A	Cl	free base	194-7

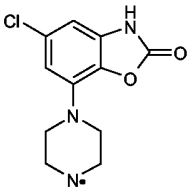
81	**II**	**59**	B		free base	153-5
82	**II**	**61**	A	I	free base	157-9
83	**III**	**16**	A	I	free base	153-154
84	**IV**	**16**	A	I	free base	163-5
85	**V**	**1**	A	I	free base	125-127
86	**V**	**3**	A	I	free base	153-155
87	**V**	**4**	A	I	HCl	182-183
88	**V**	**5**	A	I	free base	113-116
89	**V**	**6**	A	I	free base	162-164
90	**V**	**8**	A	I	free base	119-121
91	**V**	**9**	A	I	free base	150-152
92	**V**	**10**	A	I	free base	141-142
93	**V**	**11**	A	I	free base	124-126
94	**V**	**12**	A	I	free base	184-186
95	**V**	**13**	A	I	HCl	107
96	**V**	**14**	A	I	HCl	197-199
97	**V**	**15**	A	I	HCl	216-218
98	**V**	**16**	A	I	HCl	199-201
99	**V**	**17**	A	I	HCl	214-218
100	**V**	**18**	A	I	free base	228-229
101	**V**	**19**	A	I	free base	132-134
102	**V**	**20**	A	I	free base	138-140
103	**V**	**22**	A	I	free base	143-145
104	**V**	**23**	A	I	free base	150-152
105	**V**	**24**	A	I	free base	179-181
106	**V**	**25**	A	I	HCl	197-199
107	**V**	**26**	A	I	free base	105-107
108	**V**	**28**	A	I	free base	146-147
109	**V**	**31**	A	I	free base	119-21
110	**V**	**33**	A	Br	HCl	>240 d
111	**V**	**34**	A	Br	free base	108-111
112	**V**	**35**	A	Br	free base	129-132
113	**V**	**36**	A	Br	HCl	>240 d
114	**V**	**37**	A	Br	free base	146-149
115	**V**	**41**	A	Br	free base	117-118
116	**V**	**42**	A	Br	free base	110-112
117	**V**	**43**	A	Cl	free base	167-170
118	**V**	**45**	A	Br	free base	111-113
119	**V**	**46**	A	Cl	free base	88-91
120	**V**	**47**	A	Br	free base	131-133
121	**V**	**49**	A	Br	free base	124-126
122	**V**	**50**	A	Cl	free base	103-105
123	**V**	**51**	A	Cl	free base	112-115
124	**V**	**52**	A	Br	free base	203-205
125	**V**	**53**	A	Br	HCl	262-264
126	**V**	**54**	B		free base	116-118
127	**V**	**55**	B		free base	104-107
128	**V**	**56**	B		free base	118-120
129	**V**	**57**	A	I	free base	108-112
130	**V**	**58**	B		free base	102-104
131	**V**	**59**	B		free base	125-128
132	**V**	**60**	A	Br	free base	202-3
133	**V**	**61**	A	I	HCl	194-7
134	**V**	**62**	A	I	HCl	274-6 (d)
135	**V**	**63**	A	I	free base	NMR**
136	**V**	**64**	A	Cl	free base	154-5
137	**VI**	**16**	A	I	free base	134-6
138	**VI**	**31**	A	I	free base	125-6
139	**VI**	**50**	A	Cl	free base	116-8

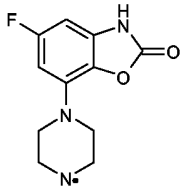
140	**VI**	**59**	B		free base	130-2
141	**VII**	**16**	A	I	HCl	274-276
142	**VIII**	**16**	A	I	free base	135-137
143	**IX**	**3**	A	I	free base	106-108
144	**IX**	**6**	A	I	free base	117-119
145	**IX**	**49**	A	Br	HCl	204-206
146	**IX**	**50**	A	Cl	free base	107-109

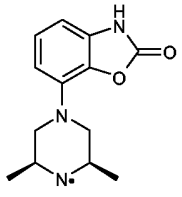
*NMR**, compound 59: (d, ppm) 3.36 (t, broad, Ph -N(C$\underline{H}_2CH_2)_2$N-)*
*NMR**, compound 135: (d, ppm) 3.29 (t, broad, Ph -N(C$\underline{H}_2CH_2)_2$N-)*
***): $CDCl_3/d^6$-DMSO = 1/4*

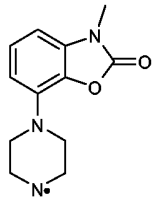
The phenylpiperazine parts of the compounds of formula (1) used in these methods are indicated as **I**-H to **IX**-H, wherein the dot on the N-atom is the attachment point for the group Q:

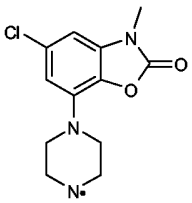

I

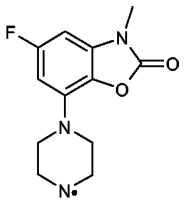

II

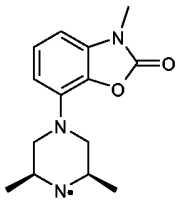

III

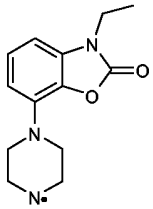

IV


V


VI

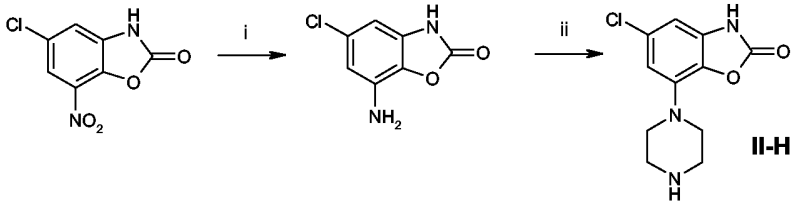

VII


VIII


IX

The syntheses of the piperazines **I**-H, **III**-H and **V**-H are described in WO97/36893.

Synthesis of amine **II**-H:



scheme II

The synthesis of the starting material has been described (patent DE487014).

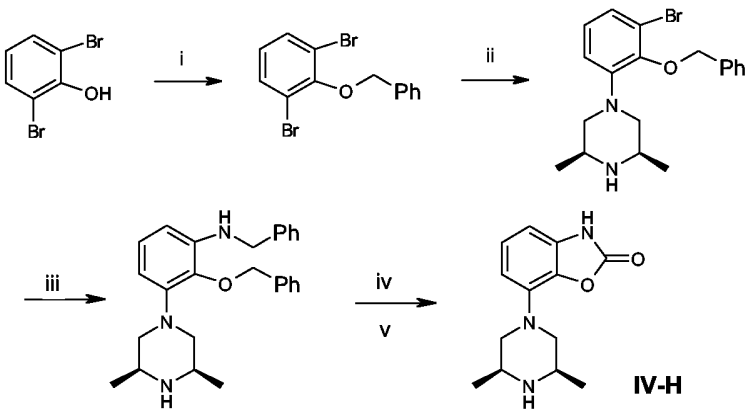
Scheme II, step i:

30 g ((0.14 mol) of the starting material was suspended in 600 ml of MeOH. Then a small amount of Raney nickel was added after which hydrogenation was started (atmospheric, room temperature). After 24 hours 7.2 liters (theoretical amount 9 .4 liters) of hydrogen was absorbed. To the reaction mixture 150 ml of THF was added and another small amount of Raney nickel. After one hour the reaction mixture was filtered over hyflo, the residue washed with THF. The filtrate was concentrated *in vacuo,* yielding 25.2 g (98%) of the correspondig aniline.

Scheme II, step ii:

24.2 g (131.2 mmol) of the aniline of the previous step and 25.8 g (144.3 mmol) of bis (2-chloroethyl)amine were suspended in 675 ml of chlorobenzene. While stirring, 25 ml of solvent were distilled off with the aid of a Dean-Stark apparatus. After removal of the Dean-Stark apparatus, the reaction was allowed to reflux for 48 hours. When the reaction mixture had come to room temperature, the mixture was decanted and the residue washed twice with Et_2O. Then 400 ml of MeOH were added after which the mixture was warmed until almost all of the residue was dissolved. Then 200 ml of silica were added after which the whole was concentrated in vacuo. Then the residue was put on top of a flash c hromatography column using DMA 0.75 as the eluent. After removal of the solvent a residue was isolated which was suspended in about 100 ml of acetonitrile and stirred for 4 hours. Filtration and drying yielded 17 g of the desired piperazine **II**-H as a free base.

Synthesis of amine **IV**-H:



scheme IV

The toluene used in this experiment was degassed for three hours prior to usage. 1.48 g (1.61 mmol) of $Pd_2(dba)_3$ and 3.02 g (4.85 mmol) of BINAP were put into 400 ml of toluene after which the mixture was stirred and heated to 105 °C for 0.5 hours after which the mixture was allowed to room temperature. Subsequently were added to the reaction mixture: 27.

Scheme IV, step i:

20.5 g (81.3 mmol) of dibromophenol and 20 g of potassium carbonate were suspended in 400 ml of aceton, after which 15.7 ml of benzylbromide were added. The reaction mixture was refluxed for 24 hours. After the mixture had reached room temperature, it was concentrated in vacuo. Subsequently water was added and CH_2Cl_2. The organic layer was filtered with a water repellant filter, the dry filtrate concentrated in vacuo after which it was dissolved again in 200 ml of acetonitrile. Subsequently, 15 ml of piperidine were added after which the temperature was raised to 60 °C for one hour. The reaction mixture was concentrated in vacuo and CH_2Cl_2 was added. The latter was washed with: 1N HCl (3x), water, 2N NaOH, and again water. The organic layer was filtered with a water repellant filter, the dry filtrate concentrated in vacuo yielding 27.6 g (99%) of the corresponding benzylated phenol.

Scheme IV, step ii:

6 g (80.7 mmol) of the benzylated compound (step i) dissolved in 50 ml of toluene, 9.2 g (80.7 mmol) of the (α,α')-dimethylpiperazine and 10.08 g (104.9 mmol) of sodium *tert*.butoxide. The resulting mixture was heated at 105 °C for 20 hours, after which it was allowed to reach room temperature. The mixture was diluted with CH_2Cl_2 after which it was filtered over hyflo and concentrated in vacuo. The residue was put on top of a flash chromatography column (SiO_2) using DMA 0.125. The combined product containing fractions yielded after concentration in vacuo 7.7 g (26%) of the almost pure phenylpiperazine.

Scheme IV, step iii:

This step was done analogously to the procedure described in the previous step ii (scheme IV). In this case benzylamine was used in the Buchwald reaction. Yield: 88%.

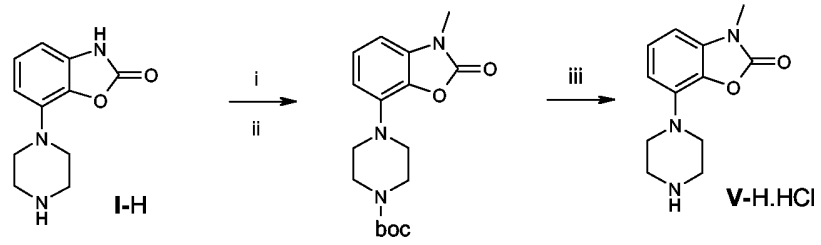
Scheme IV, step iv:

7 ml (98 mmol) of acetyl chloride was added dropwise to 70 ml of cooled absolute ethanol, stirring was continued for 15 minutes. The latter solution was added to a solution of 11.5 g (28.7 mmol) of the dibenzyl product of step iii in 250 ml of methanol. Subsequently 1.5 g of Pd/C (10%) was added, after which the reaction mixture was hydrogenated for 24 hours. The mixture was filtered over hyflo, the filtrate concentrated in vacuo. The residue containing the amino phenol HCl salt was *directly* used in step v.

Scheme IV, step v:

The residue (28.7 mmol) obtained in step iv, 52 ml of DIPEA (298 mmol), and 20.9 g (129 mmol) of CDI were added to 750 ml of THF after which the mixture was refluxed for 20 hours under a nitrogen atmosphere. After cooling to room temperature, the mixture was concentrated in vacuo, to the residue CH_2Cl_2 and 5% $NaHCO_3$ were added, the whole being stirred for one hour. Extraction with CH_2Cl_2 (3x), the water fraction was concentrated and extracted again (CH_2Cl_2, 3x). The combined organic fractions were concentrated in vacuo, the residue contained a considerable amount of imidazol. The whole was solved in 120 ml of acetonitrile after which the solution was allowed to reach room temperature. The precipitate which formed was filtered yielding almost pure piperazine **IV**.

Synthesis of amine **V**-H:

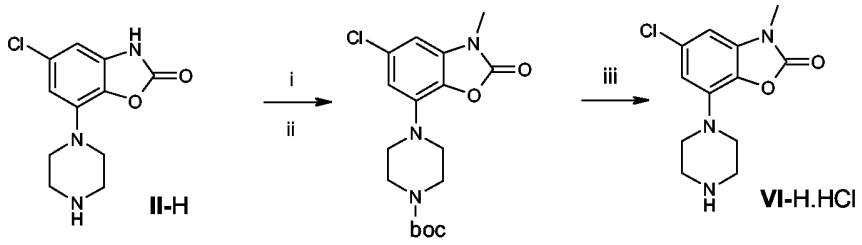


scheme V

Scheme V, steps i, ii and iii:

Synthesis of **V**-H has been described in WO97/36893. The steps i, ii and iii were done analogously to steps i, ii and iii in scheme VI.

Synthesis of amine **VI**-H:



scheme VI

Scheme VI, step i:

While stirring, 3.8 g (15 mmol) of piperazine **II**-H were suspended in 5.48 ml (31.5 mmol) of DIPEA and the mixture was brought to -40 °C. A solution of 3.14 g (14.4 mmol, 0.96 eq) of Boc-anhydride in 30 ml of CH_2Cl_2 was added dropwise in 100 minutes. Stirring was continued at -40 °C (1 hour), then at -30 °C (2 hours), and the reaction mixture was allowed to come to room temperature (16 hours). Then water and some MeOH were added after which it was extracted with CH_2Cl_2. The combined organic fractions were filtered with a water repellant filter, the dry filtrate mixed with 50 ml of silica after which the whole was concentrated in vacuo. Then the residue was put on top of a dry chromatography column (SiO_2) using CH_2Cl_2/MeOH (98/2) as the eluent. The part of the column containing the product was cut out, and the product washed out of the column material with CH_2Cl_2/MeOH (98/2) yielding 3.55 g (67%) of the desired N-Boc **II**.

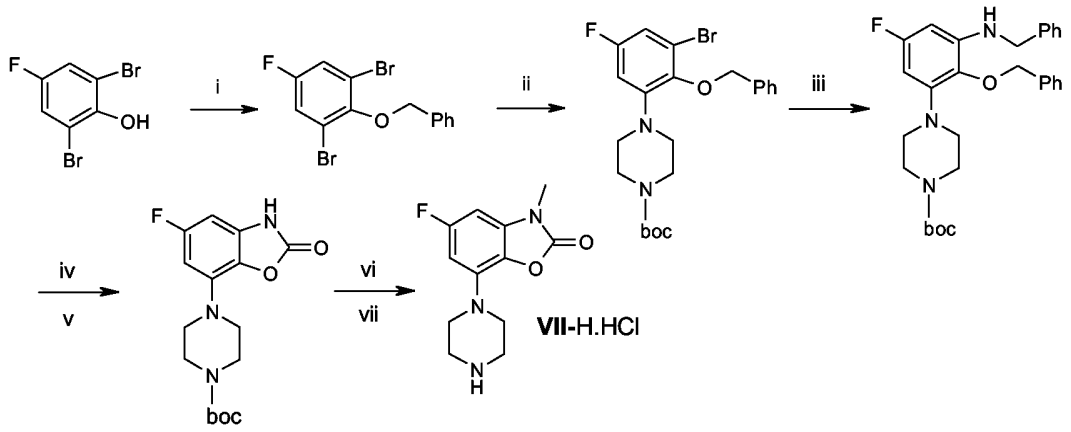
Scheme VI, step ii:

4.5 g (12.7 mmol) N-Boc **II** together with 5.8 g (3.3 eq) of potassium carbonate were suspended in 100 ml of aceton. While stirring, the reaction mixture was cooled to -10 °C after which 0.87 ml (14 mmol, 1.1 eq) of methyl iodide was added dropwise. After 15 minutes, the reaction mixture was allowed to reach room temperature and stirring was continued for 14 hours. Subsequently, the reaction mixture was concentrated in vacuo, the residue mixed with water and CH_2Cl_2. The water layer was separated and extracted twice with CH_2Cl_2. The combined organic layers were filtered with a water repellant filter, the dry filtrate concentrated in vacuo yielding 4.5 g (98%) of the corresponding N'-methylated N-Boc **II**.

Scheme VI, step iii:

While stirring at -10 °C, 5 ml of acetyl chloride (70.4 mmol, 5.8 eq) was added dropwise to 65 ml of ethanol. The latter solution was added to 4.5 g (12.2 mmol)of the N'-methylated N-Boc **II** isolated in step *ii*. The resulting mixture was stirred for 3 hours at 55 °C, then the reaction mixture was allowed to reach room temperature and stirring was continued for 14 hours. Subsequently, the mixture was concentrated in vacuo after which the residue was suspended in di-isopropyl ether and stirred for 2 hours. The precipitate was isolated by filtration yielding 3.6 g (97%) of piperazine **VI**-H.HCl.

Synthesis of amine **VII**-H:



scheme VII

Scheme VII, step i:

This step was done analogously to step i in scheme IV. After chromatograhic purification an oil containing the benzylated product, was isolated in 88% yield. The oil solidified upon standing.

Scheme VII, step ii:

This step was done analogously to step ii in scheme IV. Boc-piperazine was used in this Buchwald reaction. Yield after chromatographic purification: 44% of a brown oil.

Scheme VII, step iii:

This step was done analogously to the procedure described in the previous step ii (scheme VII). In this case benzylamine was used in the Buchwald reaction. Yield after chromatographic purification: 73% of a brown oil.

Scheme VII, step iv:

11.91 g (24.3 mmol) of the dibenzylated product isolated in previous step iii (scheme VII) was suspended in a mixture of 110 ml of ethanol, 72 ml of water and 11 ml of acetic acid. While stirring, 0.5 g of $Pd(OH)_2/C$ was added and hydrogenation was started for 6 days. After one day and after 3 days an additional small amount of $Pd(OH)_2/C$ was added. The reaction mixture was filtered over hyflo, the filtrate concentrated in vacuo. The residue was treated with toluene and concentrated in vacuo, this procedure was repeated, leaving a dark sirup 7.9 g (88%), containing the amino phenol.

Scheme VII, step v:

This step (ring closure with CDI) was done analogously to step v in scheme IV. The crude product after work up was chromatographed (flash column, SiO_2, eluent DCM/MeOH 97/3) yielding 7.6 g of an impure brown foam. A second chromatography (flash column, SiO_2, eluent EtOAc/petroleum ether 1/2) yielded 3.3 g (42%) of pure brown foam, containing the N-Boc protected benzoxazolinone piperazine.

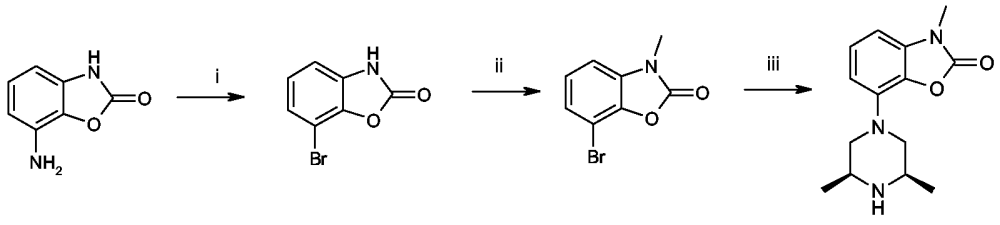
Scheme VII, step vi:

This methylation step was done analogously to the procedure described in step ii (scheme VI). Yield: 98% of a brown foam of 97% purity.

Scheme VII, step vii:

This deprotection step was done analogously to the procedure described in step iii (scheme VI). Yield: 94% of a light pink solid of 98% purity, containing the product **VII**-H.HCl.

Synthesis of amine **VIII**-H:



scheme VIII **VIII**-H

Scheme VIII, step i:

The starting material synthesis has been described in EP0189612.

4.91 g (32.7 mmol) of the anilin was suspended in 75 ml of 48% of HBr/water, while it was cooled to -5 °C. Subsequently 2.27 g (33 mmol) of sodium nitrite dissolved in 4 ml of water, were added dropwise during 15 minutes. Stirring was continued at 0 oC for 15 minutes.

Subsequently, the reaction mixture was added, in one time, to a 0 °C solution of 2.42 g (16.9 mmol) CuBr in 20 ml of 48% HBr/water. After 30 minutes the reaction mixture was heated to 85 oC for one hour, after which it was allowed to reach room temperature, stirring was continued for 14 hours. To the mixture diethyl ether and water were added, after shaking the organic layer was isolated which was washed with water. The organic layer, together with some silica, was concentrated in vacuo, and the residue was put on top of a flash chromatography column (SiO_2) using Et_2O/petroleum ether (1/1), and later on pure Et_2O as the eluent. The combined product containing fractions yielded after concentration in vacuo 3.3 g (47%) of the desired corresponding bromo product.

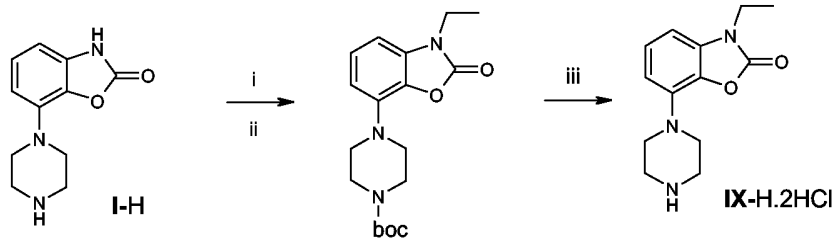
Scheme VIII, step ii:

This step was carried out identical to step *ii* in scheme VI. Yield: 92% of the corresponding methylated bromo compound.

Scheme VIII, step iii:

In the following order 6.82 g (29.9 mmol) of the methylated bromo compound, 4.03 g (35.9 mmol) of the dimethyl piperazine, 13.6 g (41.9 mmol) of Cs_2CO_3, 1.42 g (2.99 mmol) of X-Phos (see Huang et al., *J. Am. Chem. Soc.*,**125**(2003)6653). and 0.55 g (0.6 mmol) of $Pd_2(dba)_3$ were added to 225 ml of toluene which was degassed for 4 hours prior to usage. While stirring and under a nitrogen atmosphere the temperature was raised to 100 °C for 20 hours, after which it was allowed to reach room temperature. The mixture was diluted with CH_2Cl_2 after which it was filtered and concentrated in vacuo. The residue was put on top of a flash chromatography column (SiO_2) using DMA 0.25. The combined product containing fractions yielded after concentration in vacuo 0.73 g (9%) of the desired pure piperazine **VIII**-H.

Synthesis of amine **IX**-H:

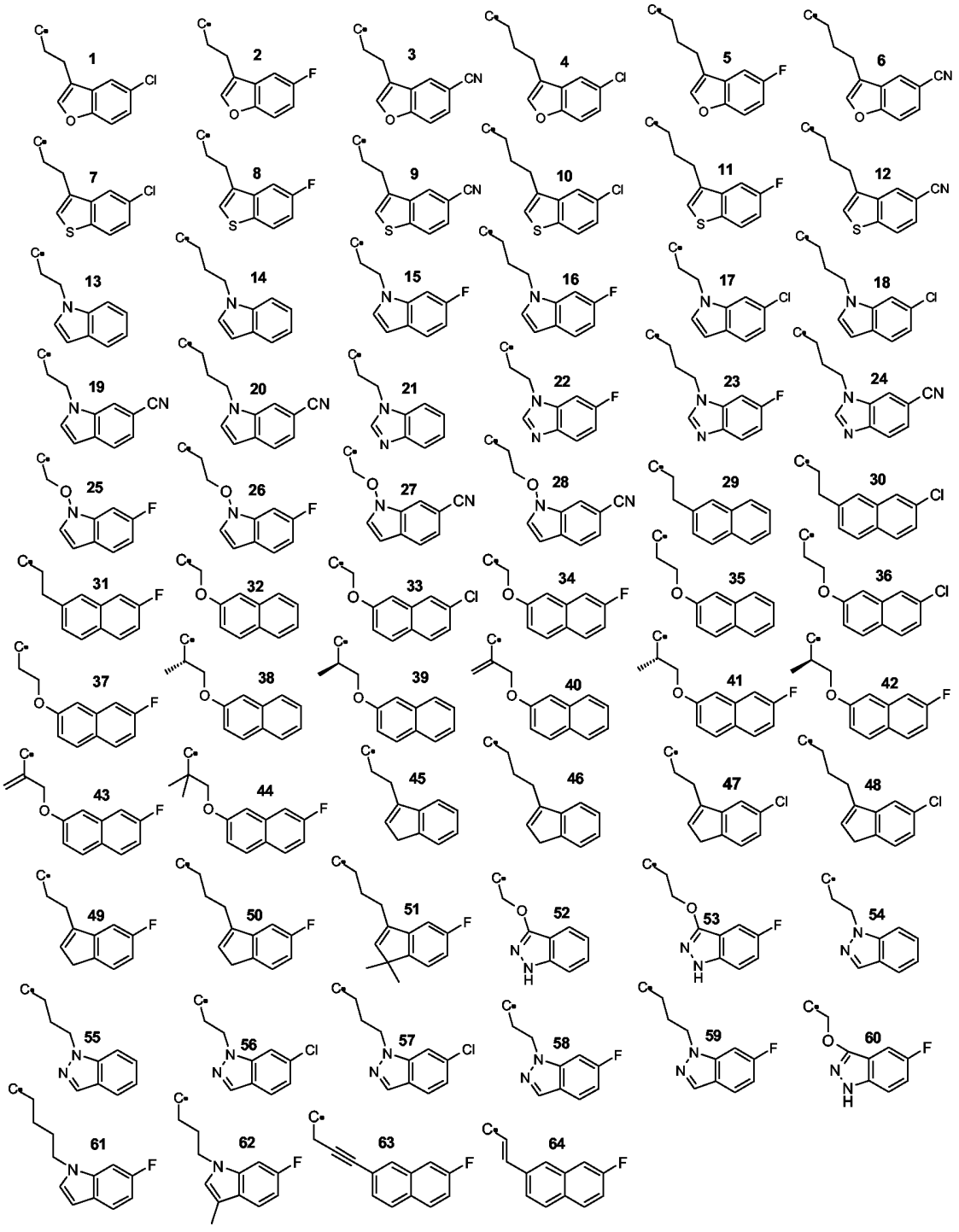


scheme IX

Scheme IX, steps i, ii and iii:

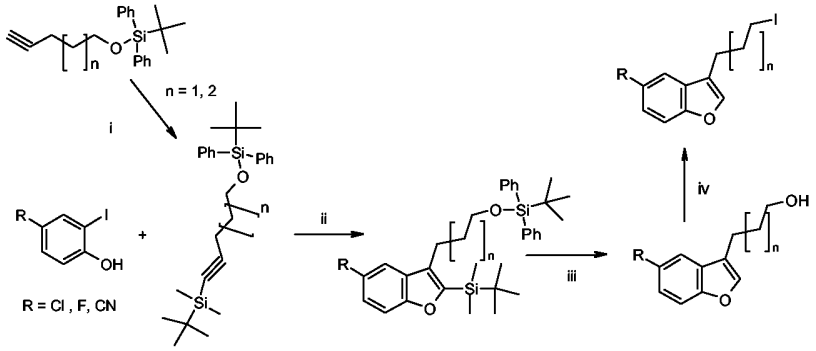
Synthesis of **I**-H has been described in WO97/36893. The steps i, ii and iii were done analogously to steps i, ii and iii in scheme VI.

Below, the different structures of **Q1** to **Q64** are given:



In these formulae 'Q', the dot represents the attachment to the phenylpiperazine part of the compounds of formula (1).

Synthesis of **Q1-6**:



scheme 1-6

All starting materials (phenols and alkynes) were prepared according to procedures described in the literature:

Alkynes: Davison, Edwin C.; Fox, Martin E.; *J. Chem. Soc. Perkin Trans. 1 ;* **12**(2002) 1494-1514. Yu, Ming; Alonso-Alicia, M.; *Bioorg. Med. Chem.;* **11** (2003)2802-2822.

Phenols: Buchan; McCombie*; J. Chem. Soc.*; **137** (1931) 144. Finger et al; *J. Amer. Chem. Soc.*; **81** (1959) 94, 95, 97. Berg; Newbery; *J. Chem. Soc.;* (1949) 642-645.

Scheme 1-6, step i:

R=CN, n=2

A stirred solution of the silylated alcohol (3.35 g, 10 mmol) in 20 ml of dry THF was cooled to -70 °C. 2.5M n-BuLi (4.8 ml, 12 mmol) was slowly added dropwise at such a rate that the temperature was kept below -65 °C. The solution was allowed to warm to -20 °C and stirring was continued for 1 hour during which the color of the solution changed from light to dark yellow. The solution is again cooled to -70 °C and a solution of tert-butyldimethylsilylchloride (1.66 g, 11 mmol) in 15 ml of dry THF is slowly added dropwise in 10 minutes. The reaction mixture was allowed to warm to room temperature and stirring was continued for 20 h. The reaction mixture was quenched by the addition of saturated NH_4Cl and extracted 2x with Et_2O. The combined Et_2O layers were washed with 5% $NaHCO_3$ (1x) and H_2O (1x) and dried (Na_2SO_4). The Et_2O fraction was concentrated under reduced pressure and the residue was chromatographed (SiO_2) using DMA/petroleum ether 1/5 as eluent to give 3.35 g (75%) of the silylated alkyne as a colorless oil.

Scheme 1-6, step ii:

A mixture of 4-cyano-2-iodophenol (1.23 g, 5 mmol), silylated alkyne (from step i) (2.18 g, 5 mmol), LiCl (0.21 g, 5 mmol) and Na_2CO_3 (2.38 g, 22.5 mmol) in 20 ml DMF was degassed by bubbling nitrogen through the solution for 2 h. $Pd(OAc)_2$ (50 mg, 0.20 mmol) was added and the reaction mixture was stirred for 7 hours at 100 °C. H_2O and hexane were added and the mixture was filtered over hyflo. After separation of the hexane layer, the aqueous layer was extracted with hexane (1x). The combined hexane layers were washed with H_2O (1x) and brine (1x). The hexane fraction was partially evaporated under reduced pressure and 8 g of silicagel was added and stirring was continued for 15 minutes. The silica is filtered off and the filtrate is concentrated under reduced pressure. The residue was chromatographed (SiO_2) using Et_2O/petroleum ether 1/9 as the eluent to give 0.93 g (35%) of the benzfurane derivative as a light yellow oil.

Scheme 1-6, step iii:

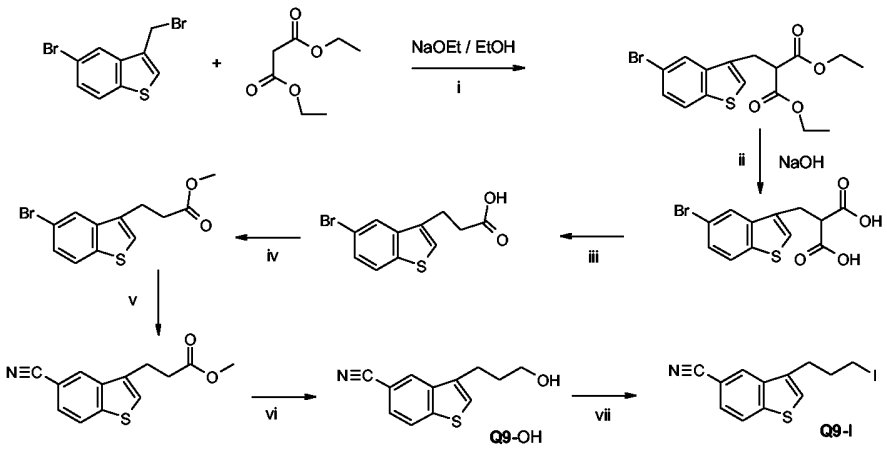
A mixture of the cyclized compound (29.58 g, 52.17 mmol), $KF.2H_2O$ (14.73 g, 156.51 mmol), benzyltriethylammoniumchloride (14.26 g, 62.60 mmol) in 450 ml of CH_3CN was refluxed for 4 h. After cooling to room temperature, CH_3CN was washed 2x with hexane. The CH_3CN fraction was evaporated under reduced pressure. H_2O was added the residue and this was extracted twice with EtOAc. The combined organic layers were washed with respectively H_2O (1x) and brine (1x). The organic layer was dried (Na_2SO_4) and concentrated *in vacuo*. The residue was subjected to column chromatography (SiO2, eluent: EtOAc/petroleum ether 1:3 → EtOAc/petroleum ether 1:1) to yield 9.20 g (82%) of the alcohol **Q3**-OH as a yellow oil.

Scheme 1-6, step iv:

PPh_3 (14.38 g, 54.84 mmol) and imidazole (3.73 g, 54.84 mmol) were dissolved in 160 ml of CH_2Cl_2. Iodine (13.92 g, 54.84 mmol) was added and the resulting suspension was stirred for 20 minutes at room temperature . A solution of the alcohol obtained at step *iii* (9.07 g, 42.19 mmol) in 70 ml of CH_2Cl_2 was added dropwise and the reaction mixture was stirred for 20 h at room temperature. Water was added and after separation the H_2O layer was extracted with CH_2Cl_2. The combined organic layers were washed with respectively 5% $NaHSO_3$ solution (1x) and H_2O (1x) and dried on Na_2SO_4. The drying agent was removed by filtration and

the solvent by concentration *in vacuo*. The residue was chromatographed (SiO_2) using CH_2Cl_2 as the eluent to give 12.9 g (94%) of the iodide **Q3**-I as a thick oil which crystallized on standing.

Synthesis of **Q7-9**:



scheme 7-9

The 5-bromobenzthiophene was prepared according to: Leclerc, V.; Beaurain, N.; *Pharm. Pharmacol. Commun.*, **6**(2000)61-66.

Scheme 7-9, step i:

Sodium metal (4.5 g, 195.9 mmol) was added in pieces to 260 ml of absolute EtOH. The malonic ester (116 ml, 779 mmol) was added and the reaction mixture was stirred under a nitrogen atmosphere for 30 minutes. The 5-bromobenzthiophene (29.5 g, 97.2 mmol) was added as a suspension in 125 ml of absolute EtOH and stirring was continued at reflux for 18 h. The solvent was evaporated under reduced pressure after which 250 ml H_2O and 15 g NH_4Cl were added to the residue. The aqueous layer was extracted with CH_2Cl_2 (2x) and the combined organic layers were dried (Water Repelling Filter) and the filtrate concentrated in vacuo (by means of an oil pump, 8 mbar). The residue was chromatographed (SiO_2) with CH_2Cl_2/petroleumether 3/2 to give 23.9 g (64%) of the di-ester.

Scheme 7-9, step ii:

This step was carried out analogous to step ii from Scheme 51.

Scheme 7-9, step ii:

This step was carried out analogous to step iii from Scheme 51.

Scheme 7-9, step iv:

This step was carried out analogous to step iii from scheme 10 -12.

Scheme 7-9, step v

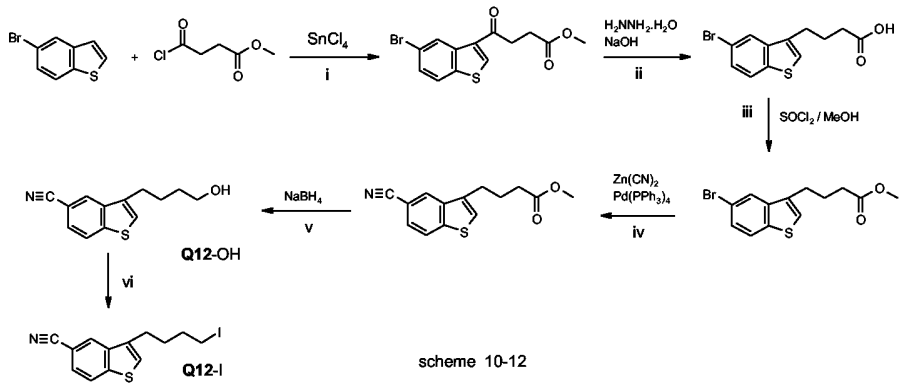
This step was carried out analogous to step v from scheme 10 -12.

Scheme 7-9, step vi:

This step was carried out analogous to step iv from s cheme 1-6.

Derivatives of **Q7**and **Q8** were prepared analogously to the above described procedures.

Synthesis of **Q10-12**:



scheme 10-12

All reagents were commercially available. The 5 -bromobenzthiophene was prepared according to Badger et al., *J. Chem. Soc.*, (1957) 2624, 2628.

Scheme 10-12, step i:

To a stirred mixture of 5-bromobenzthiophene (22.5 g, 105.6 mmol) and the acid chloride (17.4 ml, 141.3 mmol) in 135 ml benzene at 0 °C, $SnCl_4$ (43.1 ml, 368 mmol) was added in 2 h. Stirring was continued f or 4 hours at the same temperature. The reaction mixture was poured into a mixture of 95 ml concentrated HCl (36-38%) in ice. The reaction mixture was extracted with EtOAc and the organic

layer was washed with H_2O (3x), 1N NaOH (1x), 5% $NaHCO_3$ and H_2O (2x). The EtOAc fraction was dried ($MgSO_4$). The drying agent was removed by filtration and the solvent by evaporation under reduced pressure. The residue was recrystallized from 950 ml MeOH and chromatographed with Et_2O/petroleum ether 1/1 as eluent to give 23.3 g (68%) of the acylated benzthiophene.

Scheme 10-12, step ii:

To a stirred mixture of the acylated benzthiophene (23.3 g, 71.3 mmol) and powdered NaOH (23 g, 575 mmol) in 285 ml diethyleneglycol, hydrazine hydrate (23 ml, 474 mmol) was added. Stirring was continued for 2 hours at 145 °C after which additional stirring for 2 hours at 180 °C was needed to complete theconversion. The reaction mixture was poured onto ice and acidified with concentrated HCl (36 -38%). The aqueous layer was extracted with Et_2O and the organic layer was washed with H_2O (3x) and brine (1x) and dried ($MgSO_4$). The drying agent was removed by filtration and the solvent by evaporation under reduced pressure yielded 19.7 g (93%) of the acid.

Scheme 10-12, step iii:

At -5 °C, 29 ml of thionyl chloride were added dropwise in 30 minutes to 250 ml of MeOH . The mixture was stirred for 15 minutes during which the temperature was kept between -10 °C and -5 °C. The acid (19.7 g, 65.9 mmol) was added in one time to the cooled solution. The reaction mixture was stirred for 1 hour after which is was allowed to warm to room temperature and stirred for an additional 20 h. The reaction mixture was concentrated in vacuo and the residue was chromatographed (SiO_2) with CH_2Cl_2 as theeluent to give 20.6 g (100%) of the methyl ester.

Scheme 10-12, step iv:

A mixture of the methyl ester (20.6 g, 65.8 mmol) and zinc cyanide (4.64 g, 39.5 mmol) in 85 ml of dry DMF was degassed by bubbling nitrogen through the solution for 1 h. Palladium tetrakis, $Pd(PPh_3)_4$, (3.8 g, 3.29 mmol) was added under a nitrogen atmosphere and the reaction mixture was stirred for 16 hours at 90 °C. The reaction mixture was diluted with 200 ml toluene and filtered through a pad of Hyflo. The organic layer was washed with 5% $NaHCO_3$ (2x) and brine (1x). The organic layer was dried ($MgSO_4$). The drying agent was removed by filtration and the solvent by evaporation under reduced pressure. The residue was chromatographed (SiO_2)

using CH_2Cl_2/petroleum ether 3/2 → CH_2Cl_2 as eluent to give 15.6 g (92%) of the 5-cyanobenzthiophene.

Scheme 10-12, step v:

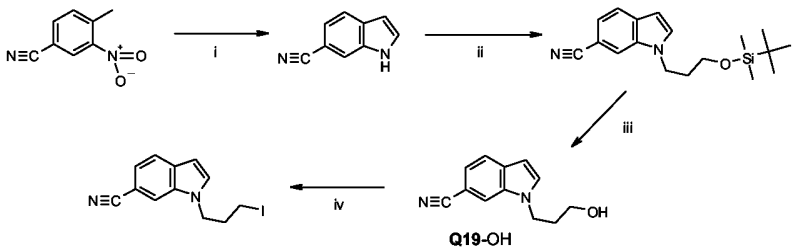
To a stirring solution of the 5-cyanobenzthiophene (15.6 g, 60.2 mmol) in 250 ml 96% EtOH at 15 °C was added sodium borohydride (22.8 g, 602 mmol) in one time. The reaction mixture was stirred at room temperature for 48 h. H_2O was added and the aqueous layer was extracted with Et_2O (3x). The combined organic layers were washed with brine (1x). The Et_2O fraction was dried ($MgSO_4$). The drying agent was removed by filtration and the solvent by evaporation under reduced pressure. The residue was chromatographed (SiO_2) with Et_2O/CH_2Cl_2 1/9 as eluent to give 9.2 g (66%) of the alcohol **Q12**-OH.

Scheme 10-12, step vi:

Was prepared according to the procedure described in Scheme 1 -6, step iii.

Q10-OH and **Q11**-OH were prepared similarly using steps i, ii, iii and v respectively.

Synthesis of **Q13-20**:



scheme 13-20

All starting materials were commercially available.

Scheme 13-20 step i:

To a stirring solution of 3-nitro-p-tolunitrile (16.58 g, 102.3 mmol) in 55 ml DMF was added DMF-dimethylacetale (15.24 g, 128.1 mmol). The reaction mixture turned dark red and was stirred at 110 °C for 3 h. The solvent was removed under reduced pressure and taken up in a mixture of 300 ml EtOH and 300 ml acetic acid. The reaction mixture was heated to 60 °C and iron powder (33 g, 594 mmol) was added in portions. The reaction mixture was refluxed for 2 hours and filtered over a pad of

Hyflo. Et_2O was added to the filtrate and the acidic layer was extracted with Et_2O (1x). The Et_2O fraction was concentrated in vacuo. The residue was chromatographed (SiO_2) with CH_2Cl_2 as the eluent to give 7.02 g (48%) of a solid, containing the 6-cyano-indole.

Scheme 13-20 step ii:

To a stirring suspension of NaH (60%) (1.13 g, 25.96 mmol) in 60 ml DMF under a nitrogen atmosphere was added 6-cyanoindole of step i (3.51 g, 24.72 mmol) in portions. After stirring at room temperature for 1 hour the 1-(dimethyl-tert.butylsilyl)-3-bromo propane (6.30 ml, 27.29 mmol) was added dropwise at -5 °C. The reaction mixture is stirred at room temperature for 20 h. 400 ml H_2O and 400 ml Et_2O were added. The Et_2O layer was separated and the aqueous layer was extracted 1x with Et_2O. The combined Et_2O layers were concentrated in vacuo. The residue was chromatographed (SiO_2) with CH_2Cl_2/petroleum ether 3/1 as the eluent to give 5.50 g (71%) as a light yellow oil.

Scheme 13-20 step iii:

Was performed analogously to step iii in scheme 1-6, and yielded **Q19**-OH.

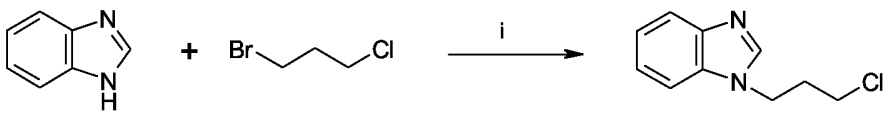
Scheme 13-20 step iv:

The conversion of the resulting alcohols to the corresponding iodo derivatives was performed analogously to the procedure described in scheme 1-6 step iv.

The 6-cyano-indole derivative **Q20**-OH was prepared according to the procedure described above.

The indole, 6-Fluoroindole and 6-Chloroindole were commercially available and were further converted to the indole derivatives **Q13-18**-OH according to the procedures given above.

Synthesis of **Q21**:

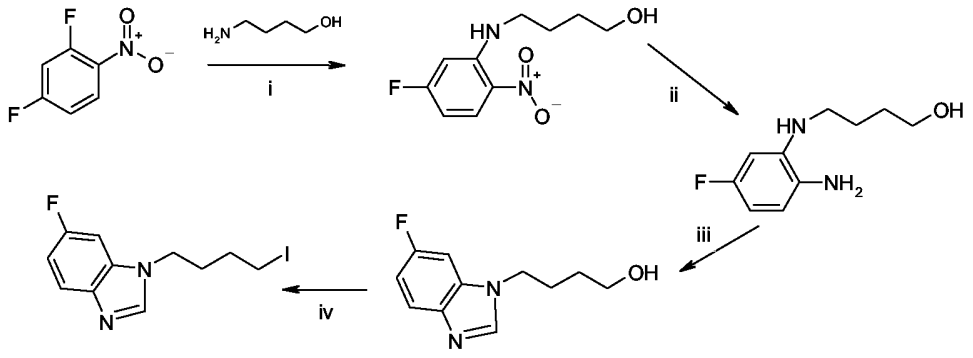


scheme 21

Scheme 21 step i:

To a stirred suspension of NaH (55%) (0.48 g, 20 mmol) in 20 ml NMP at room temperature was added dropwise a solution of benzimidazole (1.18 g, 10 mmol) in 20 ml NMP. The reaction mixture turned light red and hydrogen forming was observed. After stirring at room temperature for 30 minutes 3-chlorobromopropane (1.08 ml, 11 mmol) in 10 ml NMP was added dropwise. The reaction mixture was stirred at room temperature for 2 hours after which the reaction mixture was heated at 100 °C for 2 h. After additional stirring at room temperature for 72 h, H_2O and EtOAc were added. The layers were separated and the aqueous layer was extracted with EtOAc (2x). The combined organic layers were washed with brine (1x) and dried ($MgSO_4$). The drying agent was removed by filtration and the solvent by evaporation under reduced pressure to give 2.9 g of **Q21**-Cl (150%, still NMP present) as an oil. This was used in coupling reactions with amines.

Synthesis of **Q22-23**:



scheme 22-23

All reagents were commercially available.

Scheme 22-23 step i:

To a stirring solution of 2,4-difluoronitrobenzene (8 g, 50.3 mmol) in 100 ml CH_3CN was added 4-aminobutanol (5.61 ml, 60.4 mmol) and DIPEA (20.9 ml, 120.7 mmol). The reaction mixture was stirred at room temperature for 72 h. The solvent was evaporated under reduced pressure and CH_2Cl_2 was added to the residue. The CH_2Cl_2 fraction was washed with H_2O (2x), dried (by a Water Repelling Filter) and the filtrate evaporated under reduced pressure. The residue was chromatographed (SiO_2) with Et_2O as the eluent to give 9.68 g (84%) of the amino-alkylated product.

Scheme 22-23 step ii:

To a solution of the amino-alkylated product (from step i) (9.68 g, 42.5 mmol) in 250 ml EtOH (96%) was added 1 g 10% Pd/C after which the mixture was hydrogenated at room temperature (1 atm) for 3 h. The reaction mixture was filtered through a pad of Hyflo and the black filtrate was concentrated in vacuo under reduced pressure to give 8.42 g (100%) of the corresponding aniline.

Scheme 22-23 step iii:

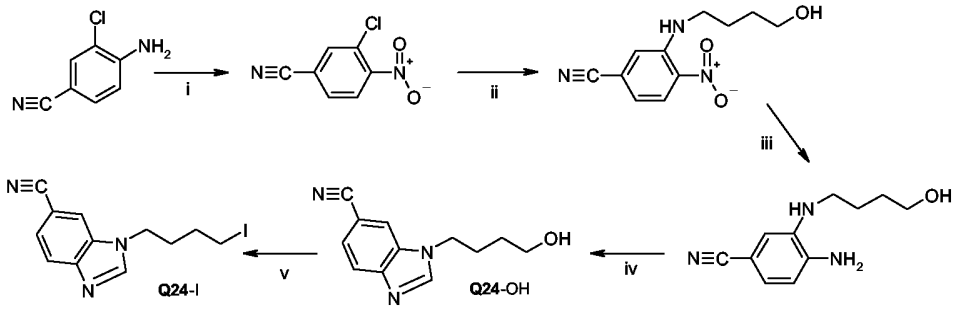
A mixture of the aniline (from step ii) (8.42 g, 42.5 mmol) in 25 ml formic acid (96%) was refluxed for 2.5 hours after which it was allowed to cool to room temperature. H_2O was added and after cooling, to the reaction mixture 50 ml of 50% NaOH was added. After stirring for 2 hours the aqueous layer was extracted with CH_2Cl_2. The CH_2Cl_2 fraction was dried (by a Water Repelling Filter) and concentrated in vacuo under reduced pressure. The residue was chromatographed (SiO_2) with CH_2Cl_2/MeOH 9:1 as the eluent to give 8.1 g (92%) of the benzimidazole.

Scheme 22-23 step iv:

The conversion of the resulting alcohols to the corresponding iodo derivatives was performed according to the procedure described in scheme 1-6 step iv. In this case triphenylphosphine on solid support was used.

Q22-OH was prepared via the same procedure as described above.

Synthesis of **Q24**:



scheme 24

All reagents were commercially available.

Scheme 24 step i:

A suspension of sodium borate tetrahydrate (32.5 g, 211.2 mmol) in 195 ml of acetic acid was heated until the temperature of the reaction mixture was above 50 °C. The reaction temperature was kept this way while 2-chloro-4-cyanoaniline (5.93 g, 38.9 mmol) was added in portions over 1 h. Stirring and heating were continued for 2 hours on an oil bath of 62°C. After cooling to room temperature the reaction mixture was poured into 1L icewater. The aqueous layer was extracted with Et_2O (3x). The combined organic layers were washed with H_2O (2x) and dried ($MgSO_4$). The drying agent was removed by filtration and the solvent by evaporation under reduced pressure. The residue was chromatographed (SiO_2) with Et_2O/petroleum ether 1/3 as eluent to give 5.27 g (74%) of the oxidized product.

Scheme 24 step ii:

To a stirring solution of 2-chloro-4-cyanonitrobenzene from step i (2.48 g, 13.6 mmol) in 12 ml DMF was cooled in ice. 4-aminobutanol (5.50 ml, 59.3 mmol) was added and the reaction mixture was slowly allowed to warm to room temperature after which stirring was continued at room temperature for 72 h. H_2O was added and the aqueous layer was extracted with CH_2Cl_2 (2x) The combined organic layers were washed with H_2O (3x), dried (by a Water Repelling Filter) and evaporated under reduced pressure. The residue was chromatographed with Et_2O/petroleum ether 4:1 as eluent to give 2.6 g (49%) of the amino-alkylated product.

Scheme 24 step iii:

Prepared according to step ii, in scheme 22-23.

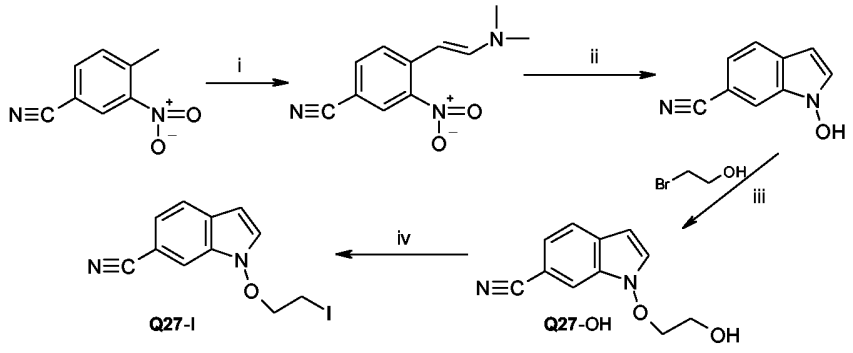
Scheme 24 step iv:

Prepared according step iii, in scheme 22-23.

Scheme 24 step v:

Prepared according step iv, in scheme 22-23.

Synthesis of **Q25-28**:



scheme 25-28

All reagents were commercially available.

Scheme 25-28 step i:

To a stirring solution of 3-nitro-p-tolunitrile (8.1 g, 50 mmol) in 30 ml DMF was added DMF-dimethylacetale (13.3 ml, 100 mmol) and the reaction mixture was stirred at 120 °C for 3 h. The solvent was evaporated under reduced pressure and the residue was taken up in CH_2Cl_2. The CH_2Cl_2 fraction was washed with H_2O (2x), dried (by a Water Repelling Filter). The drying agent was removed by filtration and the solvent by evaporation under reduced pressure to give 10.6 g (98%) of the adduct.

Scheme 25-28 step ii:

To a stirring emulsion of the adduct (from step i) (6 g, 27.6 mmol) in 175 ml Et_2O was added 8.1 g NH_4Cl and 29 g zinc granules (40 mesh). After stirring at room temperature for 2 hours 100 ml THF was added to dissolve the starting material. After an additional stirring for 6 hours the reaction mixture was filtered over a pad of Hyflo. Half of the resulting filtrate was used in the next step.

Scheme 25-28 step iii:

To the filtrate of the former step ii was added 2-bromoethanol (7.9 ml, 112 mmol), Aliquat (0.6 g, 10 mol%) and 90 ml 10% NaOH. The reaction mixture was stirred at room temperature for 20 h. After separation of the layers, the aqueous layer was extracted with Et_2O (1x). The combined organic layers were washed with H_2O (4x) and dried ($MgSO_4$). The drying agent was removed by filtration and the solvent by

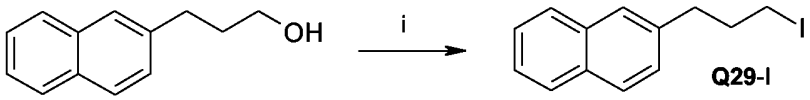
evaporation under reduced pressure (by means of an oil pump). The residue was chromatographed (SiO_2, eluent: CH_2Cl_2 → CH_2Cl_2/Et_2O 4:1) to give 1 g (36%) of the corresponding alcohol **Q27**-OH.

Scheme 25-28 step iv:

The conversion of the resulting alcohols to the corresponding iodo derivatives was performed according to the procedure described in scheme 1 -6 step iv.

Q25-OH, **Q26**-OH and **Q28**-OH were prepared analogously to the procedure described above.

Synthesis of **Q29**:



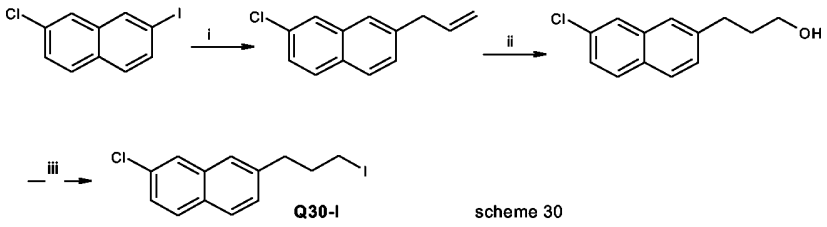
scheme 29

The naphtylpropylalcohol was prepared according to: Searles, *J.Amer.Chem.Soc.*, 73 (1951) 124.

Scheme 29 step i:

The conversion of the resulting alcohol to the corresponding iodo derivative was performed according to the procedure described in scheme 1 -6 step iv.

Synthesis of **Q30**:



scheme 30

2-chloro-7-iodo-naphtalene was prepared according to the literature (Beattie; Whitmore; *J. Chem. Soc. 1934*, 50,51,52)

Scheme 30 step i:

A 100 ml roundbottom flask under an nitrogen atmosphere was charged with 2-chloro-7-iodo-napthalene (11 mmol, 3,60g), allyl-tributyltin (13 mmol, 4.30g, 3.96 ml), tetrakis(triphenylphosphine)palladium(0) (0.55 mmol, 0.635g) and 10 ml degassed benzene. The mixture was heated to relfux under a nitrogen atmosphere and after 20 hours another portion of tetrakis(triphenylphosphine)palladium(0) (0.55 mmol, 0.635g) was added. The mixture was again heated at reflux for 20 hours after which it was allowed to cool to room temperature after which it was poured into 70 ml of a 10% KF-solution. After 30 min stirring at room temperature the suspension was filtered over Hyflo Supercel®. The filtrate was washed with water, brine and dried (Na_2SO_4). Column chromatography on silica gel (eluens 1/9 toluene/petroleum ether) afforded almost pure 2-allyl-7-chloro-napthalene (1.80g, 80%).

Scheme 30 step ii:

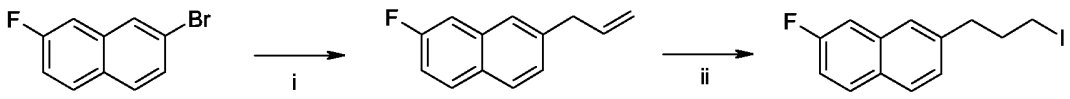
A 100 ml threeneck roundbottom flask under a nitrogen atmosphere was charged with 2-allyl-7-chloro-napthalene (1.80g, 8.9 mmol) and 12 ml of dry THF. The mixture was cooled in an ice-bath and borane-THF (3.05 mmol, 3.05 ml 1.0 M borane in THF) was added dropwise in about 20 minutes After the addition the mixture was allowed to warm to room temperature and stirred for 20 hours. 3.0 N NaOH solution (2.65 mmol, 0.89 ml) was then added to the solution and the mixture was cooled in a waterbath while adding 30% hydrogenperoxide (10.62 mmol, 1.1 ml) dropwise at such a rate that the temperature did not exceed 30 °C. After the addition the mixture was stirred for 6 hours at room temperature.

Water and diethyl ether were added and the organic layer was separated. The water layer was extracted again with ethyl ether and the combined organic extracts were washed with water, brine and dried (Na_2SO_4). The drying agent was removed by filtration and the solvent by evaporation *in vacuo*. Flash column chromatography on silica gel (eluent: 1/99 methanol/dichloromethane) afforded 3-(7-chloro-napthalene-2-yl)-propan-1-ol (0.79 g, 40%) **Q30**-OH.

Scheme 30 step iii:

The conversion of the resulting alcohol to the corresponding iodo derivative was performed according to the procedure described in scheme 79-84 step iii, yielding **Q30**-I.

Synthesis of **Q31**:



Q31-I

scheme 31

The fluorobromonaphtalene was prepared according to: Adcock,W. et al., *Aust.J.Chem.*, **23** (1970)1921-1937.

Scheme 31 step i:

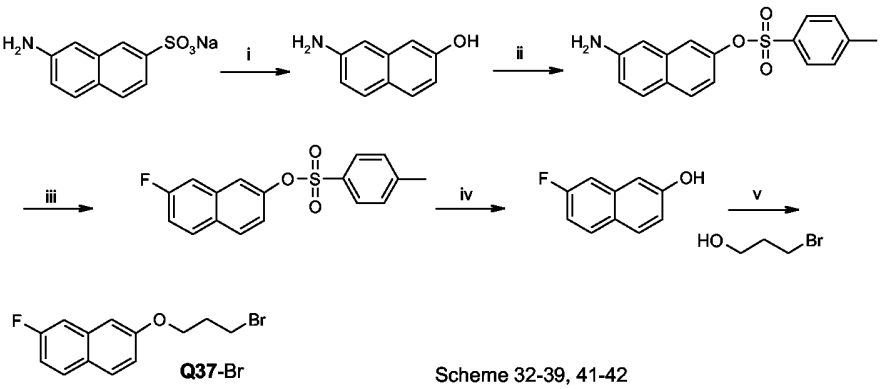
To a stirred suspension of magnesium turnings (0.49 g, 20 mmol) and 0.1 ml 1,2 - dibromoethane in 20 ml THF was added the fluoronaphtalene (0.45 g, 2 mmol) in one time. After the start of the grignard a solution of the fluoronaphtalene (4.06 g, 18 mmol) in 25 ml THF was slowly added dropwise. The temperature rose during the addition to 40 °C. The reaction mixture was stirred at room temperature for 2 hours until all the magnesium had disappeared. A freshly prepared solution from LiCl and CuCN in THF was added dropwise at -10 °C which resulted in a dark green solution. At the same temperature was added dropwise a solution of allyl bromide (1.9 ml, 22 mmol) in 15 ml THF. After the complete addition the reaction mixture was stirred at -10-0 °C for 30 minutes. The green color disappeared and stirring was continued at room temperature for 20 h. The reaction mixture was poured into 200 ml of saturated NH_4Cl and extracted with CH_2Cl_2 (3x). The combined organic layers were washed with brine and dried ($MgSO_4$). The drying agent was removed by filtration and the solvent by evaporation under reduced pressure. The residue was chromatographed (SiO_2) using petroleum ether as eluent to give 1.65 g (44%) of the corresponding allylfluoro-naphtalene.

Scheme 31 step ii:

To a cooled stirring solution of the allyl-fluoronaphtalene (1.65 g, 8.8 mmol) in 10 ml THF at -5 °C was slowly added dropwise 3.05 ml 1.0 M Borane.THF-complex. After stirring for 20 minutes at the same temperature and additional stirring at room temperature iodine (2.11 g, 8.6 mmol) was added in one time. 3.1 ml of a freshly prepared 2.7 M solution of sodium metal in MeOH) was slowly added dropwise (exothermic) after which the reaction mixture is stirred at room temperature for 20 h. 75 ml $NaHSO_3$ was added and the aqueous layer was extracted with CH_2Cl_2 (3x).

The organic layer was washed with brine (1x) and dried ($MgSO_4$). The drying agent was removed by filtration and the solvent by evaporation under reduced pressure. The residue was chromatographed (SiO_2) using petroleum ether as eluent to give 1.25 g (46%) of the iodide **Q31**-I as a white solid.

Synthesis of **Q32-39, Q41-42**:



Scheme 32-39, 41-42

Scheme 32-39, 41-42 step i:

A mixture of KOH pellets (140 g, 2.5 mol) and 10 ml H_2O in a nickel crucible was heated to 250 °C with a Bunsen burner while being stirred with a stainless steel stirrer. The flame is removed and 7-amino-2-naphtalenesulfonic acid sodium salt (0.245 mol, 60.0 g) was added to the clear liquid in 3 portions. The clear liquid changes into a thick black slurry which is again strongly heated with a Bunsen burner. At about 280°C gas evolved and the temperature of the mixture quickly rises to 310-320°C. This temperature was maintained for 8 minutes after which the mixture was allowed to cool to about 200 °C. The thick black paste was carefully transferred to a 3 litre beaker filled with ice. The product of 2 runs were combined and neutralized with concentrated HCl under cooling with an ice-salt bath. The suspension wa filtered and the black solid wa washed with 4 500 ml portions of 1.0 *N* HCl and discarded. The brown, clear filtrate that is obtained was cooled in an ice-salt bath and KOH-pellets are added until a light suspension was obtained. After addition of a saturated NH_4OAc-solution the green-grey solid fully precipitates and was collected through filtration to obtain 7-amino-naphtalene-2-ol (27.9 g, 36%) after drying in the air.

Scheme 32-39, 41-42 step ii:

7-amino-naphtalene-2-ol (0.169 mol, 27.0 g) is suspended in 750 ml DCM and TEA (0.169 mol, 17.2 g, 23.6 ml) was added. The mixturewais stirred for 30 min at room temperature after which it was cooled to -5°C in an ice-salt bath. A solution of p-Tosylchloride (0.17 mol, 32.4 g) in 250 ml DCM was added over a period of 2.5 hours at -5-0 °C. The mixture was stirred for 10 minutes at -5-0 °C after which it was allowed to warm to room temperature and stirred for 18 hours. 1L of H_2O was added to the mixture and the resulting suspension was filtered over Hyflo Super Cel® and the filtrate was transferred to a separatory funnel. After extracting the organic layer, the water-layer was again extracted with DCM (2x). The combined organic layers are washed with brine, dried (Na_2SO_4) and concentrated *in vacuo* to give 51.5 g of a black oil which was purified by column chromatography on silica gel (eluens 1/1 ethylacetate/petroleum ether) to afford toluene-4-sulfonic acid-7-amino-napthalene-2-yl-ester (12.1 g, 23%).

Scheme 32-39, 41-42 step iii:

A 500 ml threeneck roundbottom flask made from PFA was charged with 100 g Pyridine/HF complex (30:70 %w/w) and cooled to -10 °C with an ice/EtOH bath. toluene-4-sulfonic acid-7-amino-napthalene-2-yl-ester (38.6 mmol, 12.1g) was added in one portion and the mixture was stirred for 10 minutes after which a clear purple solution was obtained. This solution was cooled to < -30 °C in an dry-ice cooling bath and sodium nitrite (42.5 mmol, 2.93 g, dried by heating at 140 °C for 3 days) was added in one portion. The dry-ice bath was replaced by a normal ice-bath and the mixture was stirred at 0°C for 20 minutes after which it was heated to 55-60°C on an oilbath (evolution of nitrogen was observed). After 1.5 hours nitrogen evolution ceased and the mixture was allowed to cool to room temperature and poured into a large beaker filled with ice. The mixture was transferred to a separatory funnel and extracted 3 times with DCM. The organic layers where pooled together, washed with brine and dried (Na_2SO_4). Concentration *in vacuo* afforded 10.4 g of a red oil which was purified by flash column chromatography on silica gel (eluens 1/4 ethylacetate/petroleum ether) to give toluene-4-sulfonic acid-7-fluoro-napthalene-2-yl-ester (7.1 g, 58%)

Scheme 32-39, 41-42 step iv:

A 500 ml roundbottom flask protected with a $CaCl_2$-tube was charged with toluene-4-sulfonic acid-7-fluoro-napthalene-2-yl-ester (22.4 mmol, 7.1 g) and 200 MeOH.

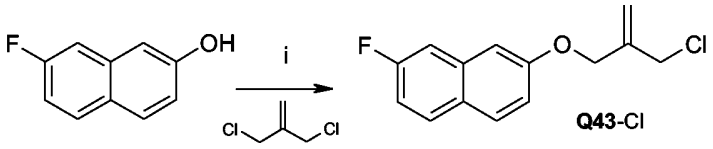
The suspension was heated until a clear solution was obtained and then cooled down to room temperature in a waterbad to afford a fine suspension. Magnesium (179 mmol, 4.36 g) was added to the mixture which was then stirred for 4 hours at room temperature. The brown suspension was cooled in an ice-EtOH bath and acidified with 6N HCl and then concentrated *in vacuo*. The mixture was transferred to a separatory funnel and extracted 3 times with ethylether. The organic extracts are pooled together, washed with brine and dried (Na_2SO_4). The drying agent was removed by filtration and the solvent by evaporation *in vacuo*. Flash column chromatography on silica gel (eluens dichloromethaan) afforded unpure 7-fluoro-napthalene-2-ol (4.69 g) as an off white solid. This solid was dissolved in DCM and extracting 3 times with 2N NaOH-solution. The basic extracts were combined and acidified with 3N HCl while cooling with an ice bath. White crystals precipitated from the solution and were collected by filtration and dried in the air to afford pure 7-fluoro-napthalene-2-ol (3.16 g, 87%)

Scheme 38-45; 47-48, step v:

To a stirred suspension at -5 °C 0.97 g (6 mmol) of 2-hydroxy-7-fluoronaphtalene, 2.83 g (10.8 mmol) of triphenylphosphine and 1.11 ml (12.6 mmol) of 3-bromo-1-propanol in 30 ml of toluene, was added dropwise a solution of 2.13 ml (10.8 mmol) DIAD in 5 ml toluene. The reaction mixture was allowed to reach room temperature after which stirring was continued overnight. The reaction mixture was concentrated *in vacuo* and the residue taken up in 30 ml of diethylether. The mixture was filtered an the filtrate concentrated *in vacuo* and the residue subjected to flash column chromatography (SiO2, eluent: CH_2Cl_2 / petroleum ether 1/5). Yield 1.28 g (75 %) of **Q37**-Br.

Q32 was synthesized as **Q32**-I, **Q33-36, Q38-39** and **Q41-42** derivatives were prepared similarly to the above described procedures (as bromides).

Synthesis of **Q40, Q43**:

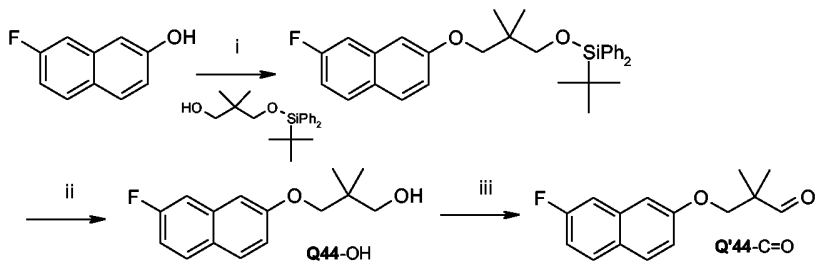


scheme 40, 43

Scheme 40, 43 step i:

A mixture of 7-fluoro-2-naphtol (see Scheme 32-39, 41-42 step iv) (0.62 g, 3.82 mmol), the alkene (1.11 ml, 9.56 mmol) and K_2CO_3 (1.58 g, 11.5 mmol) in 35 ml CH_3CN was refluxed for 3 hours after which was was cooled to room temperature and evaporated under reduced pressure. The residue was taken up in H_2O and Et_2O and extracted with Et_2O (2x). The combined organic layers were washed with H_2O (1x) and brine (1x) after which it was dried (Na_2SO_4). The drying agent was removed by filtration and the solvent by evaporation under reduced pressure. The residue was chromatographed (SiO_2) with CH_2Cl_2/petroleum ether 1/5 as eluent to give 0.56 g (58%) of the fluoronaphthol derivative **Q43**-Cl as a colorless oil.

Synthesis of **Q44**:



scheme 44

Scheme 44 step i:

For the fluornaphtol, see Scheme 32-39, 41-42 step iv. This Mitsunobu reaction was performed analogously to step v in scheme 32-39, 41-42.

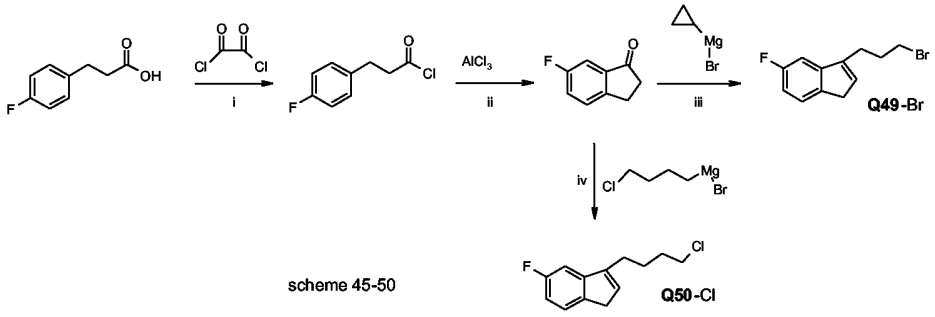
Scheme 44 step ii:

This step can be performed similar to step iii in scheme 1-6, and yielded **Q44**-OH.

Scheme 44 step iii:

Q44-OH was oxidized following the procedure of step i in scheme B2. The product, **Q'44**-C=O was used in the reductive alkylation of amines.

Synthesis of **Q45-50**:



scheme 45-50

The starting acid and reagents were commercially available. The Cl-C4-MgBr was prepared according to: C.R. Hebd, *Seances Acad. Ser. C*, **268** (1969)1152-1154.

Scheme 45-50 step i:

To a solution of the acid (25 g, 148.8 mmol) in 140 ml benzene was added 0.07 ml DMF after which oxalylchloride was added all at once. Immediate foaming of the reaction mixture was observed. The reaction mixture was stirred for at room temperature 18 hours and the solvent was removed by evaporation under reduced pressure. Acetonitrile was added to the residue for co-evaporation and again removed by evaporation under reduced pressure to give 27.75 g (100%).

Scheme 45-50 step ii:

$AlCl_3$ (27.8 g, 208 mmol) was suspended in 200 ml 1,2-dichloroethane. The mixture was cooled under a nitrogen atmosphere to 0-5 °C and a solution of the acid chloride (27.75 g, 148.8 mmol) in 140 ml 1,2-dichloroethane was added dropwise in 1 h. The cooling bath was removed and after stirring for 30 min., stirring was continued for 2 hours at 70 °C. After cooling to room temperature the reaction mixture was poured into a mixture of ice and 330 ml concentrated HCl (36-38%). The aqueous layer was extracted with CH_2Cl_2 and the resulting organic layer was washed with H_2O (2x), 5% $NaHCO_3$ and brine. The organic layer was dried ($MgSO_4$). The drying agent was removed by filtration and the solvent by evaporation under reduced pressure to give 19.02 g (85%).

Scheme 45-50 step iii:

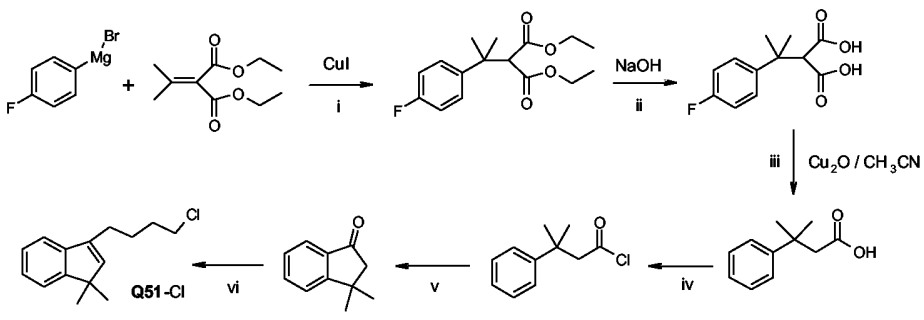
To a cooled solution of 0.5M cyclopropyl magnesiumbromide in THF (100 ml, 50 mmol) at 15 °C was added a solution of the ketone (5.3 g, 35.3 mmol) in 40 ml THF. The reaction mixture was stirred at reflux for 2 hours after which was was cooled in an ice bath. 50 ml saturated NH_4Cl was added dropwise and the aqueous layer was extracted with Et_2O. The Et_2O was washed with brine (1x), dried ($MgSO_4$) and evaporated under reduced pressure. The residue was dissolved in 85 ml acetic acid and 62 ml of a 20% HBr solution was added. The reaction mixture was stirred for 20 h. H_2O was added and the aqueous layer was extracted with CH_2Cl_2. The organic layer was further washed with H_2O (1x) and 5% $NaHCO_3$ (1x). The organic layer was dried (by a Water Repelling Filter) and evaporated under reduced pressure. The residue was chromatographed with CH_2Cl_2/petroleum ether 2.5/97.5 as eluent to give 4.44 g (49%) of the indene **Q49**-Br.

Scheme 45-50 step iv:

Was prepared according to the procedure as described for step iii, yielding **Q50**-Cl

Q45, **Q46**, **Q47**, and **Q48** derivatives were made analogously to the above described procedure.

Synthesis of **Q51**:



scheme 51

The starting materials were commercially available.

Scheme 51 step i:

A mixture of the Grignard reagent (90 ml, 90 mmol) and CuI (18 mg, 0.02 mmol) was stirred for 15 minutes after which it was cooled in an ice bath. A solution of the

di-ester (18.9 ml, 96.7 mmol) in 25 ml THF was added in 90 min and the reaction mixture was stirred at 0 °C for 2 h. 100 ml saturated NH_4Cl was added dropwise and the aqueous layer was extracted with Et_2O. The Et_2O fraction was washed with brine (1x) and dried ($MgSO_4$). The drying agent was removed by filtration and the solvent by evaporation under reduced pressure. The residue was chromatographed with CH_2Cl_2/petroleum ether 1/1 as eluent to give 26.17 g (98%) of the adduct.

Scheme 51 step ii:

To a stirring solution of the adduct (26.17 g, 88.4 mmol) in 222 ml EtOH was added 265 ml 10% NaOH. The reaction mixture was refluxed for 3 hours and the solvent was evaporated under reduced pressure. The residue was cooled in ice and acidified with concentrated HCl (36-38%). The aqueous layer was extracted with EtOAc. The EtOAc fraction was washed with brine (1x) and dried ($MgSO_4$). The drying agent was removed by filtration and the solvent by evaporation under reduced pressure to give 20.9 g (99%) of the di-acid.

Scheme 51 step iii:

A mixture of the di-acid (20.9 g, 87.1 mmol) and Cu_2O (0.62 g, 4.34 mmol) in 600 ml CH_3CN was refluxed for 16 h. The solvent was removed by evaporation under reduced pressure and 125 ml 3N HCl was added to the residue. The aqueous layer was extracted with EtOAc. The EtOAc fraction was washed with brine (1x) and dried ($MgSO_4$). The drying agent was removed by filtration and the solvent by evaporation under reduced pressure to give 16.9 g (99%) of the de-carboxylated product.

Scheme 51 step iv:

Was prepared according to step i in scheme 45-50.

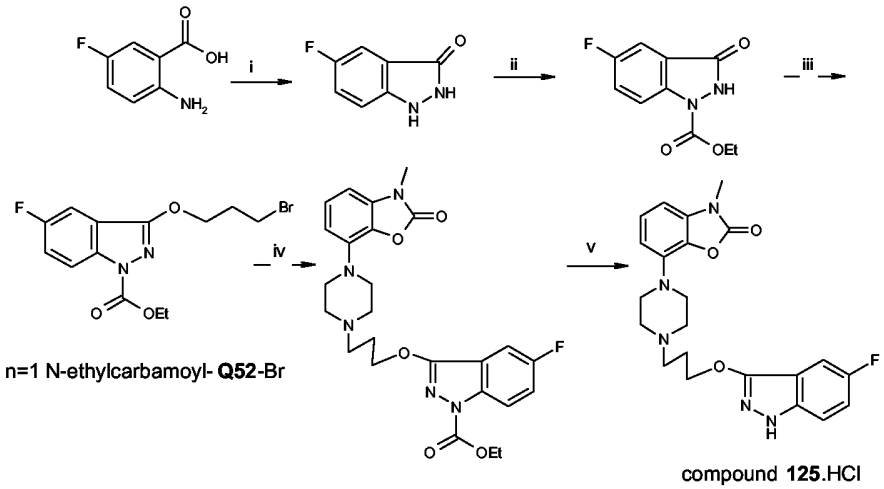
Scheme 51 step v:

Was prepared according to step ii in scheme 45-50.

Scheme 51 step vi:

Was prepared according to step iii in scheme 45-50, yielding **Q51**-Cl.

Synthesis of **Q52-53**:



scheme 52-53

Scheme 52-53 step i:

A 3 litre beaker was charged with 2-amino-5-fluoro-benzoic acid (64 mmol, 10 g), 100 ml H_2O and 110 ml concentrated HCl and the suspension was cooled to 0 °C in an ice/aceton bath. A solution of natrium nitrite (64 mmol, 4.44 g) in 68 ml H_2O was added dropwise to the mixture while the temperature was maintained at b elow 3 °C. After the addition was complete the brown solution was added in portions over 20 minutes, under a stream of sulfurdioxide, to a solution of 760 ml H_2O saturated with sulfurdioxide cooled at 0-5°C with an ice-bath. After the addition was complete the ice-bath was removed and the solution was allowed to warm to room temperature while the stream of sulfurdioxide was maintained. After 1 hour the supply of sulfurdioxide was discontinued and the solution was allowed to stand at room temperature overnight. To the dark yellow solution which was obtained was added 620 ml concentrated HCl and after cooling the mixture a yellow precipitate separates which was collected on a cooled buchner funnel. The solid was suspended in a solution of 2 ml concentrated HCl and 200 ml H_2O and the mixture was heated to reflux. After a time the solid dissolves and a clear solution was obtained. After 1.5 hours of reflux a orange/brown solid has crystallized and the mixture was allowed to cool to room temperature and was conc entrated to about 50 ml *in vacuo*. The solid was collected and dried in the air to afford 5-fluoro-1,2-dihydro-indazol-3-one (5.05 g, 52%)

Scheme 52-53 step ii:

5-fluoro-1,2-dihydro-indazol-3-one (32 mmol 5.05 g) was suspended in 30 ml pyridine and under cooling with an ice-bath chloroethylformiate (64 mmol, 6.94 g, 6.09 ml) was added dropwise. The mixture was heated to reflux for 3 hours and was then allowed to cool to room temperature ad concentrated *in vacuo* to afford a dark red oil which crystallizes after the addition of water. The solid was filtered and dried in the air to afford the corresponding urethane (5.52 g, 77%)

Scheme 52-53 step iii:

To 20 ml toluene under a nitrogen atmosphere was added the urethane derivative (from step ii) (0.45 g, 2 mmol), 3-bromopropanol (0.18 ml, 2.1 mmol), Bu_3P (0.40 g, 2 mmol) and ADDP (0.5 g, 2 mmol). After the addition of ADDP the solution turned clear. The reaction mixture was heated at 85 °C for 20 hours and cooled to room temperature. 2N NaOH and EtOAc were added and the aqueous layer was extracted with EtOAc (2x). The combined organic layers were washed with 2N NaOH (1x), H_2O (1x) and brine (1x) after which the EtOAc was dried (Na_2SO_4) and evaporated under reduced pressure. The residue was chromatographed with CH_2Cl_2/MeOH 99:1 as eluent to give 0.22 g (32%) of the alkylated indazol-3-one.

Scheme 52-53 step iv:

Was performed according to the procedure as described in scheme A2, step i.

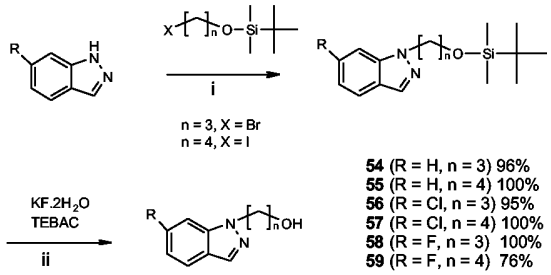
Scheme 52-53 step v:

A mixture of the ethyl carbamate (0.38 g, 0.79 mmol) and K_2CO_3 (0.38 g, 2.74 mmol) in 21 ml of MeOH/DME/H_2O (5/1/1) was stirred at room temperature for 4 h. The reaction mixture was further purified using a SCX-column (ion exchange column) with 1N NH_3/MeOH as eluent to rinse the product off the column. The eluate was evaporated under reduced pressure and the residue refluxed in 20 ml CH_3CN. The suspension was filtered by suction to give 0.28 g (86%) of the de-protected product as a light orange solid containing compound **125** which was later transformed into its mono HCl salt (AcCl/MeOH), **125**-HCl.

The **Q53** analogue can be synthesized as well, as described above.

Compounds **48**, **49** and **124** were prepared analogously to the procedures given above.

Synthesis of **Q54-59**:



scheme 54-59

The indazoles were preapared according to Christoph Rüchardt, Volkert Hassemann; *Liebigs Ann. Chem.*; (1980) 908-927.

Scheme 54-59, step i:

56; R=Cl, n=3:

NaH (55%) (2.14 g, 49.15 mmol) was suspended in 70 ml of dry DMF under a N_2 atmosphere. 6-chloro-indazole (7,5 g, 49,15 mmol) was added at room temperature. The mixture was stirred for 1 hour before cooling with an ice bath and (3 -bromo-propoxy)-tert-butyl-dimethyl-silane (11.4 ml, 49.15 mmol) was added dropwise. After stirring for an additional 15 minutes the mixture was allowed to reach room temperature, stirring was continued for another 8 hours. Subsequently, the mixture was concentrated in vacuo and the residue was dissolved in DCM, the organic layer was then washed with water (3x). The organic layer was concentrated in va cuo. The crude product was purified by column chromatography on silica gel (SiO_2, eluent: petroleum ether/diethyl ether 5/1 ? 4/1) to afford the N1 substituted indazole in 61% yield.

Scheme 54-59, step ii:

To a stirred solution of $KF.2H_2O$ (4.3 g, 45,24 mmol) and benzyl tri-ethyl ammonium chloride (7.6 g, 33.18 mmol) in 300 ml acetonitrile, the N1 substituted indazole (from step i) (9.8 g, 30.16 mmol) was added. The mixture was warmed to reflux and stirred for 8 hours. The solvent was evaporated and DCM was added to the residue. The organic layer was washed with water (3x). De organic layer was concentrated in vacuo. The crude product was purified by flash chromatography on silica (eluent:

diethylether → 1% MeOH in diethylether) to afford the 3-(indazol-1-yl)-propanol in 95% yield.

The other indazolyl alcohols were prepared analogously. In step ii, tetrabutyl ammonium chloride in THF can be used instead of the combination $KF.2H_2O$/ benzyl tri-ethyl ammonium chloride.

Synthesis of **Q60**:

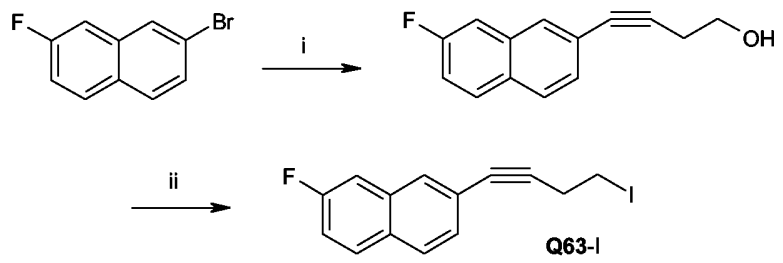
Q60-Br was synthesized analogously to the synthesis depicted in Scheme 52-53, using bromoethanol in the Mitsunobu step iii.

Synthesis of **Q61-62**:

Q61-I and **Q62**-I were synthesized analogously to the synthesis depicted in scheme 13-20, steps ii, iii and iv.

Synthesis of **Q63**:

Q63-I was synthesized as depicted in scheme 63:



scheme 63

Scheme 63, step i:

Through a suspension containing the fluorobromonapthalene (0.90 g, 4 mmol), tri-phenylphospine (0.21 g, 0.8 mmol), dichlorobis(tri-phenylphospine)palladium (0.28 g, 0.4 mmol) in 15 ml Et_3N, nitrogen was bubbled for 1 hour. 3-Butyn-1-ol (0.42 g, 0.45 ml, 6 mmol) was added and the mixture was heated to 40-50 °C on an oilbath. After 15 minutes of stirring at this temperature, CuI (0.15 g, 0.8 mmol) was added and the mixture was heated at 70 °C and stirred for 48 hours.

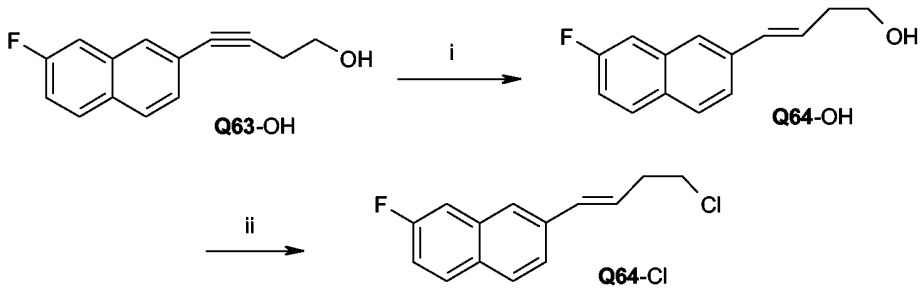
The resulting black suspension was allowed to reach room temperature and diethyl ether and water were added. The fractions were separated and the water layer was extracted twice with diethyl ether. The combined organic extracts were washed with

water, brine and dried (Na_2SO_4). After removal of the drying agent by filtration and solvent by concentration *in vacuo,* the residue was subjected to flash chromatography (SiO_2, eluent: DCM) affording **Q63**-OH, 4-(2-fluoro-napthalene-7-yl)-3-butyne-1-ol (0.30g, 1.46 mmol).

Scheme 63, step ii:

The conversion of the alcohol of step i to the corresponding iodo -derivative was performed according to scheme 1-6 step iv, yielding **Q63**-I.

Synthesis of **Q64**:



scheme 64

Scheme 64, step i:

A solution of Red-Al (4.47 ml of a 3.4 M solution in toluene) in 25 ml of dry diethyl ether was cooled in an ice-bath under nitrogen to which a solution of **Q63**-OH (1.90 g, 9.5 mmol) in 40 ml of diethylther (dry) was added dropwise. After the addition was complete, the resulting mixture is stirred for 10 min at 0 °C after which it was allowed to reach room temperature and stirred for an additional 2.5 hours. The reaction mixture was again cooled in a ice-bath and quenched by the careful addition of 50 ml of 3.6 M H_2SO_4. The reaction mixture was extracted three times with diethyl ether. The combined organic extracts are washed with water, brine, and dried Na_2SO_4). After removal of the drying agent by filtration and solvent by concentration *in vacuo,* the residue was subjected to flash chromatography (SiO_2, eluent: DCM) affording 1.17 g of **Q64**-OH, 4-(2-fluoro-naphtalene-7-yl)-3-butene-1-ol (5.8 mmol).

Scheme 64, step ii:

5 ml of concentrated hydrochloric acid is added to a solution of **Q64**-OH (1.17 g, 5.8 mmol) in 5 ml of THF. The mixture is stirred for 4.5 hours at room temperature after which another 2 ml of concentrated hydrochloric acid and 2 ml of THF are added. After another 30 minutes diethyl ether and water are added and the resulting fractions were separated. The water layer is extracted twice with diethyl ether. The combined organic fractions are washed with water, brine, dried (Na_2SO_4). After removal of the drying agent by filtration and solvent by concentration *in vacuo,* the residue was subjected to flash chromatography (SiO_2, eluent: DCM) affording 1.03 g of **Q64**-Cl (4.67 mmol).

The specific compounds of which the synthesis is described above are intended to further illustrate the invention in more detail, and therefore are not deemed to restrict the scope of the invention in any way. Other embodiments of the invention will be apparent to those skilled in the art from consideration of the specification and practice of the invention disclosed herein. It is thus intended that the specifi cation and examples be considered as exemplary only, with a true scope and spirit of the invention being indicated by the claims.

ABBREVIATIONS

AcCl	acetylchloride
ADDP	1,1'-(azodicarbonyl)dipiperidine
CDI	carbonyldiimidazol
Dba	see Huang et al., *J. Am.Chem.Soc.*, **125**(2003)6653
DCE	dichloroethane
DCM	dichloromethane
DIAD	diisopropyldiazodicarboxylate
DIPE	diisopropylether
DIPEA	diisopropylethylamine

	CH_2Cl_2(ml)	MeOH(ml)	NH_4OH(ml)
DMA 0.125	980	18.75	1.25
DMA 0.187	970	28.13	1.87
DMA 0.25	960	37.5	2.5
DMA 0.50	920	75.0	5.0

DMA 0.75	880	112.5	7.5
DMA 1.00	840	150.0	10.0

DMAP	4-dimethylaminopyridin
DME	dimethoxyethane
DMF	N,N-dimethylformamide
EtOH	ethanol
MeOH	methanol
MTBE	methyl(*tert.*)-butylether
NMP	N-methylpyrrolidon
PA	petroleum ether
TBAB	tetrabutylammoniumbromide
TBAC	tetrabutylammoniumchloride
TBAF	tetrabutylammoniumfluoride
THF	tetrahydrofurane
XPHOS	see Huang et al., *J. Am.Chem.Soc.*, **125**(2003)6653

EXAMPLE: FORMULATION OF COMPOUND 56 USED IN ANIMAL STUDIES

For oral *(p.o.)* administration : to the desired quantity (0.5-5 mg) of the solid compound 56 in a glass tube, some glass beads were added and the solid was milled by vortexing for 2 minutes. After addition of 1 ml of a solution of 1% methylcellulose in water and 2% (v/v) of Poloxamer 188 (Lutrol F68), the compound was suspended by vortexing for 10 minutes. The pH was adjusted to 7 with a few drops of aqueous NaOH (0.1N). Remaining particles in the suspension were further suspended by using an ultrasonic bath.

For intraperitoneal *(i.p.)* administration: to the desired quantity (0.5-15 mg) of the solid compound 56 in a glass tube, some glass beads were added and the solid was milled by vortexing for 2 minutes. After addition of 1 ml of a solution of 1% methylcellulose and 5% mannitol in water, the compound was suspended by vortexing for 10 minutes. Finally the pH was adjusted to 7.

EXAMPLE: PHARMACOLOGICAL TESTRESULTS

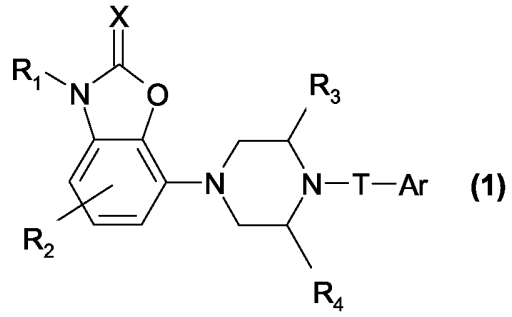
Table 2. *In vitro* affinities and functional activity of compounds of the in vention

Dopamine-D_2 and serotonin reuptake receptor affinity data obtained according to the protocols given above are shown in the table below. *In vitro* functional activity at cloned human dopamine $D_{2,L}$ receptors as measured by accumulation of radiolabeled cAMP (potency: pEC_{50}, intrinsic activity **ε**)

	Dopamine-D_2	5-HT reuptake	Dopamine-D_2
	binding	binding	cAMP accum
compound	pK_i	pK_i	ε (intrinsic activity)
6	7.7	9.8	0.85
7	8.2	8.5	0.39
8	8.3	8.9	0.10
16	8.5	9.1	0.73
53	8.8	8.8	0.62
56	8.9	8.1	0.38
79	7.1	8.5	0.10
94	7.8	8.5	0.70
98	6.9	9.0	0.75
102	7.4	9.0	0.81
108	7.7	8.1	0.95
117	8.1	> 9.0	0.29
135	7.2	8.7	0.45
140	7.0	7.3	0.24

CLAIMS

1. Compounds of the general formula (1):



(1)

wherein: X = S or O,

R_1 is H, $(C_1\text{-}C_6)$alkyl, CF_3, CH_2CF_3, OH or O-$(C_1\text{-}C_6)$alkyl

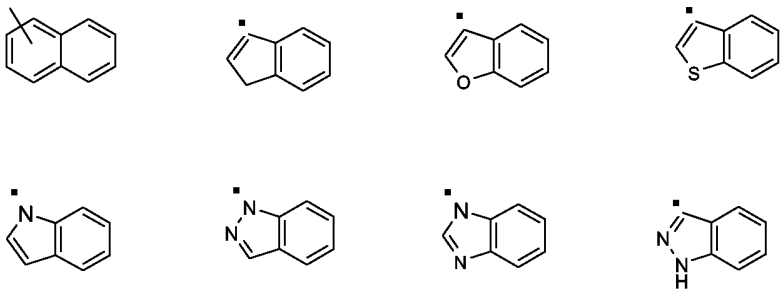
R_2 is H, $(C_1\text{-}C_6)$alkyl, halogen or cyano

R_3 is H or $(C_1\text{-}C_6)$alkyl

R_4 is H, $(C_1\text{-}C_6)$alkyl, optionally substituted with a halogen atom

T is a saturated or unsaturated carbon chain of 2-7 atoms, wherein one carbon atom may be replaced with a nitrogen atom optionally substituted with an $(C_1\text{-}C_3)$alkyl, CF_3 or CH_2CF_3 group, an oxygen atom or a sulphur atom, which chain is optionally substituted with one or more substituents selected from the group consisting of $(C_1\text{-}C_3)$alkyl, $(C_1\text{-}C_3)$alkoxy, halogen, cyano, trifluoromethyl, OCF_3, SCF_3, $OCHF_2$ and nitro,

Ar is selected from the groups:

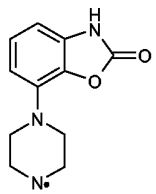


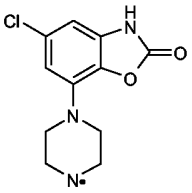
which Ar group is optionally further substituted with one or more substituents selected from the group consisting of (C_1-C_3)alkyl, (C_1-C_3)alkoxy, halogen, cyano, trifluoromethyl, OCF_3, SCF_3 $OCHF_2$ and nitro,

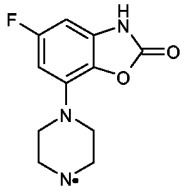
and in which Ar groups that contain a five-membered ring, the double bond in the five-membered ring may be saturated,

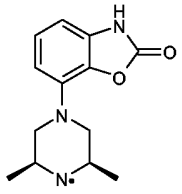
and tautomers, stereoisomers and N-oxides thereof, as well as pharmacologically acceptable salts, hydrates and solvates of said compounds of formula (1) and its tautomers, stereoisomers and N-oxides.

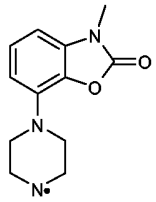
2. Compounds of the formula (1) as claimed in claim 1, wherein the phenylpiperazine part of the molecule is selected from the group consisting of:

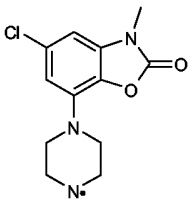

I

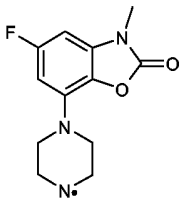

II

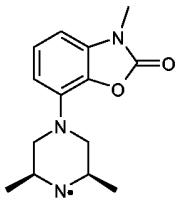

III

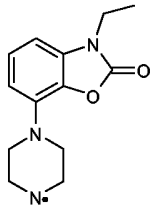

IV


V


VI

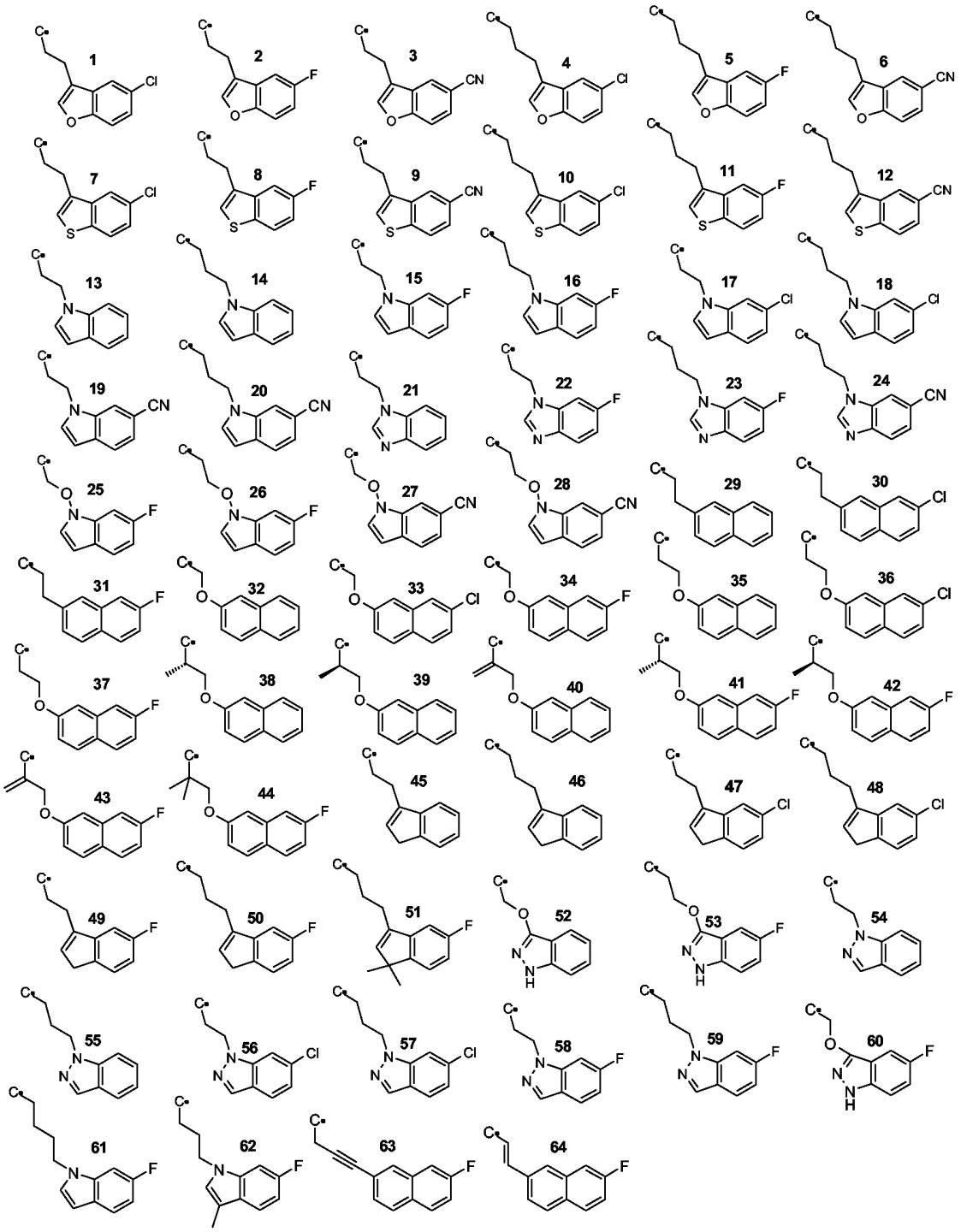

VII


VIII


IX

in which formulae the dot represents the attachment to 'T' of formula (1),

and wherein the second part of the molecule, represented by the symbols –T-Ar in formula (1), is selected from the group consisting of:



in which formulae the dot represents the attachment to the phenylpiperazine part of the compounds of formula (1),

and tautomers, stereoisomers and N-oxides thereof, as well as pharmacologically acceptable salts, hydrates and solvates of said compounds of formula (1) and its tautomers, stereoisomers and N-oxides.

3. A pharmaceutical composition comprising, in addition to a pharmaceutically acceptable carrier and/or at least one pharmaceutically acceptable auxiliary substance, a pharmacologically active amount of at least one compound of claim 1, or a salt thereof, as an active ingredient.

4. A method of preparing a composition as claimed in claim 3, characterised in that at least one compound of claims 1 or a salt thereof, is brought into a form suitable for administration

5. A compound as claimed in claim 1, or a salt thereof, for use as a medicament.

6. Use of a compound as claimed in claim 1 for the preparation of a pharmaceutical composition for the treatment of CNS disorders.

7. Use as claimed in claim 6, characterized in that said disorders are aggression, anxiety disorders, autism, vertigo, depression, disturbances of cognition or memory, Parkinson's disease, schizophrenia and other psychotic disorders.

8. Use as claimed in claim 6, characterized in that said disorder is depression.

9. Use as claimed in claim 6, characterized in that said disorders are schizophrenia and other psychotic disorders.

10. Use as claimed in claim 6, characterized in that said disorder is Parkinson's disease.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2005/056506

A. CLASSIFICATION OF SUBJECT MATTER
A61K31/423 C07D263/58 C07D413/12 A61P25/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 01/14330 A (SOLVAY PHARMACEUTICALS B.V; VAN HES, ROELOF; VAN DER HEIJDEN, JOHANNES) 1 March 2001 (2001-03-01) cited in the application page 4, line 10 - page 5, line 10; claims 1,7 pages 13-15	1-10
Y	WO 00/43382 A (H. LUNDBECK A/S; MOLTZEN, EJNER, KNUD; KROG-JENSEN, CHRISTIAN; BJOERNH) 27 July 2000 (2000-07-27) claims 1-3,12,13	1-10
Y	WO 99/67237 A (H. LUNDBECK A/S; MOLTZEN, EJNER, KNUD; MIKKELSEN, IVAN; KROG-JENSEN, C) 29 December 1999 (1999-12-29) claims 1-8,15,16	1-10

-/--

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
16 February 2006	22/02/2006

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Seymour, L

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2005/056506

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5 464 834 A (PEGLION ET AL) 7 November 1995 (1995-11-07) claims 1,9,10	1-10

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2005/056506

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
WO 0114330	A	01-03-2001	AT	299142 T	15-07-2005
			AU	772189 B2	08-04-2004
			AU	7411800 A	19-03-2001
			BR	0013498 A	14-05-2002
			CA	2379021 A1	01-03-2001
			CN	1390214 A	08-01-2003
			CZ	20020619 A3	14-08-2002
			DE	60021194 D1	11-08-2005
			DE	60021194 T2	22-12-2005
			ES	2244469 T3	16-12-2005
			HK	1051199 A1	10-12-2004
			HU	0203194 A2	28-01-2003
			JP	2003507454 T	25-02-2003
			MX	PA02001919 A	21-07-2003
			NO	20020810 A	19-02-2002
			NZ	517900 A	29-08-2003
			PL	364821 A1	13-12-2004
			PT	1212320 T	30-11-2005
			SK	2492002 A3	10-09-2002
			TR	200200460 T2	21-06-2002
WO 0043382	A	27-07-2000	AT	263763 T	15-04-2004
			AU	767377 B2	06-11-2003
			AU	2278100 A	07-08-2000
			BG	105781 A	31-05-2002
			BR	0009007 A	27-11-2001
			CA	2361059 A1	27-07-2000
			CN	1344265 A	10-04-2002
			CZ	20012657 A3	13-02-2002
			DE	60009663 D1	13-05-2004
			DE	60009663 T2	14-04-2005
			EP	1149087 A1	31-10-2001
			HU	0105065 A2	29-07-2002
			JP	2002535322 T	22-10-2002
			MX	PA01007226 A	24-04-2002
			NO	20013538 A	17-09-2001
			NZ	512732 A	31-10-2003
			PL	349909 A1	07-10-2002
			SK	10302001 A3	07-01-2002
			TR	200102089 T2	22-07-2002
			US	2002035113 A1	21-03-2002
			ZA	200105548 A	05-07-2002
WO 9967237	A	29-12-1999	AU	765317 B2	18-09-2003
			AU	4359299 A	10-01-2000
			BG	105136 A	28-09-2001
			CA	2335711 A1	29-12-1999
			EP	1089997 A1	11-04-2001
			HR	20000847 A1	31-12-2001
			HU	0101475 A2	28-10-2001
			JP	2003521443 T	15-07-2003
			NO	20006460 A	19-02-2001
			NZ	508506 A	30-01-2004
US 5464834	A	07-11-1995	AT	185345 T	15-10-1999
			AU	658512 B2	13-04-1995
			AU	4017893 A	16-12-1993
			CA	2098252 A1	13-12-1993

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2005/056506

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5464834 A		DE 69326637 D1	11-11-1999
		DE 69326637 T2	18-05-2000
		DK 574313 T3	03-04-2000
		EP 0574313 A1	15-12-1993
		ES 2139638 T3	16-02-2000
		FR 2692264 A1	17-12-1993
		GR 3031492 T3	31-01-2000
		JP 2634370 B2	23-07-1997
		JP 6179670 A	28-06-1994
		NZ 247854 A	27-09-1994
		ZA 9304143 A	17-01-1994