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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
10 July 2003 (10.07.2003)

PCT

(10) International Publication Number
WO 03/055492 A1

(51) International Patent Classification⁷: **A61K 31/517**, C07D 403/04, 403/14, A61P 25/28, 25/14, 25/18, 25/24, 15/16, 9/10

(21) International Application Number: PCT/SE02/02370

(22) International Filing Date: 18 December 2002 (18.12.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/344,887 21 December 2001 (21.12.2001) US

(71) Applicant *(for all designated States except US)*: **ASTRAZENECA AB** [SE/SE]; S-151 85 Södertälje (SE).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **BERG, Stefan** [SE/SE]; AstraZeneca R & D Södertälje, S-151 85 Södertälje (SE). **BHAT, Ratan** [US/SE]; AstraZeneca R & D Södertälje, S-151 85 Södertälje (SE). **EDWARDS, Philip** [US/US]; AstraZeneca Wilmington, P.O. Box 15437, Wilmington, DE 19850-5437 (US). **HELLBERG, Sven** [SE/SE]; AstraZeneca R & D Södertälje, S-151 85 Södertälje (SE).

(74) Agent: GLOBAL INTELLECTUAL PROPERTY; AstraZeneca AB, S-151 85 Södertälje (SE).

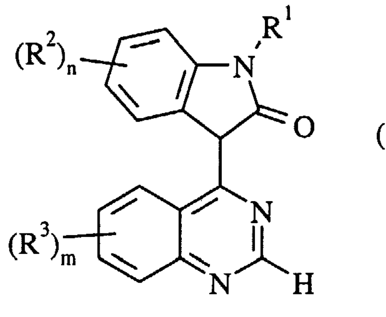
(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT,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

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

Published:
- *with international search report*
- *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

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: USE OF OXINDOLE DERIVATIVES IN THE TREATMENT OF DEMENTIA RELATED DISEASES, ALZHEIMER'S DISEASE AND CONDITIONS ASSOCIATED WITH GLYCOGEN SYNTHASE KINASE-3



(I)

(57) Abstract: The present invention relates to a new use of oxindole derivatives of formula I, as a free base or a pharmaceutically acceptable salt thereof, [Chemical formula should be inserted here. Please see paper copy.]wherein R^1, R^2, R^3, m and n are as defined as in claim 1, as well as to new compounds, a process for their preparation and new intermediates used in the preparation thereof, pharmaceutical compositions containing said therapeutically active compounds and to the use of said active compounds in therapy, especially in the prevention and/or treatment of dementia related diseases, Alzheimer's Disease and conditions associated with glycogen synthase kinase-3.

WO 03/055492 A1

USE OF OXINDOLE DERIVATIVES IN THE TREATMENT OF DEMENTIA RELATED DISEASES, ALZHEIMER'S DISEASE AND CONDITIONS ASSOCIATED WITH GLYCOGEN SYNTHASE KINASE-3

FIELD OF THE INVENTION

The present invention relates to a new use of oxindole derivatives of formula **I**, as a free base or a pharmaceutically acceptable salt thereof, as well as to new compounds, a process for their preparation and new intermediates used in the preparation thereof, pharmaceutical compositions containing said therapeutically active compounds and to the use of said active compounds in therapy, especially in the prevention and/or treatment of dementia related diseases, Alzheimer's Disease and conditions associated with glycogen synthase kinase-3.

BACKGROUND OF THE INVENTION

Glycogen synthase kinase 3 (GSK3) is a serine / threonine protein kinase composed of two isoforms (α and β), which are encoded by distinct genes but are highly homologous within the catalytic domain. GSK3 is highly expressed in the central and peripheral nervous system. GSK3 phosphorylates several substrates including tau, ß-catenin, glycogen synthase, pyruvate dehydrogenase and elongation initiation factor 2b (eIF2b). Insulin and growth factors activate protein kinase B, which phosphorylates GSK3 on the serine 9 residue and inactivates it.

Alzheimer's Disease (AD) dementias, and taupathies.

AD is characterized by cognitive decline, cholinergic dysfunction and neuronal death, neurofibrillary tangles and senile plaques consisting of amyloid-β deposits. The sequence of these events in AD is unclear, but believed to be related. Glycogen synthase kinase 3β (GSK3β) or Tau (τ) phosphorylating kinase selectively phosphorylates the microtubule associated protein τ in neurons at sites that are hyperphosphorylated in AD brains. Hyperphosphorylated protein τ has lower affinity for microtubules and accumulates as paired helical filaments, which are the main components that constitute neurofibrillary tangles and neuropil threads in AD brains. This results in depolymerization of microtubules, which leads to dying back of axons and neuritic dystrophy. Neurofibrillary tangles are consistently found in diseases such as AD, amyotrophic lateral sclerosis, parkinsonism-dementia complex of Gaum, corticobasal degeneration, dementia pugilistica and head trauma, Down's syndrome, postencephalatic parkinsonism, progressive supranuclear palsy, Niemann-Pick's Disease and Pick's Disease. Addition of amyloid-β to primary hippocampal cultures results in hyperphosphorylation of τ and a paired helical filaments-like state via induction of GSK3β activity, followed by disruption of axonal transport and neuronal death (Imahori and Uchida., J. Biochem 121:179-188, 1997). GSK3β preferentially labels neurofibrillary tangles and has been shown to be active in pre-tangle neurons in AD brains. GSK3 protein levels are also increased by 50% in brain tissue from AD patients. Furthermore, GSK3β phosphorylates pyruvate dehydrogenase, a key enzyme in the glycolytic pathway and prevents the conversion of pyruvate to acetyl-Co-A (Hoshi et al., PNAS 93:2719-2723, 1996). Acetyl-Co-A is critical for the synthesis of acetylcholine, a neurotransmitter with cognitive functions. Thus, GSK3β inhibition may have beneficial effects in progression as well as the cognitive deficits associated with Alzheimer's disease and other above-referred to diseases.

Chronic and Acute Neurodegenerative Diseases.

Growth factor mediated activation of the PI3K /Akt pathway has been shown to play a key role in neuronal survival. The activation of this pathway results in GSK3β inhibition. Recent studies (Bhat et. al., PNAS 97:11074-11079 (2000)) indicate that GSK3β activity is increased in cellular and animal models of neurodegeneration such as cerebral ischemia or after growth factor deprivation. For example, the active site phosphorylation was increased in neurons vulnerable to apoptosis, a type of cell death commonly thought to occur in chronic and acute degenerative diseases such as Alzheimer's Disease, Parkinson's Disease, amyotrophic lateral sclerosis, Huntington's Disease and HIV dementia, ischemic stroke and head trauma. Lithium was neuroprotective in inhibiting apoptosis in cells and in the brain at doses that resulted in the inhibition of GSK3β. Thus, GSK3β inhibitors could be useful in attenuating the course of neurodegenerative diseases.

Bipolar Disorders (BD)

Bipolar Disorders are characterised by manic episodes and depressive episodes. Lithium has been used to treat BD based on its mood stabilising effects. The disadvantage of lithium is the narrow therapeutic window and the danger of overdosing, that can lead to lithium intoxication. The recent discovery that lithium inhibits GSK3 at therapeutic concentrations has raised the possibility that this enzyme represents a key target of lithium's action in the brain (Stambolic et al., Curr. Biol. 6:1664-1668, 1996; Klein and Melton; PNAS 93:8455-8459, 1996). Inhibition of GSK3β may therefore be of therapeutic relevance in the treatment of BD as well as in AD patients that have affective disorders.

Schizophrenia

GSK3 is involved in signal transduction cascades of multiple cellular processes, particularly during neural development. Kozlovsky et al (Am J Psychiatry 2000 May;157(5):831-3) found that GSK3β levels were 41% lower in the schizophrenic patients than in comparison subjects. This study indicates that schizophrenia involves neurodevelopmental pathology and that abnormal GSK3 regulation could play a role in schizophrenia. Furthermore, reduced β-catenin levels have been reported in patients exhibiting schizophrenia (Cotter et al., Neuroreport 9:1379-1383 (1998)).

Diabetes

Insulin stimulates glycogen synthesis in skeletal muscles via the dephosphorylation and thus activation of glycogen synthase. Under resting conditions, GSK3 phosphorylates and inactivates glycogen synthase via dephosphorylation. GSK3 is also over-expressed in muscles from Type II diabetic patients (Nikoulina et al., Diabetes 2000 Feb;49(2):263-71). Inhibition of GSK3 increases the activity of glycogen synthase thereby decreasing glucose levels by its conversion to glycogen. GSK3 inhibition may therefore be of therapeutic relevance in the treatment of Type I and Type II diabetes and diabetic neuropathy.

Hair Loss

GSK3 phosphorylates and degrades β-catenin. β-catenin is an effector of the pathway for keratonin synthesis. β-catenin stabilisation may be lead to increase hair development. Mice expressing a stabilised β-catenin by mutation of sites phosphorylated by GSK3 undergo a process resembling de novo hair morphogenesis (Gat et al., Cell 1998 Nov 25;95 (5):605-14)). The new follicles formed sebaceous glands and dermal papilla, normally established only in embryogenesis. Thus GSK3 inhibition may offer treatment for baldness.

Oral contraceptives

Vijajaraghavan et al. (Biol Reprod 2000 Jun; 62 (6):1647-54) reported that GSK3 is high in motile versus immotile sperm. Immunocytochemistry revealed that GSK3 is present in the flagellum and the anterior portion of the sperm head. These data suggest that GSK3 could be a key element underlying motility initiation in the epididymis and regulation of mature sperm function. Inhibitors of GSK3 could be useful as contraceptives for males.

DETAILED DESCRIPTION OF THE INVENTION

Compounds of general formula **I** below are disclosed in WO 97/42187. According to WO 97/42187 the effect of the compounds on reducing antiangiogenic and/or vascular permeability in mammals has been investigated.

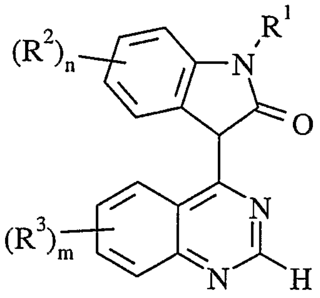
It has now surprisingly been found that the group of oxindole derivatives as decribed in WO 97/42187 are well suited for inhibiting glycogen synthase kinase-3. Said glycogen synthase kinase-3 inhibitors are suitable in the prevention and/or treatment of conditions associated with glycogen synthase kinase-3 in the central and peripheral nervous system. In particular, the compounds of the invention are expected to be suitable for prevention and/or treatment of especially dementia related diseases and Alzheimer's Disease.

The dementia related diseases are selected from the group consisting of Frontotemporal dementia Parkinson's Type, Parkinson dementia complex of Guam, HIV dementia, diseases with associated neurofibrillar tangle pathologies, predemented states, vascular dementia, dementia with Lewy bodies, Frontotemporal dementia and dementia pugilistica.

The compounds of the invention are also expected to be suitable for prevention and/or treatment of amyotrophic lateral sclerosis, corticobasal degeneration, Down syndrome, Huntington's Disease, Parkinson's Disease, postencephelatic parkinsonism, progressive supranuclear palsy, Pick's Disease, Niemann-Pick's Disease, stroke, head trauma and other chronic neurodegenerative diseases, Bipolar Disease, affective disorders, depression, schizophrenia, cognitive disorders, hair loss and contraceptive medication.

The compounds of the invention are further expected to be suitable for prevention and/or treatment of Mild Cognitive Impairment, Age-Associated Memory Impairment, Age-Related Cognitive Decline, Cognitive Impairement No Dementia, mild cognitive decline, mild neurocognitive decline, Late-Life Forgetfulness, memory impairment and cognitive impairment and androgenetic alopecia.

In the present invention a compound of the general formula **I**, as a free base or salts thereof, may be used, in the manufacturing of a medicament for the prevention and/or treatment of conditions associated with glycogen synthase kinase-3:



(I)

wherein:

R^1 is hydrogen or C_{1-3}alkyl;

R^2 is hydroxy, halogeno, trifluoromethyl, cyano, amino, nitro, carboxy, C_{1-3}alkyl, C_{1-3}alkoxy, C_{1-3}alkanoyloxy, C_{2-4}alkanoyl, C_{1-4}alkanoylamino, C_{1-4}alkoxycarbonyl, C_{1-4}alkylthio, C_{1-4}alkylsulphinyl, C_{1-4}alkylsulphonyl, carbamoyl, *N*-C_{1-4}alkylcarbamoyl, *N,N*-di(C_{1-4}alkyl)carbamoyl, aminosulphonyl, *N*-C_{1-4}alkylaminosulphonyl, *N,N*-di(C_{1-4}alkyl)aminosulphonyl, C_{1-4}alkylsulphonylamino, or a group R^4X^1,

wherein X^1 is a direct bond, C_{2-4}alkanoyl, $CONR^5R^6$, $SO_2NR^7R^8$ or SO_2R^9 (wherein R^5 and R^7 each independently are hydrogen or C_{1-2}alkyl, and R^6, R^8 and R^9 each independently are C_{1-4}alkyl, and wherein R^4 is linked to R^6, R^8 or R^9); and

R^4 is phenyl or a 5 or 6 membered heterocyclic group with one or two heteroatoms, selected independently from O, S and N, which heterocyclic group may be saturated or unsaturated and which phenyl or heterocyclic group may be substituted with one or two substituents selected independently from hydroxy, halogeno, C_{1-3}alkyl, C_{1-3}alkoxy, C_{1-3}alkanoyloxy, trifluoromethyl, cyano, amino, nitro and C_{1-4}alkoxycarbonyl;

R^3 is hydroxy, halogeno, nitro, trifluoromethyl, C_{1-3}alkyl, cyano, amino or $R^{10}X^2$, wherein X^2 is O, CH_2, S, SO, SO_2, $NR^{11}CO$, $CONR^{12}$, SO_2NR^{13}, $NR^{14}SO_2$ or NR^{15} (wherein R^{11}, R^{12}, R^{13}, R^{14} and R^{15} each independently are hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl), or X^2 is a direct bond; and

R^{10} is selected from one of the following groups:

1) hydrogen or C_{1-5}alkyl which may be substituted with one or more groups selected independently from hydroxy, fluoro and amino;

2) C_{1-5}alkylX^3COR^{16} (wherein X^3 is O or NR^{17} (wherein R^{17} is hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{16} is C_{1-3}alkyl, $NR^{18}R^{19}$ or OR^{20} (wherein R^{18}, R^{19} and R^{20} each independently are hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl));

3) C_{1-5}alkylX^4R^{21} (wherein X^4 is O, S, SO, SO_2, OCO, $NR^{22}CO$, $CONR^{23}$, SO_2NR^{24}, $NR^{25}SO_2$ or NR^{26} (wherein R^{22}, R^{23}, R^{24}, R^{25} and R^{26} each independently are hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{21} is hydrogen, C_{1-3}alkyl, cyclopentyl, cyclohexyl or a 5 or 6 membered saturated heterocyclic group with one or two heteroatoms selected independently from O, S and N, which C_{1-3}alkyl group may be substituted with one or two substituents selected independently from oxo, hydroxy, halogeno and C_{1-4}alkoxy and which heterocyclic group may be substituted with one or two substituents selected independently from oxo, hydroxy, halogeno, C_{1-4}alkyl, C_{1-4}hydroxyalkyl and C_{1-4}alkoxy);

4) C_{1-5}alkylX^5C_{1-5}alkylX^6R^{27} (wherein X^5 and X^6 each independently are O, S, SO, SO_2, $NR^{28}CO$, $CONR^{29}$, SO_2NR^{30}, $NR^{31}SO_2$ or NR^{32} (wherein R^{28}, R^{29}, R^{30}, R^{31} and R^{32} each independently are hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{27} is hydrogen or C_{1-3}alkyl);

5) C_{1-5}alkylR^{33} (wherein R^{33} is a 5 or 6 membered saturated heterocyclic group with one or two heteroatoms selected independently from O, S and N, which heterocyclic group may be substituted with one or two substituents selected independently from oxo, hydroxy, halogeno, C_{1-4}alkyl, C_{1-6}carbonyl, C_{1-4}hydroxyalkyl and C_{1-4}alkoxy);

6) C_{2-5}alkenylR^{33} (wherein R^{33} is as defined hereinbefore);

7) C_{2-5}alkynylR^{33} (wherein R^{33} is as defined hereinbefore);

8) R^{34} (wherein R^{34} is a pyridone group, a phenyl group or a 5 or 6 membered aromatic heterocyclic group with 1 to 3 heteroatoms selected independently from O, N and S, which pyridone, phenyl or heterocyclic group may carry up to 5 substituents selected independently from hydroxy, halogeno, amino, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}hydroxyalkyl, C_{1-4}aminoalkyl, C_{1-4}alkylamino, C_{1-4}hydroxyalkoxy, carboxy, cyano, $CONR^{35}R^{36}$ and $NR^{37}COR^{38}$ (wherein R^{35}, R^{36}, R^{37} and R^{38} each independently are hydrogen, C_{1-4}alkyl or C_{1-3}alkoxyC_{2-3}alkyl));

9) C_{1-5}alkylR^{34} (wherein R^{34} is as defined hereinbefore);

10) C_{2-5}alkenylR^{34} (wherein R^{34} is as defined hereinbefore);

11) C_{2-5}alkynylR^{34} (wherein R^{34} is as defined hereinbefore);

12) C_{1-5}alkylX^7R^{34} (wherein X^7 is O, S, SO, SO_2, $NR^{39}CO$, $CONR^{40}$, SO_2NR^{41}, $NR^{42}SO_2$ or NR^{43} (wherein R^{39}, R^{40}, R^{41}, R^{42} and R^{43} each independently are hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{34} is as defined hereinbefore);

13) C_{2-5}alkenylX^8R^{34} (wherein X^8 is O, S, SO, SO_2, $NR^{44}CO$, $CONR^{45}$, SO_2NR^{46}, $NR^{47}SO_2$ or NR^{48} (wherein R^{44}, R^{45}, R^{46}, R^{47} and R^{48} each independently are hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{34} is as defined hereinbefore);

14) C_{2-5}alkynylX^9R^{34} (wherein X^9 is O, S, SO, SO_2, $NR^{49}CO$, $CONR^{50}$, SO_2NR^{51}, $NR^{52}SO_2$ or NR^{53} (wherein R^{49}, R^{50}, R^{51}, R^{52} and R^{53} each independently are hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{34} is as defined hereinbefore);

15) C_{1-3}alkyl$X^{10}C_{1-3}$alkylR^{34} (wherein X^{10} is O, S, SO, SO_2, $NR^{54}CO$, ONR^{55}, SO_2NR^{56}, $NR^{57}SO_2$ or NR^{58} (wherein R^{54}, R^{55}, R^{56}, R^{57} and R^{58} each independently are hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{34} is as defined hereinbefore);

16) R^{33} (wherein R^{33} is as defined hereinbefore); and

17) C_{1-3}alkyl$X^{10}C_{1-3}$alkylR^{33} (wherein X^{10} and R^{33} are as defined hereinbefore);

18) C_{1-5}alkylCOR^{33} (wherein R^{33} is as defined hereinbefore);

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

m is 0, 1, 2, 3 or 4;

as a free base or a pharmaceutically acceptable salt thereof.

One aspect of the invention relates to the use of compounds of formula **I**, wherein R^3 is $R^{10}X^2$, wherein X^2 is O, CH_2, S, SO, SO_2, $NR^{11}CO$, $CONR^{12}$, SO_2NR^{13}, $NR^{14}SO_2$ or NR^{15} (wherein R^{11}, R^{12}, R^{13}, R^{14} and R^{15} each independently are hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl), or X^2 is a direct bond; and

R^{10} is selected from one of the following groups:

1) hydrogen or C_{1-5}alkyl which may be substituted with one or more groups selected independently from hydroxy, fluoro and amino;

2) C_{1-5}alkylX^3COR^{16} (wherein X^3 is O or NR^{17} (wherein R^{17} is hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{16} is C_{1-3}alkyl, $NR^{18}R^{19}$ or OR^{20} (wherein R^{18}, R^{19} and R^{20} each independently are hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl));

3) C_{1-5}alkylX^4R^{21} (wherein X^4 is O, S, SO, SO_2, OCO, $NR^{22}CO$, $CONR^{23}$, SO_2NR^{24}, $NR^{25}SO_2$ or NR^{26} (wherein R^{22}, R^{23}, R^{24}, R^{25} and R^{26} each independently are hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{21} is hydrogen, C_{1-3}alkyl, cyclopentyl, cyclohexyl or a 5 or 6 membered saturated heterocyclic group with one or two heteroatoms selected independently from O, S and N, which C_{1-3}alkyl group may be substituted with one or two substituents selected independently from oxo, hydroxy, halogeno and C_{1-4}alkoxy and which heterocyclic group may be substituted with one or two substituents selected independently from oxo, hydroxy, halogeno, C_{1-4}alkyl, C_{1-4}hydroxyalkyl and C_{1-4}alkoxy);

4) C_{1-5}alkylX^5C_{1-5}alkylX^6R^{27} (wherein X^5 and X^6 each independently are O, S, SO, SO_2, $NR^{28}CO$, $CONR^{29}$, SO_2NR^{30}, $NR^{31}SO_2$ or NR^{32} (wherein R^{28}, R^{29}, R^{30}, R^{31} and R^{32} each independently are hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{27} is hydrogen or C_{1-3}alkyl);

5) C_{1-5}alkylR^{33} (wherein R^{33} is a 5 or 6 membered saturated heterocyclic group with one or two heteroatoms selected independently from O, S and N, which heterocyclic group may be substituted with one or two substituents selected independently from oxo, hydroxy, halogeno, C_{1-4}alkyl, C_{1-4}hydroxyalkyl and C_{1-4}alkoxy);

6) C_{2-5}alkenylR^{33} (wherein R^{33} is as defined hereinbefore);

7) C_{2-5}alkynylR^{33} (wherein R^{33} is as defined hereinbefore);

8) R^{34} (wherein R^{34} is a pyridone group, a phenyl group or a 5 or 6 membered aromatic heterocyclic group with 1 to 3 heteroatoms selected independently from O, N and S, which pyridone, phenyl or heterocyclic group may carry up to 5 substituents selected independently from hydroxy, halogeno, amino, C_{1-4}alkyl,

C_{1-4}alkoxy, C_{1-4}hydroxyalkyl, C_{1-4}aminoalkyl, C_{1-4}alkylamino, C_{1-4}hydroxyalkoxy, carboxy, cyano, CONR^{35}R^{36} and NR^{37}COR^{38} (wherein R^{35}, R^{36}, R^{37} and R^{38} each independently are hydrogen, C_{1-4}alkyl or C_{1-3}alkoxyC_{2-3}alkyl));

9) C_{1-5}alkylR^{34} (wherein R^{34} is as defined hereinbefore);

10) C_{2-5}alkenylR^{34} (wherein R^{34} is as defined hereinbefore);

11) C_{2-5}alkynylR^{34} (wherein R^{34} is as defined hereinbefore);

12) C_{1-5}alkylX^{7}R^{34} (wherein X^{7} is O, S, SO, SO$_2$, NR^{39}CO, CONR^{40}, SO$_2$NR^{41}, NR^{42}SO$_2$ or NR^{43} (wherein R^{39}, R^{40}, R^{41}, R^{42} and R^{43} each independently are hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{34} is as defined hereinbefore);

13) C_{2-5}alkenylX^{8}R^{34} (wherein X^{8} is O, S, SO, SO$_2$, NR^{44}CO, CONR^{45}, SO$_2$NR^{46}, NR^{47}SO$_2$ or NR^{48} (wherein R^{44}, R^{45}, R^{46}, R^{47} and R^{48} each independently are hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{34} is as defined hereinbefore);

14) C_{2-5}alkynylX^{9}R^{34} (wherein X^{9} is O, S, SO, SO$_2$, NR^{49}CO, CONR^{50}, SO$_2$NR^{51}, NR^{52}SO$_2$ or NR^{53} (wherein R^{49}, R^{50}, R^{51}, R^{52} and R^{53} each independently are hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{34} is as defined hereinbefore);

15) C_{1-3}alkylX^{10}C_{1-3}alkylR^{34} (wherein X^{10} is O, S, SO, SO$_2$, NR^{54}CO, ONR^{55}, SO$_2$NR^{56}, NR^{57}SO$_2$ or NR^{58} (wherein R^{54}, R^{55}, R^{56}, R^{57} and R^{58} each independently are hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{34} is as defined hereinbefore);

16) R^{33} (wherein R^{33} is as defined hereinbefore); and

17) C_{1-3}alkylX^{10}C_{1-3}alkylR^{33} (wherein X^{10} and R^{33} are as defined hereinbefore).

Another aspect of the invention relates to the use of compounds of formula **I**, wherein R^{1} is hydrogen.

In a further aspect of the invention compounds of formula **I** may be used, wherein R^{2} is halogeno, cyano, nitro, carboxy, C_{1-4}alkoxycarbonyl, trifluoromethyl, C_{1-3}alkyl, C_{1-3}alkoxy, *N*-C_{1-4}alkylcarbamoyl, *N*,*N*-di(C_{1-4}alkyl)carbamoyl, aminosulphonyl, or a group R^{4}X^{1},

wherein X^{1} is CONR^{5}R^{6}, (wherein R^{5} is hydrogen or C_{1-2}alkyl, and R^{6} is C_{1-4}alkyl, and wherein R^{4} is linked to R^{6}); and

R^{4} is phenyl or a 5 or 6 membered heterocyclic group with one or two heteroatoms, selected independently from O and N, which heterocyclic group may be saturated or unsaturated and which phenyl or heterocyclic group may be substituted with one or two substituents selected independently from hydroxy, halogeno, C_{1-3}alkyl, C_{1-3}alkoxy, C_{1-3}alkanoyloxy, trifluoromethyl, cyano, amino, nitro and C_{1-4}alkoxycarbonyl;

n is 0, 1 or 2.

In one aspect of the invention compounds of formula **I** may be used,
wherein R^3 is $R^{10}X^2$,
wherein X^2 is O; and
R^{10} is selected from one of the following groups:
1) hydrogen or C_{1-5}alkyl;
3) C_{1-5}alkylX^4R^{21} (wherein X^4 is O or NR^{26} (wherein R^{21} and R^{26} each independently are hydrogen, C_{1-3}alkyl, cyclopentyl or cyclohexyl));
4) C_{1-5}alkylX^5C_{1-5}alkylX^6R^{27} (wherein X^5 and X^6 are O and R^{27} is hydrogen or C_{1-3}alkyl);
5) C_{1-5}alkylR^{33} (wherein R^{33} is a 5 or 6 membered saturated heterocyclic group with one or two heteroatoms, selected independently from O, S and N, which heterocyclic group may be substituted with one or two substituents selected independently from oxo, hydroxy, halogeno, C_{1-4}alkyl, C_{1-6}carbonyl, C_{1-4}hydroxyalkyl and C_{1-4}alkoxy);
9) C_{1-5}alkylR^{34} (wherein R^{34} is a 5 membered aromatic heterocyclic group with 1 to 3 heteroatoms selected independently from O and N, which heterocyclic group may carry up to 5 substituents selected independently from halogeno, amino, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}hydroxyalkyl, C_{1-4}aminoalkyl, C_{1-4}alkylamino, C_{1-4}hydroxyalkoxy, carboxy, hydoxy, cyano, $CONR^{35}R^{36}$ and $NR^{37}COR^{38}$ (wherein R^{35}, R^{36}, R^{37} and R^{38} each independently are hydrogen, C_{1-4}alkyl or C_{1-3}alkoxyC_{2-3}alkyl)); and
17) C_{1-3}alkyl$X^{10}C_{1-3}$alkylR^{33} (wherein X^{10} is O and R^{33} are as defined hereinbefore);
18) C_{1-5}alkylCOR^{33} (wherein R^{33} is as defined hereinbefore);
m is 0, 1 or 2.

In another aspect of the invention compounds of formula **I** may be used,
wherein R^3 is $R^{10}X^2$,
wherein X^2 is O; and R^{10} is

4) C_{1-5}alkylX^5C_{1-5}alkylX^6R^{27} (wherein X^5 and X^6 are O and R^{27} is hydrogen or C_{1-3}alkyl).

In yet another aspect of the invention compounds of formula **I** may be used, wherein the R^2 is substituted on position 5 and/or 6 and R^3 is substituted on position 6, 7 and/or 8.

The present invention further relates to novel compounds, which are
4-(6-Fluorooxindol-3-yl)-6-methoxy-7-(3-morpholinopropoxy)quinazoline,
4-(5-Cyanooxindol-3-yl)-6-methoxy-7-(2-methoxyethoxy)quinazoline,
4-(5-Cyanooxindol-3-yl)-7-(2-methoxyethoxy)quinazoline,
4-(5-Cyanooxindol-3-yl)-7-(2-(imidazol-1-yl)ethoxy)-6-methoxyquinazoline,
4-(5-Cyanooxindol-3-yl)-7-(3-morpholinopropoxy)quinazoline,
4-(5-Carbamoyloxindol-3-yl)-6-methoxy-7-(3-morpholinopropoxy)quinazoline,
4-(6-Cyanooxindol-3-yl)-6-methoxy-7-(3-morpholinopropoxy)quinazoline, ,
4-(6-Bromooxindol-3-yl)-7-(3-morpholinopropoxy)quinazoline,
2-Hydroxy-3-[7-(2-methoxyethoxy)quinazolin-4-yl]-1*H*-indole-5-carboxylic acid (4-phenylbutyl)amide,
6-Chloro-3-[7-(3-morpholin-4-yl-propoxy)quinazolin-4-yl]-1,3-dihydro-indol-2-one hydrochloride,
3-{7-[2-(2-Methoxyethoxy)ethoxy]quinazolin-4-yl}-1,3-dihydroindol-2-one hydrochloride,
6-Fluoro-3-[7-(3-morpholin-4-ylpropoxy)quinazolin-4-yl]-1,3-dihydro-indol-2-one dihydrochloride,
7-Fluoro-3-[6-methoxy-7-(3-morpholin-4-ylpropoxy)quinazolin-4-yl]-1,3-dihydroindol-2-one dihydrochloride,
3-[7-(3-Morpholin-4-ylpropoxy)quinazolin-4-yl]-2-oxo-2,3-dihydro-1*H*-indole-5-carboxylic acid dimethylamide,
3-[7-(3-Morpholin-4-ylpropoxy)quinazolin-4-yl]-6-propyl-1*H*-indol-2-ol hydrochloride,
6-Ethyl-3-[7-(3-morpholin-4ylpropoxy)quinazolin-4-yl]-1*H*-indol-2-ol hydrochloride,
2-Hydroxy-3-[7-(2-methoxyethoxy)quinazolin-4-yl]-1*H*-indole-5-carboxylic acid [2-(1-methylpyrrolidin-2-yl)ethyl]amide,

2-Hydroxy-3-[7-(2-morpholin-4-ylethoxy)quinazolin-4-yl]-1*H*-indole-5-carbonitril dihydrochloride,

2-Hydroxy-3-[7-(2-methoxyethoxy)quinazolin-4-yl]-1*H*-indole-5-carboxylic acid (tetrahydrofuran-2-ylmethyl)amide,

2-Hydroxy-3-[7-(2-methoxyethoxy)quinazolin-4-yl]-1*H*-indole-5-carboxylic acid (3-morpholin-4-ylpropyl)amide,

2-Hydroxy-3-[7-(2-methoxyethoxy)quinazolin-4-yl]-1*H*-indole-5-carboxylic acid [2-(1*H*-imidazol-4-yl)ethyl]amide,

2-Hydroxy-3-{7-[2-(2-methoxyethoxy)ethoxy]quinazolin-4-yl}-1*H*-indole-5-carbonitrile hydrochloride,

3-[7-(2-Imidazol-1-yl-ethoxy)-6-methoxyquinazolin-4-yl]-2-oxo-2,3-dihydro-1*H*-indole-5-sulfonamide acetate,

6-Bromo-3-[6-methoxy-7-(3-morpholin-4-yl-propoxy)quinazolin-4-yl]-1,3-dihydroindol-2-one dihydrochloride,

6-Bromo-3-quinazolin-4-yl-1,3-dihydroindol-2-one,

6-Bromo-3-{6-methoxy-7-[2-(2-methoxyethoxy)ethoxy]quinazolin-4-yl}-1,3-dihydroindol-2-one hydrochloride,

3-{7-[2-(2-Morpholin-4-yl-ethoxy)ethoxy]quinazolin-4-yl}-2-oxo-2,3-dihydro-1*H*-indole-5-carbonitrile hydrochloride,

6-Chloro-3-{7-[2-(2-methoxyethoxy)ethoxy]quinazolin-4-yl}-1,3-dihydroindol-2-one hydrochloride,

3-{7-[2-(4-Acetylpiperazin-1-yl)ethoxy]quinazolin-4-yl}-2-oxo-2,3-dihydro-1*H*-indole-5-carbonitrile hydrochloride,

5-Chloro-3-{7-[2-(2-methoxyethoxy)ethoxy]quinazolin-4-yl}-1,3-dihydroindol-2-one hydrochloride,

3-{7-[2-(4-Butyrylpiperazin-1-yl)ethoxy]quinazolin-4-yl}-2-oxo-2,3-dihydro-1*H*-indole-5-carbonitrile hydrochloride,

3-{7-[2-(4-Acetylpiperazin-1-yl)-2-oxoethoxy]quinazolin-4-yl}-2-oxo-2,3-dihydro-1*H*-indole-5-carbonitrile hydrochloride,

3-{7-[4-(4-Acetylpiperazin-1-yl)-4-oxobutoxy]quinazolin-4-yl}-2-oxo-2,3-dihydro-1*H*-indole-5-carbonitrile hydrochloride, 6-Bromo-3-[7-(2-imidazol-1-ylethoxy)-6-methoxyquinazolin-4-yl]-1,3-dihydro-indol-2-one dihydrochloride,

3-[7-(2-Imidazol-1-ylethoxy)-6-methoxyquinazolin-4-yl]-2-oxo-2,3-dihydro-1*H*-indole-6-carbonitrile dihydrochloride,

3-[7-(3-Morpholin-4-ylpropoxy)quinazolin-4-yl]-2-oxo-2,3-dihydro-1*H*-indole-5-carboxylic acid methylamide,

3-{7-[3-(4-Methylpiperazin-1-yl)propoxy]quinazolin-4-yl}-2-oxo-2,3-dihydro-1*H*-indole-5-carbonitrile hydrochloride,

2-Hydroxy-3-[8-(2-morpholin-4-ylethoxy)quinazolin-4-yl]-1*H*-indole-5-carbonitrile hydrochloride,

6-Bromo-3-[7-(3-morpholin-4-ylpropoxy)quinazolin-4-yl]-2-oxo-2,3-dihydro-1*H*-indole-5-carboxylic acid methylamide,

6-Methyl-3-[7-(3-morpholin-4-ylpropoxy)quinazolin-4-yl]-1*H*-indol-2-ol,

5-Bromo-6-methyl-3-[7-(3-morpholin-4-ylpropoxy)quinazolin-4-yl]-1*H*-indol-2-ol dihydrochloride,

6-Bromo-3-[7-(3-morpholin-4-ylpropoxy)quinazolin-4-yl]-5-nitro-1*H*-indol-2-ol dihydrochloride,

2-Hydroxy-3-[7-(2-methoxyethoxy)quinazolin-4-yl]-1*H*-indole-5-carboxylic acid,

3-[7-(3-Dimethylaminopropoxy)quinazolin-4-yl]-2-hydoxy-1*H*-indol-5-carbonitrile hydrochloride,

3-[7-(2-Dimethylaminoethoxy)quinazolin-4-yl]-2-hydoxy-1*H*-indol-5-carbonitrile fumarate,

3-{7-[2-(Isopropylmethylamino)ethoxy]quinazolin-4-yl]-2-oxo-2,3-dihydro-1*H*-indol-5-carbonitrile fumarate and

3-[7-(2-Diisopropylamino)ethoxy)quinazolin-4-yl]-2-hydroxy-1*H*-indol-5-carbonitrile fumarate,

as a free base or salts thereof.

In another aspect of the invention the compounds listed hereinbefore may be used in the manufacturing of a medicament for the prevention and/or treatment of conditions associated with glycogen synthase kinase-3.

For the avoidance of doubt it is to be understood that where in this specification a group is qualified by 'hereinbefore defined' or 'defined hereinbefore' the said group encompasses the first occurring and broadest definition as well as each and all of the preferred definitions of that group.

For the avoidance of doubt it is to be understood that in this specification 'C_{1-5}' means a carbon group having 1, 2, 3, 4 or 5 carbon atoms.

In this specification, unless stated otherwise, the term "alkyl" includes both straight and branched chain alkyl groups. C_{1-5}alkyl may be methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, n-pentyl, i-pentyl, t-pentyl, neo-pentyl.

The term "alkoxy" as used herein, unless stated otherwise includes "alkyl"O groups in which "alkyl" is as hereinbefore defined. C_{1-5}alkoxy may be methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, i-butoxy, s-butoxy, t-butoxy, n-pentyloxy, i-pentyloxy, t-pentyloxy, neo-pentyloxy.

The term "alkanoyl" as used herein, unless otherwise stated includes formyl and alkylC=O groups in which "alkyl" is as defined hereinbefore, for example C_2alkanoyl is ethanoyl and refers to $CH_3C=O$, C_1alkanoyl is formyl and refers to CHO.

In this specification, unless stated otherwise, the term "alkenyl" includes both straight and branched chain alkenyl groups but references to individual alkenyl groups such as 2-butenyl are specific for the straight chain version only. Unless otherwise stated, the term "alkenyl" advantageously refers to chains with 2 to 5 carbon atoms, preferably 3 to 4 carbon atoms.

In this specification, unless stated otherwise, the term "alkynyl" includes both straight and branched chain alkynyl groups but references to individual alkynyl groups such as 2-butynyl are specific for the straight chain version only. Unless otherwise stated, the term "alkynyl" advantageously refers to chains with 2 to 5 carbon atoms, preferably 3 to 4 carbon atoms.

In this specification, unless stated otherwise, the term "5 or 6 membered heterocyclic group with one or two heteroatoms, selected independently from O, S and N, which heterocyclic group may be saturated or unsaturated" includes both heteroaromatic rings and heterocyclic rings that are saturated. Examples of such heterocyclic groups includes, but are not limited to, furyl, imidazolyl, isoxazolyl, isothiazolyl, oxazolyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridyl, pyrimidyl, pyrrolyl, thiazolyl, thienyl, imidazolidinyl, imidazolinyl, morpholinyl, piperazinyl, piperidyl, piperidonyl, pyrazolidinyl, pyrazolinyl, pyrrolidinyl, pyrrolinyl, tetrahydropyranyl or thiomorpholinyl.

In this specification, unless stated otherwise, the term "5 or 6 membered saturated heterocyclic group with one or two heteroatoms, selected independently from O, S and N" may be, but are not limited to, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, morpholinyl, piperidinyl, oxathianyl, thiomorpholinyl, piperazinyl. In this specification, unless stated otherwise, the term "5 or 6 membered aromatic heterocyclic group with 1 to 3 heteroatoms, selected independently from O, N and S" may be, but are not limited to, furyl, imidazolyl, isoxazolyl, isothiazolyl, oxazolyl, pyrazinyl, triazinyl, pyrazolyl, pyridazinyl, pyridyl, pyrimidyl, pyrrolyl, thiazolyl or thienyl.

In this specification, unless stated otherwise, the term halogeno may be fluor, chlorine, bromine or iodine.

For the avoidance of any doubt, it is to be understood that when X^2 is, for example, a group of formula $NR^{11}CO$, it is the nitrogen atom be substituted withing the R^{11} group which is attached to the quinazoline ring and the carbonyl (CO) group is attached to R^{10}, whereas when X^2 is, for example, a group of formula $CONR^{12}$, it is the carbonyl group which is attached to the quinazoline ring and the nitrogen atom be substituted withing the R^{12} group is attached to R^{10}. A similar convention applies to the other two atoms X^2 linking groups such as $NR^{14}SO_2$ and SO_2NR^{13}. When X^2 is NR^{15} it is the nitrogen atom be substituted withing the R^{15} group which is linked to the quinazoline ring and to R^{10}. An analogous convention applies to other groups. It is further to be understood that when X^2 is NR^{15} and R^{15} is C_{1-3}alkoxyC_{2-3}alkyl it is the C_{2-3}alkyl moiety, which is linked to the nitrogen atom of X^2 and an analogous convention applies to other groups.

For the avoidance of any doubt, it is to be understood that in a compound of the formula **I** when R^{10} is, for example, a group of formula C_{1-5}alkyl$X^{10}C_{1-5}$alkylR^{34}, it is the terminal C_{1-5}alkyl moiety, which is linked to X^2, similarly when R^{10} is, for example, a group of formula C_{2-5}alkenylR^{34} it is the C_{2-5}alkenyl moiety which is linked to X^2 and an analogous convention applies to other groups.

For the avoidance of any doubt, it is to be understood that when R^{34} carries a

C_{1-4}aminoalkyl substituent it is the C_{1-4}alkyl moiety which is attached to R^{34} whereas when R^{34} carries a C_{1-4}alkylamino substituent it is the amino moiety which is attached to R^{34} and an analogous convention applies to other groups.
For the avoidance of any doubt when X^1 is C_{2-4}alkanoyl it is the carbonyl moiety which is linked to the benzen ring of the oxindole group and it is the alkyl moiety which is linked to R^4 and an analogous convention applies to other groups.

Some compounds of formula **I** may have chiral centres and/or geometric isomeric centres (E- and Z- isomers), and it is to be understood that the invention encompasses all such optical, diastereoisomers and geometric isomers that possess GSK3 inhibitory activity.

It is to be understood that the present invention also relates to any and all tautomeric forms of the compounds of formula **I**.

The present invention relates to the use of compounds of formula **I** and to new compounds as hereinbefore defined as well as to the salts thereof. Salts for use in pharmaceutical compositions will be pharmaceutically acceptable salts, but other salts may be useful in the production of the compounds of formula **I** and their pharmaceutically acceptable salts. Both organic and inorganic acids can be employed to form non-toxic pharmaceutically acceptable acid addition salts of the compounds of this invention. In addition, a suitable pharmaceutically acceptable salt of the compounds of the invention is an alkali metal salt, an alkaline earth metal salt or a salt with an organic base.

The present invention further relates to intermediates used for the preparation of compounds of formula **I**.
The intermediates are
2-Hydroxy-3-[7-(2-methoxyethoxy)quinazolin-4-yl]-1*H*-indole-5-carboxylic acid,
Methyl 2-Hydroxy-3-[7-(2-methoxyethoxy)quinazolin-4-yl]-1*H*-indole-5-carboxylate,
7-(2-Morpholin-4-yl)ethoxy)-3*H*-quinazolin-4-one,
4-Chloro-7-[(2-morpholin-4-yl)ethoxy]quinazoline,
7-[2-(2-Methoxyethoxy)ethoxy]-3*H*-quinazolin-4-one,
4-Chloro-7-[2-(2-methoxyethoxy)ethoxy]quinazoline,

4-(Methylthio)-7-[2-(2-morpholin-4-ylethoxy)ethoxy]quinazoline,
7-[2-(4-Acetylpiperazin-1-yl)ethoxy]-4-methylthioquinazoline,
7-(2-Bromoethoxy)-4-(methylthio)quinazoline,
7-[2-(4-Butyrylpiperazin-1-yl)ethoxy]-4-(methylthio)quinazoline,
7-[2-(4-Acetylpiperazin-1-yl)-2-oxoethoxy]-4-(methylthio)quinazoline,
1-Acetyl-4-(4-chlorobutanoyl)piperazine,
7-[4-(4-Acetylpiperazin-1-yl)-4-oxobutoxy]-4-(methylthio)quinazoline,
2-Oxo-2,3-dihydro-1*H*-indole-5-carboxylic acid dimethylamide,
2-Oxo-2,3-dihydro-1*H*-indole-5-carboxylic acid methylamide,
7-[3-(4-Methylpiperazin-1-yl)propoxy]-3*H*-quinazolin-4-one,
4-Chloro-7-[3-(4-methylpiperazin-1-yl)propoxy]quinazoline,
4-Chloro-8-(2-morpholin-4-ylethoxy)quinazoline,
6-Bromo-5-(2-chloroacetyl)1,3-dihydroindol-2-one,
6-Bromo-2-oxo-2,3-dihydro-1*H*-indole-5-carboxylic acid,
6-Bromo-2-oxo-2,3-dihydro-1*H*-indole-5-carboxylic acid methylamide,
2-(4-Ethylphenyl)-*N*-methoxyacetamide,
6-Ethyl-1-methoxy-1,3-dihydroindol-2-one,
6-Ethyl-1,3-dihydroindol-2-one,
N-Methoxy-2-(4-propylphenyl)acetamide,
1-Methoxy-6-propyl-1,3-dihydroindol-2-one,
6-Propyl-1,3-dihydroindol-2-one,
5-Bromo-6-methyl-1,3-dihydroindol-2-one,
6-Bromo-5-nitro-1,3-dihydroindol-2-one,
7-(3-Dimethylaminopropoxy)-3*H*-quinazolin-4-one,
7-(2-Dimethylaminoethoxy)-3*H*-quinazolin-4-one,
7-[2-(Isopropylmethylamino)ethoxy]-3*H*-quinazolin-4-one,
7-(2-Diisopropylaminoethoxy)-3*H*-quinazolin-4-one,
[3-(4-Chloroquinazolin-7-yloxy)propyl]dimethylamine,
[2-(4-Chloroquinazolin-7-yloxy)ethyl]dimethylamine,
[2-(4-Chloroquinazolin-7-yloxy)ethyl]isopropylmethylamine and
[2-(4-Chloro-quinazolin-7-yloxy)ethyl]diisopropylamine.

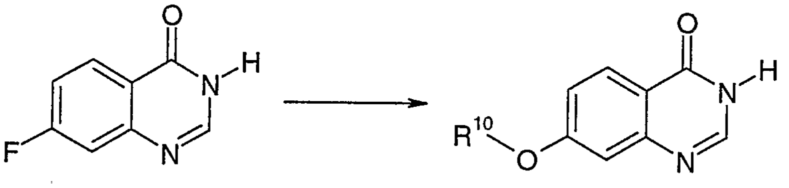
Methods of Preparation

Compounds of formula **I**, or salt thereof, may be prepared by any process known to be applicable to the preparation of chemically-related compounds. Such processes include, for example, those illustrated in European Patent Applications Publication Nos. 0520722, 0566226, 0602851, 0635498 and 0636608 and PCT application WO 97/42187.

The present invention also relates to processes for preparing the compounds of formula **I**. Throughout the following description of such processes it is understood that, where appropriate, suitable protecting groups will be added to, and subsequently removed from, the various reactants and intermediates in a manner that will be readily understood by one skilled in the art of organic synthesis. Conventional procedures for using such protecting groups as well as examples of suitable protecting groups are described, for example, in "Protective Groups in Organic Synthesis" T.W. Greene, P.G.M. Wuts, Wiley-Interscience, New York, 1999.

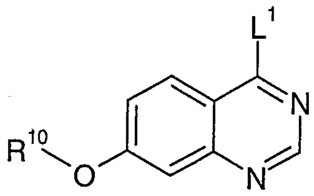
The terms "room" and "ambient" temperature refer to a temperature between 16°C and 25°C.

Methods of Preparation of Intermediates



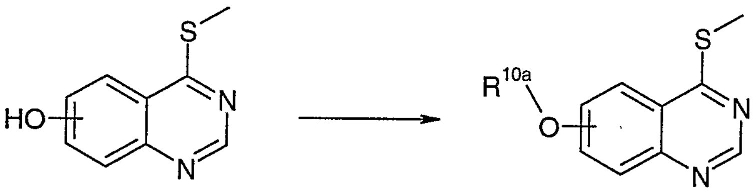
(II) **(III)**

(i) Conversion of a compound of formula **II** to a compound of formula **III**, wherein R^{10} is as defined in formula **I**, may be carried with a suitable reagent R^{10}-OH in a suitable solvent such as dimethylsulphoxide, dioxane or *N,N*-dimethylformamide in the presence of a suitable base such as an alkali metal or alkaline earth metal carbonate or hydroxide such as sodium carbonate, potassium carbonate, calcium carbonate, sodium hydroxide or potassium hydroxide or an alkali metal hydride such as sodium hydride, or an alkali metal or alkaline earth metal amide such as sodium amide, sodium bis(trimethylsilyl)amide, potassium amide or potassium bis(trimethylsilyl)amide and the reaction may occur at a temperature between 0 °C and +150 °C.



(IV)

(ii) Conversion of a compound of formula **III** to a compound of formula **IV**, wherein L^1 is a suitable leaving group such as a halogeno e.g. chlorine or bromine, may be carried with a suitable halogenation reagent such as thionyl chloride, oxalyl chloride, phosphorus oxychloride, phosphoric trichloride or aluminum tribromide in a suitable solvent such as methylene chloride, chloroform, toluene or using the halogenation reagent neat and the reaction may occur at a temperature between +20 °C and +130 °C.

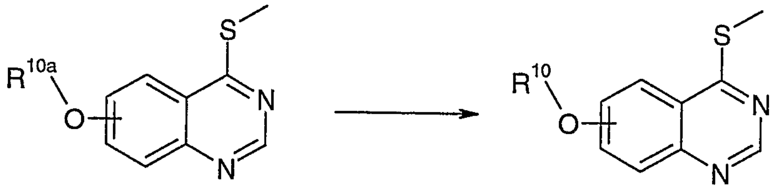


(V) (VI)

(iii) Conversion of a compound of formula **V** to a compound of formula **VI**, wherein R^{10a} is C_2-C_5alkyl-L^2, wherein L^2 is a suitable leaving group such as a halogeno e.g. chlorine or bromine, or R^{10a} is R^{10} wherein R^{10} is as defined in formula **I**, may be carried out with a suitable reagent such as

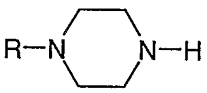
a) an alkylating reagent of the formula **IX** or a reagent L^2-C_2-C_5alkyl-L^3, wherein L^2 and L^3 may be the same or different, e.g. halogeno e.g. chlorine or bromine, in a suitable solvent such as *N,N*-dimethylformamide, methylene chloride or acetonitrile in the presence of a suitable base such as an alkali metal or alkaline earth metal carbonate or hydroxide such as sodium carbonate, potassium carbonate, calcium carbonate, sodium hydroxide or potassium hydroxide or an alkyl amine base such as triethyl amine and the reaction may occur between +20 °C and +150 °C, or

b) R^{10}-OH in a suitable solvent such as methylene chloride, chloroform, diethyl ether or tetrahydrofuran in the presence of a suitable coupling reagent such as diisopropyl azocarbodiimide or diethyl azocarbodiimide and triphenylphosphine and the reaction may occur at a temperature between +10 and +150 °C.



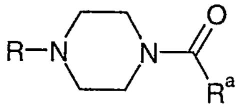
(VI) **(VII)**

(iv) Conversion of a compound of formula **VI**, wherein R^{10a} is C_2-C_5alkyl-L^2, wherein L^2 is a suitable leaving group such as a halogeno e.g. chlorine or bromine, to a compound of formula **VII**, wherein R^{10} is as defined in formula **I**, may be carried out by



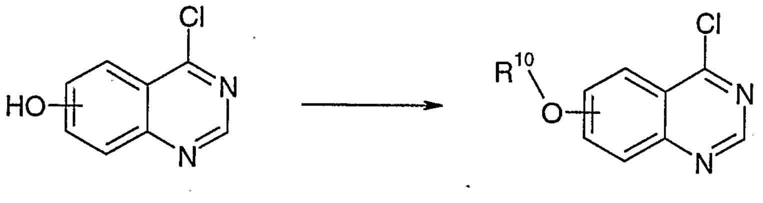
(VIII)

alkylation of a compound of formula **VIII**, wherein R is an alkanoyl group, in a suitable solvent such as *N,N*-dimethylformamide, methylene chloride or acetonitrile or using a compound of formula **VIII** neat and the reaction may occur at a temperature between +20 and +150 °C.



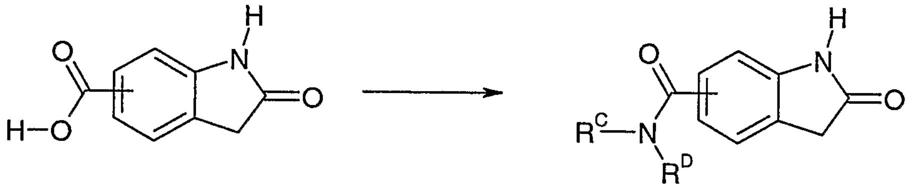
(IX)

(v) Conversion of a compound of formula **VIII**, wherein R is an alkanoyl group, to a compound of formula **IX**, wherein R^a is C_1-C_5alkylL^3 and L^3 is as defined above may be carried out by reaction with a reagent $L^2(CO)C_1$-C_5alkylL^3, wherein L^2 and L^3 may be the same or different and are defined as above, in a suitable solvent such as methylene chloride, chloroform or acetonitrile in the presence of a suitable base such as an alkali metal or alkaline earth metal carbonate or hydroxide such as sodium carbonate, potassium carbonate, calcium carbonate, sodium hydroxide or potassium hydroxide or an alkyl amine base such as triethyl amine and the reaction may occur at a temperature between -70 °C and +80 °C.



(X) (XI)

(vi) Conversion of a compound of formula **X** to a compound of formula **XI**, wherein R^{10} is as defined in formula **I**, may be carried out with a suitable reagent such as R^{10}-OH in as suitable solvent such as methylene chloride, chloroform, diethyl ether or tetrahydrofuran in the presence of a suitable coupling reagent such as diisopropyl azocarbodiimide or diethyl azocarbodiimide and triphenylphosphine and the reaction may occur at a temperature between +10 and +150 °C.

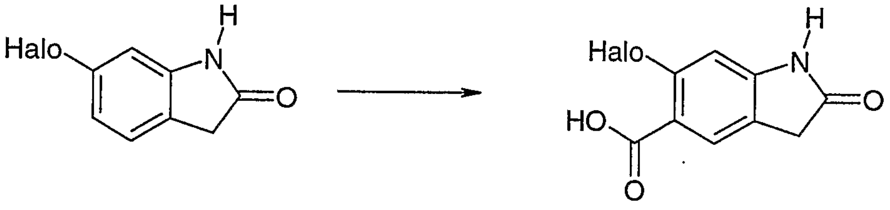


(XII) (XIII)

(vii) Conversion of a compound of formula **XII** to a compound of formula **XIII**, wherein R^C and R^D is hydrogen or $C_{1\text{-}4}$alkyl, may be carried out by activation of the acid function in a compound of formula **XII**

a) with a halogenation reagent such as thionyl chloride or oxalyl chlorid in a suitable solvent such as methylene chloride or toluene or using the reagent neat folllowed by a reaction with the appropriate substituted amine R^CR^DNH in a suitable solvent such as methylene chloride, chloroform or acetonitrile in the presence of a suitable base such as an alkali metal or alkaline earth metal carbonate or hydroxide such as sodium carbonate, potassium carbonate, calcium carbonate, sodium hydroxide or potassium hydroxide or an alkyl amine base such as triethyl amine and the reaction may occur at a temperature between -70 °C and +80 °C, or

b) with a suitable coupling reagent such as 1,1'-carbonyldiimidazole or 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide in a suitable solvent such as *N,N*-dimethylformamide or tetrahydrofuran followed by addition and reaction with the appropriate substituted amine R^CR^DNH and at a reaction temperature between +20 °C and +130 °C.

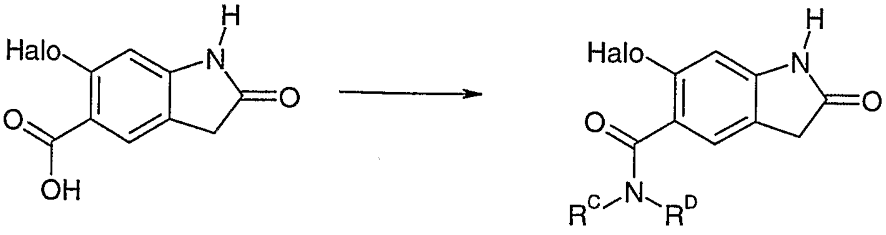


(XIV) (XV)

(viii) Conversion of a compound of formula **XIV** to a compound of formula **XV**, wherein halo is halogeno and is as defined in formula **I**, may be carried out by

a) a Friedel-Craft acylation using acylating reagent such as chloroacetyl chloride and aluminum trichloride in a suitable solvent such as methylene chloride, chloroform or nitrobenzene and at a reaction temperature between ±0 °C and 60 °C, followed by,

b) reaction of the formed chloroketone with pyridine followed by hydrolysis in a suitable solvent such as water or a mixture of water and an alcohol such as ethanol or methanol in the presence of a suitable base such as sodium hydroxide or potassium hydroxide and at a reaction temperature between +20 °C and reflux resulting in a compound of formula **XV**.



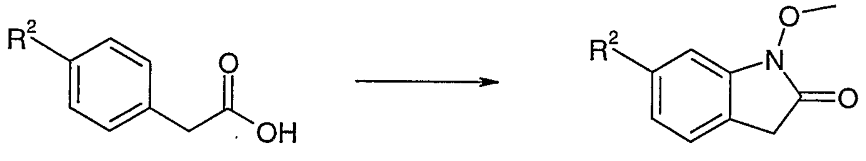
(XV) (XVI)

(ix) Conversion of a compound of formula **XV** to a compound of formula **XVI**, wherein R^C and R^D are as defined hereinbefore,

may be carried out by activation of the acid function in a compound of formula **XV**,

a) with a halogenation reagent such as thionyl chloride or oxalyl chlorid in a suitable solvent such as methylene chloride or toluene or using the reagent neat followed by reaction with the appropriate substituted amine R^CR^DNH in a suitable solvent such as methylene chloride, chloroform or acetonitrile in the presence of a suitable base such as an alkali metal or alkaline earth metal carbonate or hydroxide such as sodium carbonate, potassium carbonate, calcium carbonate, sodium hydroxide or potassium hydroxide or an alkyl amine base such as triethyl amine and the reaction may occur at a temperature between -70 °C and +80 °C, or

b) with a suitable coupling reagent such as 1,1'-carbonyldiimidazole or 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide in a suitable solvent such as *N,N*-dimethylformamide or tetrahydrofuran followed by addition and reaction with the appropriate substituted amine R^CR^DNH and at a reaction temperature between +20 °C and +130 °C.



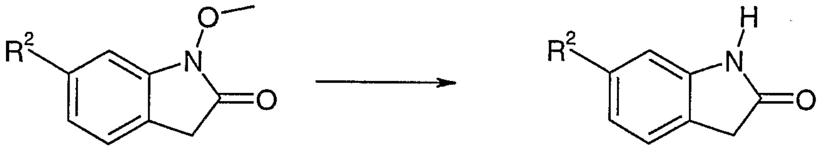
(XVII) **(XVIII)**

(x) Conversion of a compound of formula **XVII** to a compound of formula **XVIII**, wherein R^2 is C_{1-3}alkyl, may be carried out by

a) activation of the acid function in a compound of formula **XVII** with a halogenation reagent such as thionyl chloride or oxalyl chlorid in a suitable solvent such as methylene chloride or toluene or using the reagent neat and at a reaction temperature between +20 °C and reflux, followed by,

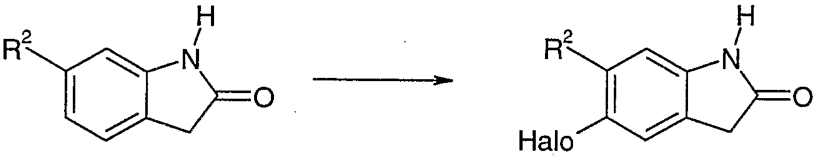
b) conversion of the acid chloride to the corresponding *N*-methoxycarboxamide by a reaction with methoxyamine hydrochloride in an appropriate solvent such as methylene chloride, chloroform or toluene or solvent mixtures with water such as toluene and water in the presence of a suitable base such as an alkali metal or alkaline earth metal carbonate or hydroxide such as sodium carbonate, potassium carbonate, calcium carbonate, sodium hydroxide or potassium hydroxide or an alkyl amine base such as triethyl amine and the reaction may occur between +20 °C and +120 °C, followed by,

c) cyclization, to form the compound of formula **XVIII**, wherein R^2 is C_{1-3}alkyl, in a suitable solvent such as methylene chloride or chloroform using a suitable reagent such as *tert*-butyl hypochlorite and at a reaction temperature between ±0 °C and reflux.



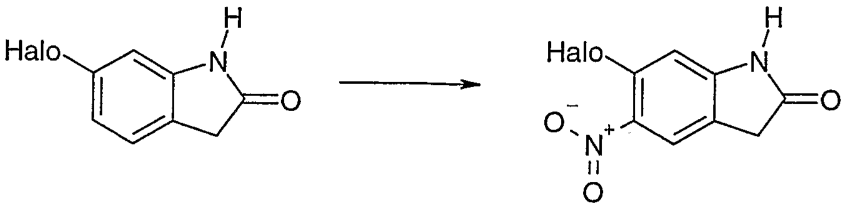
(XVIII) **(XIX)**

(xi) Conversion of a compound of formula **XVIII** to a compound of formula **XIX**, wherein R^2 is C_{1-3}alkyl, may be carried out by hydrogenation using a catalyst containing palladium, platinum, rhodium or nickel in a suitable solvent such as acetic acid or an alcohol e.g. ethanol or methanol at atmospheric or elevated pressure and at a reaction temperature between +20 °C and +120 °C.



(XIX) **(XX)**

(xii) Halogenation of the compound of formula **XIX**, wherein R_2 is C_1-$_3$alkyl and halo is halogeno as defined hereinbefore, to obtain a compound of formula **XX** may be performed by aromatic electrophilic substitution using a suitable halogenation agent such as Br_2, Cl_2, I_2, ICl, or SO_2Cl_2 or another suitable halogenation agent such as *N*-bromosuccinimid in an appropriate solvent e.g. acetonitrile, acetic acid, HCl/ethanol or water with or without a suitable base e.g. alkali metal acetate such as sodium acetate and at a reaction temperature between -20 °C and room temperature.



(XIV) **(XXI)**

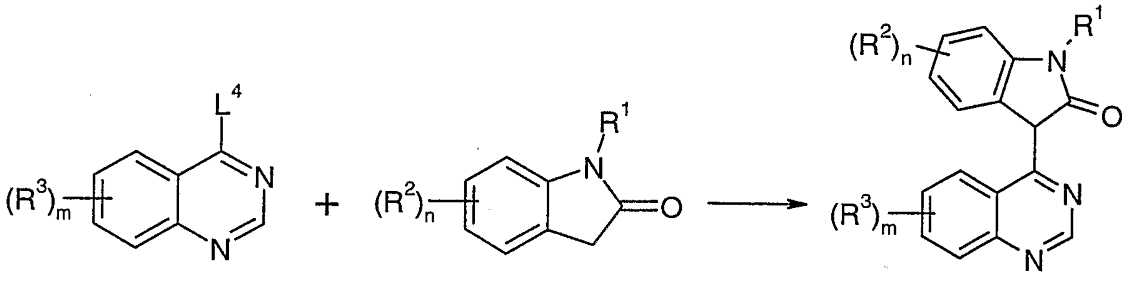
(xiii) Nitration of a compound of formula **XIV** wherein halo is halogeno, as defined hereinbefore, to obtain a compound of formula **XXI**, may be carried out by aromatic electrophilic substitution using a suitable nitration reagent such as potassium nitrate, nitric acid and sulphuric acid in a suitable solvent such as acetic acid, acetic anhydride, sulphuric acid or water at a reaction temperature between -20 °C and room temperature.

Methods of Preparation of End products

Another object of the invention is a process for the preparation of a compound of general formula **I**, as a free base or a pharmaceutically acceptable salt thereof, by

i)

Reacting a compound of formula **B (IV, VI, VII, XI)**, wherein L^4 is a leaving group L^1 or SCH_3, with a compound of formula **C**, to obtain a compound of formula **I**, and R^1, R^2, R^3, m and n are as defined in general formula **I**



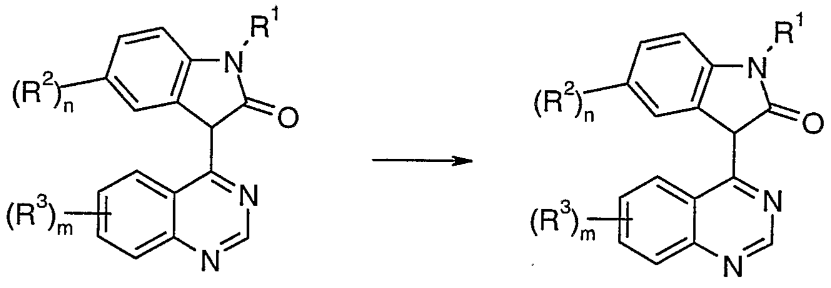
(B (IV, VI, VII, XI)) (C) (I)

Thus, the reaction of the process may be carried out in an appropriate solvent such as an ether e.g. tetrahydrofuran or 1,4-dioxan, an aromatic hydrocarbon solvent such as toluene, or a dipolar aprotic solvent such as *N,N*-dimethylformamide, *N,N*-dimethylacetamide, *N*-methylpyrrolidin-2-one or dimethyl sulphoxide and the reaction is conveniently effected at a temperature in the range of +10 to +150 °C, preferably in the range of +20 to +90 °C. The reaction is advantageously effected in the presence of a base. Such a base may be an organic amine base such as pyridine, 2,6-lutidine, collidine, 4-dimethylaminopyridine,

triethylamine, morpholine, *N*-methylmorpholine or diazabicyclo[5.4.0]undec-7-ene, tetramethylguanidine, an alkali metal or alkaline earth metal carbonate or hydroxide such as sodium carbonate, potassium carbonate, calcium carbonate, sodium hydroxide or potassium hydroxide. Alternatively, such a base is an alkali metal hydride such as sodium hydride, or an alkali metal or alkaline earth metal amide such as sodium amide, sodium bis(trimethylsilyl)amide, potassium amide or potassium bis(trimethylsilyl)amide.
When it is desired to obtain the acid salt, the free base may be treated with an acid, using a conventional procedure.

ii)

Hydrolysis of a compound of formula **Ia**, wherein R^2 is $C_{1\text{-}4}$alkoxycarbonyl to obtain a compound of formula **Ib**, wherein R^2 is carboxy and R^1, R^3, m and n are as defined in general formula **I.**

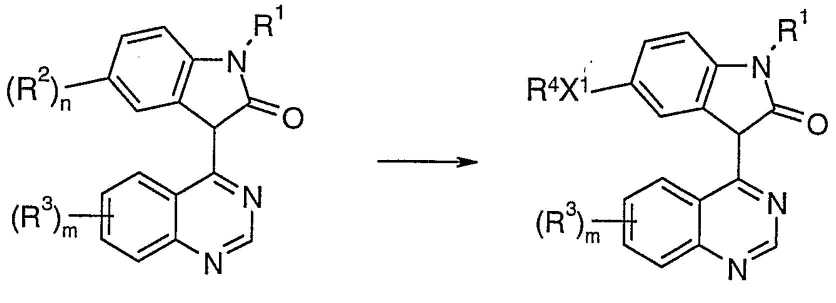


(Ia) **(Ib)**

This reaction may be carried out under acidic conditions using acids such as sulfuric acid, hydrochloride or hydrobromide in a suitable solvent e.g. water, ethanol, methanol or mixtures thereof and the reaction may occur between +20 °C and +100 °C or under basic conditions using bases such as sodium hydroxide or potassium hydroxide in a suitable solvent e.g. water, ethanol, methanol or mixtures thereof and the reaction may occur between +20 °C and +100 °C.

iii)

Amidation of a compound of formula **Ib,** wherein R^2 is carboxy to obtain a compound of formula **Ic**, wherein R^2 is R^4X^1 and X^1 is $CONR^5R^6$ and R^1, R^3, R^4, R^5, R^6, m and n are as defined in general formula **I**



(Ib) **(Ic)**

This reaction may be performed by activation of a compound of formula **Ib**, wherein R^2 is carboxy, by treating the compound with coupling reagents e.g. 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride and 1-hydroxybenzotriazole hydrate or hydroxybenzimidazole, 1,3-dicyclohexylcarbodiimide and 1-hydroxybenzotriazole hydrate, 1,1'-carbonyldiimidazole or *O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate, or using an acyl halide reagent e.g. cyanuric chloride, oxalyl chloride, thionyl chloride or bromotrispyrrolidinophosphonium hexafluorophosphate, followed by treatment with the appropriate amine with or without the presence of *N,N*-dimethylaminopyridine, in a suitable solvent such as *N,N*-dimethylformamide, tetrahydrofuran, *N*-methylpyrrolidone, methylene chloride or chloroform at a reaction temperature between 0 °C and +80 °C.

Examples

The invention will now be illustrated by the following non-limiting Examples.

Example 1

7-(2-Morpholin-4-yl)ethoxy)-3*H*-quinazolin-4-one

A mixture of sodium hydride (12.7 g, 0.317 mol, 60% oil dispersion) and dimethyl sulfoxide (60 mL, 0.84 mol) was heated at 75 °C. After 30 min the hydrogen gas evolution had ceased and the reaction was cooled to room temperature.

4-(2-Hydroxyethyl)morpholine (48 mL, 0.40 mol) was added portionwise to the reaction mixture. After stirring for 30 min, 7-fluoro-3*H*-quinazolin-4-one (13.0 g, 79.2 mmol; described in Rewcastle G. et al *J. Med. Chem*, 1996, *39*, 4, 918-928) was added and the reaction solution was heated for 3 h at 150 °C. The reaction mixture was cooled to room temperature and the resulting syrup was dissolved in ethyl acetate (500 mL) and triturated with diethyl ether (2 L). The solid was filtered off under a nitrogen atmosphere and washed several times with diethyl ether to obtain the crude product as a powder. The crude product was purified by flash chromatography (500 g silica gel column topped with a layer of celite) using methanol/methylene chloride systems (methanol/methylene chloride: 7:93 (4 L); 10:90 (2 L); 15:85 (2 L); 25:75 (4 L)) as stepwise gradient eluents. The fraction containing the product was concentrated to dryness, triturated with acetone and filtered to give 21.8 g (65% yield) of the title compound as an off-white solid: MS (AP+) *m/z* 276.0 (M^++1).

Example 2

4-Chloro-7-[(2-morpholin-4-yl)ethoxy]quinazoline

Oxalyl chloride (4.55 mL, 52 mmol) was added dropwise to a suspension of 7-(2-morpholin-4-yl)ethoxy)-3*H*-quinazolin-4-one (11.9 g, 43.3 mmol) in methylene chloride (175 mL) followed by dropwise addition of *N*,*N*-dimethylformamide (1.5 mL). The reaction mixture was heated for 2 h at reflux. The solvent was removed *in vacuo* and the resulting solid was triturated with diethyl ether. The pale yellow solid was filtered off under nitrogen atmosphere to give 17.2 g (99% yield) of the title compound as a pale yellow powder: MS (AP+) *m/z* 294.0 (M^++1).

Example 3

2-Hydroxy-3-[7-(2-morpholin-4-ylethoxy)quinazolin-4-yl]-1*H*-indole-5-carbonitril dihydrochloride

Sodium hydride (490 mg, 12.2 mmol, 60% oil dispersion) was washed with petroleum ether (2x10 mL) and dried under vacuum and the obtained material was suspended in anhydrous *N*,*N*-dimethylformamide (5 mL) and 5-cyanooxindole (323 mg, 2.04 mmol) in *N*,*N*-dimethylformamide (3 mL) was added. The resulting suspension was stirred for 30 min at room temperature and 4-chloro-7-[(2-morpholin-4-yl)ethoxy]quinazoline (200 mg, 0.68 mmol) in *N*,*N*-dimethylformamide (5 mL) was added. The reaction mixture was stirred for 1 h at room temperature. The reaction was quenched with aqueous hydrochloric acid (5 mL, 1 M) and *N*,*N*-dimethylformamide was removed *in vacuo*. To the resulting syrup was added water (50 mL) and the mixture were stirred vigorously. The solid formed was filtered off and dried at 70 °C under vacuum over night. The crude product was refluxed in methanol for 15 min and the insoluble material was filtered off and dried at 85 °C under vacuum over night to give 225 mg (68% yield) of the title compound as an orange powder: MS (AP-) *m/z* 413.9 (M-1); Anal. ($C_{23}H_{21}N_5O_3$x2HClx0.1H_2O) C, H, N.

Example 4

Methyl 2-Hydroxy-3-[7-(2-methoxyethoxy)quinazolin-4-yl]-1*H*-indole-5-carboxylate

Sodium hydride (58 mg, 1.45 mmol, 60% in oil) was washed with petroleum ether (3x5 mL) and dried *in vacuo*. The solid was suspended in tetrahydrofuran (3 mL) and methyl 2-oxo-5-indolinecarboxylate (140 mg, 0.73 mmol) in tetrahydrofuran (2 mL) and *N*-methylpyrrolidinone (2 mL) was added. The reaction mixture was stirred for 30 min at room temperature. A solution of 4-chloro-7-(2-methoxyethoxy)quinazoline (183 mg, 0.77 mmol, described in WO 97/42187) in tetrahydrofuran (2 mL) and *N*-methylpyrrolidinone (1 mL) was added and the reaction mixture was stirred for 1.5 h at room temperature. The solvent was removed *in vacuo* and 1 M hydrochloric acid was added. The precipitate formed was filtered off and dried at 40 °C *in vacuo* over night to give 150 mg (99% yield) of the title compound as an orange solid: MS (AP+) *m/z* 394.2 (M^++1).

Example 5

2-Hydroxy-3-[7-(2-methoxyethoxy)quinazolin-4-yl]-1*H*-indole-5-carboxylic Acid

To a mixture of methyl 2-hydroxy-3-[7-(2-methoxyethoxy)quinazolin-4-yl]-1*H*-indole-5-carboxylate (5.15 g, 13.1 mmol), methanol (100 mL) and water (50 mL) was added aqueous sodium hydroxide (92 mL, 1 M) and the reaction mixture was stirred at 40°C over night. Methanol was removed *in vacuo* and the basic aqueous layer was acidified with 1 M hydrochloric acid and stirred for 30 min. The precipitate formed was filtered off, washed with hydrochloric acid (50 mL, 1 M) and water (2x50 mL) and dried *in vacuo* at 50 °C over night. The crude product was stirred in methanol at room temperature over night. The solid was filtered off to give 4.23 g (85% yield) of the title compound as an orange solid: MS (AP+) *m/z* 380.3 (M^++1).

Examples 6-11

General Method A

Stock solution A was prepared by dissolving 2-hydroxy-3-[7-(2-methoxyethoxy)-quinazolin-4-yl]-1*H*-indole-5-carboxylic acid (2.0 g), (3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (2.2 g) and hydroxybenzimidazole (1.54 g) in *N*-methylpyrrolidinone (160 mL). Stock solution B was prepared by dissolving *N,N*-dimethylaminopyridine (2.8 g) in *N*-methylpyrrolidinone (40 mL).

The amidation reaction was performed by adding solution A (8 mL, corresponding to 2-hydroxy-3-[7-(2-methoxyethoxy)-quinazolin-4-yl]-1*H*-indole-5-carboxylic acid: 100 mg, 0.26 mmol, 1eq; (3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride: 110 mg, 0.51 mmol, 2.2 eq; hydroxybenzimidazole: 77 mg, 0.57 mmol, 2.2 eq) to a reaction vessel containing the desired amine (0.4 mmol, 1.5 eq). Solution B (2 mL, corresponing to *N,N*-dimethylaminopyridine: 140 mg, 1.14 mmol, 4.4 eq) was added and the resulting solution was stirred at room temperature over night. The solvent was removed *in vacuo* to give the crude product.

Example 6

2-Hydroxy-3-[7-(2-methoxyethoxy)quinazolin-4-yl]-1*H*-indole-5-carboxylic Acid [2-(1-Methylpyrrolidin-2-yl)ethyl]amide

The reaction was performed as described in method A using 2-(2-aminoethyl)-1-methylpyrrolidine (0.06 mL, 0.40 mmol). The crude product was triturated with acetonitrile. The solid was decanted and washed with methanol/diethyl ether to give 36 mg (28% yield) of the title compound: MS (AP+) *m/z* 490.4 (M^++1).

Example 7

2-Hydroxy-3-[7-(2-methoxyethoxy)quinazolin-4-yl]-1*H*-indole-5-carboxylic Acid (Tetrahydrofuran-2-ylmethyl)amide

The reaction was performed as described in method A using tetrahydro-2-furanylmethylamine (0.06 mL, 0.395 mmol). The crude product was triturated with acetone and the solid was washed with hot methanol to give 19 mg (16 % yield) of the title compound: MS (AP+) *m/z* 537.3 (M^++1).

Example 8

2-Hydroxy-3-[7-(2-methoxyethoxy)quinazolin-4-yl]-1*H*-indole-5-carboxylic Acid (3-Morpholin-4-yl-propyl)amide

The reaction was performed as described in method A using 3-(morpholin-4-yl)propanamine (0.06 mL, 0.395 mmol). The crude product was triturated with acetonitrile and the solid was washed with hot methanol to give 15 mg (12% yield) of the title compound: MS (AP+) *m/z* 506.3 (M^++1).

Example 9

2-Hydroxy-3-[7-(2-methoxyethoxy)quinazolin-4-yl]-1*H*-indole-5-carboxylic Acid (4-Phenylbutyl)amide

The reaction was performed as described in method A using 4-phenylbutylamine (0.06 mL, 0.395 mmol). The crude product was triturated with acetone and the solid was washed with hot methanol to give 38 mg (29% yield) of the title compound: MS (AP+) *m/z* 511.3 (M^++1).

Example 10

2-Hydroxy-3-[7-(2-methoxyethoxy)quinazolin-4-yl]-1*H*-indole-5-carboxylic Acid [2-(1*H*-Imidazol-4-yl)ethyl]amide

The reaction was performed as described in method A using 2-(1*H*-imidazol-4-yl)ethylamine dihydrochloride (73 mg, 0.395 mmol). The crude product was triturated with acetonitril. The solid decanted and triturated with acetonitrile/methanol/diethyl ether and washed with hot methanol to give 26 mg (21% yield) of the title compound: MS (AP+) *m/z* 473.3 (M^++1).

Example 11

7-[2-(2-Methoxyethoxy)ethoxy]-3*H*-quinazolin-4-one

Dimethyl sulfoxide (6.9 mL, 97 mmol) was added to sodium hydride (1.46 g, 36.6 mmol) and the formed foamy suspension was heated at 75 °C for 30 min until the gas evolution had ceased. The formed green cloudy solution was cooled to room temperature and

2-(2-methoxyethoxy)ethanol (5.44 mL, 45.7 mmol) was added slowly and the mixture was stirred for 30 min. 7-Fluoro-3*H*-quinazolin-4-one (1.5 g, 9.14 mmol; described in Rewcastle G. et al *J. Med. Chem*, 1996, *39*, 4, 918-928) was added and heated at 150 °C for 4 h. The reaction mixture was cooled and diluted with ethyl acetate (60 mL) followed by the addition of diethyl ether (200 mL). The formed precipitate was filtered under nitrogen atmosphere and washed with diethyl ether. The hygroscopic crude product was purified on a silica gel column using chloroform/methanol (20:1), as the eluent to give 1.2 gram (50% yield) of the title compound as a slightly coloured solid: MS (TSP) *m/z* 265 (M^++1).

Example 12

4-Chloro-7-[2-(2-methoxyethoxy)ethoxy]quinazoline

To a solution of 7-[2-(2-methoxyethoxy)ethoxy]-3*H*-quinazolin-4-one (0.86 g, 3.25 mmol) in methylene chloride (15 mL) was added oxalyl chloride (0.34 mL, 3.9 mmol) and dimethyl sulfoxide (0.1 mL) and the reaction was heated at reflux for 2 h. The solvent was evaporated *in vacuo* and the residue was washed with diethyl ether and dried *in vacuo* to give 0.9 gram of the title compound as a semi-solid: MS (TSP) *m/s* 283 (M^++1).

Example 13

2-Hydroxy-3-{7-[2-(2-methoxyethoxy)ethoxy]quinazolin-4-yl}-1*H*-indole-5-carbonitrile hydrochloride

To a suspension of sodium hydride (0.52 g, 12.8 mmol, pre-washed with hexane) in tetrahydrofuran (6 mL) was added a solution of 5-cyanooxindole (1 g, 6.4 mmol) in tetrahydrofuran (11 mL) and 1-methyl-2-pyrrolidone (11 mL). The mixture was stirred for 30 min under nitrogen atmosphere. 4-Chloro-7-[2-(2-methoxyethoxy)ethoxy]quinazoline (0.9 g, 3.2 mmol) dissolved in 1-methyl-2-pyrrolidone (10 mL) was added dropwise and the dark red solution was stirred at ambient temperature for 1.5 h. The solvent was evaporated *in vacuo* until approximately 10 mL of 1-methyl-2-pyrrolidone remained, whereupon aqueous hydrochloric acid (1 M, 25 mL) was added. The formed precipitation was filtered and washed with 1 M hydrochloric acid. Drying *in vacuo* afforded 1.1 gram (78% yield) of the title compound as an orange solid: MS (TSP) *m/s* 405 (M^++1)

Example 14

3-[7-(2-Imidazol-1-yl-ethoxy)-6-methoxyquinazolin-4-yl]-2-oxo-2,3-dihydro-1*H*-indole-5-sulfonamide acetate

Sodium hydride (59 mg, 1.48 mmol, pre-washed with pentane) was added to a suspension of 2-oxo-2,3-dihydro-1*H*-indole-5-sulfonamide (313 mg, 1.48 mmol; described in WO 9742187) in *N,N*-dimethylformamide (2.5 mL). After stirring 30 min at ambient temperature, 4-chloro-7-(2-(imidazol-1-yl)ethoxy)-6-methoxyquinazoline (150 mg, 0.49 mmol; described in WO 97/42187) was added followed by dimethyl sulfoxide (0.5 mL). After stirring for 10 min at ambient temperature, the mixture was stirred at 60 °C for 2 h. The mixture was poured onto diethyl ether/water (1:1, 100 mL). The organic layer was separated and the aqueous layer was adjusted to pH 6.3 (5 M $HCl_{(aq)}$). The precipitate was filtered, washed with water, followed by diethyl ether, methylene chloride and dried *in vacuo*. The solid was dissolved in water adjusted to pH 1.5 (5 M $HCl_{(aq)}$) and the solution was purified by preparative C18 HPLC eluting with methanol/water (1:9, containing 1% acetic acid) followed by 15:85 followed by 4:6. The fractions containing the expected product were combined, concentrated and the product was freeze-dried and dried *in vacuo* at 60 °C for 48 h to give 133 mg (54% yield) of the title compound: EIMS *m/z* 480 (M^+).

Example 15

6-Chloro-3-[7-(3-morpholin-4-yl-propoxy)quinazolin-4-yl]-1,3-dihydro-indol-2-one hydrochloride

6-Chlorooxindole (383 mg, 2.28 mmol) was added to a suspension of sodium hydride (92 mg, 2.28 mmol) in *N,N*-dimethylformamide (3 mL). After stirring for 20 min at ambient temperature, 4-chloro-7-(3-(morpholin-4-yl)propoxy)quinazoline (233 mg, 0.76 mmol; described in WO 97/42187) in *N,N*-dimethylformamide (3 mL) was added. The mixture was stirred at 70 °C for 45 min. After cooling, the volatiles were removed *in vacuo* and the residue was partitioned between ethyl acetate and water. The pH of the aqueous layer was adjusted to 8.4 with 2 M HCl. The organic layer was separated and washed with brine, dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography eluting with methanol/methylene chloride, 5:95, followed by 10:90. The fractions containing the expected product were combined and evaporated. The residue was dissolved in methylene chloride (10 mL) and methanol (3 mL) and HCl in diethyl ether (3.8 M, 0.5 mL) was added. The precipitate was filtered, washed with diethyl ether and dried *in vacuo* to give 141 mg (34% yield) of the title compound: ESI-MS 439 (M^++1).

Example 16

6-Bromo-3-[6-methoxy-7-(3-morpholin-4-ylpropoxy)quinazolin-4-yl]-1,3-dihydro-indol-2-one dihydrochloride

Sodium hydride (71 mg, 1.78 mmol, 60% in oil) was added to a solution of 6-bromooxindole (126 mg, 0.59 mmol) in *N*,*N*-dimethylformamide (3mL). After stirring for 15 min at ambient temperature, 4-chloro-6-methoxy-7-(3-(morpholin-4-yl)propoxy)quinazoline (200 mg, 0.59 mmol; described in WO 97/42187) in *N*,*N*-dimethylformamide (4 mL) and tetrahydrofuran (4 mL) was added. After stirring at 60 °C for 2.5 h, water was added and the volatiles were removed *in vacuo*. Water (50 mL) was added and the pH of the solution was adjusted to 8.5 with aqueous hydrochloric acid (2 M). Ethyl acetate was added. The organic layer was separated, washed with brine, dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography eluting with methanol/ methylene chloride, 5:95, followed by 8:92. The fractions containing the expected product were combined and evaporated. The solid was dissolved in methylene chloride (10 mL) and methanol (3 mL) and 3.8 M HCl in diethyl ether (1 mL) was added. The solution was concentrated and the solid was filtered to give 70 mg (23% yield) of the title compound: ESI-MS: 513-515 (M^++1).

Example 17

6-Bromo-3-quinazolin-4-yl-1,3-dihydroindol-2-one hydrochloride

To a suspension of sodium hydride (117 mg, 2.9 mmol, pre-washed with pentane) in *N*,*N*-dimethylformamide (1.5 mL was added a solution of 6-bromooxindole (618 mg, 2.9 mmol) in *N*,*N*-dimethylformamide (4 mL). After stirring 15 min at ambient temperature, 4-chloroquinazoline (618 mg, 2.9 mmol) in *N*,*N*-dimethylformamide (4 mL) was added and the mixture was stirred at 80 °C for 45 min. After cooling, the volatiles were removed under vacuum and the residue was suspended in water and the pH was adjusted to 7 with aqueous hydrochloric acid (2 M). The precipitate was filtered, washed with water and dried over P_2O_5 over night. The solid was dissolved in methanol/methylene chloride and adsorbed on silica and purified by column chromatography, eluting with methylene chloride/methanol, 99:1, followed by 98:2 and 95:5. The fractions containing the expected product were combined and evaporated. The product was purified a second time on silica eluting with methylene chloride/methanol, 97:3, followed by 95:5. The solid was the suspended in methylene chloride/methanol, 1:1, and HCl in diethyl ether (3.6 M, 1 mL) was added. The precipitate was filtered, washed with diethyl ether and dried *in vacuo* to give 270 mg (74% yield) of the title compound: ESI-MS 340-342 (M^{+}+1)

Example 18

6-Bromo-3-{6-methoxy-7-[2-(2-methoxyethoxy)ethoxy]quinazolin-4-yl}-1,3-dihydroindol-2-one hydrochloride

To a suspension of sodium hydride (48 mg, 1.2 mmol, pre-washed with pentane) in dimethyl sulfoxide (1 mL) was added a solution of 6-bromooxindole (255 mg, 1.2 mmol) in dimethyl sulfoxide (2 mL). After stirring for 15 min, 6-methoxy-7-[2-(2-methoxyethoxy)ethoxy]-4-(methylthio)quinazoline (130 mg, 0.4 mmol; described in WO 97/42187) was added. The mixture was stirred at 100 °C for 3 h. After cooling, the mixture was partitioned between ethyl acetate and water. The pH of the aqueous layer was adjusted to 7 with aqueous hydrochloric acid (2 M). The organic layer was separated, washed with brine, dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography eluting with methylene chloride/methanol, 93:7. The fractions containing the expected product were combined and evaporated. The solid was dissolved in methylene chloride/methanol and HCl in diethyl ether (3.8 M, 2 mL) was added. The solution was concentrated under vacuum and the solid was filtered, washed with diethyl ether and dried *in vacuo* to give 109 mg (52% yield) of the title compound: ESI-MS 488-490 (M^{+}+1).

Example 19

3-{7-[2-(2-Morpholin-4-yl-ethoxy)ethoxy]quinazolin-4-yl}-2-oxo-2,3-dihydro-1*H*-indole-5-carbonitrile hydrochloride

A solution of 5-cyanooxindole (240 mg, 1.5 mmol) was added portion wise to a suspension of sodium hydride (60 mg, 1.5 mmol, pre-washed with pentane) in dimethyl sulfoxide (2 mL). After stirring for 30 min at ambient temperature, 4-(methylthio)-7-[2-(2-morpholin-4-ylethoxy)ethoxy]quinazoline (175 mg, 0.5 mmol) was added. The mixture was stirred at 100 °C for 2 h. After cooling, water was added and the pH was adjusted to 7 with aqueous hydrochloric acid (2.5 M). The precipitate was filtered, washed with water and dried over night *in vacuo* over P_2O_5. The solid was purified by column chromatography eluting with methanol/methylene chloride, 5:95, followed by 10:90. The fractions containing the expected product were combined and evaporated. The solid was dissolved in methanol/methylene chloride, 1:1, and HCl in diethyl ether (3.5 M, 0.5 mL) was added, followed by diethyl ether. The precipitate was filtered, washed with diethyl ether and dried *in vacuo* to give 155 mg (53% yield) of the title compound: ESI-MS 460 (M^++1).

Example 20

4-(Methylthio)-7-[2-(2-morpholin-4-ylethoxy)ethoxy]quinazoline

Diethyl azodicarboxylate (2.46 mL, 15.6 mmol) was added dropwise to a suspension of 4-(methylthio)-7-hydroxyquinazoline (1.2 g, 6.25 mmol; described in WO 99/10349), triphenylphosphine (4.09 g, 15.6 mmol) and 2-(2-morpholin-4 ylethoxy)ethanol (1.42 g, 8.12 mmol; described in *J. Med. Chem*,. 1994, *37, 15*, 2285-2291) in methylene chloride (30 mL). After stirring 1.5 h at ambient temperature, the volatiles were removed *in vacuo*. The residue was dissolved in ethyl acetate/methylene chloride, filtered and poured onto a column of silica. The product was eluted with methylene chloride/methanol, 97:3, followed by 95:5. The fractions containing the expected product were combined and evaporated. The residue was triturated with diethyl ether and the solid was filtered and dried *in vacuo* to give 1.1 g (49% yield) of the title compound: ESI-MS 350 (M^++1).

Example 21

6-Chloro-3-{7-[2-(2-methoxyethoxy)ethoxy]quinazolin-4-yl}-1,3-dihydro-indol-2-one hydrochloride

6-Chlorooxindole (285 mg, 1.7 mmol) was added to a suspension of sodium hydride (102 mg, 2.55 mmol, pre-washed with pentane) in dimethyl sulfoxide (4 mL). After stirring 30 min at ambient temperature, a solution of 7-[2-(2-methoxyethoxy)ethoxy]-4-(methylthio)quinazoline (250 mg, 0.85 mmol; described in WO 99/10349) in dimethyl sulfoxide (2 mL) was added and the mixture was stirred at 90 °C for 1 h. The mixture was poured onto water (20 mL) and aqueous hydrochloric acid (2 M, 5 mL). The precipitate was filtered, washed with water and dried over P_2O_5. The solid was triturated with diethyl ether, filtered, washed with diethyl ether and dried *in vacuo* over night. The solid was dissolved in methylene chloride/methanol and HCl in diethyl ether (3.8 M) was added. The solution was concentrated and the solid was filtered and dried *in vacuo* to give 231 mg (60% yield) of the title compound: ESI-MS 414-416 (M^++1).

Example 22

3-{7-[2-(2-Methoxyethoxy)ethoxy]quinazolin-4-yl}-1,3-dihydroindol-2-one hydrochloride

The compound was prepared as descirbed for Example 29 using 7-[2-(2-methoxyethoxy)ethoxy]-4-(methylthio)quinazoline (257 mg, 1.93 mmol; described in WO 99/10349) and oxindole (190 mg, 0.64 mmol) to give 191 mg (70% yield) of the title compound as the hydrochloride: ESI-MS 380 (M^++1).

Example 23

3-{7-[2-(4-Acetylpiperazin-1-yl)ethoxy]quinazolin-4-yl}-2-oxo-2,3-dihydro-1*H*-indole-5-carbonitrile hydrochloride

A solution of 5-cyanooxindol (260 mg, 1.64 mmol) in dimethyl sulfoxide (2 mL) was added to a suspension of sodium hydride (66 mg, 1.64 mmol, pre-washed with pentane) in dimethyl sulfoxide (0.8 mL). The mixture was stirred for 20 min at ambient temperature and 7-[2-(4-acetylpiperazin-1-yl)ethoxy]-4-methylthioquinazoline (190 mg, 0.55 mmol) was added and stirring was continued for 3 h at 100 °C. The mixture was poured onto a saturated aqueous solution of ammonium chloride and ethyl acetate was added. The formed precipitate was filtered and the filtrate was extracted with ethyl acetate. The ethyl acetate layers were dried (Na_2SO_4) and evaporated to give a solid. The solid and the initial precipitate were dissolved in methylene chloride/methanol and adsorbed on silica. The product was purified by column chromatography eluting with methylene chloride/methanol, 9:1. The fractions containing the expected product were combined and evaporated. The oily residue was dissolved in methylene chloride/methanol, 1:1, and 3.8 M HCl in diethyl ether (2 mL) was added. The solution was concentrated and the precipitate was filtered, washed with diethyl ether and dried *in vacuo* to give 189 mg (63% yield) of the title compound: ESI-MS 457 (M^{+}+1).

Example 24

7-[2-(4-Acetylpiperazin-1-yl)ethoxy]-4-methylthioquinazoline

7-(2-Bromoethoxy)-4-methylthioquinazoline (250 mg, 0.83 mmol) and acetylpiperazine (225 mg, 1.75 mmol) was stirred at 120 °C for 10 min. The solid was dissolved in ethyl acetate and water and the pH of the aqueous layer was adjusted to 9 with 2 M $NaOH_{(aq)}$. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The organic layers were combined, washed with brine, dried ($MgSO_4$) and evaporated and the residue was purified by column chromatography eluting with methylene chloride/methanol, 92:8, to give 226 mg (78% yield) of the title compound: ESI-MS 347 (M^{+}+1).

Example 25

5-Chloro-3-{7-[2-(2-methoxyethoxy)ethoxy]quinazolin-4-yl}-1,3-dihydro-indol-2-one hydrochloride

5-Chlorooxindol (230 mg, 1.14 mmol) was added to a suspension of sodium hydride (92mg, 2.28 mmol; 60% in oil) in dimethyl sulfoxide (4 mL). After stirring 15 min at ambient temperature, 7-[2-(2-methoxyethoxy)ethoxy]-4-(methylthio)quinazoline (223 mg, 0.76 mmol, described in WO 99/10349) was added. The mixture was stirred at 110 °C for 1 h and then poured onto water (75 mL). The pH was adjusted to 8 with aqueous hydrochloric acid (2 M). The precipitate was filtered, washed with water and dried *in vacuo*. The solid was dissolved in methylene chloride/methanol and HCl in diethyl ether (3.8 M, 2 mL) was added. The volatiles were removed *in vacuo* to give 233 mg (67% yield) of the title compound: ESI-MS 414 (M^{+}+1).

Example 26

3-{7-[2-(4-Butyrylpiperazin-1-yl)ethoxy]quinazolin-4-yl}-2-oxo-2,3-dihydro-1*H*-indole-5-carbonitrile hydrochloride

5-Cyanooxindol (221 mg, 1.4 mmol) in dimethyl sulfoxide (1.7 mL) was added to a suspension of sodium hydride (56 mg, 1.4 mmol, pre-washed with pentane) in dimethyl sulfoxide (0.8 mL). After stirring 10 min at ambient temperature, 7-[2-(4-butyrylpiperazin-1-yl)ethoxy]-4-(methylthio)quinazoline (175 mg, 0.47 mmol) was added and the mixture was stirred at 100 °C for 3 h. After cooling, the mixture was partitioned between ethyl acetate and water and the pH was adjusted to 8.2 with aqueous hydrochloric acid (2 M). The precipitate was filtered, washed with water followed by ethyl acetate. The aqueous layer was extracted with ethyl acetate and the ethyl acetate layers were combined and evaporated to give a solid. The solid and the first precipitate were combined, dissolved in ethyl acetate and methanol and adsorbed on silica. The product was purified by column chromatography eluting with methylene chloride/acetonitrile/methanol, 60:42:8 followed by 70:20:10. The fractions containing the expected product were combined and evaporated. The solid was dissolved in methylene chloride/methanol and 3.8 M HCl in diethyl ether was added. The volatiles were removed under vacuum and the solid was filtered, washed with diethyl ether and dried *in vacuo* to give 195 mg (74% yield) of the title compound: ^{1}HNMR (DMSO-*d6*, TFA-*d*) δ 0.92 (t, 3 H), 1.55 (m, 2 H), 2.38 (dd, 2 H), 2.9-3.7 (br m, 6 H), 3.72 (br s, 2 H), 4.05-4.2 (br s, 1 H), 4.4-4.6 (br s, 1 H), 4.65 (m, 2 H), 7.1 (d, 1 H), 7.25 (d, 1 H), 7.38 (dd, 1 H), 7.5 (d, 1 H), 8.1 (s, 1 H), 8.65 (d, 1 H), 8.7 (s, 1 H); ESI-MS 485 (M^++1).

Example 27

7-(2-Bromoethoxy)-4-(methylthio)quinazoline

7-Hydroxy-4-(methylthio)quinazoline (1 g, 5.2 mmol; described in WO 99/10349), 1,2-dibromoethane (673 µL, 7.8 mmol) and potassium carbonate (2.1 g, 15 mmol) in *N,N*-dimethylformamide (15 mL) was stirred for 6 h at ambient temperature. Additional 1,2-dibromoethane (224 µL) was added and stirring was continued over night. The solid was filtered and washed with ethyl acetate. The filtrate was washed with water, brine, dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography eluting with methylene chloride/methanol, 98:2. The fraction containing the expected product were combined and evaporated to give 179 mg (11% yield) of the title compound: ESI-MS 299-301 (M^++1).

Example 28

7-[2-(4-Butyrylpiperazin-1-yl)ethoxy]-4-(methylthio)quinazoline

7-(2-Bromoethoxy)-4-(methylthio)quinazoline (0.55 g, 1.8 mmol) and 1-butyrylpiperazine (0.6 g, 3.86 mmol) was stirred at 120 °C. The mixture was then diluted with water and methylene chloride and the pH was adjusted to 9 with 2 N aqueous Na_2CO_3. The organic layer was separated and the aqueous layer was further extracted with methylene chloride. The organic layer was combined, washed with brine, dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography eluting with methylene chloride/methanol, 94:6. The fractions containing the expected product were combined and evaporated to give 461 mg (68% yield) of the title compound: ESI-MS 375 (M^++1).

Example 29

3-{7-[2-(4-Acetylpiperazin-1-yl)-2-oxoethoxy]quinazolin-4-yl}-2-oxo-2,3-dihydro-1*H*-indole-5-carbonitrile hydrochloride

A solution of 5-cyanooxindol (329 mg, 2.1 mmol) in dimethyl sulfoxide (3 mL) was added to a suspension of sodium hydride (83 mg, 2.1 mmol, 60% in oil) in dimethyl sulfoxide (1 mL). After stirring 10 min at ambient temperature, 7-[2-(4-acetylpiperazin-1-yl)-2-oxoethoxy]-4-(methylthio)quinazoline (250 mg, 0.69 mmol) was added. After stirring at 100 °C for 2 h, the mixture was poured onto saturated aqueous ammonium chloride. The precipitate was filtered, washed with water followed by ethyl acetate and dried *in vacuo*. The solid was dissolved in methylene chloride/methanol and dried over Na_2SO_4. After filtration, the filtrate was concentrated and the residue was adsorbed onto silica. The product was purified by column chromatography, eluting with methylene chloride/methanol, 93:7, followed by 90:10. The fractions containing the expected product were combined and evaporated. The solid was dissolved in methylene chloride/methanol and 3.8 M HCl in diethyl ether was added (2 mL). The volatiles were removed *in vacuo* and the solid was filtered, washed with diethyl ether and dried *in vacuo* to give 189 mg (52% yield) of the title compound: ESI-MS 471 (M^++1).

Example 30

7-[2-(4-Acetylpiperazin-1-yl)-2-oxoethoxy]-4-(methylthio)quinazoline

7-Hydroxy-4-methylthioquinazoline (600 mg, 3.12 mmol; described in WO 99/10349) was added to a suspension of sodium hydride (131 mg, 3.28 mmol, pre-washed with pentane) in *N,N*-dimethylformamide (7mL). After stirring for 15 min, 1-acetyl-4-bromoacetylpiperazine (855 mg, 3.43 mmol; described in *Chem. Europ. J.*, 2001, *7, 1*, 288-296) was added and the mixture was stirred at 50 °C for 1 h. The mixture was poured onto water containing some ethyl acetate.The precipitate was filtered , washed with water followed by diethyl ether and dried over night *in vacuo* over P_2O_5 to give 975 mg (99% yield) of the title compound: ESI-MS 361 (M^++1).

Example 31

3-{7-[4-(4-Acetylpiperazin-1-yl)-4-oxobutoxy]quinazolin-4-yl}-2-oxo-2,3-dihydro-1*H*-indole-5-carbonitrile hydrochloride

The compound was prepared as described for Example 29 using 5-cyanooxindole (221 mg, 1.4 mmol) and 7-[4-(4-acetylpiperazin-1-yl)-4-oxobutoxy]-4-(methylthio)quinazoline (181 mg, 0.466 mmol). After extraction and purification by column chromatography eluting with methylene chloride/ acetonitrile/methanol, 60:32:8, followed by 70:20:10 and trituation with HCl in diethyl ether to give 165 mg (62% yield) of the title compound: ESI-MS 499 (M^++1).

Example 32

1-Acetyl-4-(4-chlorobutanoyl)piperazine

A solution of 4-chlorobutanoyl chloride (1.54 mL, 13.7 mmol) in methylene chloride (5 mL) was added dropwise over 30 min to a solution of acetylpiperazine (1.6 g, 12.5 mmol) in methylene chloride (25 mL) cooled at -70 °C. After stirring 1 h at -70 °C and 2.5 h at ambient temperature, the mixture was poured onto a saturated solution of ammonium chloride and the pH of the aqueous layer was adjusted to 8 with solid Na_2CO_3. The organic layer was separated and the aqueous layer was extracted with methylene chloride. The organic layers were combined, dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography eluting with methylene chloride/methanol, 98:2, followed by 96:2 to give 2.51 g (86% yield) of the title compound: ESI-MS 233-235 (M^++1).

Example 33

7-[4-(4-Acetylpiperazin-1-yl)-4-oxobutoxy]-4-(methylthio)quinazoline

7-Hydroxy-4-(methylthio)quinazoline (600 mg, 3.12 mmol; described in WO 99/10349) was added to a suspension of sodium hydride (131 mg, 3.28 mmol, pre-washed with pentane) in *N*,*N*-dimethylformamide (7 mL). After stirring for 15 min, a solution of 1-acetyl-4-(4-chlorobutanoyl)piperazine (1.1 g, 3.43 mmol) in *N*,*N*-dimethylformamide (2 mL) was added. The mixture was stirred for 4 h at 50 °C and 1 h at 70 °C. The mixture was poured onto a saturated aqueous solution of ammonium chloride and extracted with ethyl acetate. The organic layer was dried ($MgSO_4$), filtered and evaporated. The residue was purified by column chromatography eluting with methylene chloride/acetonitrile/methanol, 60:39:1, to give 400 mg (33% yield) of the title compound: ESI-MS 389 (M^++1).

Example 34

6-Fluoro-3-[7-(3-morpholin-4-ylpropoxy)quinazolin-4-yl]-1,3-dihydro-indol-2-one dihydrochloride

To a suspension of sodium hydride (36 mg, 1.5 mmol, pre-washed with pentane) in dimethyl sulfoxide (2 mL) was added 6-fluorooxindole (226 mg, 1.5 mmol). The mixture was stirred 30 min at ambient temperature and 4-methylsulfanyl-7-(3-morpholin-4-ylpropoxy)quinazoline (182 mg, 0.5 mmol; described in WO 97/42187) was added. The mixture was stirred at 80 °C for 1.5 h and 6-fluorooxindole (76 mg, 0.5 mmol) was further added. The mixture was stirred at 80 °C for 30 min. After cooling the mixture was poured onto a column of silica and was eluted with methylene chloride/methanol (gradient from 100->0 to 94->6). The fractions containing the expected product were combined and concentrated. 3.8 M HCl in diethyl ether (2 mL) was added and the volatiles were removed *in vacuo*. The solid was filtered, washed with diethyl ether and dried *in vacuo* to give 52 mg (34% yield) of the title compound: ^{1}HNMR (DMSO-*d6*, TFA-*d*) δ 2.2-2.35 (m, 2 H), 3.1-3.2 (m, 2 H), 3.3-3.4 (m, 2 H), 3.51 (d, 2 H), 3.75 (dd, 2 H), 4.02 (d, 2 H), 4.3 (dd, 2 H), 6.72-6.85 (m, 2 H), 7.22 (s, 1 H), 7.3 (d, 1 H), 7.68 (m, 1 H), 8.42 (d, 1 H), 8.8 (s, 1 H).

Example 35

7-Fluoro-3-[6-methoxy-7-(3-morpholin-4-ylpropoxy)quinazolin-4-yl]-1,3-dihydroindol-2-one dihydrochloride

A stirred solution of 7-fluorooxindole (570 mg, 3.77 mmol) in *N,N*-dimethylformamide (15 mL) was degassed by subjecting it to several cycles of vacuum and argon and stirred in an argon atmosphere whilst sodium hydride (175 mg, 4.38 mmol, 60% dispersion in oil) was added in one portion. After stirring for a further 30 min , 4-chloro-6-methoxy-7-(3-(4-morpholinyl)propoxy)quinazoline (420 mg, 1.24 mmol; described in WO 97/42187) was added, the reaction mixture stirred at 90 °C for 1 h and allowed to cool to room temperature. The solvent was evaporated *in vacuo* and the residue absorbed onto silica from a methylene chloride/methanol, 95:5, solvent mixture. The product was purified by column chromatography eluting initially with methylene chloride/methanol, 95:5, and then with methylene chloride/methanol, 90:10. After evaporation of the solvent, the formed solid was triturated with acetone, filtered and dried to give 220 mg (39% yield) of the title compound: mp 211 – 214 °C; ESI-MS 453 (M^++1).

Example 36

6-Bromo-3-[7-(2-imidazol-1-ylethoxy)-6-methoxyquinazolin-4-yl]-1,3-dihydroindol-2-one dihydrochloride

7-(2-Imidazol-1-yl-ethoxy)-6-methoxy-3*H*-quinazolin-4-one (300 mg, 1.05 mmol, described in WO 97/42187) and thionyl chloride (10 mL) containing *N,N*-dimethylformamide (5 drops) was refluxed for 1 h. The volatiles were removed *in vacuo* and the residue was dissolved in ethyl acetate. The organic layer was washed with aqueous sodium bicarbonate and dried ($MgSO_4$). The 4-chloroquinazoline was used in the next step without further purification. Sodium hydride (126 mg, 3.15 mmol, 60% in oil) was added to a suspension of 6-bromooxindole (660 mg, 3.15 mmol) in *N,N*-dimethylformamide (25 mL) and the 4-chloroquinazoline previously prepared was added dropwise and the mixture was stirred at 90 °C for 2 h. After cooling, the mixture was worked-up as described for Example 44 and the residue was purified by column chromatography eluting with methylene chloride followed by methylene chloride/methanol/sat. $NH_{3(aq)}$, 100:10:1. The fractions containing the expected product were combined and evaporated. The solid was dissolved in methylene chloride/methanol, 1:1, and 1 M hydrogen chloride in diethyl ether (5 mL) was added. The solid was filtered, washed with diethyl ether and dried *in vacuo* to give 225 mg (46% yield) of the title compound: EIS-MS 480 (M^{+}+1).

Example 37

3-[7-(2-Imidazol-1-ylethoxy)-6-methoxyquinazolin-4-yl]-2-oxo-2,3-dihydro-1*H*-indole-6-carbonitrile dihydrochloride

The compound was prepared as described for Example 44 using 6-methoxy-7-(2-(imidazol-1-yl)ethoxy)-4-chloroquinazoline and 6-cyanooxindole to give 160 mg of the title compound: EIS-MS 427 (M^{+}+1).

Example 38

2-Oxo-2,3-dihydro-1*H*-indole-5-carboxylic acid dimethylamide

To a solution of 2-oxo-2,3-dihydro-1*H*-indole-5-carboxylic acid (1.36 g, 7.68 mmol; described in Sun, L. *J. Med. Chem.*, 1999, *42*, 5120) in *N,N*-dimethylformamide (25 mL) was added 1,1'-carbonyldiimidazole (1.24 g, 7.68 mmol), and the mixture was heated at 70 °C under nitrogen for 15 min. The solution was allowed to cool for 25 min, and dimethylamine (40% in water, 1.1 mL, 8.44 mmol) was added. The reaction mixture was stirred at room temperature over night. The solvent was removed *in vacuo*, and the residual oil was partitioned between chloroform and an aqueous hydrochloric acid solution (2 M). The aqueous layer was extracted several times with chloroform. The combined organic layers were dried ($MgSO_4$), and the solvent was removed *in vacuo*. The crude product was purified by column chromatography on silica using chloroform/ethanol, 95:5, as the eluent affording 0.69 g (44% yield) of the title compound as a pale pink solid: mp 147.2-147.5 °C; MS (ESP) *m/z* 205 (M^{+}+1).

Example 39

2-Oxo-2,3-dihydro-1*H*-indole-5-carboxylic acid methylamide

To a solution of 2-oxo-2,3-dihydro-1*H*-indole-5-carboxylic acid (293 mg, 1.65 mmol) in *N,N*-dimethylformamide (15 mL) were added methylamine (2 M solution in tetrahydrofuran, 0.91 mL, 1.82 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (698 mg, 3.64 mmol), and 4-dimethylaminopyridine (882 mg, 7.28 mmol).

The reaction mixture was stirred at room temperature over night. The solvent was removed *in vacuo*, and the residue was dissolved in 5 mL of a chloroform/methanol mixture (85:15). HCl in diethyl ether (3 M) was added until acidic pH. The solution was placed on a short column of silica (glass sinter funnel d=70 mm, using chloroform/ethanol, 90:10, as the eluent affording 195 mg (62% yield) of the pure product as a pale pink solid: mp 295 °C (decomp.); MS (EI) *m/z* (relative intensity) 190 (66, M^+), 160 (100), 132 (35), 104 (15), 77 (14).

Example 40

7-[3-(4-Methylpiperazin-1-yl)propoxy]-3*H*-quinazolin-4-one

To a solution of 3-(4-methylpiperazin-1-yl)propan-1-ol (1.19 g, 7.52 mmol; described in Brundage, Steck. *J. Am. Chem. Soc.*, 1959, *81*, 6511) in *N,N*-dimethylformamide (5 mL) was added sodium hydride (300 mg, 7.52 mmol, 60% dispersion in oil), and the mixture was stirred at room temperature for 55 min. 7-fluoro-3*H*-quinazolin-4-one (411 mg, 2.51 mmol; described in Rewcastle G. et al *J. Med. Chem.*, 1996, *39*, 4, 918-928) was added in portions, and the mixture was heated at 140 °C for 1.5 h. The mixture was allowed to cool, and the solvent was removed *in vacuo*. The residue was partitioned between ethyl acetate and water at pH 7 (adjusted by adding an aqueous hydrochloric acid solution, 2 M). The aqueous layer was extracted with another portion of ethyl acetate. To the aqueous layer was added a saturated $NaHCO_3$ solution followed by extraction with tetrahydrofuran. The combined organic layers were dried (Na_2SO_4), and the solvent was removed *in vacuo* affording 0.55 g of a yellowish semi-solid which was used in the next step without further purification.

Example 41

4-Chloro-7-[3-(4-methylpiperazin-1-yl)propoxy]quinazoline

A mixture of crude 7-[3-(4-methylpiperazin-1-yl)propoxy]-3*H*-quinazolin-4-one from Example 40 and phosphorous oxychloride (3 mL) was heated at reflux for 30 min. *N,N*-Dimethylaniline (0.3 mL) was added whereby the solubility increased. The mixture was heated for another 30 min, and the excess of phosphorous oxychloride was removed *in vacuo*. The residue was partitioned between ethyl acetate and a saturated $NaHCO_3$ solution. The organic layer was dried ($MgSO_4$), and the solvent was removed *in vacuo*. The crude product was purified on a silica column using chloroform/methanol, 85:15, as the eluent affording 69 mg (9% yield) of the title compound as a white solid: MS (ESP) *m/z* 321 (M $^{+}$+1).

Example 42

4-Chloro-8-(2-morpholin-4-ylethoxy)quinazoline

To a solution of 4-chloroquinazolin-8-ol (203 mg, 1.12 mmol; described in US 5270466), triphenylphosphine (442 mg, 1.69 mmol), and *N*-(2-hydroxyethyl)morpholine (221 mg, 1.69 mmol) in anhydrous tetrahydrofuran (5 mL) was added dropwise a solution of diethyl azodicarboxylate (294 mg, 1.69 mmol) in tetrahydrofuran (3 mL). The reaction mixture was stirred at ambient temperature for 45 min. The solvent was removed *in vacuo*, and the residue was purified by column chromatography on silica using chloroform/ethanol, 95:5, as the eluent to give 280 g (85% yield) of the title compound as a orange oil: MS (ESP) *m/z* 294 (M $^{+}$+1).

Example 43

3-[7-(3-Morpholin-4-yl-propoxy)quinazolin-4-yl]-2-oxo-2,3-dihydro-1*H*-indole-5-carboxylic acid dimethylamide

To a suspension of sodium hydride (20 mg, 0.495 mmol, 60% dispersion in oil) in *N,N*-dimethylformamide (2 mL) was added 2-oxo-2,3-dihydro-1*H*-indole-5-carboxylic acid dimethylamide (81 mg, 0.396 mmol) under argon atmosphere. The mixture was stirred for 20 min, and then a solution of 4-chloro-7-(3-morpholin-4-ylpropoxy)quinazoline (61 mg, 0.198 mmol) in *N,N*-dimethylformamide (2.2 mL) was added dropwise over 5 min. The obtained red solution was stirred at room temperature for 3 h. The solvent was removed *in vacuo*, and the mixture was partitioned between ethyl acetate and water. A few drops of an aqueous hydrochloric acid solution (2 M) was added and the pH was adjusted to 8 by the addition of an aqueous solution of saturated $NaHCO_3$. The product was separated in a separator funnel, and filtered and washed with water and diethyl ether. After drying *in vacuo*, 55 mg (60% yield) of the title compound was obtained as a yellow powder: mp 167.5-168.7 °C; MS (ESP) *m/z* 476 (M $^{+}$+1).

Example 44

3-[7-(3-Morpholin-4-yl-propoxy)-quinazolin-4-yl]-2-oxo-2,3-dihydro-1*H*-indole-5-carboxylic acid methylamide

To a suspension of sodium hydride (21 mg, 0.526 mmol, 60% dispersion in oil) in *N,N*-dimethylformamide (4 mL) was added 2-oxo-2,3-dihydro-1*H*-indole-5-carboxylic acid methylamide (80 mg, 0.421 mmol). 4-Chloro-7-(3-morpholin-4-ylpropoxy)quinazoline (65 mg, 0.210 mmol; described in WO 97/42187) was added in portions after 25 min. The dark red solution was stirred at room temperature over night. The solvent was removed *in vacuo*, and the residue was dissolved in a mixture of methanol, ethyl acetate, and chloroform. The HCl-salt was prepared by adding HCl in diethyl ether (3 M) followed by evaporation of about 75% of the solvent volume. Ethyl acetate was added, and the precipitated HCl-salt was filtered, washed with ethyl acetate, and dried. The HCl-salt was dissolved in an aqueous 2 M NaOH solution and extracted two times with ethyl acetate. The pH was adjusted to 8 followed by three extractions with ethyl acetate. The phases were combined and dried (Na_2SO_4). After filtration, the solvent was removed *in vacuo* affording 40 mg (41% yield) of the title compound as a yellow solid: mp 195-198 °C; MS (ESP) *m/z* 462 (M^++1).

Example 45

3-{7-[3-(4-Methylpiperazin-1-yl)propoxy]quinazolin-4-yl}-2-oxo-2,3-dihydro-1*H*-indole-5-carbonitrile dihydrochloride

To a suspension of sodium hydride (22 mg, 0.538 mmol, 60% dispersion in oil) in *N,N*-dimethylformamide (1.5 mL) was added 5-cyanooxindole (68 mg, 0.430 mmol). A dark yellow solution was obtained after 15 min, and a solution of 4-chloro-7-[3-(4-methylpiperazin-1-yl)propoxy]quinazoline (69 mg, 0.215 mmol) in *N,N*-dimethylformamide (1.5 mL) was added dropwise. A clear red solution was initially formed and by the end of the addition a precipitate was formed. The reaction mixture was stirred at room temperature for 2 h. The solvent was removed *in vacuo*, and the residue was partitioned between ethyl acetate and an aqueous hydrochloric acid solution (2 M). The aqueous layer was washed with another portion of ethyl acetate. The pH of the aqueous layer was adjusted to 6 by adding a 2 M $NaOH_{(aq)}$ solution. After washing with ethyl acetate, the aqueous layer was alkalized to pH 8 by addition of a saturated $NaHCO_{3(aq)}$

solution followed by two extractions of chloroform and one with tetrahydrofuran. The chloroform- and tetrahydrofuran layers were dried (Na_2SO_4), combined, and the solvent was removed *in vacuo*. The residue was dissolved in a mixture of methanol, chloroform, and ethyl acetate. A solution of HCl in diethyl ether was added at 0°C. Half the volume was removed *in vacuo*, and ethyl acetate was added. The precipitated HCl-salt was filtered and washed with ethyl acetate. Drying *in vacuo* at 40 °C afforded 51 mg (43% yield) of the title compound as an orange solid: mp 200 °C (decomp.); MS (ESP) *m/z* 443 (M^++1).

Example 46

2-Hydroxy-3-[8-(2-morpholin-4-ylethoxy)quinazolin-4-yl]-1*H*-indole-5-carbonitrile hydrochloride

To a solution of 5-cyanooxindole (226 mg, 1.43 mmol) in *N,N*-dimethylformamide (4 mL) was added sodium hydride (76 mg, 1.91 mmol, 60% dispersion in oil). A solution of 4-chloro-8-(2-morpholin-4-ylethoxy)quinazoline (0.28 g, 0.95 mmol) in *N,N*-dimethylformamide (3 mL) was added dropwise after 10 min. The colour changed to red, and the mixture was stirred at room temperature for 30 min. The solvent was removed *in vacuo*, and the residue was suspended in an aqueous hydrochloric acid solution (2 M) and ethyl acetate. The heterogeneous aqueous layer was washed with another portion of ethyl acetate. To the aqueous mixture was added $NaHCO_3$(s) until pH 8, followed by five extractions with chloroform. The combined chloroform layers were dried (Na_2SO_4), and the solvent was removed *in vacuo* affording 256 mg of an orange crude product. Part of this material (61 mg) was dissolved in a 1:1 mixture of methanol and dichloromethane, and a solution of HCl in diethyl ether (3 M) was added dropwise at 0°C until slightly acidic. About 60-75% of the solvent volume was removed *in vacuo*, and ethyl acetate was added. The precipitated HCl-salt was filtered and washed with ethyl acetate and dried *in vacuo* affording 49 mg of the title compound as a red solid: MS (ESP) m/z 416 (M^++1).

Example 47

3-[7-(3-Morpholin-4-yl-propoxy)quinazolin-4-yl]-6-propyl-1*H*-indol-2-ol hydrochloride

To a suspension of sodium hydride (30 mg, 0.756 mmol, 60% dispersion in oil) in *N,N*-dimethylformamide (2 mL) was added 6-propyl-1,3-dihydro-indol-2-one (106 mg, 0.605 mmol). The mixture was stirred at room temperature for 1 h, and a solution of

4-chloro-7-(3-morpholin-4-ylpropoxy)quinazoline (93 mg, 0.302 mmol; described in WO 97/42187) in *N,N*-dimethylformamide (1.2 mL) was added dropwise. The obtained red solution was stirred for 2 h. The solvent was removed *in vacuo*, and the residue was partitioned between an aqueous hydrochloric acid solution (2 M) and ethyl acetate. Some solid material remained. The aqueous layer together with insoluble material was washed with another portion of ethyl acetate. The aqueous mixture was alkalized to pH 8 by adding an aqueous 45% NaOH solution and extracted with ethyl acetate. The organic phase was dried (Na_2SO_4), and the solvent was removed *in vacuo*. The crude product was dissolved in ethyl acetate, isopropyl ether, and a few drops of ethanol. A solution of HCl in diethyl ether (3 M) was added at 0°C. The precipitated HCl-salt was filtered and washed with ethyl acetate affording 98 mg (62% yield) of the title compound as an orange powder: MS (ESP) *m/z* 447 (M^++1).

Example 48

6-Bromo-5-(2-chloroacetyl)1,3-dihydroindol-2-one

6-Bromooxindole (500 mg, 2.4 mmol) was added to aluminum trichloride (1.08 g, 8.1 mmol) in dichloroethane (1.5 mL). Chloroacetylchloride was slowly added under gas evolution and the mixture was heated at 50 °C for 18 h. The reaction was cooled to room temperature and poured into ice water. The precipitate was collected and purified by flash silica gel chromatography using chloroform/methanol (50:1->20:1->10:1->5:1) as the eluent to give 429 mg (63% yield) the title compound as a white powder: mp 238-239 °C; ESMS *m/z* 289.92 (M^++1).

Example 49

6-Bromo-2-oxo-2,3-dihydro-1*H*-indole-5-carboxylic acid

6-Bromo-5-(2-chloroacetyl)1,3-dihydroindol-2-one (422 mg, 1.46 mmol) in pyridine (5 mL) was heated at 70 °C for 3.5 h. The mixture was allowed to cool, the precipitate was filtered and washed with ethanol. The solid was dissolved in 2 M $NaOH_{(aq)}$ (8 mL) and heated to 70 °C for 1 h and 20 min, cooled on an ice bath and acidified with conc. $HCl_{(aq)}$ to pH 2. The brown precipitate was collected by filtration. This, and additional precipitate which was formed in the motherliquor over night, was dried *in vacuo* at 35 °C to give 315 mg (84% yield) of the title compound as a brown powder: mp 294 °C (decomp.); MS (TSP) *m/z* 257 (M^++1).

Example 50

6-Bromo-2-oxo-2,3-dihydro-1*H*-indole-5-carboxylic acid methylamide

6-Bromo-2-oxo-2,3-dihydro-1*H*-indole-5-carboxylic acid (510 mg, 2.0 mmol) was dissolved in *N*,*N*-dimethylformamide (20 mL) and methylamine in tetrahydrofuran (2 M, 1095 μL), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (840 mg, 4.4 mmol) and dimethylaminopyridin (1.062 g, 8.8 mmol) were added sequentially and the mixture was stirred at room temperature for 19 h. The mixture was acidified with an aqueous hydrochloric acid solution (1 M), concentrated and co-evaporated with toluene three times. The residue was dissolved in an aqueous hydrochloric acid solution (1 M), NaCl (s) was added and the solution was extracted several times with tetrahydrofuran. The organic phase was washed with an aqueous hydrochloric acid solution (1 M) and the combined aqueous phases were washed with tetrahydrofuran. The combined tetrahydrofuran phases were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was purified by flash silica gel chromatography using ethyl acetate/methanol/water (15:1:0->10:1:0->5:1:0->2:1:0->7:2:1). The fractions containing the product were concentrated, dissolved in methanol and filtered to remove silica gel. After evaporation of the solvent, the residue was crystallized from methanol to give 137 mg (26% yield) of the title compound as a pink solid: mp 279 °C (decomp.); ESMS *m/z* 271.0 (M^++1).

Example 51

6-Bromo-3-[7-(3-morpholin-4-yl-propoxy)quinazolin-4-yl]-2-oxo-2,3-dihydro-1*H*-indole-5-carboxylic acid methylamide

6-Bromo-2-oxo-2,3-dihydro-1*H*-indole-5-carboxylic acid methylamide (73 mg, 271 μmol) in *N*,*N*-dimethylformamide (3 mL) was added to sodium hydride (12.9 mg, 323 μmol, pre-washed with hexane). After stirring for 10 min, 4-chloro-7-(3-morpholin-4-ylpropoxy)quinazoline (39.8 mg, 123 μmol; described in WO 97/42187) was added. The reaction was stirred at room temperature for 2.5 h, concentrated and co-evaporated with toluene three times. The residue was dissolved in 10% $NaOH_{(aq)}$ and extracted with ethyl acetate and the organic phases were washed with 10% $NaOH_{(aq)}$. The combined aqueous phases were acidified with 1 M HCl to pH 2 and extracted with ethyl acetate. Using a 10% aqueous solution of NaOH and $NaHCO_3$ (s) the pH of the aqueous phase was adjusted to 8.5 and extracted with tetrahydrofuran. The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was dissolved in methanol and HCl in diethyl ether (1 M, 3 mL) was added. The hydrochloride salt was precipitated by the addition of diethyl ether, filtered and washed with diethyl ether. After drying *in vacuo* at 35 °C the crude product was purified by preparative HPLC (X-Terra C8 column, 19x 300 mm), using a gradient of A (water 95%, containing NH_4OAc (0.01 M), and 5% acetonitrile) and B (acetonitrile), going from 0% to 100% B over a period of 22 min. The fractions were collected and concentrated *in vacuo* to give 21 mg (30% yield) of the title compound as a yellow semi-solid: ESMS *m/z* 542.3 (M^++1).

Example 52

2-(4-Ethylphenyl)-*N*-methoxyacetamide

(4-Ethylphenyl)acetyl chloride (2.9 g, 16 mmol; described in Shah, S. et al. *J. Med. Chem.*, 1992, *35*, 3745-3754) was added to a vigorously stirred solution of methoxyamine hydrochloride (1.5 g, 17.6 mmol) and sodium carbonate (3.4 g, 32 mmol) in a mixture of toluene (15 mL) and water (15 mL). The reaction mixture was stirred for 4 h at room temperature and then extracted with ethyl acetate (3×30 mL). The combined extracts were washed with brine (30 mL), dried ($MgSO_4$), and the solvent was removed *in vacuo* and dried at 25 °C *in vacuo* over night to afford 2.7 g. The residue was purified on a silica gel column using ethyl acetate as the eluent to afford 2.4 g (77% yield) of title compound as a colorless oil: MS (TSP) *m/z* 194 (M^++1).

Example 53

6-Ethyl-1-methoxy-1,3-dihydroindol-2-one

To a solution of 2-(4-ethylphenyl)-*N*-methoxyacetamide (2.4 g, 12.4 mmol) in methylene chloride (35 mL), cooled on an ice-bath, was added *tert*-butyl hypochlorite (1.7 mL, 14.9 mmol). The ice-bath was removed and the solution was allowed to reach room temperature. After 1.5 h reaction time, the solvent was removed *in vacuo*. The residue was dissolved in nitromethane (3 mL) and added to nitromethane (100 mL) containing zinc acetate (11.4 g, 62 mmol) at 95 °C. After 30 min, insoluble materials were filtered off, washed with ethyl acetate, and the combined solvents were removed *in vacuo*. The residue was dissolved in ethyl acetate (200 mL) and washed with 5% aqueous solution of $NaHCO_3$ (150 mL), brine (50 mL), dried ($MgSO_4$), and concentrated to afford 2.2 g of a crude residue. The residue was purified on a silica gel column using diethyl ether as the eluent to afford 1.8 g (76% yield) of title compound as a brownish oil: MS (TSP) *m/z* 192 (M^++1).

Example 54

6-Ethyl-1,3-dihydroindol-2-one

6-Ethyl-1-methoxy-1,3-dihydroindol-2-one (0.5 g, 2.6 mmol) was dissolved in methanol (15 mL), palladium (10%) on charcoal (0.3 g) was added and the mixture was hydrogenated at atmospheric pressure and room temperature. After 3 h the mixture was filtered through silica to remove the catalyst and the solvent was evaporated *in vacuo*. The residue was dried at 25 °C *in vacuo* over night to afford 0.27 g (64% yield) of title compound as a white solid: MS (TSP) *m/z* 162 (M^++1).

Example 55

6-Ethyl-3-[7-(3-morpholin-4-ylpropoxy)quinazolin-4-yl]-1*H*-indol-2-ol hydrochloride

A mixture of sodium hydride (31 mg, 0.78 mmol, pre-washed with hexane) in *N,N*-dimethylformamide (1 mL) was added to 6-ethyl-1,3-dihydroindol-2-one (100 mg, 0.62 mmol) in *N,N*-dimethylformamide (2 mL). The formed yellow mixture was stirred at room temperature for 5 min and 4-chloro-7-(3-morpholin-4-yl-propoxy)quinazoline (95 mg, 0.31 mmol; described in: WO 97/42187) in *N,N*-dimethylformamide (1 mL) was added. The obtained red solution was stirred for 1 h and the solvent was removed *in vacuo*. The residue was partitioned between an aqueous solution of hydrochloric acid (2 M) and ethyl acetate. Some solid material remained and the aqueous layer together with the insoluble material was washed with another portion of ethyl acetate. The aqueous mixture was alkalized to pH 10 by adding 2 M $NaOH_{(aq)}$, and extracted with ethyl acetate (3x5 mL). The combined organic layers were dried (Na_2SO_4), and the solvent was removed *in vacuo* and dried at 25 °C *in vacuo* over night to afford 80 mg. The residue was purified on a silica gel column using chloroform/ methanol, 23:2, as an eluent. Fractions containing the product were collected and evaporated *in vacuo* and dried at 25 °C *in vacuo* over night. The residue was dissolved in diethyl ether and treated with HCl in diethyl ether (5 M). The hydrochloride was dried at 25 °C *in vacuo* over night to afford 30 mg (19% yield) of title compound as an orange powder: MS (ESP) *m/z* 433 (M^{+}+1).

Example 56

<u>*N*-Methoxy-2-(4-propylphenyl)acetamide</u>

The reaction was performed as described in Example 52 using (4-propylphenyl)acetic acid (described in Kindler, et al *Chem. Ber.*, 1943, 76, 308) that was converted to the acid chloride using thionyl chloride to afford 5.8 g (58% yield) of title compound as a colorless oil: MS (TSP) *m/z* 208 (M^{+}+1).

Example 57

<u>1-Methoxy-6-propyl-1,3-dihydroindol-2-one</u>

The reaction was performed as described in Example 53 using *N*-methoxy-2-(4-propylphenyl)acetamide to afford 4.4 g (76% yield) of title compound as a brownish oil: MS (TSP) *m/z* 206 (M^{+}+1).

Example 58

<u>6-Propyl-1,3-dihydroindol-2-one</u>

1-Methoxy-6-propyl-1,3-dihydroindol-2-one (1.54 g, 7.5 mmol) was dissolved in methanol (10 mL), palladium (10%) on charcoal (0.7 g) was added and the mixture was hydrogenated at 3.5 kg pressure and at room temperature. After 20 h the mixture was filtered through silica to remove the catalyst and the solvent was evaporated *in vacuo* to afford 1.18 g (90% yield) of title compound: MS (TSP) *m/z* 176 (100, M^{+}+1).

Example 59

<u>6-Methyl-3-[7-(3-morpholin-4-yl-propoxy)-quinazolin-4-yl]-1*H*-indol-2-ol</u>

The reaction was performed as described in Example 55 using 6-methyl-1,3-dihydroindol-2-one (described in Kawase M. et al *J. Org. Chem.*, 1989, *54*, 3394-3403) and 4-chloro-7-(3-morpholin-4-yl-propoxy)quinazoline (described in: WO 97/42187). The crude product was purified by preparative HPLC (X-Terra C8 column, 19x 300 mm), using a gradient of water/acetonitrile, 70/30, to water/acetonitrile, 30/70, to afford 8 mg (6% yield) of title compound as a orange solid: MS (ESP) *m/z* 419 (M^{+}+1).

Example 60

5-Bromo-6-methyl-1,3-dihydroindol-2-one.

6-Methyl-1,3-dihydro-2*H*-indol-2-one (0.107 g, 0.73 mmol) was dissolved in acetonitrile (3 mL) and stirred for 5 min at 0 °C. *N*-Bromosuccinimide (0.129 g, 0.73 mmol) was added and the resulting reaction mixture was stirred for 4 h at 0 °C. The reaction mixture was poured onto water and the resulting crystals were collected by vacuum filtration, followed by drying over night in a vacuum desiccator over $MgSO_4/CaSO_4$ to afford 0.091 g (55% yield) of the title compound as a reddish-brown solid: ^1H NMR (400 MHz, DMSO-*d6*) δ 10.50 (s, 1 H), 7.41 (s, 1 H), 6.82 (s, 1 H), 3.49 (s, 2 H), 2.34 (s, 3 H).

Example 61

6-Bromo-5-nitro-1,3-dihydroindol-2-one.

6-Bromo-1,3-dihydro-2*H*-indol-2-one (0.500 g, 2.36 mmol) was dissolved in conc. sulfuric acid (6 mL) and stirred for 10 min at room temperature and solid potassium nitrate (0.238 g, 2.36 mmol) was added in two portions. The resulting reaction mixture was stirred over night at room temperature. The mixture was poured onto ice-water and the reddish-brown precipitates were collected by vacuum filtration and dried over night at a vacuum desiccator over $MgSO_4/CaSO_4$ to afford 0.535 g (88 % yield) of the title compound: ^1H NMR (400 MHz, DMSO-*d6*) δ 11.04 (s, 1 H), 8.01 (s, 1 H), 7.20 (s, 1 H), 3.62 (s, 2 H).

Example 62

5-Bromo-6-methyl-3-[7-(3-morpholin-4-ylpropoxy)quinazolin-4-yl]-1*H*-indol-2-ol dihydrochloride.

To a *N,N*-dimethylformamide (1.3 mL) suspension of sodium hydride (0.011 mg, 0.44 mmol, 60% in oil, pre-washed with hexane) was added 5-bromo-6-methyl-1,3-dihydroindol-2-one (0.079 g, 0.35 mmol). The formed red mixture was stirred for 10 min at room temperature and 4-chloro-7-(3-morpholin-4-ylpropoxy)quinazoline (0.055 g, 0.18 mmol; described in WO97/42187) was added. The resulting reaction mixture was stirred for 2 h and then the solvent was removed *in vacuo*. The residue was purified on a silica gel column using dichloromethane/methanol, 10:1, as an eluent to afford, after drying, 0.036 g (40% yield) of the title compound as the free base (yellow solid). This residue (0.026 g, 0.05 mmol) was dissolved in dichloromethane/methanol, 1:1, and treated with 1 M HCl in diethyl ether at 0 °C. The resulting orange solids were collected by vacuum filtration and washed with diethyl ether to afford 0.016 g of the title compound: MS (CI) *m/z* 498 (M^+ +1).

Example 63

6-Bromo-3-[7-(3-morpholin-4-ylpropoxy)quinazolin-4-yl]-5-nitro-1*H*-indol-2-ol dihydrochloride.

Sodium hydride (0.013 mg, 0.5 mmol, 60% in oil, pre-washed with hexane) was suspended in *N,N*-dimethylformamide (2.0 mL) and to this stirred mixture, 6-bromo-5-nitro-1,3-dihydroindol-2-one (0.103 g, 0.4 mmol) was added. The formed red mixture was stirred for 10 min at room temperature and 4-chloro-7-(3-morpholin-4-ylpropoxy)quinazoline (0.062 g, 0.2 mmol; described in WO97/42187) was added. The resulting reaction mixture was stirred for 2 h and the solvent was removed *in vacuo*. The residue was purified on a silica gel column using dichloromethane/methanol, 15:1, as eluent to afford, after drying, 0.039 g (37% yield) of the title compound as the free base (yellow solid). This residue (0.03 g, 0.057 mmol) was dissolved in dichloromethane/methanol, 1:1, and treated with 1 M HCl in diethyl ether at 0 °C. The resulting orange crystals were collected by vacuum filtration and washed with diethyl ether to afford 0.028 g (81% yield) of the title compound: MS (CI) *m/z* 529 (M^+ +1).

Example 64

7-(3-Dimethylaminopropoxy)-3*H*-quinazolin-4-one.

3-Dimethylaminopropan-1-ol (0.95 mL, 8.0 mmol) was dissolved in *N,N*-dimethylformamide (5 mL) under N_2 atmosphere and stirred for 10 min at 0 °C. To this solution, sodium hydride (60 % dispersion in oil, 0.35 g, 8.8 mmol) was added and the resulting reaction mixture was allowed to warm up to room temperature and stirred for 1 h. A solution of 7-fluoro-3*H*-quinazolin-4-one (328 mg, 2 mmol; described in Rewcastle G. et al *J. Med Chem.*, 1996, *39*, 4, 918-928) in *N,N*-dimethylformamide (5 mL) was added and the mixture was stirred for 2 h at 140 °C. The reaction mixture was cooled down to room temperature and diluted with aqueous saturated $NaHCO_3$ solution followed by extraction with ethyl acetate (3x50mL). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residual oil was re-concentrated with toluene and the semisolid product crystallised upon treatment with diethyl ether. The crystals were collected by vacuum filtration and dried in a desiccator to give 0.41 g (83 % yield) of the title compound as a solid: ^{1}H NMR (DMSO-d6, 300 MHz) δ 12.00 (br s, 1 H), 8.04 (s, 1 H), 8.01 (dd, *J*= 8 and 2 Hz, 1 H), 7.09 (d, *J*= 3 Hz, 1 H), 7.06 (s, 1 H), 4.13 (t, *J*= 6 Hz, 2 H), 2.36 (t, *J*= 7 Hz, 2 H), 2.14 (s, 6 H), 1.88 (m, 2 H).

Example 65

7-(2-Dimethylaminoethoxy)-3*H*-quinazolin-4-one.

The compound was prepared as described in Example 64 using 2-dimethylaminoethanol (1.5 mL, 15 mmol) and 7-fluoro-3*H*-quinazolin-4-one (0.492 g, 3 mmol) affording 0.52 g (75% yield) of the title compound as a solid: MS (ES) *m/z* 234 (M^++1).

Example 66

7-[2-(Isopropylmethylamino)ethoxy]-3*H*-quinazolin-4-one.

The compound was prepared as described in Example 64 using 2-(isopropylmethylamino)ethanol (1.168 g, 10.0 mmol) and 7-fluoro-3*H*-quinazolin-4-one (0.41 g, 2.5 mmol) to give 0.512 g (78 % yield) of the title compound as a solid. MS (ES) *m/z* 262 (M^++1).

Example 67

7-(2-Diisopropylaminoethoxy)-3*H*-quinazolin-4-one.

The compound was prepared as described in Example 64 using 2-(diisopropylamino)ethanol (1.59 mL, 9.0 mmol) and 7-fluoro-3*H*-quinazolin-4-one (0.492 g, 3.0 mmol) to give 0.66 g (76 % yield) of the title compound as white fluffy crystals: ^{1}H NMR (DMSO-d6, 300 MHz) δ 12.07 (br s, 1 H), 8.04 (s, 1 H), 8.01 (dd, *J*= 6 and 4 Hz, 1 H), 7.07 (d, *J*= 4 Hz, 1 H), 7.05 (s, 1 H), 4.01 (t, *J*= 7 Hz, 2 H), 3.01 (m, 2 H), 2.80 (t, *J*=7 Hz, 2 H), 0.99 (d, *J*=7 Hz, 12 H).

Example 68

[3-(4-Chloroquinazolin-7-yloxy)propyl]dimethylamine.

7-(3-Dimethylaminopropoxy)-3*H*-quinazolin-4-one (0.2 g, 0.21 mmol) was added to stirred phosphorus oxychloride (5 mL). The vessel was closed and the mixture was heated to 110 °C and kept stirring for 2 h. The excess of the phosphorus oxychloride was removed *in vacuo* and the residue was dissolved in a water/chloroform mixture. The aqueous layer was alkalyzed with an aqueous saturated $NaHCO_3$ solution and the organic layer was separated. The water layer was extracted two times with chloroform and the combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The material was used in the next step without further purification.

Example 69

[2-(4-Chloroquinazolin-7-yloxy)ethyl]dimethylamine.

The compound was prepared as described in Example 68 using 7-(3-dimethylaminoethoxy)-3*H*-quinazolin-4-one (0.270g, 1.16 mmol). The material was used in the next step without further purification.

Example 70

[2-(4-Chloroquinazolin-7-yloxy)ethyl]isopropylmethylamine.

The compound was prepared as described in Example 68 using 7-[2-(isopropylmethylamino)ethoxy]-3*H*-quinazolin-4-one (0.300g, 1.15 mmol). The material was used in the next step without further purification.

Example 71

[2-(4-Chloro-quinazolin-7-yloxy)ethyl]diisopropylamine.

The compound was prepared as described in Example 68 using 7-(2-diisopropylaminoethoxy)-3*H*-quinazolin-4-one (0.330g, 1.14 mmol). The material was used in the next step without further purification.

Example 72

3-[7-(3-Dimethylaminopropoxy)quinazolin-4-yl]-2-hydoxy-1*H*-indol-5-carbonitrile hydrochloride.

To an ice-bath cooled solution of 5-cyano-1,3-dihydroindol-2-one (0.255 g, 1.62 mmol) in *N,N*-dimethylformamide (3 mL) was added sodium hydride (60 % dispersion in oil, 0.078 g, 1.94 mmol) and the ice-bath was removed. After 15 min stirring, the ice-bath cooling was resumed and a solution of [3-(4-chloroquinazolin-7-yloxy)propyl]dimethylamine (0.265 g, 0.81 mmol) in *N,N*-dimethylformamide (6 mL) was slowly added. The reaction mixture was stirred for 12 h and quenched with aqueous saturated $NaHCO_3$ solution followed by extraction with ethyl acetate (3x100 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated *in vacuo* affording the free base as a yellow solid. The residue was dissolved in chloroform/ethanol, 1:1, and treated with 1 M HCl in diethyl ether at 0 °C. The resulting solid were collected by vacuum filtration and washed with diethyl ether to obtain 0.14 g (41 % yield) of the title compound as a solid: ^{1}H NMR (DMSO-d6, 300 MHz) δ 11.02 (br s, 1 H), 10.42 (br s, 1 H), 8.72 (br s, 1 H), 8.49 (s, 1 H), 8.15 (s, 1 H), 7.44 (dd, *J*=8 and 1 Hz, 1 H), 7.22 (d, *J*=9 Hz, 1 H), 7.11 (s, 1 H), 7.01 (d, *J*=8 Hz, 1 H), 4.29 (t, *J*=6 Hz, 2 H), 3.25 (m, 2 H), 2.80 (s, 6 H), 2.24 (m, 2 H).

Example 73

3-[7-(2-Dimethylaminoethoxy)quinazolin-4-yl]-2-hydoxy-1*H*-indol-5-carbonitrile fumarate.

The compound was prepared as described in Example 72 using [2-(4-chloroquinazolin-7-yloxy)-ethyl]dimethylamine (1.15 mmol) and fumaric acid to give 0.22 g (40% yield) of the title compound as a solid. ^{1}H NMR (DMSO-d6, 300 MHz) δ 10.85 (br s, 1 H), 8.81 (br s, 1 H), 8.47 (s, 1 H), 8.20 (b s, 1 H), 7.38 (d, *J*=8 Hz, 1 H), 7.18 (d, *J*=6 Hz, 1 H), 7.07 (s, 1 H), 6.97 (d, *J*=8 Hz, 1 H), 6.58 (s, 1 H), 4.30 (t, *J*=5 Hz, 2 H), 2.87 (t, *J*=5 Hz, 2 H), 2.37 (s, 6 H).

Example 74

3-{7-[2-(Isopropylmethylamino)ethoxy]quinazolin-4-yl]-2-oxo-2,3-dihydro-1*H*-indol-5-carbonitrile fumarate.

The compound was prepared as described in Example 72 using [2-(4-chloroquinazolin-7-yloxy)ethyl]-isopropylmethylamine (1.15 mmol) and fumaric acid to give 0.185 g (32% yield) of the title compound as a solid: ^{1}H NMR (DMSO-d6, 300 MHz) δ 10.84 (br s, 1 H), 8.80 (br s, 1 H), 8.46 (s, 1 H), 8.19 (br s, 1 H), 7.37 (d, *J*=8 Hz, 1 H), 7.17 (d, *J*=9 Hz, 1 H), 7.06 (s, 1 H), 6.95 (d, *J*=8 Hz, 1 H), 6.56 (s, 1 H), 4.29 (t, *J*=5 Hz, 2 H), 3.08 (t, *J*=7 Hz, 1 H), 3.00 (t, *J*=6 Hz, 2 H), 2.40 (s, 3 H), 1.06 (d, *J*=6 Hz, 6 H).

Example 75

3-[7-(2-Diisopropylamino)ethoxy)quinazolin-4-yl]-2-hydroxy-1*H*-indol-5-carbonitrile fumarate.

The compound was prepared as described in Example 72 using [2-(4-chloroquinazolin-7-yloxy)-ethyl]diisopropylamine (1.14 mmol) and fumaric acid to give 0.20 g (35% yield) of the title compound as a solid: ^{1}H NMR (DMSO-d6, 300 MHz) δ 11.00 (b s, 1 H), 8.84 (br s, 1 H), 8.57 (s, 1 H), 8.29 (br s, 1 H), 7.50 (d, *J*=8 Hz, 1 H), 7.29 (d, *J*=9 Hz, 1 H), 7.15 (s, 1 H), 7.08 (d, *J*=8 Hz, 1 H), 6.70 (s, 1 H), 4.26 (br s, 2 H), 3.29 (t, *J*=6 Hz, 2 H), 3.10 (br s, 2 H), 1.19 (d, *J*=6 Hz, 6 H), 1.16 (d, *J*=7 Hz, 6 H).

Pharmaceutical composition

According to one aspect of the present invention there is provided a pharmaceutical composition comprising a compound of the present invention, as hereinbefore defined, for use in prevention and/or treatment of dementia related diseases, Alzheimer's Disease and conditions associated with glycogen synthase kinase-3 and other conditions listed below.

The composition may be in a form suitable for oral administration, for example as a tablet, pill, syrup, powder, granule or capsule, for parenteral injection (including intravenous, subcutaneous, intramuscular, intravascular or infusion) as a sterile solution, suspension or emulsion, for topical administration e.g. as an ointment, patch or cream or for rectal administration e.g. as a suppository.

In general the above compositions may be prepared in a conventional manner using pharmaceutically acceptable carriers or diluents.

Suitable daily doses of the compounds of formula **I** in the treatment of a mammal, including man, are approximately 0.01 to 250 mg/kg bodyweight at peroral administration and about 0.001 to 250 mg/kg bodyweight at parenteral administration. The typical daily dose of the active ingredients varies within a wide range and will depend on various factors such as the relevant indication, severity of the illness treated, the specific compound used, the route of administration, the age, weight and sex of the patient and may be determined by a physician.

Illustrate representative pharmaceutical dosage forms containing a compound of formula **I**, as a free base or a pharmaceutically acceptable salt thereof, are described in WO 97/42187.

Medical use

Surprisingly, it has been found that the compounds defined in the present invention, as hereinbefore defined, are useful in therapy. The compounds of the present invention are well suited for inhibiting glycogen synthase kinase-3 (GSK3). Accordingly, the compounds of the present invention are expected to be useful in the prevention and/or treatment of conditions associated with glycogen synthase kinase-3 activity, i.e. the compounds may be used to produce an inhibitory effect of GSK3 in mammals, including man, in need of such prevention and/or treatment.

GSK3 is highly expressed in the central and peripheral nervous system and in other tissues. Thus, it is expected that compounds of the invention are well suited for the prevention and/or treatment of conditions associated with glycogen synthase kinase-3 in the central and peripheral nervous system. In particular, the compounds of the invention are expected to be suitable suitable in the manufacture of a medicament for the prevention and/or treatment of dementia related diseases and Alzheimer's Disease.

The dementia related diseases are selected from the group consisting of Frontotemporal dementia Parkinson's Type, Parkinson dementia complex of Guam, HIV dementia, diseases with associated neurofibrillar tangle pathologies, predemented states, vascular dementia, dementia with Lewy bodies, Frontotemporal dementia and dementia pugilistica.

The compounds of the invention are also expected to be suitable in the manufacture of a medicament for the prevention and/or treatment of amyotrophic lateral sclerosis, corticobasal degeneration, Down syndrome, Huntington's Disease, Parkinson's Disease, postencephelatic parkinsonism, progressive supranuclear palsy, Pick's Disease, Niemann-Pick's Disease, stroke, head trauma and other chronic neurodegenerative diseases, Bipolar Disease, affective disorders, depression, schizophrenia, cognitive disorders, hair loss and contraceptive medication.

The compounds of the invention are further expected to be suitable in the manufacture of a medicament for the prevention and/or treatment of Mild Cognitive Impairment, Age-Associated Memory Impairment, Age-Related Cognitive Decline, Cognitive Impairement No Dementia, mild cognitive decline, mild neurocognitive decline, Late-Life Forgetfulness, memory impairment and cognitive impairment and androgenetic alopecia.

The invention also provides for a method of prevention and/or treatment of dementia related diseases, Alzheimer's Disease and conditions associated with glycogen synthase kinase-3 and other conditions listed above comprising administrering to a mammal, including man, in need of such prevention and/or treatment a therapeutically effective amount of compounds of the present invention, as hereinbefore defined.

The present invention relates also to the use of a compound of the present invention as defined hereinbefore, in the manufacture of a medicament for the prevention and/or treatment of conditions associated with glycogen synthase kinase-3.

In the context of the present specification, the term "therapy" includes treatment as well as prevention, unless there are specific indications to the contrary. The terms "therapeutic" and "therapeutically" should be construed accordingly.

Non- Medical use

In addition to their use in therapeutic medicine, the compounds of the present invention as a free base or salts thereof, are also useful as pharmacological tools in the development and standardisation of *in vitro* and *in vivo* test systems for the evaluation of the effects of inhibitors of GSK3 related activity in laboratory animals such as cats, dogs, rabbits, monkeys, rats and mice, as part of the search for new therapeutics agents.

Pharmacology

Determination of ATP competition in Scintillation Proximity GSK3β Assay.

GSK3β scintillation proximity assay.

The competition experiments were carried out in duplicate with 10 different concentrations of the inhibitors in clear-bottom microtiter plates (Wallac, Finland). A biotinylated peptide substrate, Biotin-Ala-Ala-Glu-Glu-Leu-Asp-Ser-Arg-Ala-Gly-Ser(PO_3H_2)-Pro-Gln-Leu (AstraZeneca, Lund), was added at a final concentration of 1 μM in an assay buffer containing 1 mU recombinant human GSK3β (Dundee University, UK), 12 mM morpholinepropanesulfonic acid (MOPS), pH 7.0, 0.3 mM EDTA, 0.01% β-mercaptorethanol, 0.004 % Brij 35 (a natural detergent), 0.5 % glycerol and 0.5 μg BSA/25 μl. The reaction was initiated by the addition of 0.04 μCi [γ-^{33}P]ATP (Amersham, UK) and unlabelled ATP at a final concentration of 1 μM and assay volume of 25 μl. After incubation for 20 min at room temperature, each reaction was terminated by the addition of 25 μl stop solution containing 5 mM EDTA, 50 μM ATP, 0.1 % Triton X-100 and 0.25 mg streptavidin coated Scintillation Proximity Assay (SPA) beads (Amersham, UK). After 6 hours the radioactivity was determined in a liquid scintillation counter (1450 MicroBeta Trilux, Wallac). The inhibition curves were analysed by non-linear regression using GraphPad Prism, USA. The K_m value of ATP for GSK3β, used to calculate the inhibition constants (K_i) of the various compounds, was 20 μM.

The following abbreviations have been used:

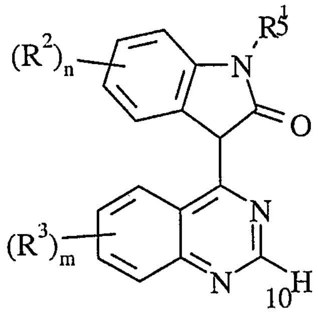
ATP	Adenosine Triphophatase
BSA	Bovin Serum Albumin
EDTA	Ethylenediaminetetraacetic acid
GSK3	Glycogen synthase kinase 3
MOPS	Morpholinepropanesulfonic acid
SPA	Scintillation Proximity Assay

Results

Typical K_i values for the compounds of the present invention are in the range of about 0.001 to about 10,000 nM. Other values for K_i are in the range of about 0.001 to about 1000 nM. Further values for K_i are in the range of about 0.001 nM to about 300 nM.

CLAIMS

1. Use of a compound of formula **I**



(I)

wherein:

R^1 is hydrogen or C_{1-3}alkyl;

R^2 is hydroxy, halogeno, trifluoromethyl, cyano, amino, nitro, carboxy, C_{1-3}alkyl, C_{1-3}alkoxy, C_{1-3}alkanoyloxy, C_{2-4}alkanoyl, C_{1-4}alkanoylamino, C_{1-4}alkoxycarbonyl, C_{1-4}alkylthio, C_{1-4}alkylsulphinyl, C_{1-4}alkylsulphonyl, carbamoyl, *N*-C_{1-4}alkylcarbamoyl, *N,N*-di(C_{1-4}alkyl)carbamoyl, aminosulphonyl, *N*-C_{1-4}alkylaminosulphonyl, *N,N*-di(C_{1-4}alkyl)aminosulphonyl, C_{1-4}alkylsulphonylamino, or a group R^4X^1,

wherein X^1 is a direct bond, C_{2-4}alkanoyl, $CONR^5R^6$, $SO_2NR^7R^8$ or SO_2R^9 (wherein R^5 and R^7 each independently are hydrogen or C_{1-2}alkyl, and R^6, R^8 and R^9 each independently are C_{1-4}alkyl, and wherein R^4 is linked to R^6, R^8 or R^9); and

R^4 is phenyl or a 5 or 6 membered heterocyclic group with one or two heteroatoms, selected independently from O, S and N, which heterocyclic group may be saturated or unsaturated and which phenyl or heterocyclic group may be substituted with one or two substituents selected independently from hydroxy, halogeno, C_{1-3}alkyl, C_{1-3}alkoxy, C_{1-3}alkanoyloxy, trifluoromethyl, cyano, amino, nitro and C_{1-4}alkoxycarbonyl;

R^3 is hydroxy, halogeno, nitro, trifluoromethyl, C_{1-3}alkyl, cyano, amino or $R^{10}X^2$,

wherein X^2 is O, CH_2, S, SO, SO_2, $NR^{11}CO$, $CONR^{12}$, SO_2NR^{13}, $NR^{14}SO_2$ or NR^{15} (wherein R^{11}, R^{12}, R^{13}, R^{14} and R^{15} each independently are hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl), or X^2 is a direct bond; and

R^{10} is selected from one of the following groups:

1) hydrogen or C_{1-5}alkyl which may be substituted with one or more groups selected independently from hydroxy, fluoro and amino;

2) C_{1-5}alkylX^3COR^{16} (wherein X^3 is O or NR^{17} (wherein R^{17} is hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{16} is C_{1-3}alkyl, $NR^{18}R^{19}$ or OR^{20} (wherein R^{18}, R^{19} and R^{20} each independently are hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl));

3) C_{1-5}alkylX^4R^{21} (wherein X^4 is O, S, SO, SO_2, OCO, $NR^{22}CO$, $CONR^{23}$, SO_2NR^{24}, $NR^{25}SO_2$ or NR^{26} (wherein R^{22}, R^{23}, R^{24}, R^{25} and R^{26} each independently are hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{21} is hydrogen, C_{1-3}alkyl, cyclopentyl, cyclohexyl or a 5 or 6 membered saturated heterocyclic group with one or two heteroatoms selected independently from O, S and N, which C_{1-3}alkyl group may be substituted with one or two substituents selected independently from oxo, hydroxy, halogeno and C_{1-4}alkoxy and which heterocyclic group may be substituted with one or two substituents selected independently from oxo, hydroxy, halogeno, C_{1-4}alkyl, C_{1-4}hydroxyalkyl and C_{1-4}alkoxy);

4) C_{1-5}alkylX^5C_{1-5}alkylX^6R^{27} (wherein X^5 and X^6 each independently are O, S, SO, SO_2, $NR^{28}CO$, $CONR^{29}$, SO_2NR^{30}, $NR^{31}SO_2$ or NR^{32} (wherein R^{28}, R^{29}, R^{30}, R^{31} and R^{32} each independently are hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{27} is hydrogen or C_{1-3}alkyl);

5) C_{1-5}alkylR^{33} (wherein R^{33} is a 5 or 6 membered saturated heterocyclic group with one or two heteroatoms selected independently from O, S and N, which heterocyclic group may be substituted with one or two substituents selected independently from oxo, hydroxy, halogeno, C_{1-4}alkyl, C_{1-6}carbonyl, C_{1-4}hydroxyalkyl and C_{1-4}alkoxy);

6) C_{2-5}alkenylR^{33} (wherein R^{33} is as defined hereinbefore);

7) C_{2-5}alkynylR^{33} (wherein R^{33} is as defined hereinbefore);

8) R^{34} (wherein R^{34} is a pyridone group, a phenyl group or a 5 or 6 membered aromatic heterocyclic group with 1 to 3 heteroatoms selected independently from O, N and S, which pyridone, phenyl or heterocyclic group may carry up to 5 substituents selected independently from hydroxy, halogeno, amino, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}hydroxyalkyl, C_{1-4}aminoalkyl, C_{1-4}alkylamino, C_{1-4}hydroxyalkoxy, carboxy, cyano, $CONR^{35}R^{36}$ and $NR^{37}COR^{38}$ (wherein R^{35}, R^{36}, R^{37} and R^{38} each independently are hydrogen, C_{1-4}alkyl or C_{1-3}alkoxyC_{2-3}alkyl));

9) C_{1-5}alkylR^{34} (wherein R^{34} is as defined hereinbefore);

10) C_{2-5}alkenylR^{34} (wherein R^{34} is as defined hereinbefore);

11) C_{2-5}alkynylR^{34} (wherein R^{34} is as defined hereinbefore);

12) C_{1-5}alkylX^7R^{34} (wherein X^7 is O, S, SO, SO_2, $NR^{39}CO$, $CONR^{40}$, SO_2NR^{41}, $NR^{42}SO_2$ or NR^{43} (wherein R^{39}, R^{40}, R^{41}, R^{42} and R^{43} each independently are hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{34} is as defined hereinbefore);

13) C_{2-5}alkenylX^8R^{34} (wherein X^8 is O, S, SO, SO_2, $NR^{44}CO$, $CONR^{45}$, SO_2NR^{46}, $NR^{47}SO_2$ or NR^{48} (wherein R^{44}, R^{45}, R^{46}, R^{47} and R^{48} each independently are hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{34} is as defined hereinbefore);

14) C_{2-5}alkynylX^9R^{34} (wherein X^9 is O, S, SO, SO_2, $NR^{49}CO$, $CONR^{50}$, SO_2NR^{51}, $NR^{52}SO_2$ or NR^{53} (wherein R^{49}, R^{50}, R^{51}, R^{52} and R^{53} each independently are hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{34} is as defined hereinbefore);

15) C_{1-3}alkyl$X^{10}C_{1-3}$alkylR^{34} (wherein X^{10} is O, S, SO, SO_2, $NR^{54}CO$, ONR^{55}, SO_2NR^{56}, $NR^{57}SO_2$ or NR^{58} (wherein R^{54}, R^{55}, R^{56}, R^{57} and R^{58} each independently are hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{34} is as defined hereinbefore);

16) R^{33} (wherein R^{33} is as defined hereinbefore); and

17) C_{1-3}alkyl$X^{10}C_{1-3}$alkylR^{33} (wherein X^{10} and R^{33} are as defined hereinbefore);

18) C_{1-5}alkylCOR^{33} (wherein R^{33} is as defined hereinbefore);

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

m is 0, 1, 2, 3 or 4;

as a free base or a pharmaceutically acceptable salt thereof, in the manufacturing of a medicament for the prevention and/or treatment of conditions associated with glycogen synthase kinase-3.

2. The use of a compound according to claim 1, wherein R^3 is $R^{10}X^2$,

wherein X^2 is O, CH_2, S, SO, SO_2, $NR^{11}CO$, $CONR^{12}$, SO_2NR^{13}, $NR^{14}SO_2$ or NR^{15} (wherein R^{11}, R^{12}, R^{13}, R^{14} and R^{15} each independently are hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl), or X^2 is a direct bond; and

R^{10} is selected from one of the following groups:

1) hydrogen or C_{1-5}alkyl which may be substituted with one or more groups selected independently from hydroxy, fluoro and amino;

2) C_{1-5}alkylX^3COR^{16} (wherein X^3 is O or NR^{17} (wherein R^{17} is hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{16} is C_{1-3}alkyl, $NR^{18}R^{19}$ or OR^{20} (wherein R^{18}, R^{19} and R^{20} each independently are hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl));

3) C_{1-5}alkylX^4R^{21} (wherein X^4 is O, S, SO, SO_2, OCO, $NR^{22}CO$, $CONR^{23}$, SO_2NR^{24}, $NR^{25}SO_2$ or NR^{26} (wherein R^{22}, R^{23}, R^{24}, R^{25} and R^{26} each independently are hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{21} is hydrogen, C_{1-3}alkyl, cyclopentyl, cyclohexyl or a 5 or 6 membered saturated heterocyclic group with one or two heteroatoms selected independently from O, S and N, which C_{1-3}alkyl group may be substituted with one or two substituents selected independently from oxo, hydroxy, halogeno and C_{1-4}alkoxy and which heterocyclic group may be substituted with one or two substituents selected independently from oxo, hydroxy, halogeno, C_{1-4}alkyl, C_{1-4}hydroxyalkyl and C_{1-4}alkoxy);

4) C_{1-5}alkylX^5C_{1-5}alkylX^6R^{27} (wherein X^5 and X^6 each independently are O, S, SO, SO_2, $NR^{28}CO$, $CONR^{29}$, SO_2NR^{30}, $NR^{31}SO_2$ or NR^{32} (wherein R^{28}, R^{29}, R^{30}, R^{31} and R^{32} each independently are hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{27} is hydrogen or C_{1-3}alkyl);

5) C_{1-5}alkylR^{33} (wherein R^{33} is a 5 or 6 membered saturated heterocyclic group with one or two heteroatoms selected independently from O, S and N, which heterocyclic group may be substituted with one or two substituents selected independently from oxo, hydroxy, halogeno, C_{1-4}alkyl, C_{1-4}hydroxyalkyl and C_{1-4}alkoxy);

6) C_{2-5}alkenylR^{33} (wherein R^{33} is as defined hereinbefore);

7) C_{2-5}alkynylR^{33} (wherein R^{33} is as defined hereinbefore);

8) R^{34} (wherein R^{34} is a pyridone group, a phenyl group or a 5 or 6 membered aromatic heterocyclic group with 1 to 3 heteroatoms selected independently from O, N and S, which pyridone, phenyl or heterocyclic group may carry up to 5 substituents selected independently from hydroxy, halogeno, amino, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}hydroxyalkyl, C_{1-4}aminoalkyl, C_{1-4}alkylamino, C_{1-4}hydroxyalkoxy, carboxy, cyano, $CONR^{35}R^{36}$ and $NR^{37}COR^{38}$ (wherein R^{35}, R^{36}, R^{37} and R^{38} each independently are hydrogen, C_{1-4}alkyl or C_{1-3}alkoxyC_{2-3}alkyl));

9) C_{1-5}alkylR^{34} (wherein R^{34} is as defined hereinbefore);

10) C_{2-5}alkenylR^{34} (wherein R^{34} is as defined hereinbefore);

11) C_{2-5}alkynylR^{34} (wherein R^{34} is as defined hereinbefore);

12) C_{1-5}alkylX^7R^{34} (wherein X^7 is O, S, SO, SO_2, $NR^{39}CO$, $CONR^{40}$, SO_2NR^{41}, $NR^{42}SO_2$ or NR^{43} (wherein R^{39}, R^{40}, R^{41}, R^{42} and R^{43} each independently are hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{34} is as defined hereinbefore);

13) C_{2-5}alkenylX^8R^{34} (wherein X^8 is O, S, SO, SO_2, $NR^{44}CO$, $CONR^{45}$, SO_2NR^{46}, $NR^{47}SO_2$ or NR^{48} (wherein R^{44}, R^{45}, R^{46}, R^{47} and R^{48} each independently are hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{34} is as defined hereinbefore);

14) C_{2-5}alkynylX^9R^{34} (wherein X^9 is O, S, SO, SO_2, $NR^{49}CO$, $CONR^{50}$, SO_2NR^{51}, $NR^{52}SO_2$ or NR^{53} (wherein R^{49}, R^{50}, R^{51}, R^{52} and R^{53} each independently are hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{34} is as defined hereinbefore);

15) C_{1-3}alkyl$X^{10}C_{1-3}$alkylR^{34} (wherein X^{10} is O, S, SO, SO_2, $NR^{54}CO$, ONR^{55}, SO_2NR^{56}, $NR^{57}SO_2$ or NR^{58} (wherein R^{54}, R^{55}, R^{56}, R^{57} and R^{58} each independently are hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{34} is as defined hereinbefore);

16) R^{33} (wherein R^{33} is as defined hereinbefore); and

17) C_{1-3}alkyl$X^{10}C_{1-3}$alkylR^{33} (wherein X^{10} and R^{33} are as defined hereinbefore).

3. The use of a compound according to claims 1 and 2, wherein R^1 is hydrogen.

4. The use of a compound according to any one of claims 1 to 3, wherein R^2 is halogeno, cyano, nitro, carboxy, C_{1-4}alkoxycarbonyl, trifluoromethyl, C_{1-3}alkyl, C_{1-3}alkoxy, *N*-C_{1-4}alkylcarbamoyl, *N,N*-di(C_{1-4}alkyl)carbamoyl, aminosulphonyl, or a group R^4X^1, wherein X^1 is $CONR^5R^6$, (wherein R^5 is hydrogen or C_{1-2}alkyl, and R^6 is C_{1-4}alkyl, and wherein R^4 is linked to R^6); and

R^4 is phenyl or a 5 or 6 membered heterocyclic group with one or two heteroatoms, selected independently from O and N, which heterocyclic group may be saturated or unsaturated and which phenyl or heterocyclic group may be substituted with one or two substituents selected independently from hydroxy, halogeno, C_{1-3}alkyl, C_{1-3}alkoxy, C_{1-3}alkanoyloxy, trifluoromethyl, cyano, amino, nitro and C_{1-4}alkoxycarbonyl;

n is 0, 1 or 2.

5. The use of a compound according to any one of claims 1 to 4, wherein R^3 is $R^{10}X^2$, wherein X^2 is O; and

R^{10} is selected from one of the following groups:

3) C_{1-5}alkylX^4R^{21} (wherein X^4 is O or NR^{26} (wherein R^{21} and R^{26} each independently are hydrogen, C_{1-3}alkyl, cyclopentyl or cyclohexyl));

4) C_{1-5}alkylX^5C_{1-5}alkylX^6R^{27} (wherein X^5 and X^6 are O and R^{27} is hydrogen or C_{1-3}alkyl);

5) C_{1-5}alkylR^{33} (wherein R^{33} is a 6 membered saturated heterocyclic group with one or two heteroatoms, selected independently from O and N, which heterocyclic group may be substituted with one or two substituents selected independently from oxo, hydroxy, halogeno, C_{1-4}alkyl, C_{1-4}hydroxyalkyl and C_{1-4}alkoxy);

9) C_{1-5}alkylR^{34} (wherein R^{34} is a 5 membered aromatic heterocyclic group with 1 to 3 heteroatoms selected independently from O and N, which heterocyclic group may carry up to 5 substituents selected independently from halogeno, amino, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}hydroxyalkyl, C_{1-4}aminoalkyl, C_{1-4}alkylamino, C_{1-4}hydroxyalkoxy, carboxy, hydoxy, cyano, $CONR^{35}R^{36}$ and $NR^{37}COR^{38}$ (wherein R^{35}, R^{36}, R^{37} and R^{38} each independently are hydrogen, C_{1-4}alkyl or C_{1-3}alkoxyC_{2-3}alkyl)); and

17) C_{1-3}alkyl$X^{10}C_{1-3}$alkylR^{33} (wherein X^{10} is O and R^{33} are as defined hereinbefore);

m is 0, 1 or 2.

6. The use of a compound according to any one of claims 1, 3 and 4, wherein R^3 is $R^{10}X^2$, wherein X^2 is O; and R^{10} is selected from one of the following groups:

1) hydrogen or C_{1-5}alkyl;

5) C_{1-5}alkylR^{33} (wherein R^{33} is a 5 or 6 membered saturated heterocyclic group with one or two heteroatoms, selected independently from O, S and N, which heterocyclic group may be substituted with one or two substituents selected independently from oxo, hydroxy, halogeno, C_{1-4}alkyl, C_{1-6}carbonyl, C_{1-4}hydroxyalkyl and C_{1-4}alkoxy);

18) C_{1-5}alkylCOR^{33} (wherein R^{33} is as defined hereinbefore).

7. The use of a compound according to any of claims 1 to 5, wherein R^3 is $R^{10}X^2$, wherein X^2 is O; and R^{10} is

4) C_{1-5}alkylX^5C_{1-5}alkylX^6R^{27} (wherein X^5 and X^6 are O and R^{27} is hydrogen or C_{1-3}alkyl).

8. The use of a compound according to any one of claims 1 to 7, wherein the R^2 is substituted on position 5 and/or 6 and R^3 is substituted on position 6, 7 and/or 8.

9. The use of a compound of formula **I** as defined in claim 1, in the manufacture of a medicament for the prevention and/or treatment of dementia related diseases and Alzheimer's Disease.

10. The use according to claim 9, wherein the dementia related diseases are selected from the group consisting of Frontotemporal dementia Parkinson's Type, Parkinson dementia complex of Guam, HIV dementia, diseases with associated neurofibrillar tangle pathologies, predemented states, vascular dementia, dementia with Lewy bodies, Frontotemporal dementia and dementia pugilistica.

11. The use of a compound of formula **I** as defined in claim 1, in the manufacture of a medicament for the prevention and/or treatment of amyotrophic lateral sclerosis, corticobasal degeneration, Down syndrome, Huntington's Disease, Parkinson's Disease, postencephelatic parkinsonism, progressive supranuclear palsy, Pick's Disease, Niemann-Pick's Disease, stroke, head trauma and other chronic neurodegenerative diseases, Bipolar Disease, affective disorders, depression, schizophrenia, cognitive disorders, hair loss and contraceptive medication.

12. The use of a compound of formula I as defined in claim 1, in the manufacture of a medicament for the prevention and/or treatment of Mild Cognitive Impairment, Age-Associated Memory Impairment, Age-Related Cognitive Decline, Cognitive Impairement No Dementia, mild cognitive decline, mild neurocognitive decline, Late-Life Forgetfulness, memory impairment and cognitive impairment and androgenetic alopecia.

13. A compound which is
4-(6-Fluorooxindol-3-yl)-6-methoxy-7-(3-morpholinopropoxy)quinazoline,
4-(5-Cyanooxindol-3-yl)-6-methoxy-7-(2-methoxyethoxy)quinazoline,
4-(5-Cyanooxindol-3-yl)-7-(2-methoxyethoxy)quinazoline,
4-(5-Cyanooxindol-3-yl)-7-(2-(imidazol-1-yl)ethoxy)-6-methoxyquinazoline,

4-(5-Cyanooxindol-3-yl)-7-(3-morpholinopropoxy)quinazoline,

4-(5-Carbamoyloxindol-3-yl)-6-methoxy-7-(3-morpholinopropoxy)quinazoline,

4-(6-Cyanooxindol-3-yl)-6-methoxy-7-(3-morpholinopropoxy)quinazoline,

4-(6-Bromooxindol-3-yl)-7-(3-morpholinopropoxy)quinazoline,

2-Hydroxy-3-[7-(2-methoxyethoxy)quinazolin-4-yl]-1*H*-indole-5-carboxylic acid (4-phenylbutyl)amide,

6-Chloro-3-[7-(3-morpholin-4-yl-propoxy)quinazolin-4-yl]-1,3-dihydro-indol-2-one hydrochloride,

3-{7-[2-(2-Methoxyethoxy)ethoxy]quinazolin-4-yl}-1,3-dihydroindol-2-one hydrochloride,

6-Fluoro-3-[7-(3-morpholin-4-ylpropoxy)quinazolin-4-yl]-1,3-dihydro-indol-2-one dihydrochloride,

7-Fluoro-3-[6-methoxy-7-(3-morpholin-4-ylpropoxy)quinazolin-4-yl]-1,3-dihydroindol-2-one dihydrochloride,

3-[7-(3-Morpholin-4-ylpropoxy)quinazolin-4-yl]-2-oxo-2,3-dihydro-1*H*-indole-5-carboxylic acid dimethylamide,

3-[7-(3-Morpholin-4-ylpropoxy)quinazolin-4-yl]-6-propyl-1*H*-indol-2-ol hydrochloride,

6-Ethyl-3-[7-(3-morpholin-4ylpropoxy)quinazolin-4-yl]-1*H*-indol-2-ol hydrochloride,

2-Hydroxy-3-[7-(2-methoxyethoxy)quinazolin-4-yl]-1*H*-indole-5-carboxylic acid [2-(1-methylpyrrolidin-2-yl)ethyl]amide,

2-Hydroxy-3-[7-(2-morpholin-4-ylethoxy)quinazolin-4-yl]-1*H*-indole-5-carbonitril dihydrochloride,

2-Hydroxy-3-[7-(2-methoxyethoxy)quinazolin-4-yl]-1H-indole-5-carboxylic acid (tetrahydrofuran-2-ylmethyl)amide,

2-Hydroxy-3-[7-(2-methoxyethoxy)quinazolin-4-yl]-1*H*-indole-5-carboxylic acid (3-morpholin-4-ylpropyl)amide,

2-Hydroxy-3-[7-(2-methoxyethoxy)quinazolin-4-yl]-1*H*-indole-5-carboxylic acid [2-(1*H*-imidazol-4-yl)ethyl]amide,

2-Hydroxy-3-{7-[2-(2-methoxyethoxy)ethoxy]quinazolin-4-yl}-1*H*-indole-5-carbonitrile hydrochloride,

3-[7-(2-Imidazol-1-yl-ethoxy)-6-methoxyquinazolin-4-yl]-2-oxo-2,3-dihydro-1*H*-indole-5-sulfonamide acetate, 6-Bromo-3-[6-methoxy-7-(3-morpholin-4-yl-propoxy)quinazolin-4-yl]-1,3-dihydroindol-2-one dihydrochloride,

6-Bromo-3-quinazolin-4-yl-1,3-dihydroindol-2-one,

6-Bromo-3-{6-methoxy-7-[2-(2-methoxyethoxy)ethoxy]quinazolin-4-yl}-1,3-dihydroindol-2-one hydrochloride,

3-{7-[2-(2-Morpholin-4-yl-ethoxy)ethoxy]quinazolin-4-yl}-2-oxo-2,3-dihydro-1*H*-indole-5-carbonitrile hydrochloride,

6-Chloro-3-{7-[2-(2-methoxyethoxy)ethoxy]quinazolin-4-yl}-1,3-dihydroindol-2-one hydrochloride,

3-{7-[2-(4-Acetylpiperazin-1-yl)ethoxy]quinazolin-4-yl}-2-oxo-2,3-dihydro-1*H*-indole-5-carbonitrile hydrochloride,

5-Chloro-3-{7-[2-(2-methoxyethoxy)ethoxy]quinazolin-4-yl}-1,3-dihydroindol-2-one hydrochloride,

3-{7-[2-(4-Butyrylpiperazin-1-yl)ethoxy]quinazolin-4-yl}-2-oxo-2,3-dihydro-1*H*-indole-5-carbonitrile hydrochloride,

3-{7-[2-(4-Acetylpiperazin-1-yl)-2-oxoethoxy]quinazolin-4-yl}-2-oxo-2,3-dihydro-1*H*-indole-5-carbonitrile hydrochloride,

3-{7-[4-(4-Acetylpiperazin-1-yl)-4-oxobutoxy]quinazolin-4-yl}-2-oxo-2,3-dihydro-1*H*-indole-5-carbonitrile hydrochloride,

6-Bromo-3-[7-(2-imidazol-1-ylethoxy)-6-methoxyquinazolin-4-yl]-1,3-dihydro-indol-2-one dihydrochloride,

3-[7-(2-Imidazol-1-ylethoxy)-6-methoxyquinazolin-4-yl]-2-oxo-2,3-dihydro-1*H*-indole-6-carbonitrile dihydrochloride,

3-[7-(3-Morpholin-4-ylpropoxy)quinazolin-4-yl]-2-oxo-2,3-dihydro-1*H*-indole-5-carboxylic acid methylamide,

3-{7-[3-(4-Methylpiperazin-1-yl)propoxy]quinazolin-4-yl}-2-oxo-2,3-dihydro-1*H*-indole-5-carbonitrile hydrochloride,

2-Hydroxy-3-[8-(2-morpholin-4-ylethoxy)quinazolin-4-yl]-1*H*-indole-5-carbonitrile hydrochloride,

6-Bromo-3-[7-(3-morpholin-4-ylpropoxy)quinazolin-4-yl]-2-oxo-2,3-dihydro-1*H*-indole-5-carboxylic acid methylamide,

6-Methyl-3-[7-(3-morpholin-4-ylpropoxy)quinazolin-4-yl]-1*H*-indol-2-ol,

5-Bromo-6-methyl-3-[7-(3-morpholin-4-ylpropoxy)quinazolin-4-yl]-1*H*-indol-2-ol dihydrochloride,
6-Bromo-3-[7-(3-morpholin-4-ylpropoxy)quinazolin-4-yl]-5-nitro-1*H*-indol-2-ol dihydrochloride and
2-Hydroxy-3-[7-(2-methoxyethoxy)quinazolin-4-yl]-1*H*-indole-5-carboxylic acid
as a free base or salts thereof.

14. A compound which is
3-[7-(3-Dimethylaminopropoxy)quinazolin-4-yl]-2-hydoxy-1*H*-indol-5-carbonitrile hydrochloride,
3-[7-(2-Dimethylaminoethoxy)quinazolin-4-yl]-2-hydoxy-1*H*-indol-5-carbonitrile fumarate,
3-{7-[2-(Isopropylmethylamino)ethoxy]quinazolin-4-yl]-2-oxo-2,3-dihydro-1*H*-indol-5-carbonitrile fumarate and
3-[7-(2-Diisopropylamino)ethoxy)quinazolin-4-yl]-2-hydroxy-1*H*-indol-5-carbonitrile fumarate,
as a free base or salts thereof.

15. Compounds according to claims 13 and 14, for use in therapy.

16. A use of a compound according to claims 13 and 14 in the manufacturing of a medicament for the prevention and/or treatment of conditions associated with glycogen synthase kinase-3.

17. A use of a compound according to claims 13 and 14 in the manufacturing of a medicament for the prevention and/or treatment of dementia related diseases and Alzheimer's Disease.

18. The use according to claim 17, wherein the dementia related diseases are selected from the group consisting of Frontotemporal dementia Parkinson's Type, Parkinson dementia complex of Guam, HIV dementia, diseases with associated neurofibrillar tangle

pathologies, predemented states, vascular dementia, dementia with Lewy bodies, Frontotemporal dementia and dementia pugilistica.

19. A use of a compound according to claims 13 and 14 in the manufacturing of a medicament for the prevention and/or treatment of amyotrophic lateral sclerosis, corticobasal degeneration, Down syndrome, Huntington's Disease, Parkinson's Disease, postencephelatic parkinsonism, progressive supranuclear palsy, Pick's Disease, Niemann-Pick's Disease, stroke, head trauma and other chronic neurodegenerative diseases, Bipolar Disease, affective disorders, depression, schizophrenia, cognitive disorders, hair loss and contraceptive medication.

20. A use of a compound according to claims 13 and 14 in the manufacturing of a medicament for the prevention and/or treatment of Mild Cognitive Impairment, Age-Associated Memory Impairment, Age-Related Cognitive Decline, Cognitive Impairement No Dementia, mild cognitive decline, mild neurocognitive decline, Late-Life Forgetfulness, memory impairment and cognitive impairment and androgenetic alopecia.

21. A pharmaceutical composition for use in prevention and/or treatment of dementia related diseases, Alzheimer's Disease and conditions associated with glycogen synthase kinase-3, comprising a therapeutically effective amount of a compound of formula **I** as defined in any one of claims 1 to 8, and pharmaceutically acceptable carriers or diluents.

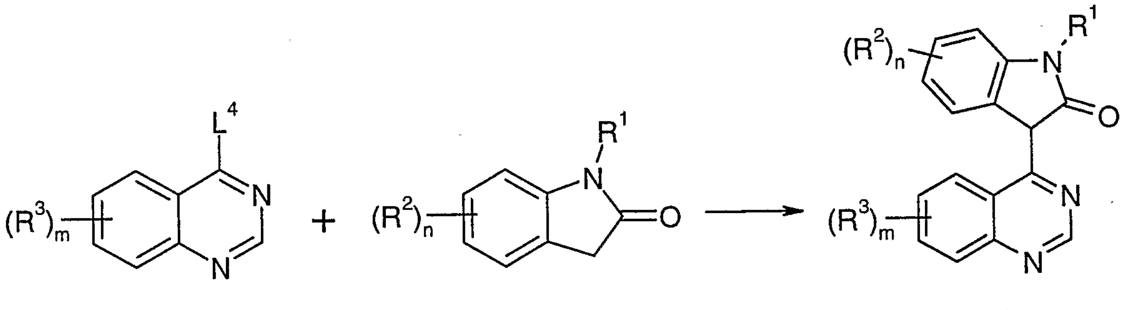
22. The pharmaceutical composition for use according to claim 21, wherein the compound is defined as in claims 13 and 14.

23. A method of prevention and/or treatment of dementia related diseases, Alzheimer's Disease and conditions associated with glycogen synthase kinase-3, comprising administering to a mammal, including man in need of such prevention and/or treatment, a therapeutically effective amount of a compound of formula **I** as defined in any one of claims 1 to 8.

24. The method according to claim 23, wherein the compound is defined as in claims 13 and 14.

25. A process for the preparation of a compound of formula **I** according to claims 13 and 14, comprising of:

i)

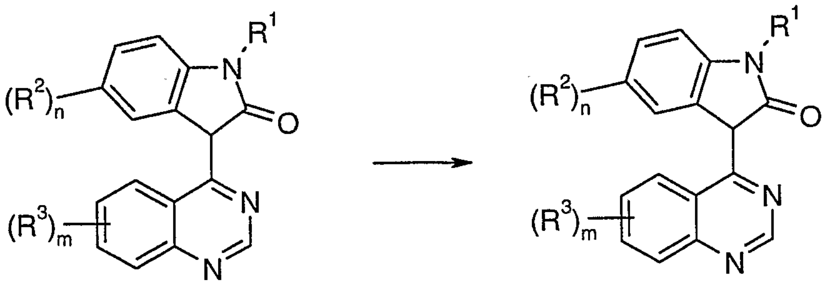


(B (IV, VI, VII, XI)) (C) (I)

reacting a compound of formula **B (IV, VI, VII, XI)**, wherein L^4 is a leaving group or SCH_3 with a compound of formula **C**, to obtain a compound of formula **I**, and R^1, R^2, R^3, m and n are as defined in general formula **I**,

or,

ii)

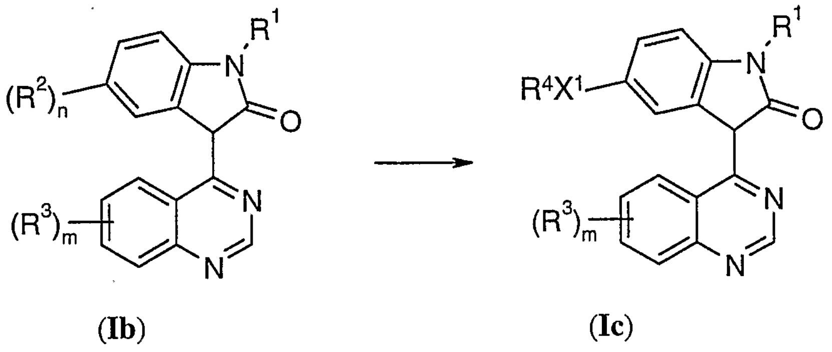


(Ia) **(Ib)**

hydrolysis of a compound of formula **Ia**, wherein R^2 is C_{1-6}alkoxycarbonyl to obtain a compound of formula **Ib**, wherein R^2 is carboxy and R^1, R^3, m and n are as defined in general formula **I** ,

or,

iii)



amidation of a compound of formula **Ib,** wherein R^2 is carboxy to obtain a compound of formula **Ic**, wherein R^2 is R^4X^1 and X^1 is $CONR^5R^6$, and R^1, R^3, R^4, R^5, R^6, m and n are as defined in general formula **I**.

26. A compound which is
7-(2-Morpholin-4-yl)ethoxy)-3*H*-quinazolin-4-one,
4-Chloro-7-[(2-morpholin-4-yl)ethoxy]quinazoline,
7-[2-(2-Methoxyethoxy)ethoxy]-3*H*-quinazolin-4-one,
4-Chloro-7-[2-(2-methoxyethoxy)ethoxy]quinazoline,
4-(Methylthio)-7-[2-(2-morpholin-4-ylethoxy)ethoxy]quinazoline,
7-[2-(4-Acetylpiperazin-1-yl)ethoxy]-4-methylthioquinazoline,
7-(2-Bromoethoxy)-4-(methylthio)quinazoline,
7-[2-(4-Butyrylpiperazin-1-yl)ethoxy]-4-(methylthio)quinazoline,
7-[2-(4-Acetylpiperazin-1-yl)-2-oxoethoxy]-4-(methylthio)quinazoline,
1-Acetyl-4-(4-chlorobutanoyl)piperazine,
7-[4-(4-Acetylpiperazin-1-yl)-4-oxobutoxy]-4-(methylthio)quinazoline,
2-Oxo-2,3-dihydro-1*H*-indole-5-carboxylic acid dimethylamide,
2-Oxo-2,3-dihydro-1*H*-indole-5-carboxylic acid methylamide,
7-[3-(4-Methylpiperazin-1-yl)propoxy]-3*H*-quinazolin-4-one,
4-Chloro-7-[3-(4-methylpiperazin-1-yl)propoxy]quinazoline,
4-Chloro-8-(2-morpholin-4-ylethoxy)quinazoline,
6-Bromo-5-(2-chloroacetyl)1,3-dihydroindol-2-one,
6-Bromo-2-oxo-2,3-dihydro-1*H*-indole-5-carboxylic acid,

6-Bromo-2-oxo-2,3-dihydro-1*H*-indole-5-carboxylic acid methylamide,
2-(4-Ethylphenyl)-*N*-methoxyacetamide,
6-Ethyl-1-methoxy-1,3-dihydroindol-2-one,
6-Ethyl-1,3-dihydroindol-2-one,
N-Methoxy-2-(4-propylphenyl)acetamide,
1-Methoxy-6-propyl-1,3-dihydroindol-2-one,
6-Propyl-1,3-dihydroindol-2-one,
5-Bromo-6-methyl-1,3-dihydroindol-2-one and
6-Bromo-5-nitro-1,3-dihydroindol-2-one,
as a free base or salts thereof.

27. A compound which is
7-(3-Dimethylaminopropoxy)-3*H*-quinazolin-4-one,
7-(2-Dimethylaminoethoxy)-3*H*-quinazolin-4-one,
7-[2-(Isopropylmethylamino)ethoxy]-3*H*-quinazolin-4-one,
7-(2-Diisopropylaminoethoxy)-3*H*-quinazolin-4-one,
[3-(4-Chloroquinazolin-7-yloxy)propyl]dimethylamine,
[2-(4-Chloroquinazolin-7-yloxy)ethyl]dimethylamine,
[2-(4-Chloroquinazolin-7-yloxy)ethyl]isopropylmethylamine and
[2-(4-Chloro-quinazolin-7-yloxy)ethyl]diisopropylamine,
as a free base or salts thereof.

28. The use of the compounds according to claims 26 and 27 for the preparation of the compounds as defined in any one of claims 13 and 14.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 02/02370

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: A61K 31/517, C07D 403/04, C07D 403/14, A61P 25/28, A61P 25/14, A61P 25/18, A61P 25/24, A61P 15/16, A61P 9/10

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)

IPC7: A61K, C07D, A61P

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

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CHEM. ABS DATA, WPI DATA, EPO-INTERNAL

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 9742187 A1 (ZENECA LIMITED), 13 November 1997 (13.11.97) --	1-8,13-16, 21-25
X	WO 9910349 A1 (ZENECA LIMTED), 4 March 1999 (04.03.99) --	1-8,13-16, 21-25
P,X	J. Med. Chem. Volume 45, 2002, Piyasena Hewawasam et al, "Synthesis and Structure-Activity Relationships of 3-Aryloxindoles: A New class of Calcium-Dependent, Large Conductance Potassium (Maxi-K) Channel Openers with Neuroprotective Properties", pages 1487-1499 --	1-8,11, 13-16,19, 23-25

☒ Further documents are listed in the continuation of Box C. ☒ 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 application or patent 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 12 May 2003	Date of mailing of the international search report 14 -05- 2003
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer VIVECA NORÉN/EÖ Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 02/02370

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 1136493 A1 (SANOFI-SYNTHELABO), 26 Sept 2001 (26.09.01) --	1-25
A	WO 9533750 A1 (PFIZER INC.), 14 December 1995 (14.12.95) --	1-25
A	WO 0010975 A1 (SUMITOMO PHARMACEUTICALS CO. LTD.), 2 March 2000 (02.03.00) -- --------	1-25

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE02/02370

Box I **Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 23-24
because they relate to subject matter not required to be searched by this Authority, namely:
see next sheet

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II **Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

see next sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: 1-25

Remark on Protest ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

`Box I.1

Claims 23-24 relate to methods of treatment of the human or animal body by surgery or by therapy/ diagnostic methods practised on the human or animal body/Rule 39.1.(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds/compositions.

Box II

According to Article 34(3)(a-c) and Rule 13.2 of PCT a patent application is allowed to comprise only one independent invention. To, when applying for patent for a process, also be able to apply for patent protection of the starting material and the intermediates of the process, it is necessary that the starting material or intermediates show a clear structural similarity with the final products. The compounds of claims 26-27 do not exhibit enough similarity with the final product (formula I) to fulfill these demands of unity. Hence the present application comprises the two independent inventions as follows:

Invention 1: Compounds according to formula I, use and processes of manufacture thereof and pharmaceutical formulation and methods of treatment comprising these compounds. Claims 1-25.
Invention 2: Remaining compounds defined in claim 26 and their use. Claims 26-27.

As no additional fee has been paid only invention 1 has been searched.

INTERNATIONAL SEARCH REPORT

Information on patent family members

29/03/03

International application No.
PCT/SE 02/02370

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9742187 A1	13/11/97	AU 2647597 A	26/11/97
		EP 0912557 A	06/05/99
		GB 9707800 D	00/00/00
		JP 2000510115 T	08/08/00
		US 6265411 B	24/07/01
		ZA 9703844 A	06/11/97
WO 9910349 A1	04/03/99	AU 8816298 A	16/03/99
		EP 1005470 A	07/06/00
		JP 2001514182 T	11/09/01
		US 6294532 B	25/09/01
EP 1136493 A1	26/09/01	AU 6215001 A	03/10/01
		WO 0170728 A	27/09/01
WO 9533750 A1	14/12/95	AT 196295 T	15/09/00
		AU 692548 B	11/06/98
		AU 2453095 A	04/01/96
		BR 9502708 A	30/04/96
		CA 2192354 A	14/12/95
		CN 1049659 B	23/02/00
		CN 1150428 A	21/05/97
		CN 1246475 A	08/03/00
		CZ 9603608 A	14/07/99
		DE 69518841 D,T	11/01/01
		DK 764166 T	09/10/00
		EP 0764166 A,B	26/03/97
		SE 0764166 T3	
		ES 2150567 T	01/12/00
		FI 964894 A	05/12/96
		GR 3034765 T	28/02/01
		HR 950321 A,B	28/02/98
		HU 75774 A	28/05/97
		HU 9603391 D	00/00/00
		IL 114004 D	00/00/00
		IL 129954 D	00/00/00
		IL 139504 D	00/00/00
		IL 139505 D	00/00/00
		JP 3193055 B	30/07/01
		JP 3223169 B	29/10/01
		JP 9507249 T	22/07/97
		JP 11246411 A	14/09/99
		JP 2000001434 A	07/01/00
		NO 2391 A	06/02/97
		NO 308994 B	27/11/00
		NO 310234 B	11/06/01
		NO 965237 A	06/02/97
		NO 20002391 D	00/00/00
		NZ 285442 A	27/05/98
		PL 320631 A	13/10/97
		PT 764166 T	31/01/01
		SK 155596 A	11/12/00
		US 5962479 A	05/10/99
		ZA 9504677 A	09/12/96

INTERNATIONAL SEARCH REPORT

Information on patent family members

29/03/03

International application No.

PCT/SE 02/02370

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0010975 A1	02/03/00	AU 5301199 A	14/03/00
		CA 2340701 A	02/03/00
		CN 1313853 T	19/09/01
		EP 1105376 A	13/06/01
		JP 2002523400 T	30/07/02