Isoquinolinone derivatives as NK3 antagonists

Field of the invention

The present invention relates to compounds useful in therapy, in particular in the treatment of psychosis, to compositions comprising said compounds, and to methods of treating diseases comprising the administration of said compounds.

Background of the invention

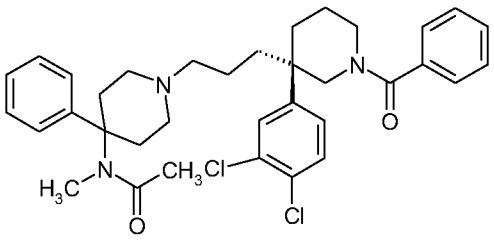
The currently approved antipsychotic drugs share the common feature of reducing the dopamine signalling in the brain. This is achieved through either a dopamine D2 receptor antagonistic or partial agonistic effect. The first generation antipsychotics (also referred to as "typical") are often associated with extra-pyrimidal side effects wherefore the use of these agents have diminished. Second generation or "atypical" antipsychotics in addition to the D2 receptor affinity have affinity to the serotonin receptor 2A (5-HT_{2A}). Some atypical antipsychotics in addition have affinity for the 5-HT_{2C}, 5-$HT_{6,}$ or 5-HT_7 receptors. Atypical antipsychotics give rise to fewer extra-pyrimidal side effects, but are still hampered by weight gain and QT_C effects. Examples of atypicals are clozapine, olanzapine and risperidone.

More recently, neurokinin receptors have been suggested as targets for CNS diseases [Albert, *Expert Opin. Ther. Patents*, 14, 1421-1433, 2004]. Neurokinins (or tachykinins) are a family of neuropeptides, which include substance P (SP), neurokinin A (NKA), and neurokinin B (NKB). The biological effects of these substances are primarily effected through binding to and activation of the three neurokinin receptors NK1, NK2, and NK3. Although some cross reactivity probably exists, SP has the highest affinity and is believed to be the endogenous ligand for NK1, and likewise for NKA and NK2, and for NKB and NK3.

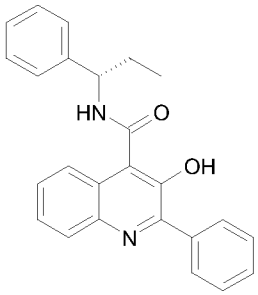
NK3 is primarily expressed centrally in regions including cortical regions, such as frontal, parietal and cingulated cortex; nuclei of the amygdale, such as the basal, central and lateral nuclei; the hippocampus; and mesencephalon structures, such as ventral tegmental area, substantia nigra pars compacta, and dorsal raphe nuclei

[Spooren et al, *Nature Reviews*, 4, 967-975, 2005]. The NK3 receptor is expressed on dopaminergic neurons, and Spooren et al has suggested that the antipsychotic effects of NK3 antagonists are mediated by an inhibition of the dopamine tone, particularly at the D2 receptor combined with a reduction of the serotonergic tone, particularly at the 5-HT_{2A} receptor.

Two structurally distinct NK3 antagonists, namely talnetant and osanetant, have been clinically tested for antipsychotic, and in particular antischizophrenic effects.



Osanetant

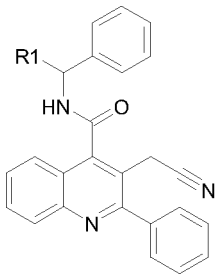


Talnetant

Osanetant proved superior to placebo in clinical trials, in particular on positive symptoms of psychosis, i.e. delusions, hallucinations and paranoia [*Am.J.Psychiatry*, 161, 2004, 975-984]. Similarly, talnetant has been shown in clinical trials to ameliorate the cognitive behaviour of schizophrenics [*Curr.Opion.Invest.Drug*, 6, 717-721, 2005]. Nevertheless, both compounds are hampered by poor pharmacokinetic and pharmacodynamic properties including poor solubility, poor bioavailability, relatively high clearance, and poor blood-brain barrier penetration [*Nature reviews*, 4, 967-975, 2005]. These results lend support to the notion that the NK3 receptor is a promising target for the treatment of e.g. psychosis, however emphasising the need for identifying compounds with adequate pharmacokinetic and pharmacodynamic properties.

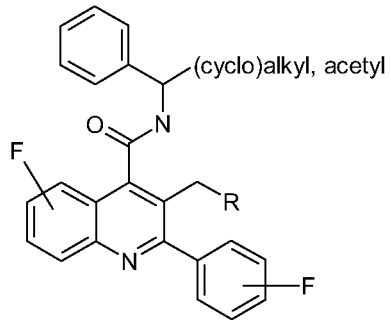
WO95/32948 discloses a range of quinoline derivatives, including talnetant as NK3 antagonists.

More recently, WO 2006/130080 discloses compounds having the core structure



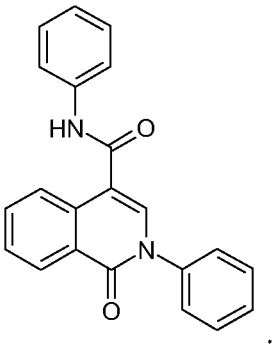
which compounds are said to be NK3 antagonists; and WO 2006/050991 and WO 2006/050992 disclose further quinolinecarboxamides derivatives, which derivatives are said to be NK3 antagonists.

WO 2005/014575 discloses compounds of the formula



wherein R represents N-containing heterocycles, i.e. pyrazolyl, triazolyl and tetrazolyl.

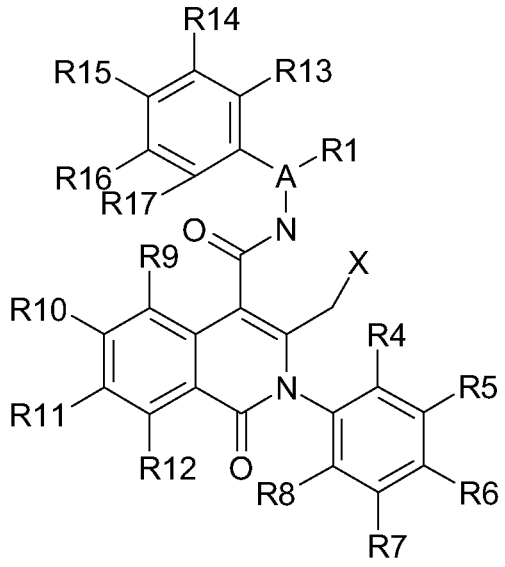
Finally, *Ind.J.Chem. Section B*, 18B, 304-306, 1979 discloses a study on the synthesis of compounds with the following core structure



Summary of the invention

The present inventors have surprisingly found that certain isoquinolinone derivatives are potent NK3 antagonists, which may as such be used in the treatment of

e.g. psychosis. Accordingly, in one embodiment the invention relates to compounds of formula I



[I]

wherein A represents N, CH or CR^1;

wherein each R^1 independently represents hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, -C(O)-C_{1-6}alkyl, -C(O)-C_{2-6}alkenyl, -C(O)-C_{2-6}alkynyl, -C(O)-O-C_{1-6}alkyl, -C(O)-O-C_{2-6}alkenyl, -C(O)-O-C_{2-6}alkynyl or phenyl, wherein said phenyl, C_{1-6}alkyl, C_{2-6}alkenyl or C_{2-6}alkynyl is optionally substituted with one or more substituents selected from halogen, hydroxyl, haloC_{1-6}alkyl, nitro, C_{1-6}alkoxy, and NR^2R^3;

wherein X represents hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, cyano, $-OR^2$, -O-C(O)R^2, -OC(O)NR^2R^3, -C(O)-NR^2R^3, -N(R^2)C(O)R^3, -N(R^2)-C(O)NR^2R^3 or NR^2R^3, or X represents a mono-cyclic, bi-cyclic or tri-cyclic moiety having 4-16 ring atoms one of which is nitrogen, and wherein one, two or three additional ring atoms may be a hetero atom selected from N, O and S, and wherein said mono-cyclic, bi-cyclic or tri-cyclic moiety may optionally be substituted with one or more substituents W,

wherein W is selected from hydrogen, hydroxy, halogen, cyano, (=O), -O-$(CH_2)_c$-O-, wherein c is 2 or 3 (spiro), $(CH_2)_d$, wherein d is 5 or 6 (spiro), C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, -C(O)-C_{1-6}alkyl, -C(O)-C_{2-6}alkenyl, -C(O)-C_{2-6}alkynyl, -C(O)-O-C_{1-6}alkyl, -C(O)-O-C_{2-6}alkenyl, -C(O)-O-C_{2-6}alkynyl, -O-C(O)-C_{1-6}alkyl, -O-

C(O)-C_{2-6}alkenyl, -O-C(O)-C_{2-6}alkynyl, -C(O)H, COOH; or wherein W represents a moiety of the formula $-(CH_2)_a$-Y-$(CH_2)_b$-Z;

wherein a and b independently represent an integer selected from 0, 1, 2 and 3;

wherein Y represents a bond, C(O), O, S, -O-C(O), -C(O)-O-, -NR^2-, -NR^2-C(O)-, -C(O)-NH-, or $S(O)_2$;

wherein Z represents hydrogen, C_{1-6}alkyl, NR^2R^3, cyano or a mono-cyclic or fused bi-cyclic moiety comprising 4 to12 ring atoms of which optionally one, two or three are hetero atoms selected from amongst N, O, and S, and wherein said mono-cyclic or fused bi-cyclic moiety is optionally substituted with one or more substituents selected from the group consisting of halogen, cyano, C_{1-6}alkyl, hydroxyl, and C_{1-6}alkoxy, pyrazinyl, phenyl, pyridyl, and halogen substituted phenyl;

wherein each of R^4-R^8, R^9-R^{12}, and R^{13}-R^{17} independently represent hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, halogen, NR^2R^3, hydroxy, cyano, nitro, C_{1-6}alkoxy, haloC_{1-6}alkyl or hydroxyC_{1-6}alkyl;

wherein R^2 and R^3 independently represent hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, hydroxyC_{1-6}alkyl, haloC_{1-6}alkyl or phenyl;

and pharmaceutically acceptable salts thereof.

In one embodiment, the invention relates to compounds of formula I and pharmaceutically acceptable salts thereof for use in therapy.

In one embodiment, the invention relates to pharmaceutical compositions comprising compounds of formula I and pharmaceutically acceptable salts thereof.

In one embodiment, the invention relates to methods of treatment, which methods comprise the administration of therapeutically effective amounts of a compound of formula I and pharmaceutically acceptable salts thereof to a patient in need thereof.

In one embodiment, the invention relates to the use of a compound of formula I and pharmaceutically acceptable salts thereof in the manufacture of a medicament.

In one embodiment, the invention relates to compounds of formula I and pharmaceutically acceptable salts thereof for use in the treatment of diseases.

Definitions

In the present context, "alkyl" is intended to indicate a straight, branched and/or cyclic saturated hydrocarbon. In particular "C_{1-6}alkyl" is intended to indicate such hydrocarbon having 1, 2, 3, 4, 5, or 6 carbon atoms. Examples of C_{1-6}alkyl include methyl, ethyl, propyl, butyl, pentyl, hexyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, 2-methyl-propyl, tert.-butyl, and cyclopropylmethyl.

In the present context, "alkenyl" is intended to indicate a straight, branched and/or cyclic hydrocarbon comprising at least one carbon-carbon double bond. In particular "C_{2-6}alkenyl" is intended to indicate such hydrocarbon having 2, 3, 4, 5, or 6 carbon atoms. Examples of C_{2-6}alkenyl include ethenyl, 1-propenyl, 2-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, and cyclohexenyl.

In the present context, "alkynyl" is intended to indicate a straight, branched and/or cyclic hydrocarbon comprising at least one carbon-carbon triple bond and optionally also one or more carbon-carbon double bonds. In particular "C_{2-6}alkynyl" is intended to indicate such hydrocarbon having 2, 3, 4, 5, or 6 carbon atoms. Examples of C_{2-6}alkynyl include ethynyl, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, 3-butynyl and 5-but-1-en-3-ynyl.

In the present context "halogen" is intended to indicate members of the 7th group of the periodic system, e.g. flouro, chloro, bromo, and iodo.

In the present context, "alkoxy" is intended to indicate a moiety of the formula –OR', wherein R' indicates alkyl as defined above. In particular "C_{1-6}alkoxy" is intended to indicate such moiety wherein the alkyl part has 1, 2, 3, 4 5, or 6 carbon atoms.

In the present context, haloalkyl is intended to indicate an alkyl as defined above substituted with one or more halogens. In particular, haloC_{1-6}alkyl is intended to indicate a moiety wherein the alkyl part has 1, 2, 3, 4, 5 or 6 carbon atoms. One example of haloalkyl is trifluoromehtyl.

In the present context, pharmaceutically acceptable salts include pharmaceutical acceptable acid addition salts, pharmaceutically acceptable metal salts, ammonium and alkylated ammonium salts. Acid addition salts include salts of inorganic acids as well as organic acids.

Examples of suitable inorganic acids include hydrochloric, hydrobromic, hydroiodic, phosphoric, sulfuric, sulfamic, nitric acids and the like.

Examples of suitable organic acids include formic, acetic, trichloroacetic, trifluoroacetic, propionic, benzoic, cinnamic, citric, fumaric, glycolic, itaconic, lactic, methanesulfonic, maleic, malic, malonic, mandelic, oxalic, picric, pyruvic, salicylic, succinic, methane sulfonic, ethanesulfonic, tartaric, ascorbic, pamoic, bismethylene salicylic, ethanedisulfonic, gluconic, citraconic, aspartic, stearic, palmitic, EDTA, glycolic, p-aminobenzoic, glutamic, benzenesulfonic, p-toluenesulfonic acids, theophylline acetic acids, as well as the 8-halotheophyllines, for example 8-bromotheophylline and the like. Further examples of pharmaceutical acceptable inorganic or organic acid addition salts include the pharmaceutically acceptable salts listed in J. Pharm. Sci. 1977,66,2, which is incorporated herein by reference.

Examples of metal salts include lithium, sodium, potassium, magnesium salts and the like.

Examples of ammonium and alkylated ammonium salts include ammonium, methyl-, dimethyl-, trimethyl-, ethyl-, hydroxyethyl-, diethyl-, n-butyl-, sec-butyl-, tert-butyl-, tetramethylammonium salts and the like.

In the present context, a ”ring atom” is intended to indicate the atoms constituting a ring, and ring atoms are selected from C, N, O and S. As an example, benzene and toluene both have 6 carbons as ring atoms whereas pyridine has 5 carbons and 1 nitrogen as ring atoms.

In the present context, a “mono-cyclic moiety” is intended to indicate a ring formed structure comprising only one ring. Similarly, a “bi-cyclic moiety” is intended to indicate a structure comprised of two joined rings. The two rings may be joined at two adjacent ring atoms in each ring in which case said bi-cyclic moiety is said to be fused. Naphthalene is an example of a fused bi-cyclic ring moiety. Alternatively, the two rings are joined at a single ring atom in which case said bi-cyclic moiety is said to be spiro. 1,4-Dioxa-8-aza-spiro[4.5]decane is an example of a bi-cyclic ring moiety in spiro form. Alternatively, the two rings may be joined at two non-adjacent ring atoms in each ring in which case said bi-cyclic ring moiety is said to be caged. 3-Aza-bicyclo[3.2.2]nonane is an example of a caged bi-cyclic moiety. A “tri-cyclic moiety” is intended to indicate a structure comprised of three joined rings. As discussed for the

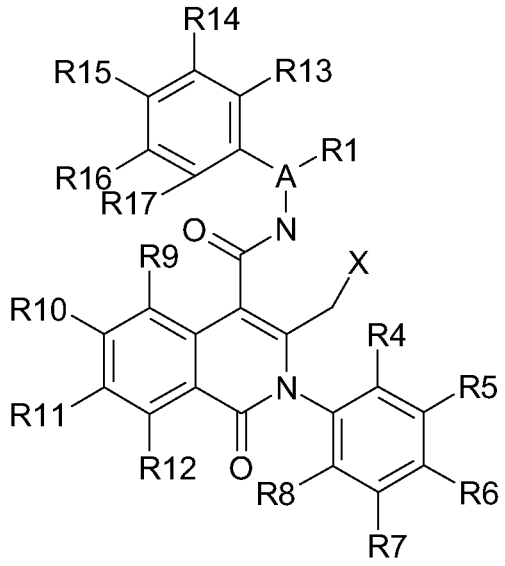
bi-ctyclic moieties above, tri-cyclic moieties may be fused, spiro or caged, or in deed, a combination thereof.

In the present context, the term "therapeutically effective amount" of a compound means an amount sufficient to cure, alleviate or partially arrest the clinical manifestations of a given disease and its complications in a therapeutic intervention comprising the administration of said compound. An amount adequate to accomplish this is defined as "therapeutically effective amount". Effective amounts for each purpose will depend on the severity of the disease or injury as well as the weight and general state of the subject. It will be understood that determining an appropriate dosage may be achieved using routine experimentation, by constructing a matrix of values and testing different points in the matrix, which is all within the ordinary skills of a trained physician.

In the present context, the term "treatment" and "treating" means the management and care of a patient for the purpose of combating a condition, such as a disease or a disorder. The term is intended to include the full spectrum of treatments for a given condition from which the patient is suffering, such as administration of the active compound to alleviate the symptoms or complications, to delay the progression of the disease, disorder or condition, to alleviate or relief the symptoms and complications, and/or to cure or eliminate the disease, disorder or condition as well as to prevent the condition, wherein prevention is to be understood as the management and care of a patient for the purpose of combating the disease, condition, or disorder and includes the administration of the active compounds to prevent the onset of the symptoms or complications. Nonetheless, prophylactic (preventive) and therapeutic (curative) treatments are two separate aspects of the invention. The patient to be treated is preferably a mammal, in particular a human being.

Detailed description of the invention

The compounds of the present invention are defined by formula I below



[I]

wherein A represents N, CH or CR^1;

wherein each R^1 independently represents hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, -C(O)-C_{1-6}alkyl, -C(O)-C_{2-6}alkenyl, -C(O)-C_{2-6}alkynyl, -C(O)-O-C_{1-6}alkyl, -C(O)-O-C_{2-6}alkenyl, -C(O)-O-C_{2-6}alkynyl or phenyl, wherein said phenyl, C_{1-6}alkyl, C_{2-6}alkenyl or C_{2-6}alkynyl is optionally substituted with one or more substituents selected from halogen, hydroxyl, haloC_{1-6}alkyl, nitro, C_{1-6}alkoxy, and NR^2R^3;

wherein X represents hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, cyano, $-OR^2$, -O-C(O)R^2, -OC(O)NR^2R^3, -C(O)-NR^2R^3, $-N(R^2)C(O)R^3$, $-N(R^2)$-C(O)NR^2R^3 or NR^2R^3, or X represents a mono-cyclic, bi-cyclic or tri-cyclic moiety having 4-16 ring atoms one of which is nitrogen, and wherein one, two or three additional ring atoms may be a hetero atom selected from N, O and S, and wherein said mono-cyclic, bi-cyclic or tri-cyclic moiety may optionally be substituted with one or more substituents W,

wherein W is selected from hydrogen, hydroxy, halogen, cyano, (=O), -O-$(CH_2)_c$-O-, wherein c is 2 or 3 (spiro), $(CH_2)_d$, wherein d is 5 or 6 (spiro), C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, -C(O)-C_{1-6}alkyl, -C(O)-C_{2-6}alkenyl, -C(O)-C_{2-6}alkynyl, -C(O)-O-C_{1-6}alkyl, -C(O)-O-C_{2-6}alkenyl, -C(O)-O-C_{2-6}alkynyl, -O-C(O)-C_{1-6}alkyl, -O-C(O)-C_{2-6}alkenyl, -O-C(O)-C_{2-6}alkynyl, -C(O)H, COOH; or wherein W represents a moiety of the formula $-(CH_2)_a$-Y-$(CH_2)_b$-Z;

wherein a and b independently represent an integer selected from 0, 1, 2 and 3;

wherein Y represents a bond, C(O), O, S, -O-C(O), -C(O)-O-, -NR^2-, -NR^2-C(O)-, -C(O)-NH-, or $S(O)_2$;

wherein Z represents hydrogen, C_{1-6}alkyl, NR^2R^3, cyano or a mono-cyclic or fused bi-cyclic moiety comprising 4 to 12 ring atoms of which optionally one, two or three are hetero atoms selected from amongst N, O, and S, and wherein said mono-cyclic or fused bi-cyclic moiety is optionally substituted with one or more substituents selected from the group consisting of halogen, cyano, C_{1-6}alkyl, hydroxyl, and C_{1-6}alkoxy, pyrazinyl, phenyl, pyridyl, and halogen substituted phenyl;

wherein each of R^4-R^8, R^9-R^{12}, and R^{13}-R^{17} independently represent hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, halogen, NR^2R^3, hydroxy, cyano, nitro, C_{1-6}alkoxy, haloC_{1-6}alkyl or hydroxyC_{1-6}alkyl;

wherein R^2 and R^3 independently represent hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, hydroxyC_{1-6}alkyl, haloC_{1-6}alkyl or phenyl;

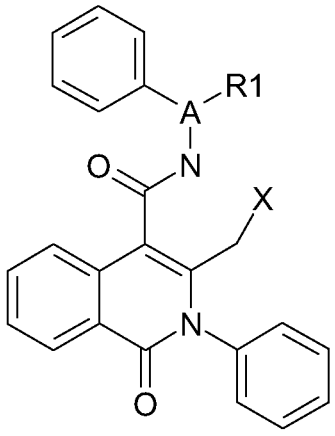
and pharmaceutically acceptable salts thereof.

In one embodiment, R^4-R^8 represent hydrogen.

In one embodiment, R^9-R^{12} represent hydrogen.

In one embodiment, R^{13}-R^{17} represent hydrogen.

In one embodiment, the compounds of the present invention are defined by formula I_a



[Ia]

wherein A represents N, CH or CR^1;

wherein each R^1 independently represents hydrogen, C_{1-6}alkyl, -C(O)-C_{1-6}alkyl,

-C(O)-O-C_{1-6}alkyl, or phenyl, wherein said phenyl or C_{1-6}alkyl, is optionally substituted with one or more substituents selected from halogen, hydroxyl, haloC_{1-6}alkyl, nitro, C_{1-6}alkoxy, and NR^2R^3;

wherein X represents hydrogen, C_{1-6}alkyl, cyano, $-OR^2$, $-O-C(O)R^2$, $-OC(O)NR^2R^3$, $-C(O)-NR^2R^3$, $-N(R^2)C(O)R^3$, $-N(R^2)-C(O)NR^2R^3$ or NR^2R^3, or X represents a mono-cyclic, bicyclic or tri-cyclic moiety having 4-16 ring atoms one of which is nitrogen, and wherein one, two or three additional ring atoms may be a hetero atom selected from N, O and S, and wherein said mono-cyclic, bi-cyclic or tri-cyclic moiety may optionally be substituted with one or more substituents W, wherein W is selected from hydrogen, hydroxy, halogen, cyano, (=O), $-O-(CH_2)_c-O-$, wherein c is 2 or 3 (spiro), $(CH_2)_d$, wherein d is 5 or 6 (spiro), C_{1-6}alkyl, C_{1-6}alkoxy, $-C(O)-C_{1-6}$alkyl, $-C(O)-O-C_{1-6}$alkyl, $-O-C(O)-C_{1-6}$alkyl, -C(O)H, COOH; or wherein W represents a moiety of the formula $-(CH_2)_a-Y-(CH_2)_b-Z$;

wherein a and b independently represent an integer selected from 0, 1, 2 and 3;

wherein Y represents a bond, C(O), O, S, -O-C(O), $-C(O)-O-$, $-NR^2-$, $-NR^2-C(O)-$, $-C(O)-NH-$, or $S(O)_2$;

wherein Z represents hydrogen, C_{1-6}alkyl, NR^2R^3, cyano or a mono-cyclic or fused bi-cyclic moiety comprising 4 to 12 ring atoms of which optionally one, two or three are hetero atoms selected from amongst N, O, and S, and wherein said mono-cyclic or fused bi-cyclic moiety is optionally substituted with one or more substituents selected from the group consisting of halogen, cyano, C_{1-6}alkyl, hydroxyl, and C_{1-6}alkoxy, pyrazinyl, phenyl, pyridyl, and halogen substituted phenyl;

wherein each of R^4-R^8, R^9-R^{12}, and R^{13}-R^{17} independently represent hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, halogen, NR^2R^3, hydroxy, cyano, nitro, C_{1-6}alkoxy, haloC_{1-6}alkyl or hydroxyC_{1-6}alkyl;

wherein R^2 and R^3 independently represent hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, hydroxyC_{1-6}alkyl, haloC_{1-6}alkyl or phenyl; and pharmaceutically acceptable salts thereof. In particular, A represents CH and R^1 represents C_{1-6}alkyl, such as ethyl or cyclopropyl.

In one embodiment wherein the compounds of the present invention are defined by formula I_a, X represents hydrogen, C_{1-6}alkyl, cyano, $-OR^2$, $-O-C(O)R^2$, $-OC(O)NR^2R^3$, $-C(O)-NR^2R^3-$, $-N(R^2)C(O)R^3$, $-N(R^2)-C(O)NR^2R^3$ or NR^2R^3, wherein

R^2 and R^3 independently represent hydrogen, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, haloC_{1-6}alkyl or phenyl. In particular, X represents hydrogen, methyl, or NR^2R^3, wherein R^2 and R^3 independently represent hydrogen, C_{1-6}alkyl, or hydroxyC_{1-6}alkyl, and particular mentioning is made of R^2 and R^3 independently representing hydrogen, cyclopropylmethyl, methyl, ethyl or cyclopropyl.

In one embodiment wherein the compounds of the present invention are defined by formula I_a, X represents a mono-cyclic, bi-cyclic or tri-cyclic moiety having 4-16 ring atoms one of which is nitrogen, and wherein one, two or three additional ring atoms may be a hetero atom selected from N, O and S, and wherein said mono-cyclic, bi-cyclic or tri-cyclic moiety may optionally be substituted with one or more substituents W, wherein W is selected from hydrogen, hydroxy, halogen, cyano, (=O), -O-$(CH_2)_c$-O-, wherein c is 2 or 3 (spiro), $(CH_2)_d$, wherein d is 5 or 6 (spiro), C_{1-6}alkyl, C_{1-6}alkoxy, -C(O)-C_{1-6}alkyl, -C(O)-O-C_{1-6}alkyl, -O-C(O)-C_{1-6}alkyl, -O-C(O)-, -C(O)H, COOH; or wherein W represents a moiety of the formula –$(CH_2)_a$-Y-$(CH_2)_b$-Z;

wherein a and b independently represent an integer selected from 0, 1, 2 and 3;

wherein Y represents a bond, C(O), O, S, -O-C(O), -C(O)-O-, -NR^2-, -NR^2-C(O)-, -C(O)-NH-, or $S(O)_2$;

wherein Z represents hydrogen, C_{1-6}alkyl, NR^2R^3, cyano or a mono-cyclic or fused bi-cyclic moiety comprising 4 to 12 ring atoms of which optionally one, two or three are hetero atoms selected from amongst N, O, and S, and wherein said mono-cyclic or fused bi-cyclic moiety is optionally substituted with one or more substituents selected from the group consisting of halogen, cyano, C_{1-6}alkyl, hydroxyl, and C_{1-6}alkoxy, pyrazinyl, phenyl, pyridyl, and halogen substituted phenyl;

wherein R^2 and R^3 independently represent hydrogen, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, haloC_{1-6}alkyl or phenyl.

In one embodiment wherein the compounds of the present invention are defined by formula I_a, X represents a mono-cyclic moiety having 5 ring atoms one of which is nitrogen, and wherein one, two or three additional ring atoms may be a hetero atom selected from N, O and S, and wherein said mono-cyclic moiety may optionally be substituted with one or more substituents W, wherein W is selected from hydrogen, hydroxy, halogen, cyano, (=O), -O-$(CH_2)_c$-O-, wherein c is 2 or 3 (spiro),

$(CH_2)_d$, wherein d is 5 or 6 (spiro), C_{1-6}alkyl, C_{1-6}alkoxy, -C(O)-C_{1-6}alkyl, -C(O)-O-C_{1-6}alkyl, -O-C(O)-C_{1-6}alkyl, -O-C(O)-, -C(O)H, COOH; or wherein W represents a moiety of the formula $-(CH_2)_a$-Y-$(CH_2)_b$-Z;

wherein a and b independently represent an integer selected from 0, 1, 2 and 3;

wherein Y represents a bond, C(O), O, S, -O-C(O), -C(O)-O-, -NR^2-, -NR^2-C(O)-, -C(O)-NH-, or $S(O)_2$;

wherein Z represents hydrogen, C_{1-6}alkyl, NR^2R^3, cyano or a mono-cyclic or fused bi-cyclic moiety comprising 4 to 12 ring atoms of which optionally one, two or three are hetero atoms selected from amongst N, O, and S, and wherein said mono-cyclic or fused bi-cyclic moiety is optionally substituted with one or more substituents selected from the group consisting of halogen, cyano, C_{1-6}alkyl, hydroxyl, and C_{1-6}alkoxy, pyrazinyl, phenyl, pyridyl, and halogen substituted phenyl;

wherein R^2 and R^3 independently represent hydrogen, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, haloC_{1-6}alkyl or phenyl. Examples of such mono-cyclic moiety having 5 ring atoms include pyrrole, 2H-pyrrole, pyrazole, isothiazole, pyrrolidine, pyrroline, tetrazole, imidazolidine, imidazoline, pyrazolidine and pyrazoline.

In one embodiment wherein the compounds of the present invention are defined by formula I_a, X represents a mono-cyclic moiety having 6 ring atoms one of which is nitrogen, and wherein one, two or three additional ring atoms may be a hetero atom selected from N, O and S, and wherein said mono-cyclic moiety may optionally be substituted with one or more substituents W, wherein W is selected from hydrogen, hydroxy, halogen, cyano, (=O), -O-$(CH_2)_c$-O-, wherein c is 2 or 3 (spiro), $(CH_2)_d$, wherein d is 5 or 6 (spiro), C_{1-6}alkyl, C_{1-6}alkoxy, -C(O)-C_{1-6}alkyl, -C(O)-O-C_{1-6}alkyl, -O-C(O)-C_{1-6}alkyl, -O-C(O)-, -C(O)H, COOH; or wherein W represents a moiety of the formula $-(CH_2)_a$-Y-$(CH_2)_b$-Z;

wherein a and b independently represent an integer selected from 0, 1, 2 and 3;

wherein Y represents a bond, C(O), O, S, -O-C(O), -C(O)-O-, -NR^2-, -NR^2-C(O)-, -C(O)-NH-, or $S(O)_2$;

wherein Z represents hydrogen, C_{1-6}alkyl, NR^2R^3, cyano or a mono-cyclic or fused bi-cyclic moiety comprising 4 to 12 ring atoms of which optionally one, two or three are hetero atoms selected from amongst N, O, and S, and wherein said mono-cyclic or fused bi-cyclic moiety is optionally substituted with one or more substituents selected

from the group consisting of halogen, cyano, C_{1-6}alkyl, hydroxyl, and C_{1-6}alkoxy, pyrazinyl, phenyl, pyridyl, and halogen substituted phenyl;
wherein R^2 and R^3 independently represent hydrogen, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, haloC_{1-6}alkyl or phenyl. Examples of such mono-cyclic moiety having 6 ring atoms include pyridine, pyrazine, pyrimidine, pyridazine, piperidine, piperazine dihydropyridine, tetrahydropyridine, and morpholine.

In one embodiment, wherein the compounds of the present invention are defined by formula I_a, X represents a mono-cyclic moiety having 7 ring atoms one of which is nitrogen, and wherein one, two or three additional ring atoms may be a hetero atom selected from N, O and S, and wherein said mono-cyclic moiety may optionally be substituted with one or more substituents W, wherein W is selected from hydrogen, hydroxy, halogen, cyano, (=O), -O-$(CH_2)_c$-O-, wherein c is 2 or 3 (spiro), $(CH_2)_d$, wherein d is 5 or 6 (spiro), C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, -C(O)-C_{1-6}alkyl, -C(O)-O-C_{1-6}alkyl, -O-C(O)-C_{1-6}alkyl, -C(O)H, COOH; or wherein W represents a moiety of the formula $-(CH_2)_a$-Y-$(CH_2)_b$-Z;
wherein a and b independently represent an integer selected from 0, 1, 2 and 3;
wherein Y represents a bond, C(O), O, S, -O-C(O), -C(O)-O-, -NR^2-, -NR^2-C(O)-, -C(O)-NH-, or $S(O)_2$;
wherein Z represents hydrogen, C_{1-6}alkyl, NR^2R^3, cyano or a mono-cyclic or fused bi-cyclic moiety comprising 4 to 12 ring atoms of which optionally one, two or three are hetero atoms selected from amongst N, O, and S, and wherein said mono-cyclic or fused bi-cyclic moiety is optionally substituted with one or more substituents selected from the group consisting of halogen, cyano, C_{1-6}alkyl, hydroxyl, and C_{1-6}alkoxy, pyrazinyl, phenyl, pyridyl, and halogen substituted phenyl;
wherein R^2 and R^3 independently represent hydrogen, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, haloC_{1-6}alkyl or phenyl. Examples of such mono-cyclic moiety having 7 ring atoms include azepane, [1,4]diazepane and 2,3,4,5-tetrahydro-1H-[1,4]diazepane.

In one embodiment wherein compounds of the present invention are defined by formula I_a, X represents a mono-cyclic or bi-cyclic moiety having 8 ring atoms one of which is nitrogen, and wherein one, two or three additional ring atoms may be a hetero atom selected from N, O and S, and wherein said cyclic or bicyclic moiety may optionally be substituted with one or more substituents W, wherein W is selected from

hydrogen, hydroxy, halogen, cyano, (=O), -O-$(CH_2)_c$-O-, wherein c is 2 or 3 (spiro), $(CH_2)_d$, wherein d is 5 or 6 (spiro), C_{1-6}alkyl, C_{1-6}alkoxy, -C(O)-C_{1-6}alkyl, -C(O)-O-C_{1-6}alkyl, -O-C(O)-C_{1-6}alkyl, -C(O)H, COOH; or wherein W represents a moiety of the formula $-(CH_2)_a$-Y-$(CH_2)_b$-Z;

wherein a and b independently represent an integer selected from 0, 1, 2 and 3;

wherein Y represents a bond, C(O), O, S, -O-C(O), -C(O)-O-, -NR^2-, -NR^2-C(O)-, -C(O)-NH-, or $S(O)_2$;

wherein Z represents hydrogen, C_{1-6}alkyl, NR^2R^3, cyano or a mono-cyclic or fused bi-cyclic moiety comprising 4 to 12 ring atoms of which optionally one, two or three are hetero atoms selected from amongst N, O, and S, and wherein said mono-cyclic or fused bi-cyclic moiety is optionally substituted with one or more substituents selected from the group consisting of halogen, cyano, C_{1-6}alkyl, hydroxyl, and C_{1-6}alkoxy, pyrazinyl, phenyl, pyridyl, and halogen substituted phenyl;

wherein R^2 and R^3 independently represent hydrogen, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, haloC_{1-6}alkyl or phenyl. Examples of such mono-cyclic or bi-cyclic moiety having 8 ring atoms include quinnuclidine, 8-aza-bicyclo[3.2.1]octane and 2-aza-bicyclo[2.2.2]octane.

In one embodiment wherein the compounds of the present invention are defined by formula I_a, X represents a mono-cyclic or bi-cyclic moiety having 9 ring atoms one of which is nitrogen, and wherein one, two or three additional ring atoms may be a hetero atom selected from N, O and S, and wherein said mono-cyclic or bi-cyclic moiety may optionally be substituted with one or more substituents W, wherein W is selected from hydrogen, hydroxy, halogen, cyano, (=O), -O-$(CH_2)_c$-O-, wherein c is 2 or 3 (spiro), $(CH_2)_d$, wherein d is 5 or 6 (spiro), C_{1-6}alkyl, C_{1-6}alkoxy, -C(O)-C_{1-6}alkyl, -C(O)-O-C_{1-6}alkyl, -O-C(O)-C_{1-6}alkyl, -C(O)H, COOH; or wherein W represents a moiety of the formula $-(CH_2)_a$-Y-$(CH_2)_b$-Z;

wherein a and b independently represent an integer selected from 0, 1, 2 and 3;

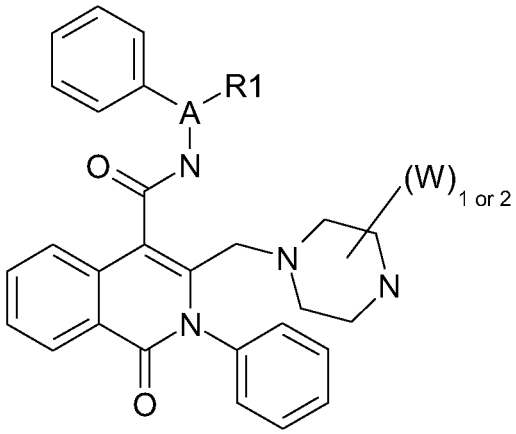
wherein Y represents a bond, C(O), O, S, -O-C(O), -C(O)-O-, -NR^2-, -NR^2-C(O)-, -C(O)-NH-, or $S(O)_2$;

wherein Z represents hydrogen, C_{1-6}alkyl, NR^2R^3, cyano or a mono-cyclic or fused bi-cyclic moiety comprising 4 to 12 ring atoms of which optionally one, two or three are hetero atoms selected from amongst N, O, and S, and wherein said mono-cyclic or

fused bi-cyclic moiety is optionally substituted with one or more substituents selected from the group consisting of halogen, cyano, C_{1-6}alkyl, hydroxyl, and C_{1-6}alkoxy, pyrazinyl, phenyl, pyridyl, and halogen substituted phenyl;
wherein R^2 and R^3 independently represent hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, hydroxyC_{1-6}alkyl, haloC_{1-6}alkyl or phenyl. Examples of such mono-cyclic or bi-cyclic moiety having 9 ring atoms include indolizine, isoindole, 3H-indole, indole, 1H-indazole, purine, indoline, and isoindoline.

In one embodiment wherein the compounds of the present invention are defined by formula I_a, X represents a mono-cyclic or bi-cyclic moiety having 10 ring atoms one of which is nitrogen, and wherein one, two or three additional ring atoms may be a hetero atom selected from N, O and S, and wherein said mono-cyclic or bi-cyclic moiety may optionally be substituted with one or more substituents W, wherein W is selected from hydrogen, hydroxy, halogen, cyano, (=O), -O-$(CH_2)_c$-O-, wherein c is 2 or 3 (spiro), $(CH_2)_d$, wherein d is 5 or 6 (spiro), C_{1-6}alkyl, C_{1-6}alkoxy, -C(O)-C_{1-6}alkyl, -C(O)-O-C_{1-6}alkyl, -O-C(O)-C_{1-6}alkyl, -C(O)H, COOH; or wherein W represents a moiety of the formula $-(CH_2)_a$-Y-$(CH_2)_b$-Z;
wherein a and b independently represent an integer selected from 0, 1, 2 and 3;
wherein Y represents a bond, C(O), O, S, -O-C(O), -C(O)-O-, -NR^2-, -NR^2-C(O)-, -C(O)-NH-, or $S(O)_2$;
wherein Z represents hydrogen, C_{1-6}alkyl, NR^2R^3, cyano or a mono-cyclic or fused bi-cyclic moiety comprising 4 to 12 ring atoms of which optionally one, two or three are hetero atoms selected from amongst N, O, and S, and wherein said mono-cyclic or fused bi-cyclic moiety is optionally substituted with one or more substituents selected from the group consisting of halogen, cyano, C_{1-6}alkyl, hydroxyl, and C_{1-6}alkoxy, pyrazinyl, phenyl, pyridyl, and halogen substituted phenyl;
wherein R^2 and R^3 independently represent hydrogen, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, haloC_{1-6}alkyl or phenyl. Examples of such mono-cyclic or bi-cyclic moiety having 10 ring atoms include 4H-quinolizine, isoquinoline, quinoline, phthalazine, naphthyridine, quinoxaline, cinnoline, pterridine, 1,2,3,4-tetrahydro-isoquinolone, 1,4,8-triaza-spiro[4.5]decane and 1,2,3,4-tetrahydro-quinoline.

In one embodiment, the compounds of the present invention are defined by formula I_b



[Ib]

wherein A represents N, CH or CR^1;

wherein each R^1 independently represents hydrogen, C_{1-6}alkyl, -C(O)-C_{1-6}alkyl, C(O)-O-C_{1-6}alkyl, or phenyl, wherein said phenyl, or C_{1-6}alkyl is optionally substituted with one or more substituents selected from halogen, hydroxyl, haloC_{1-6}alkyl, nitro, C_{1-6}alkoxy, and NR^2R^3;

wherein W is selected from hydrogen, hydroxy, halogen, cyano, (=O), -O-$(CH_2)_c$-O-, wherein c is 2 or 3 (spiro), $(CH_2)_d$, wherein d is 5 or 6 (spiro), C_{1-6}alkyl, C_{1-6}alkoxy, -C(O)-C_{1-6}alkyl, -C(O)-O-C_{1-6}alkyl, -O-C(O)-C_{1-6}alkyl, -C(O)H, COOH; or wherein W represents a moiety of the formula $-(CH_2)_a$-Y-$(CH_2)_b$-Z;

wherein a and b independently represent an integer selected from 0, 1, 2 and 3;

wherein Y represents a bond, C(O), O, S, -O-C(O), -C(O)-O-, $-NR^2$-, $-NR^2$-C(O)-, -C(O)-NH-, or $S(O)_2$;

wherein Z represents hydrogen, C_{1-6}alkyl, NR^2R^3, cyano or a mono-cyclic or fused bi-cyclic moiety comprising 4 to 12 ring atoms of which optionally one, two or three are hetero atoms selected from amongst N, O, and S, and wherein said mono-cyclic or fused bi-cyclic moiety is optionally substituted with one or more substituents selected from the group consisting of halogen, cyano, C_{1-6}alkyl, hydroxyl, and C_{1-6}alkoxy, pyrazinyl, phenyl, pyridyl, and halogen substituted phenyl;

wherein R^2 and R^3 independently represent hydrogen, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, haloC_{1-6}alkyl or phenyl; and pharmaceutically acceptable salts thereof. In particular, A represent CH, and R^1 represents C_{1-6}alkyl, such as ethyl or cyclopropyl.

In one embodiment wherein the compounds of the present invention are defined by formula I_b, W represents a moiety of the formula $-(CH_2)_a$-Y-$(CH_2)_b$-Z; wherein a and b independently represent an integer selected from 0, 1, 2 and 3; wherein Y represents a bond, C(O), O, S, -O-C(O), -C(O)-O-, -NR^2-, -NR^2-C(O)-, -C(O)-NH-, or $S(O)_2$;

wherein Z represents hydrogen, C_{1-6}alkyl, NR^2R^3, cyano or a mono-cyclic or fused bi-cyclic moiety comprising 4 to 12 ring atoms of which optionally one, two or three are hetero atoms selected from amongst N, O, and S, and wherein said mono-cyclic or fused bi-cyclic moiety is optionally substituted with one or more substituents selected from the group consisting of halogen, cyano, C_{1-6}alkyl, hydroxyl, and C_{1-6}alkoxy, pyrazinyl, phenyl, pyridyl, and halogen substituted phenyl;

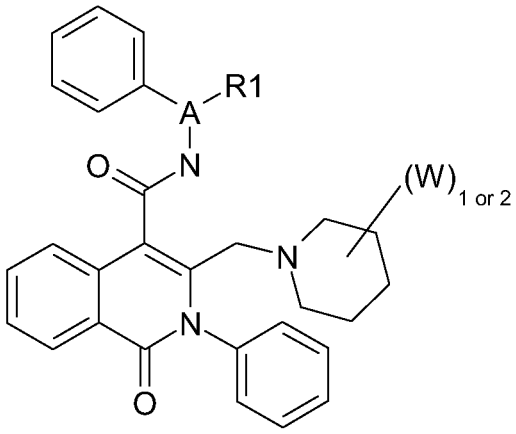
wherein R^2 and R^3 independently represent hydrogen, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, haloC_{1-6}alkyl or phenyl. In a further embodiment, Y represents a bond, C(O) or $S(O)_2$; wherein a+b is 0, 1, 2, 3, or 4; and wherein Z represents mono-cyclic or fused bi-cyclic moiety comprising 5 to 12 carbon ring atoms and optionally one, two or three hetero atoms selected from amongst N, O, and S, and wherein said cyclic or bicyclic moiety is optionally substituted with one or more substituents selected from the group consisting of halogen, cyano, C_{1-6}alkyl, hydroxyl, and C_{1-6}alkoxy, phenyl, pyrazinyl, pyridyl, and halogen substituted phenyl. Particular mentioning is made of the embodiment, wherein Y represents a bond or C(O), and a+b is 0, 1, 2, or 3. In particular, Z comprises 5-9 ring atoms, such as e.g. 5, 6, or 9 ring atoms. Examples of Z with 5 ring atoms include pyrrolide and cyclopentyl; examples of Z with 6 ring atoms include phenyl, pyrimidinyl, morpholinyl and pyridyl; examples of Z with 9 ring atoms include furo [3.2-c]pyridyl. A particular example of Z is morpholinyl, e.g. attached to the rest of the W moiety via the nitrogen, and optionally substituted with one or more substituents selected from the group consisting of halogen, cyano, C_{1-6}alkyl, hydroxyl, and C_{1-6}alkoxy, phenyl, pyrazinyl, pyridyl, and halogen substituted phenyl. Another particular example of Z is piperidyl, e.g. attached to the rest of the W moiety via the nitrogen, and optionally substituted with one or more substituents

selected from the group consisting of halogen, cyano, C_{1-6}alkyl, hydroxyl, and C_{1-6}alkoxy, phenyl, pyrazinyl, pyridyl, and halogen substituted phenyl. Another particular example of Z is pyridyl, e.g. attached to the rest of the W moiety via the nitrogen. Another particular example of Z is pyridyl, e.g. attached to the rest of the W moiety at the 2, 3 or 4 position, and optionally substituted with one or more substituents selected from the group consisting of halogen, cyano, C_{1-6}alkyl, hydroxyl, and C_{1-6}alkoxy, pyrazinyl, phenyl, pyridyl, and halogen substituted phenyl. Another particular example of Z is phenyl, optionally substituted with one or more substituents selected from the group consisting of halogen, cyano, C_{1-6}alkyl, hydroxyl, and C_{1-6}alkoxy, phenyl, pyrazinyl, pyridyl, and halogen substituted phenyl. Another particular example of Z is pyrrolidinyl, optionally substituted with one or more substituents selected from the group consisting of halogen, cyano, C_{1-6}alkyl, hydroxyl, and C_{1-6}alkoxy, pyrazinyl, phenyl, pyridyl, and halogen substituted phenyl. Another particular example of Z is indolyl, e.g. attached to the rest of the W moiety at the 4, 5, 6, or 7 position, and optionally substituted with one or more substituents selected from the group consisting of halogen, cyano, C_{1-6}alkyl, hydroxyl, and C_{1-6}alkoxy, phenyl, pyrazinyl, pyridyl, and halogen substituted phenyl. Other particular examples of Z include cyclopentyl, furopyridyl, tetrahydrofuranyl, benzo[1.4]oxazinyl, benzo[1.4]dioxinyl, benzo[1.2.5]thiadiazol, and quinazolinyl.

In one embodiment wherein the compounds of the present invention are defined by formula I_b, Y represents a bond, C(O), -C(O)-O-, C(O)-NH-, -O-, or $S(O)_2$; a+b is 0, 1, 2, 3 or 4; and wherein Z represents hydrogen, C_{1-6}alkyl, such as methyl, iso-propyl, iso-butyl, or tert.-butyl, NR^2R^3 or cyano.

In one embodiment wherein the compounds of the present invention are defined by formula I_b, A represents CH; R^1 represents C_{1-6}alkyl, such as ethyl or cyclopropyl, W is selected from hydrogen, hydroxy, halogen, cyano, (=O), -O-$(CH_2)_c$-O-, wherein c is 2 or 3 (spiro), $(CH_2)_d$, wherein d is 5 or 6 (spiro), C_{1-6}alkyl, C_{1-6}alkoxy, -C(O)-C_{1-6}alkyl, -C(O)-O-C_{1-6}alkyl, -O-C(O)-C_{1-6}alkyl, -C(O)H, COOH.

In one embodiment the compounds of the present invention are defined by formula I_c



[Ic]

wherein A represents N, CH or CR^1;

wherein each R^1 independently represents hydrogen, C_{1-6}alkyl, -C(O)-C_{1-6}alkyl, C(O)-O-C_{1-6}alkyl, or phenyl, wherein said phenyl, or C_{1-6}alkyl is optionally substituted with one or more substituents selected from halogen, hydroxyl, haloC_{1-6}alkyl, nitro, C_{1-6}alkoxy, and NR^2R^3;

wherein W is selected from hydrogen, hydroxy, halogen, cyano, (=O), -O-$(CH_2)_c$-O-, wherein c is 2 or 3 (spiro), $(CH_2)_d$, wherein d is 5 or 6 (spiro), C_{1-6}alkyl, C_{1-6}alkoxy, -C(O)-C_{1-6}alkyl, -C(O)-O-C_{1-6}alkyl, -O-C(O)-C_{1-6}alkyl, -C(O)H, COOH; or wherein W represents a moiety of the formula $–(CH_2)_a$-Y-$(CH_2)_b$-Z;

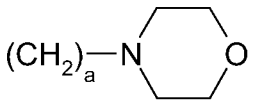
wherein a and b independently represent an integer selected from 0, 1, 2 and 3;

wherein Y represents a bond, C(O), O, S, -O-C(O), -C(O)-O-, -NR^2-, -NR^2-C(O)-, -C(O)-NH-, or $S(O)_2$;

wherein Z represents hydrogen, C_{1-6}alkyl, NR^2R^3, cyano or a mono-cyclic or fused bi-cyclic moiety comprising 4 to 12 ring atoms of which optionally one, two or three are hetero atoms selected from amongst N, O, and S, and wherein said mono-cyclic or fused bi-cyclic moiety is optionally substituted with one or more substituents selected from the group consisting of halogen, cyano, C_{1-6}alkyl, hydroxyl, and C_{1-6}alkoxy, pyrazinyl, phenyl, pyridyl, and halogen substituted phenyl;

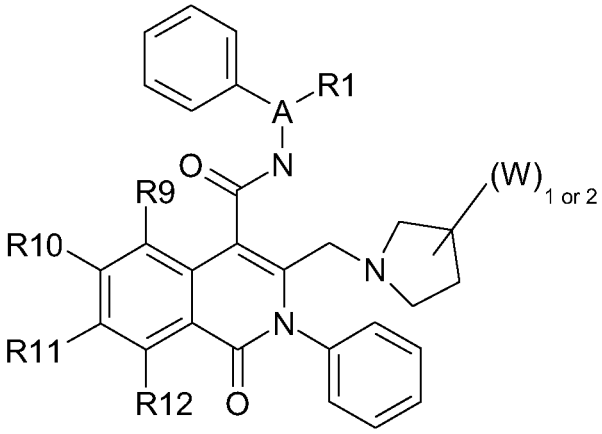
wherein R^2 and R^3 independently represent hydrogen, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, haloC_{1-6}alkyl or phenyl; and pharmaceutically acceptable salts thereof. In particular, A represent CH, and R^1 represents C_{1-6}alkyl, such as ethyl or cyclopropyl.

In one embodiment wherein the compounds of the present invention are defined by formula I_c, W independently represents hydrogen, hydroxyl, phenyl, phenyl substituted with C_{1-6}alkoxy, piperidyl, pyridyl, -O-$(CH_2)_c$-O-, wherein c is 2 or 3 (spiro), $N(CH_3)_2$, C_{1-6}alkyl, –$(CH_2)_a$-C(O)-O-$(CH_2)_b$-H, wherein a+b is 1, 2, or 3, or



, wherein a represents 1, 2, or 3.

In one embodiment, the compounds of the present invention are defined by formula I_d



[Id]

wherein A represents N, CH or CR^1;

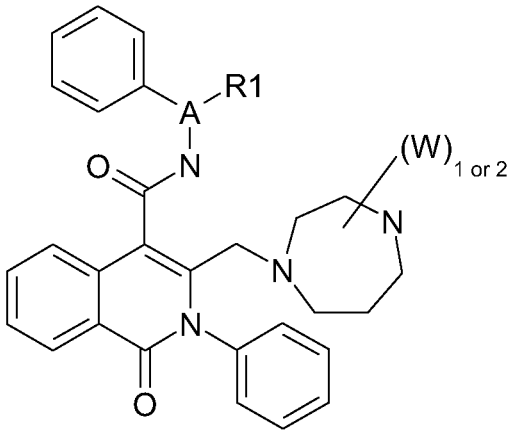
wherein each R^1 independently represents hydrogen, C_{1-6}alkyl, -C(O)-C_{1-6}alkyl, C(O)-O-C_{1-6}alkyl, or phenyl, wherein said phenyl, or C_{1-6}alkyl is optionally substituted with one or more substituents selected from halogen, hydroxyl, haloC_{1-6}alkyl, nitro, C_{1-6}alkoxy, and NR^2R^3;

wherein W is selected from hydrogen, hydroxy, halogen, cyano, (=O), -O-$(CH_2)_c$-O-, wherein c is 2 or 3 (spiro), $(CH_2)_d$, wherein d is 5 or 6 (spiro), C_{1-6}alkyl, C_{1-6}alkoxy, -C(O)-C_{1-6}alkyl, -C(O)-O-C_{1-6}alkyl, -O-C(O)-C_{1-6}alkyl, -C(O)H, COOH;

wherein R^2 and R^3 independently represent hydrogen, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, haloC_{1-6}alkyl or phenyl; wherein R^9-R^{12} independently represent hydrogen or halogen;

and pharmaceutically acceptable salts thereof. In particular, A is CH; R^1 represents C_{1-6}alkyl, such as ethyl or cyclopropyl; and each of R^9-R^{12} independently represent hydrogen or halogen.

In one embodiment, the compounds of the present invention are defined by formula I_e



[Ie]

wherein A represents N, CH or CR^1;

wherein each R^1 independently represents hydrogen, C_{1-6}alkyl, -C(O)-C_{1-6}alkyl, C(O)-O-C_{1-6}alkyl, or phenyl, wherein said phenyl, or C_{1-6}alkyl is optionally substituted with one or more substituents selected from halogen, hydroxyl, haloC_{1-6}alkyl, nitro, C_{1-6}alkoxy, and NR^2R^3;

wherein W is selected from hydrogen, hydroxy, halogen, cyano, (=O), -O-$(CH_2)_c$-O-, wherein c is 2 or 3 (spiro), $(CH_2)_d$, wherein d is 5 or 6 (spiro), C_{1-6}alkyl, C_{1-6}alkoxy, -C(O)-C_{1-6}alkyl, -C(O)-O-C_{1-6}alkyl, -O-C(O)-C_{1-6}alkyl, -C(O)H, COOH; or wherein W represents a moiety of the formula $-(CH_2)_a$-Y-$(CH_2)_b$-Z;

wherein a and b independently represent an integer selected from 0, 1, 2 and 3;

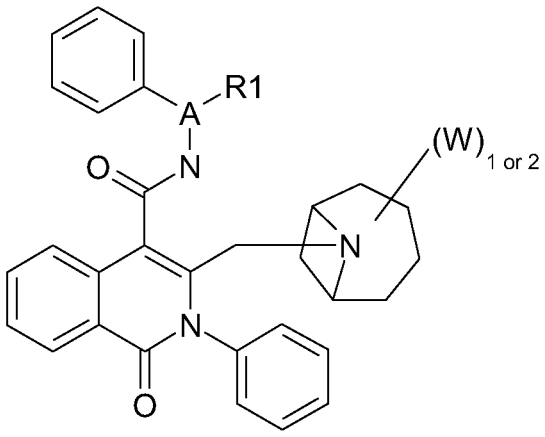
wherein Y represents a bond, C(O), O, S, -O-C(O), -C(O)-O-, NR^2, -NR^2-C(O)-, -C(O)-NH-, or $S(O)_2$;

wherein Z represents hydrogen, C_{1-6}alkyl, NR^2R^3, cyano or a mono-cyclic or fused bi-cyclic moiety comprising 4 to 12 ring atoms of which optionally one, two or three are hetero atoms selected from amongst N, O, and S, and wherein said mono-cyclic or fused bi-cyclic moiety is optionally substituted with one or more substituents selected

from the group consisting of halogen, cyano, C_{1-6}alkyl, hydroxyl, and C_{1-6}alkoxy, pyrazinyl, phenyl, pyridyl, and halogen substituted phenyl;

wherein R^2 and R^3 independently represent hydrogen, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, haloC_{1-6}alkyl or phenyl; and pharmaceutically acceptable salts thereof. In particular, A is CH, and R^1 represents C_{1-6}alkyl, such as ethyl or cyclopropyl. In particular, Z comprises 5-9 ring atoms, such as e.g. 5, 6, or 9 ring atoms. Examples of Z with 5 ring atoms include pyrrolide and cyclopentyl; examples of Z with 6 ring atoms include phenyl, pyrimidinyl, morpholinyl and pyridyl; examples of Z with 9 ring atoms include furo [3.2-c]pyridyl.

In one embodiment, the compounds of the present invention are defined by formula I_f



[If]

wherein A represents N, CH or CR^1;

wherein each R^1 independently represents hydrogen, C_{1-6}alkyl, -C(O)-C_{1-6}alkyl, C(O)-O-C_{1-6}alkyl, or phenyl, wherein said phenyl, or C_{1-6}alkyl is optionally substituted with one or more substituents selected from halogen, hydroxyl, haloC_{1-6}alkyl, nitro, C_{1-6}alkoxy, and NR^2R^3;

wherein W is selected from hydrogen, hydroxy, halogen, cyano, (=O), -O-$(CH_2)_c$-O-, wherein c is 2 or 3 (spiro), $(CH_2)_d$, wherein d is 5 or 6 (spiro), C_{1-6}alkyl, C_{1-6}alkoxy, -C(O)-C_{1-6}alkyl, -C(O)-O-C_{1-6}alkyl, -O-C(O)-C_{1-6}alkyl, -C(O)H, COOH; or wherein W represents a moiety of the formula $-(CH_2)_a$-Y-$(CH_2)_b$-Z;

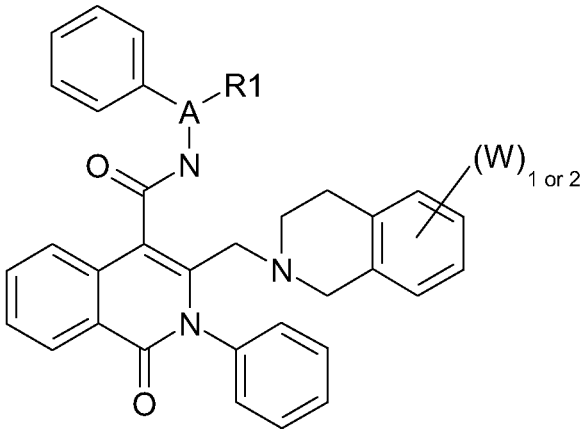
wherein a and b independently represent an integer selected from 0, 1, 2 and 3;

wherein Y represents a bond, C(O), O, S, -O-C(O), -C(O)-O-, NR^2, -NR^2-C(O)-, -C(O)-NH-, or $S(O)_2$;

wherein Z represents hydrogen, C_{1-6}alkyl, NR^2R^3, cyano or a mono-cyclic or fused bi-cyclic moiety comprising 4 to 12 ring atoms of which optionally one, two or three are hetero atoms selected from amongst N, O, and S, and wherein said mono-cyclic or fused bi-cyclic moiety is optionally substituted with one or more substituents selected from the group consisting of halogen, cyano, C_{1-6}alkyl, hydroxyl, and C_{1-6}alkoxy, pyrazinyl, phenyl, pyridyl, and halogen substituted phenyl;

wherein R^2 and R^3 independently represent hydrogen, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, haloC_{1-6}alkyl or phenyl; and pharmaceutically acceptable salts thereof. In particular, A is CH, and R^1 represents C_{1-6}alkyl, such as ethyl or cyclopropyl. In particular, Z comprises 5-9 ring atoms, such as e.g. 5, 6, or 9 ring atoms. Examples of Z with 5 ring atoms include pyrrolide and cyclopentyl; examples of Z with 6 ring atoms include phenyl, pyrimidinyl, morpholinyl and pyridyl; examples of Z with 9 ring atoms include furo [3.2-c]pyridyl.

In one embodiment, the compounds of the present invention are defined by formula I_g



[Ig]

wherein A represents N, CH or CR^1;

wherein each R^1 independently represents hydrogen, C_{1-6}alkyl, -C(O)-C_{1-6}alkyl, C(O)-O-C_{1-6}alkyl, or phenyl, wherein said phenyl, or C_{1-6}alkyl is optionally substituted with

one or more substituents selected from halogen, hydroxyl, haloC_{1-6}alkyl, nitro, C_{1-6}alkoxy, and NR^2R^3;

wherein W is selected from hydrogen, hydroxy, halogen, cyano, (=O), -O-$(CH_2)_c$-O-, wherein c is 2 or 3 (spiro), $(CH_2)_d$, wherein d is 5 or 6 (spiro), C_{1-6}alkyl, C_{1-6}alkoxy, -C(O)-C_{1-6}alkyl, -C(O)-O-C_{1-6}alkyl, -O-C(O)-C_{1-6}alkyl, -N(R^2)-C(O)-R^3, -C(O)H, COOH; or wherein W represents a moiety of the formula –$(CH_2)_a$-Y-$(CH_2)_b$-Z;

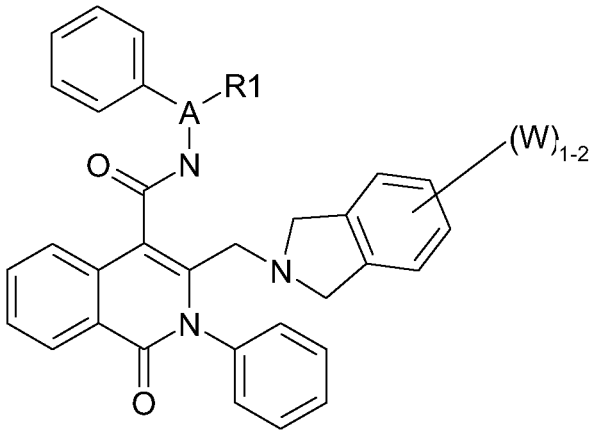
wherein a and b independently represent an integer selected from 0, 1, 2 and 3;

wherein Y represents a bond, C(O), O, S, -O-C(O), -C(O)-O-, NR^2, -NR^2-C(O)-, -C(O)-NH-, or $S(O)_2$;

wherein Z represents hydrogen, C_{1-6}alkyl, NR^2R^3, cyano or a mono-cyclic or fused bi-cyclic moiety comprising 4 to 12 ring atoms of which optionally one, two or three are hetero atoms selected from amongst N, O, and S, and wherein said mono-cyclic or fused bi-cyclic moiety is optionally substituted with one or more substituents selected from the group consisting of halogen, cyano, C_{1-6}alkyl, hydroxyl, and C_{1-6}alkoxy, pyrazinyl, phenyl, pyridyl, and halogen substituted phenyl;

wherein R^2 and R^3 independently represent hydrogen, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, haloC_{1-6}alkyl or phenyl; and pharmaceutically acceptable salts thereof. In particular, A is CH, and R^1 represents C_{1-6}alkyl, such as ethyl or cyclopropyl. In particular, Z comprises 5-9 ring atoms, such as e.g. 5, 6, or 9 ring atoms. Examples of Z with 5 ring atoms include pyrrolide and cyclopentyl; examples of Z with 6 ring atoms include phenyl, pyrimidinyl, morpholinyl and pyridyl; examples of Z with 9 ring atoms include furo [3.2-c]pyridyl.

In one embodiment, the compounds of the present invention are defined by formula I_h



[I_h]

wherein A represents N, CH or CR^1;

wherein each R^1 independently represents hydrogen, C_{1-6}alkyl, -C(O)-C_{1-6}alkyl, C(O)-O-C_{1-6}alkyl, or phenyl, wherein said phenyl, or C_{1-6}alkyl is optionally substituted with one or more substituents selected from halogen, hydroxyl, haloC_{1-6}alkyl, nitro, C_{1-6}alkoxy, and NR^2R^3;

wherein W is selected from hydrogen, hydroxy, halogen, cyano, (=O), -O-$(CH_2)_c$-O-, wherein c is 2 or 3 (spiro), $(CH_2)_d$, wherein d is 5 or 6 (spiro), C_{1-6}alkyl, C_{1-6}alkoxy, -C(O)-C_{1-6}alkyl, -C(O)-O-C_{1-6}alkyl, -O-C(O)-C_{1-6}alkyl, -C(O)H, COOH; or wherein W represents a moiety of the formula –$(CH_2)_a$-Y-$(CH_2)_b$-Z;

wherein a and b independently represent an integer selected from 0, 1, 2 and 3;

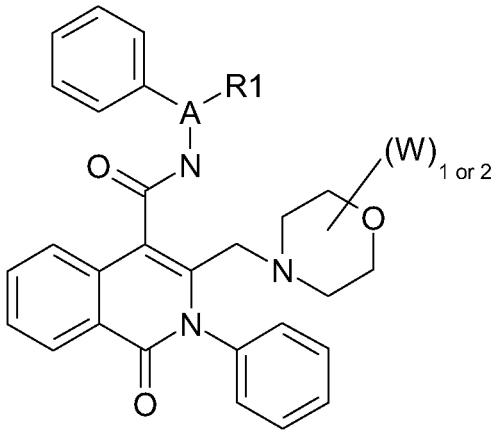
wherein Y represents a bond, C(O), O, S, -O-C(O), -C(O)-O-, NR^2, -NR^2-C(O)-, -C(O)-NH-, or $S(O)_2$;

wherein Z represents hydrogen, C_{1-6}alkyl, NR^2R^3, cyano or a mono-cyclic or fused bi-cyclic moiety comprising 4 to 12 ring atoms of which optionally one, two or three are hetero atoms selected from amongst N, O, and S, and wherein said mono-cyclic or fused bi-cyclic moiety is optionally substituted with one or more substituents selected from the group consisting of halogen, cyano, C_{1-6}alkyl, hydroxyl, and C_{1-6}alkoxy, pyrazinyl, phenyl, pyridyl, and halogen substituted phenyl;

wherein R^2 and R^3 independently represent hydrogen, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, haloC_{1-6}alkyl or phenyl; and pharmaceutically acceptable salts thereof. In particular, A is CH, and R^1 represents C_{1-6}alkyl, such as ethyl or cyclopropyl. In particular, Z comprises 5-9 ring atoms, such as e.g. 5, 6, or 9 ring atoms. Examples of Z with 5 ring

atoms include pyrrolide and cyclopentyl; examples of Z with 6 ring atoms include phenyl, pyrimidinyl, morpholinyl and pyridyl; examples of Z with 9 ring atoms include furo [3.2-c]pyridyl.

In one embodiment, the compounds of the present invention are defined by formula I_i



[Ii]

wherein A represents N, CH or CR^1;

wherein each R^1 independently represents hydrogen, C_{1-6}alkyl, -C(O)-C_{1-6}alkyl, C(O)-O-C_{1-6}alkyl, or phenyl, wherein said phenyl, or C_{1-6}alkyl is optionally substituted with one or more substituents selected from halogen, hydroxyl, haloC_{1-6}alkyl, nitro, C_{1-6}alkoxy, and NR^2R^3;

wherein W is selected from hydrogen, hydroxy, halogen, cyano, (=O), -O-$(CH_2)_c$-O-, wherein c is 2 or 3 (spiro), $(CH_2)_d$, wherein d is 5 or 6 (spiro), C_{1-6}alkyl, C_{1-6}alkoxy, -C(O)-C_{1-6}alkyl, -C(O)-O-C_{1-6}alkyl, -O-C(O)-C_{1-6}alkyl, -C(O)H, COOH; or wherein X represents a moiety of the formula –$(CH_2)_a$-Y-$(CH_2)_b$-Z;

wherein a and b independently represent an integer selected from 0, 1, 2 and 3;

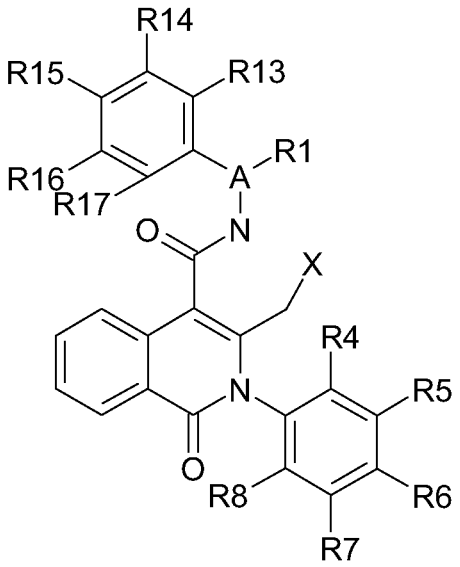
wherein Y represents a bond, C(O), O, S, -O-C(O), -C(O)-O-, NR^2, -NR^2-C(O)-, -C(O)-NH-, or $S(O)_2$;

wherein Z represents hydrogen, C_{1-6}alkyl, NR^2R^3, cyano or a mono-cyclic or fused bi-cyclic moiety comprising 4 to 12 ring atoms of which optionally one, two or three are hetero atoms selected from amongst N, O, and S, and wherein said mono-cyclic or fused bi-cyclic moiety is optionally substituted with one or more substituents selected

from the group consisting of halogen, cyano, C_{1-6}alkyl, hydroxyl, and C_{1-6}alkoxy, pyrazinyl, phenyl, pyridyl, and halogen substituted phenyl;

wherein R^2 and R^3 independently represent hydrogen, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, haloC_{1-6}alkyl or phenyl; and pharmaceutically acceptable salts thereof. In particular, A is CH, and R^1 represents C_{1-6}alkyl, such as ethyl or cyclopropyl. In particular, Z comprises 5-9 ring atoms, such as e.g. 5, 6, or 9 ring atoms. Examples of Z with 5 ring atoms include pyrrolide and cyclopentyl; examples of Z with 6 ring atoms include phenyl, pyrimidinyl, morpholinyl and pyridyl; examples of Z with 9 ring atoms include furo [3.2-c]pyridyl.

In one embodiment, the compounds of the present invention are defined by formula Ij



[Ij]

wherein A represents N, CH or CR^1;

wherein each R^1 independently represents hydrogen, C_{1-6}alkyl, -C(O)-C_{1-6}alkyl, -C(O)-O-C_{1-6}alkyl, or phenyl, wherein said phenyl or C_{1-6}alkyl is optionally substituted with one or more substituents selected from halogen, hydroxyl, haloC_{1-6}alkyl, nitro, C_{1-6}alkoxy, and NR^2R^3;

wherein X represents hydrogen, C_{1-6}alkyl, cyano, $-OR^2$, -O-C(O)R^2, -OC(O)NR^2R^3, -C(O)-NR^2R^3, -N(R^2)C(O)R^3, -N(R^2)-C(O)NR^2R^3 or NR^2R^3, or X represents a mono-cyclic, bicyclic or tri-cyclic moiety having 4-16 ring atoms one of which is nitrogen, and wherein one, two or three additional ring atoms may be a hetero atom selected

from N, O and S, and wherein said mono-cyclic, bi-cyclic or tri-cyclic moiety may optionally be substituted with one or more substituents W, wherein W is selected from hydrogen, hydroxy, halogen, cyano, (=O), -O-$(CH_2)_c$-O-, wherein c is 2 or 3 (spiro), $(CH_2)_d$, wherein d is 5 or 6 (spiro), C_{1-6}alkyl, C_{1-6}alkoxy, -C(O)-C_{1-6}alkyl, -C(O)-O-C_{1-6}alkyl, -O-C(O)-C_{1-6}alkyl, -C(O)H, COOH; or wherein W represents a moiety of the formula $-(CH_2)_a$-Y-$(CH_2)_b$-Z;

wherein a and b independently represent an integer selected from 0, 1, 2 and 3;

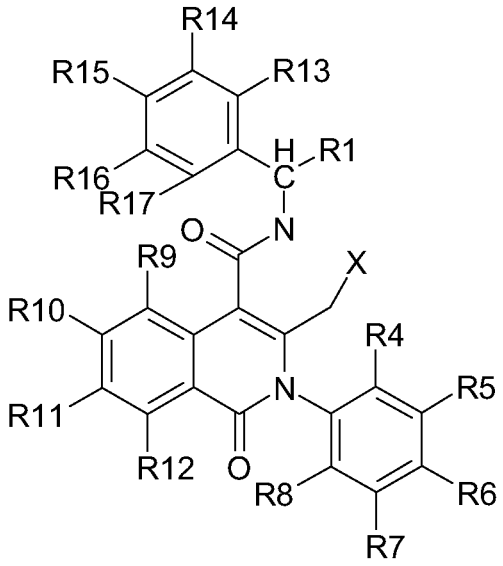
wherein Y represents a bond, C(O), O, S, -O-C(O), -C(O)-O-, -NR^2-, -NR^2-C(O)-, -C(O)-NH-, or $S(O)_2$;

wherein Z represents hydrogen, C_{1-6}alkyl, NR^2R^3, cyano or a mono-cyclic or fused bi-cyclic moiety comprising 4 to 12 ring atoms of which optionally one, two or three are hetero atoms selected from amongst N, O, and S, and wherein said mono-cyclic or fused bi-cyclic moiety is optionally substituted with one or more substituents selected from the group consisting of halogen, cyano, C_{1-6}alkyl, hydroxyl, and C_{1-6}alkoxy, phenyl, pyridyl, and halogen substituted phenyl;

wherein one of R^4-R^8 represents halogen and the other represent hydrogen; wherein one of R^{13}-R^{17} represents halogen and the other represent hydrogen;

wherein R^2 and R^3 independently represent hydrogen, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, haloC_{1-6}alkyl or phenyl; and pharmaceutically acceptable salts thereof. In particular, A represents CH; R^1 represents C_{1-6}alkyl, such as ethyl or cyclopropyl; R^{14} represents halogen; and R^5 or R^8 represents halogen. Particular mentioning is made of the embodiment wherein X represents piperazinyl or 1-piperidyl substituted with one or two substituents W, wherein said W is a moiety of the formula $-(CH_2)_a$-Y-$(CH_2)_b$-Z, wherein a and b independently represent 0, 1, 2 or 3; Y represents a bond, O, -NR^2-C(O)-; and wherein Z represents hydrogen, C_{1-6}alkyl, piperidyl, morpholinyl, pyridyl, phenyl, phenyl substituted with C_{1-6}alkoxy, or pyrrolidinyl.

In one embodiment, the compounds of the invention are defined by formula I_k



[Ik]

wherein R^1 represents hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl or C_{2-6}alkynyl;

wherein X represents hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl or NR^2R^3, or X represents a mono-cyclic or bi-cyclic moiety having 5-9 ring atoms one of which is nitrogen, and wherein one, two or three additional ring atoms may be a hetero atom selected from N, O and S, and wherein said mono-cyclic or bi-cyclic moiety may optionally be substituted with one or more substituents W, wherein W is selected from hydrogen, halogen, hydroxy, (=O), C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, or wherein W represents a moiety of the formula $-(CH_2)_a$-Y-$(CH_2)_b$-Z;

wherein a and b independently represent an integer selected from 0, 1, 2 and 3;

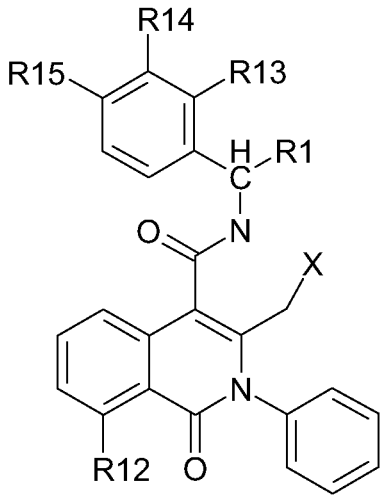
wherein Y represents a bond, and wherein Z represents a mono-cyclic moiety comprising 5 to 6 ring atoms of which optionally one, two or three are hetero atoms selected from amongst N, O, and S, and wherein said mono-cyclic moiety is optionally substituted with one or more substituents selected from the group consisting of halogen, C_{1-6}alkyl, hydroxyl, and C_{1-6}alkoxy;

wherein each of R^4-R^8 independently represents hydrogen or halogen;

wherein each of R^9-R^{12} independently represents hydrogen or halogen provided that at least one of R^9-R^{12} represents halogen;

wherein each of R^{13}-R^{17} independently represent hydrogen or halogen;

wherein R^2 and R^3 independently represent hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl; and pharmaceutically acceptable salts thereof. In particular, the compounds defined by formula I_k may be further defined by formula I_k'



[Ik']

wherein R^1 is selected from C_{1-6}alkyl;

wherein X is selected from hydrogen, C_{1-6}alkyl or NR^2R^3, or X represents a mono-cyclic or bi-cyclic moiety having 5-9 ring atoms one of which is nitrogen, and wherein one additional ring atoms may be a hetero atom selected from N, and wherein said mono-cyclic or bi-cyclic moiety may optionally be substituted with one or more substituents W, wherein W is selected from hydrogen, hydroxy, (=O), C_{1-6}alkyl or wherein W represents a moiety of the formula $-(CH_2)_a$-Y-$(CH_2)_b$-Z;

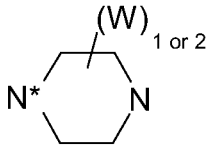
wherein a and b independently represent an integer selected from 0, 1, 2 and 3;

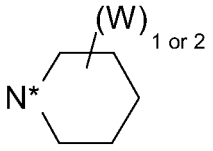
wherein Y represents a bond, and wherein Z represents a mono-cyclic moiety comprising 5 to 6 ring atoms of which optionally one is a hetero atom selected from amongst N, O, and S, and wherein said mono-cyclic moiety is optionally substituted with one or more substituents selected from the group consisting of halogen, C_{1-6}alkyl, hydroxyl, and C_{1-6}alkoxy;

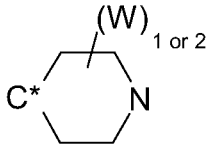
wherein R^{12} represents halogen;

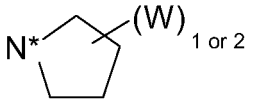
R^{13}-R^{15} each independently represents hydrogen or halogen;

and pharmaceutically acceptable salts thereof. In particular, R^1 represents methyl, ethyl, cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl, and X represents



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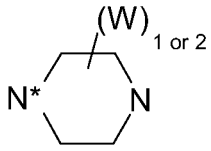
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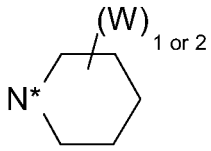
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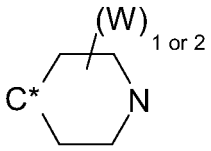
$-NR^2R^3$, or Hydrogen

* indicates the point of attachment

In one embodiment, wherein the compounds of the invention are defined by formula I_k' and R^1 represents methyl, ethyl, cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl, X represents 

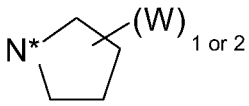
, and wherein W represents hydrogen, (=O), C_{1-6}-alkyl, or $-(CH_2)_a$-Y-$(CH_2)_b$-Z. In particular, W represents hydrogen, methyl, cyclopropylmethyl, isopropyl, isobutyl, tert-butyl, (=O), or or $-(CH_2)_a$-Y-$(CH_2)_a$-Z, wherein a+b is 2 and Z is selected from 4-morpholinyl, phenyl, 1-piperidine or 1-pyrrolidinyl.

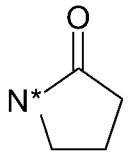
In one embodiment, wherein the compounds of the invention are defined by formula I_k' and R^1 represents methyl, ethyl, cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl, X represents 

or 

, wherein W represents hydrogen, hydroxyl, C_{1-6}-alkyl or $-(CH_2)_a$-Y-$(CH_2)_a$-Z. In particular, W represents hydrogen, hydroxyl, tert-butyl, or a+b is 0 or 2 and Z represents 4-morpholinyl, phenyl, optionally substituted with C_{1-6}alkoxy, or 4-piperidyl.

In one embodiment, wherein the compounds of the invention are defined by formula I_k' and R^1 represents methyl, ethyl, cyclopropyl, cyclobutyl, cyclopentyl or

cyclohexyl, X represent 

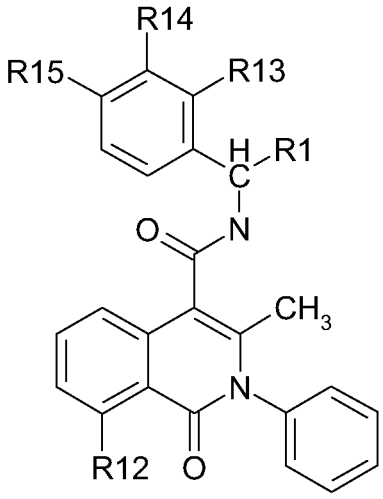
, and W represents (=O), and in particular, X represents 

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In one embodiment, wherein the compounds of the invention are defined by formula I_k' and R^1 represents methyl, ethyl, cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl, X represents $-NR^2R^3$. In particular, R^2 and R^3 independently represents hydrogen or C_{1-6}-alkyl, and special mention is made of the compounds wherein R^2 represents hydrogen, and R^3 represents cyclopropyl, isobutyl or tert-butyl.

In one embodiment, wherein the compounds of the invention are defined by formula I_k' and R^1 represents methyl, ethyl, cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl, X is hydrogen.

In one embodiment, the compounds of the invention are defined by formula I_k''



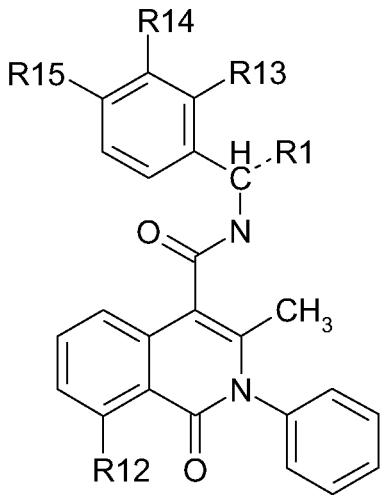
[Ik"]

wherein R^1 represents ethyl, cylopropyl or cyclobutyl;

wherein R^{12} represents flouro or chloro; and

R^{13}, R^{14} and R^{15} each individually represent hydrogen, fluoro or chloro, wherein two of R^{13}, R^{14} and R^{15} represent hydrogen, and pharmaceutically acceptable salts thereof.

In particular, said compound is essentially the S enantiomers as depicted in formula I_k'''



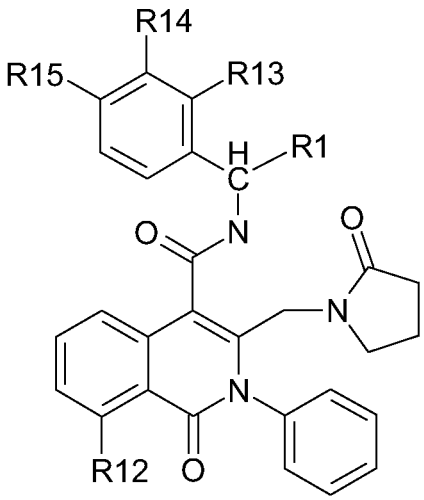
[Ik'"]

wherein R^1 represents ethyl or cylopropyl;

wherein R^{12} represents flouro or chloro; and

R^{13}, R^{14} and R^{15} each individually represent hydrogen, fluoro or chloro, wherein two of R^{13}, R^{14} and R^{15} represent hydrogen.

In one embodiment, the compounds of the inventions are defined by formula I_d'



[Id']

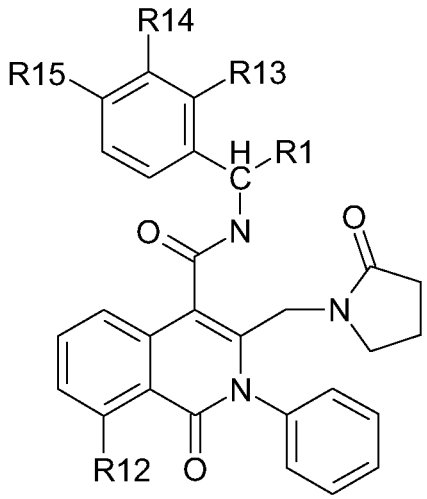
wherein R^1 represents ethyl or cyclopropyl;

R^{12} represent halogen;

R^{13}, R^{14} and R15 each independently represents hydrogen, or halogen;

and pharmaceutically acceptable salts thereof.

In one embodiment, the compounds of the inventiion are defined by formula I_d''



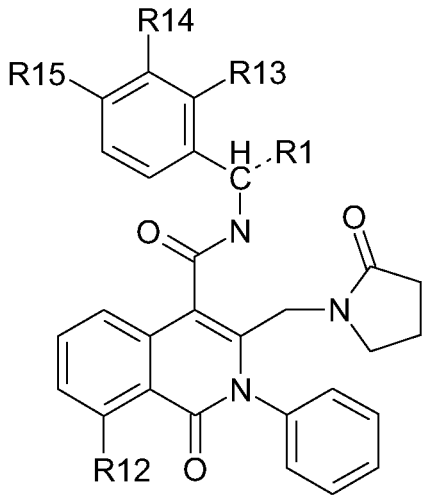
[Id"]

wherein R^1 represents ethyl or cyclopropyl;

R^{12} represent chloro or fluoro;

R^{12}, R^{14} and R^{15} each independently represent hydrogen, chloro or fluoro, wherein two of R^{12}, R^{14} and R^{15} represent hydrogen;

and pharmaceutically acceptable salts thereof. In particular, said compound is essentially the S enantiomer as depicted in formula Id'''



[Id'"]

wherein R^1 represents ethyl or cyclopropyl;

R^{12} represent chloro or fluoro;

R^{12}, R^{14} and R^{15} each independently represent hydrogen, chloro or fluoro, wherein two of R^{12}, R^{14} and R^{15} represent hydrogen;

and pharmaceutically acceptable salts thereof.

In one embodiment the compounds of the present invention are selected from the below list. For convenience, the number indicated in bold in front of the compound name refers to the corresponding example number.

1a 3-Methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

1b 3,6-Dimethyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

1c 7-Chloro-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

1d 7-Bromo-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

1e 6-Fluoro-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

1f 3,5-Dimethyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

1g 7-Fluoro-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

1h 3,7-Dimethyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

1i 8-Chloro-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

1r 3-Methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-cyclopropyl-phenyl-methyl)-amide

1s 3-Methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-cyclopropyl-(3-fluoro-phenyl)-methyl]-amide

1j 3,8-Dimethyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

1k 2-(2-Fluoro-phenyl)-3-methyl-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

1l 3-Methyl-1-oxo-2-o-tolyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

1m 2-(2-Chloro-phenyl)-3-methyl-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

1n 2-(2,6-Difluoro-phenyl)-3-methyl-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

1o 2-(3-Fluoro-phenyl)-3-methyl-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

1p 3-Methyl-1-oxo-2-m-tolyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

1q 2-(3-Chloro-phenyl)-3-methyl-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

1t 8-Chloro-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-cyclopropyl-(3-fluoro-phenyl)-methyl]-amide

2a 3-Dimethylaminomethyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2b 3-Methylaminomethyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2c 3-Ethylaminomethyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2d 3-Cyclopropylaminomethyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2e 3-[(Cyclopropylmethyl-amino)-methyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2f 3-(3,6-Dihydro-2H-pyridin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2g 3-[4-(2-Methoxy-phenyl)-piperazin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2h 3-[4-(4-Fluoro-phenyl)-piperazin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2i 3-(4-Formyl-piperazin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2j 4-[1-Oxo-2-phenyl-4-(1-phenyl-propylcarbamoyl)-1,2-dihydro-isoquinolin-3-ylmethyl]-piperazine-1-carboxylic acid ethyl ester

2k 3-(4-Methyl-piperazin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2l 1-Oxo-2-phenyl-3-(1,3,4,9-tetrahydro-beta-carbolin-2-ylmethyl)-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2m 1-Oxo-2-phenyl-3-piperazin-1-ylmethyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2n 3-(3-Methyl-piperazin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2o 3-(3,5-Dimethyl-piperazin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2p 3-(4-Benzyl-piperazin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2q 1-Oxo-3-[4-(2-oxo-2-pyrrolidin-1-yl-ethyl)-piperazin-1-ylmethyl]-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2r 3-Morpholin-4-ylmethyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2s 3-(2,6-Dimethyl-morpholin-4-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2t 1-Oxo-2-phenyl-3-thiomorpholin-4-ylmethyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2u 3-(1,4-Dioxa-8-aza-spiro[4.5]dec-8-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2v 1-Oxo-2-phenyl-3-piperidin-1-ylmethyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2w 3-(2-Methyl-piperidin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2x 3-(2,6-Dimethyl-piperidin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2y 3-(2-Hydroxymethyl-piperidin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2z 1-[1-Oxo-2-phenyl-4-(1-phenyl-propylcarbamoyl)-1,2-dihydro-isoquinolin-3-ylmethyl]-piperidine-3-carboxylic acid ethyl ester

2aa 3-(3-Methyl-piperidin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2ab 3-(4-Hydroxy-piperidin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2ac 1-Oxo-2-phenyl-3-(4-phenyl-piperidin-1-ylmethyl)-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2ad 1-[1-Oxo-2-phenyl-4-(1-phenyl-propylcarbamoyl)-1,2-dihydro-isoquinolin-3-ylmethyl]-piperidine-4-carboxylic acid ethyl ester

2ae 3-(4-Methyl-piperidin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2af 1-Oxo-2-phenyl-3-(4-pyridin-2-yl-piperazin-1-ylmethyl)-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2ag 3-(Octahydro-quinolin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2ah 3-Azepan-1-ylmethyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2ai 3-(3-Hydroxy-piperidin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2aj 3-[4-(2,4-Dimethyl-phenyl)-piperazin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2ak 3-[4-(3,4-Dimethyl-phenyl)-piperazin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2al 3-(4-Dimethylamino-piperidin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2am 3-[4-(2,5-Dimethyl-phenyl)-piperazin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2an 3-[4-(2-Fluoro-phenyl)-piperazin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2ao 3-[4-(3-Methoxy-phenyl)-piperazin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2ap 1-Oxo-2-phenyl-3-(4-m-tolyl-piperazin-1-ylmethyl)-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2aq 3-[4-(4-Methoxy-phenyl)-piperazin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2ar 1-Oxo-3-(4-phenethyl-piperazin-1-ylmethyl)-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2as 1-Oxo-2-phenyl-3-(4-pyrimidin-2-yl-piperazin-1-ylmethyl)-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2at 3-[4-(2-Cyano-phenyl)-piperazin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2au 3-[4-(4-Chloro-phenyl)-piperazin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2av 3-((1S,3R,5R)-3-Hydroxy-8-aza-bicyclo[3.2.1]oct-8-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2aw 3-(4-Acetyl-piperazin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2ax 3-(4-Methyl-[1,4]diazepan-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2ay 3-(4-Ethyl-piperazin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2az 3-((2S,6R)-2,6-Dimethyl-morpholin-4-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2ba 3-[4-(2,4-Difluoro-phenyl)-piperazin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2bb 3-[4-(3-Dimethylamino-propyl)-piperazin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2bc 3-(4-Isopropyl-piperazin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2bd 3-(3-Aza-bicyclo[3.2.2]non-3-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2be 3-(4-Cyclopentyl-piperazin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2bf 3-[1,4']Bipiperidinyl-1'-ylmethyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2bg 3-(3,4-Dihydro-1H-isoquinolin-2-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2bh 3-[4-(2-Dimethylamino-ethyl)-piperazin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2bi 3-(4-Hydroxymethyl-piperidin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2bj 1-Oxo-2-phenyl-3-[4-(tetrahydro-furan-2-carbonyl)-piperazin-1-ylmethyl]-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2bk 3-(4-Isobutyl-piperazin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2bl 3-[4-(2-Methoxy-ethyl)-piperazin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2bm 3-[4-(2-Morpholin-4-yl-ethyl)-piperazin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2bn 3-(1,3-Dihydro-isoindol-2-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2bo 3-[4-(1-Methyl-piperidin-4-yl)-piperazin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2bp 1-Oxo-2-phenyl-3-[4-(2-piperidin-1-yl-ethyl)-piperazin-1-ylmethyl]-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2bq 1-Oxo-2-phenyl-3-[4-(2-pyrrolidin-1-yl-ethyl)-piperazin-1-ylmethyl]-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2br 3-(4-Dimethylcarbamoylmethyl-piperazin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2bs 3-(Octahydro-pyrido[1,2-a]pyrazin-2-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2bt 3-(4-Formyl-[1,4]diazepan-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2bu 3-[4-(4-Cyano-phenyl)-piperazin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2bv 1-Oxo-2-phenyl-3-(4-pyridin-4-ylmethyl-piperazin-1-ylmethyl)-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2bw 1-Oxo-2-phenyl-3-[4-(3-pyrrolidin-1-yl-propyl)-piperazin-1-ylmethyl]-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2bx 1-Oxo-2-phenyl-3-(4-pyridin-2-ylmethyl-piperazin-1-ylmethyl)-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2by 3-(4-Ethanesulfonyl-piperazin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2bz 3-(4-sec-Butyl-piperazin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2ca 3-[4-(1-Ethyl-propyl)-piperazin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2cb 3-[4-(2-Cyano-ethyl)-piperazin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2cc 3-(4-Methanesulfonyl-piperazin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2cd {1-[1-Oxo-2-phenyl-4-(1-phenyl-propylcarbamoyl)-1,2-dihydro-isoquinolin-3-ylmethyl]-piperidin-4-yl}-acetic acid ethyl ester

2ce 3-[4-(3-Fluoro-phenyl)-piperazin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2cf 1-Oxo-2-phenyl-3-((S)-3-phenyl-piperidin-1-ylmethyl)-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2cg 1-Oxo-2-phenyl-3-[4-(pyrrolidine-1-carbonyl)-piperazin-1-ylmethyl]-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2ch 3-[4-(Morpholine-4-carbonyl)-piperazin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2ci 3-(4-Methoxy-piperidin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2cj 3-(4'-Hydroxy-3',4',5',6'-tetrahydro-2'H-[3,4']bipyridinyl-1'-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2ck 3-(4-Hydroxy-3,4,5,6-tetrahydro-2H-[4,4']bipyridinyl-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2cl 3-(3H-spiro[isobenzofuran-1,4'-piperidin]-1'-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2cm 3-(4-Hydroxy-4-methyl-piperidin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2cn 3-(hexahydro-spiro[benzo[1,3]dioxole-2,4'-piperidin]-1'-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2co 1-Oxo-2-phenyl-3-(3,4,5,6-tetrahydro-2H-[4,4']bipyridinyl-1-ylmethyl)-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2cp 3-[4-(2-Dimethylamino-ethyl)-piperidin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2cq 3-(4-Dimethylsulfamoyl-piperazin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2cr 3-(1,1-Dioxo-thiomorpholin-4-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2cs 1-Oxo-2-phenyl-3-(2-pyridin-2-ylmethyl-piperidin-1-ylmethyl)-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2ct 3-(2-Morpholin-4-ylmethyl-piperidin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2cu 3-(4-Furo[3,2-c]pyridin-4-yl-piperazin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2cv 3-(4-Cyclopropylmethyl-piperazin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2cw 3-[4-(2-Morpholin-4-yl-ethyl)-piperidin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2cx 1-Oxo-2-phenyl-3-(4-pyrimidin-2-yl-[1,4]diazepan-1-ylmethyl)-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2cy 3-(4-Methyl-6,7-dihydro-4H-thieno[3,2-c]pyridin-5-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2cz 3-[1,4]Diazepan-1-ylmethyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2da 3-((2S,5R)-2,5-Dimethyl-piperazin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2db 3-((S)-3-Methyl-piperazin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2dc 3-((R)-3-Methyl-piperazin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2dd 3-[3-(3-Chloro-phenyl)-piperazin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2de 3-[4-(1H-Indol-4-yl)-piperazin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2df 1-Oxo-3-(3-oxo-piperazin-1-ylmethyl)-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2dg 3-[4-(1H-Indol-5-yl)-piperazin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2dh 3-(6,9-Diaza-spiro[4.5]dec-9-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2di 3-(1,4-Diaza-spiro[5.5]undec-4-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2dj 3-(3-Isopropyl-piperazin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2dk 3-(3,3-Dimethyl-piperazin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2dl 3-[3-(4-Fluoro-phenyl)-piperazin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2dm 1-Oxo-2-phenyl-3-(3-p-tolyl-piperazin-1-ylmethyl)-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2dn 4-[1-Oxo-2-phenyl-4-(1-phenyl-propylcarbamoyl)-1,2-dihydro-isoquinolin-3-ylmethyl]-piperazine-1-carboxylic acid tert-butyl ester

2do 3-(4-Methylcarbamoylmethyl-piperazin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2dp 8-Chloro-3-dimethylaminomethyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2dr 3-Cyclopentylaminomethyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2ds 3-Cyclohexylaminomethyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2dt 3-{[(2-Hydroxy-ethyl)-methyl-amino]-methyl}-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2du 3-Imidazol-1-ylmethyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2dv 3-(2-Methyl-imidazol-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2dw 3-(4-Methyl-imidazol-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2dx 3-(2,5-Dihydro-pyrrol-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2dy 3-(2,5-Dimethyl-2,5-dihydro-pyrrol-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2dz 1-Oxo-2-phenyl-3-pyrrolidin-1-ylmethyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2ea 1-Oxo-2-phenyl-3-(thiazol-2-ylaminomethyl)-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2eb 1-Oxo-2-phenyl-3-(pyrimidin-4-ylaminomethyl)-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2ec 3-(tert-Butylamino-methyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2ed 3-[(2-Hydroxy-1,1-dimethyl-ethylamino)-methyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2ee 3-(Isopropylamino-methyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2ef 3-[(2-Hydroxy-1-methyl-ethylamino)-methyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2eg 3-[(1-Hydroxymethyl-propylamino)-methyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2eh 3-[(2,2-Dimethyl-propylamino)-methyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2ei 1-Oxo-2-phenyl-3-prop-2-ynylaminomethyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2ej 3-Allylaminomethyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2ek 3-[(Methyl-prop-2-ynyl-amino)-methyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2el 3-Diallylaminomethyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2em 3-Diethylaminomethyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2en 3-[(Isopropyl-methyl-amino)-methyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2eo 3-[((S)-2-Hydroxy-1-methyl-ethylamino)-methyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2ep 3-[((R)-2-Hydroxy-1-methyl-ethylamino)-methyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2eq 3-{[(2-Methoxy-ethyl)-methyl-amino]-methyl}-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2er 3-((R)-3-Hydroxy-pyrrolidin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2es 3-((S)-3-Hydroxy-pyrrolidin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2et 3-[(Cyclopentyl-methyl-amino)-methyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2eu 3-{[(2-Hydroxy-1-methyl-ethyl)-methyl-amino]-methyl}-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2ev 3-{[Ethyl-(2-hydroxy-ethyl)-amino]-methyl}-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2ew 3-[(Ethyl-methyl-amino)-methyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2ex 3-Cyclobutylaminomethyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2ey 3-Azetidin-1-ylmethyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2ez 3-(4-tert-Butyl-piperazin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2fa 3-[4-(2-Hydroxy-ethyl)-piperazin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2fb 3-{4-[2-(2-Hydroxy-ethoxy)-ethyl]-piperazin-1-ylmethyl}-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2fc 3-[4-(3-Chloro-5-trifluoromethyl-pyridin-2-yl)-piperazin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2fd 3-[4-(3,5-Dichloro-pyridin-4-yl)-piperazin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2fe 4-[1-Oxo-2-phenyl-4-((S)-1-phenyl-propylcarbamoyl)-1,2-dihydro-isoquinolin-3-ylmethyl]-piperazine-1-carboxylic acid benzyl ester

2ff 3-[4-(3-Morpholin-4-yl-propyl)-piperazin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2fg 1-Oxo-2-phenyl-3-[4-(3-piperidin-1-yl-propyl)-piperazin-1-ylmethyl]-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2fh 3-[4-(4,6-Dimethoxy-pyrimidin-2-ylmethyl)-piperazin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2fi 3-[4-(3-Hydroxy-propyl)-piperazin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2fj 3-[4-(2,3-Dihydroxy-propyl)-piperazin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2fk (2-Oxo-2-{4-[1-oxo-2-phenyl-4-(1-phenyl-propylcarbamoyl)-1,2-dihydro-isoquinolin-3-ylmethyl]-piperazin-1-yl}-ethyl)-carbamic acid tert-butyl ester

2fl 3-[4-(1H-Indazol-5-yl)-piperazin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2fm 1-Oxo-2-phenyl-3-(4-quinolin-6-yl-piperazin-1-ylmethyl)-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2fn 3-[4-(6,7-Dimethoxy-quinazolin-4-yl)-piperazin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2fo 4-{4-[1-Oxo-2-phenyl-4-(1-phenyl-propylcarbamoyl)-1,2-dihydro-isoquinolin-3-ylmethyl]-piperazin-1-yl}-piperidine-1-carboxylic acid tert-butyl ester

2fp 3-{4-[2-(4-Chloro-phenoxy)-ethyl]-piperazin-1-ylmethyl}-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2fq {4-[1-Oxo-2-phenyl-4-(1-phenyl-propylcarbamoyl)-1,2-dihydro-isoquinolin-3-ylmethyl]-piperazin-1-yl}-acetic acid tert-butyl ester

2fr 1-Oxo-2-phenyl-3-[4-(3,3,3-trifluoro-2-hydroxy-propyl)-piperazin-1-ylmethyl]-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2fs 3-[4-(2-Hydroxy-propyl)-piperazin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2fu 3-[4-(4-Amino-6,7-dimethoxy-quinazolin-2-yl)-piperazin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2fv (2-{4-[1-Oxo-2-phenyl-4-(1-phenyl-propylcarbamoyl)-1,2-dihydro-isoquinolin-3-ylmethyl]-piperazin-1-yl}-ethyl)-carbamic acid tert-butyl ester

2fw 1-Oxo-3-{4-[2-(2-oxo-imidazolidin-1-yl)-ethyl]-piperazin-1-ylmethyl}-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2fx 3-{4-[(4,6-Dimethoxy-pyrimidin-2-yl)-phenyl-methyl]-piperazin-1-ylmethyl}-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2fy 3-(4-Benzo[1,2,5]thiadiazol-4-yl-piperazin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2fz 3-[4-(2,3-Dihydro-benzo[1,4]dioxin-5-yl)-piperazin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2ga 3-[4-(4-Methyl-quinolin-2-yl)-piperazin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2gb 1-Oxo-2-phenyl-3-[4-(pyridin-2-ylcarbamoylmethyl)-piperazin-1-ylmethyl]-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2gc 3-[4-(6-Chloro-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-8-yl)-piperazin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2gd 3-(4-Carbamoylmethyl-piperazin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2ge 3-(4-Hydroxy-4-phenyl-piperidin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2gf 3-[4-(4-Chloro-phenyl)-4-hydroxy-piperidin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2gg 1-[1-Oxo-2-phenyl-4-(1-phenyl-propylcarbamoyl)-1,2-dihydro-isoquinolin-3-ylmethyl]-piperidine-4-carboxylic acid

2gh 3-(4-Cyano-4-phenyl-piperidin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2gi 3-(4-Benzyl-4-hydroxy-piperidin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2gj 1-[1-Oxo-2-phenyl-4-(1-phenyl-propylcarbamoyl)-1,2-dihydro-isoquinolin-3-ylmethyl]-4-phenyl-piperidine-4-carboxylic acid ethyl ester

2gk 1-Oxo-2-phenyl-3-[4-(phenyl-propionyl-amino)-piperidin-1-ylmethyl]-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2gl Methyl-{1-[1-oxo-2-phenyl-4-(1-phenyl-propylcarbamoyl)-1,2-dihydro-isoquinolin-3-ylmethyl]-piperidin-4-yl}-carbamic acid tert-butyl ester

2gm 1-Oxo-2-phenyl-3-[4-(2-pyrrolidin-1-yl-ethyl)-piperidin-1-ylmethyl]-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2gn 3-{4-[5-(4-Fluoro-phenyl)-[1,3,4]oxadiazol-2-yl]-piperidin-1-ylmethyl}-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2go 1-Oxo-2-phenyl-3-[4-(3-pyridin-4-yl-[1,2,4]oxadiazol-5-yl)-piperidin-1-ylmethyl]-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2gp 1-Oxo-2-phenyl-3-[4-(3-pyrazin-2-yl-[1,2,4]oxadiazol-5-yl)-piperidin-1-ylmethyl]-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2gq 1-Oxo-2-phenyl-3-[4-(3-pyridin-4-yl-[1,2,4]oxadiazol-5-yl)-piperidin-1-ylmethyl]-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2gr 3-(4'-Hydroxy-3',4',5',6'-tetrahydro-2'H-[2,4']bipyridinyl-1'-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2gs 3-(spiro[isochroman-1,4'-piperidin]-1'-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2gt 3-[4-Hydroxy-4-(3-methoxy-phenyl)-piperidin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2gu 3-[4-(3-Chloro-phenyl)-4-hydroxy-piperidin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2gv 3-(6-chloro-3H-spiro[isobenzofuran-1,4'-piperidin]-1'-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2gw 3-(4-{[4-Chloro-3-(4-fluoro-phenyl)-indan-1-yl]-methyl-amino}-piperidin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2gx 3-(1-acetyl-spiro[indoline-3,4'-piperidin]-1'-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2gy 3-(1-acetyl-5-fluoro-spiro[indoline-3,4'-piperidin]-1'-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2gz 1-Oxo-3-(4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-8-ylmethyl)-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2ha 3-(4-Acetylamino-piperidin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2hb 1-Oxo-3-(1-oxo-2,8-diaza-spiro[4.5]dec-8-ylmethyl)-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2hc 3-[4-Hydroxy-4-(3-trifluoromethyl-phenyl)-piperidin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2hd 1-Oxo-2-phenyl-3-(4-trifluoromethyl-piperidin-1-ylmethyl)-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2he 3-[4-(4-Methyl-piperazine-1-carbonyl)-piperidin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2hf 3-(5-isopropyl-3H-spiro[isobenzofuran-1,4'-piperidin]-1'-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2hg 3-[4-(Acetyl-methyl-amino)-4-phenyl-piperidin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2hh 4-{1-[1-Oxo-2-phenyl-4-(1-phenyl-propylcarbamoyl)-1,2-dihydro-isoquinolin-3-ylmethyl]-piperidin-4-yl}-piperazine-1-carboxylic acid tert-butyl ester

2hi (2-{1-[1-Oxo-2-phenyl-4-(1-phenyl-propylcarbamoyl)-1,2-dihydro-isoquinolin-3-ylmethyl]-piperidin-4-yl}-ethyl)-carbamic acid tert-butyl ester

2hj 3-(4-Methylamino-4-phenyl-piperidin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2hk 3-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2hl 3-[4-Acetylamino-4-(3-fluoro-phenyl)-piperidin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2hm 1-Oxo-3-[4-(4-oxo-piperidine-1-carbonyl)-piperidin-1-ylmethyl]-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2hn 3-[4,4']Bipiperidinyl-1-ylmethyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2ho {1-[1-Oxo-2-phenyl-4-(1-phenyl-propylcarbamoyl)-1,2-dihydro-isoquinolin-3-ylmethyl]-piperidin-4-yl}-carbamic acid tert-butyl ester

2hp 3-[1,4']Bipiperidinyl-1'-ylmethyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid [cyclopropyl-(3-fluoro-phenyl)-methyl]-amide

2hq 1-Oxo-3-(4-phenethyl-piperazin-1-ylmethyl)-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid [cyclopropyl-(3-fluoro-phenyl)-methyl]-amide

2hr 3-(4-Isopropyl-piperazin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid [cyclopropyl-(3-fluoro-phenyl)-methyl]-amide

2hs 3-[4-(2-Morpholin-4-yl-ethyl)-piperazin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid [cyclopropyl-(3-fluoro-phenyl)-methyl]-amide

2ht 3-[4-(1-Methyl-piperidin-4-yl)-piperazin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid [cyclopropyl-(3-fluoro-phenyl)-methyl]-amide

2hu 1-Oxo-2-phenyl-3-[4-(2-piperidin-1-yl-ethyl)-piperazin-1-ylmethyl]-1,2-dihydro-isoquinoline-4-carboxylic acid [cyclopropyl-(3-fluoro-phenyl)-methyl]-amide

2hv 1-Oxo-2-phenyl-3-[4-(2-pyrrolidin-1-yl-ethyl)-piperazin-1-ylmethyl]-1,2-dihydro-isoquinoline-4-carboxylic acid [cyclopropyl-(3-fluoro-phenyl)-methyl]-amide

2hw 1-Oxo-2-phenyl-3-(4-pyridin-4-ylmethyl-piperazin-1-ylmethyl)-1,2-dihydro-isoquinoline-4-carboxylic acid [cyclopropyl-(3-fluoro-phenyl)-methyl]-amide

2hx 3-(4-Hydroxy-3,4,5,6-tetrahydro-2H-[4,4']bipyridinyl-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid [cyclopropyl-(3-fluoro-phenyl)-methyl]-amide

2hy 3-[4-(2-Morpholin-4-yl-ethyl)-piperidin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid [cyclopropyl-(3-fluoro-phenyl)-methyl]-amide

2hz 3-[4-Hydroxy-4-(3-methoxy-phenyl)-piperidin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid [cyclopropyl-(3-fluoro-phenyl)-methyl]-amide

2ia 3-[4-(Acetyl-methyl-amino)-4-phenyl-piperidin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid [cyclopropyl-(3-fluoro-phenyl)-methyl]-amide

2ib 2-(2-Fluoro-phenyl)-1-oxo-3-(4-phenethyl-piperazin-1-ylmethyl)-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2ic 2-(2-Fluoro-phenyl)-3-(4-isopropyl-piperazin-1-ylmethyl)-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2id 3-[1,4']Bipiperidinyl-1'-ylmethyl-2-(2-fluoro-phenyl)-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2ie 2-(2-Fluoro-phenyl)-3-[4-(2-morpholin-4-yl-ethyl)-piperazin-1-ylmethyl]-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2if 2-(2-Fluoro-phenyl)-3-[4-(1-methyl-piperidin-4-yl)-piperazin-1-ylmethyl]-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2ig 2-(2-Fluoro-phenyl)-1-oxo-3-[4-(2-piperidin-1-yl-ethyl)-piperazin-1-ylmethyl]-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2ih 2-(2-Fluoro-phenyl)-1-oxo-3-[4-(2-pyrrolidin-1-yl-ethyl)-piperazin-1-ylmethyl]-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2ii 2-(2-Fluoro-phenyl)-1-oxo-3-(4-pyridin-4-ylmethyl-piperazin-1-ylmethyl)-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2ij 2-(2-Fluoro-phenyl)-3-(4-hydroxy-3,4,5,6-tetrahydro-2H-[4,4']bipyridinyl-1-ylmethyl)-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2ik 2-(2-Fluoro-phenyl)-3-[4-(2-morpholin-4-yl-ethyl)-piperidin-1-ylmethyl]-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2il 2-(2-Fluoro-phenyl)-3-[4-hydroxy-4-(3-methoxy-phenyl)-piperidin-1-ylmethyl]-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2im 3-[4-(2-Morpholin-4-yl-ethyl)-piperazin-1-ylmethyl]-1-oxo-2-o-tolyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2in 1-Oxo-3-[4-(2-piperidin-1-yl-ethyl)-piperazin-1-ylmethyl]-2-o-tolyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2io 1-Oxo-3-(4-pyridin-4-ylmethyl-piperazin-1-ylmethyl)-2-o-tolyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2ip 2-(3-Fluoro-phenyl)-1-oxo-3-(4-phenethyl-piperazin-1-ylmethyl)-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2iq 2-(3-Fluoro-phenyl)-3-(4-isopropyl-piperazin-1-ylmethyl)-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2ir 3-[1,4']Bipiperidinyl-1'-ylmethyl-2-(3-fluoro-phenyl)-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2is 2-(3-Fluoro-phenyl)-3-[4-(2-morpholin-4-yl-ethyl)-piperazin-1-ylmethyl]-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2it 2-(3-Fluoro-phenyl)-3-[4-(1-methyl-piperidin-4-yl)-piperazin-1-ylmethyl]-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2iu 2-(3-Fluoro-phenyl)-1-oxo-3-[4-(2-piperidin-1-yl-ethyl)-piperazin-1-ylmethyl]-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2iv 2-(3-Fluoro-phenyl)-1-oxo-3-[4-(2-pyrrolidin-1-yl-ethyl)-piperazin-1-ylmethyl]-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2iw 2-(3-Fluoro-phenyl)-1-oxo-3-(4-pyridin-4-ylmethyl-piperazin-1-ylmethyl)-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2ix 2-(3-Fluoro-phenyl)-3-[4-(2-morpholin-4-yl-ethyl)-piperidin-1-ylmethyl]-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2iy 2-(3-Fluoro-phenyl)-3-[4-hydroxy-4-(3-methoxy-phenyl)-piperidin-1-ylmethyl]-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2iz 3-[4-(Acetyl-methyl-amino)-4-phenyl-piperidin-1-ylmethyl]-2-(3-fluoro-phenyl)-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2ja 2-(3-Chloro-phenyl)-1-oxo-3-(4-phenethyl-piperazin-1-ylmethyl)-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2jb 2-(3-Chloro-phenyl)-3-(4-isopropyl-piperazin-1-ylmethyl)-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2jc 3-[1,4']Bipiperidinyl-1'-ylmethyl-2-(3-chloro-phenyl)-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2jd 2-(3-Chloro-phenyl)-3-[4-(2-morpholin-4-yl-ethyl)-piperazin-1-ylmethyl]-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2je 2-(3-Chloro-phenyl)-3-[4-(1-methyl-piperidin-4-yl)-piperazin-1-ylmethyl]-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2jf 2-(3-Chloro-phenyl)-1-oxo-3-[4-(2-piperidin-1-yl-ethyl)-piperazin-1-ylmethyl]-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2jg 2-(3-Chloro-phenyl)-1-oxo-3-[4-(2-pyrrolidin-1-yl-ethyl)-piperazin-1-ylmethyl]-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2jh 2-(3-Chloro-phenyl)-1-oxo-3-(4-pyridin-4-ylmethyl-piperazin-1-ylmethyl)-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2ji 2-(3-Chloro-phenyl)-3-[4-(2-morpholin-4-yl-ethyl)-piperidin-1-ylmethyl]-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2jj 2-(3-Chloro-phenyl)-3-[4-hydroxy-4-(3-methoxy-phenyl)-piperidin-1-ylmethyl]-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2jk 3-[4-(Acetyl-methyl-amino)-4-phenyl-piperidin-1-ylmethyl]-2-(3-chloro-phenyl)-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2jl 1-Oxo-3-(4-phenethyl-piperazin-1-ylmethyl)-2-m-tolyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2jm 3-[1,4']Bipiperidinyl-1'-ylmethyl-1-oxo-2-m-tolyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2jn 3-[4-(2-Morpholin-4-yl-ethyl)-piperazin-1-ylmethyl]-1-oxo-2-m-tolyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2jo 3-[4-(1-Methyl-piperidin-4-yl)-piperazin-1-ylmethyl]-1-oxo-2-m-tolyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2jp 1-Oxo-3-[4-(2-piperidin-1-yl-ethyl)-piperazin-1-ylmethyl]-2-m-tolyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2jq 1-Oxo-3-[4-(2-pyrrolidin-1-yl-ethyl)-piperazin-1-ylmethyl]-2-m-tolyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2jr 1-Oxo-3-(4-pyridin-4-ylmethyl-piperazin-1-ylmethyl)-2-m-tolyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2js 3-[4-(2-Morpholin-4-yl-ethyl)-piperidin-1-ylmethyl]-1-oxo-2-m-tolyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2jt 3-[4-Hydroxy-4-(3-methoxy-phenyl)-piperidin-1-ylmethyl]-1-oxo-2-m-tolyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2ju 3-[4-(Acetyl-methyl-amino)-4-phenyl-piperidin-1-ylmethyl]-1-oxo-2-m-tolyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

3a 1-Oxo-3-(2-oxo-pyrrolidin-1-ylmethyl)-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

3b 8-Chloro-1-oxo-3-(2-oxo-pyrrolidin-1-ylmethyl)-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

4a 3-Cyanomethyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

5a 3-Methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid N,N-diphenyl-hydrazide

5b N'-(3-Methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carbonyl)-N-phenyl-hydrazinecarboxylic acid methyl ester

1aa 2-(3-Methoxy-phenyl)-3-methyl-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

1ab 2-(4-Methoxy-phenyl)-3-methyl-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

1ac 2-(4-Fluoro-phenyl)-3-methyl-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

1ad 2-(4-Chloro-phenyl)-3-methyl-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

1ae 3-Methyl-1-oxo-2-p-tolyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

1af 2-(3-Methoxy-phenyl)-3-methyl-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-cyclopropyl-(3-fluoro-phenyl)-methyl]-amide

1ag 2-(4-Methoxy-phenyl)-3-methyl-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-cyclopropyl-(3-fluoro-phenyl)-methyl]-amide

1ah 2-(4-Fluoro-phenyl)-3-methyl-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-cyclopropyl-(3-fluoro-phenyl)-methyl]-amide

1ai 2-(4-Chloro-phenyl)-3-methyl-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-cyclopropyl-(3-fluoro-phenyl)-methyl]-amide

1aj 3-Methyl-1-oxo-2-p-tolyl-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-cyclopropyl-(3-fluoro-phenyl)-methyl]-amide

1ak 2-(2-Methoxy-phenyl)-3-methyl-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

1al 2-(2-Methoxy-phenyl)-3-methyl-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-cyclopropyl-(3-fluoro-phenyl)-methyl]-amide

1am 3-Methyl-8-nitro-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

1an 3-Methyl-8-nitro-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-cyclopropyl-(3-fluoro-phenyl)-methyl]-amide

1ao 8-Methoxy-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

1ap 8-Methoxy-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-cyclopropyl-(3-fluoro-phenyl)-methyl]-amide

1aq 8-Amino-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

1ar 8-Cyano-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

1as 8-Chloro-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-1-(4-chloro-phenyl)-propyl]-amide

1at 8-Chloro-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-1-(4-fluoro-phenyl)-propyl]-amide

1au 8-Chloro-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-1-(2-fluoro-phenyl)-propyl]-amide

1av 8-Chloro-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-1-(3-chloro-phenyl)-propyl]-amide

1aw 8-Chloro-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-(3-chloro-phenyl)-cyclopropyl-methyl]-amide

1ax 8-Chloro-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-(4-chloro-phenyl)-cyclopropyl-methyl]-amide

1ay 8-Chloro-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-1-(3-fluoro-phenyl)-propyl]-amide

1az 8-Chloro-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-2-methyl-1-phenyl-propyl)-amide

1ba 8-Chloro-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-cyclopropyl-(4-fluoro-phenyl)-methyl]-amide

1bb 8-Chloro-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-1-(2-chloro-phenyl)-propyl]-amide

1bc 8-Chloro-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-cyclopentyl-phenyl-methyl)-amide

1bd 8-Chloro-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-(2-chloro-phenyl)-cyclopropyl-methyl]-amide

1be 8-Chloro-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-cyclopropyl-(2-fluoro-phenyl)-methyl]-amide

1bf 8-Chloro-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-cyclohexyl-phenyl-methyl)-amide

1bg 8-Chloro-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-cyclopropyl-phenyl-methyl)-amide

1bh 8-Chloro-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-cyclobutyl-(3-fluoro-phenyl)-methyl]-amide

1bi 8-Chloro-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-cyclobutyl-(4-fluoro-phenyl)-methyl]-amide

1bl 8-Chloro-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid [(R)-cyclopropyl-(3-fluoro-phenyl)-methyl]-amide

1bn 8-Chloro-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)cyclobutyl-phenyl-methyl)-amide

1bo 8-Chloro-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid [cyclobutyl-(2-fluoro-phenyl)-methyl]-amide

2ka 3-(4-tert-Butyl-piperazin-1-ylmethyl)-8-chloro-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-cyclopropyl-(3-fluoro-phenyl)-methyl]-amide

2kb 8-Chloro-3-(4-isopropyl-piperazin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2kc 8-Chloro-3-(4-isobutyl-piperazin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2kd 8-Chloro-3-(octahydro-pyrido[1,2-a]pyrazin-2-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2ke 8-Chloro-3-(4-hydroxy-3,4,5,6-tetrahydro-2H-[4,4']bipyridinyl-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2kf 8-Chloro-3-(4-cyclopropylmethyl-piperazin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2kg 8-Chloro-3-[4-(2-morpholin-4-yl-ethyl)-piperidin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2kh 8-Chloro-3-[1,4]diazepan-1-ylmethyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2ki 8-Chloro-3-((S)-3-methyl-piperazin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2kj 8-Chloro-3-imidazol-1-ylmethyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2kk 8-Chloro-3-(4-methyl-imidazol-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2kl 3-(tert-Butylamino-methyl)-8-chloro-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2km 8-Chloro-3-(isopropylamino-methyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2kn 8-Chloro-3-[4-hydroxy-4-(3-methoxy-phenyl)-piperidin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2ko 3-(4-tert-Butyl-piperazin-1-ylmethyl)-8-chloro-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2kp 3-Benzoimidazol-1-ylmethyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2kq 1-Oxo-2-phenyl-3-pyrazol-1-ylmethyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2kr 3-(4-Methyl-pyrazol-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2ks 1-Oxo-2-phenyl-3-[1,2,3]triazol-1-ylmethyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2kt 2-(3-Methoxy-phenyl)-1-oxo-3-(4-pyridin-4-ylmethyl-piperazin-1-ylmethyl)-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2ku 2-(4-Methoxy-phenyl)-3-[4-(2-morpholin-4-yl-ethyl)-piperazin-1-ylmethyl]-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2kv 2-(4-Fluoro-phenyl)-1-oxo-3-(4-phenethyl-piperazin-1-ylmethyl)-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2kw 2-(4-Fluoro-phenyl)-3-(4-isopropyl-piperazin-1-ylmethyl)-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2kx 3-[1,4']Bipiperidinyl-1'-ylmethyl-2-(4-fluoro-phenyl)-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2ky 2-(4-Fluoro-phenyl)-3-[4-(2-morpholin-4-yl-ethyl)-piperazin-1-ylmethyl]-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2kz 2-(4-Fluoro-phenyl)-3-[4-(1-methyl-piperidin-4-yl)-piperazin-1-ylmethyl]-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2la 2-(4-Fluoro-phenyl)-1-oxo-3-[4-(2-pyrrolidin-1-yl-ethyl)-piperazin-1-ylmethyl]-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2lb 2-(4-Fluoro-phenyl)-3-[4-hydroxy-4-(3-methoxy-phenyl)-piperidin-1-ylmethyl]-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2lc 2-(4-Chloro-phenyl)-1-oxo-3-(4-phenethyl-piperazin-1-ylmethyl)-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2ld 2-(4-Chloro-phenyl)-3-(4-isopropyl-piperazin-1-ylmethyl)-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2le 3-[1,4']Bipiperidinyl-1'-ylmethyl-2-(4-chloro-phenyl)-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2lf 2-(4-Chloro-phenyl)-3-[4-(2-morpholin-4-yl-ethyl)-piperazin-1-ylmethyl]-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2lg 2-(4-Chloro-phenyl)-3-[4-(1-methyl-piperidin-4-yl)-piperazin-1-ylmethyl]-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2lh 2-(4-Chloro-phenyl)-1-oxo-3-[4-(2-piperidin-1-yl-ethyl)-piperazin-1-ylmethyl]-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2li 2-(4-Chloro-phenyl)-1-oxo-3-[4-(2-pyrrolidin-1-yl-ethyl)-piperazin-1-ylmethyl]-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2lj 3-(4-tert-Butyl-piperazin-1-ylmethyl)-8-fluoro-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2lk 8-Chloro-3-cyclopropylaminomethyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2ll 3-(4-tert-Butyl-piperazin-1-ylmethyl)-8-fluoro-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-cyclopropyl-(3-fluoro-phenyl)-methyl]-amide

2lm 8-Fluoro-1-oxo-2-phenyl-3-piperazin-1-ylmethyl-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-cyclopropyl-(3-fluoro-phenyl)-methyl]-amide

2ln 8-Fluoro-1-oxo-3-(3-oxo-pyrazolidin-1-ylmethyl)-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-cyclopropyl-(3-fluoro-phenyl)-methyl]-amide

2lo 8-Fluoro-1-oxo-3-(3-oxo-piperazin-1-ylmethyl)-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-cyclopropyl-(3-fluoro-phenyl)-methyl]-amide

3c 1-Oxo-2-phenyl-3-(1H-[1,2,4]triazol-3-ylsulfanylmethyl)-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

3d 8-Chloro-1-oxo-3-(2-oxo-pyrrolidin-1-ylmethyl)-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-cyclopropyl-(3-fluoro-phenyl)-methyl]-amide

3e 8-Fluoro-1-oxo-3-(2-oxo-pyrrolidin-1-ylmethyl)-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

3f 8-Fluoro-1-oxo-3-(2-oxo-pyrrolidin-1-ylmethyl)-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-cyclopropyl-(3-fluoro-phenyl)-methyl]-amide

3g 8-Fluoro-1-oxo-3-(5-oxo-pyrazolidin-1-ylmethyl)-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-cyclopropyl-(3-fluoro-phenyl)-methyl]-amide

3h 8-Fluoro-1-oxo-3-(2-oxo-piperazin-1-ylmethyl)-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-cyclopropyl-(3-fluoro-phenyl)-methyl]-amide

3i 8-Fluoro-1-oxo-3-(2-oxo-piperidin-1-ylmethyl)-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-cyclopropyl-(3-fluoro-phenyl)-methyl]-amide

4b 8-Chloro-3-cyanomethyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-cyclopropyl-(3-fluoro-phenyl)-methyl]-amide

6a 2-(3,4-Dichloro-phenyl)-3-methyl-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

6b 8-Fluoro-1-oxo-3-(2-oxo-pyrrolidin-1-ylmethyl)-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-cyclopropyl-phenyl-methyl)-amide

6c 8-Fluoro-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-cyclopropyl-phenyl-methyl)-amide

7a 3-Ethyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

7b 8-Fluoro-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

7c 8-Fluoro-2-(3-fluoro-phenyl)-3-methyl-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

7d 8-Fluoro-2-(4-fluoro-phenyl)-3-methyl-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

7e 8-Fluoro-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-cyclopropyl-(3-fluoro-phenyl)-methyl]-amide

7f 8-Fluoro-2-(3-fluoro-phenyl)-1-oxo-3-(2-oxo-pyrrolidin-1-ylmethyl)-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-cyclopropyl-(3-fluoro-phenyl)-methyl]-amide

7g 8-Fluoro-2-(4-fluoro-phenyl)-1-oxo-3-(2-oxo-pyrrolidin-1-ylmethyl)-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-cyclopropyl-(3-fluoro-phenyl)-methyl]-amide

7h 8-Fluoro-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-cyclobutyl-(3-fluoro-phenyl)-methyl]-amide

7i 8-Fluoro-2-(2-fluoro-phenyl)-3-methyl-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-cyclopropyl-(3-fluoro-phenyl)-methyl]-amide

7j 8-Fluoro-2-(3-fluoro-phenyl)-3-methyl-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-cyclopropyl-(3-fluoro-phenyl)-methyl]-amide

7k 8-Fluoro-2-(4-fluoro-phenyl)-3-methyl-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-cyclopropyl-(3-fluoro-phenyl)-methyl]-amide

7l 6,8-Difluoro-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-cyclopropyl-(3-fluoro-phenyl)-methyl]-amide

7m 5,8-Difluoro-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-cyclopropyl-(3-fluoro-phenyl)-methyl]-amide

7n 3-Methyl-1-oxo-2-phenyl-8-trifluoromethyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

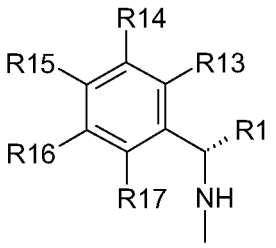
8a 3-(1-tert-Butyl-piperidin-4-ylmethyl)-8-chloro-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-cyclopropyl-(3-fluoro-phenyl)-methyl]-amide

and pharmaceutically acceptable salts thereof.

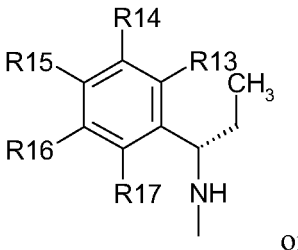
Further, the compounds of this invention may exist in unsolvated as well as in solvated forms with pharmaceutically acceptable solvents such as water, ethanol and the like. In general, the solvated forms are considered equivalent to the unsolvated forms for the purposes of this invention.

The compounds of the present invention may have one or more asymmetric centres and it is intended that any optical isomers (i.e. enantiomers or diastereomers), as separated, pure or partially purified optical isomers and any mixtures thereof including racemic mixtures, i.e. a mixture of stereoisomeres, are included within the scope of the invention. In particular, when A represents CH or CR^1, A may be an optical centre giving rise to two optical isomers, an R form and an S form. In one embodiment, the compounds of the present invention have the S form.

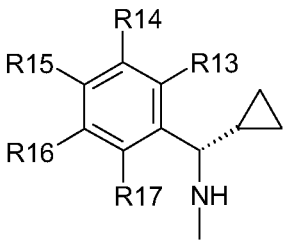
In a particular embodiment, the compounds of the present invention have the following absolute configuration around A, A being CH



, e.g.



or



In this context is understood that when specifying the enantiomeric form, then the compound is in enantiomeric excess, e.g. essentially in a pure form. Accordingly, one embodiment of the invention relates to a compound of the invention having an enantiomeric excess of at least 60%, at least 70%, at least 80%, at least 85%, at least 90%, at least 96%, preferably at least 98%.

Racemic forms can be resolved into the optical antipodes by known methods, for example by separation of diastereomeric salts thereof with an optically active acid, and liberating the optically active amine compound by treatment with a base. Another method for resolving racemates into the optical antipodes is based upon chromatography of an optically active matrix. The compounds of the present invention may also be resolved by the formation of diastereomeric derivatives. Additional methods for the resolution of optical isomers, known to those skilled in the art, may be used. Such methods include those discussed by J. Jaques, A. Collet and S. Wilen in "Enantiomers, Racemates, and Resolutions", John Wiley and Sons, New York (1981). Optically active compounds can also be prepared from optically active starting materials.

Furthermore, when a double bond or a fully or partially saturated ring system is present in the molecule geometric isomers may be formed. It is intended that any geometric isomers, as separated, pure or partially purified geometric isomers or mixtures thereof are included within the scope of the invention. Likewise, molecules having a bond with restricted rotation may form geometric isomers. These are also intended to be included within the scope of the present invention.

Furthermore, some of the compounds of the present invention may exist in different tautomeric forms and it is intended that any tautomeric forms that the compounds are able to form are included within the scope of the present invention.

NK3 receptor antagonists have been implicated in various diseases in addition to psychosis and schizophrenia discussed above. Langlois et al in *J.Pharm.Exp.Ther.*, 299, 712-717, 2001, concludes that NK3 antagonists may be applicable in CNS diseases in general, and in anxiety and depression in particular. Yip et al in *Br.J.Phar.*, 122, 715-722, 1997 further implicates NK3 antagonists in diverse brain functions, such as cortical processing, learning and memory, neuroendocrine and behavioral regulation. Additional studies have shown that NKB and NK3 receptors are involved in pain, and that NK3 antagonists have an antinociceptive and analgesic effect [Fioramonti, *Neurogastroenterol.Motil.*,15, 363-369, 2003]. Mazelin et al in *Life Sci.*, 63, 293-304, 1998 show that NK3 antagonists have an effect in gut inflammation and concludes that such antagonists may be used in the treatment of irritable bowel syndrome (IBS). In addition, NK3 antagonists have in *in vivo* models been demonstrated to be useful in the treatment of airway related diseases, such as asthma, airway hyperresponsiveness, cough, and bronchorestriction [Daoui, *Am.J.Respir.Crit.Care Med.*, 158, 42-48, 1998]. Maubach et al in *Neurosci.*, 83, 1047-1062, 1998 show that NKB and the NK3 agonist senktide increase the frequency and duration of epileptiform discharges, and thus by inference that NK3 antagonists have a anticonvulsive potential. Finally, Kemel et al in *J.Neurosci.*, 22, 1929-1936, 2002, suggests the use of NK3 antagonists in the treatment of Parkinson's Disease.

Accordingly, clinical, pre-clinical, *in vivo* and *in vitro* studies support that NK3 receptor antagonists are of relevance for the treatment or prevention of various disorders including psychosis, schizophrenia, depression, anxiety, cognitive impairment, obesity, Alzheimer's disease, Parkinson's disease, pain, convulsions,

cough, asthma, airway hyperresponsiveness, microvascular hypersensitivity, bronchoconstriction, gut inflammation, and inflammatory bowel syndrome.

Schizophrenia is classified into subgroups. The paranoid type is characterised by delusions and hallucinations and absence of thought disorder, disorganized behavior, and affective flattening. The disorganized type, which is also named 'hebephrenic schizophrenia' in the ICD, in which thought disorder and flat affect are present together. The cataconic type, in which prominent psychomotor disturbances are evident, and symptoms may include catatonic stupor and waxy flexibility. The undifferentiated type in which psychotic symptoms are present but the criteria for paranoid, disorganized, or catatonic types have not been met. The symptoms of schizophrenia normally manifest themselves in three broad categories, i.e. positive, negative and cognitive symptoms. Positive symptoms are those, which represent an "excess" of normal experiences, such as hallucinations and delusions. Negative symptoms are those where the patient suffers from a lack of normal experiences, such as anhedonia and lack of social interaction. The cognitive symptoms relate to cognitive impairment in schizophrenics, such as lack of sustained attention and deficits in decision making. The current antipsychotics are fairly successful in treating the positive symptoms but fare less well for the negative and cognitive symptoms. Contrary to that, NK3 antagonists have been shown clinically to improve on both positive and negative symptoms in schizophrenics [*Am.J.Psychiatry*, 161, 975-984, 204], and according to the above discussion they are also expected to deliver an effect on the cognitive symptoms.

Cognitive impairment include a decline in cognitive functions or cognitive domains, e.g. working memory, attention and vigilance, verbal learning and memory, visual learning and memory, reasoning and problem solving e.g. executive function, speed of processing and/or social cognition. In particular, cognitive impairment may indicate deficits in attention, disorganized thinking, slow thinking, difficulty in understanding, poor concentration, impairment of problem solving, poor memory, difficulties in expressing thoughts and/or difficulties in integrating thoughts, feelings and behaviour, or difficulties in extinction of irrelevant thoughts.

In one embodiment, the present invention relates to the compounds of the present invention for use in therapy.

In one embodiment, the present invention relates to a method of treating a disease selected from psychosis; schizophrenia; schizophrenoform disorder; schizoaffective disorder; delusional disorder; brief psychotic disorder; shared psychotic disorder; psychotic disorder due to a general medical condition; substance or drug induced psychotic disorder (cocaine, alcohol, amphetamine etc); schizoid personality disorder; schizoptypal personality disorder; psychosis or schizophrenia associated with major depression, bipolar disorder, Alzheimer's disease or Parkinson's disease; major depression; general anxiety disorder; bipolar disorder (maintenance treatment, recurrence prevention and stabilization); mania; hypomania; cognitive impairment; ADHD; obesity; appetite reduction; Alzheimer's disease; Parkinson's disease; pain; convulsions; cough; asthma; airway hyperresponsiveness; microvascular hypersensitivity; bronchoconstriction; chronic obstructive pulmonary disease; urinary incontinence; gut inflammation; and inflammatory bowel syndrome the method comprising the administration of a therapeutically effective amount of a compound of the present invention to a patient in need thereof.

In one embodiment, the present invention relates to a method for the treatment of schizophrenia, the method comprising the administration of a therapeutically effective amount of a compound of the present invention to a patient in need thereof. In particular, said treatment includes the treatment of the positive, negative and/or cognitive symptoms of schizophrenia.

In one embodiment, the present invention relates to a method of treating cognitive impairment, the method comprising the administration of a therapeutically effective amount of a compound of the present invention to a patient in need thereof. In particular, said cognitive impairment is manifested as a decline in working memory, attention and vigilance, verbal learning and memory, visual learning and memory, reasoning and problem solving e.g. executive function, speed of processing and/or social cognition.

The antipsychotic effect of typical and atypical anti-psychotics, in particular D2 antagonists is exerted via an inhibition of the post-synaptic D2 receptors. Pre-synaptic D2 auto-receptors, however, are also affected by the administration of these compounds giving rise to an increase in the dopamine neuron firing rate, which, in fact, counteracts the antipsychotic effects. The increased firing rate continues until the

effect of the pre-synaptic auto-receptors is blocked (the depolarization block), typically after approximately 3 weeks of chronic treatment with typical or atypical anti-psychotics. This model explains the up to 3 weeks delay of clinical effect normally seen when D2 antagonist treatment is initiated. NK3 antagonists seem to inhibit the increase in the dopamine neuron firing mediated by the pre-synaptic D2 auto-receptors brought about by D2 antagonists, wherefore the combined administration of NK3 antagonists and D2 antagonists is expected to give rise to a faster onset of the clinical effect. Moreover, D2 antagonists are known to increase prolactin levels, which may give rise to serious side effects, such as osteoporosis. It is known that NK3 agonists give rise to an increase in prolactin from which it may be deduced that a NK3 antagonist will lower an increased, i.e. normalise the prolactin level. A combined use of NK3 antagonists and D2 antagonists may thus address some of the safety aspects associated with D2 antagonists administration. Similarly, NK3 antagonists may be administered together with antagonists/inverse agonists/negative modulators/partial agonists of one or more of the targets dopamine D2 receptor, dopamine D3 receptor, dopamine D4 receptor, phosphodiesterase PDE10, serotonin 5-HT_{1A} receptor, serotonin 5-HT_{2A} receptor, serotonin 5-HT_6 receptor, adrenergic alpha 2 receptor, cannabinoid type 1 receptor, histamine H3 receptor, cyclooxygenases, sodium channels or glycine transporter GlyT1; or with agonists/positive modulators/partial agonists of one or more of the targets serotonin 5-HT_{2C} receptor, KCNQ channels, NMDA receptor, AMPA receptor, nicotinic alpha-7 receptor, muscarinic M1 receptor, muscarinic M4 receptor, metabotropic glutamate receptor mGluR2, metabotropic glutamate receptor mGluR5, dopamine D1 receptor or dopamine D5 receptor.

Such combined administration of compounds of the present invention and other anti-psychotic compounds, such as D2 antagonists, D2 partial agonists, PDE10 antagonists, 5-HT_{2A} antagonists, 5-HT_6 antagonists or KCNQ4 antagonists may be sequential or concomitant. Examples of D2 antagonists or partial agonists include haloperidol, chlorpromazine, sulpirid, risperidone, ziprasidon, olanzapine, quetiapin, and clozapine.

In one embodiment, the compound of the present invention is administered in an amount from about 0.001 mg/kg body weight to about 100 mg/kg body weight per

day. In particular, daily dosages may be in the range of 0.01 mg/kg body weight to about 50 mg/kg body weight per day. The exact dosages will depend upon the frequency and mode of administration, the sex, the age the weight, and the general condition of the subject to be treated, the nature and the severity of the condition to be treated, any concomitant diseases to be treated, the desired effect of the treatment and other factors known to those skilled in the art.

A typical oral dosage for adults will be in the range of 1-1000 mg/day of a compound of the present invention, such as 1-500 mg/day.

In one embodiment, the present invention relates to the use of the compounds of the present invention in the manufacture of a medicament for the treatment of a disease selected from psychosis; schizophrenia; schizophrenoform disorder; schizoaffective disorder; delusional disorder; brief psychotic disorder; shared psychotic disorder; psychotic disorder due to a general medical condition; substance or drug induced psychotic disorder (cocaine, alcohol, amphetamine etc); schizoid personality disorder; schizoptypal personality disorder; psychosis or schizophrenia associated with major depression, bipolar disorder, Alzheimer's disease or Parkinson's disease; major depression; general anxiety disorder; bipolar disorder (maintenance treatment, recurrence prevention and stabilization); mania; hypomania; cognitive impairment; ADHD; obesity; appetite reduction; Alzheimer's disease; Parkinson's disease; pain; convulsions; cough; asthma; airway hyperresponsiveness; microvascular hypersensitivity; bronchoconstriction; chronic obstructive pulmonary disease; urinary incontinence; gut inflammation; and inflammatory bowel syndrome.

In one embodiment, the present invention relates to the use of a compound of the present invention in the manufacture of a medicament for the treatment of schizophrenia. In particular, said treatment includes the treatment of the positive, negative and/or cognitive symptoms of schizophrenia.

In one embodiment, the present invention relates to the use of a compound of the present invention in the manufacture of a medicament for the treatment of cognitive impairment. In particular, said cognitive impairment is manifested as a decline in working memory, attention and vigilance, verbal learning and memory, visual learning and memory, reasoning and problem solving e.g. executive function, speed of processing and/or social cognition.

In one embodiment, the present invention relates to a compound of the present invention for use in the treatment of a disease selected from psychosis; schizophrenia; schizophrenoform disorder; schizoaffective disorder; delusional disorder; brief psychotic disorder; shared psychotic disorder; psychotic disorder due to a general medical condition; substance or drug induced psychotic disorder (cocaine, alcohol, amphetamine etc); schizoid personality disorder; schizoptypal personality disorder; psychosis or schizophrenia associated with major depression, bipolar disorder, Alzheimer's disease or Parkinson's disease; major depression; general anxiety disorder; bipolar disorder (maintenance treatment, recurrence prevention and stabilization); mania; hypomania; cognitive impairment; ADHD; obesity; appetite reduction; Alzheimer's disease; Parkinson's disease; pain; convulsions; cough; asthma; airway hyperresponsiveness; microvascular hypersensitivity; bronchoconstriction; chronic obstructive pulmonary disease; urinary incontinence; gut inflammation; and inflammatory bowel syndrome.

In one embodiment, the present invention relates to a compound of the present invention for use in the treatment of schizophrenia. In particular, said treatment includes the treatment of the positive, negative and/or cognitive symptoms of schizophrenia.

In one embodiment, the present invention relates to a compound of the present invention for use in the treatment of cognitive impairment. In particular, said cognitive impairment is manifested as a decline in working memory, attention and vigilance, verbal learning and memory, visual learning and memory, reasoning and problem solving e.g. executive function, speed of processing and/or social cognition.

The compounds of the present invention may be administered alone as a pure compound or in combination with pharmaceutically acceptable carriers or excipients, in either single or multiple doses. The pharmaceutical compositions according to the invention may be formulated with pharmaceutically acceptable carriers or diluents as well as any other known adjuvants and excipients in accordance with conventional techniques such as those disclosed in Remington: The Science and Practice of Pharmacy, 19 Edition, Gennaro, Ed., Mack Publishing Co., Easton, PA, 1995.

The pharmaceutical compositions may be specifically formulated for administration by any suitable route such as the oral, rectal, nasal, pulmonary, topical

(including buccal and sublingual), transdermal, intracisternal, intraperitoneal, vaginal and parenteral (including subcutaneous, intramuscular, intrathecal, intravenous and intradermal) route, the oral route being preferred. It will be appreciated that the preferred route will depend on the general condition and age of the subject to be treated, the nature of the condition to be treated and the active ingredient chosen.

Pharmaceutical compositions for oral administration include solid dosage forms such as capsules, tablets, dragees, pills, lozenges, powders and granules. Where appropriate, they can be prepared with coatings.

Liquid dosage forms for oral administration include solutions, emulsions, suspensions, syrups and elixirs.

Pharmaceutical compositions for parenteral administration include sterile aqueous and nonaqueous injectable solutions, dispersions, suspensions or emulsions as well as sterile powders to be reconstituted in sterile injectable solutions or dispersions prior to use.

Other suitable administration forms include suppositories, sprays, ointments, cremes, gels, inhalants, dermal patches, implants, etc.

Conveniently, the compounds of the invention are administered in a unit dosage form containing said compounds in an amount of about 0.1 to 500 mg, such as 10 mg, 50 mg 100 mg, 150 mg, 200 mg or 250 mg of a compound of the present invention.

For parenteral routes such as intravenous, intrathecal, intramuscular and similar administration, typically doses are in the order of about half the dose employed for oral administration.

For parenteral administration, solutions of the compound of the invention in sterile aqueous solution, aqueous propylene glycol, aqueous vitamin E or sesame or peanut oil may be employed. Such aqueous solutions should be suitably buffered if necessary and the liquid diluent first rendered isotonic with sufficient saline or glucose. The aqueous solutions are particularly suitable for intravenous, intramuscular, subcutaneous and intraperitoneal administration. The sterile aqueous media employed are all readily available by standard techniques known to those skilled in the art.

Suitable pharmaceutical carriers include inert solid diluents or fillers, sterile aqueous solution and various organic solvents. Examples of solid carriers are lactose, terra alba, sucrose, cyclodextrin, talc, gelatine, agar, pectin, acacia, magnesium stearate, stearic acid and lower alkyl ethers of cellulose. Examples of liquid carriers are syrup, peanut oil, olive oil, phospho lipids, fatty acids, fatty acid amines, polyoxyethylene and water. The pharmaceutical compositions formed by combining the compound of the invention and the pharmaceutical acceptable carriers are then readily administered in a variety of dosage forms suitable for the disclosed routes of administration.

Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules or tablets, each containing a predetermined amount of the active ingredient, and which may include a suitable excipient. Furthermore, the orally available formulations may be in the form of a powder or granules, a solution or suspension in an aqueous or non-aqueous liquid, or an oil-in-water or water-in-oil liquid emulsion.

If a solid carrier is used for oral administration, the preparation may be tablet, e.g. placed in a hard gelatine capsule in powder or pellet form or in the form of a troche or lozenge. The amount of solid carrier may vary but will usually be from about 25 mg to about 1 g.

If a liquid carrier is used, the preparation may be in the form of a syrup, emulsion, soft gelatine capsule or sterile injectable liquid such as an aqueous or non-aqueous liquid suspension or solution.

Tablets may be prepared by mixing the active ingredient with ordinary adjuvants and/or diluents followed by the compression of the mixture in a conventional tabletting machine. Examples of adjuvants or diluents comprise: Corn starch, potato starch, talcum, magnesium stearate, gelatine, lactose, gums, and the like. Any other adjuvants or additives usually used for such purposes such as colourings, flavourings, preservatives etc. may be used provided that they are compatible with the active ingredients.

In one embodiment, the invention relates to a pharmaceutical composition comprising a compound of the present invention together with a second anti-psychotic agent. In one embodiment, said second anti-psychotic agent is selected from

antagonists/inverse agonists/negative modulators/partial agonists of the targets dopamine D2 receptor, dopamine D3 receptor, dopamine D4 receptor, phosphodiesterase PDE10, serotonin 5-HT_{1A} receptor, serotonin 5-HT_{2A} receptor, serotonin 5-HT_6 receptor, adrenergic alpha 2 receptor, cannabinoid type 1 receptor, histamine H3 receptor, cyclooxygenases, sodium channels or glycine transporter GlyT1; or from agonists/positive modulators/partial agonists of the targets serotonin 5-HT_{2C} receptor, KCNQ channels, NMDA receptor, AMPA receptor, nicotinic alpha-7 receptor, muscarinic M1 receptor, muscarinic M4 receptor, metabotropic glutamate receptor mGluR2, metabotropic glutamate receptor mGluR5, dopamine D1 receptor or dopamine D5 receptor. In one embodiment, said second anti-psychotic agent is selected from typical anti-psychotics, atypical anti-psychotics, D2 antagonists, partial D2 agonists, PDE10 antagonists, 5-HT_{2A} antagonists, 5-HT_6 antagonists and KCNQ4 antagonists, and in particular atypical anti-psychotics, D2 antagonists, partial D2 agonists. Particular examples of such anti-psychotics include haloperidol, chlorpromazine, sulpirid, risperidone, ziprasidon, olanzapine, quetiapine, and clozapine.

In one embodiment, the invention relates to a pharmaceutical kit comprising a container comprising a compound of the present invention and a separate container comprising an anti-psychotic drug. Typical anti-psychotics, atypical anti-psychotics, D2 antagonists, partial D2 agonists, PDE10 antagonists, 5-HT_{2A} antagonists, 5-HT_6 antagonists and KCNQ4 antagonists, and in particular atypical anti-psychotics, D2 antagonists, partial D2 agonists. Particular examples of such anti-psychotics include haloperidol, chlorpromazine, sulpirid, risperidone, ziprasidon, olanzapine, quetiapine, and clozapine.

All references, including publications, patent applications, and patents, cited herein are hereby incorporated by reference in their entirety and to the same extent as if each reference were individually and specifically indicated to be incorporated by reference and were set forth in its entirety herein (to the maximum extent permitted by law), regardless of any separately provided incorporation of particular documents made elsewhere herein.

The use of the terms “a” and “an” and “the” and similar referents in the context of describing the invention are to be construed to cover both the singular and

the plural, unless otherwise indicated herein or clearly contradicted by context. For example, the phrase "the compound" is to be understood as referring to various "compounds" of the invention or particular described aspect, unless otherwise indicated.

Unless otherwise indicated, all exact values provided herein are representative of corresponding approximate values (e.g., all exact exemplary values provided with respect to a particular factor or measurement can be considered to also provide a corresponding approximate measurement, modified by "about," where appropriate).

The description herein of any aspect or aspect of the invention using terms such as “comprising”, “having,” “including,” or “containing” with reference to an element or elements is intended to provide support for a similar aspect or aspect of the invention that “consists of”, “consists essentially of”, or “substantially comprises” that particular element or elements, unless otherwise stated or clearly contradicted by context (e.g., a composition described herein as comprising a particular element should be understood as also describing a composition consisting of that element, unless otherwise stated or clearly contradicted by context).

SYNTHETIC ROUTES

The compounds of the present invention of the general formula I, wherein R^1-R^{17}, A, and X are as defined above can be prepared by the methods outlined in the following reaction schemes and examples. In the described methods it is possible to make use of variants or modifications, which are themselves known to chemists skilled in the art or could be apparent to the person of ordinary skill in this art. Furthermore, other methods for preparing compounds of the invention will be readily apparent to the person skilled in the art in light of the following reaction schemes and examples.

In the intermediate compounds of the general formulae I – XX, R1-R17, A, and X are as defined under formula I.

For compounds, which can exist as a mixture or equilibrium between two or more tautomers, only one tautomer is represented in the schemes, although it may not be the most stable tautomer. For compounds, which can exist in enantiomeric, stereoisomeric or geometric isomeric forms their geometric configuration is specified; otherwise the structure represents a mixture of stereoisomers. Such compounds

include, but not limited to 1,3-ketoesters or enamines of the general formula IV and VII, which can exist in equilibrium between keto or enol forms and the latter may also exist in isomeric Z- and E-forms as well-known to chemists skilled in the art. Such compounds also include compounds of the present invention of the general formula I, which may exist as a mixture of atropisomers due to restricted rotation around carbon-carbon single bonds similar to atropisomerism in ortho, ortho′-disubstituted biaryl compounds also well-known to the person skilled in the art.

Starting materials of the general formulae III, VI, and XI are either obtained from commercial sources as summarized in the Table 2 or they can be readily prepared by standard methods or their modifications described in the literature.

2-Bromobenzoic acids of the general formula II are coupled with keto-esters of the general formula III in the presence of a strong base such as sodium hydride and copper or copper salts such as copper (I) bromide in a suitable solvent such as 1,4-dioxane, acetonitrile or an excess of the above keto-esters at suitable temperature such as reflux or at 70°C with the formation of compounds of the general formula IV. Such arylation reaction is well-known in general as copper-catalyzed Ullmann-type coupling reaction (review: S.V. Ley, A.W. Thomas *Angew. Chem. Int. Ed.* **2003**, *42*, 5400). Also, in this particular case when the coupling reaction involves activated methylene compounds such as compounds of the general formula IV in the presence of copper or copper salts the reaction is known as the Hurtley reaction (W.R.H. Hurtley *J. Chem. Soc.* **1929**, 1870).

The obtained compounds of the general formula IV are then reacted with anilines of the general formula VI with or without appropriate solvent under the heating conditions with the formation of isoquinolones of the general formula VIII via intermediate formation of enamines of the general formula VII which are usually not separated from the reaction mixture. Alternatively, the enamines of the general formula VII can be obtained from anilines of the general VI in the presence of the appropriate dehydrating agent such as tetraethoxysilane under heating conditions or at ambient temperature in the presence of a catalytic amount of acid such as acetic acid. Then, the cyclisation reaction with the formation of isoquinolones of the general formula VIII can be carried out under the heating conditions as mentioned above or at

ambient temperature in the presence of an appropriate coupling reagent such as EDC/HOBT.

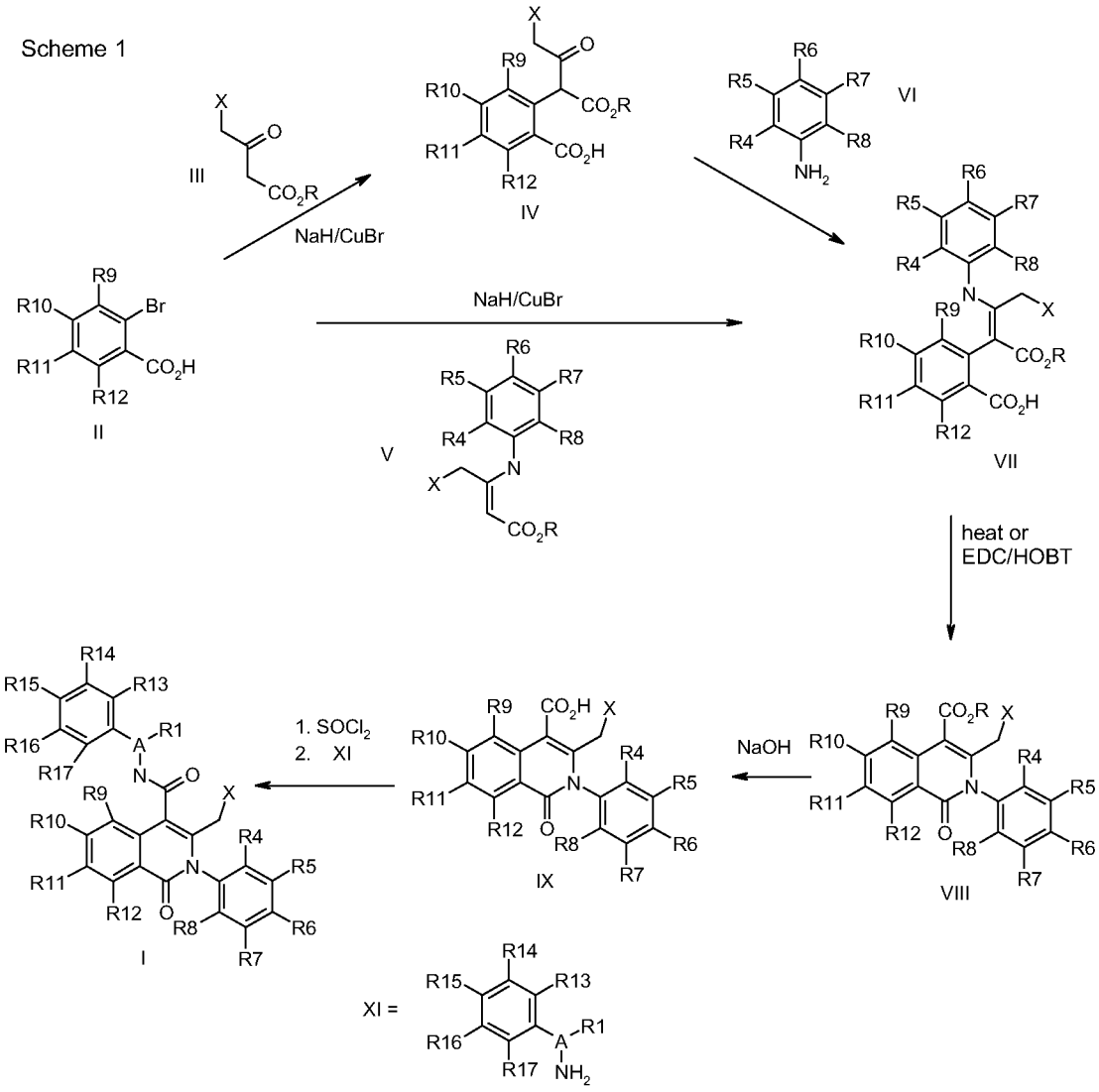
Furthermore, isoquinolinones of the general formula VIII can be obtained directly from the starting 2-bromobenzoic acids of the general formula II and deprotonated enamines of the general formula V in a modified one-pot procedure involving Hurtley reaction performed at 70°C with the formation of the compounds of the general formula VII and subsequent cyclisation performed at higher temperature. Enamines of the general formula V are readily available from ketoesters III and anilines VI under conditions described above for preparation of enamines of the general formula VII.

Compounds of the general formula VIII are readily hydrolyzed to acids of the general formula IX under conditions for ester hydrolysis well-known to chemists skilled in the art. Finally, the subsequent coupling with amines (A = C) or hydrazines (A = N) of the general formula XI leads to the formation of the compounds of the invention of the general formula I. Such coupling reactions usually performed via activation of the acid with an appropriate coupling or activation reagent such as but not limited to thionyl chloride with the formation of corresponding acid chloride. Hydrazines of the general formula I where R1 = H can be converted to disubstituted hydrazides of the same general formula where R1 is not hydrogen by acylation, alkylation or arylation reactions with appropriate acylation or alkylation reagents such as but not limited to acid chlorides, carbamoyl chlorides, chloroformates or alkylhalogenides.

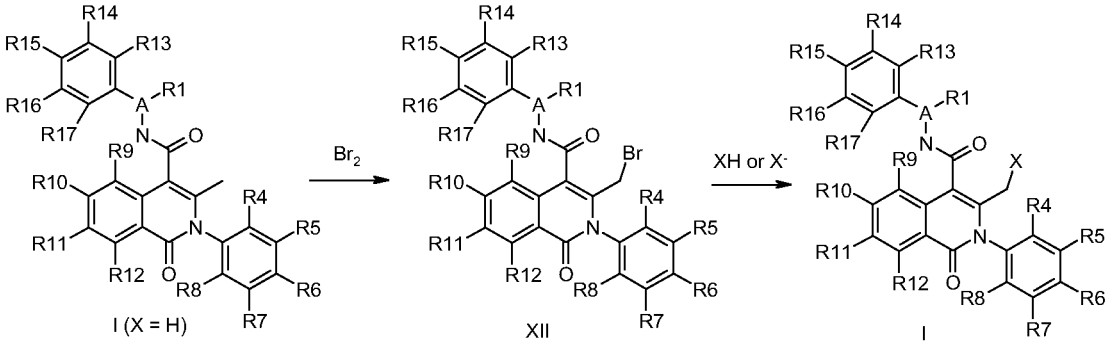
Compounds of the general formula I where X is hydrogen can be converted to the compounds of the general formula XII by regioselective bromination reaction in the presence of bromination reagent such as bromine. Then the bromine atom can be substituted by various nucleophiles of the general formula X-H or X^- with the formation of the compounds of the invention of the general formula I. Those skilled in the art will readily appreciate that many nitrogen, carbon and sulphur nucleophiles such as but not limited to amines, aromatic amines, amides, heterocycles, alcohols, phenols, cyanides or thiols are commercially or readily available in the neutral or in the deprotonated anionic form required for such transformation.

If necessary, further derivatisation or transformation can be performed in the substituents R4-R12 and X using standard methods of organic synthesis known to the person of ordinary skill in the art.

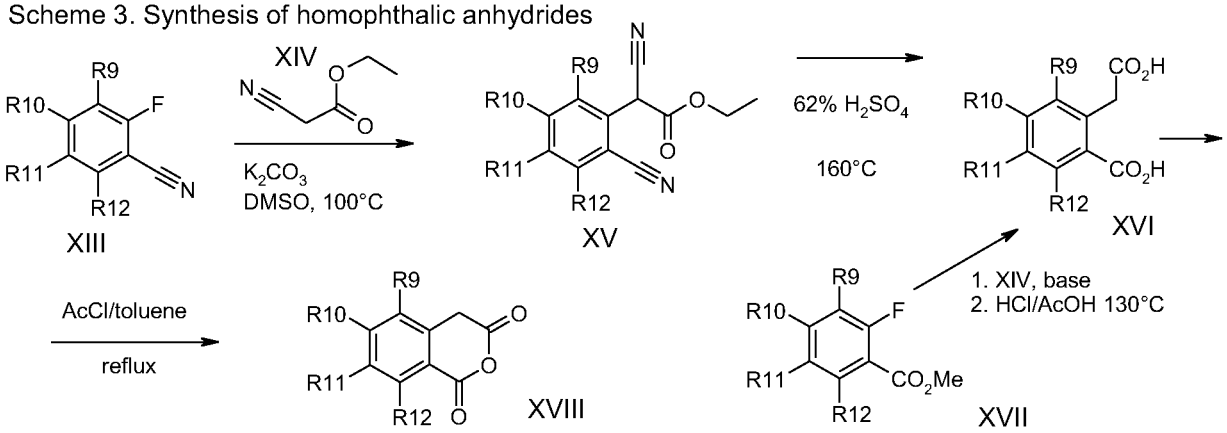
Scheme 1



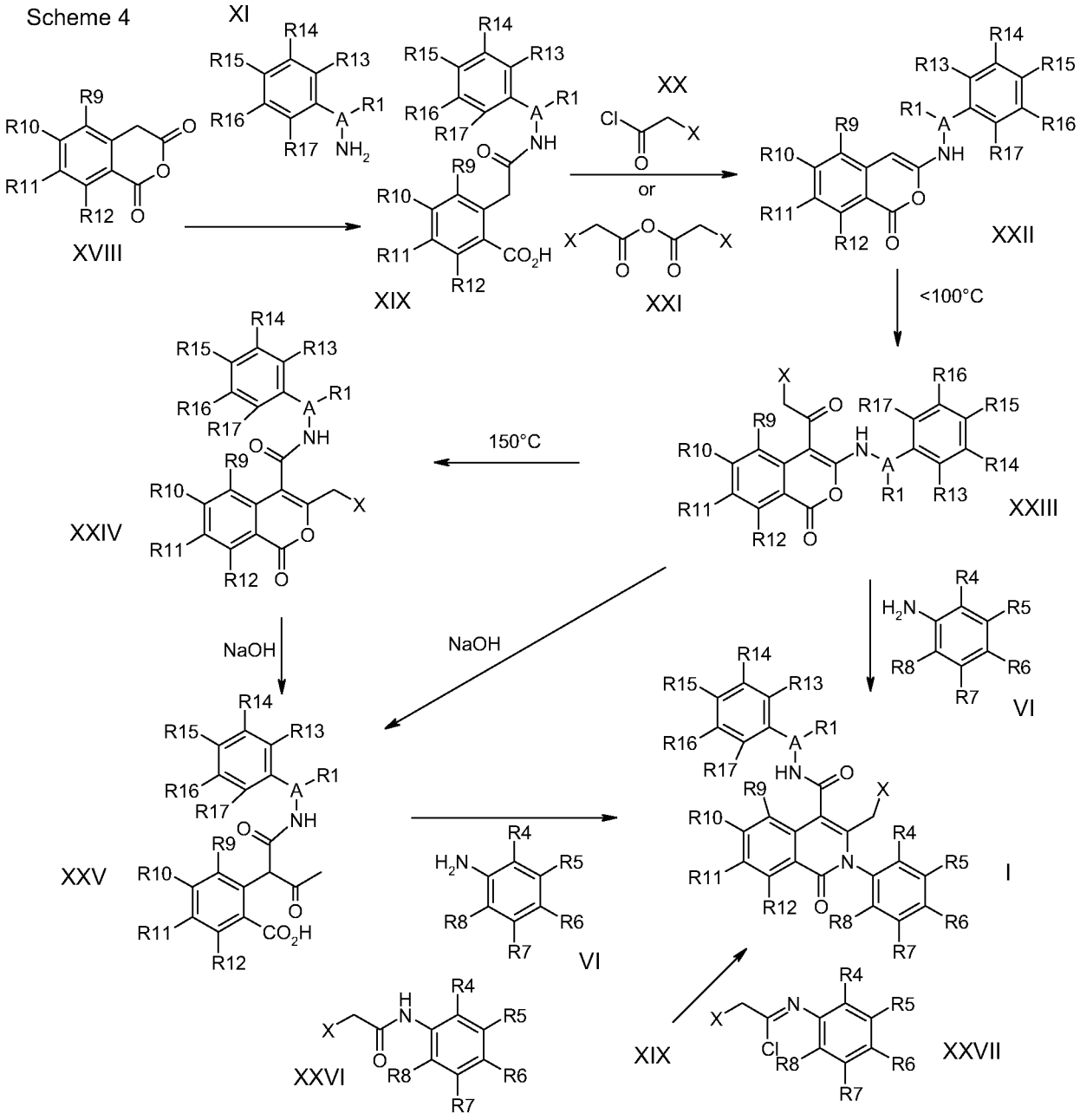
Scheme 2


R14
R15
R13
R16
A
R1
R17
N
O
R9
R10
R4
R5
R11
N
R12
O
R8
R6
R7
I (X = H)
Br2
Br
XII
XH or X-
X
I

Scheme 3. Synthesis of homophthalic anhydrides



Scheme 4



Alternatively, compounds of the general formula I can be prepared starting from substituted homophthalic anhydrides of the general formula XVIII as shown in Scheme 4. Homophthalic anhydrides are either commercially available or can be prepared as shown in scheme 3 starting from corresponding fluorobenzonitriles or fluorobenzoates of the general formula XIII and XVII, respectively. They undergo aromatic nucleophilic substitution reaction with ethyl cyanoacetate XIV in the presence of base such as potassium carbonate or cesium carbonate under heating conditions in appropriate solvent such as dimethylsulfoxide. The coupling products are hydrolyzed in the presence of the strong acids such as sulphuric or hydrochloric acids in water under heating conditions with the formation of diacids of the general formula XVI. Finally, the diacids are converted into the homophthalic anhydrides of the general formula XVIII in the presence of dehydrating agent such as but not limited to acetyl chloride without a solvent or in the appropriate solvent such as toluene under heating conditions such as reflux.

Homophthalic anhydrides of the general formula XVIII can be regioselectively converted into the acid-amides of the general formula XIX at room temperature or under heating conditions in the appropriate solvent such as acetonitrile. Then they are treated with appropriate acid anhydrides or acid chlorides of the general formula XX and XXI, respectively, in the absence or presence of base such as triethyl amine and DMAP in the appropriated solvent, usually in acetonitrile, at room temperature or under mild heating conditions ($T < +100°C$). This transformation first provides intermediate ketene-aminals of the general formula XXII, which undergo further acylation reaction with the formation of compounds of the general formula XXIII. Further heating at higher temperature such as at +150°C leads to the rearrangement with the formation of amides of the general formula XIV. Both compounds of the general formula XXIII and XXIV can be readily hydrolyzed at ambient temperature with an appropriate base such as sodium hydroxide in aqueous methanol or aqueous tetrahydrofurane as a solvent. The obtained keto-acids of the general formula XXV or ketene-aminals of the general formula XXIII are converted to the final compounds of the invention of the general formula I by condensation with anilines of the general formula VI under the same conditions as described above for condensation with keto-acids of the general formula IV.

Alternatively, acid-amides of the general formula XIX can be converted directly to the compounds of the invention of the general formula I by condensation with appropriate imidoyl chlorides of the general formula XXVII which are readily available from corresponding amide of the general formula XXVI, which are easily prepared by well-known coupling between aniline of the general formula VI and corresponding carboxylic acids or their anhydrides or acid chlorides of the general formula XX and XXI, respectively.

Examples

Analytical LC-MS, method A (used in most cases unless noted otherwise): data were obtained on a Sciex API 150EX analytical LC/MS system equipped with Applied Biosystems API150EX single qaudrupole mass spectrometer and atmospheric pressure photo ionisation (APPI) ion source, Shimadzu LC10ADvp LC pumps (3X), Shimadzu SPD-M20A photodiode array detector, SEDERE Sedex 85 - low temperature Evaporative Light Scattering Detector (ELSD), Shimadzu CBM-20A system controller, Gilson 215 autosampler and Gilson 864 degasser controlled by Analyst Software. Column: 30 X 4.6 mm Waters Symmetry C18 column with 3.5 µm particle size; Injection Volume: 15 µL; Column temperature: 60°C; Solventsystem: A = water/trifluoroacetic acid (100:0.05) and B = water/acetonitrile/trifluoroacetic acid (5:95:0.035); Method: Linear gradient elution with 10% B to 100% B in 2.4 minutes then with 10% B in 0.4 minutes and with a flow rate of 3.3 mL/minute. The retention times (t_R) are expressed in minutes based on UV-trace at 254 nm.

Analytical LC-MS, method B: data were obtained on a Sciex API300 analytical LC/MS system equipped with Applied Biosystems API300 triple qaudrupole mass spectrometer with atmospheric pressure photo ionisation (APPI) ion source, Shimadzu LC10ADvp LC pumps (3X), Shimadzu SPD-M20A photodiode array detector, Polymer Labs PL-ELS 2100 - low temperature Evaporative Light Scattering Detector (ELSD), Shimadzu SCL10A VP system controller, Gilson 215 autosampler and Gilson 864 degasser controlled by Analyst Software. Column: Symmetry C18 3.5 µm, 4.6 x 30 mm 30 X 4.6 mm; Injection Volume: 5 µL; Column temperature: 60°C; Solventsystem: A = water/trifluoroacetic acid (100:0.05) and B =

water/acetonitrile/trifluoroacetic acid (5:95:0.035); Method: Linear gradient elution with 10% B to 100% B in 1.45 minutes then with 10% B in 0.55 minutes and with a flow rate of 5.5 mL/minute:

Time, min.	%B
0.00	10.0
1.45	100.0
1.55	10.0
2.0	10.0

The retention times (t_R) are expressed in minutes based on UV-trace at 254 nm.

Preparative LC-MS purification was performed on the same Sciex API 150EX system equipped with Gilson 333 and 334 pumps, Shimadzu LC10ADvp pump, Gilson UV/VIS 155 UV detector, Gilson 233XL autosampler, Gilson FC204 fraction, Gilson 506C system interface, Gilson 864 degasser, DIY flowsplitter (approx. 1:1000), and LC Packings Accurate flowsplitter (1:10.000 @ 140 ml/min). The MS and fraction collector was controlled by Masschrom software (Macintosh PC), the LC system was controlled by Unipoint software. For a small scale (<20 mg) purification fractions were collected in 4 ml vials using Symmetry C18 5 µm, 10 x 50 mm column, injection volume of 0-300 µL, flow rate of 5.7 ml/min and duration of 8 min. Gradient:

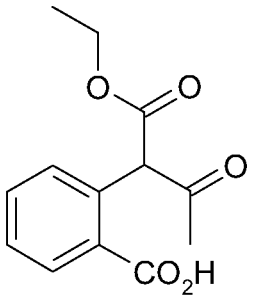
Time, min.	%B
0.00	10.0-50.0 (variable, depending on the sample)
7.00	100.0
7.10	10.0-50.0
8.00	10.0-50.0

^{1}H NMR spectra were recorded at 500.13 MHz on a Bruker Avance DRX-500 instrument at T=303.3 K. Variable temperature ^{1}H NMR spectra were recorded at 250 MHz on a Bruker Avance DPX-250 instrument. Deuterated dimethyl sulfoxide (DMSO-d_6, 99.8%D) was used as solvent unless noted otherwise. Tetramethylsilane was used as internal reference standard. Chemical shift values are expressed in ppm-

values relative to tetramethylsilane. The following abbreviations or their combinations are used for multiplicity of NMR signals: s = singlet, d = doublet, t = triplet, q = quartet, qui = quintet, h = heptet, dd = double doublet, ddd = double double doublet, dt = double triplet, dq = double quartet, tt = triplet of triplets, m = multiplet and br = broad or broad singlet.

Microwave experiments were performed in sealed process vials or reactors using an Emrys Synthesizer or Emrys Optimizer EXP from Personal Chemistry or a Milestone Microsynth instrument from Milestone. Before sealing the process vial it was flashed with argon. When a reaction was heated in a microwave instrument, it was cooled to 25°C before the next process step.

Preparation of intermediates

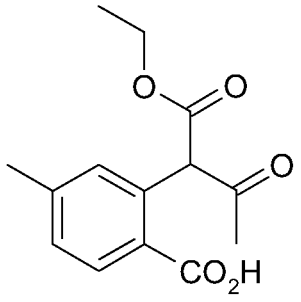


2-(1-Ethoxycarbonyl-2-oxo-propyl)-benzoic acid.

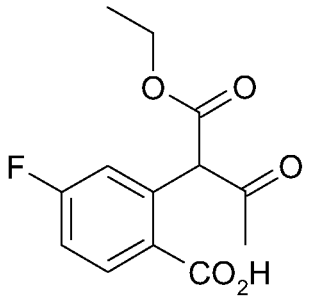
To a cold (ice/water bath) stirred mixture of 2-bromobenzoic acid (20.1g, 0.1 mol) and ethyl acetoacetate (13.01 g, 0.1 mol) in 1,4-dioxane (200 ml) sodium hydride (8 g, 0.2 mol, 60% dispersion in mineral oil) was added in small portions. After addition the cold bath was removed and the reaction mixture was allowed to stir at ambient temperature for 10 min. Copper (I) bromide (15.2 g, 0.106 mol) was added in portions and the obtained mixture was heated at reflux for 1 h. It was allowed to cool and stirred overnight at ambient temperature. The obtained green suspension was quenched with ethyl acetate (200 ml) and ice (300 g) and acidified with concentrated HCl (50 ml). The organic phase was washed with aq. 2 M HCl (2x100 ml) and brine, dried (Na_2SO_4) and evaporated in vacuo. The remaining mineral oil was removed by decantation after shaking with heptane (3x100 ml) and evaporation. Yield ca. 20g, pale-yellow oil. The crude product was used in the next step without further

purification. LC-MS (m/z) 205 ($[M-CO_2]^+$); t_R = 0.91. ^1H NMR (500 MHz, DMSO-d_6): mixture of at least 3 tautomers.

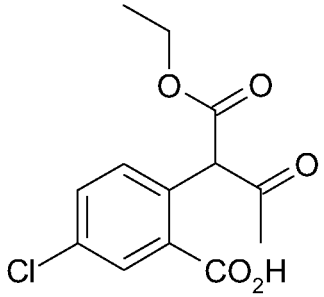
The following compounds were prepared analogously from corresponding 2-bromobenzoic acids and used in the next step without further purification and characterisation unless noted otherwise:



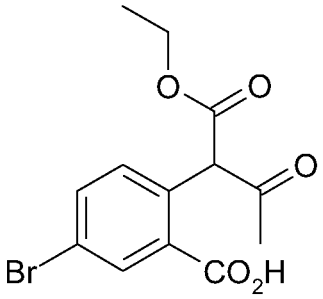
2-(1-Ethoxycarbonyl-2-oxo-propyl)-4-methyl-benzoic acid.
LC-MS (m/z) 247.2 ($[MH-H_2O]^+$); t_R = 1.05.



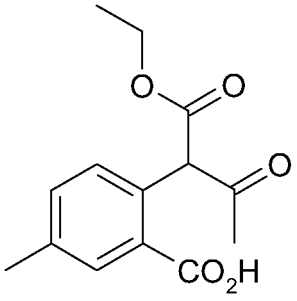
2-(1-Ethoxycarbonyl-2-oxo-propyl)-4-fluoro-benzoic acid.



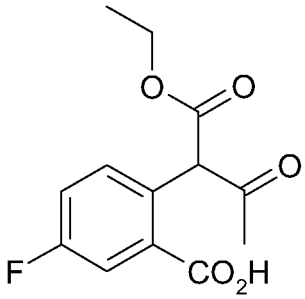
5-Chloro-2-(1-ethoxycarbonyl-2-oxo-propyl)-benzoic acid.



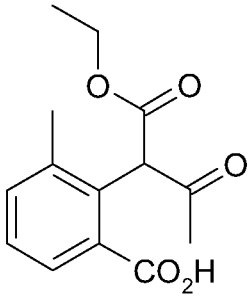
5-Bromo-2-(1-ethoxycarbonyl-2-oxo-propyl)-benzoic acid.



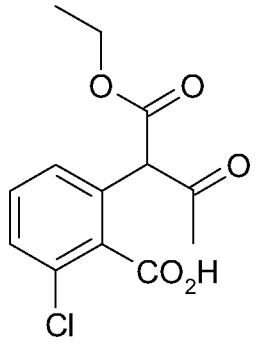
2-(1-Ethoxycarbonyl-2-oxo-propyl)-5-methyl-benzoic acid.



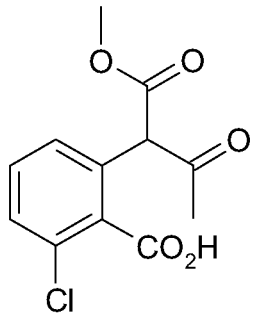
2-(1-Ethoxycarbonyl-2-oxo-propyl)-5-fluoro-benzoic acid.



2-(1-Ethoxycarbonyl-2-oxo-propyl)-3-methyl-benzoic acid.

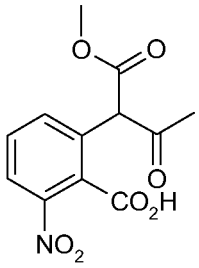


2-Chloro-6-(1-ethoxycarbonyl-2-oxo-propyl)-benzoic acid.

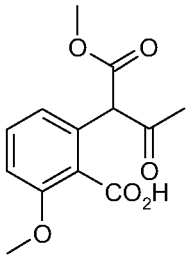


2-Chloro-6-(1-methoxycarbonyl-2-oxo-propyl)-benzoic acid.

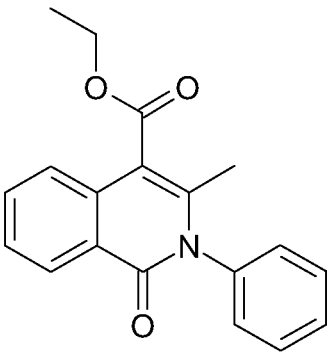
To a stirred mixture of 2-bromo-6-chlorobenzoic acid (20 g, 85 mmol), methylacetoacetate (310 ml, excess), and copper (I) bromide 12.2 g, 85 mmol) sodium hydride (8.5 g, 212 mmol, 60% in oil) was added by portions and then heated at 70°C for 16 hours. The resulting mixture was diluted with water (600 ml) and extracted with diethyl ether (3 x 500 ml). Aqueous phase was acidified with 2M HCl and extracted with ethyl acetate (2 x 800 ml). The combined organic solution was washed with brine (100 ml), dried (Na_2SO_4) and evaporated. The obtained oil was treated with a hot mixture of ethyl acetate (20 ml) and heptane (200 ml) and decanted for 2 times, dried in vacuo to give 8 g of yellow-brown solid, yield 34%. ^{1}H NMR (500 MHz, DMSO-d_6): 1.73 (s, 3H), 3.6 (s, 3H), 7.24 (d, 1H), 7.44 (t, 2H), 7.5 (d, 1H), 12.85 (s, 1H, OH of enol form), 13.4 (br, 1H, CO_2H).



2-(1-Methoxycarbonyl-2-oxo-propyl)-6-nitro-benzoic acid.



2-Methoxy-6-(1-methoxycarbonyl-2-oxo-propyl)-benzoic acid.

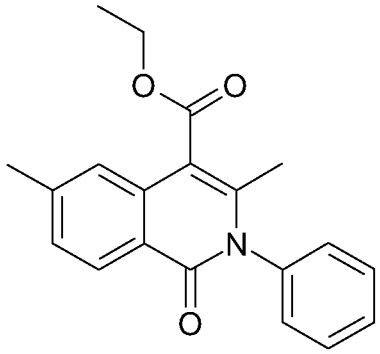


3-Methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ethyl ester.

A mixture of 2-(1-ethoxycarbonyl-2-oxo-propyl)-benzoic acid (7.6 g, 30.4 mmol) and aniline (10 ml, 108 mmol) was flushed with argon, sealed in the Emrys process vial and heated at 150°C for 15 min under microwave irradiation. The volatiles were removed in vacuo and the obtained residue was partitioned between ethyl acetate (100 ml) and 2M HCl (100 ml). The organic layer was washed with brine (2 x 20 ml), dried (Na_2SO_4) and evaporated to give 8.7 g of brown oil that solidified. The obtained crude product was of ca. 90% purity according to ^1H NMR and can be used in the next step without further purification. Alternatively, the crude product was dissolved in hot ethyl acetate (20 ml), precipitated with heptane (60 ml), allowed to cool, filtered and

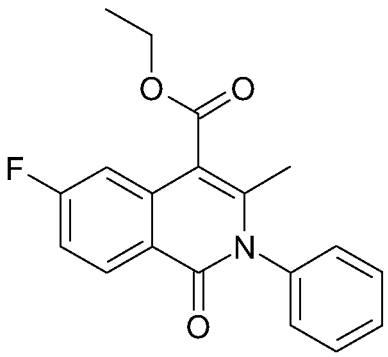
washed with diethyl ether to give 4.2 g of a pale-brown crystalline solid, yield 45%. LC-MS (m/z) 308.2 (MH^+); t_R = 1.43. ^{1}H NMR (500 MHz, DMSO-d_6): 1.34 (t, 3H), 1.97 (s, 3H), 4.41 (q, 2H), 7.38 (d, 2H), 7.51 (t, 1H), 7.56 (t (overlapping m), 3H), 7.62 (d, 1H), 7.8 (t, 1H), 8.22 (d, 1H).

The following compounds were prepared analogously from corresponding crude 2-(1-ethoxycarbonyl-2-oxo-propyl)-4-methylbenzoic acids and corresponding anilines.



3,6-Dimethyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ethyl ester.

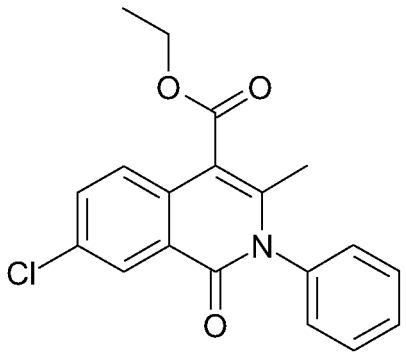
The crude product was used in the next step without crystallization. LC-MS (m/z) 322.1 (MH^+); t_R = 1.53. ^{1}H NMR (500 MHz, DMSO-d_6): 1.34 (t, 3H), 1.96 (s, 3H), 2.47 (s, 3H), 4.41 (q, 2H), 7.28 (t, 1H), 7.37 (m, 3H), 7.50 (d, 1H), 7.56 (m, 2H), 8.11 (d, 1H).



6-Fluoro-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ethyl ester.

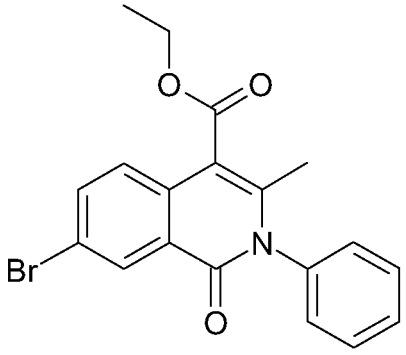
The crude product was used in the next step without crystallization. LC-MS (m/z) 326.3 (MH^+); t_R = 1.54. ^{1}H NMR (500 MHz, DMSO-d_6): 1.33 (t, 3H), 2.0 (s, 3H),

4.41 (q, 2H), 7.28 (t, 1H), 7.39 (d, 2H), 7.42 (m, 1H), 7.51 (t, 1H), 7.57 (t, 2H), 8.29 (dd, 1H).



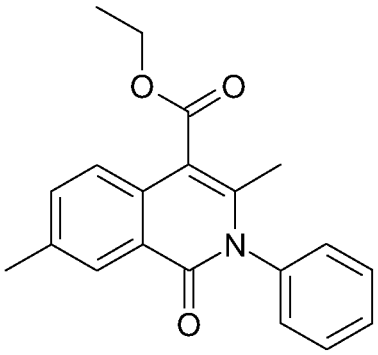
7-Chloro-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ethyl ester.

The crude product was used in the next step without crystallization. LC-MS (m/z) 342.0 (MH^+); t_R = 1.67. ^1H NMR (500 MHz, DMSO-d_6): 1.33 (t, 3H), 1.98 (s, 3H), 4.41 (q, 2H), 7.4 (d, 2H), 7.51 (t, 1H), 7.57 (t, 2H), 7.7 (d, 1H), 7.85 (dd, 1H), 8.15 (d, 1H).



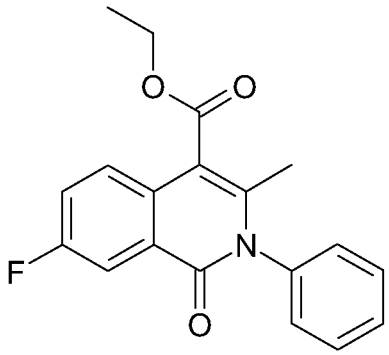
7-Bromo-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ethyl ester.

The crude product was used in the next step without crystallization. LC-MS (m/z) 386.1 (MH^+, ^{79}Br); t_R = 1.71. ^1H NMR (500 MHz, DMSO-d_6): 1.33 (t, 3H), 1.98 (s, 3H), 4.4 (q, 2H), 7.39 (d, 2H), 7.51 (t, 1H), 7.57 (t, 2H), 7.62 (d, 1H), 7.96 (dd, 1H), 8.29 (d, 1H).



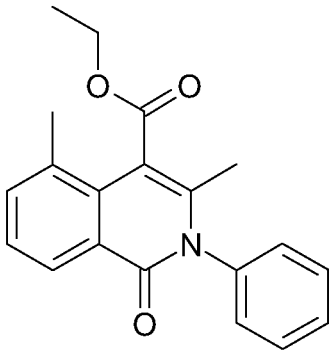
3,7-Dimethyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ethyl ester.

The crude product as a brown oil was used in the next step without purification. LC-MS (m/z) 322.2 (MH^+); t_R = 1.59.



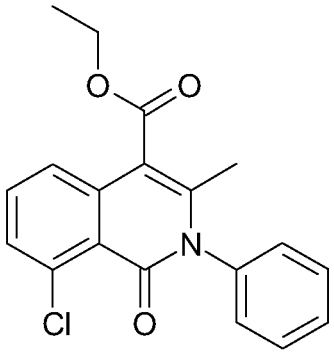
7-Fluoro-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ethyl ester.

The crude product as a brown oil was used in the next step without purification. LC-MS (m/z) 326.1 (MH^+); t_R = 0.79 (method B).



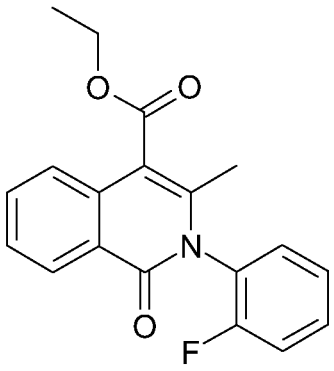
3,5-Dimethyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ethyl ester.

The crude product was used in the next step without purification. LC-MS (m/z) 322.1 (MH^+); t_R = 1.63.



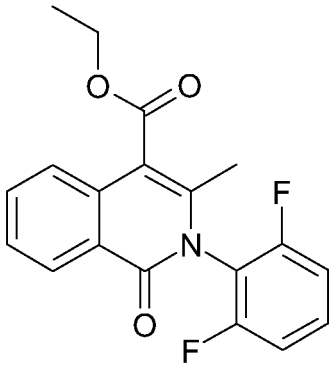
8-Chloro-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ethyl ester.

The crude product was used in the next step without purification. LC-MS (m/z) 342.0 (MH^+); t_R = 1.55.



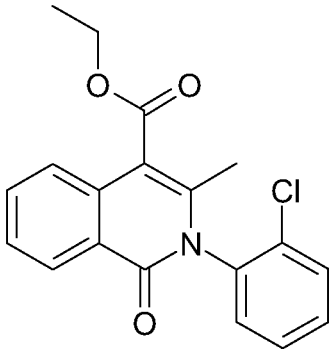
2-(2-Fluoro-phenyl)-3-methyl-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ethyl ester.

LC-MS (m/z) 326.5 (MH^+); t_R = 1.46.



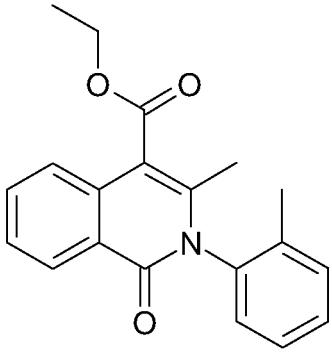
2-(2,6-Difluoro-phenyl)-3-methyl-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ethyl ester.

The crude product was used in the next step without purification and characterization.



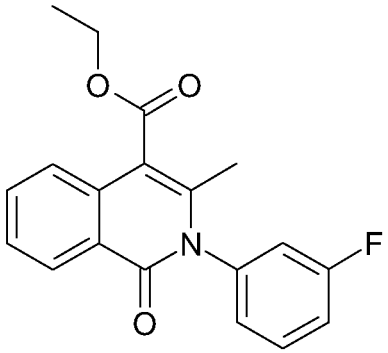
2-(2-Chloro-phenyl)-3-methyl-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ethyl ester.

The crude product was used in the next step without purification and characterization.



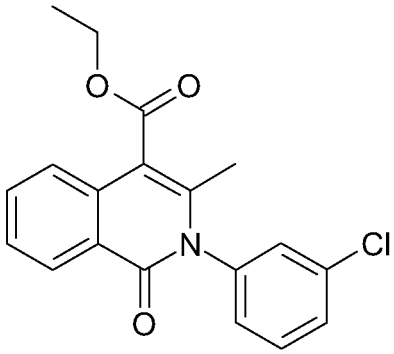
3-Methyl-1-oxo-2-o-tolyl-1,2-dihydro-isoquinoline-4-carboxylic acid ethyl ester.

The crude product was used in the next step without purification and characterization.



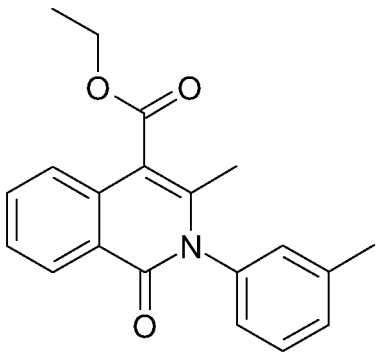
2-(3-Fluoro-phenyl)-3-methyl-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ethyl ester.

LC-MS (m/z) 326.3 (MH^+); t_R = 1.47.



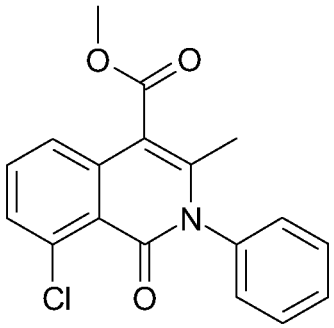
2-(3-Chloro-phenyl)-3-methyl-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ethyl ester.

LC-MS (m/z) 342.1 (MH^+); t_R = 1.61.



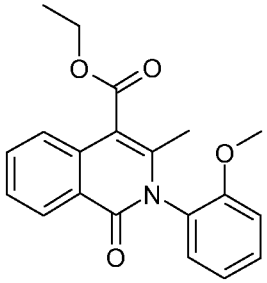
3-Methyl-1-oxo-2-m-tolyl-1,2-dihydro-isoquinoline-4-carboxylic acid ethyl ester.

LC-MS (m/z) 322.1 (MH^+); t_R = 1.57.



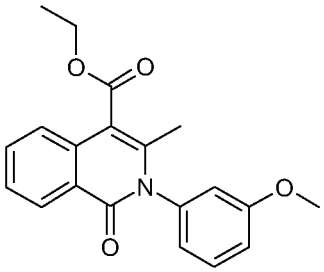
8-Chloro-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid methyl ester.

A mixture of 2-chloro-6-(1-methoxycarbonyl-2-oxo-propyl)-benzoic acid (4 g, 15 mmol), aniline (1.369 ml, 15 mmol) and tetraethoxysilane (6.65 ml, 30 mmol) in methanol (20 ml) was sealed and heated under microwave irradiation at +150°C for 20 min. The obtained solution was diluted with water (150 ml) and extracted with ethyl acetate (2x300 ml). The combined organic solution was dried ($MgSO_4$) and evaporated. The obtained crude enamine (2-chloro-6-(1-methoxycarbonyl-2-phenylamino-propenyl)-benzoic acid) was dissolved in dimethylformamide (80 ml) followed by addition of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC, 4.3 g, 22.5 mmol) and 1-hydroxybenzotriazole (HOBT, 3.04 g, 22.5 mmol). It was stirred for 16 hours and partitioned between water (250 ml), diethyl ether (250 ml) and ethyl acetate (150 ml). The organic phase was washed with 0.5 M NaOH (2x100 ml), brine (2x200 ml), dried ($MgSO_4$) and evaporated to give 4.25 g of brown oil, which was used in the next step without further purification. Yield 87%. LC-MS (m/z) 328.0 (MH^+); t_R = 1.36. ^1H NMR (500 MHz, $CDCl_3$): 2.02 (s, 3H), 3.98 (s, 3H), 7.23 (d, 2H), 7.44-7.55 (m, 6H).



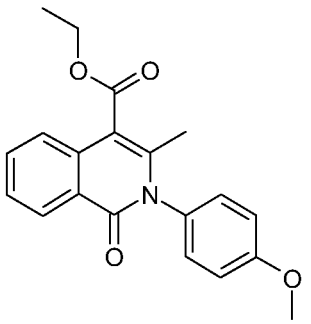
2-(2-Methoxy-phenyl)-3-methyl-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ethyl ester.

The title compound was used in the next step without purification. LC-MS (m/z) 338.3 (MH^+); t_R = 1.38.



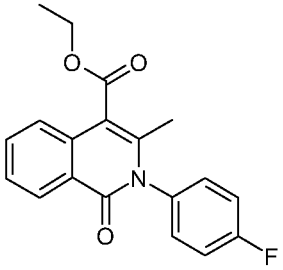
2-(3-Methoxy-phenyl)-3-methyl-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ethyl ester.

The title compound was used in the next step without purification. LC-MS (m/z) 338.5 (MH^+); t_R = 1.41.



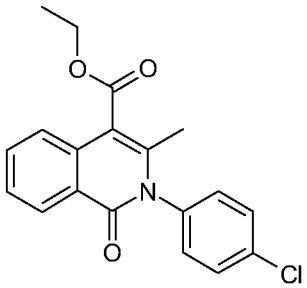
2-(4-Methoxy-phenyl)-3-methyl-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ethyl ester.

The title compound was used in the next step without purification. LC-MS (m/z) 338.5 (MH^+); t_R = 1.4.



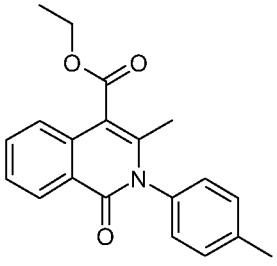
2-(4-Fluoro-phenyl)-3-methyl-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ethyl ester.

The title compound was used in the next step without purification. LC-MS (m/z) 326.2 (MH^+); t_R = 1.41.



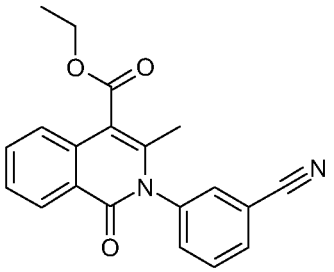
2-(4-Chloro-phenyl)-3-methyl-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ethyl ester.

The title compound was used in the next step without purification. LC-MS (m/z) 342.2 (MH^+); t_R = 1.53.



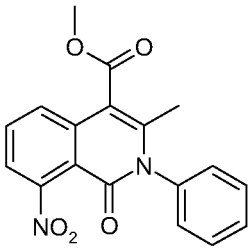
3-Methyl-1-oxo-2-p-tolyl-1,2-dihydro-isoquinoline-4-carboxylic acid ethyl ester.

The title compound was used in the next step without purification. LC-MS (m/z) 321.7 (MH^+); t_R = 1.51.



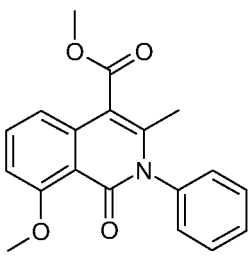
2-(3-Cyano-phenyl)-3-methyl-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ethyl ester.

The title compound was used in the next step without purification. LC-MS (m/z) 333.0 (MH^+); t_R = 1.3.



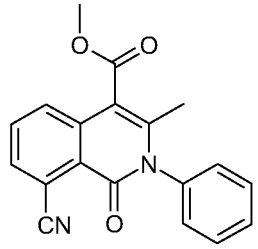
3-Methyl-8-nitro-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid methyl ester.

The title compound was used in the next step without purification. LC-MS (m/z) 339.3 (MH^+); t_R = 1.26.



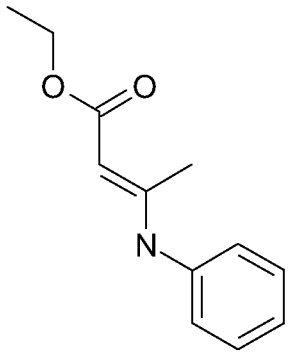
8-Methoxy-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid methyl ester.

The title compound was used in the next step without purification. LC-MS (m/z) 324.3 (MH^+); t_R = 1.12.



8-Cyano-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid methyl ester.

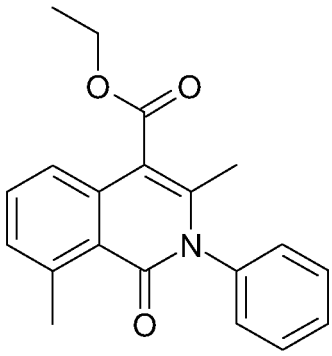
A suspension of 3-methyl-8-nitro-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid methyl ester (320 mg, 0.95 mmol) and Zn (898 mg, 13.8 mmol) in THF (4.5 ml) and 2M aq. HCl (4.5 ml) was stirred for 10 min, filtered and partitioned between ethyl acetate (3x150 ml) and sat. aq. $NaHCO_3$ (100 ml). The combined organic solution was dried ($MgSO_4$) and evaporated to give 8-amino-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid methyl ester as a dark oil (200 mg, 0.645 mmol, 69% yield. LC-MS (m/z) 309.4 (MH^+); t_R = 1.2. It was dissolved in conc. aq. HCl (0.4 ml) and H_2O (3.25 ml). To the obtained solution $NaNO_2$ (46.3 mg, 0.645 mmol, in 0.12 ml H_2O) was added dropwise at 0°C. After 15 min it was neutralized (pH = 6-7) with sat. aq. $NaHCO_3$ to give diazonium salt solution. To a solution of KCN (202 mg, 3 mmol) in water (0.4 ml) solution of $CuSO_4x5H_2O$ (197 mg, 0.774 mmol) in water (0.8 ml) was added dropwise at 0°C. After addition completion benzene (2 ml) was added and the mixture was warmed to +60°C. To this mixture diazonium salt solution was added dropwise during 15 min then kept at 70°C for 85 min. It was allowed to cool to r.t., diluted with ethyl acetate (10 ml) and filtered via plug of cellite. The organic layer was washed with brine (10 ml), dried ($MgSO_4$) and evaporated to give 97.9 mg of the title compound (48% yield). LC-MS (m/z) 319.2 (MH^+); t_R = 1.15.



3-Phenylamino-but-2-enoic acid ethyl ester.

The compound was prepared according to the described procedure (Q. Dai, W. Yang, and X. Zhang *Org. Letters* **2005**, 5343).

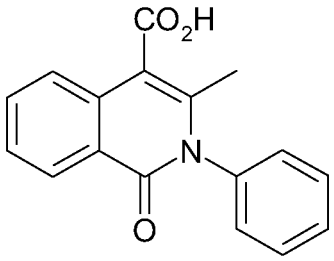
^{1}H NMR (500 MHz, DMSO-d_6): 1.19 (t, 3H), 2.01 (s, 3H), 4.06 (q, 2H), 4.7 (s, 1H), 7.17 (overlapping t, 1H), 7.18 (overlapping d, 2H), 7.36 (t, 2H), 10.36 (s, 1H).



3,8-Dimethyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ethyl ester.

To a cold (ice/water bath) solution of 2-bromo-6-methyl-benzoic acid (650 mg, 3.023 mmol) and 3-phenylamino-but-2-enoic acid ethyl ester (750 mg, 3.65 mmol) in acetonitrile (10 ml), sodium hydride (267 mg, 6.67 mmol, 60% dispersion in mineral oil) was added in portions. The cold bath was removed and the mixture was sonicated at ambient temperature until gas evolution ceased (10 min). Copper (I) bromide was added (957 mg, 6.67 mmol) and the obtained suspension was flushed with argon, sealed and heated under microwave irradiation at +80°C for 30 min. LC-MS indicated a full conversion to 2-(1-ethoxycarbonyl-2-phenylamino-propenyl)-6-methyl-benzoic acid (LC-MS (m/z) 340.4 (MH^+); t_R = 1.59. The obtained suspension was heated at +160°C under microwave irradiation for 30 min. It was diluted with ethyl acetate (50 ml) and filtered. The obtained organic solution was washed with 1M HCl (3 x 50 ml),

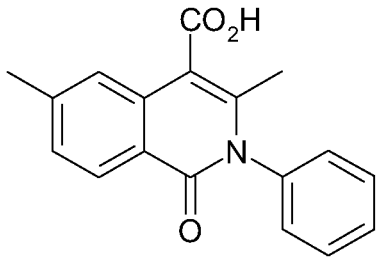
water (2 x 10 ml) and sat. aq. $NaHCO_3$ solution (30 ml), absorbed on SiO_2 (3 g) and flash chromatographed on SiO_2 (50 g, gradient heptane – 30% ethyl acetate in heptane) to give 217 mg of yellow oil. Yield 22%. LC-MS (m/z) 322.2 (MH^+); t_R = 1.62. ^1H NMR (500 MHz, DMSO-d_6): 1.32 (t, 3H), 1.91 (s, 3H), 2.74 (s, 3H), 4.39 (q, 2H), 7.3 (d, 1H), 7.36 (overlapping m, 3H), 7.49 (m, 1H), 7.55 (t, 2H), 7.61 (t, 1H).



3-Methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid.

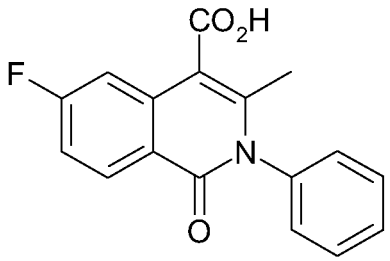
3-Methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ethyl ester (4.2 g, 13.7 mmol) was dissolved in 100 ml of hot methanol and a solution of NaOH (6 g) in water (20 ml) was added. The reaction mixture was heated at reflux for 2 hrs, diluted with water (200 ml) and stirred overnight at ambient temperature. Organic volatiles were removed under reduced pressure and the obtained aqueous solution was extracted with ethyl acetate (2 x 50 ml). The aqueous solution was poured into ice/2M HCl (150 ml). The obtained suspension was sonicated, and the product was separated by filtration, washed with water and dried in vacuo to give 2.9 g of a colourless solid, yield 76%. LC-MS (m/z) 280.2 (MH^+); t_R = 0.9. ^1H NMR (500 MHz, DMSO-d_6): 2.01 (s, 3H), 7.36 (d, 2H), 7.50 (t, 1H), 7.56 (q (overlapping m), 3H), 7.72 (d, 1H), 7.81 (t, 1H), 8.22 (d, 1H), 13.5 (br, 1H).

The following acids were prepared analogously from corresponding ethyl esters:



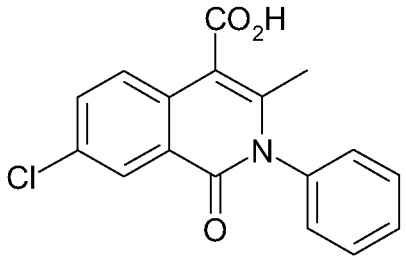
3,6-Dimethyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid.

LC-MS (m/z) 293.9 (MH^+); t_R = 0.99. ^1H NMR (500 MHz, DMSO-d_6): 2.0 (s, 3H), 2.47 (s, 3H), 7.34 (d, 2H), 7.38 (d, 1H), 7.47 (s, 1H), 7.50 (d, 1H), 7.56 (t, 2H), 8.11 (d, 1H), 13.4 (br, 1H).



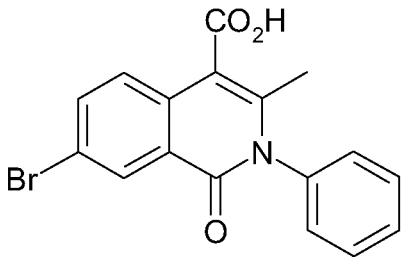
6-Fluoro-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid.

LC-MS (m/z) 298.4 (MH^+); t_R = 0.99. ^1H NMR (500 MHz, DMSO-d_6): 2.05 (s, 3H), 7.37 (d, 2H), 7.41 (dt, 1H), 7.48 (dd, 1H), 7.51 (t, 1H), 7.57 (t, 2H), 8.28 (dd, 1H), 13.6 (b, 1H).



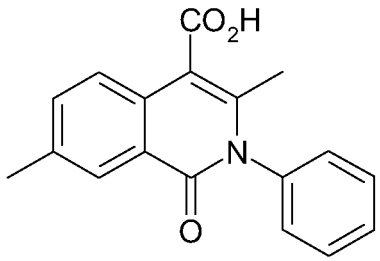
7-Chloro-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid.

The crude product was used in the next step without crystallization. LC-MS (m/z) 314.2 (MH^+); t_R = 1.13. ^1H NMR (500 MHz, DMSO-d_6): ^1H NMR (500 MHz, DMSO-d_6): 2.03 (s, 3H), 7.38 (d, 2H), 7.51 (t, 1H), 7.57 (t, 2H), 7.79 (d, 1H), 7.86 (dd, 1H), 8.15(d, 1H), 13.55 (b, 1H).



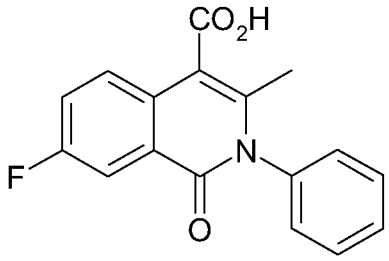
7-Bromo-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid.

LC-MS (m/z) 358.1 (MH^+, ^{79}Br); t_R = 1.2. ^1H NMR (500 MHz, DMSO-d_6): 2.02 (s, 3H), 7.38 (d, 2H), 7.51 (t, 1H), 7.57 (t, 2H), 7.72 (d, 1H), 7.97 (dd, 1H), 8.29 (d, 1H), 13.55 (b, 1H).



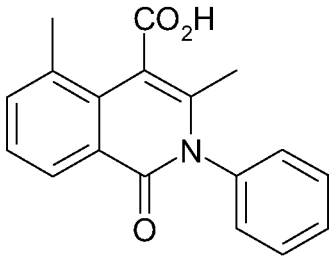
3,7-Dimethyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid.

LC-MS (m/z) 293.9 (MH^+); t_R = 1.02. ^1H NMR (500 MHz, DMSO-d_6): 2.0 (s, 3H), 2.45 (s, 3H), 7.34 (d, 2H), 7.5 (t, 1H), 7.56 (t, 2H), 7.63 (m, 2H), 8.02 (s, 1H), 13.38 (br, 1H).



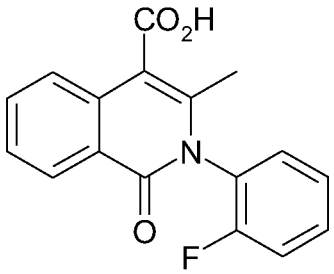
7-Fluoro-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid.

LC-MS (m/z) 298.2 (MH^+); t_R = 1.01. ^1H NMR (500 MHz, DMSO-d_6): 2.02 (s, 3H), 7.37 (d, 2H), 7.51 (t, 1H), 7.57 (t, 2H), 7.71 (dt, 1H), 7.83 (dd, 1H), 7.88 (dd, 1H), 13.54 (br, 1H).



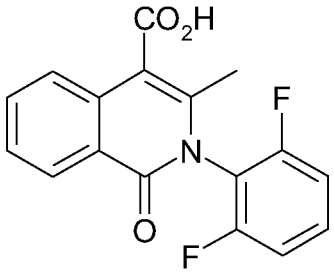
3,5-Dimethyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid.

LC-MS (m/z) 294.1 (MH^+); t_R = 1.09. ^1H NMR (500 MHz, DMSO-d_6): 1.95 (s, 3H), 2.74 (s, 3H), 7.27-7.64 (m, 8H), 13.35 (b, 1H).



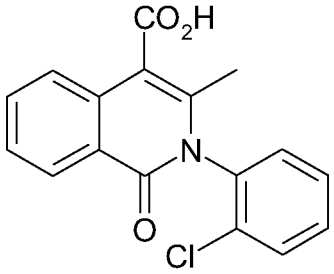
2-(2-Fluoro-phenyl)-3-methyl-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid.

LC-MS (m/z) 298.4 (MH^+); t_R = 0.83.



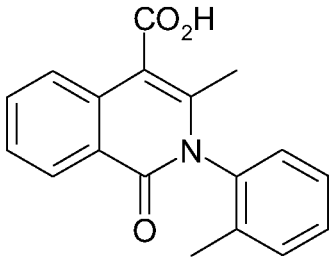
2-(2,6-Difluoro-phenyl)-3-methyl-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid.

LC-MS (m/z) 316.2 (MH^+); t_R = 1.03.



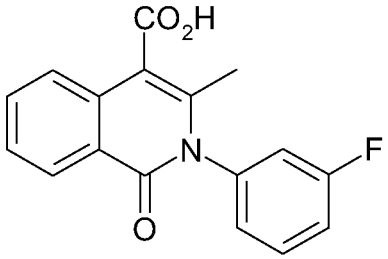
2-(2-Chloro-phenyl)-3-methyl-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid.

LC-MS (m/z) 314.2 (MH^+); t_R = 1.0.



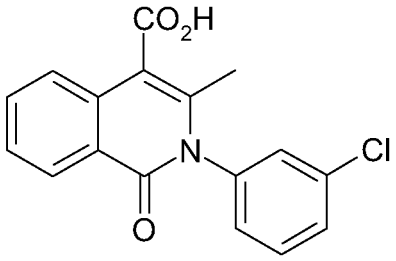
3-Methyl-1-oxo-2-o-tolyl-1,2-dihydro-isoquinoline-4-carboxylic acid.

LC-MS (m/z) 294.1 (MH^+); t_R = 0.99.



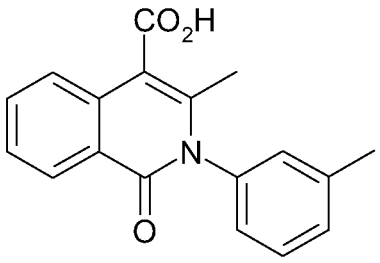
2-(3-Fluoro-phenyl)-3-methyl-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid.

LC-MS (m/z) 298.4 (MH^+); t_R = 0.96. ^{1}H NMR (250 MHz, DMSO-d_6): 2.02 (s, 3H), 7.24 (d, 1H), 7.32-7.42 (m, 2H), 7.5-7.65 (m, 2H), 7.71 (d, 1H), 7.81 (m, 1H), 8.21 (d, 1H), 13.49 (br, 1H).



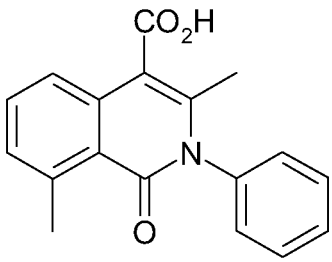
2-(3-Chloro-phenyl)-3-methyl-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid.

LC-MS (m/z) 314.2 (MH^+); t_R = 1.09. ^{1}H NMR (500 MHz, DMSO-d_6): 2.04 (s, 3H), 7.39 (t, 1H), 7.56 (t, 1H), 7.58-7.62 (m, 3H), 7.72 (d, 1H), 7.81 (t, 1H), 8.21 (d, 1H), 13.5 (br, 1H).



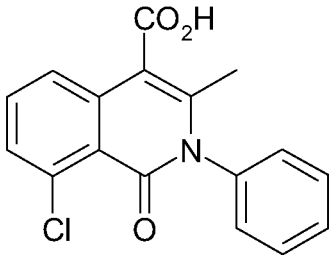
3-Methyl-1-oxo-2-m-tolyl-1,2-dihydro-isoquinoline-4-carboxylic acid.

LC-MS (m/z) 293.9 (MH^+); t_R = 1.03. ^1H NMR (250 MHz, DMSO-d_6): 2.02 (s, 3H), 2.38 (s, 3H), 7.14 (overlapping d, 1H), 7.16 (overlapping s, 1H), 7.31 (d, 1H), 7.44 (t, 1H), 7.54 (t, 1H), 7.71 (d, 1H), 7.8 (t, 1H), 8.21 (d, 1H), 13.46 (br, 1H).



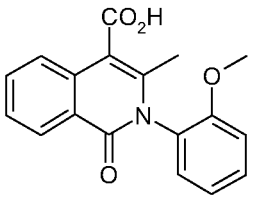
3,8-Dimethyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid.

A solution of 3,8-dimethyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ethyl ester (200 mg, 0.62 mmol) in DMSO (3 ml) and aqueous 1N NaOH (2 ml, 2 mmol) was heated under microwave irradiation at +120°C for 20 min and diluted with water (30 ml). Uncharged impurities were extracted with diethyl ether (30 ml) and the aqueous solution was poured into ice (50 g) with aqueous 2M HCl (10 ml). The obtained precipitate was filtered, washed with water and dried in vacuo to give 75 mg of yellow solid. Yield 41%. LC-MS (m/z) 293.9 (MH^+); t_R = 1.09. ^1H NMR (500 MHz, DMSO-d_6): 1.95 (s, 3H), 2.74 (s, 3H), 7.3 (d, 1H), 7.32 (d, 2H), 7.48 (two overlapping m, 2H), 7.55 (t, 2H), 7.62 (t, 1H), 13.42 (b, 1H).



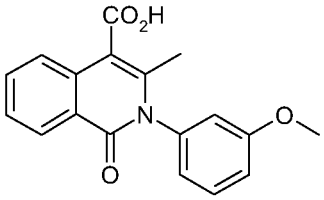
8-Chloro-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid.

The title compound was prepared analogously by hydrolysis of the corresponding methyl or ethyl ester at 100°C. LC-MS (m/z) 314.1 (MH^+); t_R = 1.03.



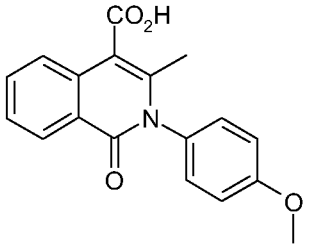
2-(2-Methoxy-phenyl)-3-methyl-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid.

The title compound was used in the next step without purification. LC-MS (m/z) 310.3 (MH^+); t_R = 0.87.



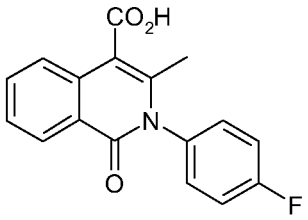
2-(3-Methoxy-phenyl)-3-methyl-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid.

The title compound was used in the next step without purification. LC-MS (m/z) 310.4 (MH^+); t_R = 0.9.



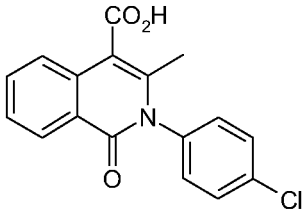
2-(4-Methoxy-phenyl)-3-methyl-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid.

The title compound was used in the next step without purification. LC-MS (m/z) 310.4 (MH^+); t_R = 0.89.



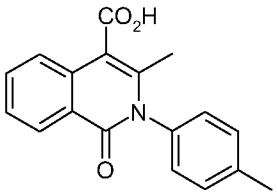
2-(4-Fluoro-phenyl)-3-methyl-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid.

The title compound was used in the next step without purification. LC-MS (m/z) 298.2 (MH^+); t_R = 0.9.



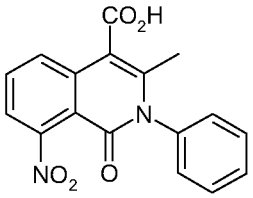
2-(4-Chloro-phenyl)-3-methyl-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid.

The title compound was used in the next step without purification. LC-MS (m/z) 314.2 (MH^+); t_R = 1.53.



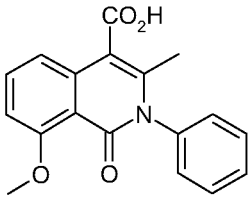
3-Methyl-1-oxo-2-p-tolyl-1,2-dihydro-isoquinoline-4-carboxylic acid.

The title compound was used in the next step without purification. LC-MS (m/z) 293.9 (MH^+); t_R = 0.99.



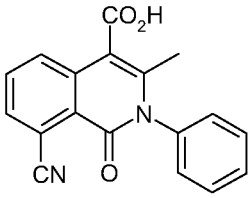
3-Methyl-8-nitro-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid.

The title compound was used in the next step without purification. LC-MS (m/z) 325.5 (MH^+); t_R = 0.94.



8-Methoxy-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid.

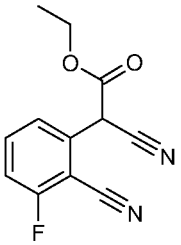
The title compound was used in the next step without purification. LC-MS (m/z) 310.6 (MH^+); t_R = 0.73.



8-Cyano-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid.

LC-MS (m/z) 305.0 (MH^+); t_R = 0.82.

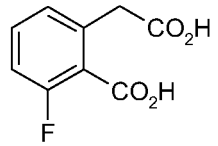
Synthesis of homophthalic anhydrides of the general formula XVIII:



Cyano-(2-cyano-3-fluoro-phenyl)-acetic acid ethyl ester.

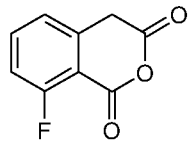
A mixture of cyanoacetic acid ethyl ester (26.7 mL, 251 mmol), 2,6-difluorobenzonitrile (33.2 g, 239 mmol) and potassium carbonate (82.5 g, 597 mmol) in dimethyl sulfoxide (120 mL) was stirred at +55°C for 16 hours and poured into ice-water mixture (ca. 400 mL). It was acidified with conc. aq. HCl with caution (CO_2

evolution) and extracted with ethyl acetate (600 ml). The organic phase was washed with brine (100 mL) and evaporated to give 55.1 g of a pale yellow solid that was used in the next step without further purification. ^{1}H NMR (500 MHz, $CDCl_3$): 1.35 (t, J=7.0 Hz, 3H), 4.34 (m, 2H), 5.13 (s, 1H), 7.33 (t, J=8.4 Hz, 1H), 7.57 (d, J=7.9 Hz, 1H), 7.33 (dd, J=7.9 Hz, J=13.9 Hz, 1H).



2-Carboxymethyl-6-fluoro-benzoic acid.

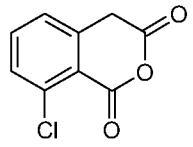
A mixture of 62% sulfuric acid (2:1 conc. H_2SO_4 in water, 400 ml) and cyano-(2-cyano-3-fluoro-phenyl)-acetic acid ethyl ester (52.0 g, 224 mmol) was stirred at +150°C overnight (16 hours). The reaction mixture was poured into ice (ca. 500 g) and neutralised with 10.8 N aq. NaOH (500 mL) with cooling. The mixture was extracted with ethyl acetate (3 x 500mL) and the combined organic solution was washed with brine, dried over $MgSO_4$ and evaporated to give 40.28 g of crude product that was used in the next step without further purification. The analytical sample was prepared by recrystallisation from toluene - ethyl acetate. ^{1}H NMR (500 MHz, DMSO-d_6): 3.4 (br, CO_2H + H_2O), 3.77 (s, 2H), 7.17 (d, J=7.9 Hz, 1H), 7.2 (overlapping t (unres. dd), 1H), 7.45 (dd, J=7.9 Hz, J=13.9 Hz, 1H), 12.95 (br, CO_2H).



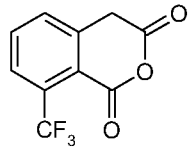
8-Fluoro-isochroman-1,3-dione.

2-Carboxymethyl-6-fluoro-benzoic acid (130 mg, 0.65 mmol) in acetyl chloride (2 ml) was heated under microwave irradiation at 150°C for 10 min then concentrated in vacuo to give the title product (120 mg, 100% yield). The compound is hydroscopic and slowly decomposes back to the starting diacid in wet solvents or under moisturised atmosphere. ^{1}H NMR (500 MHz, DMSO-d_6): 4.29 (s, 2H), 7.27 (d, J=7.8 Hz, 1H), 7.34 (dd, J=8.5 Hz, J=11 Hz, 1H), 7.76 (dt, J=5.3 Hz, J=8 Hz, 1H).

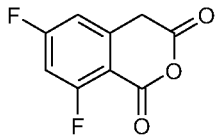
The following homophthalic anhydrides were obtained analogously by the described above 3-step procedure from corresponding fluorobenzonitriles and ethyl cyanoacetate:



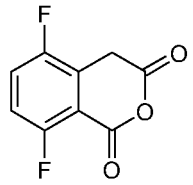
8-Chloro-isochroman-1,3-dione.



8-Trifluoromethyl-isochroman-1,3-dione.

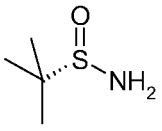


6,8-Difluoro-isochroman-1,3-dione.



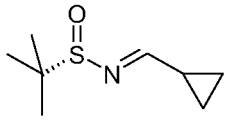
5,8-Difluoro-isochroman-1,3-dione.

Synthesis of chiral and racemic amines of the general formula XI:



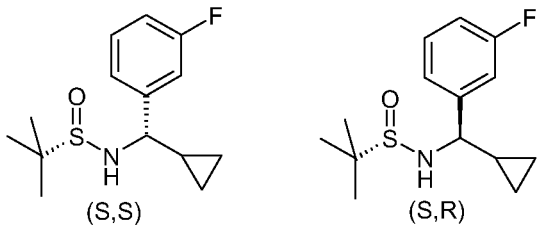
(S)-(–)-2-Methyl-2-propanesulfinamide.

The title chiral auxiliary was prepared according to a described procedure for the (R)-(+)-enantiomer by D.J. Weix and J.A. Ellman *Organic Syntheses* **2005**, *82*, 157.



(S)-2-Methyl-2-propanesulfinic acid 1-cyclopropyl-methylideneamide.

The title compound was prepared according to a general procedure described by G. Liu, D.A. Cogan, T.D. Owens, T.P. Tang, and J.A. Ellman *J. Org. Chem.* **1999**, *64*, 1278: A mixture of cyclopropanecarboxaldehyde (35.0 g, 0.5 mol), 2-methyl-2-propanesulfinic acid 1-cyclopropyl-methylideneamide (30 g, 0.25 mol) and anhydrous $CuSO_4$ (120 g, 0.75 mol) in CH_2Cl_2 (1500 mL) was stirred at room temperature overnight. The reaction mixture was filtered and evaporated to give the title compound (39 g, yield 95%), which was used in the next step without further purification.



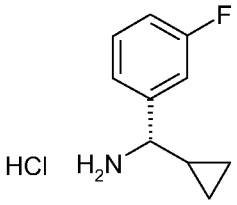
(S)-2-Methyl-2-propanesulfinic acid [(S)-cyclopropyl-(3-fluoro-phenyl)-methyl]-amide and *(S)-2-Methyl-2-propanesulfinic acid [(R)-cyclopropyl-(3-fluoro-phenyl)-methyl]-amide.*

The title compounds were obtained according to a general described procedure for 1,2-stereoselective addition of organometallic reagents to sulfinyl imines by D.A. Cogan, G. Liu, J.A. Ellman, *Tetrahedron* **1999**, *55*, 8883.

Procedure A: To an anhydrous lithium chloride (1.7 g, 40 mmol) THF (20 ml) was added under nitrogen followed by slow addition of *i*-PrMgCl (22 mL, 2 M in THF) and the obtained mixture was stirred at r.t. overnight. The obtained *i*-PrMgCl·LiCl solution was added dropwise to a stirred solution of 1-bromo-3-fluorobenzene (5.6 g, 33 mmol) in THF (25 ml) at 0°C and stirring continued for 2 hours. The obtained Grignard reagent was added to a solution of (S)-2-methyl-2-propanesulfinic acid 1-

cyclopropyl-methylideneamide (2.5 g, 14 mmol) in CH_2Cl_2 (60 mL) at -48°C. The mixture was stirred at -48°C for 5 hours and then at room temperature overnight. The reaction mixture was quenched by addition of aq. sat. NH_4Cl (50 mL) and extracted with CH_2Cl_2 (3x100 mL). The combined organic solution was dried (Na_2SO_4) and evaporated to give a crude mixture, which was purified by column chromatography on silica gel (EtOAc/petroleum ether = 1/10). The obtained mixture of diastereoisomers was resolved by SFC to give the title (S,S)-isomer as the major product (1.5 g, yield 37.5%) and the title (S,R)-isomer (0.16 g, yield: 4.0%).

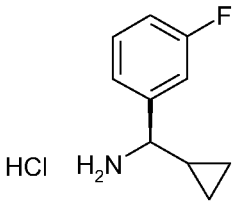
Procedure B: Alternatively, to a suspension of Mg (13.4 g, 0.55 mol) in 50 mL of anhydrous THF at 50°C a solution of 1-bromo-3-fluorobenzene (89.0 g, 0.50 mol) was added dropwise. The mixture was stirred for 2 hours at +50°C and then it was added dropwise to a solution of (S)-2-methyl-2-propanesulfinic acid 1-cyclopropyl-methylideneamide (78.0 g, 0.46 mol) in 100 mL of THF at 50-60°C and stirred for 2 hours. It was quenched with aq. sat. NH_4Cl (100 ml), water (300 mL), filtered, and the both solid and filtrate were extracted with hot ethyl acetate (600 mL) and evaporated in vacuo. The residue was crystallized from a mixture of ethyl acetate and petroleum ether (1:1, 200 mL) at -20°C to give 80 g of the title (S,S)-isomer as a white powder, 66% yield, de 100% according to chiral HPLC. ^{1}H NMR ($CDCl_3$, 400 MHz, TMS=0 ppm): 7.34-7.28 (m, 1H), 7.16-7.12 (m, 2H), 7.00-6.96 (m, 1H), 3.68 (dd, J = 8.8 Hz, 3.2 Hz, 1H), 3.52 (s, 1H), 1.42 (s, 9H), 1.15-1.08 (m, 1H), 0.84-0.75 (m, 1H), 0.69-0.61 (m, 1H), 0.55-0.46 (m, 1H), 0.28-0.21 (m, 1H).



(S)-(+)-C-[C-Cyclopropyl-C-(3-fluoro-phenyl)]-methylamine hydrochloride

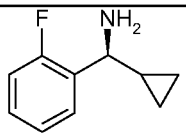
To a saturated solution of HCl in anhydrous dioxane (400 ml) (S)-2-methyl-2-propanesulfinic acid [(S)-cyclopropyl-(3-fluoro-phenyl)-methyl]-amide (80 g, 0.3 mol) was added at 0°C. After stirring at r.t. for 1 hour, the reaction mixture was evaporated in vacuo. The residue was washed with anhydrous ether (2x100 ml) and dried in vacuo to give 56 g of the title compound as a white solid, yield 93%, ee 100% according to chiral HPLC. $[\alpha]^{20}_{D}$ = + 52.69 (c = 10 mg/mL, CH_3OH). ^{1}H NMR

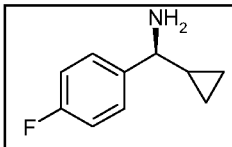
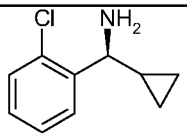
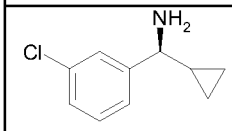
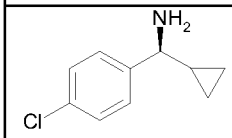
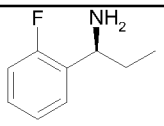
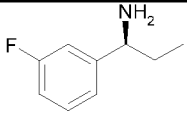
(CD_3OD, 400 MHz, TMS=0): 7.44-7.39 (m, 1H), 7.25-7.19 (m, 2H), 7.12-7.07 (m, 1H), 3.56 (d, J = 10.0 Hz, 1H), 1.37-1.28 (m, 1H), 0.78-0.75 (m, 1H), 0.61-0.55 (m, 2H), 0.39-0.36 (m, 1H).

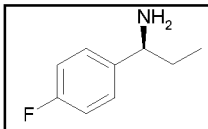
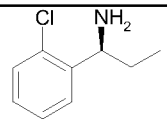
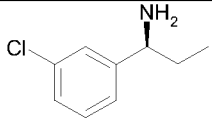
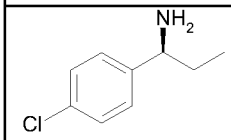
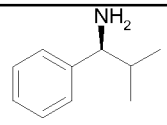
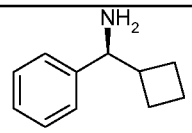
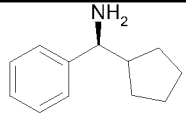


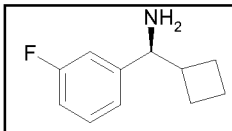
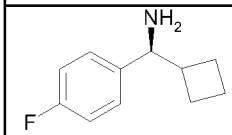
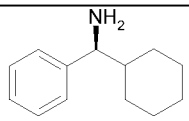
(R)-(–)-C-[C-Cyclopropyl-C-(3-fluoro-phenyl)]-methylamine hydrochloride.
The title compound was prepared according to the above identical procedure from (S)-2-methyl-2-propanesulfinic acid [(R)-cyclopropyl-(3-fluoro-phenyl)-methyl]-amide (0.16g, 0.6 mmol) to give 0.116 g of the title compound as a white solid. $[\alpha]^{20}_{\cdot D}$ = – 49.18 (c = 10 mg/mL, CH_3OH), ee 100%. ^1H NMR (CD_3OD, 400 MHz, TMS=0): identical with (S)-enantiomer.

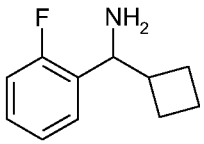
The following enantiomerically pure amine hydrochlorides were obtained analogously in three-step procedure starting from condensation of the corresponding aldehyde with chiral auxiliary, stereoselctive Grignard addition where the mixture of diastereoisomers was resolved either by recrystallisation or by chromatography (SFC or column) and the major (S,S)-diastereoisomer was finally converted to a chiral amine with HCl.

Structure (HCl salt)	**Chemical name**	**$[\alpha]^{20}_{\cdot D}$, (10mg/ml) MeOH**	**ee (chiral HPLC)**	**^1H NMR (CD_3OD, 400 MHz)**
	*C-[(S)-C-cyclopropyl-C-(2-fluoro-phenyl)]-methylamine*	+19.61	100	7.31-7.28 (m, 1H), 7.14-7.01 (m, 3H), 3.74 (d, J = 9.6 Hz, 1H), 1.12-1.05 (m, 1H), 0.47-0.42 (m, 1H), 0.29-0.28 (m, 2H), 0.10-0.07 (m, 1H)

	*C-[(S)-C-Cyclopropyl-C-(4-fluoro-phenyl)]-methylamine*	+47.25	98.9	7.50-7.46 (m, 2H), 7.19-7.14 (m, 2H), 3.56 (d, *J* = 10.0 Hz, 1H), 1.40-1.31 (m, 1H), 0.83-0.76 (m, 1H), 0.67-0.54 (m, 2H), 0.40-0.31 (m, 1H)
	*C-[(S)-C-(2-Chloro-phenyl)-C-cyclopropyl]-methylamine*	+20.56	100	7.68 (dd, *J* = 7.6 Hz, 1.6 Hz, 1H), 7.52-7.38 (m, 3H), 4.12 (d, *J* = 9.6 Hz, 1H), 1.51-1.42 (m, 1H), 0.86-0.80 (m, 1H), 0.68-0.58 (m, 2H), 0.49-0.41 (m, 1H)
	*C-[(S)-C-(3-Chloro-phenyl)-C-cyclopropyl]-methylamine*	+54.25	96.9	7.55 (s, 1H), 7.50-7.42 (m, 3H), 3.61 (d, *J* = 10.0 Hz, 1H), 1.42-1.34 (m, 1H), 0.89-0.83 (m, 1H), 0.74-0.62 (m, 2H).
	*C-[(S)-C-(4-Chloro-phenyl)-C-cyclopropyl]-methylamine*	+59.1	96.2	7.47 (s, 4H), 3.60 (d, *J* = 10.4 Hz, 1H), 1.41-1.34 (m, 1H), 0.86-0.81 (m, 1H), 0.71-0.66 (m, 2H), 0.43-0.39 (m, 1H).
	*(S)-1-(2-Fluoro-phenyl)-propylamine*	–9.71	100	7.54-7.46 (m, 2H), 7.34-7.22 (m, 2H), 4.49 (dd, *J* = 9.2 Hz, 6.0 Hz, 1H), 2.13-1.96 (m, 2H), 0.95 (t, *J* = 6.8 Hz, 3H).
	*(S)-1-(3-Fluoro-phenyl)-propylamine*	+13.9	100	7.51-7.46 (m, 1H), 7.27-7.14 (m, 3H), 4.20 (dd, *J* = 9.2 Hz, 6.0 Hz, 1H), 2.07-1.89 (m, 2H), 0.89 (t, *J* = 7.2 Hz, 3H).

	*(S)-1-(4-Fluoro-phenyl)-propylamine*	+14.83	98.7	7.53-7.50 (m, 2H), 7.24-7.19 (m, 2H), 4.21 (dd, J = 9.2 Hz, 5.6 Hz, 1H), 2.13-1.91 (m, 2H), 0.89 (t, *J* = 7.2 Hz, 3H).
	*(S)-1-(2-Chloro-phenyl)-propylamine*	–1.64	100	7.56-7.38 (m, 4H), 4.73 (dd, *J* = 8.8 Hz, 6.4 Hz, 1H), 2.08-1.96 (m, 2H), 0.92 (t, *J* = 7.6 Hz, 3H).
	*(S)-1-(3-Chloro-phenyl)-propylamine*	+14.46	100	7.48-7.35 (m, 4H), 4.17 (dd, *J* = 9.2 Hz, 6.0 Hz, 1H), 2.06-1.88 (m, 2H), 0.88 (t, *J* = 7.2 Hz, 3H).
	*(S)-1-(4-Chloro-phenyl)-propylamine*	+14.73	100	7.50-7.47 (m, 2H), 7.44-7.41 (m, 2H), 4.18 (dd, *J* = 9.6 Hz, 6.0 Hz, 1H), 2.07-1.90 (m, 2H), 0.89 (t, *J* = 7.6 Hz, 3H).
	*(S)-2-Methyl-1-phenyl-propylamine*	+7.12	100	7.47-7.37 (m, 5H), 3.91 (d, *J* = 9.2 Hz, 1H), 2.21-2.16 (m, 1H), 1.13 (d, *J* = 6.8 Hz, 3H), 0.78 (d, *J* = 6.8 Hz, 3H).
	*C-((S)-C-Cyclobutyl-C-phenyl)-methylamine*	+17.57	95.4	7.37-7.31 (m, 5H), 4.12 (d, *J* = 10.4 Hz, 1H), 2.84-2.75 (m, 1H), 2.21-2.13 (m, 1H), 1.99-1.64 (m, 5H).
	*C-((S)-C-Cyclopentyl-C-phenyl)-methylamine*	+6.97	99.2	7.43 (br, 5H), 3.99 (d, *J* = 10.4 Hz, 1H), 2.46-2.40 (m, 1H), 2.02 (br, 1H), 1.76-1.08 (m, 8H).

	*C-[(S)-C-Cyclobutyl-C-(3-fluoro-phenyl)]-methylamine*	+19.45	100	7.48-7.44 (m, 1H), 7.24-7.15 (m, 3H), 4.26 (d, *J* = 10.4 Hz, 1H), 2.87-2.84 (m, 1H), 2.25-2.24 (m, 1H), 2.05-1.76 (m, 5H).
	*C-[(S)-C-Cyclobutyl-C-(4-fluoro-phenyl)]-methylamine*	+26.98	100	7.45-7.41 (m, 2H), 7.18-7.14 (m, 2H), 4.22 (d, *J* = 10.6 Hz, 1H), 2.89-2.81 (m, 1H), 2.28-2.21 (m, 1H), 2.05-1.71 (m, 5H).
	*C-((S)-C-Cyclohexyl-C-phenyl)-methylamine*	+4.8	100	7.46-7.34 (m, 5H), 3.92 (d, *J* = 9.2 Hz, 1H), 1.97-1.94 (m, 1H), 1.86-1.83 (m, 2H), 1.68-1.66 (m, 2H), 1.33-1.30 (m, 2H), 1.20-1.11 (m, 3H), 0.91-0.88 (m, 1H).

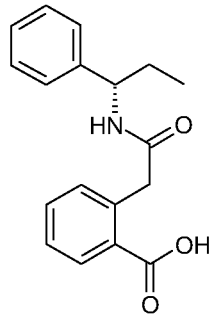


C-Cyclobutyl-C-(2-fluoro-phenyl)-methylamine.

One third of a solution of cyclobutyl bromide (5.0 g, 41.3 mmol) in anhydrous tetrahydrofuran (24 mL) was stirred with magnesium (1.11 g, 46.3 mmol) under reflux. The remaining solution was added dropwise over a period of 15 minutes, and the stirring at reflux continued for 30 min. To the obtained solution 2-fluorobenzonitrile (1.2 g) in THF (15 ml) was added dropwise at 0°C. The mixture was stirred for 5.5 h at 0°C followed by addition of methanol (30 ml) and sodium borohydride (1.13 g). The reaction mixture was stirred for 16 hours at ambient temperature and concentrated. The residue was partitioned between chloroform (3x100 ml) and water, and the pH was adjusted to 1. The mixture was extracted with chloroform. The aqueous phase was adjusted to pH=10, and extracted with chloroform (3 x 100 ml). The combined organic layers were dried, evaporated and

purified by column chromatography on silica gel (ethyl acetate/petroleum ether = 1/1) to afford the title amine (0.45 g, yield: 7.9%) ^{1}H NMR (CD_3OD, 400 MHz) 7.49-7.38 (m, 2H), 7.30-7.15 (m, 2H), 4.50 (d, J = 10.4 Hz, 1H), 3.00-2.90 (m, 1H), 2.29-2.21 (m, 1H), 2.09-1.71 (m, 5H).

Synthesis of acid-amides of the general formula XIX:

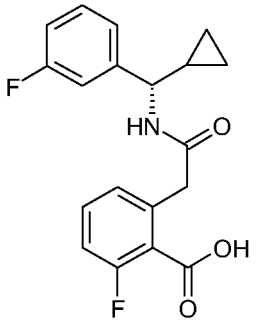


2-[((S)-1-Phenyl-propylcarbamoyl)-methyl]-benzoic acid.

A mixture of homophthalic anhydride (810 mg, 5 mmol) and (S)-(–)-1-phenylpropylamine (676 mg, 5 mmol) in acetonitrile (15 ml) was heated under microwave irradiation at +150°C for 15 min. White precipitate was collected by filtration, washed with heptane and dried in vacuo to give pure title compound in 72% yield (1.065g). Alternatively, to a stirred solution of homophthalic anhydride (16.214 g, 0.1 mol) in acetonitrile (100 ml) (S)-(–)-1-phenylpropylamine (13.83 g, 0.102 mol) was added dropwise (exothermic reaction) and the obtained reaction mixture was refluxed for 5 min. It was allowed to cool and the product was isolated by filtration as above to give 23.4 g of colourless solid, 79% yield. LC-MS (m/z) 298.5 (MH^+); t_R = 1.11. ^{1}H NMR (500 MHz, DMSO-d_6): 0.84 (t, J=7.3 Hz, 3H), 1.67 (quintet, J=7.3 Hz, 2H), 3.85 (d of AB system, J=15.1 Hz, 1H), 3.95 (d of AB system, J=15.1 Hz, 1H), 4.66 (q, J=7.6 Hz, 1H), 7.2 (unres. m, 1H), 7.25-7.34 (m, 5H), 7.45 (t, J=7.3 Hz, 1H), 7.8 (d, J=7.8 Hz, 1H), 8.39 (br. d, J=7.7 Hz, 1H, NH).

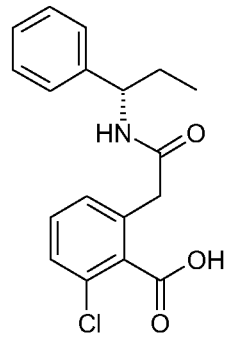
The following compounds were obtained analogously from corresponding homophthalic anhydrides of general formula and amines of the general formula XVIII and XI, respectively. The reactions were usually run at room temperature and the products were isolated by extraction or filtration and used in the next steps without

further purification.



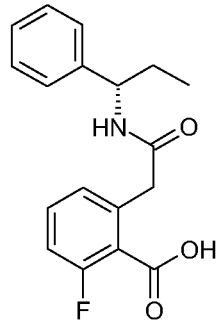
2-({[(S)-Cyclopropyl-(3-fluoro-phenyl)-methyl]-carbamoyl}-methyl)-6-fluoro-benzoic acid.

LC-MS (m/z) 346.2 (MH^+); t_R = 1.14. ^{1}H NMR (500 MHz, DMSO-d_6): 0.35 (m, 1H), 0.39 (m, 1H), 0.5 (m, 2H), 1.12 (m, 1H), 3.68 & 3.74 (two d of AB system, J= 15.2 Hz, 2H, CH_2), 4.25 (t, J= 8.5 Hz, 1H), 7.05 (dt, J=2.2, 8.05 Hz, 1H), 7.13 (d, J= 8.1 Hz, 1H), 7.16-7.21 (m, 2H), 7.35 (m, 1H), 7.42 (m, 1H), 8.66 (d, J= 8.2 Hz, 1H, NH), 13.44 (br., CO_2H).



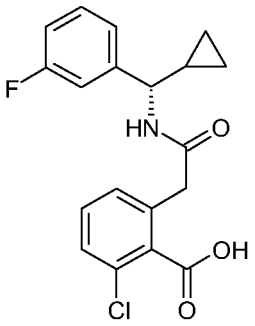
2-Chloro-6-[((S)-1-phenyl-propylcarbamoyl)-methyl]-benzoic acid.

LC-MS (m/z) 332.2 (MH^+); t_R = 1.19. ^{1}H NMR (500 MHz, DMSO-d_6): 0.84 (t, J=7.3 Hz, 3H), 1.68 (quintet, J=7.3 Hz, 2H), 3.54 & 3.61 (two d of AB system, J=15.3 Hz, 2H, CH_2), 4.67 (q, J=7.5 Hz, 1H), 7.19-7.4 (m, 8H), 8.48 (d, J=8.3 Hz, 1H, NH), 13.64 (br., CO_2H).

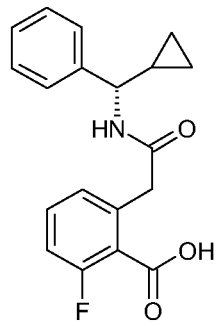


2-Fluoro-6-[((S)-1-phenyl-propylcarbamoyl)-methyl]-benzoic acid.

LC-MS (m/z) 316.3 (MH^+); t_R = 1.13. ^1H NMR (500 MHz, $CDCl_3$): 0.79 (t, J= 7.4 Hz, 3H), 1.76 (d of quintet, 2H, diastereotopic CH_2 of Et), 3.64 (s, 2H, CH_2), 4.75 (q, J= 7.7 Hz, 1H), 7.04 (t, J=8.5 Hz, 1H), 7.08 (d, J=7.7 Hz, 1H), 7.17-7.23 (overlapping m, 3H), 7.24-7.28 (overlapping m, 2H), 7.32 (m, 1H), 7.45 (br d, J= 8.1 Hz, 1H, NH). 8.48 (d, J=8.3 Hz, 1H, NH), 11.14 (br., CO_2H).

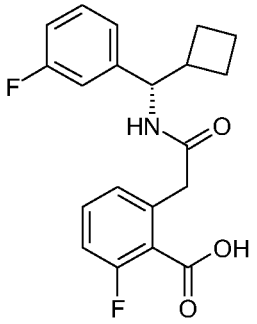


2-Chloro-6-({[(S)-cyclopropyl-(3-fluoro-phenyl)-methyl]-carbamoyl}-methyl)-benzoic acid.



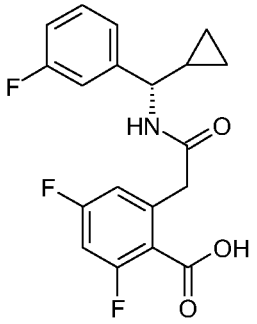
2-{[((S)-Cyclopropyl-phenyl-methyl)-carbamoyl]-methyl}-6-fluoro-benzoic acid.

LC-MS (m/z) 328.4 (MH^+); t_R = 1.12.

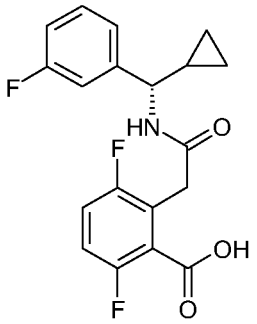


2-({[(S)-Cyclobutyl-(3-fluoro-phenyl)-methyl]-carbamoyl}-methyl)-6-fluoro-benzoic acid.

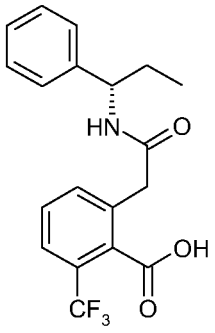
LC-MS (m/z) 360.2 (MH^+); t_R = 1.31.



2-({[(S)-Cyclopropyl-(3-fluoro-phenyl)-methyl]-carbamoyl}-methyl)-4,6-difluoro-benzoic acid.



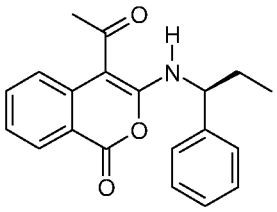
2-({[(S)-Cyclopropyl-(3-fluoro-phenyl)-methyl]-carbamoyl}-methyl)-3,6-difluoro-benzoic acid.



2-[((S)-1-Phenyl-propylcarbamoyl)-methyl]-6-trifluoromethyl-benzoic acid.

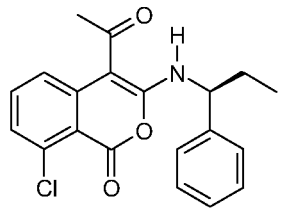
LC-MS (m/z) 366.4 (MH^+); t_R = 1.24.

Synthesis of compounds of the general formula XXIII:



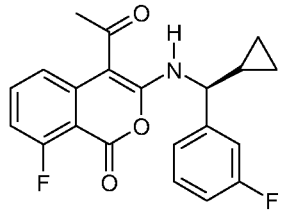
4-Acetyl-3-((S)-1-phenyl-propylamino)-isochromen-1-one.

A mixture of 2-[((S)-1-phenyl-propylcarbamoyl)-methyl]-benzoic acid (10 g), acetic anhydride (50 ml), and N,N-dimethylaminopyridine (100 mg) was heated at gentle reflux (T_{max} = +124°C) for 7 min and evaporated in vacuo at +50°C to give the title compound as a yellow-brown solid (11.1 g, purity 98% by NMR). LC-MS (m/z) 322.3 (MH^+); t_R = 1.72. ^{1}H NMR (500 MHz, DMSO-d_6): 0.89 (t, J=7.2 Hz, 3H), 1.86-1.97 (m, 2H), 2.56 (s, 3H), 4.95 (q, J= 7.1 Hz, 1H, CH-NH), 7.26 (t, J=7.5 Hz, 1H), 7.29 (unres. m, 1H), 7.36-7.41 (unres m., 3H), 7.71 (t, J=7.5 Hz, 1H), 7.75 (d, J=8.3 Hz, 1H), 7.98 (d, J=7.8 Hz, 1H), 11.53 (d, J=7.6 Hz, 1H, NH). ^{13}C APT NMR (125 MHz, DMSO-d_6, δ(DMSO-d_6)=39.87 ppm): 10.68 (CH_3), 30.0 (CH_2), 31.57 (CH_3), 57.01 (CH), 92.44 (C), 114.88 (C), 124.2 (CH), (CH), 124.26 (CH), 126.65 (CH), 127.8 (CH), 129.05 (CH), 129.93 (CH), 135.71 (CH), 138.68 (C), 141.86 (C), 158.51 (C), 160.55 (C), 194.82 (C, MeCO).



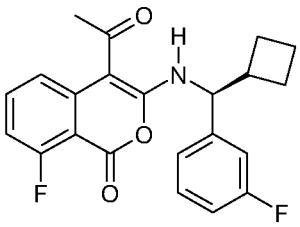
4-Acetyl-8-chloro-3-((S)-1-phenyl-propylamino)-isochromen-1-one.

2-Chloro-6-[((S)-1-phenyl-propylcarbamoyl)-methyl]-benzoic acid (11.4 g) and acetic anhydride (50 ml) were heated at 103°C for 60 min and evaporated to give 12.45 g of brown oil (purity ca 95% according to ^{1}H NMR). LC-MS (m/z) 355.2 (MH^+); t_R = 1.82. Analytically pure sample was prepared by recrystallisation (9 g from 30 ml of hot MeCN) to give the title compound (4.41 g) as a pale yellow solid after cooling (dry ice – EtOH bath) and filtration. LC-MS (m/z) 355.2 (MH^+); t_R = 1.82. ^{1}H NMR (500 MHz, DMSO-d_6): 0.88 (t, J=7.4 Hz, 3H), 1.92 (m, 2H), 2.5 (s, 3H), 4.92 (q, J=7.3 Hz, 1H, CH-NH), 7.27-7.33 (m, 2H), 7.39 (d (unres. m), J= 4.3 Hz, 4H), 7.59-7.66 (m, 2H), 11.11 (d, J=7.8 Hz, 1H, NH).



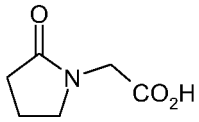
4-Acetyl-3-{[(S)-cyclopropyl-(3-fluoro-phenyl)-methyl]-amino}-8-fluoro-isochromen-1-one.

A mixture of 2-({[(S)-cyclopropyl-(3-fluoro-phenyl)-methyl]-carbamoyl}-methyl)-6-fluoro-benzoic acid (12.92 g, 37.41 mmol) and acetic anhydride (100 mL, 1 mol) was stirred at +65°C for 20 hours and evaporated in vacuo (65°C, 10 mbar, 2 hours) to give the title compound as a thick brown oil, which was used in the next step without purification (14.30 g, yield 103.5%, purity 95% according to ^{1}H NMR). LC-MS (m/z) 370.1 (MH^+); t_R = 1.65. ^{1}H NMR (500 MHz, DMSO-d_6): 0.45-0.59 (m, 3H), 0.64 (m, 1H), 1.41 (m, 1H), 2.53 (s, 3H), 4.36 (t (unres. dd), 1H), 7.03 (dd, J = 8.3, 10.7 Hz, 1H), 7.12 (dt, J = 1.9, 8.5Hz, 1H), 7.27 (d, J=10.2 Hz, 1H), 7.3 (d, J=7.8 Hz, 1H), 7.42 (q, J=7.8 Hz, 1H), 7.53 (d, 8.5 Hz, 1H), 7.7 (m, 1H), 11.3 (d, J=7.3 Hz, 1H, NH).



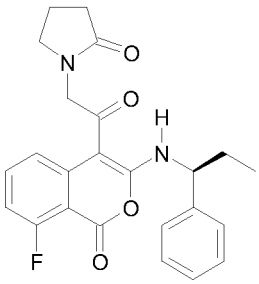
4-Acetyl-3-{[(S)-cyclobutyl-(3-fluoro-phenyl)-methyl]-amino}-8-fluoro-isochromen-1-one.

LC-MS (m/z) 384.4 (MH^+); t_R = 1.82.



(2-Oxo-pyrrolidin-1-yl)-acetic acid.

A mixture of 2-pyrrolidone (2.66 ml, 34 mmol) and NaH (60% in oil, 1.25 g, 31.3 mmol) in THF (75 ml) was stirred until gas evolution ceased (30 min). tert-Butyl 2-bromoacetate (4.45 ml, 30 mmol) was added and stirred at r.t. overnight then partitioned between water (200 ml) and ethyl acetate (200 ml) to give intermediate 2-(oxo-pyrrolidin-1-yl)-acetic acid tert-butyl ester (5.8 g). It was dissolved in acetic acid (40 ml) and conc. aq. HCl (6 ml) with gas evolution observed. After stirring at r.t. for 2 hours it was evaporated and recrystallized from toluene/ethanol to give 2.58 g of the title compound (60% yield). ^{1}H NMR (500 MHz, DMSO-d_6): 1.95 (quintet, J= 7.7 Hz, 2H), 2.24 (t, J= 8.1 Hz, 2H), 3.38 (m, overalapping with H_2O (3.35 ppm), 2H), 3.91 (s, 2H), 12.77 (br., 1H).

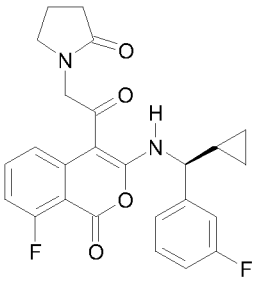


1-{2-[8-Fluoro-1-oxo-3-((S)-1-phenyl-propylamino)-1H-isochromen-4-yl]-2-oxo-ethyl}-pyrrolidin-2-one.

To a solution of 2-oxo-pyrrolidin-1-yl-acetic acid (1.56 g, 10.9 mmol) in 1,2-dichloroethane (40 ml) oxalyl chloride (0.95 ml, 10.9 mmol) and DMF (1 drop) were

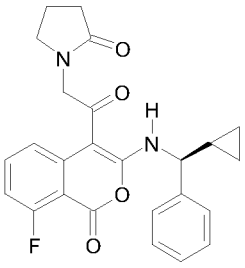
added with gas evolution observed. After stirring at r.t. for 1 hour, 2-fluoro-6-[((S)-1-phenyl-propylcarbamoyl)-methyl]-benzoic acid (1.56 g, 4.95 mmol), triethylamine (2.1 ml, 14.9 mmol) and DMAP (85 mg, 0.1 eq.) were added and stirred at r.t. overnight. It was partitioned between mixture of 0.2 M aq. HCl (100 ml) – brine (100 ml) and ethyl acetate (250 ml), washed with water and evaporated to give 1.89 g of crude title compound used in the next step without further purification.

^{1}H NMR (500 MHz, DMSO-d_6, selected resonances): 4.51 & 4.58 (two d of AB system, J=16.3 Hz, N-CH_2-CO), 4.99 (q, J= 7.5 Hz, 1H, C<u>H</u>-NH), 11.31 (d, J= 7.9 Hz, 1H, NH).



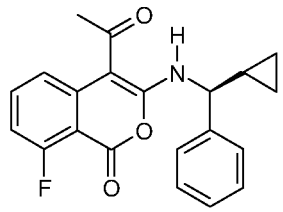
1-[2-(3-{[(S)-Cyclopropyl-(3-fluoro-phenyl)-methyl]-amino}-8-fluoro-1-oxo-1H-isochromen-4-yl)-2-oxo-ethyl]-pyrrolidin-2-one.

The title compound was prepared analogously and purified by flash chromatography on SiO_2. LC-MS (m/z) 453.3 (MH^+); t_R = 1.48.



1-(2-{3-[((S)-Cyclopropyl-phenyl-methyl)-amino]-8-fluoro-1-oxo-1H-isochromen-4-yl}-2-oxo-ethyl)-pyrrolidin-2-one.

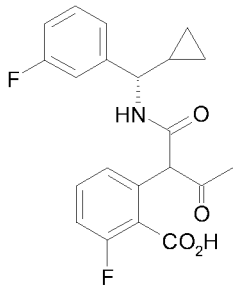
The title compound was prepared analogously. LC-MS (m/z) 435.3 (MH^+); t_R = 1.43.



4-Acetyl-3-[((S)-cyclopropyl-phenyl-methyl)-amino]-8-fluoro-isochromen-1-one.

LC-MS (m/z) 352.6 (MH^+); t_R = 1.62. ^{1}H NMR (500 MHz, DMSO-d_6): 0.48 (m, 2H), 0.54 (m, 1H), 0.64 (m, 1H), 1.39 (m, 1H), 2.53 (s, 3H), 4.39 (t (unres. dd), 1H), 7.04 (dd, J = 8.2, 10.8 Hz, 1H), 7.3 (t, J=7.3 Hz, 1H), 7.39 (t, J=7.6 Hz, 2H), 7.43 (d, J=7.3 Hz, 2H), 7.53 (d, 8.5 Hz, 1H), 7.7 (m, 1H), 11.39 (d, J=7.5 Hz, 1H, NH).

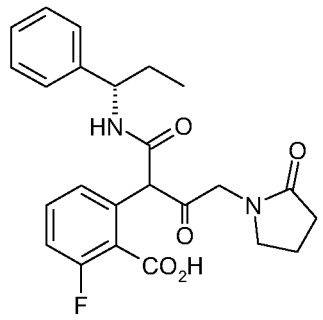
Hydrolysis of compounds of the general formula XXIII into compounds of the general formula XXV:



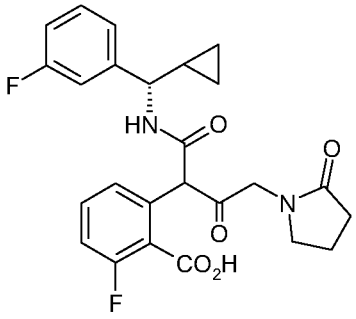
2-(1-{[(S)-Cyclopropyl-(3-fluoro-phenyl)-methyl]-carbamoyl}-2-oxo-propyl)-6-fluoro-benzoic acid.

4-Acetyl-3-{[(S)-cyclopropyl-(3-fluoro-phenyl)-methyl]-amino}-8-fluoro-2-benzopyran-1-one (14.30 g, 38.72 mmol) was dissolved in a mixture of tetrahydrofuran (50 mL) and methanol (50 mL) and placed on an ice/water bath with stirring. NaOH (1 M in H_2O, 100 ml) was added and stirring continued for 1 hour. The cold bath removed and the mixture was allowed to warm to r.t. (20°C) during 1 hour. The reaction mixture was poored into ice-water mixture (200 g + 200 ml), followed by slow addition of 2 M aq. HCl (200 mL) and extracted with ethyl acetate (200 mL), washed with sat. aq. NaCl, dried (Na_2SO_4), filtered and evaporated to give the title compound (14.65 g, yield 97.7%) as a pale brown foam. The crude product was used in the next step without further purification. LC-MS (m/z) 388.3 (MH^+); t_R = 1.2. ^{1}H NMR (500 MHz, DMSO-d_6): a mixture of tautomers and diastereoisomers.

The following compounds were prepared analogously:

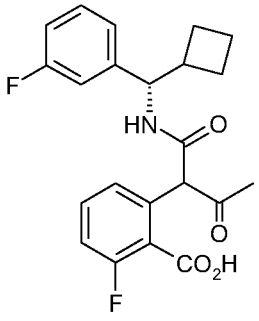


2-Fluoro-6-[2-oxo-3-(2-oxo-pyrrolidin-1-yl)-1-((S)-1-phenyl-propylcarbamoyl)-propyl]-benzoic acid.



2-[1-{[(S)-Cyclopropyl-(3-fluoro-phenyl)-methyl]-carbamoyl}-2-oxo-3-(2-oxo-pyrrolidin-1-yl)-propyl]-6-fluoro-benzoic acid.

LC-MS (m/z) 471.4 (MH^+); t_R = 1.17.

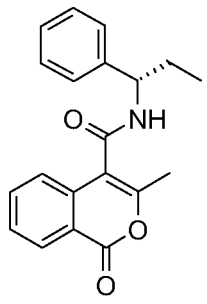


2-(1-{[(S)-Cyclobutyl-(3-fluoro-phenyl)-methyl]-carbamoyl}-2-oxo-propyl)-6-fluoro-benzoic acid.

LC-MS (m/z) 402.2 (MH^+); t_R = 1.36.

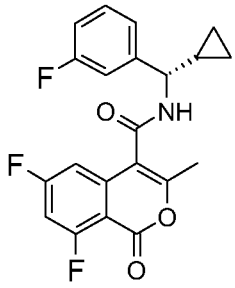
Synthesis of compounds of the general formula XXIV and XXV: Compounds of general formula XXIV obtained analogously as described above for compounds of

general formula XXIII but at higher temperature (150°C, 15 min) and they are usually hydrolyzed to compounds of the general formula XXV without isolation and characterization, so only two examples of compounds XXIV are given below.



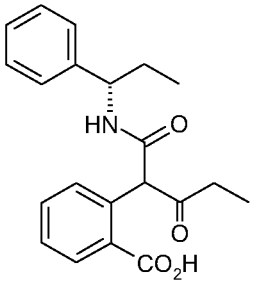
3-Methyl-1-oxo-1H-isochromene-4-carboxylic acid ((S)-1-phenyl-propyl)-amide.

The title compound was purified by flash chromatography on SiO_2. LC-MS (m/z) 322.1 (MH^+); t_R = 1.27. ^1H NMR (500 MHz, $CDCl_3$): 1.03 (t, J=7.3 Hz, 3H), 1.91-2.06 (complex m, 2H, CH_2), 2.19 (s, 3H), 5.11 (q, J=7.8 Hz, 1H), 7.06 (br. d, J=8.3 Hz, 1H, NH), 7.22-7.33 (m, 3H), 7.36-7.43 (m, 4H), 7.54 (t, J= 7.6 Hz, 1H), 7.95 (d, J= 7.8 Hz, 1H). ^1H NMR (500 MHz, DMSO-d_6): 0.92 (t, J= 7.3 Hz, 3H), 1.76 (m, 2H), 2.18 (s, 3H), 4.93 (q, J=8.3 Hz, 1H), 7.21-7.41 (m, 6H), 7.59 (t, J=7.7 Hz, 1H), 7.82 (t, J=7.2 Hz, 1H), 8.17 (d, J=7.8 Hz, 1H), 9.1 (br. d, J=8.4 Hz, 1H, NH).



6,8-Difluoro-3-methyl-1-oxo-1H-isochromene-4-carboxylic acid [(S)-cyclopropyl-(3-fluoro-phenyl)-methyl]-amide.

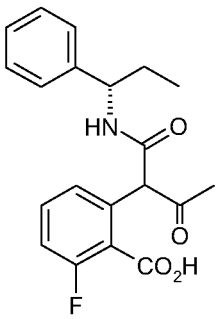
The title compound was purified by flash chromatography on SiO_2. LC-MS (m/z) 388.4 (MH^+); t_R = 1.39.



2-[2-Oxo-1-((S)-1-phenyl-propylcarbamoyl)-butyl]-benzoic acid.

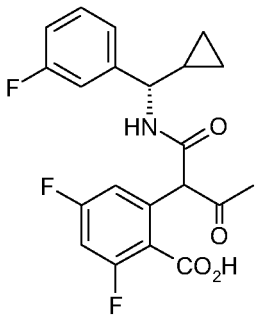
A sealed mixture of 2-[((S)-1-phenyl-propylcarbamoyl)-methyl]-benzoic acid (409 mg, 1.38 mmol), propionic anhydride (10 ml) and 4-N,N-dimethylaminopyridine (15 mg) was heated under microwave irradiation at 150°C for 20 min and partitioned between 1M HCl (50 ml) and ethyl acetate (100 ml). The organic layer was washed with sat. aq. $NaHCO_3$ (2x50 ml) and brine and concentrated in vacuo. To the obtained residue methanol (25 ml) tetrahydrofurane (25 ml) and 2M aq. NaOH (50 ml) was added and stirred at r.t. for 1 hour. The organic volatiles were removed in vacuo and the pH was adjusted to 1 with 3M aq. HCl. The crude title product (495 mg) was separated by extraction with ethyl acetate (150 ml) and used in the next step without further purification. ^{1}H NMR (500 MHz, DMSO-d_6): a mixture of tautomers and diastereoisomers.

The following compounds were obtained analogously:



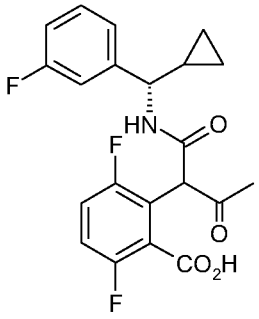
2-Fluoro-6-[2-oxo-1-((S)-1-phenyl-propylcarbamoyl)-propyl]-benzoic acid.

LC-MS (m/z) 358.4 (MH^+); t_R = 1.17.



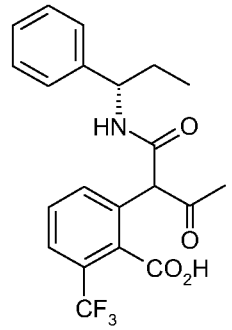
2-(1-{[(S)-Cyclopropyl-(3-fluoro-phenyl)-methyl]-carbamoyl}-2-oxo-propyl)-4,6-difluoro-benzoic acid.

LC-MS (m/z) 406.7 (MH^+); t_R = 1.3.



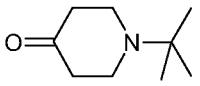
2-(1-{[(S)-Cyclopropyl-(3-fluoro-phenyl)-methyl]-carbamoyl}-2-oxo-propyl)-3,6-difluoro-benzoic acid.

LC-MS (m/z) 406.0 (MH^+); t_R = 0.72 (method B).



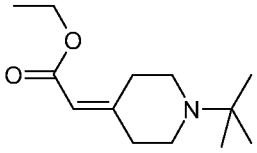
2-[2-Oxo-1-((S)-1-phenyl-propylcarbamoyl)-propyl]-6-trifluoromethyl-benzoic acid.

The title compound was used in the next step directly.



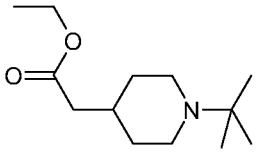
1-tert-Butyl-piperidin-4-one.

The title compound was prepared according to the described procedure: J.S. Amato, J.Y.L. Chung, R.J. Cvetovich, X. Gong, M. McLaughlin, R.A. Reamer *J. Org. Chem.* **2005**, *70*, 1930.



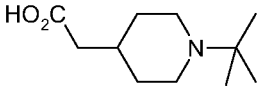
(1-tert-Butyl-piperidin-4-ylidene)-acetic acid ethyl ester.

A mixture of 1-tert-Butyl-piperidin-4-one (4.59 g, 23.6 mmol) and ethyl (triphenylphosphorylidene)acetate (10.3 g, 23.6 mmol) in toluene (100 mL) was stirred at reflux for 24 hours under nitrogen and evaporated in vacuo. The residue was purified by column chromatography on silica gel (petroleum ether/triethylamine = 100/1) to afford 5.1 g of the title compound as a pale yellow oil, 76.5% yield.



(1-tert-Butyl-piperidin-4-yl)-acetic acid ethyl ester.

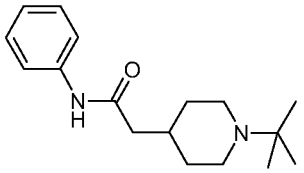
To a solution of (1-tert-butyl-piperidin-4-ylidene)-acetic acid ethyl ester (5.1 g, 22.7 mmol) in ethanol (50 mL) 10% Pd/C (0.6 g) was added and the mixture was stirred under the hydrogen atmosphere (42 psi) at ambient temperature for 14 hours. The catalyst was removed by filtration, and the filtrate was concentrated to give the title (4.03 g, yield 78%), which was used in the next step directly.



(1-tert-Butyl-piperidin-4-yl)-acetic acid.

To a solution of NaOH in water/ethanol (v/v = 40/10, 50 mL) (1-tert-butyl-piperidin-4-yl)-acetic acid ethyl ester (4.03 g, 17.8 mmol) was added and the mixture was stirred at r.t. overnight. 1 N aq. HCl was added to adjust the pH to 5. Volotiles were evaporated in vacuo, the residue was diluted with methanol (30 mL), and the insoluble inorganic salts were removed by filtration. The filtrate was concentrated and purified by column chromatography on silica gel (CH_2Cl_2/MeOH = 20/1 to 5/1) to give 0.7 g of title compound as a light grey powder. ^{1}H NMR (400 MHz, DMSO-d_6): 3.15-3.08

(br m, 2H), 2.30 (br t, J = 11.2 Hz, 2H), 2.05 (d, J = 6.4 Hz, 2H), 1.71-1.68 (m, 3H), 1.30-1.27 (m, 2H), 1.10 (s, 9H).

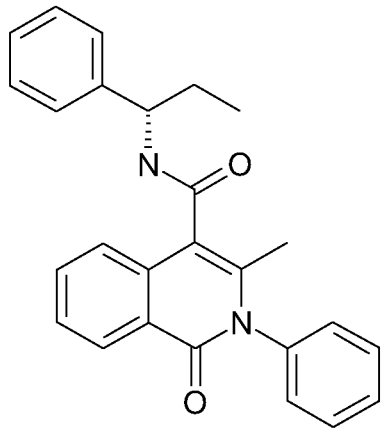


2-(1-tert-Butyl-piperidin-4-yl)-N-phenyl-acetamide.

To a mixture of (1-tert-butyl-piperidin-4-yl)-acetic acid (672 mg, 3.37 mmol), aniline (0.32 ml, 3.5 mmol), and HOBt (568 mg, 4.2 mmol) in DMF (20 ml), EDC (805 mg, 4.2 mmol) was added. It was stirred at r.t. for 2 hours and partitioned between water (200 ml) and ethyl acetate (200 ml). The organic phase was washed with 0.5 N aq. NaOH (2x50 ml) and brine (3x50 ml), dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by flash chromatography on (SiO_2, gradient heptane - ethyl acetate) to give 250 mg of the title compound. ^{1}H NMR (500 MHz, DMSO-d_6): 1.07 (s, 9H), 1.32 (br. m, 2H), 1.81 (br. d, 2H), 1.89 (m, 1H), 2.11 (br. t, 2H), 2.25 (d, 2H), 3.03 (br. d, 2H), 7.1 (t, 1H), 7.24 (br., 1H), 7.31 (t, 2H), 7.52 (d, 2H).

Compounds of the invention

Example 1

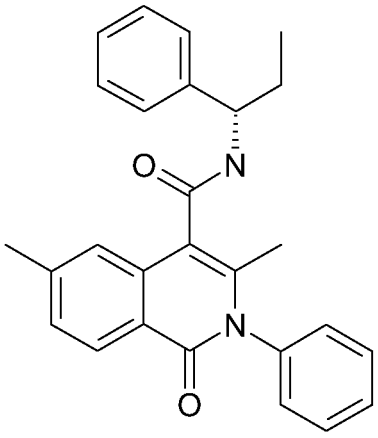


1a *3-Methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide.*

A solution of 3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid (212 mg, 0.76 mmol) in $SOCl_2$ (1.5 ml) and dimethylformamide (ca. 5 µL) was heated

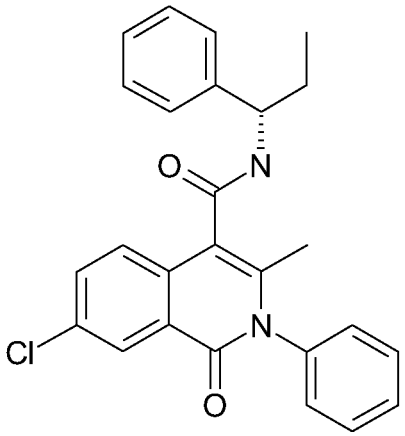
at reflux for 5 min. Volatiles were removed in vacuo to give 228 mg of the corresponding acid chloride as a pale brown solid. A portion of the acid chloride (110 mg, 0.37 mmol) was dissolved in 1,2-dichloroethane (2 ml) and (S)-(–)-1-phenylpropylamine (150 µL, 1.1 mmol) was added. The obtained suspension was shaked for 5 min, diluted with 1,2-dichloroethane (10 ml), washed with 1M aqueous HCl (3 x 5 ml) and water (5 ml). The organic phase was poured into SiO_2 (5 g), eluted with 1,2-dichloroethane (50 ml) and the product was eluted with 1:1 ethyl acetate – heptane to give 140 mg of colourless crystalline solid. Yield 95%. Alternatively, in another run the reaction mixture was partitioned between 2M HCl and heptane (10 ml) and the product was separated by filtration from the obtained biphasic system. LC-MS (m/z) 397.1 (MH^+); t_R = 1.44. ^{1}H NMR (500 MHz, $CDCl_3$): 1.0 (t, 3H), 1.93 (m, 5H), 5.16 (q, 1H), 6.7 (d, 1H), 7.07 (d, 2H), 7.31 (m, 1H), 7.36 (d, 4H), 7.4-7.5 (m, 5H), 7.63 (unres. t, 1H), 8.31 (d, 1H).

The following compounds were obtained analogously from the corresponding acid and amine and purified by preparative LC-MS:



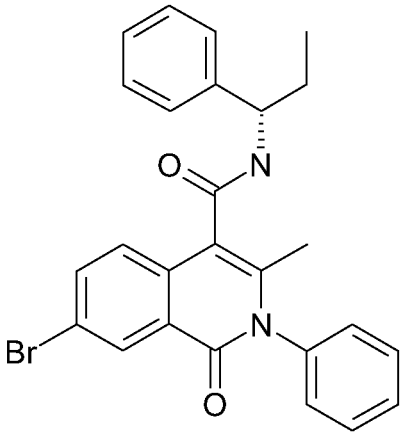
1b *3,6-Dimethyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide.*

LC-MS (m/z) 411.3 (MH^+); t_R = 0.8 (method B).



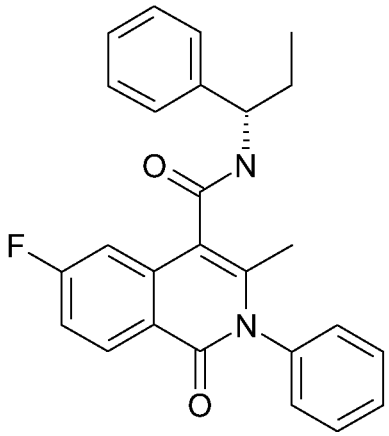
1c *7-Chloro-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide.*

LC-MS (m/z) 431.3 (MH^+); t_R = 0.86 (method B).



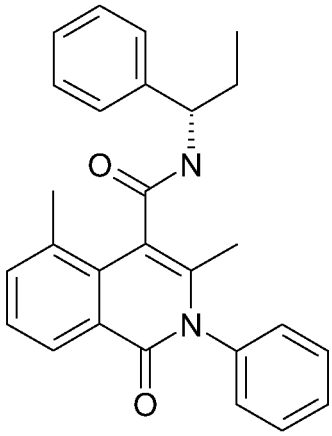
1d *7-Bromo-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide.*

LC-MS (m/z) 475.1 (MH^+, ^{79}Br); t_R = 0.87 (method B).



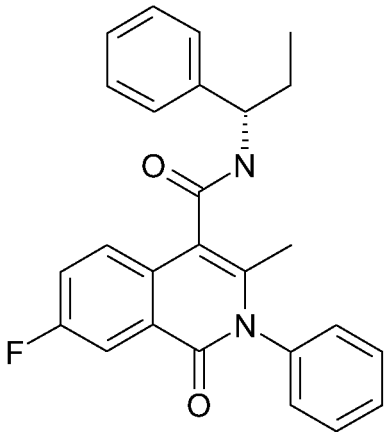
1e *6-Fluoro-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide.*

LC-MS (m/z) 415.5 (MH^+); t_R = 0.80 (method B).



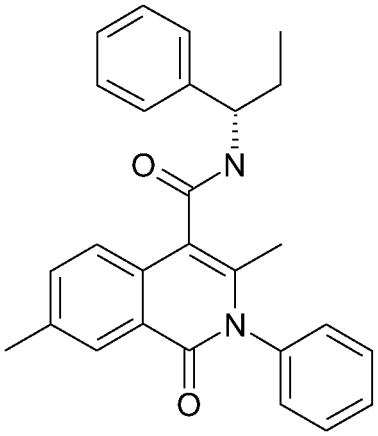
1f *3,5-Dimethyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide.*

LC-MS (m/z) 411.3 (MH^+); t_R = 0.84 (method B).



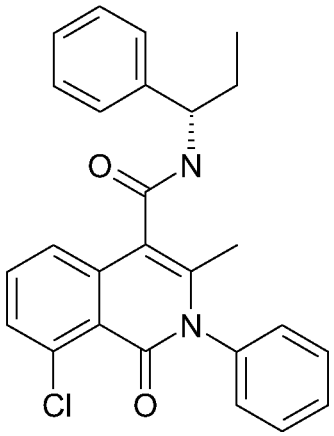
1g *7-Fluoro-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide.*

LC-MS (m/z) 415.4 (MH^+); t_R = 1.49.



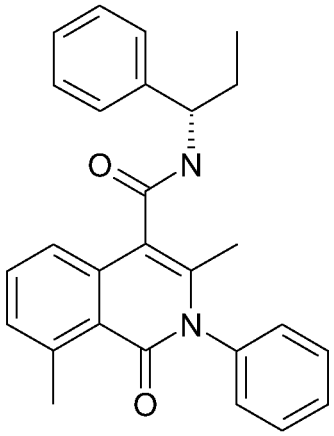
1h *3,7-Dimethyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide.*

LC-MS (m/z) 411.4 (MH^+); t_R = 1.5.



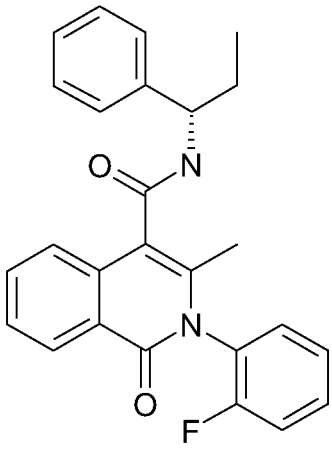
1i *8-Chloro-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide.*

LC-MS (m/z) 431.4 (MH^+); t_R = 1.54.



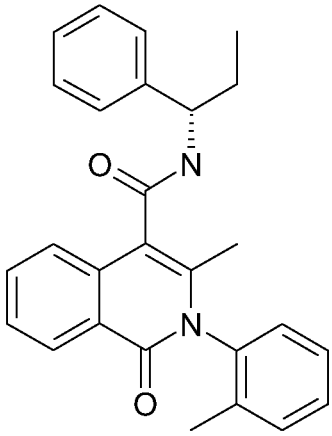
1j *3,8-Dimethyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide.*

LC-MS (m/z) 411.4 (MH^+); t_R = 1.5. ^{1}H NMR (250 MHz, DMSO-d_6, T=343K): 0.91 (t, 3H), 1.78 (overlapping s, 3H), 1.79 (overlapping m, 1H), 2.75 (s, 3H), 4.94 (q, 1H), 7.15-7.27 (m, 5H), 7.27-7.39 (m, 4H), 7.41-7.58 (m, 4H), 8.67 (d, 1H).



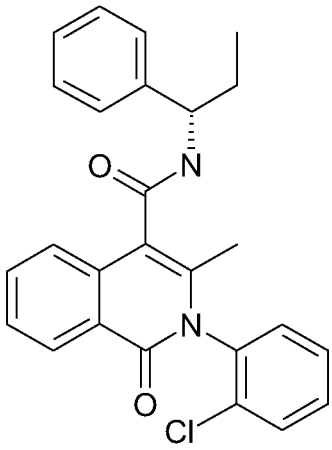
1k *2-(2-Fluoro-phenyl)-3-methyl-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide.*

LC-MS (m/z) 415.5 (MH^+); t_R = 1.49.



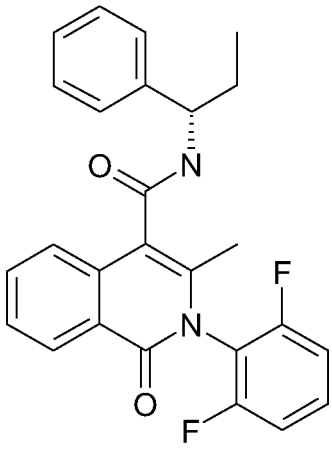
1l *3-Methyl-1-oxo-2-o-tolyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide.*

LC-MS (m/z) 411.5 (MH^+); t_R = 1.5.



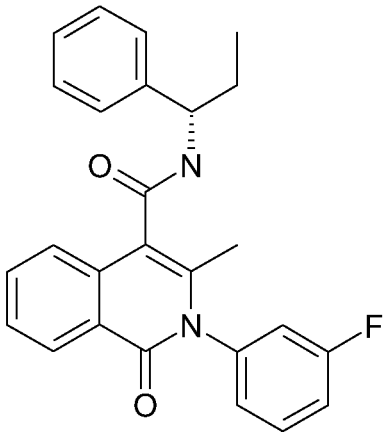
1m *2-(2-Chloro-phenyl)-3-methyl-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide.*

LC-MS (m/z) 431.2 (MH^+); t_R = 1.51.



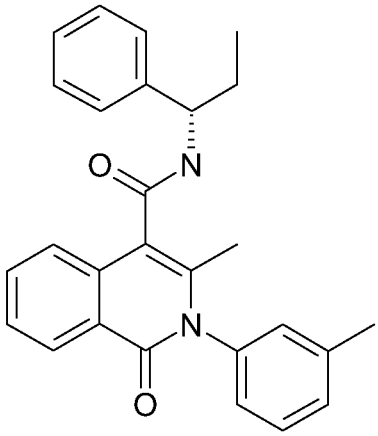
1n *2-(2,6-Difluoro-phenyl)-3-methyl-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide.*

LC-MS (m/z) 433.4 (MH^+); t_R = 1.54.



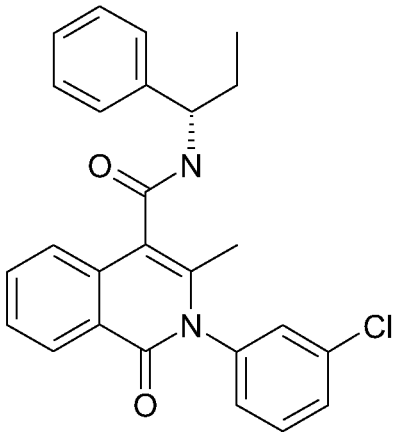
1o *2-(3-Fluoro-phenyl)-3-methyl-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide.*

LC-MS (m/z) 415.1 (MH^+); t_R = 1.48.



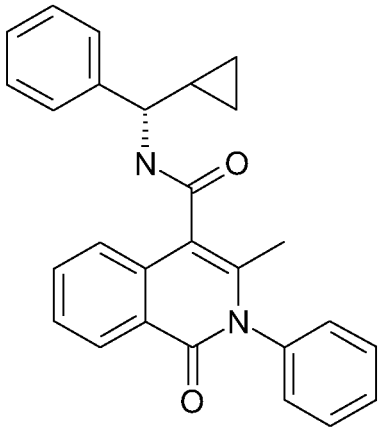
1p *3-Methyl-1-oxo-2-m-tolyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide.*

LC-MS (m/z) 411.5 (MH^+); t_R = 1.53.



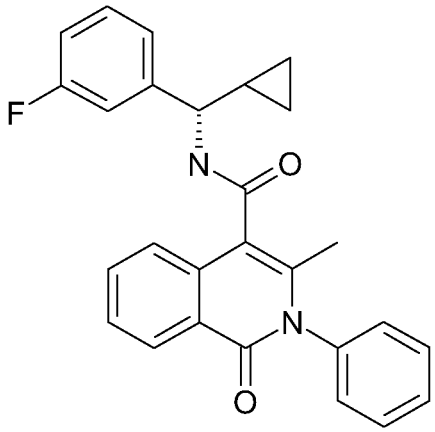
1q *2-(3-Chloro-phenyl)-3-methyl-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide.*

LC-MS (m/z) 431.2 (MH^+); t_R = 1.57.



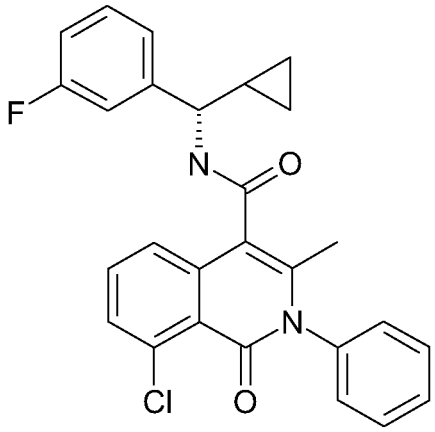
1r *3-Methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-cyclopropyl-phenyl-methyl)-amide.*

LC-MS (m/z) 409.4 (MH^+); t_R = 1.43. ^{1}H NMR (250 MHz, DMSO-d_6, T=343K): 0.45 (m, 2H), 0.56 (m, 2H), 1.25 (m, 1H), 1.88 (s, 3H), 4.51 (t, 1H), 7.21-7.37 (m, 5H), 7.42-7.59 (m, 7H), 7.7 (dt, 1H), 8.21 (dd, 1H), 8.89 (d, 1H).



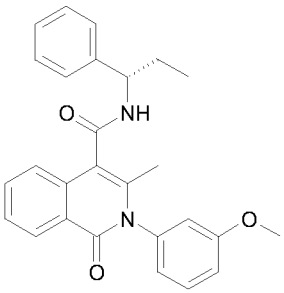
1s *3-Methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-cyclopropyl-(3-fluoro-phenyl)-methyl]-amide.*

LC-MS (m/z) 427.1 (MH^+); t_R = 1.48. ^{1}H NMR (250 MHz, DMSO-d_6, T=343K): 0.48 (m, 2H), 0.57 (m, 2H), 1.24 (m, 1H), 1.89 (s, 3H), 4.51 (t, 1H), 7.05 (m, 1H), 7.21-7.31 (m, 4H), 7.33-7.6 (m, 6H), 7.7 (dt, 1H), 8.21 (dd, 1H), 8.94 (d, 1H).



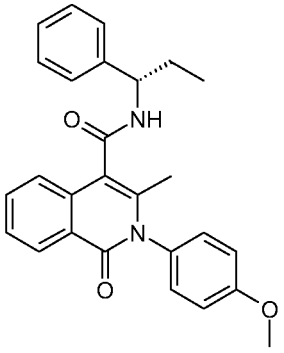
1t *8-Chloro-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-cyclopropyl-(3-fluoro-phenyl)-methyl]-amide.*

LC-MS (m/z) 461.6 (MH^+); t_R = 1.51. ^{1}H NMR (250 MHz, DMSO-d_6, T=343K): 0.48 (m, 2H), 0.58 (m, 2H), 1.27 (m, 1H), 1.87 (s, 3H), 4.5 (t, 1H), 7.06 (m, 1H), 7.21-7.32 (m, 4H), 7.32-7.45 (m, 2H), 7.45-7.66 (m, 5H), 8.95 (d, 1H).



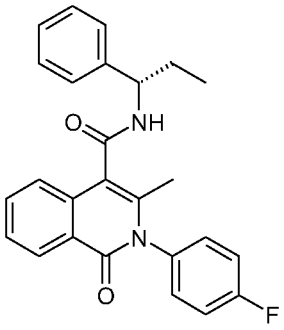
1aa 2-(3-Methoxy-phenyl)-3-methyl-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide.

LC-MS (m/z) 426.7 (MH^+); t_R = 1.43.



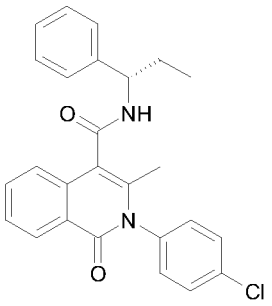
1ab 2-(4-Methoxy-phenyl)-3-methyl-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide.

LC-MS (m/z) 427.0 (MH^+); t_R = 1.43.



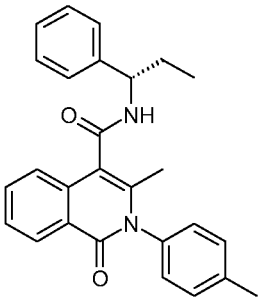
1ac 2-(4-Fluoro-phenyl)-3-methyl-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide.

LC-MS (m/z) 415.0 (MH^+); t_R = 1.43.



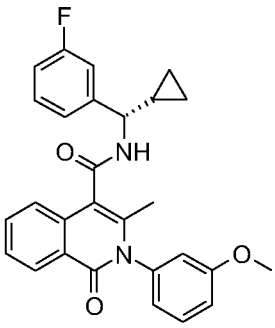
1ad 2-(4-Chloro-phenyl)-3-methyl-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide.

LC-MS (m/z) 431.1 (MH^+); t_R = 1.54.



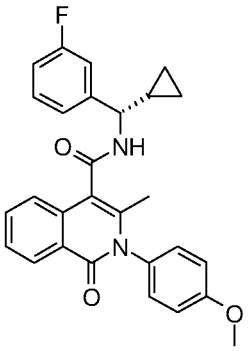
1ae 3-Methyl-1-oxo-2-p-tolyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide.

LC-MS (m/z) 411.2 (MH^+); t_R = 1.51.



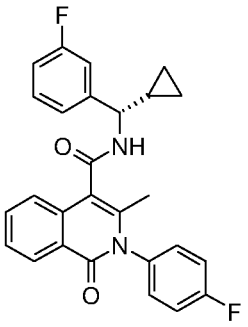
1af 2-(3-Methoxy-phenyl)-3-methyl-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-cyclopropyl-(3-fluoro-phenyl)-methyl]-amide.

LC-MS (m/z) 457.0 (MH^+); t_R = 1.47.



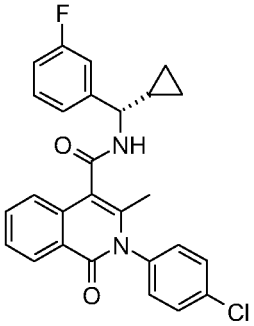
1ag 2-(4-Methoxy-phenyl)-3-methyl-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-cyclopropyl-(3-fluoro-phenyl)-methyl]-amide.

LC-MS (m/z) 457.1 (MH^+); t_R = 1.46.



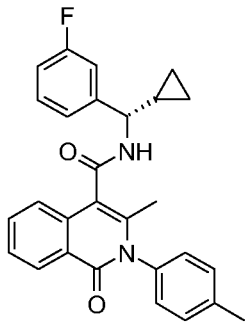
1ah 2-(4-Fluoro-phenyl)-3-methyl-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-cyclopropyl-(3-fluoro-phenyl)-methyl]-amide.

LC-MS (m/z) 445.6 (MH^+); t_R = 1.48.



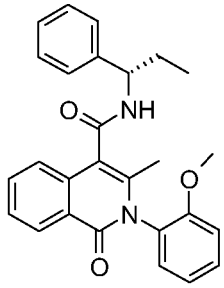
1ai 2-(4-Chloro-phenyl)-3-methyl-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-cyclopropyl-(3-fluoro-phenyl)-methyl]-amide.

LC-MS (m/z) 461.3 (MH^+); t_R = 1.57.



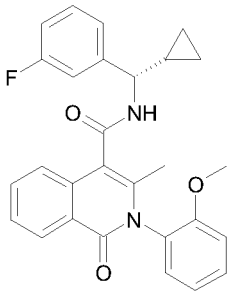
1aj 3-Methyl-1-oxo-2-p-tolyl-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-cyclopropyl-(3-fluoro-phenyl)-methyl]-amide.

LC-MS (m/z) 440.9 (MH^+); t_R = 1.54.



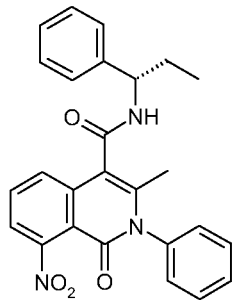
1ak 2-(2-Methoxy-phenyl)-3-methyl-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide.

LC-MS (m/z) 427.0 (MH^+); t_R = 1.39.



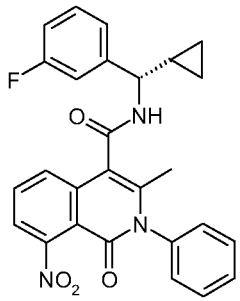
1al 2-(2-Methoxy-phenyl)-3-methyl-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-cyclopropyl-(3-fluoro-phenyl)-methyl]-amide.

LC-MS (m/z) 457.4 (MH^+); t_R = 1.43.



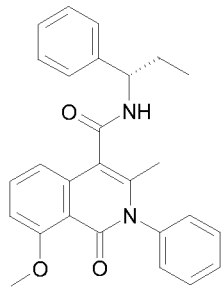
1am *3-Methyl-8-nitro-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide.*

LC-MS (m/z) 442.4 (MH^+); t_R = 1.46.



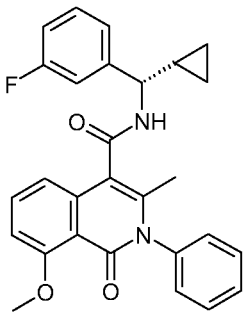
1an *3-Methyl-8-nitro-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-cyclopropyl-(3-fluoro-phenyl)-methyl]-amide.*

LC-MS (m/z) 442.4 (MH^+); t_R = 1.46.



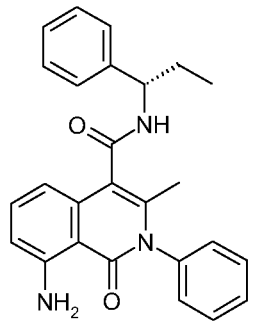
1ao *8-Methoxy-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide.*

LC-MS (m/z) 427.1 (MH^+); t_R = 1.32.



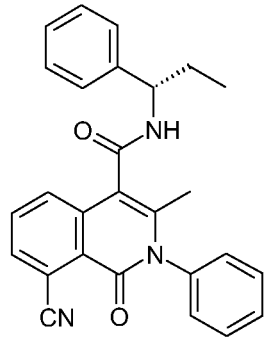
1ap *8-Methoxy-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-cyclopropyl-(3-fluoro-phenyl)-methyl]-amide.*

LC-MS (m/z) 457.4 (MH^+); t_R = 1.36.



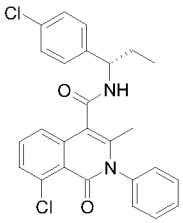
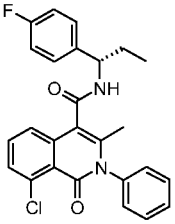
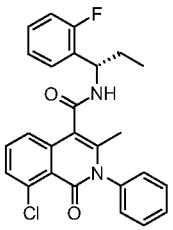
1aq *8-Amino-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide.*

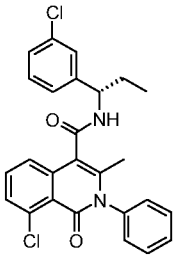
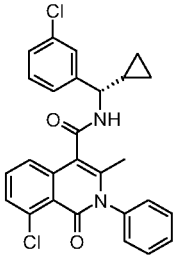
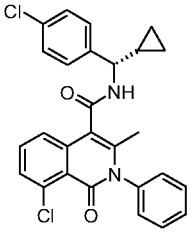
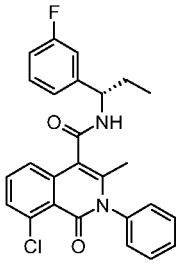
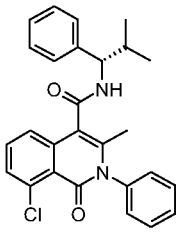
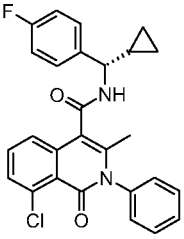
To a stirred solution of 3-methyl-8-nitro-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide (**1am,** 10 mg, 0.023 mmol) in tetrahydrofurane (0.15 ml) 2M aq. HCl (0.12 ml, 0.25 mmol) and Zn powder (45 mg, 0.69 mmol) was added. After 30 min the mixture was filtered and partitioned between ethyl acetate (4 ml) and sat. aq. $NaHCO_3$ (2 ml), then brine (3 ml). The organic solution was dried ($MgSO_4$) and evaporated to afford 5.9 mg of the title compound (70% yield). LC-MS (m/z) 412.4 (MH^+); t_R = 1.37.

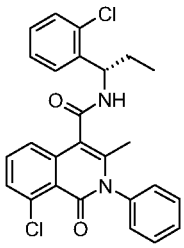
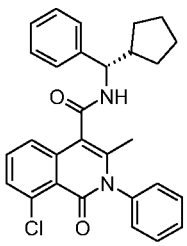
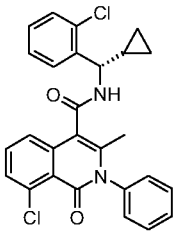
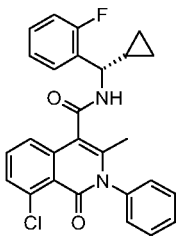
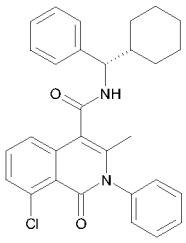
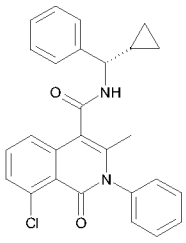


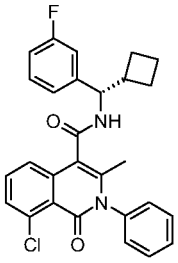
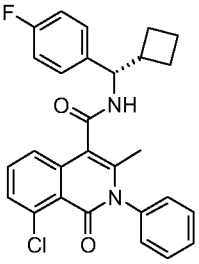
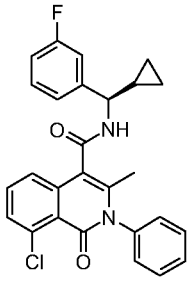
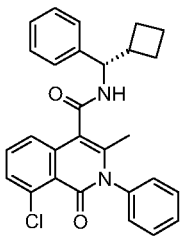
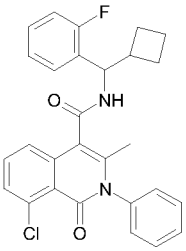
1ar *8-Cyano-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide.*
LC-MS (m/z) 422.1 (MH^+); t_R = 1.37.

The following compounds were obtained according to the general procedure: the corresponding acid of the general formula IX (0.04 mmol) and amine of the general formula XI (0.06 mmol) in DMF (0.5 ml) was stirred in the presence of Et_3N (3 eq.), EDC (1.5 eq.), and HOBT (1.5 eq.) at r.t. overnight followed by partitioning between ethyl acetate (2 ml) and 0.5 M NaOH (1 ml) and flash chromatography on SiO_2.

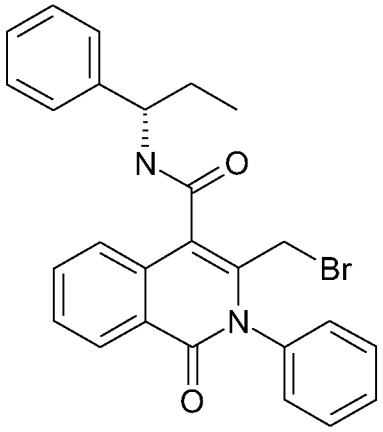
	Chemical name	**structure**	**t_R (min)**	**MW**	**m/z (MH^+)**
1as	*8-Chloro-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-1-(4-chloro-phenyl)-propyl]-amide*		1.63	465.4	465.4
1at	*8-Chloro-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-1-(4-fluoro-phenyl)-propyl]-amide*		1.52	448.9	449.3
1au	*8-Chloro-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-1-(2-fluoro-phenyl)-propyl]-amide*		1.52	448.9	449.4

1av	*8-Chloro-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-1-(3-chloro-phenyl)-propyl]-amide*		1.62	465.4	465.3
1aw	*8-Chloro-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-(3-chloro-phenyl)-cyclopropyl-methyl]-amide*		1.64	477.4	477.3
1ax	*8-Chloro-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-(4-chloro-phenyl)-cyclopropyl-methyl]-amide*		1.64	477.4	477.4
1ay	*8-Chloro-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-1-(3-fluoro-phenyl)-propyl]-amide*		1.53	448.9	449.3
1az	*8-Chloro-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-2-methyl-1-phenyl-propyl)-amide*		1.59	444.96	445.7
1ba	*8-Chloro-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-cyclopropyl-(4-fluoro-phenyl)-methyl]-amide*		1.53	460.9	461.5

1bb	*8-Chloro-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-1-(2-chloro-phenyl)-propyl]-amide*		1.61	465.4	465.3
1bc	*8-Chloro-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-cyclopentyl-phenyl-methyl)-amide*		1.72	470.99	471.8
1bd	*8-Chloro-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-(2-chloro-phenyl)-cyclopropyl-methyl]-amide*		1.6	477.4	477.2
1be	*8-Chloro-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-cyclopropyl-(2-fluoro-phenyl)-methyl]-amide*		1.6	460.9	461.6
1bf	*8-Chloro-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-cyclohexyl-phenyl-methyl)-amide*		1.8	485.0	485.4
1bg	*8-Chloro-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-cyclopropyl-phenyl-methyl)-amide*		1.5	442.9	443.5

1bh	*8-Chloro-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-cyclobutyl-(3-fluoro-phenyl)-methyl]-amide*		1.65	474.96	475.5
1bi	*8-Chloro-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-cyclobutyl-(4-fluoro-phenyl)-methyl]-amide*		1.64	474.96	475.5
1bl	*8-Chloro-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid [(R)-cyclopropyl-(3-fluoro-phenyl)-methyl]-amide*		1.52	460.9	461.5
1bn	*8-Chloro-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)cyclobutyl-phenyl-methyl)-amide*		1.61	456.97	457.3
1bo	*8-Chloro-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid [cyclobutyl-(2-fluoro-phenyl)-methyl]-amide*		1.64	474.96	475.4

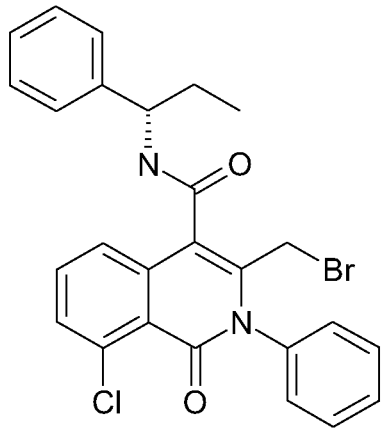
Example 2: Preparation of intermediates



3-Bromomethyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide.

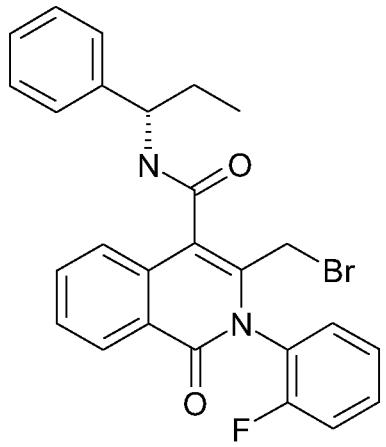
To a suspension of $CaCO_3$ (500 mg, 5 mmol) and 3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide (115 mg, 0.29 mmol) in 1,2-dichloroethane (5 ml) bromine (600 mg, 3.75 mmol) was added. The obtained mixture was sonicated at +33°C for 2 hours, diluted with 1,2-dichloroethane (20 ml) and poured into silica gel column (5 g). The excess of bromine was eluted with 1,2-dichloroethane and the product was eluted with 1:1 ethyl acetate – heptane to give 135 mg of brown solid. It was dissolved in ethyl acetate (0.5 ml) and precipitated with heptane (20 ml) to give 100 mg of yellow-brown solid. Yield 72%. LC-MS (m/z) 475.2 (MH^+, ^{79}Br); t_R = 1.59. ^1H NMR (500 MHz, DMSO-d_6, a mixture of two interconverting rotamers): 0.95 (br, 3H, CH_3), 1.74 and 1.82 (two unres. m, 2 x 1H, CH_2), 4.0 (unres. m, 1H, CH_2Br), 4.21 and 4.35 (two unres. m, 2 x 0.5H, CH_2Br), 4.97 (q, 1H, CH), 7.1 (br, 0.5H), 7.24 (br, 0.5H), 7.28-7.21 (br m, 11.5H), 7.89 (br, 0.5H), 8.25 (br, 1H), 9.28 (d, 1H, NH).

The following compounds were obtained analogously:



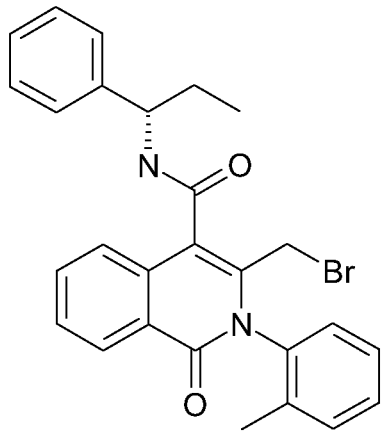
3-Bromomethyl-8-chloro-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide.

The crude product was used in the next step without further purification. LC-MS (m/z) 511.3 (MH^+, ^{79}Br); t_R = 1.68.



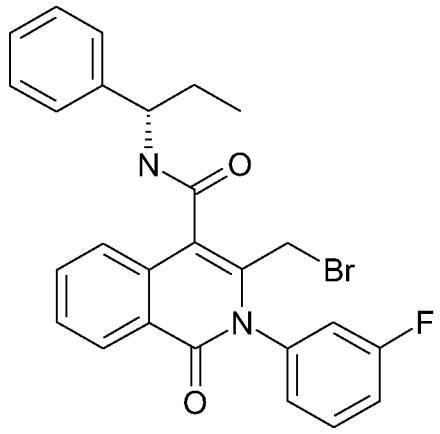
3-Bromomethyl-2-(2-fluoro-phenyl)-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide.

The crude product was used in the next step without further purification. LC-MS (m/z) 493.3 (MH^+, ^{79}Br); t_R = 1.62.



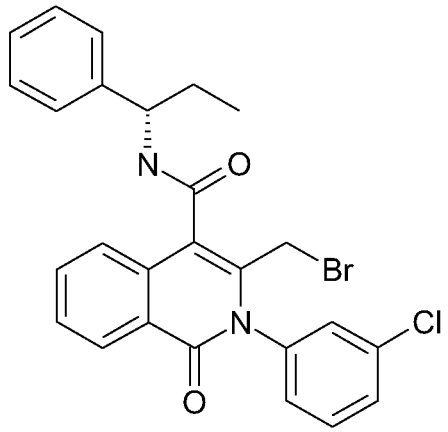
3-Bromomethyl-1-oxo-2-o-tolyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide.

The crude product was used in the next step without further purification. LC-MS (m/z) 489.3 (MH^+, ^{79}Br); t_R = 1.65.



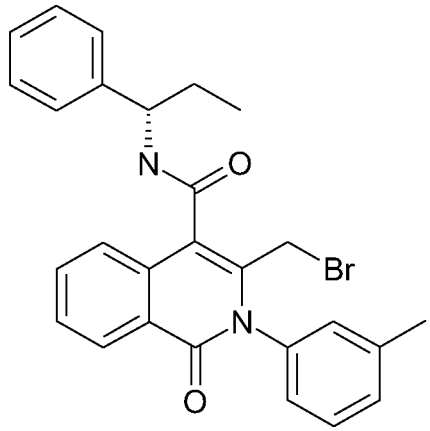
3-Bromomethyl-2-(3-fluoro-phenyl)-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide.

LC-MS (m/z) 493.5 (MH^+, ^{79}Br); t_R = 0.80 (method B).



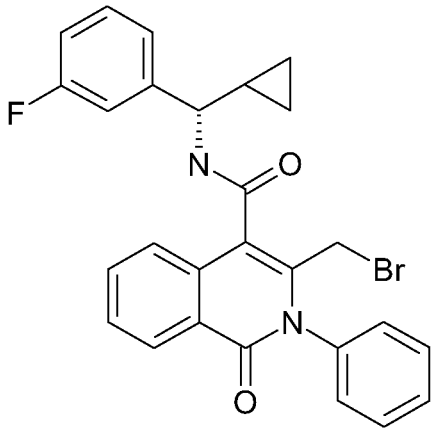
3-Bromomethyl-2-(3-chloro-phenyl)-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide.

LC-MS (m/z) 511.5 (MH^+, ^{81}Br); t_R = 0.84 (method B).



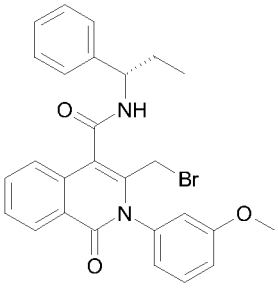
3-Bromomethyl-1-oxo-2-m-tolyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide.

LC-MS (m/z) 489.2 (MH^+, ^{79}Br); t_R = 0.86 (method B).



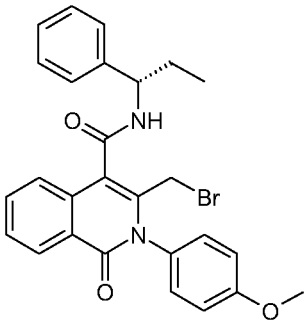
3-Bromomethyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-cyclopropyl-(3-fluoro-phenyl)-methyl]-amide.

LC-MS (m/z) 505.1 (MH^+); t_R = 1.62.



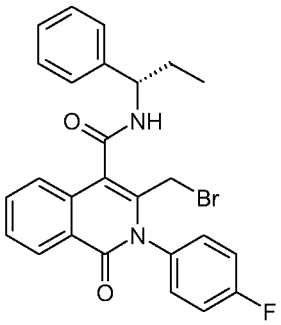
3-Bromomethyl-2-(3-methoxy-phenyl)-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide.

The product was purified by flash chromatography on SiO_2 (gradient heptane - ethyl acetate) and used in the next step directly.



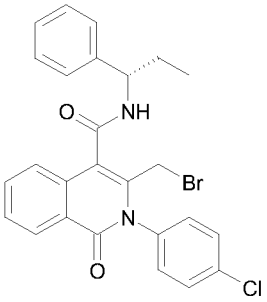
3-Bromomethyl-2-(4-methoxy-phenyl)-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide.

The product was purified by flash chromatography on SiO_2 (gradient heptane - ethyl acetate). LC-MS (m/z) 505.1 & 507.2 (MH^+); t_R = 1.52.



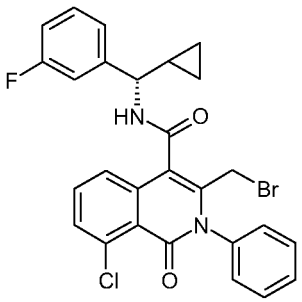
3-Bromomethyl-2-(4-fluoro-phenyl)-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide.

The product was purified by flash chromatography on SiO_2 (gradient heptane - ethyl acetate). LC-MS (m/z) 493.3 & 495.3 (MH^+); t_R = 1.54.



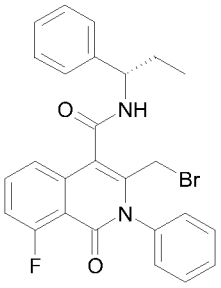
3-Bromomethyl-2-(4-chloro-phenyl)-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide.

LC-MS (m/z) 509.2 & 511.1 (MH^+); t_R = 1.63.



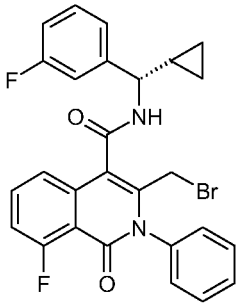
3-Bromomethyl-8-chloro-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-cyclopropyl-(3-fluoro-phenyl)-methyl]-amide.

LC-MS (m/z) 539.1 & 541.4 (MH^+); t_R = 1.69.



3-Bromomethyl-8-fluoro-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide.

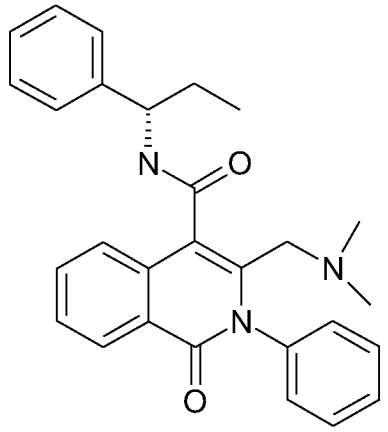
LC-MS (m/z) 493.3 & 495.2 (MH^+); t_R = 1.52.



3-Bromomethyl-8-fluoro-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-cyclopropyl-(3-fluoro-phenyl)-methyl]-amide.

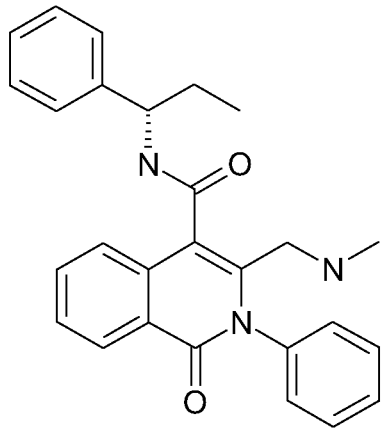
LC-MS (m/z) 523.5 & 525.6 (MH^+); t_R = 1.56.

Compounds of the invention



2a *3-Dimethylaminomethyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide.*

A mixture of 3-bromomethyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide (70 mg, 0.147 mmol) and dimethylamine (1 ml of 33% solution in abs. ethanol, excess) was kept at 50°C for 10 min and then evaporated in vacuo. The residue was dissolved in methanol and passed through SCX cation exchange column (1 g, RSO_3H form). Uncharged impurities were eluted with methanol and the product was eluted with 4M NH_3 in methanol to give 53 mg of colourless glass-like solid. It was further purified by flash chromatography on SiO_2 (5 g, gradient 1,2-dichloroethane – 10% ethyl acetate in 1,2-dichloroethane) to give 45 mg of colourless solid. Yield 70%. LC-MS (m/z) 440.1 (MH^+); t_R = 0.88. ^1H NMR (250 MHz, DMSO-d_6, T = 333 K): 0.92 (t, 2H), 1.83 (two overlapping m, 2H), 1.66 (s, 6H), 2.96 and 3.08 (two d of CH_AH_BN, 2H), 4.96 (q, 1H), 7.19-7.56 (m, 12H), 7.68 (t, 1H), 8.21 (d, 1H), 8.75 (d, 1H).



2b *3-Methylaminomethyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide.*

A mixture of 3-bromomethyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide (4.7 mg, 0.01 mmol) and methylamine (1 ml of 2M solution in tetrahydrofurane, excess) was kept at ambient temperature for 20 min and then evaporated in vacuo. The product was used for biological testing without further purification. LC-MS (m/z) 426.3 (MH^+); t_R = 0.85.

The following 3-aminomethyl derivatives were prepared analogously from corresponding 3-bromomethyl derivatives and 1.2 - 5 molar equivalents of appropriate aliphatic or aromatic primary or secondary amine in tetrahydrofurane as a solvent at ambient temperature. The reactions were monitored by LC-MS. In several cases longer reaction times were used or the reaction mixture was heated to 50°C and/or diisopropylethylamine (2 eq.) was added as a base. After evaporation of the reaction mixture the compounds were of sufficient purity as detected by analytical LC-MS; otherwise further purification by SCX column or by preparative LC-MS was performed.

List of compounds from example 2

	Chemical name	t_R (min)	MW	m/z (MH+)
2c	3-Ethylaminomethyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	0.45 (method B)	439.6	440.6
2d	3-Cyclopropylaminomethyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	0.49 (method B)	451.6	452.1
2e	3-[(Cyclopropylmethyl-amino)-methyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	0.51 (method B)	465.6	466.4
2f	3-(3,6-Dihydro-2H-pyridin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	0.99	477.6	478.1
2g	3-[4-(2-Methoxy-phenyl)-piperazin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	1.14	586.7	587.5
2h	3-[4-(4-Fluoro-phenyl)-piperazin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	1.35	574.7	575.6
2i	3-(4-Formyl-piperazin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	1.12	508.6	509.3
2j	4-[1-Oxo-2-phenyl-4-(1-phenyl-propylcarbamoyl)-1,2-dihydro-isoquinolin-3-ylmethyl]-piperazine-1-carboxylic acid ethyl ester	1.33	552.7	553.7
2k	3-(4-Methyl-piperazin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	0.87	494.6	495.7
2l	1-Oxo-2-phenyl-3-(1,3,4,9-tetrahydro-beta-carbolin-2-	1.27	566.7	567.7

	ylmethyl)-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide			
2m	1-Oxo-2-phenyl-3-piperazin-1-ylmethyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	0.86	480.6	481.2
2n	3-(3-Methyl-piperazin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	0.88	494.6	495.7
2o	3-(3,5-Dimethyl-piperazin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	0.9	508.7	509.3
2p	3-(4-Benzyl-piperazin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	1.02	570.7	571.5
2q	1-Oxo-3-[4-(2-oxo-2-pyrrolidin-1-yl-ethyl)-piperazin-1-ylmethyl]-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	0.92	591.8	592.4
2r	3-Morpholin-4-ylmethyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	1.08	481.6	482.2
2s	3-(2,6-Dimethyl-morpholin-4-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	1.21	509.6	510.2
2t	1-Oxo-2-phenyl-3-thiomorpholin-4-ylmethyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	1.22	497.7	498.8
2u	3-(1,4-Dioxa-8-aza-spiro[4.5]dec-8-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	1.01	537.7	538.4
2v	1-Oxo-2-phenyl-3-piperidin-1-ylmethyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-	1	479.6	480.3

	amide			
2w	3-(2-Methyl-piperidin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	1.07	493.6	494.4
2x	3-(2,6-Dimethyl-piperidin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	1.09	507.7	508.4
2y	3-(2-Hydroxymethyl-piperidin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	0.93	509.6	510.3
2z	1-[1-Oxo-2-phenyl-4-(1-phenyl-propylcarbamoyl)-1,2-dihydro-isoquinolin-3-ylmethyl]-piperidine-3-carboxylic acid ethyl ester	1.14	551.7	552.4
2aa	3-(3-Methyl-piperidin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	1.09	493.6	494.5
2ab	3-(4-Hydroxy-piperidin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	0.83	495.6	496.5
2ac	1-Oxo-2-phenyl-3-(4-phenyl-piperidin-1-ylmethyl)-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	1.27	555.7	556.5
2ad	1-[1-Oxo-2-phenyl-4-(1-phenyl-propylcarbamoyl)-1,2-dihydro-isoquinolin-3-ylmethyl]-piperidine-4-carboxylic acid ethyl ester	1.11	551.7	552.5
2ae	3-(4-Methyl-piperidin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	1.1	493.6	494.6
2af	1-Oxo-2-phenyl-3-(4-pyridin-2-yl-piperazin-1-ylmethyl)-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	0.97	557.7	558.4

2ag	3-(Octahydro-quinolin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	1.18	533.7	534.4
2ah	3-Azepan-1-ylmethyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	1.08	493.6	494.6
2ai	3-(3-Hydroxy-piperidin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	0.88	495.6	496.5
2aj	3-[4-(2,4-Dimethyl-phenyl)-piperazin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	1.45	584.8	585.5
2ak	3-[4-(3,4-Dimethyl-phenyl)-piperazin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	1.29	584.8	585.6
2al	3-(4-Dimethylamino-piperidin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	0.81	522.7	523.5
2am	3-[4-(2,5-Dimethyl-phenyl)-piperazin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	1.47	584.8	585.6
2an	3-[4-(2-Fluoro-phenyl)-piperazin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	1.42	574.7	575.4
2ao	3-[4-(3-Methoxy-phenyl)-piperazin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	1.32	586.7	587.3
2ap	1-Oxo-2-phenyl-3-(4-m-tolyl-piperazin-1-ylmethyl)-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	1.33	570.7	571.7
2aq	3-[4-(4-Methoxy-phenyl)-piperazin-1-ylmethyl]-1-oxo-2-	1.11	586.7	587.6

	phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide			
2ar	1-Oxo-3-(4-phenethyl-piperazin-1-ylmethyl)-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	1.09	584.8	585.5
2as	1-Oxo-2-phenyl-3-(4-pyrimidin-2-yl-piperazin-1-ylmethyl)-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	1.18	558.7	559.3
2at	3-[4-(2-Cyano-phenyl)-piperazin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	1.43	581.7	582.7
2au	3-[4-(4-Chloro-phenyl)-piperazin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	1.54	591.2	591.3
2av	3-((1S,3R,5R)-3-Hydroxy-8-aza-bicyclo[3.2.1]oct-8-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	0.88	521.7	522.7
2aw	3-(4-Acetyl-piperazin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	1.07	522.6	523.5
2ax	3-(4-Methyl-[1,4]diazepan-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	0.89	508.7	509.2
2ay	3-(4-Ethyl-piperazin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	0.89	508.7	509.2
2az	3-((2S,6R)-2,6-Dimethyl-morpholin-4-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	1.21	509.6	510.2
2ba	3-[4-(2,4-Difluoro-phenyl)-piperazin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-	1.48	592.7	593.6

	phenyl-propyl)-amide			
2bb	3-[4-(3-Dimethylamino-propyl)-piperazin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	0.76	565.8	566.7
2bc	3-(4-Isopropyl-piperazin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	0.91	522.7	523.5
2bd	3-(3-Aza-bicyclo[3.2.2]non-3-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	1.21	519.7	520.4
2be	3-(4-Cyclopentyl-piperazin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	0.98	548.7	549.6
2bf	3-[1,4']Bipiperidinyl-1'-ylmethyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	0.86	562.8	563.2
2bg	3-(3,4-Dihydro-1H-isoquinolin-2-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	1.22	527.7	528.7
2bh	3-[4-(2-Dimethylamino-ethyl)-piperazin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	0.74	551.7	552.5
2bi	3-(4-Hydroxymethyl-piperidin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	0.86	509.6	510.3
2bj	1-Oxo-2-phenyl-3-[4-(tetrahydro-furan-2-carbonyl)-piperazin-1-ylmethyl]-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	1.16	578.7	579.9
2bk	3-(4-Isobutyl-piperazin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	0.98	536.7	537.4

2bl	3-[4-(2-Methoxy-ethyl)-piperazin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	0.91	538.7	539.6
2bm	3-[4-(2-Morpholin-4-yl-ethyl)-piperazin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	0.75	593.8	594.7
2bn	3-(1,3-Dihydro-isoindol-2-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	1.16	513.6	514.8
2bo	3-[4-(1-Methyl-piperidin-4-yl)-piperazin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	0.72	577.8	578.5
2bp	1-Oxo-2-phenyl-3-[4-(2-piperidin-1-yl-ethyl)-piperazin-1-ylmethyl]-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	0.75	591.8	592.5
2bq	1-Oxo-2-phenyl-3-[4-(2-pyrrolidin-1-yl-ethyl)-piperazin-1-ylmethyl]-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	0.74	577.8	578.4
2br	3-(4-Dimethylcarbamoylmethyl-piperazin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	0.89	565.7	566.6
2bs	3-(Octahydro-pyrido[1,2-a]pyrazin-2-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	0.93	534.7	535.4
2bt	3-(4-Formyl-[1,4]diazepan-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	0.94	522.6	523.6
2bu	3-[4-(4-Cyano-phenyl)-piperazin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	1.46	581.7	582.6
2bv	1-Oxo-2-phenyl-3-(4-pyridin-4-ylmethyl-piperazin-1-	0.77	571.7	572.4

	ylmethyl)-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide			
2bw	1-Oxo-2-phenyl-3-[4-(3-pyrrolidin-1-yl-propyl)-piperazin-1-ylmethyl]-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	0.75	591.8	592.6
2bx	1-Oxo-2-phenyl-3-(4-pyridin-2-ylmethyl-piperazin-1-ylmethyl)-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	0.93	571.7	572.5
2by	3-(4-Ethanesulfonyl-piperazin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	1.38	572.7	573.7
2bz	3-(4-sec-Butyl-piperazin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	0.96	536.7	537.4
2ca	3-[4-(1-Ethyl-propyl)-piperazin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	1.01	550.7	551.8
2cb	3-[4-(2-Cyano-ethyl)-piperazin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	0.9	533.7	534.4
2cc	3-(4-Methanesulfonyl-piperazin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	1.31	558.7	559.2
2cd	{1-[1-Oxo-2-phenyl-4-(1-phenyl-propylcarbamoyl)-1,2-dihydro-isoquinolin-3-ylmethyl]-piperidin-4-yl}-acetic acid ethyl ester	1.12	565.7	566.7
2ce	3-[4-(3-Fluoro-phenyl)-piperazin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	1.48	574.7	575.5
2cf	1-Oxo-2-phenyl-3-((S)-3-phenyl-piperidin-1-ylmethyl)-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-	1.27	555.7	556.5

	propyl)-amide			
2cg	1-Oxo-2-phenyl-3-[4-(pyrrolidine-1-carbonyl)-piperazin-1-ylmethyl]-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	1.11	577.7	578.6
2ch	3-[4-(Morpholine-4-carbonyl)-piperazin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	1.04	593.7	594.7
2ci	3-(4-Methoxy-piperidin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	0.98	509.6	510.2
2cj	3-(4'-Hydroxy-3',4',5',6'-tetrahydro-2'H-[3,4']bipyridinyl-1'-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	0.71	572.7	573.8
2ck	3-(4-Hydroxy-3,4,5,6-tetrahydro-2H-[4,4']bipyridinyl-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	0.71	572.7	573.8
2cl	3-(3H-spiro[isobenzofuran-1,4'-piperidin]-1'-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	1.25	583.7	584.5
2cm	3-(4-Hydroxy-4-methyl-piperidin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	0.91	509.6	510.1
2cn	3-(hexahydro-spiro[benzo[1,3]dioxole-2,4'-piperidin]-1'-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	1.27	591.7	592.5
2co	1-Oxo-2-phenyl-3-(3,4,5,6-tetrahydro-2H-[4,4']bipyridinyl-1-ylmethyl)-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	0.71	556.7	557.4
2cp	3-[4-(2-Dimethylamino-ethyl)-piperidin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	0.68	550.7	551.4

2cq	3-(4-Dimethylsulfamoyl-piperazin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	1.43	587.7	588.3
2cr	3-(1,1-Dioxo-thiomorpholin-4-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	1.29	529.7	530.3
2cs	1-Oxo-2-phenyl-3-(2-pyridin-2-ylmethyl-piperidin-1-ylmethyl)-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	1.05	570.7	571.6
2ct	3-(2-Morpholin-4-ylmethyl-piperidin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	1.08	578.8	579.8
2cu	3-(4-Furo[3,2-c]pyridin-4-yl-piperazin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	1.01	597.7	598.5
2cv	3-(4-Cyclopropylmethyl-piperazin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	0.95	534.7	535.3
2cw	3-[4-(2-Morpholin-4-yl-ethyl)-piperidin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	0.69	592.8	593.5
2cx	1-Oxo-2-phenyl-3-(4-pyrimidin-2-yl-[1,4]diazepan-1-ylmethyl)-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	1.05	572.7	573.5
2cy	3-(4-Methyl-6,7-dihydro-4H-thieno[3,2-c]pyridin-5-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	1.23	547.7	548.5
2cz	3-[1,4]Diazepan-1-ylmethyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	0.89	494.6	495.7
2da	3-((2S,5R)-2,5-Dimethyl-piperazin-1-ylmethyl)-1-oxo-2-	0.92	508.7	509.2

	phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide			
2db	3-((S)-3-Methyl-piperazin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	0.88	494.6	495.7
2dc	3-((R)-3-Methyl-piperazin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	0.88	494.6	495.7
2dd	3-[3-(3-Chloro-phenyl)-piperazin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	1.11	591.2	591.4
2de	3-[4-(1H-Indol-4-yl)-piperazin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	1.1	595.7	596.6
2df	1-Oxo-3-(3-oxo-piperazin-1-ylmethyl)-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	1.09	494.6	495.7
2dg	3-[4-(1H-Indol-5-yl)-piperazin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	1.04	595.7	596.7
2dh	3-(6,9-Diaza-spiro[4.5]dec-9-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	0.97	534.7	535.3
2di	3-(1,4-Diaza-spiro[5.5]undec-4-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	1.01	548.7	549.7
2dj	3-(3-Isopropyl-piperazin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	0.96	522.7	523.5
2dk	3-(3,3-Dimethyl-piperazin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-	0.9	508.7	509.2

	propyl)-amide			
2dl	3-[3-(4-Fluoro-phenyl)-piperazin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	1.05	574.7	575.4
2dm	1-Oxo-2-phenyl-3-(3-p-tolyl-piperazin-1-ylmethyl)-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	1.08	570.7	571.7
2dn	4-[1-Oxo-2-phenyl-4-(1-phenyl-propylcarbamoyl)-1,2-dihydro-isoquinolin-3-ylmethyl]-piperazine-1-carboxylic acid tert-butyl ester	1.49	580.7	581.9
2do	3-(4-Methylcarbamoylmethyl-piperazin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	0.86	551.7	552.9
2dp	8-Chloro-3-dimethylaminomethyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	0.95	474.0	474.6
2dr	3-Cyclopentylaminomethyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	1.03	479.6	480.4
2ds	3-Cyclohexylaminomethyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	1.1	493.6	494.4
2dt	3-{[(2-Hydroxy-ethyl)-methyl-amino]-methyl}-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	0.84	469.6	470.6
2du	3-Imidazol-1-ylmethyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	0.86	462.6	463.4
2dv	3-(2-Methyl-imidazol-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	0.88	476.6	477.3

2dw	3-(4-Methyl-imidazol-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	0.89	476.6	477.3
2dx	3-(2,5-Dihydro-pyrrol-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	0.92	463.6	464.5
2dy	3-(2,5-Dimethyl-2,5-dihydro-pyrrol-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	1.06	491.6	492.4
2dz	1-Oxo-2-phenyl-3-pyrrolidin-1-ylmethyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	0.92	465.6	466.3
2ea	1-Oxo-2-phenyl-3-(thiazol-2-ylaminomethyl)-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	0.88	494.6	495.6
2eb	1-Oxo-2-phenyl-3-(pyrimidin-4-ylaminomethyl)-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	0.85	489.6	490.4
2ec	3-(tert-Butylamino-methyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	1	467.6	468.7
2ed	3-[(2-Hydroxy-1,1-dimethyl-ethylamino)-methyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	0.91	483.6	484.3
2ee	3-(Isopropylamino-methyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	0.93	453.6	454.3
2ef	3-[(2-Hydroxy-1-methyl-ethylamino)-methyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	0.86	469.6	470.5
2eg	3-[(1-Hydroxymethyl-propylamino)-methyl]-1-oxo-2-	0.92	483.6	484.4

	phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide			
2eh	3-[(2,2-Dimethyl-propylamino)-methyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	1.13	481.6	482.2
2ei	1-Oxo-2-phenyl-3-prop-2-ynylaminomethyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	0.95	449.6	450.2
2ej	3-Allylaminomethyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	0.94	451.6	452.4
2ek	3-[(Methyl-prop-2-ynyl-amino)-methyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	1.22	463.6	464.5
2el	3-Diallylaminomethyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	1.19	491.6	492.4
2em	3-Diethylaminomethyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	0.98	467.6	468.5
2en	3-[(Isopropyl-methyl-amino)-methyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	0.96	467.6	468.7
2eo	3-[((S)-2-Hydroxy-1-methyl-ethylamino)-methyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	0.86	469.6	470.5
2ep	3-[((R)-2-Hydroxy-1-methyl-ethylamino)-methyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	0.87	469.6	470.5
2eq	3-{[(2-Methoxy-ethyl)-methyl-amino]-methyl}-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-	0.96	483.6	484.4

	phenyl-propyl)-amide			
2er	3-((R)-3-Hydroxy-pyrrolidin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	0.85	481.6	482.3
2es	3-((S)-3-Hydroxy-pyrrolidin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	0.84	481.6	482.3
2et	3-[(Cyclopentyl-methyl-amino)-methyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	1.09	493.6	494.5
2eu	3-{[(2-Hydroxy-1-methyl-ethyl)-methyl-amino]-methyl}-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	0.89	483.6	484.4
2ev	3-{[Ethyl-(2-hydroxy-ethyl)-amino]-methyl}-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	0.89	483.6	484.4
2ew	3-[(Ethyl-methyl-amino)-methyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	0.92	453.6	454.4
2ex	3-Cyclobutylaminomethyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	0.98	465.6	466.4
2ey	3-Azetidin-1-ylmethyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	0.86	451.6	452.3
2ez	3-(4-tert-Butyl-piperazin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	0.91	536.7	537.3
2fa	3-[4-(2-Hydroxy-ethyl)-piperazin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	0.86	524.7	525.6

2fb	3-{4-[2-(2-Hydroxy-ethoxy)-ethyl]-piperazin-1-ylmethyl}-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	0.86	568.7	569.6
2fc	3-[4-(3-Chloro-5-trifluoromethyl-pyridin-2-yl)-piperazin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	1.77	660.1	660.8
2fd	3-[4-(3,5-Dichloro-pyridin-4-yl)-piperazin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	1.45	626.6	626.5
2fe	4-[1-Oxo-2-phenyl-4-((S)-1-phenyl-propylcarbamoyl)-1,2-dihydro-isoquinolin-3-ylmethyl]-piperazine-1-carboxylic acid benzyl ester	1.57	614.7	615.4
2ff	3-[4-(3-Morpholin-4-yl-propyl)-piperazin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	0.74	607.8	609.0
2fg	1-Oxo-2-phenyl-3-[4-(3-piperidin-1-yl-propyl)-piperazin-1-ylmethyl]-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	0.76	605.8	607.1
2fh	3-[4-(4,6-Dimethoxy-pyrimidin-2-ylmethyl)-piperazin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	1.05	632.8	633.9
2fi	3-[4-(3-Hydroxy-propyl)-piperazin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	0.86	538.7	539.4
2fj	3-[4-(2,3-Dihydroxy-propyl)-piperazin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	0.84	554.7	555.7
2fk	(2-Oxo-2-{4-[1-oxo-2-phenyl-4-(1-phenyl-propylcarbamoyl)-1,2-dihydro-isoquinolin-3-ylmethyl]-piperazin-1-yl}-ethyl)-carbamic acid tert-butyl ester	1.39	637.8	638.5
2fl	3-[4-(1H-Indazol-5-yl)-piperazin-1-ylmethyl]-1-oxo-2-	0.99	596.7	597.7

	phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide			
2fm	1-Oxo-2-phenyl-3-(4-quinolin-6-yl-piperazin-1-ylmethyl)-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	0.95	607.8	608.7
2fn	3-[4-(6,7-Dimethoxy-quinazolin-4-yl)-piperazin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	1.06	668.8	669.3
2fo	4-{4-[1-Oxo-2-phenyl-4-(1-phenyl-propylcarbamoyl)-1,2-dihydro-isoquinolin-3-ylmethyl]-piperazin-1-yl}-piperidine-1-carboxylic acid tert-butyl ester	1.09	663.9	664.8
2fp	3-{4-[2-(4-Chloro-phenoxy)-ethyl]-piperazin-1-ylmethyl}-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	1.19	635.2	635.9
2fq	{4-[1-Oxo-2-phenyl-4-(1-phenyl-propylcarbamoyl)-1,2-dihydro-isoquinolin-3-ylmethyl]-piperazin-1-yl}-acetic acid tert-butyl ester	1.08	594.8	595.9
2fr	1-Oxo-2-phenyl-3-[4-(3,3,3-trifluoro-2-hydroxy-propyl)-piperazin-1-ylmethyl]-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	0.96	592.7	593.6
2fs	3-[4-(2-Hydroxy-propyl)-piperazin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	0.86	538.7	539.5
2fu	3-[4-(4-Amino-6,7-dimethoxy-quinazolin-2-yl)-piperazin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	1.03	683.8	684.7
2fv	(2-{4-[1-Oxo-2-phenyl-4-(1-phenyl-propylcarbamoyl)-1,2-dihydro-isoquinolin-3-ylmethyl]-piperazin-1-yl}-ethyl)-carbamic acid tert-butyl ester	1.06	623.8	624.5
2fw	1-Oxo-3-{4-[2-(2-oxo-imidazolidin-1-yl)-ethyl]-piperazin-1-ylmethyl}-2-phenyl-1,2-dihydro-isoquinoline-4-	0.85	592.7	593.7

	carboxylic acid ((S)-1-phenyl-propyl)-amide			
2fx	3-{4-[(4,6-Dimethoxy-pyrimidin-2-yl)-phenyl-methyl]-piperazin-1-ylmethyl}-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	1.21	708.9	709.4
2fy	3-(4-Benzo[1,2,5]thiadiazol-4-yl-piperazin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	1.48	614.8	615.4
2fz	3-[4-(2,3-Dihydro-benzo[1,4]dioxin-5-yl)-piperazin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	1.2	614.7	615.3
2ga	3-[4-(4-Methyl-quinolin-2-yl)-piperazin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	1.15	621.8	622.7
2gb	1-Oxo-2-phenyl-3-[4-(pyridin-2-ylcarbamoylmethyl)-piperazin-1-ylmethyl]-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	0.93	614.7	615.4
2gc	3-[4-(6-Chloro-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-8-yl)-piperazin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	1.21	662.2	662.8
2gd	3-(4-Carbamoylmethyl-piperazin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	0.85	537.7	538.5
2ge	3-(4-Hydroxy-4-phenyl-piperidin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	1.12	571.7	572.6
2gf	3-[4-(4-Chloro-phenyl)-4-hydroxy-piperidin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	1.23	606.2	606.8
2gg	1-[1-Oxo-2-phenyl-4-(1-phenyl-propylcarbamoyl)-1,2-	0.9	523.6	524.5

	dihydro-isoquinolin-3-ylmethyl]-piperidine-4-carboxylic acid			
2gh	3-(4-Cyano-4-phenyl-piperidin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	1.59	580.7	581.9
2gi	3-(4-Benzyl-4-hydroxy-piperidin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	1.16	585.7	586.0
2gj	1-[1-Oxo-2-phenyl-4-(1-phenyl-propylcarbamoyl)-1,2-dihydro-isoquinolin-3-ylmethyl]-4-phenyl-piperidine-4-carboxylic acid ethyl ester	1.35	627.8	628.5
2gk	1-Oxo-2-phenyl-3-[4-(phenyl-propionyl-amino)-piperidin-1-ylmethyl]-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	1.17	626.8	627.6
2gl	Methyl-{1-[1-oxo-2-phenyl-4-(1-phenyl-propylcarbamoyl)-1,2-dihydro-isoquinolin-3-ylmethyl]-piperidin-4-yl}-carbamic acid tert-butyl ester	1.25	608.8	609.8
2gm	1-Oxo-2-phenyl-3-[4-(2-pyrrolidin-1-yl-ethyl)-piperidin-1-ylmethyl]-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	0.72	576.8	577.5
2gn	3-{4-[5-(4-Fluoro-phenyl)-[1,3,4]oxadiazol-2-yl]-piperidin-1-ylmethyl}-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	1.22	641.7	642.3
2go	1-Oxo-2-phenyl-3-[4-(3-pyridin-4-yl-[1,2,4]oxadiazol-5-yl)-piperidin-1-ylmethyl]-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	0.96	624.7	625.5
2gp	1-Oxo-2-phenyl-3-[4-(3-pyrazin-2-yl-[1,2,4]oxadiazol-5-yl)-piperidin-1-ylmethyl]-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	1.04	625.7	626.5
2gq	1-Oxo-2-phenyl-3-[4-(3-pyridin-4-yl-[1,2,4]oxadiazol-5-	1.04	624.7	625.5

	yl)-piperidin-1-ylmethyl]-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide			
2gr	3-(4'-Hydroxy-3',4',5',6'-tetrahydro-2'H-[2,4']bipyridinyl-1'-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	0.83	572.7	573.5
2gs	3-(spiro[isochroman-1,4'-piperidin]-1'-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	1.24	597.8	598.6
2gt	3-[4-Hydroxy-4-(3-methoxy-phenyl)-piperidin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	1.13	601.7	602.4
2gu	3-[4-(3-Chloro-phenyl)-4-hydroxy-piperidin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	1.23	606.2	606.8
2gv	3-(6-chloro-3H-spiro[isobenzofuran-1,4'-piperidin]-1'-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	1.36	618.2	618.4
2gw	3-(4-{[4-Chloro-3-(4-fluoro-phenyl)-indan-1-yl]-methyl-amino}-piperidin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	1.36	753.4	753.4
2gx	3-(1-acetyl-spiro[indoline-3,4'-piperidin]-1'-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	1.15	624.8	625.6
2gy	3-(1-acetyl-5-fluoro-spiro[indoline-3,4'-piperidin]-1'-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	1.2	642.8	643.4
2gz	1-Oxo-3-(4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-8-ylmethyl)-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	1.15	625.8	626.6
2ha	3-(4-Acetylamino-piperidin-1-ylmethyl)-1-oxo-2-phenyl-	0.83	536.7	537.4

	1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide			
2hb	1-Oxo-3-(1-oxo-2,8-diaza-spiro[4.5]dec-8-ylmethyl)-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	0.85	548.7	549.7
2hc	3-[4-Hydroxy-4-(3-trifluoromethyl-phenyl)-piperidin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	1.29	639.7	640.3
2hd	1-Oxo-2-phenyl-3-(4-trifluoromethyl-piperidin-1-ylmethyl)-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	1.3	547.6	548.4
2he	3-[4-(4-Methyl-piperazine-1-carbonyl)-piperidin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	0.7	605.8	607.0
2hf	3-(5-isopropyl-3H-spiro[isobenzofuran-1,4'-piperidin]-1'-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	1.48	625.8	626.6
2hg	3-[4-(Acetyl-methyl-amino)-4-phenyl-piperidin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	1.13	626.8	627.7
2hh	4-{1-[1-Oxo-2-phenyl-4-(1-phenyl-propylcarbamoyl)-1,2-dihydro-isoquinolin-3-ylmethyl]-piperidin-4-yl}-piperazine-1-carboxylic acid tert-butyl ester	1.03	663.9	664.7
2hi	(2-{1-[1-Oxo-2-phenyl-4-(1-phenyl-propylcarbamoyl)-1,2-dihydro-isoquinolin-3-ylmethyl]-piperidin-4-yl}-ethyl)-carbamic acid tert-butyl ester	1.19	622.8	623.5
2hj	3-(4-Methylamino-4-phenyl-piperidin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	1.01	584.8	585.5
2hk	3-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-	1.06	612.8	613.3

	phenyl-propyl)-amide			
2hl	3-[4-Acetylamino-4-(3-fluoro-phenyl)-piperidin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	1.06	630.8	631.5
2hm	1-Oxo-3-[4-(4-oxo-piperidine-1-carbonyl)-piperidin-1-ylmethyl]-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	0.89	604.7	605.3
2hn	3-[4,4']Bipiperidinyl-1-ylmethyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	0.7	562.8	563.2
2ho	{1-[1-Oxo-2-phenyl-4-(1-phenyl-propylcarbamoyl)-1,2-dihydro-isoquinolin-3-ylmethyl]-piperidin-4-yl}-carbamic acid tert-butyl ester	1.15	594.8	595.8
2hp	3-[1,4']Bipiperidinyl-1'-ylmethyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid [cyclopropyl-(3-fluoro-phenyl)-methyl]-amide	0.95	592.8	593.5
2hq	1-Oxo-3-(4-phenethyl-piperazin-1-ylmethyl)-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid [cyclopropyl-(3-fluoro-phenyl)-methyl]-amide	1.15	614.8	615.5
2hr	3-(4-Isopropyl-piperazin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid [cyclopropyl-(3-fluoro-phenyl)-methyl]-amide	0.97	552.7	553.8
2hs	3-[4-(2-Morpholin-4-yl-ethyl)-piperazin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid [cyclopropyl-(3-fluoro-phenyl)-methyl]-amide	0.81	623.8	624.6
2ht	3-[4-(1-Methyl-piperidin-4-yl)-piperazin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid [cyclopropyl-(3-fluoro-phenyl)-methyl]-amide	0.78	607.8	608.9
2hu	1-Oxo-2-phenyl-3-[4-(2-piperidin-1-yl-ethyl)-piperazin-1-ylmethyl]-1,2-dihydro-isoquinoline-4-carboxylic acid [cyclopropyl-(3-fluoro-phenyl)-methyl]-amide	0.82	621.8	622.6

2hv	1-Oxo-2-phenyl-3-[4-(2-pyrrolidin-1-yl-ethyl)-piperazin-1-ylmethyl]-1,2-dihydro-isoquinoline-4-carboxylic acid [cyclopropyl-(3-fluoro-phenyl)-methyl]-amide	0.8	607.8	608.8
2hw	1-Oxo-2-phenyl-3-(4-pyridin-4-ylmethyl-piperazin-1-ylmethyl)-1,2-dihydro-isoquinoline-4-carboxylic acid [cyclopropyl-(3-fluoro-phenyl)-methyl]-amide	0.84	601.7	602.6
2hx	3-(4-Hydroxy-3,4,5,6-tetrahydro-2H-[4,4']bipyridinyl-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid [cyclopropyl-(3-fluoro-phenyl)-methyl]-amide	0.77	602.7	603.7
2hy	3-[4-(2-Morpholin-4-yl-ethyl)-piperidin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid [cyclopropyl-(3-fluoro-phenyl)-methyl]-amide	0.75	622.8	623.7
2hz	3-[4-Hydroxy-4-(3-methoxy-phenyl)-piperidin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid [cyclopropyl-(3-fluoro-phenyl)-methyl]-amide	1.17	631.7	632.6
2ia	3-[4-(Acetyl-methyl-amino)-4-phenyl-piperidin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid [cyclopropyl-(3-fluoro-phenyl)-methyl]-amide	1.18	656.8	657.8
2ib	2-(2-Fluoro-phenyl)-1-oxo-3-(4-phenethyl-piperazin-1-ylmethyl)-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	1.12	602.8	603.8
2ic	2-(2-Fluoro-phenyl)-3-(4-isopropyl-piperazin-1-ylmethyl)-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	0.96	540.7	541.7
2id	3-[1,4']Bipiperidinyl-1'-ylmethyl-2-(2-fluoro-phenyl)-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	1	580.7	581.7
2ie	2-(2-Fluoro-phenyl)-3-[4-(2-morpholin-4-yl-ethyl)-	0.82	611.8	612.5

	piperazin-1-ylmethyl]-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide			
2if	2-(2-Fluoro-phenyl)-3-[4-(1-methyl-piperidin-4-yl)-piperazin-1-ylmethyl]-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	0.76	595.8	596.8
2ig	2-(2-Fluoro-phenyl)-1-oxo-3-[4-(2-piperidin-1-yl-ethyl)-piperazin-1-ylmethyl]-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	0.81	609.8	610.5
2ih	2-(2-Fluoro-phenyl)-1-oxo-3-[4-(2-pyrrolidin-1-yl-ethyl)-piperazin-1-ylmethyl]-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	0.8	595.8	596.7
2ii	2-(2-Fluoro-phenyl)-1-oxo-3-(4-pyridin-4-ylmethyl-piperazin-1-ylmethyl)-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	0.84	589.7	590.4
2ij	2-(2-Fluoro-phenyl)-3-(4-hydroxy-3,4,5,6-tetrahydro-2H-[4,4']bipyridinyl-1-ylmethyl)-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	0.85	590.7	591.3
2ik	2-(2-Fluoro-phenyl)-3-[4-(2-morpholin-4-yl-ethyl)-piperidin-1-ylmethyl]-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	0.76	610.8	611.7
2il	2-(2-Fluoro-phenyl)-3-[4-hydroxy-4-(3-methoxy-phenyl)-piperidin-1-ylmethyl]-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	1.21	619.7	620.3
2im	3-[4-(2-Morpholin-4-yl-ethyl)-piperazin-1-ylmethyl]-1-oxo-2-o-tolyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	0.82	607.8	608.8
2in	1-Oxo-3-[4-(2-piperidin-1-yl-ethyl)-piperazin-1-ylmethyl]-2-o-tolyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	0.81	605.8	606.9
2io	1-Oxo-3-(4-pyridin-4-ylmethyl-piperazin-1-ylmethyl)-2-o-	0.84	585.7	586.4

	tolyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide			
2ip	2-(3-Fluoro-phenyl)-1-oxo-3-(4-phenethyl-piperazin-1-ylmethyl)-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	1.13	602.8	603.8
2iq	2-(3-Fluoro-phenyl)-3-(4-isopropyl-piperazin-1-ylmethyl)-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	0.96	540.7	541.3
2ir	3-[1,4']Bipiperidinyl-1'-ylmethyl-2-(3-fluoro-phenyl)-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	0.98	580.7	581.8
2is	2-(3-Fluoro-phenyl)-3-[4-(2-morpholin-4-yl-ethyl)-piperazin-1-ylmethyl]-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	0.81	611.8	612.6
2it	2-(3-Fluoro-phenyl)-3-[4-(1-methyl-piperidin-4-yl)-piperazin-1-ylmethyl]-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	0.75	595.8	596.8
2iu	2-(3-Fluoro-phenyl)-1-oxo-3-[4-(2-piperidin-1-yl-ethyl)-piperazin-1-ylmethyl]-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	0.8	609.8	610.7
2iv	2-(3-Fluoro-phenyl)-1-oxo-3-[4-(2-pyrrolidin-1-yl-ethyl)-piperazin-1-ylmethyl]-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	0.79	595.8	596.8
2iw	2-(3-Fluoro-phenyl)-1-oxo-3-(4-pyridin-4-ylmethyl-piperazin-1-ylmethyl)-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	0.83	589.7	590.2
2ix	2-(3-Fluoro-phenyl)-3-[4-(2-morpholin-4-yl-ethyl)-piperidin-1-ylmethyl]-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	0.73	610.8	611.6
2iy	2-(3-Fluoro-phenyl)-3-[4-hydroxy-4-(3-methoxy-phenyl)-piperidin-1-ylmethyl]-1-oxo-1,2-dihydro-isoquinoline-4-	1.18	619.7	620.7

	carboxylic acid ((S)-1-phenyl-propyl)-amide			
2iz	3-[4-(Acetyl-methyl-amino)-4-phenyl-piperidin-1-ylmethyl]-2-(3-fluoro-phenyl)-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	1.2	644.8	645.7
2ja	2-(3-Chloro-phenyl)-1-oxo-3-(4-phenethyl-piperazin-1-ylmethyl)-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	1.17	619.2	619.4
2jb	2-(3-Chloro-phenyl)-3-(4-isopropyl-piperazin-1-ylmethyl)-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	1	557.1	557.5
2jc	3-[1,4']Bipiperidinyl-1'-ylmethyl-2-(3-chloro-phenyl)-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	1.04	597.2	597.8
2jd	2-(3-Chloro-phenyl)-3-[4-(2-morpholin-4-yl-ethyl)-piperazin-1-ylmethyl]-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	0.86	628.2	628.6
2je	2-(3-Chloro-phenyl)-3-[4-(1-methyl-piperidin-4-yl)-piperazin-1-ylmethyl]-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	0.79	612.2	612.2
2jf	2-(3-Chloro-phenyl)-1-oxo-3-[4-(2-piperidin-1-yl-ethyl)-piperazin-1-ylmethyl]-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	0.84	626.2	626.7
2jg	2-(3-Chloro-phenyl)-1-oxo-3-[4-(2-pyrrolidin-1-yl-ethyl)-piperazin-1-ylmethyl]-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	0.83	612.2	612.4
2jh	2-(3-Chloro-phenyl)-1-oxo-3-(4-pyridin-4-ylmethyl-piperazin-1-ylmethyl)-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	0.88	606.2	606.1
2ji	2-(3-Chloro-phenyl)-3-[4-(2-morpholin-4-yl-ethyl)-piperidin-1-ylmethyl]-1-oxo-1,2-dihydro-isoquinoline-4-	0.78	627.2	627.4

	carboxylic acid ((S)-1-phenyl-propyl)-amide			
2jj	2-(3-Chloro-phenyl)-3-[4-hydroxy-4-(3-methoxy-phenyl)-piperidin-1-ylmethyl]-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	1.23	636.2	636.7
2jk	3-[4-(Acetyl-methyl-amino)-4-phenyl-piperidin-1-ylmethyl]-2-(3-chloro-phenyl)-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	1.26	661.2	662.0
2jl	1-Oxo-3-(4-phenethyl-piperazin-1-ylmethyl)-2-m-tolyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	1.15	598.8	599.6
2jm	3-[1,4']Bipiperidinyl-1'-ylmethyl-1-oxo-2-m-tolyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	0.96	576.8	577.5
2jn	3-[4-(2-Morpholin-4-yl-ethyl)-piperazin-1-ylmethyl]-1-oxo-2-m-tolyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	0.83	607.8	609.0
2jo	3-[4-(1-Methyl-piperidin-4-yl)-piperazin-1-ylmethyl]-1-oxo-2-m-tolyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	0.78	591.8	592.6
2jp	1-Oxo-3-[4-(2-piperidin-1-yl-ethyl)-piperazin-1-ylmethyl]-2-m-tolyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	0.83	605.8	607.1
2jq	1-Oxo-3-[4-(2-pyrrolidin-1-yl-ethyl)-piperazin-1-ylmethyl]-2-m-tolyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	0.81	591.8	592.6
2jr	1-Oxo-3-(4-pyridin-4-ylmethyl-piperazin-1-ylmethyl)-2-m-tolyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	0.85	585.7	586.0
2js	3-[4-(2-Morpholin-4-yl-ethyl)-piperidin-1-ylmethyl]-1-oxo-2-m-tolyl-1,2-dihydro-isoquinoline-4-carboxylic acid	0.73	606.8	608.1

	((S)-1-phenyl-propyl)-amide			
2jt	3-[4-Hydroxy-4-(3-methoxy-phenyl)-piperidin-1-ylmethyl]-1-oxo-2-m-tolyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	1.18	615.8	616.3
2ju	3-[4-(Acetyl-methyl-amino)-4-phenyl-piperidin-1-ylmethyl]-1-oxo-2-m-tolyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	1.19	640.8	641.7

List of compounds from example **2**, continued

	Chemical name	**t_R (min)**	**MW**	**m/z (MH+)**
2ka	3-(4-tert-Butyl-piperazin-1-ylmethyl)-8-chloro-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-cyclopropyl-(3-fluoro-phenyl)-methyl]-amide	1.06	601.2	601.5
2kb	8-Chloro-3-(4-isopropyl-piperazin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	1.01	557.1	557.5
2kc	8-Chloro-3-(4-isobutyl-piperazin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	1.07	571.2	571.7
2kd	8-Chloro-3-(octahydro-pyrido[1,2-a]pyrazin-2-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	1.03	569.1	569.6
2ke	8-Chloro-3-(4-hydroxy-3,4,5,6-tetrahydro-2H-[4,4']bipyridinyl-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	0.8	607.2	607.9
2kf	8-Chloro-3-(4-cyclopropylmethyl-piperazin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	1.04	569.1	569.8
2kg	8-Chloro-3-[4-(2-morpholin-4-yl-ethyl)-piperidin-1-	0.75	627.2	627.4

	ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide			
2kh	8-Chloro-3-[1,4]diazepan-1-ylmethyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	0.98	529.1	529.3
2ki	8-Chloro-3-((S)-3-methyl-piperazin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	0.98	529.1	529.2
2kj	8-Chloro-3-imidazol-1-ylmethyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	0.92	497.0	497.4
2kk	8-Chloro-3-(4-methyl-imidazol-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	0.97	511.0	511.3
2kl	3-(tert-Butylamino-methyl)-8-chloro-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	1.06	502.1	502.5
2km	8-Chloro-3-(isopropylamino-methyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	1	488.0	488.6
2kn	8-Chloro-3-[4-hydroxy-4-(3-methoxy-phenyl)-piperidin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	1.2	636.2	636.8
2ko	3-(4-tert-Butyl-piperazin-1-ylmethyl)-8-chloro-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	1.03	571.2	571.4
2kp	3-Benzoimidazol-1-ylmethyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	1.02	512.6	513.3
2kq	1-Oxo-2-phenyl-3-pyrazol-1-ylmethyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-	1.54	462.6	463.4

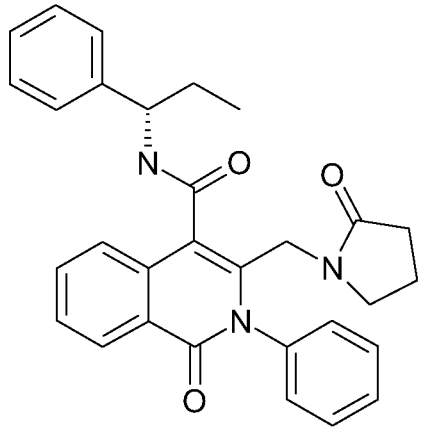
	amide			
2kr	3-(4-Methyl-pyrazol-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	1.65	476.6	477.3
2ks	1-Oxo-2-phenyl-3-[1,2,3]triazol-1-ylmethyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	1.23	463.5	464.4
2kt	2-(3-Methoxy-phenyl)-1-oxo-3-(4-pyridin-4-ylmethyl-piperazin-1-ylmethyl)-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	0.82	601.7	602.7
2ku	2-(4-Methoxy-phenyl)-3-[4-(2-morpholin-4-yl-ethyl)-piperazin-1-ylmethyl]-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	0.8	623.8	624.5
2kv	2-(4-Fluoro-phenyl)-1-oxo-3-(4-phenethyl-piperazin-1-ylmethyl)-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	1.13	602.8	603.8
2kw	2-(4-Fluoro-phenyl)-3-(4-isopropyl-piperazin-1-ylmethyl)-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	0.95	540.7	541.7
2kx	3-[1,4']Bipiperidinyl-1'-ylmethyl-2-(4-fluoro-phenyl)-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	0.98	580.7	581.9
2ky	2-(4-Fluoro-phenyl)-3-[4-(2-morpholin-4-yl-ethyl)-piperazin-1-ylmethyl]-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	0.79	611.8	612.6
2kz	2-(4-Fluoro-phenyl)-3-[4-(1-methyl-piperidin-4-yl)-piperazin-1-ylmethyl]-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	0.74	595.8	596.8
2la	2-(4-Fluoro-phenyl)-1-oxo-3-[4-(2-pyrrolidin-1-yl-ethyl)-piperazin-1-ylmethyl]-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	0.78	595.8	596.7

2lb	2-(4-Fluoro-phenyl)-3-[4-hydroxy-4-(3-methoxy-phenyl)-piperidin-1-ylmethyl]-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	1.18	619.7	620.4
2lc	2-(4-Chloro-phenyl)-1-oxo-3-(4-phenethyl-piperazin-1-ylmethyl)-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	1.17	619.2	619.3
2ld	2-(4-Chloro-phenyl)-3-(4-isopropyl-piperazin-1-ylmethyl)-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	0.99	557.1	557.4
2le	3-[1,4']Bipiperidinyl-1'-ylmethyl-2-(4-chloro-phenyl)-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	1.04	597.2	597.8
2lf	2-(4-Chloro-phenyl)-3-[4-(2-morpholin-4-yl-ethyl)-piperazin-1-ylmethyl]-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	0.85	628.2	628.6
2lg	2-(4-Chloro-phenyl)-3-[4-(1-methyl-piperidin-4-yl)-piperazin-1-ylmethyl]-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	0.77	612.2	612.3
2lh	2-(4-Chloro-phenyl)-1-oxo-3-[4-(2-piperidin-1-yl-ethyl)-piperazin-1-ylmethyl]-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	0.84	626.2	626.8
2li	2-(4-Chloro-phenyl)-1-oxo-3-[4-(2-pyrrolidin-1-yl-ethyl)-piperazin-1-ylmethyl]-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	0.81	612.2	612.6
2lj	3-(4-tert-Butyl-piperazin-1-ylmethyl)-8-fluoro-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	0.96	554.7	555.7
2lk	8-Chloro-3-cyclopropylaminomethyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	0.61 (method B)	486.0	486.4
2ll	3-(4-tert-Butyl-piperazin-1-ylmethyl)-8-fluoro-1-oxo-2-	0.98	584.7	585.5

	phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-cyclopropyl-(3-fluoro-phenyl)-methyl]-amide			
2lm	8-Fluoro-1-oxo-2-phenyl-3-piperazin-1-ylmethyl-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-cyclopropyl-(3-fluoro-phenyl)-methyl]-amide (*)	0.89	528.6	529.4
2ln	8-Fluoro-1-oxo-3-(3-oxo-pyrazolidin-1-ylmethyl)-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-cyclopropyl-(3-fluoro-phenyl)-methyl]-amide	1.14	528.6	528.8
2lo	8-Fluoro-1-oxo-3-(3-oxo-piperazin-1-ylmethyl)-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-cyclopropyl-(3-fluoro-phenyl)-methyl]-amide	1.13	542.6	543.5

(*): 1-(tert-Butoxycarbonyl)piperazine was used as amine and the BOC-group was removed in the next step by 2M HCl in diethyl ether and methanol (1:1) at r.t.

Example 3

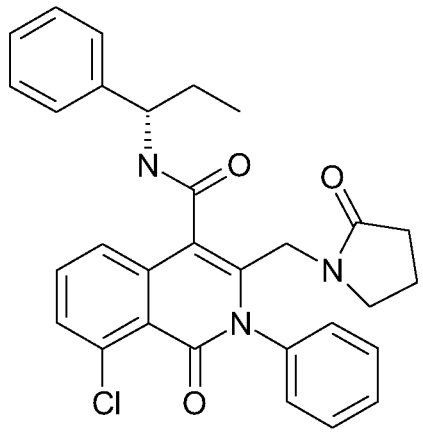


3a *1-Oxo-3-(2-oxo-pyrrolidin-1-ylmethyl)-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide.*

To a solution of 2-pyrrolidinone (0.1 ml) in tetrahydrofurane (2 ml) sodium hydride (20 mg, 60% dispersion in mineral oil) was added. The reaction mixture was stirred at ambient temperature until the gas evolution ceased then 3-bromomethyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide (30 mg) was added. After 30 min acetic acid (0.05 ml) was added and volatiles were removed in vacuo. The product was purified by flash chromatography on SiO_2 (5 g,

1,2-dichloroethane then gradient 50% to 100% ethyl acetate in heptane) to give 17 mg of white solid. Yield 56%. LC-MS (m/z) 480.5 (MH^+); t_R = 1.21.

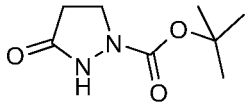
The following compound was obtained analogously:



3b *8-Chloro-1-oxo-3-(2-oxo-pyrrolidin-1-ylmethyl)-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide.*

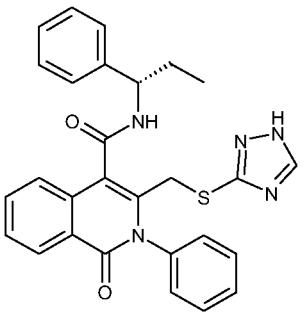
LC-MS (m/z) 514.7 (MH^+); t_R = 1.33.

Synthesis of intermediates:



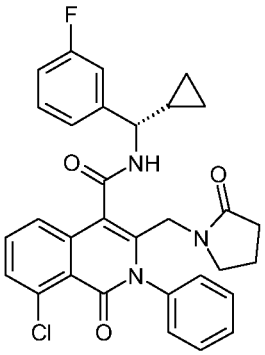
3-Oxo-pyrazolidine-1-carboxylic acid tert-butyl ester.

To a mixture of 3-pyrazolidinone hydrochloride (55.3 mg, 0.45 mmol), Na_2CO_3 (133 mg, 1.24 mol), water (0.5 ml) and dioxane (0.054 ml) BOC-anhydride (101 mg, 0.46 mmol) in dioxane (0.16 ml) was added and stirred at r.t. overnight. It was filtered, evaporated and used in the next step without further purification. ^1H NMR (500 MHz, DMSO-d_6): 1.4 (s, 9H), 2.32 (t, J=9 Hz, 2H), 3.6 (t, J=9 Hz, 2H).



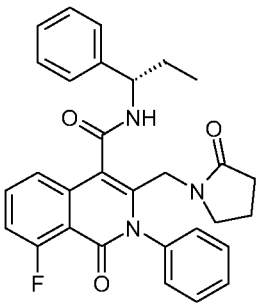
3c *1-Oxo-2-phenyl-3-(1H-[1,2,4]triazol-3-ylsulfanylmethyl)-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide.*

LC-MS (m/z) 496.6 (MH^+); t_R = 0.64 (method B).



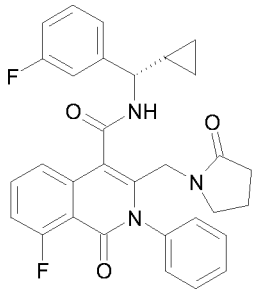
3d *8-Chloro-1-oxo-3-(2-oxo-pyrrolidin-1-ylmethyl)-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-cyclopropyl-(3-fluoro-phenyl)-methyl]-amide.*

LC-MS (m/z) 544.3 (MH^+); t_R = 1.39. ^{1}H NMR (250 MHz, 70°C, DMSO-d_6): 0.4-0.64 (m, 4H), 1.28 (m, 1H), 1.74 (m, 2H), 1.97 (m, 2H), 2.89 (br, 1H), 3.06 (H_2O), 4.02-4.14 (br, 2H), 4.51 (t, J=8.6 Hz, 1H), 7.08 (dt, 1H), 7.2-7.3 (m, 4H), 7.37-7.7 (m, 7H), 9.07 (d, J=8.1 Hz, 1H, NH).

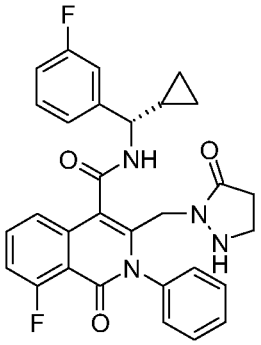


3e *8-Fluoro-1-oxo-3-(2-oxo-pyrrolidin-1-ylmethyl)-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide.*

LC-MS (m/z) 498.8 (MH^+); t_R = 1.23, t_R = 0.68 (method B). ^1H NMR (250 MHz, 70°C, DMSO-d_6): 0.93 (t, J=7.3 Hz, 3H), 1.66-2.0 (m, 6H), 2.84 (br t, 1H), 3.01 (overlapped H_2O signal), 3.98-4.08 (br, 2H), 4.97 (t, J=7.6 Hz, 1H), 7.2-7.54 (m, 12 H), 7.69 (m, 1H), 8.77 (d, J=7.9 Hz, 1H, NH).

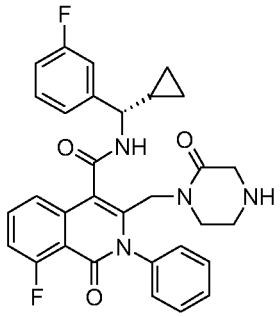


3f *8-Fluoro-1-oxo-3-(2-oxo-pyrrolidin-1-ylmethyl)-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-cyclopropyl-(3-fluoro-phenyl)-methyl]-amide.* LC-MS (m/z) 528.7 (MH^+); t_R = 1.29, t_R = 0.7 (method B). ^1H NMR (250 MHz, 80°C, DMSO-d_6): 0.37-0.62 (m, 4H), 1.25 (m, 1H), 1.71 (quintet, J=7.5 Hz, 2H), 1.94 (t, J=7.9 Hz, 2H), 2.85 (br, 2H), 2.94 (H_2O), 4.05 (br, 2H), 4.5 (t, J=8.6 Hz, 1H), 7.04 (m, 1H), 7.17-7.32 (m, 5H), 7.32-7.52 (m, 5H), 7.7 (m, 1H), 8.97 (d, J=8.1 Hz, 1H, NH).



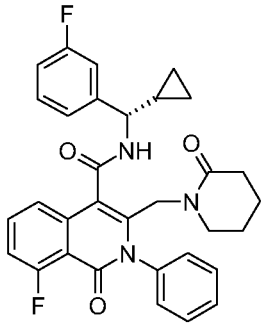
3g *8-Fluoro-1-oxo-3-(5-oxo-pyrazolidin-1-ylmethyl)-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-cyclopropyl-(3-fluoro-phenyl)-methyl]-amide.* 3-Oxo-pyrazolidine-1-carboxylic acid tert-butyl ester was used in the coupling reaction promoted by NaH. The BOC-group in the obtained intermediate 2-(4-{[(S)-cyclopropyl-(3-fluoro-phenyl)-methyl]-carbamoyl}-8-fluoro-1-oxo-2-phenyl-1,2-dihydro-isoquinolin-3-ylmethyl)-3-oxo-yrazolidine-1-carboxylic acid tert-butyl ester

was removed with 2M HCl in ethyl ether – methanol (1:1) at r.t., 30 min and the title compound was purified by preparative LC-MS. LC-MS (m/z) 529.3 (MH^+); t_R = 1.15.



3h *8-Fluoro-1-oxo-3-(2-oxo-piperazin-1-ylmethyl)-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-cyclopropyl-(3-fluoro-phenyl)-methyl]-amide.*

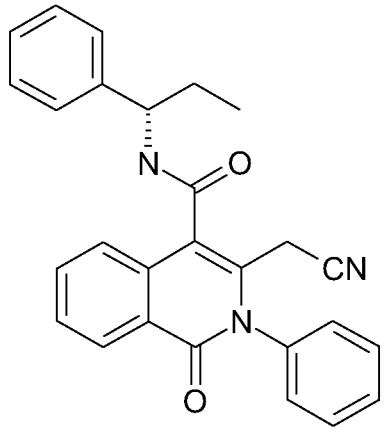
The title compound was prepared analogously from 2-oxo-4-(tert-butoxycarbonyl)piperazine followed by BOC group removal. LC-MS (m/z) 543.6 (MH^+); t_R = 0.84.



3i *8-Fluoro-1-oxo-3-(2-oxo-piperidin-1-ylmethyl)-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-cyclopropyl-(3-fluoro-phenyl)-methyl]-amide.*

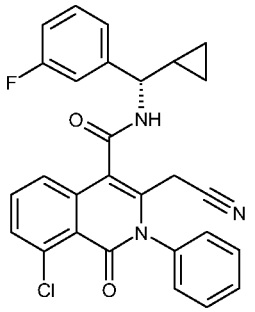
The title compound was prepared analogously from 2-piperidone. LC-MS (m/z) 542.5 (MH^+); t_R = 1.35.

Example 4



4a *3-Cyanomethyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide.*

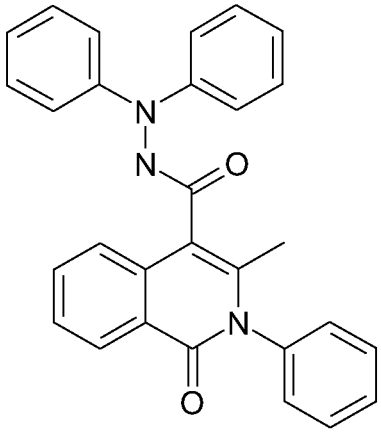
To a solution of 3-bromomethyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide (83 mg, 0.174 mmol) in THF (1.5 ml, anhydrous) and DMF (1.5 ml, anhydrous) sodium cyanide (83 mg, excess) was added. After 5 min the obtained suspension was poured into water (50 ml) followed by addition of heptane (20 ml). The crude product was separated by filtration and purified by flash chromatography on SiO_2 (5g, 1:1 EA-heptane) to give 50 mg of colourless solid, yield 68%. LC-MS (m/z) 422.4 (MH^+); t_R = 1.39. ^1H NMR (250 MHz, DMSO-d_6, T = 343 K): 0.94 (t, 3H), 1.78 and 1.85 (two overlapping qui of ABX_4, 2H, CH_2 of Et), 3.45 and 3.54 (two d of AB, 2H, CH_2CN), 4.98 (q, 1H), 7.22-7.44 (m, 8H), 7.53-7.64 (m, 4H), 7.72 (dt, 1H), 8.25 (dd, 1H), 9.05 (d, 1H).



4b *8-Chloro-3-cyanomethyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-cyclopropyl-(3-fluoro-phenyl)-methyl]-amide.*

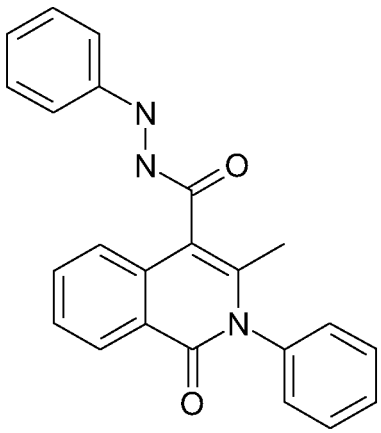
LC-MS (m/z) 486.5 (MH^+); t_R = 1.81.

Example 5



5a *3-Methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid N',N'-diphenyl-hydrazide.*

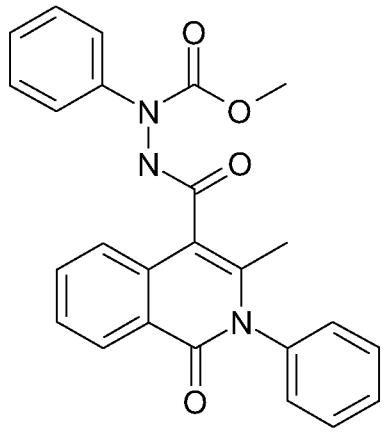
A mixture of 3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carbonyl chloride (the synthesis is described above in example **1a**) (25 mg, 0.08 mmol) and 1,1-diphenylhydrazine hydrochloride (56 mg, 0.25 mmol) in 1,2-dichloroethane (1 ml) was heated under microwave irradiation for 20 min at 140°C. Volatiles were removed in vacuo and the product was purified by preparative LC-MS to give 14 mg of colorless solid. LC-MS (m/z) 446.7 (MH^+); t_R = 1.58.



3-Methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid N'-phenyl-hydrazide. [740-170]

The title compound was prepared analogously. LC-MS (m/z) 370.2 (MH^+); t_R = 1.15. ^{1}H NMR (500 MHz, DMSO-d_6): 2.01 (s, 3H), 6.76 (t, 1H), 6.83 (d, 2H), 7.2 (t, 2H),

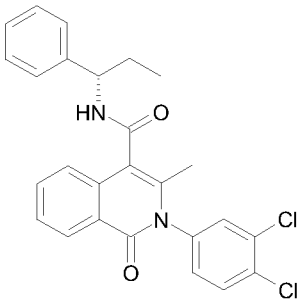
7.33 (br, 2H), 7.5-7.62 (m, 5H), 7.83 (t, 1H), 8.11 (br, 1H), 8.24 (d, 1H), 10.33 (s, 1H).



5b *N'-(3-Methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carbonyl)-N-phenyl-hydrazinecarboxylic acid methyl ester.*

A mixture of 3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid N'-phenyl-hydrazide (**5a**, 490 mg, 1.3 mmol) and methyl chloroformate (0.6 ml, 8 mmol) in 1,2-dichloroethane (10 ml) was heated under microwave irradiation for 10 min at 100°C. Volatiles were removed in vacuo and the product was purified by flash chromatography (SiO_2, gradient heptane – 1:1 ethyl acetate/heptane) to give 190 mg of solid. LC-MS (m/z) 428.8 (MH^+); t_R = 1.22.

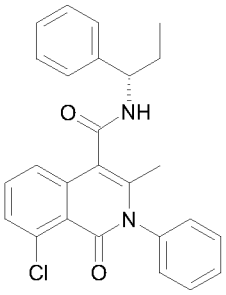
Example 6



6a *2-(3,4-Dichloro-phenyl)-3-methyl-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide.*

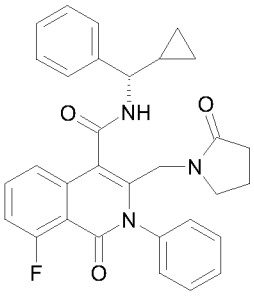
A mixture of 4-acetyl-3-((S)-1-phenyl-propylamino)-isochromen-1-one (60 mg) and 3,4-dichloroaniline (250 mg) in acetonitrile (0.5 ml) were heated under microwave irradiation at 160°C for 15 min. The reaction mixture was partitioned between 2M HCl (3 ml) and ethyl acetate (3 ml). The organic solution was absorbed on SiO_2 (600 mg) and flash chromatographed on SiO_2 (20g) with gradient heptane - ethyl acetate to give 22 mg of the title compound as a white solid. LC-MS (m/z) 465.4 & 467.4 (MH^+); t_R = 1.63.

The following compounds were obtained analogously from corresponding compounds of the general formula XXIII and appropriate anilines of the general formula VI:



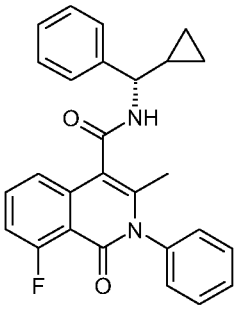
8-Chloro-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide (1i).

The title compound and its alternative method of preparation was described in the example 1i.



6b *8-Fluoro-1-oxo-3-(2-oxo-pyrrolidin-1-ylmethyl)-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-cyclopropyl-phenyl-methyl)-amide.*

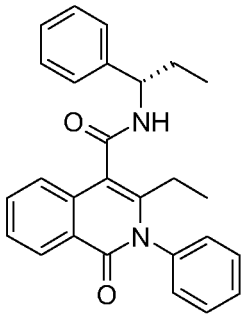
LC-MS (m/z) 510.3 (MH^+); t_R = 1.25.



6c *8-Fluoro-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-cyclopropyl-phenyl-methyl)-amide.*

LC-MS (m/z) 427.3 (MH^+); t_R = 1.39.

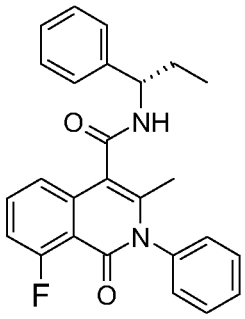
Example 7



7a *3-Ethyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide.*

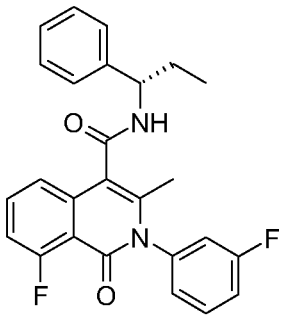
A sealed mixture of 2-[2-oxo-1-((S)-1-phenyl-propylcarbamoyl)-butyl]-benzoic acid (82 mg, 0.2 mmol) and aniline (0.3 ml, 3.3 mmol) in acetonitrile (0.3 ml) was heated under microwave irradiation at +160°C for 10 min. The mixture was partitioned between ethyl acetate (20 ml) and 3M aq. HCl (2 x 8 ml), sat. aq. $NaHCO_3$ (2 x 10 ml and brine, dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography (SiO_2, gradient heptane – ethyl acetate) to give 32 mg of the title compound. LC-MS (m/z) 411.5 (MH^+); t_R = 1.48. ^1H NMR (500 MHz, DMSO-d_6): a mixture of two atropisomers.

The following compounds were obtained analogously by condensation of compounds of the general formula XXV with appropriate aniline of the general formula VI:



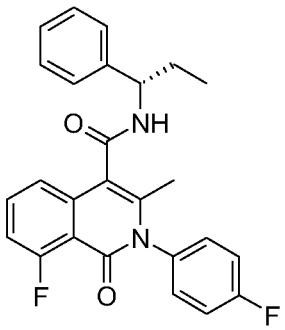
7b *8-Fluoro-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide.*

LC-MS (m/z) 415.5 (MH^+); t_R = 1.39.



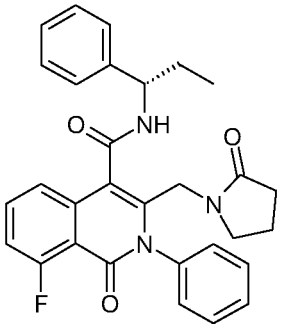
7c 8-Fluoro-2-(3-fluoro-phenyl)-3-methyl-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide.

LC-MS (m/z) 433.5 (MH^+); t_R = 1.41.



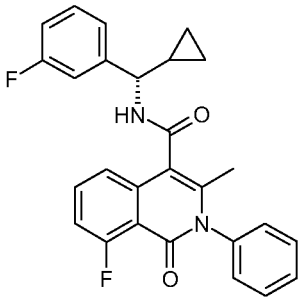
7d 8-Fluoro-2-(4-fluoro-phenyl)-3-methyl-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide.

LC-MS (m/z) 433.6 (MH^+); t_R = 1.4.



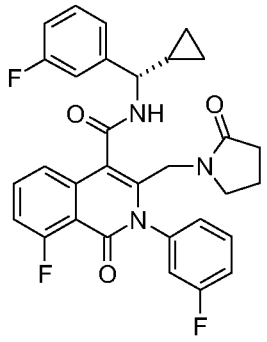
8-Fluoro-1-oxo-3-(2-oxo-pyrrolidin-1-ylmethyl)-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide (3e).

The title compound and its alternative method of preparation was described above in the example 3.



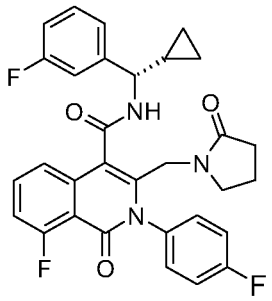
7e *8-Fluoro-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-cyclopropyl-(3-fluoro-phenyl)-methyl]-amide.*

LC-MS (m/z) 445.6 (MH^+); t_R = 1.44. ^{1}H NMR (250 MHz, 70°C, DMSO-d_6): 0.41-0.61 (m, 4H), 1.25 (m, 1H), 1.86 (s, 3H), 4.49 (t, J=8.9 Hz, 1H), 7.04 (m, 1H), 7.13-7.31 (m, 6H), 7.37 (m, 1H), 7.42-7.6 (m, 3H), 7.67 (m, 1H), 8.93 (br d, J=8.5 Hz, 1H, NH).



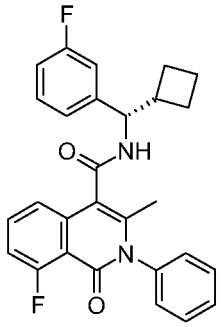
7f 8-Fluoro-2-(3-fluoro-phenyl)-1-oxo-3-(2-oxo-pyrrolidin-1-ylmethyl)-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-cyclopropyl-(3-fluoro-phenyl)-methyl]-amide.

The title product was isolated by preparative TLC on silica gel. LC-MS (m/z) 546.4 (MH^+); t_R = 0.71 (method B).



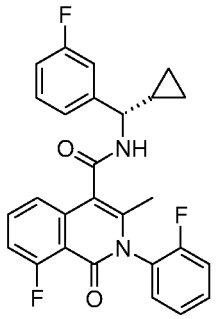
7g 8-Fluoro-2-(4-fluoro-phenyl)-1-oxo-3-(2-oxo-pyrrolidin-1-ylmethyl)-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-cyclopropyl-(3-fluoro-phenyl)-methyl]-amide.

The title product was isolated by preparative TLC on silica gel. LC-MS (m/z) 546.3 (MH^+); t_R = 0.71 (method B).



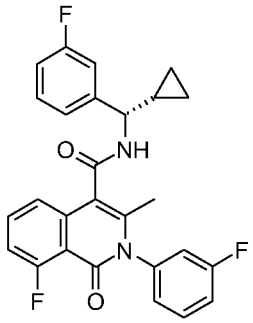
***7h** 8-Fluoro-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-cyclobutyl-(3-fluoro-phenyl)-methyl]-amide.*

LC-MS (m/z) 459.4 (MH^+); t_R = 1.54.



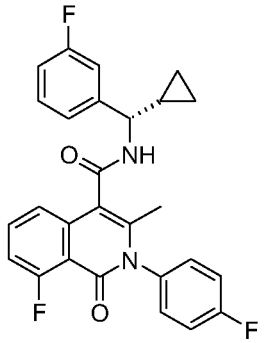
7i *8-Fluoro-2-(2-fluoro-phenyl)-3-methyl-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-cyclopropyl-(3-fluoro-phenyl)-methyl]-amide.*

LC-MS (m/z) 463.3 (MH^+); t_R = 1.46.



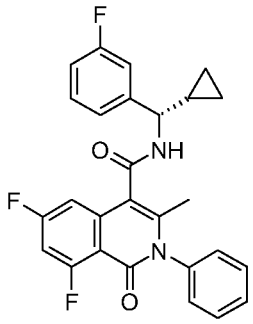
7j *8-Fluoro-2-(3-fluoro-phenyl)-3-methyl-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-cyclopropyl-(3-fluoro-phenyl)-methyl]-amide.*

LC-MS (m/z) 463.3 (MH^+); t_R = 1.46.



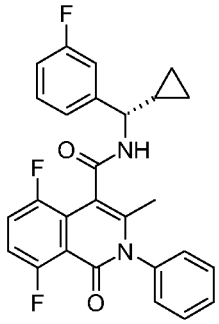
7k *8-Fluoro-2-(4-fluoro-phenyl)-3-methyl-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-cyclopropyl-(3-fluoro-phenyl)-methyl]-amide.*

LC-MS (m/z) 463.4 (MH^+); t_R = 1.45.



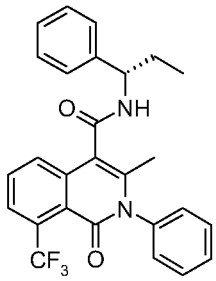
7l *6,8-Difluoro-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-cyclopropyl-(3-fluoro-phenyl)-methyl]-amide.*

LC-MS (m/z) 463.2 (MH^+); t_R = 0.82 (method B).



7m *5,8-Difluoro-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-cyclopropyl-(3-fluoro-phenyl)-methyl]-amide.*

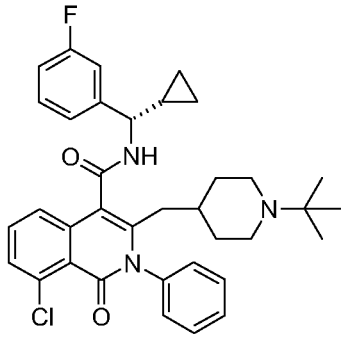
LC-MS (m/z) 463.4 (MH^+); t_R = 1.39.



7n 3-Methyl-1-oxo-2-phenyl-8-trifluoromethyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide.

LC-MS (m/z) 465.3 (MH^+); t_R = 1.57.

Example 8



8a *3-(1-tert-Butyl-piperidin-4-ylmethyl)-8-chloro-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-cyclopropyl-(3-fluoro-phenyl)-methyl]-amide.*

To a cold (ice bath) mixture of 2-(1-tert-butyl-piperidin-4-yl)-N-phenyl-acetamide (250 mg, 0.91 mmol) and 2,6-dimethylpyridine (0.139 ml, 1.2 mmol) in 1,2-dichloroethane (8 ml) oxalyl chloride (0.07 ml, 0.8 mmol) was added and stirred at 0°C for 15 min. 2-Chloro-6-({[(S)-cyclopropyl-(3-fluoro-phenyl)-methyl]-carbamoyl}-methyl)-benzoic acid (70 mg, 0.2 mmol) was added and the reaction mixture was stirred in a sealed vessel at 90°C for 15 hours. It was partitioned between 0.5 M aq. NaOH (40 ml) and ethyl acetate (200 ml), the organic phase washed with water, dried and evaporated. The residue was purified by flash chromatography (SiO_2, ethyl acetate – methanol) to give 19 mg of the title compound. LC-MS (m/z) 600.6 (MH^+); t_R = 1.1. ^1H NMR (500 MHz, r.t., DMSO-d_6): broad signals, a mixture of two atropisomers.

Reagents used for the preparation of the compounds.

Name	Supplier	CAS no.	Cat.no.
Ethyl acetoacetate	Aldrich	141-97-9	E 964-1
Methyl acetoacetate	Aldrich	105-45-3	53,736-5
Sodium hydride, 60% dispersion in mineral oil	Aldrich	7646-69-7	45,291-2
Copper (I) bromide	Aldrich	7787-70-4	21,286-5
2-Bromobenzoic acid	Janssen Chimica	88-65-3	41066/1

2-Bromo-4-methylbenzoic acid	Matrix Scientific	7697-27-0	001816
2-Bromo-6-methylbenzoic acid	Matrix Scientific	90259-31-7	001819
2,5-Dibromobenzoic acid	ABCR	610-71-9	AV15077
2-Bromo-4-fluorobenzoic acid	Fluorochem	1006-41-3	005470
2-Bromo-5-chlorobenzoic acid	ABCR	21739-93-5	AV10103
2-Bromo-5-fluorobenzoic acid	Aldrich	394-28-5	56,349-8
2-Bromo-3-methylbenzoic acid	Fluorochem	53663-39-1	112800
2-Bromo-5-methylbenzoic acid	Fluorochem	6967-82-4	B2947-E
2-Bromo-6-chlorobenzoic acid	Fluorochem	93224-85-2	19332
Aniline	Aldrich	62-53-3	13,293-4
2-Fluoroaniline	Lancaster	348-54-9	1236
2,6-Difluoroaniline	Aldrich	5509-65-9	196614
2-Chloroaniline	Aldrich	95-51-2	23300
o-Toluidine	Aldrich	95-53-4	18,542-6
3-Fluoroaniline	Flrochem	372-19-0	1438
3-Chloroaniline	Fluka	108-42-9	23330
m-Toluidine	Aldrich	108-44-1	511218
(S)-(-)-1-Phenylpropylamine	Lancaster	3789-59-1	X16320G002 5
C-((S)-*C*-Cyclopropyl-*C*-phenyl)-methylamine	The compound was prepared according to a described procedure in WO 2005/014575		
C-[(S)-*C*-Cyclopropyl-*C*-(3-fluoro-phenyl)]-methylamine	The compound was prepared according to a described procedure in WO 2005/014575		
Tetraethoxysilane	Aldrich	78-10-4	236209
1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC)	Aldrich	25952-53-8	16,146-2
1-Hydroxybenzotriazole (HOBT)	ABCR	2592-95-2	AV21700
Dimethylamine, 33% solution in abs. Ethanol	Fluka	124-40-3	38950

Methylamine, 2M solution in THF	Aldrich	74-89-5	42,646-6
2-Pyrrolidone	Aldrich	616-45-5	240338
1,1-Diphenylhydrazine hydrochloride	Aldrich	530-47-2	11,459-6
Phenylhydrazine	Aldrich	100-63-0	P2,625-2
Methyl chloroformate	Aldrich	79-22-1	M35304
Sodium cyanide	Aldrich	143-33-9	380970

Reagents used for the preparation of the compounds, continued.

Name	**Supplier**	**CAS no.**	**Cat.no.**
Homophthalic anhydride	ABCR	703-59-3	AV15538
Cyclopropanecarboxaldehyde	Aldrich	1489-69-6	27,221-3
1-Bromo-3-fluorobenzene	Aldrich	1073-06-9	B67007
(S)-3-Amino-3-phenylpropanenitrile	Netchem	-	331516
3,4-Dichloroaniline	Aldrich	95-76-1	56042
2-Bromo-6-nitrobenzoic acid	Ref. 1	38876-67-4	-
2-Bromo-6-methoxybenzoic acid	Ref. 2	31786-45-5	-
tert-Butyl 2-bromoacetate	Aldrich	5292-43-3	12,426-0
Ethyl (triphenylphosphorylidene)acetate	Aldrich	1099-45-2	C510-6
1-(tert-Butoxycarbonyl)piperazine	Lancaster	57260-71-6	13363
3-Pyrazolidinone hydrochloride	Acros	1752-88-1	335490050
2-Oxo-4-(tert-butoxycarbonyl)piperazine	Aldrich	76003-29-7	64,105-7
2-Piperidone	Aldrich	675-20-7	V20-9

Ref. 1. The compound was prepared according to a described procedure: S.C. Glossop *Synthesis* **2007**, *7,* 981.

Ref. 2. The compound was prepared according to a described procedure: T. Sugaya, Y. Mimura, N. Kato, M. Ikuta, T. Mimura et al. *Synthesis* **1994**, 73.

Example 9 NK3 receptor binding assay

Membranepreparation: BHK cells stably expressing the human NK3 receptor were seeded in harvesting plates in Dulbeccos MEM containing GlutaMax (862 mg/l), 1mM sodium pyruvate, 10% fetal calf serum, 1% Pen/Strep, 1 mg/ml G418 and were grown at 34 °C in a humidified atmosphere containing 10% CO_2. To increase receptor expression, 10 µM trichotatin A was added to the media 24 hours before harvest of the cells at a confluency of app 90%. Prior to the harvesting, the cells were washed twice with PBS without Mg^{2+} og Ca^{2+} and subsequently scrapped of in 10 ml PBS pr harvesting plate. The cells suspension were centrifuged at 1500xG in three minutes before resuspension in 15 mM Tris-HCl pH 7,5 buffer containing 2 mM $MgCl_2$; 0,3 mM EDTA and 1 mM EGTA (buffer A). The cell suspention was homogenised and subsequently centrifuged at 40000xG in 30 minutes. The membrane-pellet was resuspended in buffer A containing 250 mM sucrose, alliquoted and stored at – 80 °C.

Affinity assay description: The assay was performed as a SPA-based competition-binding assay in a 50 mM Tris pH 7.4 assay buffer containing 120 mM NaCl, 3 mM $MnCl_2$, 40 µg/ml bacitracin, 2 µg/ml Chymostatin, 1 µg/ml Phosphoramidon and 4 µg/ml Leupeptin. App 0.02 nM ^{125}I-NKB was mixed with test compounds before addition of 4 µg of the homogenised NK3 membrane preparation and 0,025 mg SPA beads in a total volume of 60 µl. The assay plate was subsequently under agitation incubated for 90 min at RT. The plate was centrifugated 10 minutes at 500xG and counted in a topcounter 5 minuttes pr well.

The total binding, which comprised less than 5 % of added radioligand, was defined using assay buffer whereas the non-specific binding was defined in the presence of 1 µM osanetant. The non-specific binding constituted app 5 % of the total binding.

Data points were expressed in percent of the specific binding of ^{125}I-NKB and the IC_{50} values (concentration causing 50 percent inhibition of ^{125}I-NKB specific binding) were determined by non-linear regression analysis using a sigmoidal variable slope curve fitting. The dissociation constant (K_i) were calculated from the Cheng Prusoff equation ($K_i = IC_{50}/(1+(L/K_D))$), where the concentration of free radioligand L is approximated to the concentration of added ^{125}I-NKB in the assay (app 0,02 nM).

The K_D of ^{125}I-NKB was determined to be 0,7 nM from three independent saturation assays each performed with duplicate determinations. Bmax was app 2 pmol/mg.

The compounds of the present invention generally have K_i values of 500 nM or less. Many compounds, in fact, have K_i values below 100 nM and down to single digit values.

The table below shows the K_i for the NK3 receptor

Compound	K_i nM
Ex 2a	180
Ex 2bm	8.2
Ex 2hs	5.3
Ex 2hz	3
Ex 3a	72
Ex 5a	55

See also the table in Example 10 for more affinity data for the compounds of the present invention.

Example 10 NK3 receptor efficacy and potency assay

BHK cells stably expressing the human NK3 receptor were seeded in 100 µl media in black walled clear-base 96-wells plates (Costar) aiming at a confluency of 95-100% at the day of assay. The assay was performed according to the FLIPR Calcium 4 Assay kit (Molecular Devices). At the day of the assay, the media was removed and the cells were washed once with the HBSS buffer (Hanks BSS buffer, pH 7,4 containing 20 mM Hepes) before 100 µl of a solution of the calcium assay reagent dissolved in the HBSS buffer containing 2,5 mM probinicid was added to the cells. The plates were incubated for 60 min at 34ºC, 10% CO_2 before use in the FLIPR for examination of fluorescence.

One representative plate was examined with a dose-response curve with NKB in a setup in which the wells initially were added HBSS buffer and 15 min later the various concentrations of NKB were added in order to determine the EC_{50} and EC_{85} of NKB. All compound plates used for NKB were precoated with a 1% BSA solution

and subsequently washed three times with H_2O. NKB was diluted in HBSS buffer containing 0,1% BSA.

For efficacy and potency evaluation of compounds, these were diluted in HBSS buffer prior to test. For test of agonist activity, 25 µl of the diluted compound solution was added and the plate was analyzed for 5 minutes in the FLIPR. For test of antagonist activity, the plate was incubated for another 45 minutes before addition of 25 µl of the EC_{85} concentration of NKB (app. 4 nM) as described above. The plates were subsequently analyzed for 5 minutes before the assay was terminated. The maximal increase in fluorescence over background following each ligand addition was determined. The IC_{50} value was calculated using sigmoidal variable slope curve fitting, and the cIC_{50} value was determined using the equation ($cIC_{50} = IC_{50}/(1+(EC_{85}/EC_{50}))$), where EC_{85} and EC_{50} for NKB were determined as described above.

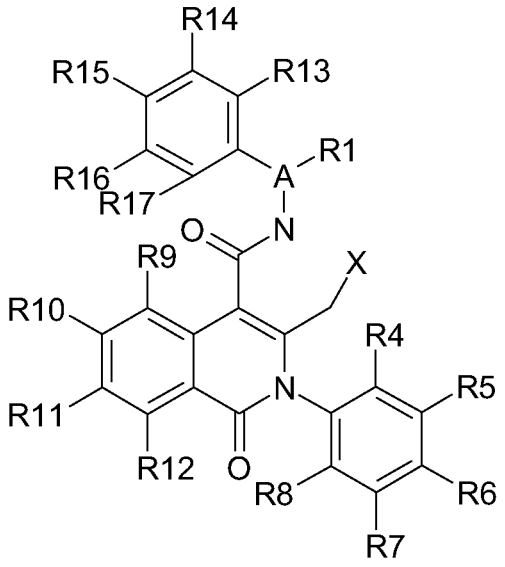
All isoquinolinones of the present invention characterized in the NK3 receptor efficacy and potency assay have been antagonists without any observed significant agonist activity at relevant doses. The table shows affinity data (obtained as described in Example 9) and potency data obtained with the compounds of the invention. Minor diffrences between the tabulated values in Example 9 and 10 only reflects that more than one batch have been tested and/or that one batch has been tested more than once.

	Affinity		Potency
Example No	**K_i/nM**		**cIC_{50}/nM**
2e	330		470
1i	41		130
3a	88		270
2r	320		420
2s	200		340
2u	90		96
2ah	290		360
2bg	160		220
2bm	8,8		14
2bn	160		300
2cw	8,4		45
2cz	76		49
2df	340		450
2ec	210		520
2eg	240		610
2es	140		240

2ey	240		480
2fm	33		140
2gt	9,2		22
2hq	10		44
2hs	7,5		21
2hu	6,2		29
2hv	14		35
2hw	8,2		63
2hx	9,3		68
2hy	8,8		63
2hz	4,5		35
2ia	12		100
2iy	17		92
1t	27		44
2kh	82		120
2kn	8,7		41
2ko	11		5,6
3d	16		46
2lj	18		16
3b	32		47
1bh	21		81
2ll	7,9		6,3
8a	7		9,9
1bn	23		23
6c	23		24
1bl	470		

Claims

1. A compound according to formula I



[I]

wherein A represents N, CH or CR^1;

wherein each R^1 independently represents hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, -C(O)-C_{1-6}alkyl, -C(O)-C_{2-6}alkenyl, -C(O)-C_{2-6}alkynyl, -C(O)-O-C_{1-6}alkyl, -C(O)-O-C_{2-6}alkenyl, -C(O)-O-C_{2-6}alkynyl or phenyl, wherein said phenyl, C_{1-6}alkyl, C_{2-6}alkenyl or C_{2-6}alkynyl is optionally substituted with one or more substituents selected from halogen, hydroxyl, haloC_{1-6}alkyl, nitro, C_{1-6}alkoxy, and NR^2R^3;

wherein X represents hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, cyano, $-OR^2$, -O-C(O)R^2, -OC(O)NR^2R^3, -C(O)-NR^2R^3, -N(R^2)C(O)R^3, -N(R^2)-C(O)NR^2R^3 or NR^2R^3, or X represents a mono-cyclic, bi-cyclic or tri-cyclic moiety having 4-16 ring atoms one of which is nitrogen, and wherein one, two or three additional ring atoms may be a hetero atom selected from N, O and S, and wherein said mono-cyclic, bi-cyclic or tri-cyclic moiety may optionally be substituted with one or more substituents W,

wherein W is selected from hydrogen, hydroxy, halogen, cyano, (=O), -O-$(CH_2)_c$-O-, wherein c is 2 or 3 (spiro), $(CH_2)_d$, wherein d is 5 or 6 (spiro), C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, -C(O)-C_{1-6}alkyl, -C(O)-C_{2-6}alkenyl, -C(O)-C_{2-6}alkynyl, -C(O)-O-C_{1-6}alkyl, -C(O)-O-C_{2-6}alkenyl, -C(O)-O-C_{2-6}alkynyl, -O-C(O)-C_{1-6}alkyl, -O-

$C(O)$-C_{2-6}alkenyl, -O-$C(O)$-C_{2-6}alkynyl, -$C(O)$H, COOH; or wherein W represents a moiety of the formula $-(CH_2)_a$-Y-$(CH_2)_b$-Z;

wherein a and b independently represent an integer selected from 0, 1, 2 and 3;

wherein Y represents a bond, $C(O)$, O, S, -O-$C(O)$, -$C(O)$-O-, -NR^2-, -NR^2-$C(O)$-, -$C(O)$-NH-, or $S(O)_2$;

wherein Z represents hydrogen, C_{1-6}alkyl, NR^2R^3, cyano or a mono-cyclic or fused bi-cyclic moiety comprising 4 to12 ring atoms of which optionally one, two or three are hetero atoms selected from amongst N, O, and S, and wherein said mono-cyclic or fused bi-cyclic moiety is optionally substituted with one or more substituents selected from the group consisting of halogen, cyano, C_{1-6}alkyl, hydroxyl, and C_{1-6}alkoxy, pyrazinyl, phenyl, pyridyl, and halogen substituted phenyl;

wherein each of R^4-R^8, R^9-R^{12}, and R^{13}-R^{17} independently represent hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, halogen, NR^2R^3, hydroxy, cyano, nitro, C_{1-6}alkoxy, haloC_{1-6}alkyl or hydroxyC_{1-6}alkyl;

wherein R^2 and R^3 independently represent hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, hydroxyC_{1-6}alkyl, haloC_{1-6}alkyl or phenyl;

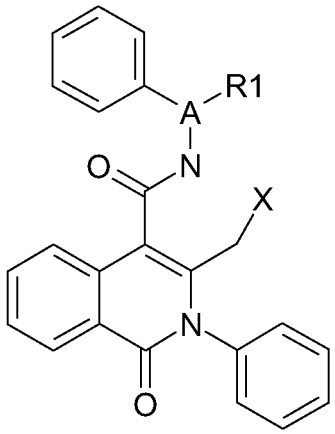
and pharmaceutically acceptable salts thereof.

2. A compound according to claim 1, wherein R^4-R^8 represent hydrogen.

3. A compound according to claim 1, wherein R^9-R^{12} represent hydrogen.

4. A compound according to claim 1, wherein R^{13}-R^{17} represent hydrogen.

5. A compound according to claim 1 of the formula I_a



[Ia]

wherein A represents N, CH or CR^1;

wherein each R^1 independently represents hydrogen, C_{1-6}alkyl, -C(O)-C_{1-6}alkyl, -C(O)-O-C_{1-6}alkyl, or phenyl, wherein said phenyl or C_{1-6}alkyl, is optionally substituted with one or more substituents selected from halogen, hydroxyl, haloC_{1-6}alkyl, nitro, C_{1-6}alkoxy, and NR^2R^3;

wherein X represents hydrogen, C_{1-6}alkyl, cyano, $-OR^2$, $-O-C(O)R^2$, $-OC(O)NR^2R^3$, $-C(O)-NR^2R^3$, $-N(R^2)C(O)R^3$, $-N(R^2)-C(O)NR^2R^3$ or NR^2R^3, or X represents a mono-cyclic, bicyclic or tri-cyclic moiety having 4-16 ring atoms one of which is nitrogen, and wherein one, two or three additional ring atoms may be a hetero atom selected from N, O and S, and wherein said mono-cyclic, bi-cyclic or tri-cyclic moiety may optionally be substituted with one or more substituents W, wherein W is selected from hydrogen, hydroxy, halogen, cyano, (=O), $-O-(CH_2)_c-O-$, wherein c is 2 or 3 (spiro), $(CH_2)_d$, wherein d is 5 or 6 (spiro), C_{1-6}alkyl, C_{1-6}alkoxy, -C(O)-C_{1-6}alkyl, -C(O)-O-C_{1-6}alkyl, -O-C(O)-C_{1-6}alkyl, -C(O)H, COOH; or wherein W represents a moiety of the formula $-(CH_2)_a-Y-(CH_2)_b-Z$;

wherein a and b independently represent an integer selected from 0, 1, 2 and 3;

wherein Y represents a bond, C(O), O, S, -O-C(O), -C(O)-O-, $-NR^2-$, $-NR^2-C(O)-$, -C(O)-NH-, or $S(O)_2$;

wherein Z represents hydrogen, C_{1-6}alkyl, NR^2R^3, cyano or a mono-cyclic or fused bi-cyclic moiety comprising 4 to 12 ring atoms of which optionally one, two or three are hetero atoms selected from amongst N, O, and S, and wherein said mono-cyclic or

fused bi-cyclic moiety is optionally substituted with one or more substituents selected from the group consisting of halogen, cyano, C_{1-6}alkyl, hydroxyl, and C_{1-6}alkoxy, pyrazinyl, phenyl, pyridyl, and halogen substituted phenyl;
wherein each of R^4-R^8, R^9-R^{12}, and R^{13}-R^{17} independently represent hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, halogen, NR^2R^3, hydroxy, cyano, nitro, C_{1-6}alkoxy, haloC_{1-6}alkyl or hydroxyC_{1-6}alkyl;
wherein R^2 and R^3 independently represent hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, hydroxyC_{1-6}alkyl, haloC_{1-6}alkyl or phenyl;
and pharmaceutically acceptable salts thereof.

6. A compound according to claim 5, wherein A represents CH.

7. A compound according to claim 6, wherein R^1 represents C_{1-6}alkyl.

8. A compound according to claim 7, wherein R^1 represents ethyl or cyclopropyl.

9. A compound according to any of claims 5-8, wherein X represents hydrogen, C_{1-6}alkyl, cyano, -OR^2, -O-C(O)R^2, -OC(O)NR^2R^3, -C(O)-NR^2R^3-, -$N(R^2)C(O)R^3$, -$N(R^2)$-C(O)NR^2R^3 or NR^2R^3, wherein R^2 and R^3 independently represent hydrogen, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, haloC_{1-6}alkyl or phenyl.

10. A compound according to claim 9, wherein X represents hydrogen, methyl, or NR^2R^3, wherein R^2 and R^3 independently represent hydrogen, C_{1-6}alkyl, or hydroxyC_{1-6}alkyl.

11. A compound according to claim 10, wherein R^2 and R^3 independently represent hydrogen, cyclopropylmethyl, methyl, ethyl or cyclopropyl.

12. A compound according to any of claims 5-8, wherein X represents a mono-cyclic, bi-cyclic or tri-cyclic moiety having 4-16 ring atoms one of which is nitrogen, and wherein one, two or three additional ring atoms may be a hetero atom selected from N, O and S, and wherein said mono-cyclic, bi-cyclic or tri-cyclic moiety may

optionally be substituted with one or more substituents W, wherein W is selected from hydrogen, hydroxy, halogen, cyano, (=O), -O-$(CH_2)_c$-O-, wherein c is 2 or 3 (spiro), $(CH_2)_d$, wherein d is 5 or 6 (spiro), C_{1-6}alkyl, C_{1-6}alkoxy, -C(O)-C_{1-6}alkyl, -C(O)-O-C_{1-6}alkyl, -O-C(O)-C_{1-6}alkyl, -O-C(O)-, -C(O)H, COOH; or wherein W represents a moiety of the formula –$(CH_2)_a$-Y-$(CH_2)_b$-Z;

wherein a and b independently represent an integer selected from 0, 1, 2 and 3;

wherein Y represents a bond, C(O), O, S, -O-C(O), -C(O)-O-, -NR^2-, -NR^2-C(O)-, -C(O)-NH-, or $S(O)_2$;

wherein Z represents hydrogen, C_{1-6}alkyl, NR^2R^3, cyano or a mono-cyclic or fused bi-cyclic moiety comprising 4 to 12 ring atoms of which optionally one, two or three are hetero atoms selected from amongst N, O, and S, and wherein said mono-cyclic or fused bi-cyclic moiety is optionally substituted with one or more substituents selected from the group consisting of halogen, cyano, C_{1-6}alkyl, hydroxyl, and C_{1-6}alkoxy, pyrazinyl, phenyl, pyridyl, and halogen substituted phenyl;

wherein R^2 and R^3 independently represent hydrogen, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, haloC_{1-6}alkyl or phenyl.

13. A compound according to any of claims 12, wherein X represents a mono-cyclic moiety having 5 ring atoms one of which is nitrogen, and wherein one, two or three additional ring atoms may be a hetero atom selected from N, O and S, and wherein said mono-cyclic moiety may optionally be substituted with one or more substituents W, wherein W is selected from hydrogen, hydroxy, halogen, cyano, (=O), -O-$(CH_2)_c$-O-, wherein c is 2 or 3 (spiro), $(CH_2)_d$, wherein d is 5 or 6 (spiro), C_{1-6}alkyl, C_{1-6}alkoxy, -C(O)-C_{1-6}alkyl, -C(O)-O-C_{1-6}alkyl, -O-C(O)-C_{1-6}alkyl, -O-C(O)-, -C(O)H, COOH; or wherein W represents a moiety of the formula –$(CH_2)_a$-Y-$(CH_2)_b$-Z;

wherein a and b independently represent an integer selected from 0, 1, 2 and 3;

wherein Y represents a bond, C(O), O, S, -O-C(O), -C(O)-O-, -NR^2-, -NR^2-C(O)-, -C(O)-NH-, or $S(O)_2$;

wherein Z represents hydrogen, C_{1-6}alkyl, NR^2R^3, cyano or a mono-cyclic or fused bi-cyclic moiety comprising 4 to 12 ring atoms of which optionally one, two or three are hetero atoms selected from amongst N, O, and S, and wherein said mono-cyclic or

fused bi-cyclic moiety is optionally substituted with one or more substituents selected from the group consisting of halogen, cyano, C_{1-6}alkyl, hydroxyl, and C_{1-6}alkoxy, pyrazinyl, phenyl, pyridyl, and halogen substituted phenyl;
wherein R^2 and R^3 independently represent hydrogen, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, haloC_{1-6}alkyl or phenyl.

14. A compound according to any of claims 12, wherein X represents a mono-cyclic moiety having 6 ring atoms one of which is nitrogen, and wherein one, two or three additional ring atoms may be a hetero atom selected from N, O and S, and wherein said mono-cyclic moiety may optionally be substituted with one or more substituents W, wherein W is selected from hydrogen, hydroxy, halogen, cyano, (=O), -O-$(CH_2)_c$-O-, wherein c is 2 or 3 (spiro), $(CH_2)_d$, wherein d is 5 or 6 (spiro), C_{1-6}alkyl, C_{1-6}alkoxy, -C(O)-C_{1-6}alkyl, -C(O)-O-C_{1-6}alkyl, -O-C(O)-C_{1-6}alkyl, -O-C(O)-, -C(O)H, COOH; or wherein W represents a moiety of the formula –$(CH_2)_a$-Y-$(CH_2)_b$-Z;
wherein a and b independently represent an integer selected from 0, 1, 2 and 3;
wherein Y represents a bond, C(O), O, S, -O-C(O), -C(O)-O-, -NR^2-, -NR^2-C(O)-, -C(O)-NH-, or $S(O)_2$;
wherein Z represents hydrogen, C_{1-6}alkyl, NR^2R^3, cyano or a mono-cyclic or fused bi-cyclic moiety comprising 4 to 12 ring atoms of which optionally one, two or three are hetero atoms selected from amongst N, O, and S, and wherein said mono-cyclic or fused bi-cyclic moiety is optionally substituted with one or more substituents selected from the group consisting of halogen, cyano, C_{1-6}alkyl, hydroxyl, and C_{1-6}alkoxy, pyrazinyl, phenyl, pyridyl, and halogen substituted phenyl;
wherein R^2 and R^3 independently represent hydrogen, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, haloC_{1-6}alkyl or phenyl.

15. A compound according to any of claims 12, wherein X represents a mono-cyclic moiety having 7 ring atoms one of which is nitrogen, and wherein one, two or three additional ring atoms may be a hetero atom selected from N, O and S, and wherein said mono-cyclic moiety may optionally be substituted with one or more substituents W, wherein W is selected from hydrogen, hydroxy, halogen, cyano, (=O),

-O-$(CH_2)_c$-O-, wherein c is 2 or 3 (spiro), $(CH_2)_d$, wherein d is 5 or 6 (spiro), C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, -C(O)-C_{1-6}alkyl, -C(O)-O-C_{1-6}alkyl, -O-C(O)-C_{1-6}alkyl, -C(O)H, COOH; or wherein W represents a moiety of the formula –$(CH_2)_a$-Y-$(CH_2)_b$-Z;

wherein a and b independently represent an integer selected from 0, 1, 2 and 3;

wherein Y represents a bond, C(O), O, S, -O-C(O), -C(O)-O-, -NR^2-, -NR^2-C(O)-, -C(O)-NH-, or $S(O)_2$;

wherein Z represents hydrogen, C_{1-6}alkyl, NR^2R^3, cyano or a mono-cyclic or fused bi-cyclic moiety comprising 4 to 12 ring atoms of which optionally one, two or three are hetero atoms selected from amongst N, O, and S, and wherein said mono-cyclic or fused bi-cyclic moiety is optionally substituted with one or more substituents selected from the group consisting of halogen, cyano, C_{1-6}alkyl, hydroxyl, and C_{1-6}alkoxy, pyrazinyl, phenyl, pyridyl, and halogen substituted phenyl;

wherein R^2 and R^3 independently represent hydrogen, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, haloC_{1-6}alkyl or phenyl.

16. A compound according to any of claims 12, wherein X represents a mono-cyclic or bi-cyclic moiety having 8 ring atoms one of which is nitrogen, and wherein one, two or three additional ring atoms may be a hetero atom selected from N, O and S, and wherein said cyclic or bicyclic moiety may optionally be substituted with one or more substituents W, wherein W is selected from hydrogen, hydroxy, halogen, cyano, (=O), -O-$(CH_2)_c$-O-, wherein c is 2 or 3 (spiro), $(CH_2)_d$, wherein d is 5 or 6 (spiro), C_{1-6}alkyl, C_{1-6}alkoxy, -C(O)-C_{1-6}alkyl, -C(O)-O-C_{1-6}alkyl, -O-C(O)-C_{1-6}alkyl, -C(O)H, COOH; or wherein W represents a moiety of the formula –$(CH_2)_a$-Y-$(CH_2)_b$-Z;

wherein a and b independently represent an integer selected from 0, 1, 2 and 3;

wherein Y represents a bond, C(O), O, S, -O-C(O), -C(O)-O-, -NR^2-, -NR^2-C(O)-, -C(O)-NH-, or $S(O)_2$;

wherein Z represents hydrogen, C_{1-6}alkyl, NR^2R^3, cyano or a mono-cyclic or fused bi-cyclic moiety comprising 4 to 12 ring atoms of which optionally one, two or three are hetero atoms selected from amongst N, O, and S, and wherein said mono-cyclic or fused bi-cyclic moiety is optionally substituted with one or more substituents selected

from the group consisting of halogen, cyano, C_{1-6}alkyl, hydroxyl, and C_{1-6}alkoxy, pyrazinyl, phenyl, pyridyl, and halogen substituted phenyl;
wherein R^2 and R^3 independently represent hydrogen, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, haloC_{1-6}alkyl or phenyl.

17. A compound according to any of claims 12, wherein X represents a mono-cyclic or bi-cyclic moiety having 9 ring atoms one of which is nitrogen, and wherein one, two or three additional ring atoms may be a hetero atom selected from N, O and S, and wherein said mono-cyclic or bi-cyclic moiety may optionally be substituted with one or more substituents W, wherein W is selected from hydrogen, hydroxy, halogen, cyano, (=O), -O-$(CH_2)_c$-O-, wherein c is 2 or 3 (spiro), $(CH_2)_d$, wherein d is 5 or 6 (spiro), C_{1-6}alkyl, C_{1-6}alkoxy, -C(O)-C_{1-6}alkyl, -C(O)-O-C_{1-6}alkyl, -O-C(O)-C_{1-6}alkyl, -C(O)H, COOH; or wherein W represents a moiety of the formula –$(CH_2)_a$-Y-$(CH_2)_b$-Z;
wherein a and b independently represent an integer selected from 0, 1, 2 and 3;
wherein Y represents a bond, C(O), O, S, -O-C(O), -C(O)-O-, -NR^2-, -NR^2-C(O)-, -C(O)-NH-, or $S(O)_2$;
wherein Z represents hydrogen, C_{1-6}alkyl, NR^2R^3, cyano or a mono-cyclic or fused bi-cyclic moiety comprising 4 to 12 ring atoms of which optionally one, two or three are hetero atoms selected from amongst N, O, and S, and wherein said mono-cyclic or fused bi-cyclic moiety is optionally substituted with one or more substituents selected from the group consisting of halogen, cyano, C_{1-6}alkyl, hydroxyl, and C_{1-6}alkoxy, pyrazinyl, phenyl, pyridyl, and halogen substituted phenyl;
wherein R^2 and R^3 independently represent hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, hydroxyC_{1-6}alkyl, haloC_{1-6}alkyl or phenyl.

18. A compound according to any of claims 12, wherein X represents a mono-cyclic or bi-cyclic moiety having 10 ring atoms one of which is nitrogen, and wherein one, two or three additional ring atoms may be a hetero atom selected from N, O and S, and wherein said mono-cyclic or bi-cyclic moiety may optionally be substituted with one or more substituents W, wherein W is selected from hydrogen, hydroxy, halogen, cyano, (=O), -O-$(CH_2)_c$-O-, wherein c is 2 or 3 (spiro), $(CH_2)_d$, wherein d is

5 or 6 (spiro), C_{1-6}alkyl, C_{1-6}alkoxy, -C(O)-C_{1-6}alkyl, -C(O)-O-C_{1-6}alkyl, -O-C(O)-C_{1-6}alkyl, -C(O)H, COOH; or wherein W represents a moiety of the formula $-(CH_2)_a$-Y-$(CH_2)_b$-Z;

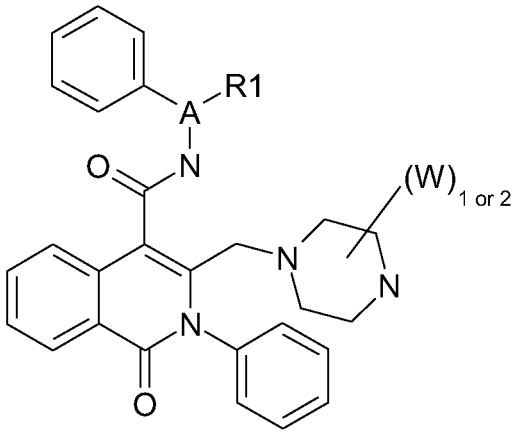
wherein a and b independently represent an integer selected from 0, 1, 2 and 3;

wherein Y represents a bond, C(O), O, S, -O-C(O), -C(O)-O-, -NR^2-, -NR^2-C(O)-, -C(O)-NH-, or $S(O)_2$;

wherein Z represents hydrogen, C_{1-6}alkyl, NR^2R^3, cyano or a mono-cyclic or fused bi-cyclic moiety comprising 4 to 12 ring atoms of which optionally one, two or three are hetero atoms selected from amongst N, O, and S, and wherein said mono-cyclic or fused bi-cyclic moiety is optionally substituted with one or more substituents selected from the group consisting of halogen, cyano, C_{1-6}alkyl, hydroxyl, and C_{1-6}alkoxy, pyrazinyl, phenyl, pyridyl, and halogen substituted phenyl;

wherein R^2 and R^3 independently represent hydrogen, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, haloC_{1-6}alkyl or phenyl.

19. A compound according to claim 1 of the formula I_b



[Ib]

wherein A represents N, CH or CR^1;

wherein each R^1 independently represents hydrogen, C_{1-6}alkyl, -C(O)-C_{1-6}alkyl, C(O)-O-C_{1-6}alkyl, or phenyl, wherein said phenyl, or C_{1-6}alkyl is optionally substituted with

one or more substituents selected from halogen, hydroxyl, haloC_{1-6}alkyl, nitro, C_{1-6}alkoxy, and NR^2R^3;

wherein W is selected from hydrogen, hydroxy, halogen, cyano, (=O), -O-$(CH_2)_c$-O-, wherein c is 2 or 3 (spiro), $(CH_2)_d$, wherein d is 5 or 6 (spiro), C_{1-6}alkyl, C_{1-6}alkoxy, -C(O)-C_{1-6}alkyl, -C(O)-O-C_{1-6}alkyl, -O-C(O)-C_{1-6}alkyl, -C(O)H, COOH; or wherein W represents a moiety of the formula –$(CH_2)_a$-Y-$(CH_2)_b$-Z;

wherein a and b independently represent an integer selected from 0, 1, 2 and 3;

wherein Y represents a bond, C(O), O, S, -O-C(O), -C(O)-O-, -NR^2-, -NR^2-C(O)-, -C(O)-NH-, or $S(O)_2$;

wherein Z represents hydrogen, C_{1-6}alkyl, NR^2R^3, cyano or a mono-cyclic or fused bi-cyclic moiety comprising 4 to 12 ring atoms of which optionally one, two or three are hetero atoms selected from amongst N, O, and S, and wherein said mono-cyclic or fused bi-cyclic moiety is optionally substituted with one or more substituents selected from the group consisting of halogen, cyano, C_{1-6}alkyl, hydroxyl, and C_{1-6}alkoxy, pyrazinyl, phenyl, pyridyl, and halogen substituted phenyl;

wherein R^2 and R^3 independently represent hydrogen, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, haloC_{1-6}alkyl or phenyl;

and pharmaceutically acceptable salts thereof.

20. A compound according to claim 19, wherein A represent CH, and R^1 represents C_{1-6}alkyl.

21. A compound according to claim 20, wherein R^1 represents ethyl or cyclopropyl.

22. A compound according to any of claims 19-21, wherein W represents a moiety of the formula –$(CH_2)_a$-Y-$(CH_2)_b$-Z;

wherein a and b independently represent an integer selected from 0, 1, 2 and 3;

wherein Y represents a bond, C(O), O, S, -O-C(O), -C(O)-O-, -NR^2-, -NR^2-C(O)-, -C(O)-NH-, or $S(O)_2$;

wherein Z represents hydrogen, C_{1-6}alkyl, NR^2R^3, cyano or a mono-cyclic or fused bi-cyclic moiety comprising 4 to 12 ring atoms of which optionally one, two or three are

hetero atoms selected from amongst N, O, and S, and wherein said mono-cyclic or fused bi-cyclic moiety is optionally substituted with one or more substituents selected from the group consisting of halogen, cyano, C_{1-6}alkyl, hydroxyl, and C_{1-6}alkoxy, pyrazinyl, phenyl, pyridyl, and halogen substituted phenyl;

wherein R^2 and R^3 independently represent hydrogen, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, haloC_{1-6}alkyl or phenyl.

23. A compound according to claim 22, wherein Y represents a bond, C(O) or $S(O)_2$; wherein a+b is 0, 1, 2, 3, or 4; and wherein Z represents mono-cyclic or fused bi-cyclic moiety comprising 4 to 12 carbon ring atoms and optionally one, two or three hetero atoms selected from amongst N, O, and S, and wherein said cyclic or bicyclic moiety is optionally substituted with one or more substituents selected from the group consisting of halogen, cyano, C_{1-6}alkyl, hydroxyl, and C_{1-6}alkoxy, phenyl, pyrazinyl, pyridyl, and halogen substituted phenyl.

24. A compound according to claim 23, wherein Y represents a bond or C(O), and a+b is 0, 1, 2, or 3.

25. A compound according to any of claims 22-24, wherein Z represents morpholinyl optionally substituted with one or more substituents selected from the group consisting of halogen, cyano, C_{1-6}alkyl, hydroxyl, and C_{1-6}alkoxy, phenyl, pyrazinyl, pyridyl, and halogen substituted phenyl.

26. A compound according to claim 25, wherein said morpholinyl is attached to the rest of the W moiety via the nitrogen

27. A compound according to any of claims 22-24, wherein Z represents piperidyl optionally substituted with one or more substituents selected from the group consisting of halogen, cyano, C_{1-6}alkyl, hydroxyl, and C_{1-6}alkoxy, phenyl, pyrazinyl, pyridyl, and halogen substituted phenyl.

28. A compound according to claim 27, wherein said piperidyl is attached to the rest of the W moiety via the nitrogen.

29. A compound according to any of claims 22-24, wherein Z represents pyridyl, optionally substituted with one or more substituents selected from the group consisting of halogen, cyano, C_{1-6}alkyl, hydroxyl, and C_{1-6}alkoxy, pyrazinyl, phenyl, pyridyl, and halogen substituted phenyl.

30. A compound according to claim 29, wherein said pyridyl is attached to the rest of the W moiety via the 2, 3, or 4-position of the pyridyl.

31. A compound according to any of claims 22-24, wherein Z represents phenyl, optionally substituted with one or more substituents selected from the group consisting of halogen, cyano, C_{1-6}alkyl, hydroxyl, and C_{1-6}alkoxy, phenyl, pyrazinyl, pyridyl, and halogen substituted phenyl.

32. A compound according to any of claims 22-24, wherein Z represents pyrrolidinyl, optionally substituted with one or more substituents selected from the group consisting of halogen, cyano, C_{1-6}alkyl, hydroxyl, and C_{1-6}alkoxy, pyrazinyl, phenyl, pyridyl, and halogen substituted phenyl.

33. A compound according to any of claims 22-24, wherein Z represents indolyl, optionally substituted with one or more substituents selected from the group consisting of halogen, cyano, C_{1-6}alkyl, hydroxyl, and C_{1-6}alkoxy, phenyl, pyrazinyl, pyridyl, and halogen substituted phenyl.

34. A compound according to claim 33, wherein said indolinyl is attached to the rest of the W moiety at the 4, 5, 6, or 7 position of the indolyl group.

35. A compound according to any of claims 22-24, wherein Z represents cyclopentyl.

36. A compound according to any of claims 22-24, wherein Z represents furopyridyl.

37. A compound according to any of claims 22-24, wherein Z represents tetrahydrofuranyl.

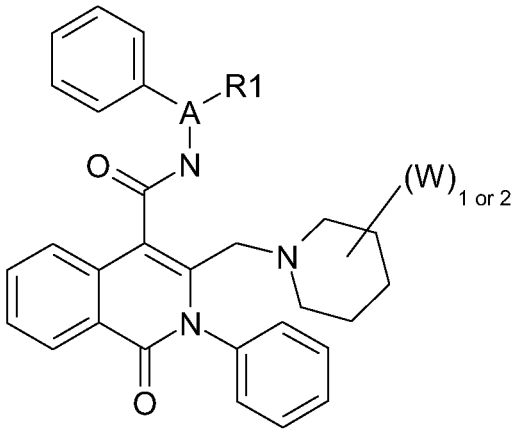
38. A compound according to claim 22, wherein Y represents a bond, C(O), -C(O)-O-, C(O)-NH-, -O-, or $S(O)_2$; a+b is 0, 1, 2, 3 or 4; and wherein Z represents hydrogen, C_{1-6}alkyl, NR^2R^3 or cyano.

39. A compound according to claim 38, wherein Y represents a bond, C(O), -C(O)-O-, C(O)-NH-, -O-, or $S(O)_2$, a+b is 0, 1, 2 or 3, and wherein Z represents hydrogen, methyl, ethyl, $-N(CH_3)_2$, cyano, iso-propyl, iso-butyl, or tert.-butyl.

40. A compound according to any of claims 19-21, wherein W is selected from hydrogen, hydroxy, halogen, cyano, (=O), $-O-(CH_2)_c-O-$, wherein c is 2 or 3 (spiro), $(CH_2)_d$, wherein d is 5 or 6 (spiro), C_{1-6}alkyl, C_{1-6}alkoxy, $-C(O)-C_{1-6}$alkyl, $-C(O)-O-C_{1-6}$alkyl, $-O-C(O)-C_{1-6}$alkyl, -C(O)H, COOH.

41. A compound according to claim 40, wherein W is selected from $-(CH_2)_d-$, wherein d is 5 or 6 (spiro) and C_{1-6}alkyl.

42. A compound according to claim 1 of formula Ic



[Ic]

wherein A represents N, CH or CR^1;

wherein each R^1 independently represents hydrogen, C_{1-6}alkyl, -C(O)-C_{1-6}alkyl, C(O)-O-C_{1-6}alkyl, or phenyl, wherein said phenyl, or C_{1-6}alkyl is optionally substituted with one or more substituents selected from halogen, hydroxyl, haloC_{1-6}alkyl, nitro, C_{1-6}alkoxy, and NR^2R^3;

wherein W is selected from hydrogen, hydroxy, halogen, cyano, (=O), -O-$(CH_2)_c$-O-, wherein c is 2 or 3 (spiro), $(CH_2)_d$, wherein d is 5 or 6 (spiro), C_{1-6}alkyl, C_{1-6}alkoxy, -C(O)-C_{1-6}alkyl, -C(O)-O-C_{1-6}alkyl, -O-C(O)-C_{1-6}alkyl, -C(O)H, COOH; or wherein W represents a moiety of the formula $-(CH_2)_a$-Y-$(CH_2)_b$-Z;

wherein a and b independently represent an integer selected from 0, 1, 2 and 3;

wherein Y represents a bond, C(O), O, S, -O-C(O), -C(O)-O-, -NR^2-, -NR^2-C(O)-, -C(O)-NH-, or $S(O)_2$;

wherein Z represents hydrogen, C_{1-6}alkyl, NR^2R^3, cyano or a mono-cyclic or fused bi-cyclic moiety comprising 4 to 12 ring atoms of which optionally one, two or three are hetero atoms selected from amongst N, O, and S, and wherein said mono-cyclic or fused bi-cyclic moiety is optionally substituted with one or more substituents selected from the group consisting of halogen, cyano, C_{1-6}alkyl, hydroxyl, and C_{1-6}alkoxy, pyrazinyl, phenyl, pyridyl, and halogen substituted phenyl;

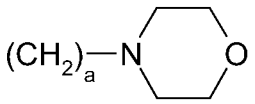
wherein R^2 and R^3 independently represent hydrogen, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, haloC_{1-6}alkyl or phenyl;

and pharmaceutically acceptable salts thereof.

43. A compound according to claim 42, wherein A represent CH, and R^1 represents C_{1-6}alkyl.

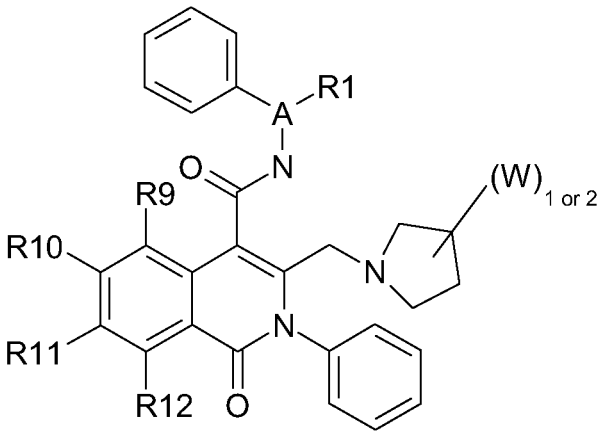
44. A compound according to claim 43, wherein R^1 represents ethyl or cyclopropyl.

45. A compound according to any of claims 42-44, wherein W independently represents hydrogen, hydroxyl, phenyl, phenyl substituted with C_{1-6}alkoxy, piperidyl, pyridyl, -O-$(CH_2)_c$-O-, wherein c is 2 or 3 (spiro), $N(CH_3)_2$, C_{1-6}alkyl, –$(CH_2)_a$-C(O)-O-$(CH_2)_b$-H, wherein a+b is 1, 2, or 3, or



, wherein a represents 1, 2, or 3.

46. A compound according to claim 1 of the formula I_d



[Id]

wherein A represents N, CH or CR^1;

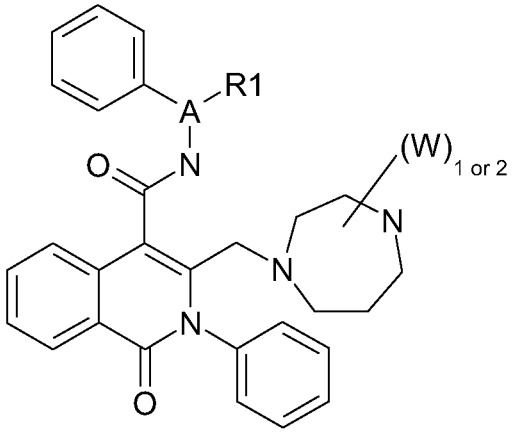
wherein each R^1 independently represents hydrogen, C_{1-6}alkyl, -C(O)-C_{1-6}alkyl, C(O)-O-C_{1-6}alkyl, or phenyl, wherein said phenyl, or C_{1-6}alkyl is optionally substituted with one or more substituents selected from halogen, hydroxyl, haloC_{1-6}alkyl, nitro, C_{1-6}alkoxy, and NR^2R^3;

wherein W is selected from hydrogen, hydroxy, halogen, cyano, (=O), -O-$(CH_2)_c$-O-, wherein c is 2 or 3 (spiro), $(CH_2)_d$, wherein d is 5 or 6 (spiro), C_{1-6}alkyl, C_{1-6}alkoxy, -C(O)-C_{1-6}alkyl, -C(O)-O-C_{1-6}alkyl, -O-C(O)-C_{1-6}alkyl, -C(O)H, COOH;
wherein R^2 and R^3 independently represent hydrogen, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, haloC_{1-6}alkyl or phenyl;
wherein R^9-R^{12} independently represent hydrogen or halogen;
and pharmaceutically acceptable salts thereof.

47. A compound according to claim 46, wherein A is CH; R^1 represents C_{1-6}alkyl; and each of R^9-R^{12} independently represent hydrogen or halogen.

48. A compound according to claim 47, wherein R^1 represents ethyl or cyclopropyl; and each of R^9-R^{12} represent hydrogen.

49. A compound according to claim 1 of the formula I_e



[Ie]

wherein A represents N, CH or CR^1;
wherein each R^1 independently represents hydrogen, C_{1-6}alkyl, -C(O)-C_{1-6}alkyl, C(O)-O-C_{1-6}alkyl, or phenyl, wherein said phenyl, or C_{1-6}alkyl is optionally substituted with one or more substituents selected from halogen, hydroxyl, haloC_{1-6}alkyl, nitro, C_{1-6}alkoxy, and NR^2R^3;

wherein W is selected from hydrogen, hydroxy, halogen, cyano, (=O), -O-$(CH_2)_c$-O-, wherein c is 2 or 3 (spiro), $(CH_2)_d$, wherein d is 5 or 6 (spiro), C_{1-6}alkyl, C_{1-6}alkoxy, -C(O)-C_{1-6}alkyl, -C(O)-O-C_{1-6}alkyl, -O-C(O)-C_{1-6}alkyl, -C(O)H, COOH; or wherein W represents a moiety of the formula $-(CH_2)_a$-Y-$(CH_2)_b$-Z;

wherein a and b independently represent an integer selected from 0, 1, 2 and 3;

wherein Y represents a bond, C(O), O, S, -O-C(O), -C(O)-O-, NR^2, -NR^2-C(O)-, -C(O)-NH-, or $S(O)_2$;

wherein Z represents hydrogen, C_{1-6}alkyl, NR^2R^3, cyano or a mono-cyclic or fused bi-cyclic moiety comprising 4 to 12 ring atoms of which optionally one, two or three are hetero atoms selected from amongst N, O, and S, and wherein said mono-cyclic or fused bi-cyclic moiety is optionally substituted with one or more substituents selected from the group consisting of halogen, cyano, C_{1-6}alkyl, hydroxyl, and C_{1-6}alkoxy, pyrazinyl, phenyl, pyridyl, and halogen substituted phenyl;

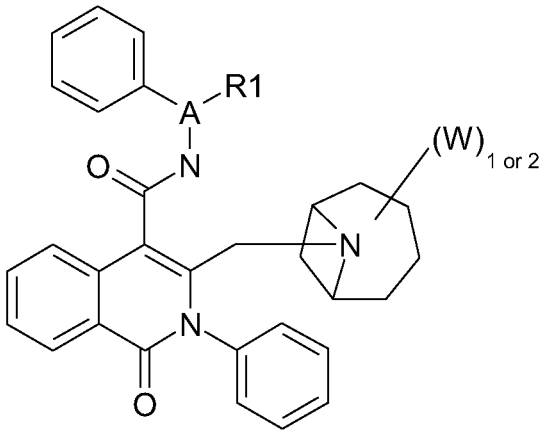
wherein R^2 and R^3 independently represent hydrogen, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, haloC_{1-6}alkyl or phenyl;

and pharmaceutically acceptable salts thereof.

50. A compound according to claim 49, wherein A is CH, and R^1 represents C_{1-6}alkyl.

51. A compound according to claim 50, wherein R^1 represents ethyl or cyclopropyl.

52. A compound according to claim 1 of the formula I_f



[If]

wherein A represents N, CH or CR^1;

wherein each R^1 independently represents hydrogen, C_{1-6}alkyl, -C(O)-C_{1-6}alkyl, C(O)-O-C_{1-6}alkyl, or phenyl, wherein said phenyl, or C_{1-6}alkyl is optionally substituted with one or more substituents selected from halogen, hydroxyl, haloC_{1-6}alkyl, nitro, C_{1-6}alkoxy, and NR^2R^3;

wherein W is selected from hydrogen, hydroxy, halogen, cyano, (=O), -O-$(CH_2)_c$-O-, wherein c is 2 or 3 (spiro), $(CH_2)_d$, wherein d is 5 or 6 (spiro), C_{1-6}alkyl, C_{1-6}alkoxy, -C(O)-C_{1-6}alkyl, -C(O)-O-C_{1-6}alkyl, -O-C(O)-C_{1-6}alkyl, -C(O)H, COOH; or wherein W represents a moiety of the formula $-(CH_2)_a$-Y-$(CH_2)_b$-Z;

wherein a and b independently represent an integer selected from 0, 1, 2 and 3;

wherein Y represents a bond, C(O), O, S, -O-C(O), -C(O)-O-, NR^2, -NR^2-C(O)-, -C(O)-NH-, or $S(O)_2$;

wherein Z represents hydrogen, C_{1-6}alkyl, NR^2R^3, cyano or a mono-cyclic or fused bi-cyclic moiety comprising 4 to 12 ring atoms of which optionally one, two or three are hetero atoms selected from amongst N, O, and S, and wherein said mono-cyclic or fused bi-cyclic moiety is optionally substituted with one or more substituents selected from the group consisting of halogen, cyano, C_{1-6}alkyl, hydroxyl, and C_{1-6}alkoxy, pyrazinyl, phenyl, pyridyl, and halogen substituted phenyl;

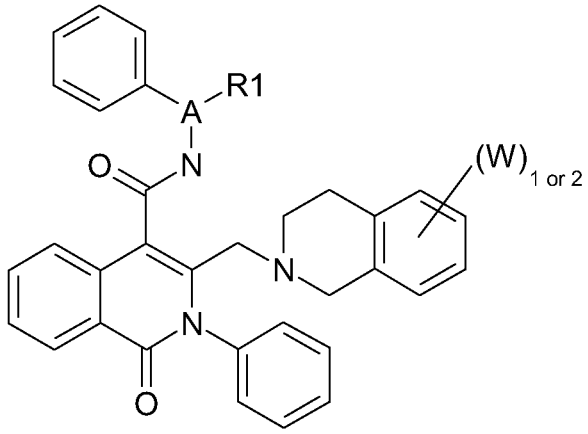
wherein R^2 and R^3 independently represent hydrogen, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, haloC_{1-6}alkyl or phenyl;

and pharmaceutically acceptable salts thereof.

53. A compound according to claim 52, wherein A is CH, and R^1 represents C_{1-6}alkyl.

54. A compound according to claim 53, wherein R^1 represents ethyl or cyclopropyl.

55. A compound according to claim 1 of the formula I_g



[Ig]

wherein A represents N, CH or CR^1;

wherein each R^1 independently represents hydrogen, C_{1-6}alkyl, -C(O)-C_{1-6}alkyl, C(O)-O-C_{1-6}alkyl, or phenyl, wherein said phenyl, or C_{1-6}alkyl is optionally substituted with one or more substituents selected from halogen, hydroxyl, haloC_{1-6}alkyl, nitro, C_{1-6}alkoxy, and NR^2R^3;

wherein W is selected from hydrogen, hydroxy, halogen, cyano, (=O), -O-$(CH_2)_c$-O-, wherein c is 2 or 3 (spiro), $(CH_2)_d$, wherein d is 5 or 6 (spiro), C_{1-6}alkyl, C_{1-6}alkoxy, -C(O)-C_{1-6}alkyl, -C(O)-O-C_{1-6}alkyl, -O-C(O)-C_{1-6}alkyl, -N(R^2)-C(O)-R^3, -C(O)H, COOH; or wherein W represents a moiety of the formula –$(CH_2)_a$-Y-$(CH_2)_b$-Z;

wherein a and b independently represent an integer selected from 0, 1, 2 and 3;

wherein Y represents a bond, C(O), O, S, -O-C(O), -C(O)-O-, NR^2, -NR^2-C(O)-, -C(O)-NH-, or $S(O)_2$;

wherein Z represents hydrogen, C_{1-6}alkyl, NR^2R^3, cyano or a mono-cyclic or fused bi-cyclic moiety comprising 4 to 12 ring atoms of which optionally one, two or three are hetero atoms selected from amongst N, O, and S, and wherein said mono-cyclic or fused bi-cyclic moiety is optionally substituted with one or more substituents selected from the group consisting of halogen, cyano, C_{1-6}alkyl, hydroxyl, and C_{1-6}alkoxy, pyrazinyl, phenyl, pyridyl, and halogen substituted phenyl;

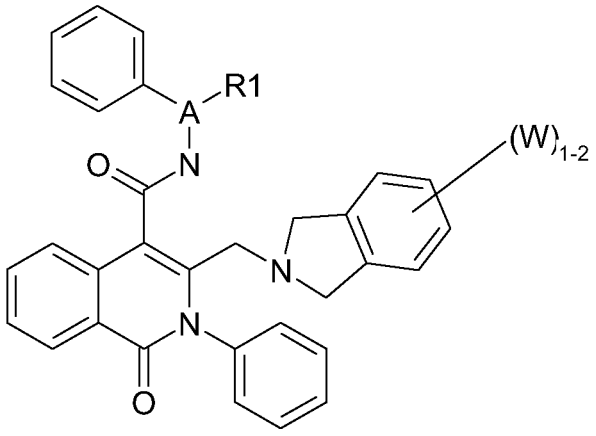
wherein R^2 and R^3 independently represent hydrogen, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, haloC_{1-6}alkyl or phenyl;

and pharmaceutically acceptable salts thereof.

56. A compound according to claim 55, wherein A is CH, and R^1 represents C_{1-6}alkyl.

57. A compound according to claim 56, wherein R^1 represents ethyl or cyclopropyl.

58. A compound according to claim 1 of formula I_h



[I_h]

wherein A represents N, CH or CR^1;

wherein each R^1 independently represents hydrogen, C_{1-6}alkyl, -C(O)-C_{1-6}alkyl, C(O)-O-C_{1-6}alkyl, or phenyl, wherein said phenyl, or C_{1-6}alkyl is optionally substituted with one or more substituents selected from halogen, hydroxyl, haloC_{1-6}alkyl, nitro, C_{1-6}alkoxy, and NR^2R^3;

wherein W is selected from hydrogen, hydroxy, halogen, cyano, (=O), -O-$(CH_2)_c$-O-, wherein c is 2 or 3 (spiro), $(CH_2)_d$, wherein d is 5 or 6 (spiro), C_{1-6}alkyl, C_{1-6}alkoxy, -C(O)-C_{1-6}alkyl, -C(O)-O-C_{1-6}alkyl, -O-C(O)-C_{1-6}alkyl, -C(O)H, COOH; or wherein W represents a moiety of the formula $-(CH_2)_a$-Y-$(CH_2)_b$-Z;

wherein a and b independently represent an integer selected from 0, 1, 2 and 3;

wherein Y represents a bond, C(O), O, S, -O-C(O), -C(O)-O-, NR^2, -NR^2-C(O)-, -C(O)-NH-, or $S(O)_2$;

wherein Z represents hydrogen, C_{1-6}alkyl, NR^2R^3, cyano or a mono-cyclic or fused bi-cyclic moiety comprising 4 to 12 ring atoms of which optionally one, two or three are hetero atoms selected from amongst N, O, and S, and wherein said mono-cyclic or fused bi-cyclic moiety is optionally substituted with one or more substituents selected from the group consisting of halogen, cyano, C_{1-6}alkyl, hydroxyl, and C_{1-6}alkoxy, pyrazinyl, phenyl, pyridyl, and halogen substituted phenyl;

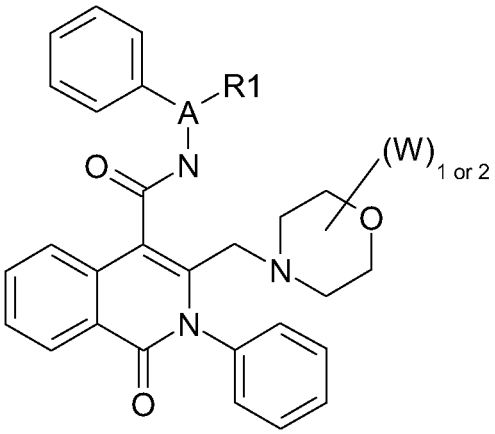
wherein R^2 and R^3 independently represent hydrogen, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, haloC_{1-6}alkyl or phenyl;

and pharmaceutically acceptable salts thereof.

59. A compound according to claim 58, wherein A is CH, and R^1 represents C_{1-6}alkyl.

60. A compound according to claim 57, wherein R^1 represents ethyl or cyclopropyl.

61. A compound according to claim 1 of formula I_i



[li]

wherein A represents N, CH or CR^1;

wherein each R^1 independently represents hydrogen, C_{1-6}alkyl, -C(O)-C_{1-6}alkyl, C(O)-O-C_{1-6}alkyl, or phenyl, wherein said phenyl, or C_{1-6}alkyl is optionally substituted with one or more substituents selected from halogen, hydroxyl, haloC_{1-6}alkyl, nitro, C_{1-6}alkoxy, and NR^2R^3;

wherein W is selected from hydrogen, hydroxy, halogen, cyano, (=O), -O-$(CH_2)_c$-O-, wherein c is 2 or 3 (spiro), $(CH_2)_d$, wherein d is 5 or 6 (spiro), C_{1-6}alkyl, C_{1-6}alkoxy, -C(O)-C_{1-6}alkyl, -C(O)-O-C_{1-6}alkyl, -O-C(O)-C_{1-6}alkyl, -C(O)H, COOH; or wherein X represents a moiety of the formula $-(CH_2)_a$-Y-$(CH_2)_b$-Z;

wherein a and b independently represent an integer selected from 0, 1, 2 and 3;

wherein Y represents a bond, C(O), O, S, -O-C(O), -C(O)-O-, NR^2, -NR^2-C(O)-, -C(O)-NH-, or $S(O)_2$;

wherein Z represents hydrogen, C_{1-6}alkyl, NR^2R^3, cyano or a mono-cyclic or fused bi-cyclic moiety comprising 4 to 12 ring atoms of which optionally one, two or three are hetero atoms selected from amongst N, O, and S, and wherein said mono-cyclic or fused bi-cyclic moiety is optionally substituted with one or more substituents selected from the group consisting of halogen, cyano, C_{1-6}alkyl, hydroxyl, and C_{1-6}alkoxy, pyrazinyl, phenyl, pyridyl, and halogen substituted phenyl;

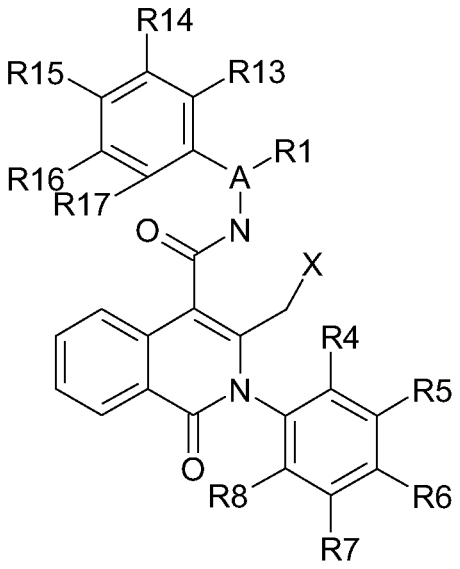
wherein R^2 and R^3 independently represent hydrogen, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, haloC_{1-6}alkyl or phenyl;

and pharmaceutically acceptable salts thereof.

62. A compound according to claim 61, wherein A is CH, and R^1 represents C_{1-6}alkyl.

63. A compound according to claim 62, wherein R^1 represents ethyl or cyclopropyl.

64. A compound according to claim 1 of formula Ij



[Ij]

wherein A represents N, CH or CR^1;

wherein each R^1 independently represents hydrogen, C_{1-6}alkyl, -C(O)-C_{1-6}alkyl, -C(O)-O-C_{1-6}alkyl, or phenyl, wherein said phenyl or C_{1-6}alkyl is optionally substituted with one or more substituents selected from halogen, hydroxyl, haloC_{1-6}alkyl, nitro, C_{1-6}alkoxy, and NR^2R^3;

wherein X represents hydrogen, C_{1-6}alkyl, cyano, $-OR^2$, -O-C(O)R^2, -OC(O)NR^2R^3, -C(O)-NR^2R^3, -N(R^2)C(O)R^3, -N(R^2)-C(O)NR^2R^3 or NR^2R^3, or X represents a mono-cyclic, bicyclic or tri-cyclic moiety having 4-16 ring atoms one of which is nitrogen, and wherein one, two or three additional ring atoms may be a hetero atom selected from N, O and S, and wherein said mono-cyclic, bi-cyclic or tri-cyclic moiety may optionally be substituted with one or more substituents W, wherein W is selected from hydrogen, hydroxy, halogen, cyano, (=O), -O-$(CH_2)_c$-O-, wherein c is 2 or 3 (spiro),

$(CH_2)_d$, wherein d is 5 or 6 (spiro), C_{1-6}alkyl, C_{1-6}alkoxy, -C(O)-C_{1-6}alkyl, -C(O)-O-C_{1-6}alkyl, -O-C(O)-C_{1-6}alkyl, -C(O)H, COOH; or wherein W represents a moiety of the formula $-(CH_2)_a$-Y-$(CH_2)_b$-Z;

wherein a and b independently represent an integer selected from 0, 1, 2 and 3;

wherein Y represents a bond, C(O), O, S, -O-C(O), -C(O)-O-, -NR^2-, -NR^2-C(O)-, -C(O)-NH-, or $S(O)_2$;

wherein Z represents hydrogen, C_{1-6}alkyl, NR^2R^3, cyano or a mono-cyclic or fused bi-cyclic moiety comprising 4 to 12 ring atoms of which optionally one, two or three are hetero atoms selected from amongst N, O, and S, and wherein said mono-cyclic or fused bi-cyclic moiety is optionally substituted with one or more substituents selected from the group consisting of halogen, cyano, C_{1-6}alkyl, hydroxyl, and C_{1-6}alkoxy, phenyl, pyridyl, and halogen substituted phenyl;

wherein one of R^4-R^8 represents halogen and the other represent hydrogen; wherein one of R^{13}-R^{17} represents halogen and the other represent hydrogen;

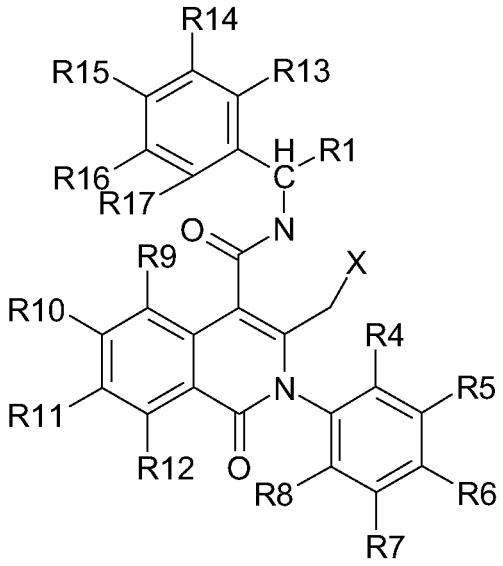
wherein R^2 and R^3 independently represent hydrogen, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, haloC_{1-6}alkyl or phenyl;

and pharmaceutically acceptable salts thereof.

65. A compound according to claim 64 wherein A represents CH; R^1 represents ethyl or cyclopropyl; R^{14} represents halogen; and R^5 or R^8 represents halogen.

66. A compound according to claim 65 wherein X represents piperazinyl or 1-piperidyl substituted with one or two substituents W, wherein said W is a moiety of the formula $-(CH_2)_a$-Y-$(CH_2)_b$-Z, wherein a and b independently represent 0, 1, 2 or 3; Y represents a bond, O, -NR^2-C(O)-; and wherein Z represents hydrogen, C_{1-6}alkyl, piperidyl, morpholinyl, pyridyl, phenyl, phenyl substituted with C_{1-6}alkoxy, or pyrrolidinyl.

67. The compound according claim 1 of the formula Ik



[Ik]

wherein R^1 represents hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl or C_{2-6}alkynyl;

wherein X represents hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl or NR^2R^3, or X represents a mono-cyclic or bi-cyclic moiety having 5-9 ring atoms one of which is nitrogen, and wherein one, two or three additional ring atoms may be a hetero atom selected from N, O and S, and wherein said mono-cyclic or bi-cyclic moiety may optionally be substituted with one or more substituents W, wherein W is selected from hydrogen, halogen, hydroxy, (=O), C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, or wherein W represents a moiety of the formula $-(CH_2)_a$-Y-$(CH_2)_b$-Z;

wherein a and b independently represent an integer selected from 0, 1, 2 and 3;

wherein Y represents a bond, and wherein Z represents a mono-cyclic moiety comprising 5 to 6 ring atoms of which optionally one, two or three are hetero atoms selected from amongst N, O, and S, and wherein said mono-cyclic moiety is optionally substituted with one or more substituents selected from the group consisting of halogen, C_{1-6}alkyl, hydroxyl, and C_{1-6}alkoxy;

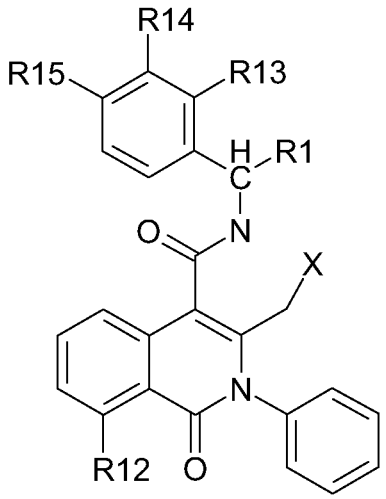
wherein each of R^4-R^8 independently represents hydrogen or halogen;

wherein each of R^9-R^{12} independently represents hydrogen or halogen provided that at least one of R^9-R^{12} represents halogen;

wherein each of R^{13}-R^{17} independently represent hydrogen or halogen;

wherein R^2 and R^3 independently represent hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl; and pharmaceutically acceptable salts thereof.

68. The compound according to claim 67 of formula Ik'

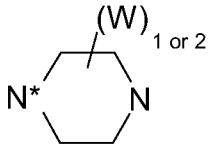


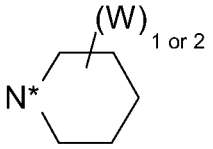
[Ik']

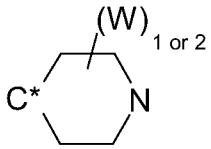
wherein R^1 is selected from C_{1-6}alkyl;
wherein X is selected from hydrogen, C_{1-6}alkyl or NR^2R^3, or X represents a mono-cyclic or bi-cyclic moiety having 5-9 ring atoms one of which is nitrogen, and wherein one additional ring atoms may be a hetero atom selected from N, and wherein said mono-cyclic or bi-cyclic moiety may optionally be substituted with one or more substituents W, wherein W is selected from hydrogen, hydroxy, (=O), C_{1-6}alkyl or wherein W represents a moiety of the formula $-(CH_2)_a$-Y-$(CH_2)_b$-Z;
wherein a and b independently represent an integer selected from 0, 1, 2 and 3;
wherein Y represents a bond, and wherein Z represents a mono-cyclic moiety comprising 5 to 6 ring atoms of which optionally one is a hetero atom selected from amongst N, O, and S, and wherein said mono-cyclic moiety is optionally substituted with one or more substituents selected from the group consisting of halogen, C_{1-6}alkyl, hydroxyl, and C_{1-6}alkoxy;
wherein R^{12} represents halogen;
R^{13}-R^{15} each independently represents hydrogen or halogen;
and pharmaceutically acceptable salts thereof.

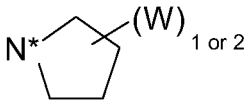
69. The compound according to any of claims 67-68, wherein R^1 represents methyl, ethyl, cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl.

70. The compound according to claim 69, wherein X represents



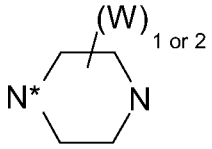
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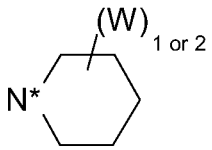
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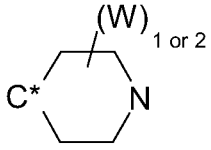
$-NR^2R^3$, or hydrogen

71. The compound according to claim 70, wherein X represents 

, and wherein W represents hydrogen, (=O), C_{1-6}-alkyl, or $-(CH_2)_a$-Y-$(CH_2)_b$-Z.

72. The compound according to claim 71, wherein W represents hydrogen, methyl, cyclopropylmethyl, isopropyl, isobutyl, tert-butyl, (=O), or or $-(CH_2)_a$-Y-$(CH_2)_a$-Z, wherein a+b is 2 and Z is selected from 4-morpholinyl, phenyl, 1-piperidine or 1-pyrrolidinyl.

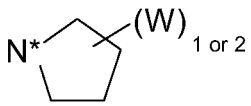
73. The compound according to claim 70, wherein X represents 

or 

, wherein W represents hydrogen, hydroxyl, C_{1-6}-alkyl or $-(CH_2)_a$-Y-$(CH_2)_a$-Z.

74. The compound according to claim 73, wherein W represents hydrogen, hydroxyl, tert-butyl, or a+b is 0 or 2 and Z represent 4-morpholinyl, phenyl, optionally substituted with C_{1-6}alkoxy, or 4-piperidyl.

75. The compound according to claim 70, wherein X represent



, and W represents (=O).

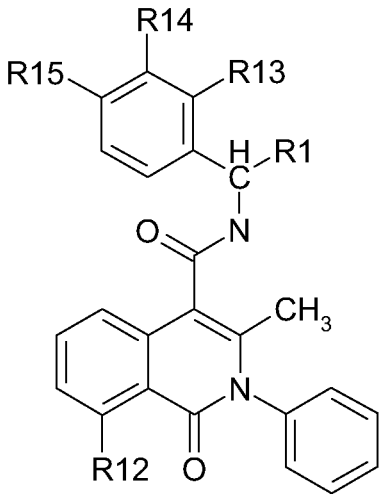
76. The compound according to claim 70, wherein X represents $-NR^2R^3$.

77. The compound according to claim 76, wherein R^2 and R^3 independently represents hydrogen or C_{1-6}-alkyl.

78. The compound according to claim 77, wherein R^2 represents hydrogen, and R^3 represents cyclopropyl, isobutyl or tert-butyl.

79. The compound according to claim 70, wherein X is hydrogen.

80. The compound according to claim 1 of the formula Ik''



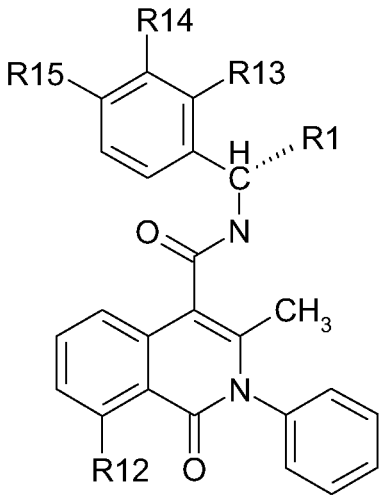
[Ik"]

wherein R^1 represents ethyl, cylopropyl or cyclobutyl;

wherein R^{12} represents flouro or chloro; and

R^{13}, R^{14} and R^{15} each individually represent hydrogen, fluoro or chloro, wherein two of R^{13}, R^{14} and R^{15} represent hydrogen.

81. The compound according to claim 80, wherein said compound is essentially the S enantiomers as depicted in formula Ik'''



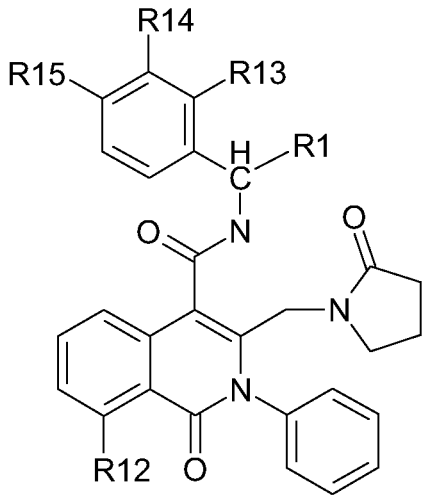
[Ik'"]

wherein R^1 represents ethyl or cylopropyl;

wherein R^{12} represents flouro or chloro; and

R^{13}, R^{14} and R^{15} each individually represent hydrogen, fluoro or chloro, wherein two of R^{13}, R^{14} and R^{15} represent hydrogen.

82. A compound according to claim 1 of the formula Id'



[Id']

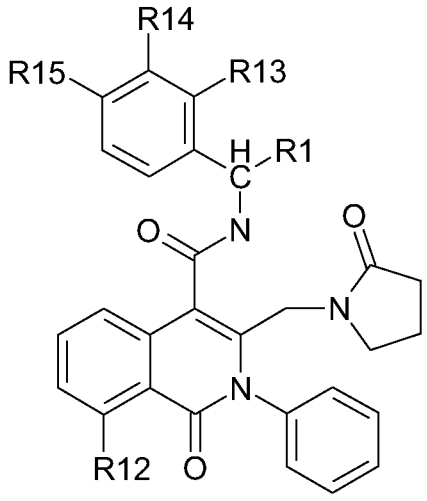
wherein R^1 represents ethyl or cyclopropyl;

R^{12} represent halogen;

R^{13}, R^{14} and R15 each independently represents hydrogen, or halogen;

and pharmaceutically acceptable salts thereof.

83. A compound according to claim 1 of the formula Id''



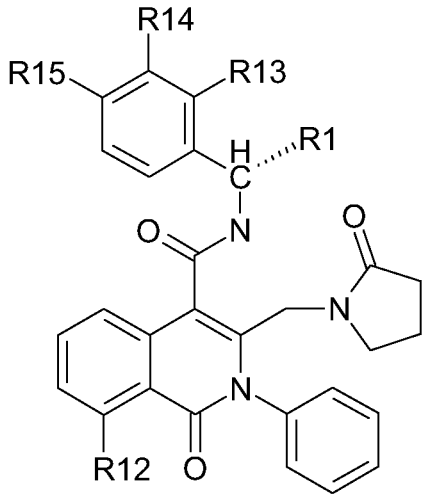
[Id'']

wherein R^1 represents ethyl or cyclopropyl;

R^{12} represent chloro or fluoro;

R^{12}, R^{14} and R^{15} each independently represent hydrogen, chloro or fluoro, wherein two of R^{12}, R^{14} and R^{15} represent hydrogen;
and pharmaceutically acceptable salts thereof.

84. A compound according to claim 83, wherein said compound is essentially the S enantiomer as depicted in formula Id'''



[Id'"]

wherein R^1 represents ethyl or cyclopropyl;
R^{12} represent chloro or fluoro;
R^{12}, R^{14} and R^{15} each independently represent hydrogen, chloro or fluoro, wherein two of R^{12}, R^{14} and R^{15} represent hydrogen;
and pharmaceutically acceptable salts thereof.

85. A compound according to claim 1 selected from

1a 3-Methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

1b 3,6-Dimethyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

1c 7-Chloro-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

1d 7-Bromo-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

1e 6-Fluoro-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

1f 3,5-Dimethyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

1g 7-Fluoro-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

1h 3,7-Dimethyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

1i 8-Chloro-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

1r 3-Methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-cyclopropyl-phenyl-methyl)-amide

1s 3-Methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-cyclopropyl-(3-fluoro-phenyl)-methyl]-amide

1j 3,8-Dimethyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

1k 2-(2-Fluoro-phenyl)-3-methyl-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

1l 3-Methyl-1-oxo-2-o-tolyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

1m 2-(2-Chloro-phenyl)-3-methyl-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

1n 2-(2,6-Difluoro-phenyl)-3-methyl-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

1o 2-(3-Fluoro-phenyl)-3-methyl-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

1p 3-Methyl-1-oxo-2-m-tolyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

1q 2-(3-Chloro-phenyl)-3-methyl-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

1t 8-Chloro-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-cyclopropyl-(3-fluoro-phenyl)-methyl]-amide

2a 3-Dimethylaminomethyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2b 3-Methylaminomethyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2c 3-Ethylaminomethyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2d 3-Cyclopropylaminomethyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2e 3-[(Cyclopropylmethyl-amino)-methyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2f 3-(3,6-Dihydro-2H-pyridin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2g 3-[4-(2-Methoxy-phenyl)-piperazin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2h 3-[4-(4-Fluoro-phenyl)-piperazin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2i 3-(4-Formyl-piperazin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2j 4-[1-Oxo-2-phenyl-4-(1-phenyl-propylcarbamoyl)-1,2-dihydro-isoquinolin-3-ylmethyl]-piperazine-1-carboxylic acid ethyl ester

2k 3-(4-Methyl-piperazin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2l 1-Oxo-2-phenyl-3-(1,3,4,9-tetrahydro-beta-carbolin-2-ylmethyl)-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2m 1-Oxo-2-phenyl-3-piperazin-1-ylmethyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2n 3-(3-Methyl-piperazin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2o 3-(3,5-Dimethyl-piperazin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2p 3-(4-Benzyl-piperazin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2q 1-Oxo-3-[4-(2-oxo-2-pyrrolidin-1-yl-ethyl)-piperazin-1-ylmethyl]-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2r 3-Morpholin-4-ylmethyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2s 3-(2,6-Dimethyl-morpholin-4-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2t 1-Oxo-2-phenyl-3-thiomorpholin-4-ylmethyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2u 3-(1,4-Dioxa-8-aza-spiro[4.5]dec-8-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2v 1-Oxo-2-phenyl-3-piperidin-1-ylmethyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2w 3-(2-Methyl-piperidin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2x 3-(2,6-Dimethyl-piperidin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2y 3-(2-Hydroxymethyl-piperidin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2z 1-[1-Oxo-2-phenyl-4-(1-phenyl-propylcarbamoyl)-1,2-dihydro-isoquinolin-3-ylmethyl]-piperidine-3-carboxylic acid ethyl ester

2aa 3-(3-Methyl-piperidin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2ab 3-(4-Hydroxy-piperidin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2ac 1-Oxo-2-phenyl-3-(4-phenyl-piperidin-1-ylmethyl)-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2ad 1-[1-Oxo-2-phenyl-4-(1-phenyl-propylcarbamoyl)-1,2-dihydro-isoquinolin-3-ylmethyl]-piperidine-4-carboxylic acid ethyl ester

2ae 3-(4-Methyl-piperidin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2af 1-Oxo-2-phenyl-3-(4-pyridin-2-yl-piperazin-1-ylmethyl)-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2ag 3-(Octahydro-quinolin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2ah 3-Azepan-1-ylmethyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2ai 3-(3-Hydroxy-piperidin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2aj 3-[4-(2,4-Dimethyl-phenyl)-piperazin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2ak 3-[4-(3,4-Dimethyl-phenyl)-piperazin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2al 3-(4-Dimethylamino-piperidin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2am 3-[4-(2,5-Dimethyl-phenyl)-piperazin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2an 3-[4-(2-Fluoro-phenyl)-piperazin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2ao 3-[4-(3-Methoxy-phenyl)-piperazin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2ap 1-Oxo-2-phenyl-3-(4-m-tolyl-piperazin-1-ylmethyl)-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2aq 3-[4-(4-Methoxy-phenyl)-piperazin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2ar 1-Oxo-3-(4-phenethyl-piperazin-1-ylmethyl)-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2as 1-Oxo-2-phenyl-3-(4-pyrimidin-2-yl-piperazin-1-ylmethyl)-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2at 3-[4-(2-Cyano-phenyl)-piperazin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2au 3-[4-(4-Chloro-phenyl)-piperazin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2av 3-((1S,3R,5R)-3-Hydroxy-8-aza-bicyclo[3.2.1]oct-8-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2aw 3-(4-Acetyl-piperazin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2ax 3-(4-Methyl-[1,4]diazepan-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2ay 3-(4-Ethyl-piperazin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2az 3-((2S,6R)-2,6-Dimethyl-morpholin-4-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2ba 3-[4-(2,4-Difluoro-phenyl)-piperazin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2bb 3-[4-(3-Dimethylamino-propyl)-piperazin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2bc 3-(4-Isopropyl-piperazin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2bd 3-(3-Aza-bicyclo[3.2.2]non-3-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2be 3-(4-Cyclopentyl-piperazin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2bf 3-[1,4']Bipiperidinyl-1'-ylmethyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2bg 3-(3,4-Dihydro-1H-isoquinolin-2-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2bh 3-[4-(2-Dimethylamino-ethyl)-piperazin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2bi 3-(4-Hydroxymethyl-piperidin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2bj 1-Oxo-2-phenyl-3-[4-(tetrahydro-furan-2-carbonyl)-piperazin-1-ylmethyl]-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2bk 3-(4-Isobutyl-piperazin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2bl 3-[4-(2-Methoxy-ethyl)-piperazin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2bm 3-[4-(2-Morpholin-4-yl-ethyl)-piperazin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2bn 3-(1,3-Dihydro-isoindol-2-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2bo 3-[4-(1-Methyl-piperidin-4-yl)-piperazin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2bp 1-Oxo-2-phenyl-3-[4-(2-piperidin-1-yl-ethyl)-piperazin-1-ylmethyl]-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2bq 1-Oxo-2-phenyl-3-[4-(2-pyrrolidin-1-yl-ethyl)-piperazin-1-ylmethyl]-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2br 3-(4-Dimethylcarbamoylmethyl-piperazin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2bs 3-(Octahydro-pyrido[1,2-a]pyrazin-2-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2bt 3-(4-Formyl-[1,4]diazepan-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2bu 3-[4-(4-Cyano-phenyl)-piperazin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2bv 1-Oxo-2-phenyl-3-(4-pyridin-4-ylmethyl-piperazin-1-ylmethyl)-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2bw 1-Oxo-2-phenyl-3-[4-(3-pyrrolidin-1-yl-propyl)-piperazin-1-ylmethyl]-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2bx 1-Oxo-2-phenyl-3-(4-pyridin-2-ylmethyl-piperazin-1-ylmethyl)-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2by 3-(4-Ethanesulfonyl-piperazin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2bz 3-(4-sec-Butyl-piperazin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2ca 3-[4-(1-Ethyl-propyl)-piperazin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2cb 3-[4-(2-Cyano-ethyl)-piperazin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2cc 3-(4-Methanesulfonyl-piperazin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2cd {1-[1-Oxo-2-phenyl-4-(1-phenyl-propylcarbamoyl)-1,2-dihydro-isoquinolin-3-ylmethyl]-piperidin-4-yl}-acetic acid ethyl ester

2ce 3-[4-(3-Fluoro-phenyl)-piperazin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2cf 1-Oxo-2-phenyl-3-((S)-3-phenyl-piperidin-1-ylmethyl)-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2cg 1-Oxo-2-phenyl-3-[4-(pyrrolidine-1-carbonyl)-piperazin-1-ylmethyl]-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2ch 3-[4-(Morpholine-4-carbonyl)-piperazin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2ci 3-(4-Methoxy-piperidin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2cj 3-(4'-Hydroxy-3',4',5',6'-tetrahydro-2'H-[3,4']bipyridinyl-1'-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2ck 3-(4-Hydroxy-3,4,5,6-tetrahydro-2H-[4,4']bipyridinyl-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2cl 3-(3H-spiro[isobenzofuran-1,4'-piperidin]-1'-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2cm 3-(4-Hydroxy-4-methyl-piperidin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2cn 3-(hexahydro-spiro[benzo[1,3]dioxole-2,4'-piperidin]-1'-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2co 1-Oxo-2-phenyl-3-(3,4,5,6-tetrahydro-2H-[4,4']bipyridinyl-1-ylmethyl)-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2cp 3-[4-(2-Dimethylamino-ethyl)-piperidin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2cq 3-(4-Dimethylsulfamoyl-piperazin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2cr 3-(1,1-Dioxo-thiomorpholin-4-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2cs 1-Oxo-2-phenyl-3-(2-pyridin-2-ylmethyl-piperidin-1-ylmethyl)-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2ct 3-(2-Morpholin-4-ylmethyl-piperidin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2cu 3-(4-Furo[3,2-c]pyridin-4-yl-piperazin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2cv 3-(4-Cyclopropylmethyl-piperazin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2cw 3-[4-(2-Morpholin-4-yl-ethyl)-piperidin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2cx 1-Oxo-2-phenyl-3-(4-pyrimidin-2-yl-[1,4]diazepan-1-ylmethyl)-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2cy 3-(4-Methyl-6,7-dihydro-4H-thieno[3,2-c]pyridin-5-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2cz 3-[1,4]Diazepan-1-ylmethyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2da 3-((2S,5R)-2,5-Dimethyl-piperazin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2db 3-((S)-3-Methyl-piperazin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2dc 3-((R)-3-Methyl-piperazin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2dd 3-[3-(3-Chloro-phenyl)-piperazin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2de 3-[4-(1H-Indol-4-yl)-piperazin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2df 1-Oxo-3-(3-oxo-piperazin-1-ylmethyl)-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2dg 3-[4-(1H-Indol-5-yl)-piperazin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2dh 3-(6,9-Diaza-spiro[4.5]dec-9-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2di 3-(1,4-Diaza-spiro[5.5]undec-4-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2dj 3-(3-Isopropyl-piperazin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2dk 3-(3,3-Dimethyl-piperazin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2dl 3-[3-(4-Fluoro-phenyl)-piperazin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2dm 1-Oxo-2-phenyl-3-(3-p-tolyl-piperazin-1-ylmethyl)-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2dn 4-[1-Oxo-2-phenyl-4-(1-phenyl-propylcarbamoyl)-1,2-dihydro-isoquinolin-3-ylmethyl]-piperazine-1-carboxylic acid tert-butyl ester

2do 3-(4-Methylcarbamoylmethyl-piperazin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2dp 8-Chloro-3-dimethylaminomethyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2dr 3-Cyclopentylaminomethyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2ds 3-Cyclohexylaminomethyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2dt 3-{[(2-Hydroxy-ethyl)-methyl-amino]-methyl}-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2du 3-Imidazol-1-ylmethyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2dv 3-(2-Methyl-imidazol-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2dw 3-(4-Methyl-imidazol-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2dx 3-(2,5-Dihydro-pyrrol-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2dy 3-(2,5-Dimethyl-2,5-dihydro-pyrrol-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2dz 1-Oxo-2-phenyl-3-pyrrolidin-1-ylmethyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2ea 1-Oxo-2-phenyl-3-(thiazol-2-ylaminomethyl)-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2eb 1-Oxo-2-phenyl-3-(pyrimidin-4-ylaminomethyl)-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2ec 3-(tert-Butylamino-methyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2ed 3-[(2-Hydroxy-1,1-dimethyl-ethylamino)-methyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2ee 3-(Isopropylamino-methyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2ef 3-[(2-Hydroxy-1-methyl-ethylamino)-methyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2eg 3-[(1-Hydroxymethyl-propylamino)-methyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2eh 3-[(2,2-Dimethyl-propylamino)-methyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2ei 1-Oxo-2-phenyl-3-prop-2-ynylaminomethyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2ej 3-Allylaminomethyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2ek 3-[(Methyl-prop-2-ynyl-amino)-methyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2el 3-Diallylaminomethyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2em 3-Diethylaminomethyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2en 3-[(Isopropyl-methyl-amino)-methyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2eo 3-[((S)-2-Hydroxy-1-methyl-ethylamino)-methyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2ep 3-[((R)-2-Hydroxy-1-methyl-ethylamino)-methyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2eq 3-{[(2-Methoxy-ethyl)-methyl-amino]-methyl}-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2er 3-((R)-3-Hydroxy-pyrrolidin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2es 3-((S)-3-Hydroxy-pyrrolidin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2et 3-[(Cyclopentyl-methyl-amino)-methyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2eu 3-{[(2-Hydroxy-1-methyl-ethyl)-methyl-amino]-methyl}-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2ev 3-{[Ethyl-(2-hydroxy-ethyl)-amino]-methyl}-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2ew 3-[(Ethyl-methyl-amino)-methyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2ex 3-Cyclobutylaminomethyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2ey 3-Azetidin-1-ylmethyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2ez 3-(4-tert-Butyl-piperazin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2fa 3-[4-(2-Hydroxy-ethyl)-piperazin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2fb 3-{4-[2-(2-Hydroxy-ethoxy)-ethyl]-piperazin-1-ylmethyl}-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2fc 3-[4-(3-Chloro-5-trifluoromethyl-pyridin-2-yl)-piperazin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2fd 3-[4-(3,5-Dichloro-pyridin-4-yl)-piperazin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2fe 4-[1-Oxo-2-phenyl-4-((S)-1-phenyl-propylcarbamoyl)-1,2-dihydro-isoquinolin-3-ylmethyl]-piperazine-1-carboxylic acid benzyl ester

2ff 3-[4-(3-Morpholin-4-yl-propyl)-piperazin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2fg 1-Oxo-2-phenyl-3-[4-(3-piperidin-1-yl-propyl)-piperazin-1-ylmethyl]-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2fh 3-[4-(4,6-Dimethoxy-pyrimidin-2-ylmethyl)-piperazin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2fi 3-[4-(3-Hydroxy-propyl)-piperazin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2fj 3-[4-(2,3-Dihydroxy-propyl)-piperazin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2fk (2-Oxo-2-{4-[1-oxo-2-phenyl-4-(1-phenyl-propylcarbamoyl)-1,2-dihydro-isoquinolin-3-ylmethyl]-piperazin-1-yl}-ethyl)-carbamic acid tert-butyl ester

2fl 3-[4-(1H-Indazol-5-yl)-piperazin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2fm 1-Oxo-2-phenyl-3-(4-quinolin-6-yl-piperazin-1-ylmethyl)-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2fn 3-[4-(6,7-Dimethoxy-quinazolin-4-yl)-piperazin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2fo 4-{4-[1-Oxo-2-phenyl-4-(1-phenyl-propylcarbamoyl)-1,2-dihydro-isoquinolin-3-ylmethyl]-piperazin-1-yl}-piperidine-1-carboxylic acid tert-butyl ester

2fp 3-{4-[2-(4-Chloro-phenoxy)-ethyl]-piperazin-1-ylmethyl}-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2fq {4-[1-Oxo-2-phenyl-4-(1-phenyl-propylcarbamoyl)-1,2-dihydro-isoquinolin-3-ylmethyl]-piperazin-1-yl}-acetic acid tert-butyl ester

2fr 1-Oxo-2-phenyl-3-[4-(3,3,3-trifluoro-2-hydroxy-propyl)-piperazin-1-ylmethyl]-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2fs 3-[4-(2-Hydroxy-propyl)-piperazin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2fu 3-[4-(4-Amino-6,7-dimethoxy-quinazolin-2-yl)-piperazin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2fv (2-{4-[1-Oxo-2-phenyl-4-(1-phenyl-propylcarbamoyl)-1,2-dihydro-isoquinolin-3-ylmethyl]-piperazin-1-yl}-ethyl)-carbamic acid tert-butyl ester

2fw 1-Oxo-3-{4-[2-(2-oxo-imidazolidin-1-yl)-ethyl]-piperazin-1-ylmethyl}-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2fx 3-{4-[(4,6-Dimethoxy-pyrimidin-2-yl)-phenyl-methyl]-piperazin-1-ylmethyl}-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2fy 3-(4-Benzo[1,2,5]thiadiazol-4-yl-piperazin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2fz 3-[4-(2,3-Dihydro-benzo[1,4]dioxin-5-yl)-piperazin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2ga 3-[4-(4-Methyl-quinolin-2-yl)-piperazin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2gb 1-Oxo-2-phenyl-3-[4-(pyridin-2-ylcarbamoylmethyl)-piperazin-1-ylmethyl]-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2gc 3-[4-(6-Chloro-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-8-yl)-piperazin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2gd 3-(4-Carbamoylmethyl-piperazin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2ge 3-(4-Hydroxy-4-phenyl-piperidin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2gf 3-[4-(4-Chloro-phenyl)-4-hydroxy-piperidin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2gg 1-[1-Oxo-2-phenyl-4-(1-phenyl-propylcarbamoyl)-1,2-dihydro-isoquinolin-3-ylmethyl]-piperidine-4-carboxylic acid

2gh 3-(4-Cyano-4-phenyl-piperidin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2gi 3-(4-Benzyl-4-hydroxy-piperidin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2gj 1-[1-Oxo-2-phenyl-4-(1-phenyl-propylcarbamoyl)-1,2-dihydro-isoquinolin-3-ylmethyl]-4-phenyl-piperidine-4-carboxylic acid ethyl ester

2gk 1-Oxo-2-phenyl-3-[4-(phenyl-propionyl-amino)-piperidin-1-ylmethyl]-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2gl Methyl-{1-[1-oxo-2-phenyl-4-(1-phenyl-propylcarbamoyl)-1,2-dihydro-isoquinolin-3-ylmethyl]-piperidin-4-yl}-carbamic acid tert-butyl ester

2gm 1-Oxo-2-phenyl-3-[4-(2-pyrrolidin-1-yl-ethyl)-piperidin-1-ylmethyl]-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2gn 3-{4-[5-(4-Fluoro-phenyl)-[1,3,4]oxadiazol-2-yl]-piperidin-1-ylmethyl}-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2go 1-Oxo-2-phenyl-3-[4-(3-pyridin-4-yl-[1,2,4]oxadiazol-5-yl)-piperidin-1-ylmethyl]-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2gp 1-Oxo-2-phenyl-3-[4-(3-pyrazin-2-yl-[1,2,4]oxadiazol-5-yl)-piperidin-1-ylmethyl]-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2gq 1-Oxo-2-phenyl-3-[4-(3-pyridin-4-yl-[1,2,4]oxadiazol-5-yl)-piperidin-1-ylmethyl]-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2gr 3-(4'-Hydroxy-3',4',5',6'-tetrahydro-2'H-[2,4']bipyridinyl-1'-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2gs 3-(spiro[isochroman-1,4'-piperidin]-1'-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2gt 3-[4-Hydroxy-4-(3-methoxy-phenyl)-piperidin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2gu 3-[4-(3-Chloro-phenyl)-4-hydroxy-piperidin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2gv 3-(6-chloro-3H-spiro[isobenzofuran-1,4'-piperidin]-1'-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2gw 3-(4-{[4-Chloro-3-(4-fluoro-phenyl)-indan-1-yl]-methyl-amino}-piperidin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2gx 3-(1-acetyl-spiro[indoline-3,4'-piperidin]-1'-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2gy 3-(1-acetyl-5-fluoro-spiro[indoline-3,4'-piperidin]-1'-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2gz 1-Oxo-3-(4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-8-ylmethyl)-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2ha 3-(4-Acetylamino-piperidin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2hb 1-Oxo-3-(1-oxo-2,8-diaza-spiro[4.5]dec-8-ylmethyl)-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2hc 3-[4-Hydroxy-4-(3-trifluoromethyl-phenyl)-piperidin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2hd 1-Oxo-2-phenyl-3-(4-trifluoromethyl-piperidin-1-ylmethyl)-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2he 3-[4-(4-Methyl-piperazine-1-carbonyl)-piperidin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2hf 3-(5-isopropyl-3H-spiro[isobenzofuran-1,4'-piperidin]-1'-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2hg 3-[4-(Acetyl-methyl-amino)-4-phenyl-piperidin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2hh 4-{1-[1-Oxo-2-phenyl-4-(1-phenyl-propylcarbamoyl)-1,2-dihydro-isoquinolin-3-ylmethyl]-piperidin-4-yl}-piperazine-1-carboxylic acid tert-butyl ester

2hi (2-{1-[1-Oxo-2-phenyl-4-(1-phenyl-propylcarbamoyl)-1,2-dihydro-isoquinolin-3-ylmethyl]-piperidin-4-yl}-ethyl)-carbamic acid tert-butyl ester

2hj 3-(4-Methylamino-4-phenyl-piperidin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2hk 3-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2hl 3-[4-Acetylamino-4-(3-fluoro-phenyl)-piperidin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2hm 1-Oxo-3-[4-(4-oxo-piperidine-1-carbonyl)-piperidin-1-ylmethyl]-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2hn 3-[4,4']Bipiperidinyl-1-ylmethyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2ho {1-[1-Oxo-2-phenyl-4-(1-phenyl-propylcarbamoyl)-1,2-dihydro-isoquinolin-3-ylmethyl]-piperidin-4-yl}-carbamic acid tert-butyl ester

2hp 3-[1,4']Bipiperidinyl-1'-ylmethyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid [cyclopropyl-(3-fluoro-phenyl)-methyl]-amide

2hq 1-Oxo-3-(4-phenethyl-piperazin-1-ylmethyl)-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid [cyclopropyl-(3-fluoro-phenyl)-methyl]-amide

2hr 3-(4-Isopropyl-piperazin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid [cyclopropyl-(3-fluoro-phenyl)-methyl]-amide

2hs 3-[4-(2-Morpholin-4-yl-ethyl)-piperazin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid [cyclopropyl-(3-fluoro-phenyl)-methyl]-amide

2ht 3-[4-(1-Methyl-piperidin-4-yl)-piperazin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid [cyclopropyl-(3-fluoro-phenyl)-methyl]-amide

2hu 1-Oxo-2-phenyl-3-[4-(2-piperidin-1-yl-ethyl)-piperazin-1-ylmethyl]-1,2-dihydro-isoquinoline-4-carboxylic acid [cyclopropyl-(3-fluoro-phenyl)-methyl]-amide

2hv 1-Oxo-2-phenyl-3-[4-(2-pyrrolidin-1-yl-ethyl)-piperazin-1-ylmethyl]-1,2-dihydro-isoquinoline-4-carboxylic acid [cyclopropyl-(3-fluoro-phenyl)-methyl]-amide

2hw 1-Oxo-2-phenyl-3-(4-pyridin-4-ylmethyl-piperazin-1-ylmethyl)-1,2-dihydro-isoquinoline-4-carboxylic acid [cyclopropyl-(3-fluoro-phenyl)-methyl]-amide

2hx 3-(4-Hydroxy-3,4,5,6-tetrahydro-2H-[4,4']bipyridinyl-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid [cyclopropyl-(3-fluoro-phenyl)-methyl]-amide

2hy 3-[4-(2-Morpholin-4-yl-ethyl)-piperidin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid [cyclopropyl-(3-fluoro-phenyl)-methyl]-amide

2hz 3-[4-Hydroxy-4-(3-methoxy-phenyl)-piperidin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid [cyclopropyl-(3-fluoro-phenyl)-methyl]-amide

2ia 3-[4-(Acetyl-methyl-amino)-4-phenyl-piperidin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid [cyclopropyl-(3-fluoro-phenyl)-methyl]-amide

2ib 2-(2-Fluoro-phenyl)-1-oxo-3-(4-phenethyl-piperazin-1-ylmethyl)-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2ic 2-(2-Fluoro-phenyl)-3-(4-isopropyl-piperazin-1-ylmethyl)-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2id 3-[1,4']Bipiperidinyl-1'-ylmethyl-2-(2-fluoro-phenyl)-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2ie 2-(2-Fluoro-phenyl)-3-[4-(2-morpholin-4-yl-ethyl)-piperazin-1-ylmethyl]-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2if 2-(2-Fluoro-phenyl)-3-[4-(1-methyl-piperidin-4-yl)-piperazin-1-ylmethyl]-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2ig 2-(2-Fluoro-phenyl)-1-oxo-3-[4-(2-piperidin-1-yl-ethyl)-piperazin-1-ylmethyl]-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2ih 2-(2-Fluoro-phenyl)-1-oxo-3-[4-(2-pyrrolidin-1-yl-ethyl)-piperazin-1-ylmethyl]-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2ii 2-(2-Fluoro-phenyl)-1-oxo-3-(4-pyridin-4-ylmethyl-piperazin-1-ylmethyl)-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2ij 2-(2-Fluoro-phenyl)-3-(4-hydroxy-3,4,5,6-tetrahydro-2H-[4,4']bipyridinyl-1-ylmethyl)-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2ik 2-(2-Fluoro-phenyl)-3-[4-(2-morpholin-4-yl-ethyl)-piperidin-1-ylmethyl]-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2il 2-(2-Fluoro-phenyl)-3-[4-hydroxy-4-(3-methoxy-phenyl)-piperidin-1-ylmethyl]-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2im 3-[4-(2-Morpholin-4-yl-ethyl)-piperazin-1-ylmethyl]-1-oxo-2-o-tolyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2in 1-Oxo-3-[4-(2-piperidin-1-yl-ethyl)-piperazin-1-ylmethyl]-2-o-tolyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2io 1-Oxo-3-(4-pyridin-4-ylmethyl-piperazin-1-ylmethyl)-2-o-tolyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2ip 2-(3-Fluoro-phenyl)-1-oxo-3-(4-phenethyl-piperazin-1-ylmethyl)-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2iq 2-(3-Fluoro-phenyl)-3-(4-isopropyl-piperazin-1-ylmethyl)-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2ir 3-[1,4']Bipiperidinyl-1'-ylmethyl-2-(3-fluoro-phenyl)-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2is 2-(3-Fluoro-phenyl)-3-[4-(2-morpholin-4-yl-ethyl)-piperazin-1-ylmethyl]-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2it 2-(3-Fluoro-phenyl)-3-[4-(1-methyl-piperidin-4-yl)-piperazin-1-ylmethyl]-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2iu 2-(3-Fluoro-phenyl)-1-oxo-3-[4-(2-piperidin-1-yl-ethyl)-piperazin-1-ylmethyl]-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2iv 2-(3-Fluoro-phenyl)-1-oxo-3-[4-(2-pyrrolidin-1-yl-ethyl)-piperazin-1-ylmethyl]-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2iw 2-(3-Fluoro-phenyl)-1-oxo-3-(4-pyridin-4-ylmethyl-piperazin-1-ylmethyl)-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2ix 2-(3-Fluoro-phenyl)-3-[4-(2-morpholin-4-yl-ethyl)-piperidin-1-ylmethyl]-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2iy 2-(3-Fluoro-phenyl)-3-[4-hydroxy-4-(3-methoxy-phenyl)-piperidin-1-ylmethyl]-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2iz 3-[4-(Acetyl-methyl-amino)-4-phenyl-piperidin-1-ylmethyl]-2-(3-fluoro-phenyl)-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2ja 2-(3-Chloro-phenyl)-1-oxo-3-(4-phenethyl-piperazin-1-ylmethyl)-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2jb 2-(3-Chloro-phenyl)-3-(4-isopropyl-piperazin-1-ylmethyl)-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2jc 3-[1,4']Bipiperidinyl-1'-ylmethyl-2-(3-chloro-phenyl)-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2jd 2-(3-Chloro-phenyl)-3-[4-(2-morpholin-4-yl-ethyl)-piperazin-1-ylmethyl]-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2je 2-(3-Chloro-phenyl)-3-[4-(1-methyl-piperidin-4-yl)-piperazin-1-ylmethyl]-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2jf 2-(3-Chloro-phenyl)-1-oxo-3-[4-(2-piperidin-1-yl-ethyl)-piperazin-1-ylmethyl]-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2jg 2-(3-Chloro-phenyl)-1-oxo-3-[4-(2-pyrrolidin-1-yl-ethyl)-piperazin-1-ylmethyl]-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2jh 2-(3-Chloro-phenyl)-1-oxo-3-(4-pyridin-4-ylmethyl-piperazin-1-ylmethyl)-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2ji 2-(3-Chloro-phenyl)-3-[4-(2-morpholin-4-yl-ethyl)-piperidin-1-ylmethyl]-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2jj 2-(3-Chloro-phenyl)-3-[4-hydroxy-4-(3-methoxy-phenyl)-piperidin-1-ylmethyl]-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2jk 3-[4-(Acetyl-methyl-amino)-4-phenyl-piperidin-1-ylmethyl]-2-(3-chloro-phenyl)-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2jl 1-Oxo-3-(4-phenethyl-piperazin-1-ylmethyl)-2-m-tolyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2jm 3-[1,4']Bipiperidinyl-1'-ylmethyl-1-oxo-2-m-tolyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2jn 3-[4-(2-Morpholin-4-yl-ethyl)-piperazin-1-ylmethyl]-1-oxo-2-m-tolyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2jo 3-[4-(1-Methyl-piperidin-4-yl)-piperazin-1-ylmethyl]-1-oxo-2-m-tolyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2jp 1-Oxo-3-[4-(2-piperidin-1-yl-ethyl)-piperazin-1-ylmethyl]-2-m-tolyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2jq 1-Oxo-3-[4-(2-pyrrolidin-1-yl-ethyl)-piperazin-1-ylmethyl]-2-m-tolyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2jr 1-Oxo-3-(4-pyridin-4-ylmethyl-piperazin-1-ylmethyl)-2-m-tolyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2js 3-[4-(2-Morpholin-4-yl-ethyl)-piperidin-1-ylmethyl]-1-oxo-2-m-tolyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2jt 3-[4-Hydroxy-4-(3-methoxy-phenyl)-piperidin-1-ylmethyl]-1-oxo-2-m-tolyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2ju 3-[4-(Acetyl-methyl-amino)-4-phenyl-piperidin-1-ylmethyl]-1-oxo-2-m-tolyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

3a 1-Oxo-3-(2-oxo-pyrrolidin-1-ylmethyl)-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

3b 8-Chloro-1-oxo-3-(2-oxo-pyrrolidin-1-ylmethyl)-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

4a 3-Cyanomethyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

5a 3-Methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid N,N-diphenyl-hydrazide

5b N'-(3-Methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carbonyl)-N-phenyl-hydrazinecarboxylic acid methyl ester

1aa 2-(3-Methoxy-phenyl)-3-methyl-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

1ab 2-(4-Methoxy-phenyl)-3-methyl-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

1ac 2-(4-Fluoro-phenyl)-3-methyl-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

1ad 2-(4-Chloro-phenyl)-3-methyl-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

1ae 3-Methyl-1-oxo-2-p-tolyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

1af 2-(3-Methoxy-phenyl)-3-methyl-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-cyclopropyl-(3-fluoro-phenyl)-methyl]-amide

1ag 2-(4-Methoxy-phenyl)-3-methyl-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-cyclopropyl-(3-fluoro-phenyl)-methyl]-amide

1ah 2-(4-Fluoro-phenyl)-3-methyl-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-cyclopropyl-(3-fluoro-phenyl)-methyl]-amide

1ai 2-(4-Chloro-phenyl)-3-methyl-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-cyclopropyl-(3-fluoro-phenyl)-methyl]-amide

1aj 3-Methyl-1-oxo-2-p-tolyl-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-cyclopropyl-(3-fluoro-phenyl)-methyl]-amide

1ak 2-(2-Methoxy-phenyl)-3-methyl-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

1al 2-(2-Methoxy-phenyl)-3-methyl-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-cyclopropyl-(3-fluoro-phenyl)-methyl]-amide

1am 3-Methyl-8-nitro-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

1an 3-Methyl-8-nitro-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-cyclopropyl-(3-fluoro-phenyl)-methyl]-amide

1ao 8-Methoxy-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

1ap 8-Methoxy-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-cyclopropyl-(3-fluoro-phenyl)-methyl]-amide

1aq 8-Amino-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

1ar 8-Cyano-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

1as 8-Chloro-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-1-(4-chloro-phenyl)-propyl]-amide

1at 8-Chloro-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-1-(4-fluoro-phenyl)-propyl]-amide

1au 8-Chloro-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-1-(2-fluoro-phenyl)-propyl]-amide

1av 8-Chloro-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-1-(3-chloro-phenyl)-propyl]-amide

1aw 8-Chloro-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-(3-chloro-phenyl)-cyclopropyl-methyl]-amide

1ax 8-Chloro-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-(4-chloro-phenyl)-cyclopropyl-methyl]-amide

1ay 8-Chloro-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-1-(3-fluoro-phenyl)-propyl]-amide

1az 8-Chloro-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-2-methyl-1-phenyl-propyl)-amide

1ba 8-Chloro-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-cyclopropyl-(4-fluoro-phenyl)-methyl]-amide

1bb 8-Chloro-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-1-(2-chloro-phenyl)-propyl]-amide

1bc 8-Chloro-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-cyclopentyl-phenyl-methyl)-amide

1bd 8-Chloro-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-(2-chloro-phenyl)-cyclopropyl-methyl]-amide

1be 8-Chloro-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-cyclopropyl-(2-fluoro-phenyl)-methyl]-amide

1bf 8-Chloro-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-cyclohexyl-phenyl-methyl)-amide

1bg 8-Chloro-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-cyclopropyl-phenyl-methyl)-amide

1bh 8-Chloro-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-cyclobutyl-(3-fluoro-phenyl)-methyl]-amide

1bi 8-Chloro-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-cyclobutyl-(4-fluoro-phenyl)-methyl]-amide

1bl 8-Chloro-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid [(R)-cyclopropyl-(3-fluoro-phenyl)-methyl]-amide

1bn 8-Chloro-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)cyclobutyl-phenyl-methyl)-amide

1bo 8-Chloro-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid [cyclobutyl-(2-fluoro-phenyl)-methyl]-amide

2ka 3-(4-tert-Butyl-piperazin-1-ylmethyl)-8-chloro-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-cyclopropyl-(3-fluoro-phenyl)-methyl]-amide

2kb 8-Chloro-3-(4-isopropyl-piperazin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2kc 8-Chloro-3-(4-isobutyl-piperazin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2kd 8-Chloro-3-(octahydro-pyrido[1,2-a]pyrazin-2-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2ke 8-Chloro-3-(4-hydroxy-3,4,5,6-tetrahydro-2H-[4,4']bipyridinyl-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2kf 8-Chloro-3-(4-cyclopropylmethyl-piperazin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2kg 8-Chloro-3-[4-(2-morpholin-4-yl-ethyl)-piperidin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2kh 8-Chloro-3-[1,4]diazepan-1-ylmethyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2ki 8-Chloro-3-((S)-3-methyl-piperazin-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2kj 8-Chloro-3-imidazol-1-ylmethyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2kk 8-Chloro-3-(4-methyl-imidazol-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2kl 3-(tert-Butylamino-methyl)-8-chloro-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2km 8-Chloro-3-(isopropylamino-methyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2kn 8-Chloro-3-[4-hydroxy-4-(3-methoxy-phenyl)-piperidin-1-ylmethyl]-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2ko 3-(4-tert-Butyl-piperazin-1-ylmethyl)-8-chloro-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2kp 3-Benzoimidazol-1-ylmethyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2kq 1-Oxo-2-phenyl-3-pyrazol-1-ylmethyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2kr 3-(4-Methyl-pyrazol-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2ks 1-Oxo-2-phenyl-3-[1,2,3]triazol-1-ylmethyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2kt 2-(3-Methoxy-phenyl)-1-oxo-3-(4-pyridin-4-ylmethyl-piperazin-1-ylmethyl)-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2ku 2-(4-Methoxy-phenyl)-3-[4-(2-morpholin-4-yl-ethyl)-piperazin-1-ylmethyl]-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2kv 2-(4-Fluoro-phenyl)-1-oxo-3-(4-phenethyl-piperazin-1-ylmethyl)-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2kw 2-(4-Fluoro-phenyl)-3-(4-isopropyl-piperazin-1-ylmethyl)-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2kx 3-[1,4']Bipiperidinyl-1'-ylmethyl-2-(4-fluoro-phenyl)-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2ky 2-(4-Fluoro-phenyl)-3-[4-(2-morpholin-4-yl-ethyl)-piperazin-1-ylmethyl]-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2kz 2-(4-Fluoro-phenyl)-3-[4-(1-methyl-piperidin-4-yl)-piperazin-1-ylmethyl]-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2la 2-(4-Fluoro-phenyl)-1-oxo-3-[4-(2-pyrrolidin-1-yl-ethyl)-piperazin-1-ylmethyl]-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2lb 2-(4-Fluoro-phenyl)-3-[4-hydroxy-4-(3-methoxy-phenyl)-piperidin-1-ylmethyl]-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2lc 2-(4-Chloro-phenyl)-1-oxo-3-(4-phenethyl-piperazin-1-ylmethyl)-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2ld 2-(4-Chloro-phenyl)-3-(4-isopropyl-piperazin-1-ylmethyl)-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2le 3-[1,4']Bipiperidinyl-1'-ylmethyl-2-(4-chloro-phenyl)-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2lf 2-(4-Chloro-phenyl)-3-[4-(2-morpholin-4-yl-ethyl)-piperazin-1-ylmethyl]-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2lg 2-(4-Chloro-phenyl)-3-[4-(1-methyl-piperidin-4-yl)-piperazin-1-ylmethyl]-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2lh 2-(4-Chloro-phenyl)-1-oxo-3-[4-(2-piperidin-1-yl-ethyl)-piperazin-1-ylmethyl]-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2li 2-(4-Chloro-phenyl)-1-oxo-3-[4-(2-pyrrolidin-1-yl-ethyl)-piperazin-1-ylmethyl]-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2lj 3-(4-tert-Butyl-piperazin-1-ylmethyl)-8-fluoro-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2lk 8-Chloro-3-cyclopropylaminomethyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

2ll 3-(4-tert-Butyl-piperazin-1-ylmethyl)-8-fluoro-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-cyclopropyl-(3-fluoro-phenyl)-methyl]-amide

2lm 8-Fluoro-1-oxo-2-phenyl-3-piperazin-1-ylmethyl-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-cyclopropyl-(3-fluoro-phenyl)-methyl]-amide

2ln 8-Fluoro-1-oxo-3-(3-oxo-pyrazolidin-1-ylmethyl)-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-cyclopropyl-(3-fluoro-phenyl)-methyl]-amide

2lo 8-Fluoro-1-oxo-3-(3-oxo-piperazin-1-ylmethyl)-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-cyclopropyl-(3-fluoro-phenyl)-methyl]-amide

3c 1-Oxo-2-phenyl-3-(1H-[1,2,4]triazol-3-ylsulfanylmethyl)-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

3d 8-Chloro-1-oxo-3-(2-oxo-pyrrolidin-1-ylmethyl)-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-cyclopropyl-(3-fluoro-phenyl)-methyl]-amide

3e 8-Fluoro-1-oxo-3-(2-oxo-pyrrolidin-1-ylmethyl)-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

3f 8-Fluoro-1-oxo-3-(2-oxo-pyrrolidin-1-ylmethyl)-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-cyclopropyl-(3-fluoro-phenyl)-methyl]-amide

3g 8-Fluoro-1-oxo-3-(5-oxo-pyrazolidin-1-ylmethyl)-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-cyclopropyl-(3-fluoro-phenyl)-methyl]-amide

3h 8-Fluoro-1-oxo-3-(2-oxo-piperazin-1-ylmethyl)-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-cyclopropyl-(3-fluoro-phenyl)-methyl]-amide

3i 8-Fluoro-1-oxo-3-(2-oxo-piperidin-1-ylmethyl)-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-cyclopropyl-(3-fluoro-phenyl)-methyl]-amide

4b 8-Chloro-3-cyanomethyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-cyclopropyl-(3-fluoro-phenyl)-methyl]-amide

6a 2-(3,4-Dichloro-phenyl)-3-methyl-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

6b 8-Fluoro-1-oxo-3-(2-oxo-pyrrolidin-1-ylmethyl)-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-cyclopropyl-phenyl-methyl)-amide

6c 8-Fluoro-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-cyclopropyl-phenyl-methyl)-amide

7a 3-Ethyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

7b 8-Fluoro-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

7c 8-Fluoro-2-(3-fluoro-phenyl)-3-methyl-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

7d 8-Fluoro-2-(4-fluoro-phenyl)-3-methyl-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

7e 8-Fluoro-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-cyclopropyl-(3-fluoro-phenyl)-methyl]-amide

7f 8-Fluoro-2-(3-fluoro-phenyl)-1-oxo-3-(2-oxo-pyrrolidin-1-ylmethyl)-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-cyclopropyl-(3-fluoro-phenyl)-methyl]-amide

7g 8-Fluoro-2-(4-fluoro-phenyl)-1-oxo-3-(2-oxo-pyrrolidin-1-ylmethyl)-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-cyclopropyl-(3-fluoro-phenyl)-methyl]-amide

7h 8-Fluoro-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-cyclobutyl-(3-fluoro-phenyl)-methyl]-amide

7i 8-Fluoro-2-(2-fluoro-phenyl)-3-methyl-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-cyclopropyl-(3-fluoro-phenyl)-methyl]-amide

7j 8-Fluoro-2-(3-fluoro-phenyl)-3-methyl-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-cyclopropyl-(3-fluoro-phenyl)-methyl]-amide

7k 8-Fluoro-2-(4-fluoro-phenyl)-3-methyl-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-cyclopropyl-(3-fluoro-phenyl)-methyl]-amide

7l 6,8-Difluoro-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-cyclopropyl-(3-fluoro-phenyl)-methyl]-amide

7m 5,8-Difluoro-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-cyclopropyl-(3-fluoro-phenyl)-methyl]-amide

7n 3-Methyl-1-oxo-2-phenyl-8-trifluoromethyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

8a 3-(1-tert-Butyl-piperidin-4-ylmethyl)-8-chloro-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-cyclopropyl-(3-fluoro-phenyl)-methyl]-amide;

and pharmaceutically acceptable salts of any of these compounds.

86. A compound according to any of claims 1-85 for use in therapy

87. A method for the treatment of a disease selected from psychosis; schizophrenia; schizophrenoform disorder; schizoaffective disorder; delusional disorder; brief psychotic disorder; shared psychotic disorder; psychotic disorder due to a general medical condition; substance or drug induced psychotic disorder (cocaine, alcohol, amphetamine etc); schizoid personality disorder; schizoptypal personality disorder; psychosis or schizophrenia associated with major depression, bipolar disorder, Alzheimer's disease or Parkinson's disease; major depression; general anxiety disorder; bipolar disorder (maintenance treatment, recurrence prevention and stabilization); mania; hypomania; cognitive impairment; ADHD; obesity; appetite reduction; Alzheimer's disease; Parkinson's disease; pain; convulsions; cough; asthma; airway hyperresponsiveness; microvascular hypersensitivity; bronchoconstriction; chronic obstructive pulmonary disease; urinary incontinence; gut inflammation; and inflammatory bowel syndrome, which method comprises the administration of a therapeutically effective amount of a compound according to any of claims 1-85 to a patient in need thereof.

88. The method according to claim 87, wherein said disease is schizophrenia

89. The method according to claim 88, wherein said treatment comprises the treatment of positive, negative and/or cognitive symptoms of schizophrenia.

90. The method according to claim 88 or 89 which additionally comprises a concomitant or sequential administration of a therapeutically effective amount of a compound selected from the list consisting of D2 antagonists, D2 partial agonists, PDE10 antagonists, 5-HT_{2A} antagonists, 5-HT_6 antagonists and KCNQ4 antagonister.

91. A compound according to any of claims 1-85 for use in the treatment of a disease selected from psychosis; schizophrenia; schizophrenoform disorder; schizoaffective disorder; delusional disorder; brief psychotic disorder; shared psychotic disorder; psychotic disorder due to a general medical condition; substance

or drug induced psychotic disorder (cocaine, alcohol, amphetamine etc); schizoid personality disorder; schizoptypal personality disorder; psychosis or schizophrenia associated with major depression, bipolar disorder, Alzheimer's disease or Parkinson's disease; major depression; general anxiety disorder; bipolar disorder (maintenance treatment, recurrence prevention and stabilization); mania; hypomania; cognitive impairment; ADHD; obesity; appetite reduction; Alzheimer's disease; Parkinson's disease; pain; convulsions; cough; asthma; airway hyperresponsiveness; microvascular hypersensitivity; bronchoconstriction; chronic obstructive pulmonary disease; urinary incontinence; gut inflammation; and inflammatory bowel syndrome.

92. The compound according to claim 91, wherein said disease is schizophrenia.

93. The compound according to claim 92, wherein said disease is the negative, positive and/or cognitive symptoms of schizophrenia.

94. The use of a compound according to any of claims 1-85 for the manufacture of a medicament for the treatment of a disease selected from psychosis; schizophrenia; schizophrenoform disorder; schizoaffective disorder; delusional disorder; brief psychotic disorder; shared psychotic disorder; psychotic disorder due to a general medical condition; substance or drug induced psychotic disorder (cocaine, alcohol, amphetamine etc); schizoid personality disorder; schizoptypal personality disorder; psychosis or schizophrenia associated with major depression, bipolar disorder, Alzheimer's disease or Parkinson's disease; major depression; general anxiety disorder; bipolar disorder (maintenance treatment, recurrence prevention and stabilization); mania; hypomania; cognitive impairment; ADHD; obesity; appetite reduction; Alzheimer's disease; Parkinson's disease; pain; convulsions; cough; asthma; airway hyperresponsiveness; microvascular hypersensitivity; bronchoconstriction; chronic obstructive pulmonary disease; urinary incontinence; gut inflammation; and inflammatory bowel syndrome.

95. The use according to claim 93, wherein said disease is schizophrenia.

96. The use according to claim 95, wherein said disease is the positive, negative and/or cognitive symptoms of schizophrenia.

97. The use according to claim 95 or 96 wherein said manufacture further comprises the use of a compound selected from the list consisting of D2 antagonists, D2 partial agonists, PDE10 antagonists, 5-HT_{2A} antagonists, 5-HT_6 antagonists and KCNQ4 antagonists

98. A pharmaceutical composition comprising a compound according to any of claims 1-85 and one or more pharmaceutically acceptable carrier or excipient.

99. A composition according to claim 98 which composition additionally comprises a compound selected from the list consisting of D2 antagonists, D2 partial agonists, PDE10 antagonists, 5-HT_{2A} antagonists, 5-HT_6 antagonists and KCNQ4 antagonists.

100. A kit comprising a compound according to any of claims 1-85 together with a compound selected from the list consisting of D2 antagonists, D2 partial agonists, PDE10 antagonists, 5-HT_{2A} antagonists, 5-HT_6 antagonists and KCNQ4 antagonists.