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División de Nuevas Creaciones

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SOLICITUD

PATENTE DE INVENCIÓN

21. **EXPEDIENTE No.** 09-120188

54. **TÍTULO** DERIVADOS DE ISOQUINOLINONA COMO ANTAGONISTAS DEL NK3

51. **CLASIFICACIÓN INTERNACIONAL**

71. **SOLICITANTE** H. LUNDBECK A/S

DOMICILIO VALBY, DINAMARCA

74. **APODERADO** LUZ CLEMENCIA DE PAEZ
C.C. 35.456.344 de Usaquén

22. **BOGOTÁ, D.C.,**

Poder, Cesión
Fec 26-11-2004

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☒ Capítulo I. ☐ Capítulo II.

2 SOLICITANTE (71)

Nombre: **H. LUNDBECK A/S**
Sociedad constituida y existente bajo las leyes de Dinamarca.

Dirección: Ottiliavej 9,
DK-2500 Valby,
Dinamarca

Domicilio: Valby
Dinamarca

IDENTIFICACIÓN
C.C. ☐ NIT ☐
C.E. ☐ Otro ☐
Cual _____
Número _____

3 REPRESENTANTE O APODERADO

Nombre: LUZ CLEMENCIA DE PAEZ
Dirección: Carrera 4ª. No. 72-35
Teléfono: 347 36 11
Fax: 211 86 50
E-mail: clientes@cavelier.com
Domicilio: Bogotá, Colombia.

IDENTIFICACIÓN
C.C. ☒ NIT ☐
C.E. ☐ Otro ☐
Cual _____
Número 35.456.344 T.P 23.555

4 INVENTOR (ES) (72)

1. **Klaus Baek SIMONSEN**
Læssøegade 75,
DK-5230 Odense M,
Dinamarca

2. **Jan KEHLER**
Nymøllevej 28,
DK-2800 Kgs. Lyngby
Dinamarca

3. **Karsten JUHL**
Brydeholm 56,
DK-2670 Greve,
Dinamarca

4. **Nikolay KHANZHIN**
Teglgårdsvej 545, 2. tv,
DK-3050 Humlebæk,
Dinamarca

5. **Søren Møller NIELSEN**
Åmosevej 15,
DK-3400 Hillerød
Dinamarca

5 PCT (86)

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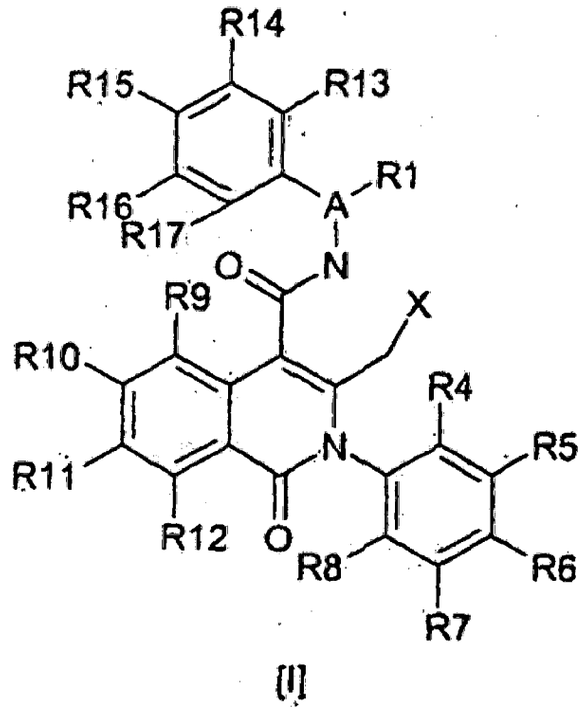
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Comprobante de pago No.: 09-77,186 **Fecha:** 13 de octubre de 2009
Comprobante de pago No.: 09-78,692 **Fecha:** 19 de octubre de 2009

(10)

Anexos:

- [x] Comprobante de pago de la tasa de presentación de la solicitud por $ 540.000.oo.
- [x] Comprobante de pago por 85 reivindicaciones adicionales después de la decimoquinta reivindicación por $2.125.000.oo.
- [ ] Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- [ ] Poderes, si fuere el caso.
- [ ] Documento de cesión del inventor al solicitante o a su causante.
- [ ] Declaraciones.
- [x] Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
- [x] Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- [ ] Copia del examen preliminar efectuado por la IPEA.
- [ ] Traducción del examen preliminar efectuado por la IPEA.
- [ ] De ser el caso, copia del contrato de acceso.
- [ ] De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
- [ ] De ser el caso, certificado de depósito del material biológico.
- [x] Arte final 12x12
- [ ] De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- [x] Otros: VER HOJA DE DOCUMENTOS ANEXOS

(11) **FIGURA CARACTERÍSTICA**



[I]

(12) Solicito la concesión de la patente,

NOMBRE: LUZ CLEMENCIA DE PÁEZ

FIRMA : Luz Clemencia de Páez

C.C. 35.456.344 de Usaquén T.P. 23.555

SCT

DOCUMENTOS ANEXOS

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   Páginas 212 en el idioma original

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(71) Applicant *(for all designated States except US)*: **H. LUNDBECK A/S** [DK/DK]; Ottiliavej 9, DK-2500 Valby (DK).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **SIMONSEN, Klaus, Bæk** [DK/DK]; Læssøegade 75, DK-5230 Odense M (DK). **KEHLER, Jan** [DK/DK]; Nymøllevej 28, DK-2800 Kgs. Lyngby (DK). **JUHL, Karsten** [DK/DK]; Brydeholm 56, DK-2670 Greve (DK). **KHANZHIN, Nikolay** [RU/DK]; Teglgårdsvej 545, 2. tv, DK-3050 Humlebæk (DK). **NIELSEN, Søren, Møller** [DK/DK]; Åmosevej 15, DK-3400 Hillerød (DK).

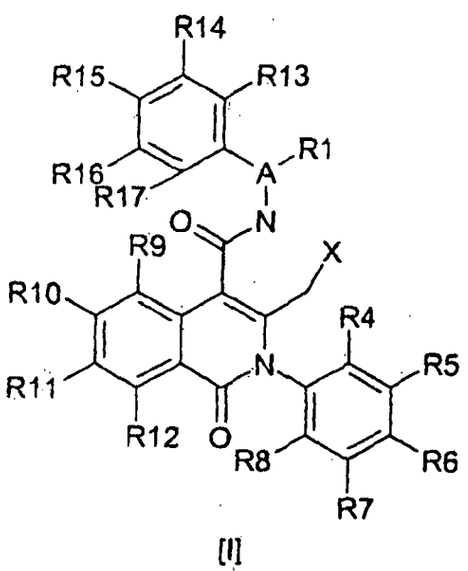
(74) Common Representative: **H. LUNDBECK A/S**; Corporate Patents, Ottiliavej 9, DK-2500 Valby (DK).

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

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(54) Title: ISOQUINOLINONE DERIVATIVES AS NK3 ANTAGONISTS



[I]

(57) Abstract: Isoquinolone derivatives of the general formula (I) are provided The compounds are NK3 antagonists and useful for the treatment of e. g. psychosis and schizophrenia.

WO 2008/131779 A1

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

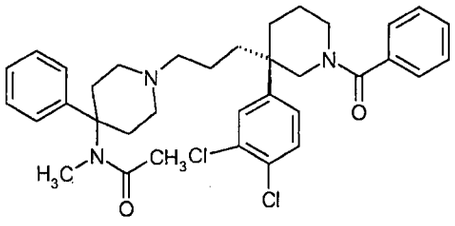
The currently approved antipsychotic drugs share the common feature of reducing the dopamine signalling in the brain. This is achieved through either a dopamine D2 receptor antagonistic or partial agonistic effect. The first generation antipsychotics (also referred to as "typical") are often associated 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.

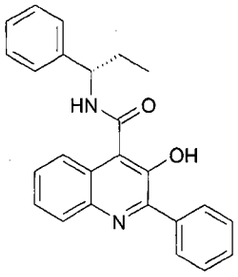
NK3 is primarily expressed centrally in regions including cortical regions, such as frontal, parietal and cingulated cortex; nuclei of the amygdale, such as the basal, central and lateral nuclei; the hippocampus; and mesencephalon structures, such as ventral tegmental area, substantia nigra pars compacta,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

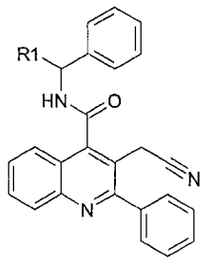


Talnetant

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 amcliorate 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.

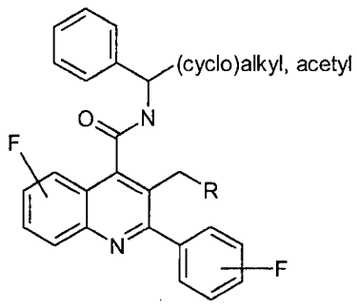
WO95/32948 discloses a range of quinoline derivatives, including talnetant as NK3 antagonists.

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



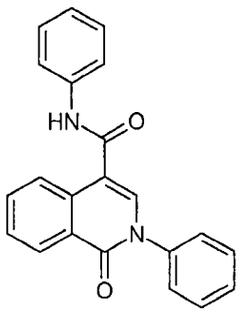
which compounds are said to be NK3 antagonists; and WO 2006/050991 and WO 2006/050992 disclose further quinolinecarboxamides derivatives, which derivatives are said to be NK3 antagonists.

WO 2005/014575 discloses compounds of the formula



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

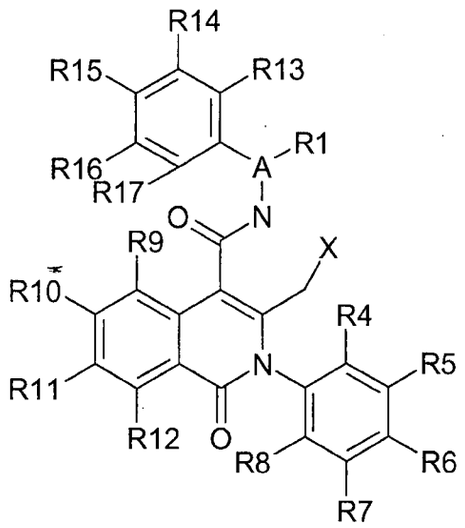
Finally, *Ind.J.Chem. Section B*, 18B, 304-306, 1979 discloses a study on the synthesis of compounds with the following core structure



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

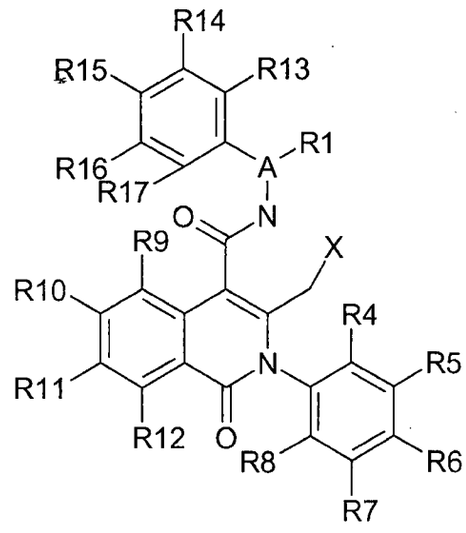
bi-ctyclic moieties above, tri-cyclic moieties may be fused, spiro or caged, or in deed, a combination thereof.

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;

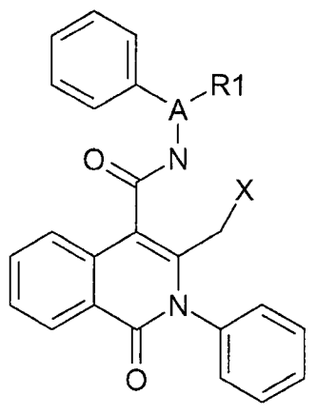
and pharmaceutically acceptable salts thereof.

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;

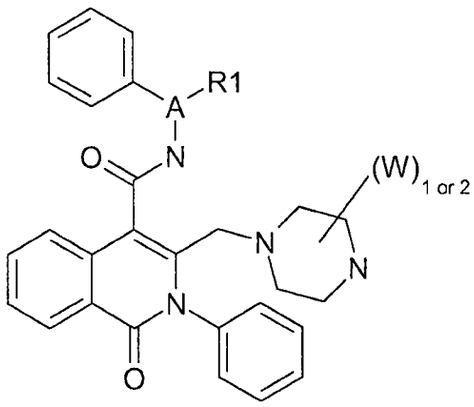
wherein Y represents a bond, C(O), O, S, -O-C(O), -C(O)-O-, -NR^2-, -NR^2-C(O)-, -C(O)-NH-, or $S(O)_2$;

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;

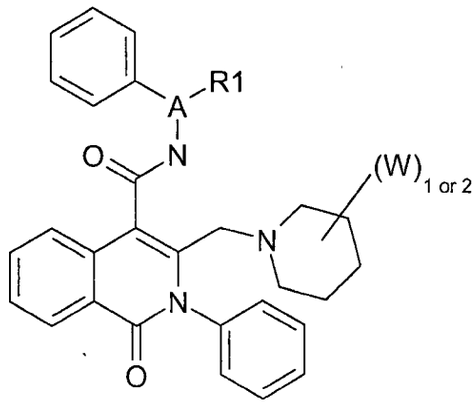
wherein R^2 and R^3 independently represent hydrogen, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, haloC_{1-6}alkyl or phenyl. In a further embodiment, Y represents a bond, C(O) or $S(O)_2$; wherein a+b is 0, 1, 2, 3, or 4; and wherein Z represents mono-cyclic or fused bi-cyclic moiety comprising 5 to 12 carbon 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;

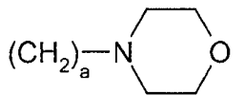
wherein a and b independently represent an integer selected from 0, 1, 2 and 3;

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;

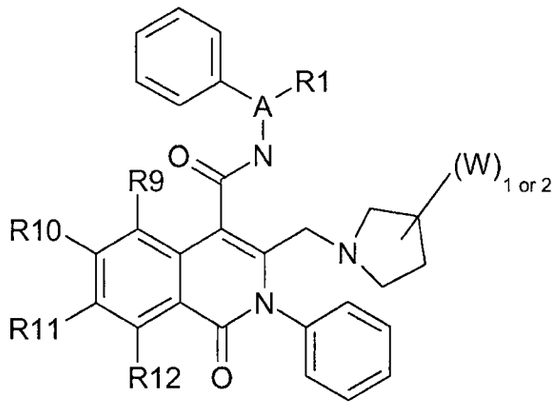
wherein R^2 and R^3 independently represent hydrogen, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, haloC_{1-6}alkyl or phenyl; and pharmaceutically acceptable salts thereof. In particular, A represent CH, and R^1 represents C_{1-6}alkyl, such as ethyl or cyclopropyl.

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;

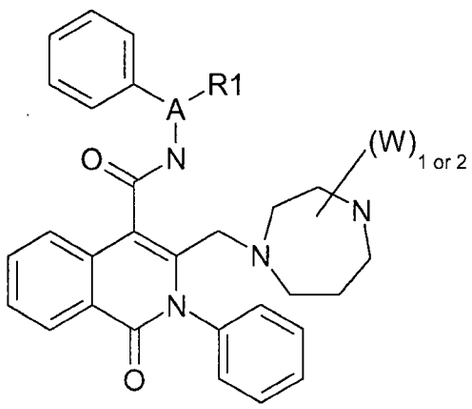
wherein each R^1 independently represents hydrogen, C_{1-6}alkyl, -C(O)-C_{1-6}alkyl, C(O)-O-C_{1-6}alkyl, or phenyl, wherein said phenyl, or C_{1-6}alkyl is optionally substituted with one or more substituents selected from halogen, hydroxyl, haloC_{1-6}alkyl, nitro, C_{1-6}alkoxy, and NR^2R^3;

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;

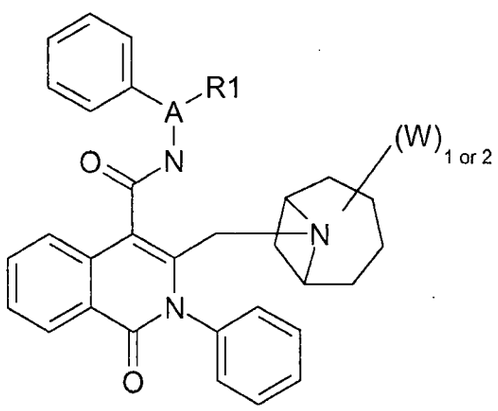
wherein Y represents a bond, C(O), O, S, -O-C(O), -C(O)-O-, NR^2, -NR^2-C(O)-, -C(O)-NH-, or $S(O)_2$;

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;

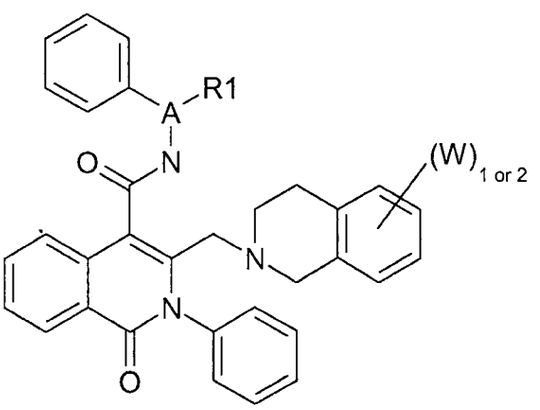
wherein a and b independently represent an integer selected from 0, 1, 2 and 3;

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;

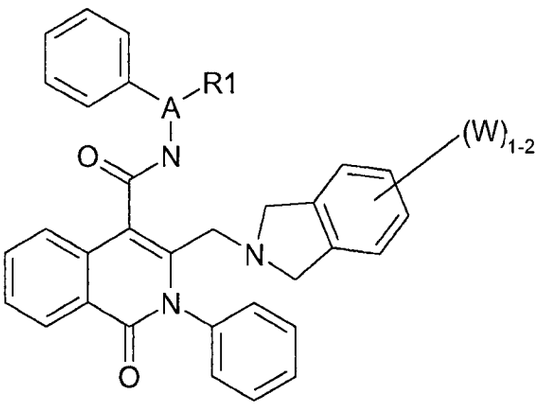
wherein a and b independently represent an integer selected from 0, 1, 2 and 3;

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;

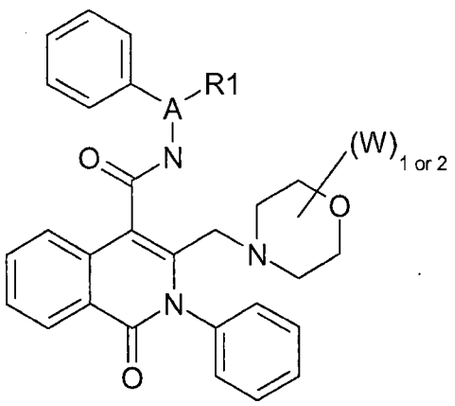
wherein Y represents a bond, C(O), O, S, -O-C(O), -C(O)-O-, NR^2, -NR^2-C(O)-, -C(O)-NH-, or $S(O)_2$;

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;

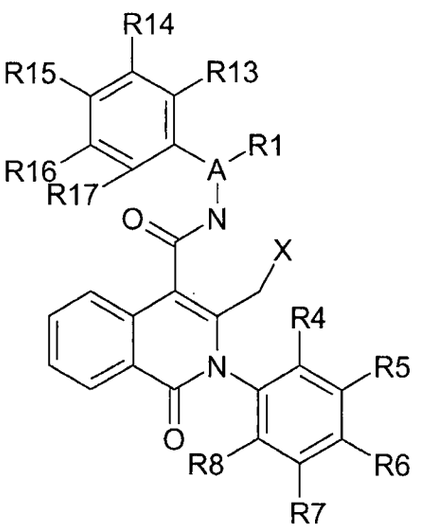
wherein a and b independently represent an integer selected from 0, 1, 2 and 3;

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;

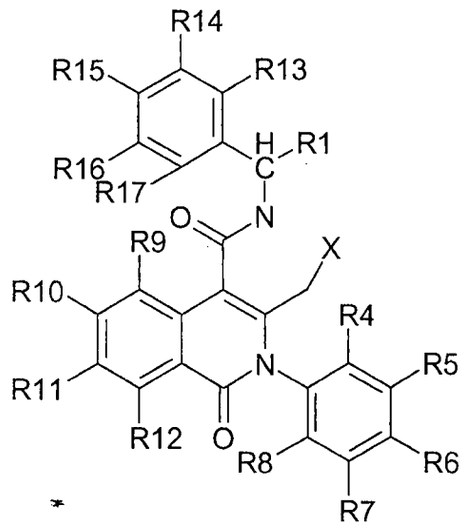
wherein Y represents a bond, C(O), O, S, -O-C(O), -C(O)-O-, -NR^2-, -NR^2-C(O)-, -C(O)-NH-, or $S(O)_2$;

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;

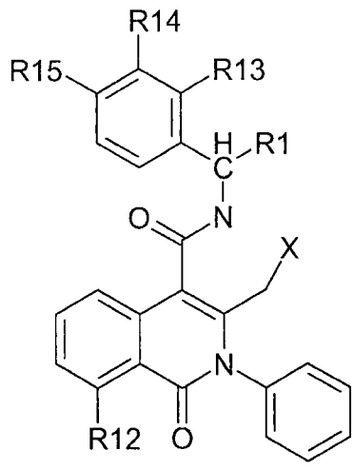
wherein Y represents a bond, and wherein Z represents a mono-cyclic moiety comprising 5 to 6 ring atoms of which optionally one, two or three are hetero atoms selected from amongst N, O, and S, and wherein said mono-cyclic moiety is optionally substituted with one or more substituents selected from the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

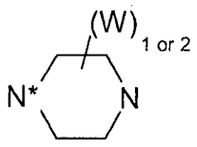
wherein a and b independently represent an integer selected from 0, 1, 2 and 3;

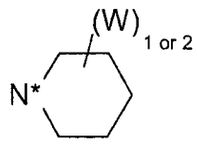
wherein Y represents a bond, and wherein Z represents a mono-cyclic moiety comprising 5 to 6 ring atoms of which optionally one is a hetero atom selected from amongst N, O, and S, and wherein said mono-cyclic moiety is optionally substituted with one or more substituents selected from the group consisting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

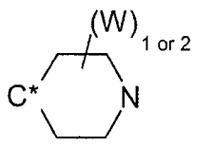
wherein R^{12} represents halogen;

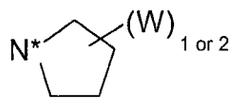
R^{13}-R^{15} each independently represents hydrogen or halogen;

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



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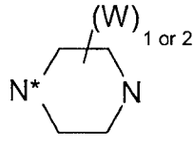
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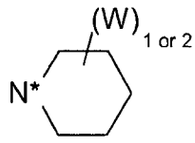
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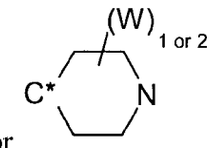
$-NR^2R^3$, or Hydrogen

* 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 

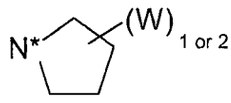
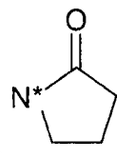
, and wherein W represents hydrogen, (=O), C_{1-6}-alkyl, or $-(CH_2)_a$-Y-$(CH_2)_b$-Z. In particular, W represents hydrogen, methyl, cyclopropylmethyl, isopropyl, isobutyl, tert-butyl, (=O), or or $-(CH_2)_a$-Y-$(CH_2)_a$-Z, wherein a+b is 2 and Z is selected from 4-morpholinyl, phenyl, 1-piperidine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

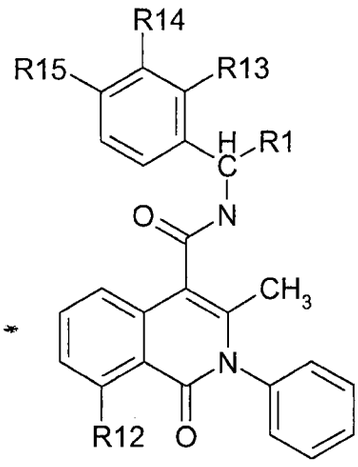
In one embodiment, wherein the compounds of the invention are defined by formula I_k' and R^1 represents methyl, ethyl, cyclopropyl, cyclobutyl, cyclopentyl or

cyclohexyl, X represent  , and W represents (=O), and in particular, X represents  .

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''



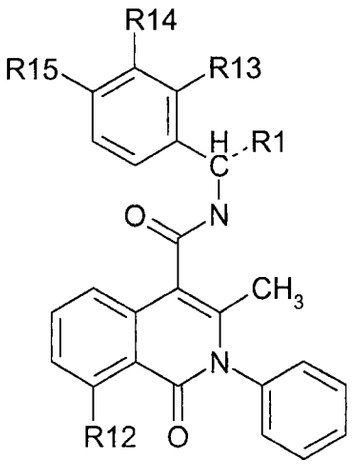
[Ik"]

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'''



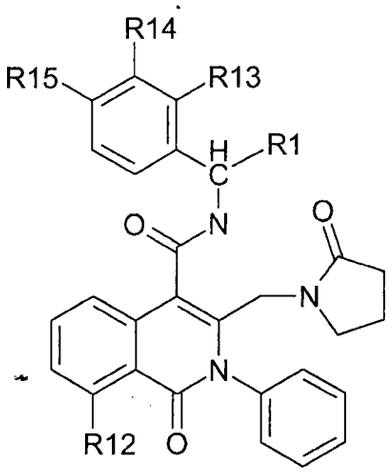
[Ik'"]

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']

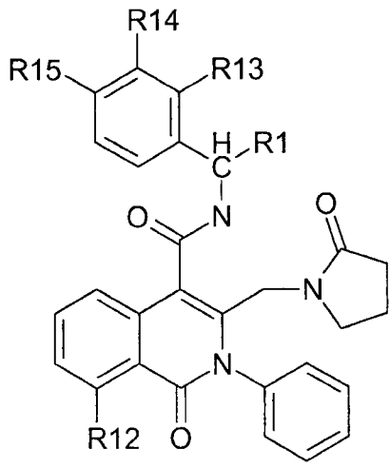
wherein R^1 represents ethyl or cyclopropyl;

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''



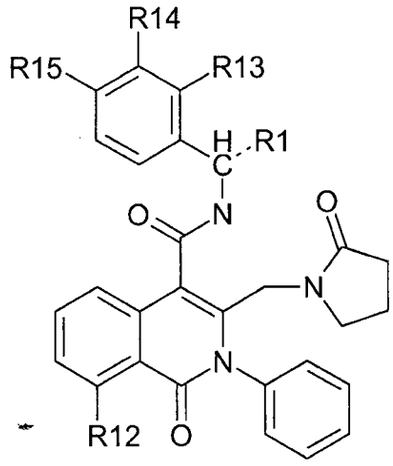
[Id"]

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

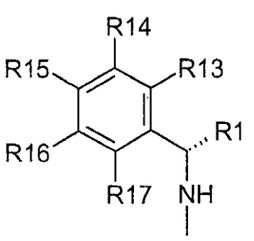
7n 3-Methyl-1-oxo-2-phenyl-8-trifluoromethyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide

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.

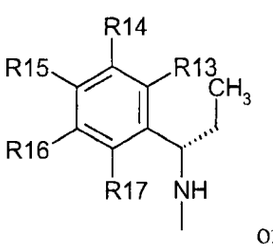
Further, the compounds of this invention may exist in unsolvated as well as in solvated forms with pharmaceutically acceptable solvents such as water, ethanol and the like. In general, the solvated forms are considered equivalent to the unsolvated forms for the purposes of this invention.

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.

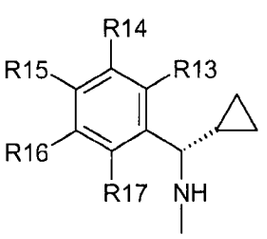
In a particular embodiment, the compounds of the present invention have the following absolute configuration around A, A being CH



, 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.

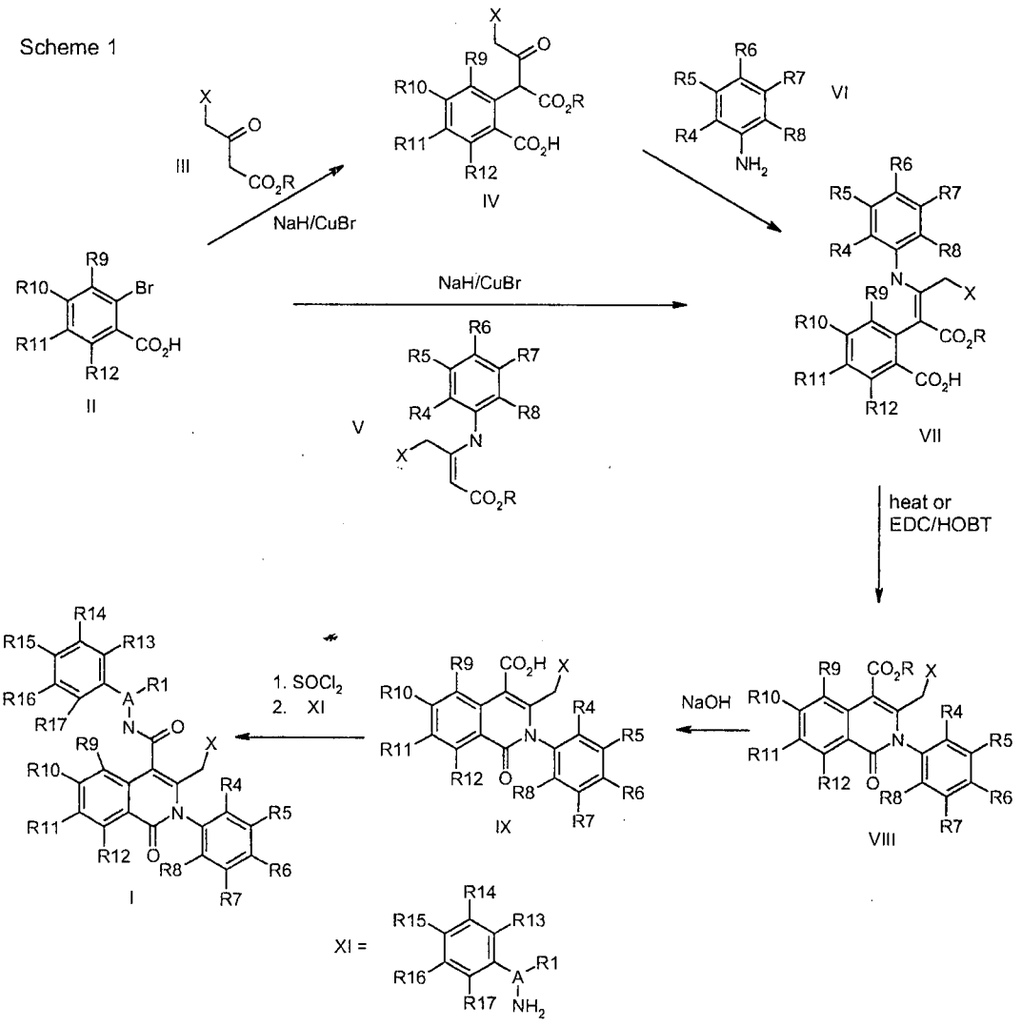
Furthermore, isoquinolinones of the general formula VIII can be obtained directly from the starting 2-bromobenzoic acids of the general formula II and deprotonated enamines of the general formula V in a modified one-pot procedure involving Hurtley reaction performed at 70°C with the formation of the 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.

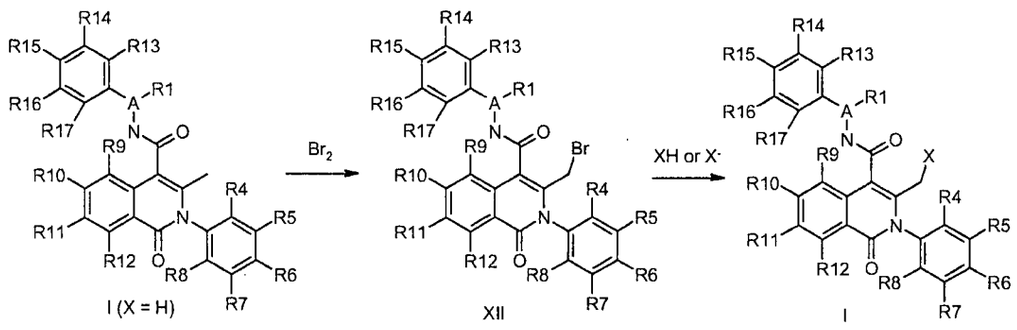
Compounds of the general formula I where X is hydrogen can be converted to the compounds of the general formula XII by regioselective bromination reaction in the presence of bromination reagent such as bromine. Then the bromine atom can be substituted by various nucleophiles of the general formula X-H 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.

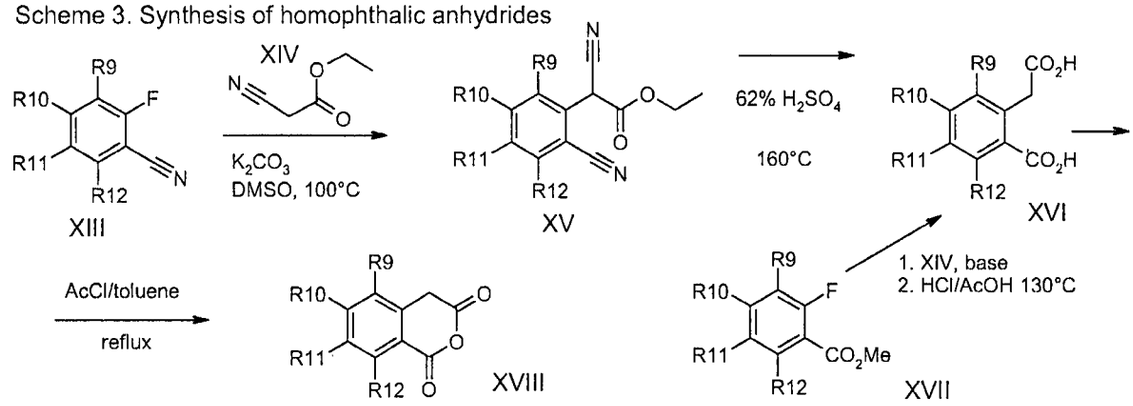
Scheme 1



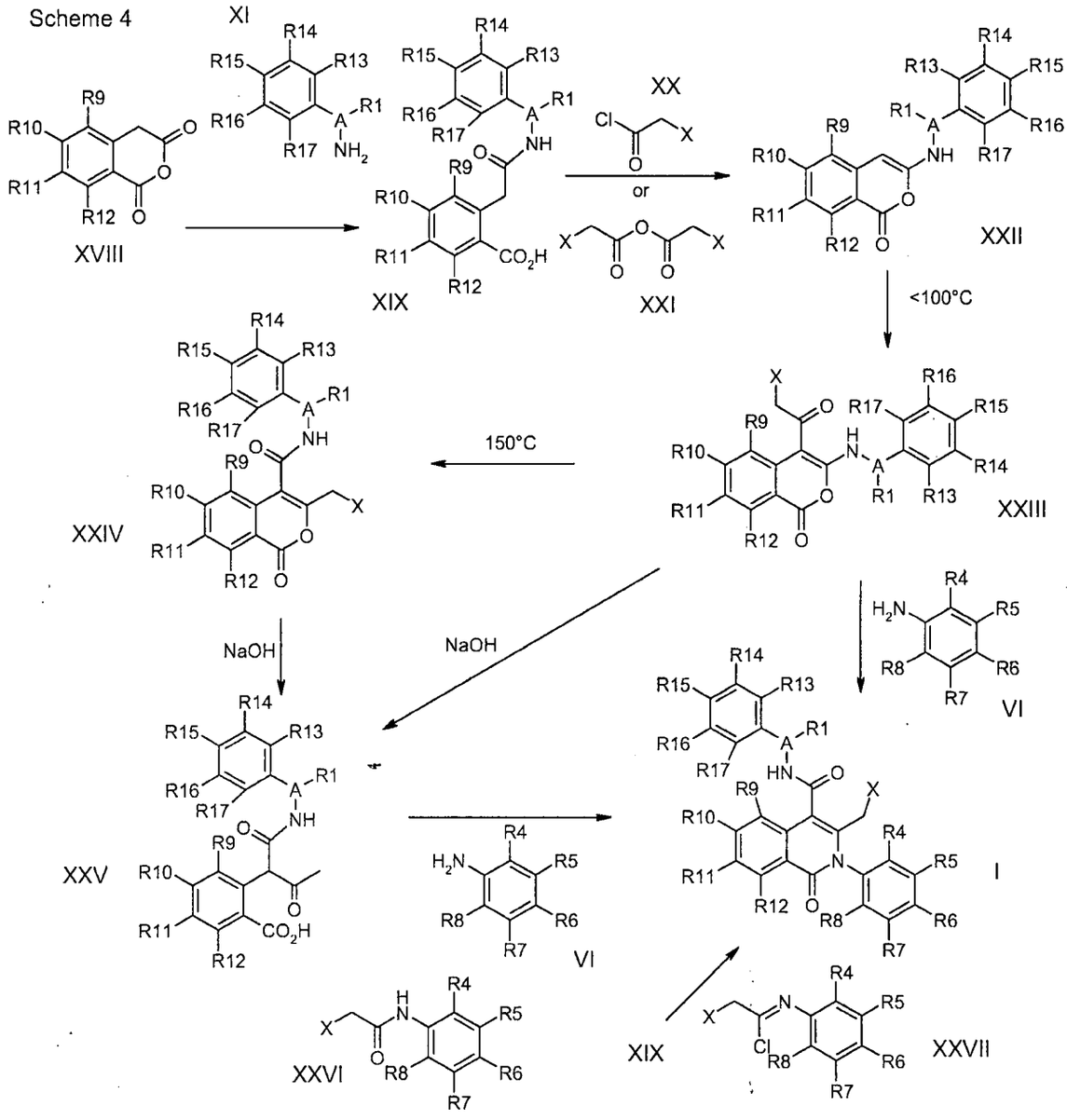
Scheme 2


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

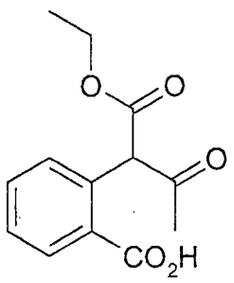
Time, min.	%B
0.00	10.0-50.0 (variable, depending on the sample)
7.00	100.0
7.10	10.0-50.0
8.00	10.0-50.0

^{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

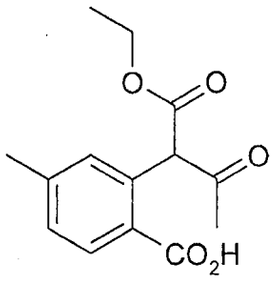


2-(1-Ethoxycarbonyl-2-oxo-propyl)-benzoic acid.

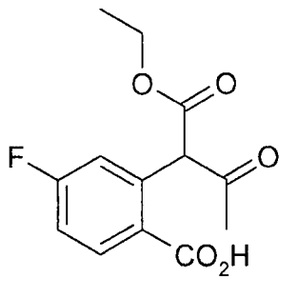
To a cold (ice/water bath) stirred mixture of 2-bromobenzoic acid (20.1g, 0.1 mol) and ethyl acetoacetate (13.01 g, 0.1 mol) in 1,4-dioxane (200 ml) sodium hydride (8 g, 0.2 mol, 60% dispersion in mineral oil) was added in small portions. After addition the cold bath was removed and the reaction mixture 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.

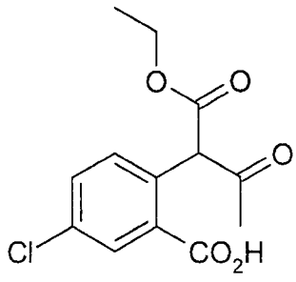
The following compounds were prepared analogously from corresponding 2-bromobenzoic acids and used in the next step without further purification and characterisation unless noted otherwise:



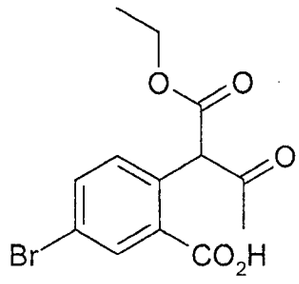
2-(1-Ethoxycarbonyl-2-oxo-propyl)-4-methyl-benzoic acid.
LC-MS (m/z) 247.2 ($[MH-H_2O]^+$); t_R = 1.05.



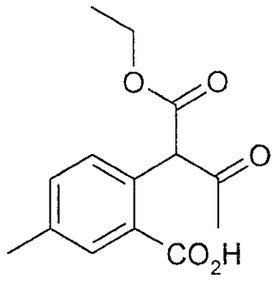
2-(1-Ethoxycarbonyl-2-oxo-propyl)-4-fluoro-benzoic acid.



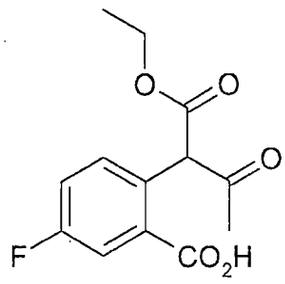
5-Chloro-2-(1-ethoxycarbonyl-2-oxo-propyl)-benzoic acid.



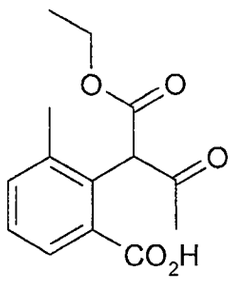
5-Bromo-2-(1-ethoxycarbonyl-2-oxo-propyl)-benzoic acid.



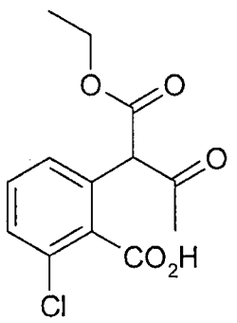
2-(1-Ethoxycarbonyl-2-oxo-propyl)-5-methyl-benzoic acid.



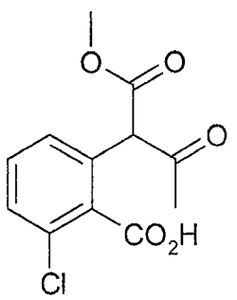
2-(1-Ethoxycarbonyl-2-oxo-propyl)-5-fluoro-benzoic acid.



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

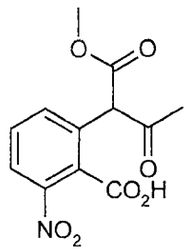


2-Chloro-6-(1-ethoxycarbonyl-2-oxo-propyl)-benzoic acid.

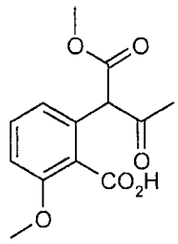


2-Chloro-6-(1-methoxycarbonyl-2-oxo-propyl)-benzoic acid.

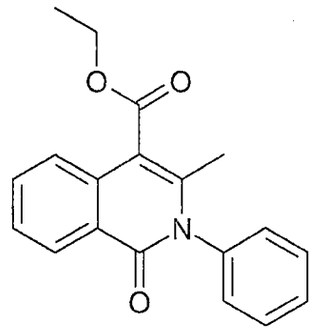
To a stirred mixture of 2-bromo-6-chlorobenzoic acid (20 g, 85 mmol), methylacetoacetate (310 ml, excess), and copper (I) bromide 12.2 g, 85 mmol) sodium hydride (8.5 g, 212 mmol, 60% in oil) was added by portions and then heated at 70°C for 16 hours. The resulting mixture was diluted with water (600 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.

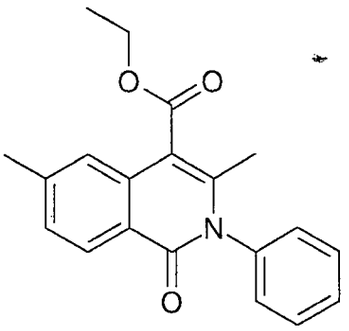


3-Methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ethyl ester.

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

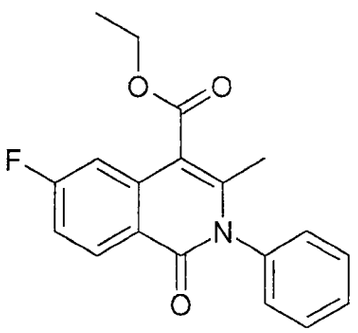
washed with diethyl ether to give 4.2 g of a pale-brown crystalline solid, yield 45%. LC-MS (m/z) 308.2 (MH^+); t_R = 1.43. ^1H NMR (500 MHz, DMSO-d_6): 1.34 (t, 3H), 1.97 (s, 3H), 4.41 (q, 2H), 7.38 (d, 2H), 7.51 (t, 1H), 7.56 (t (overlapping m), 3H), 7.62 (d, 1H), 7.8 (t, 1H), 8.22 (d, 1H).

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.

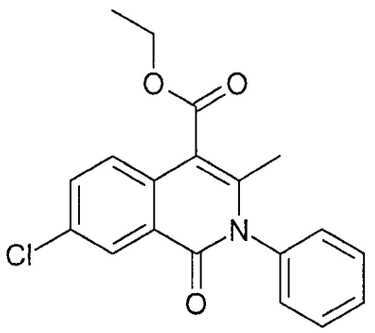
The crude product was used in the next step without crystallization. LC-MS (m/z) 322.1 (MH^+); t_R = 1.53. ^1H NMR (500 MHz, DMSO-d_6): 1.34 (t, 3H), 1.96 (s, 3H), 2.47 (s, 3H), 4.41 (q, 2H), 7.28 (t, 1H), 7.37 (m, 3H), 7.50 (d, 1H), 7.56 (m, 2H), 8.11 (d, 1H).



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

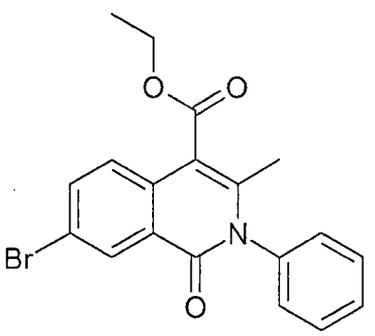
The crude product was used in the next step without crystallization. LC-MS (m/z) 326.3 (MH^+); t_R = 1.54. ^1H NMR (500 MHz, DMSO-d_6): 1.33 (t, 3H), 2.0 (s, 3H),

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).



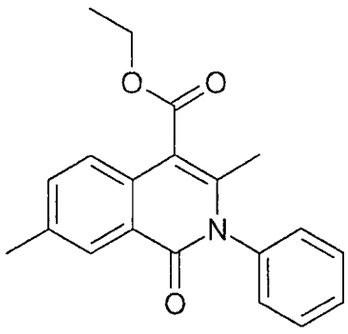
7-Chloro-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ethyl ester.

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).



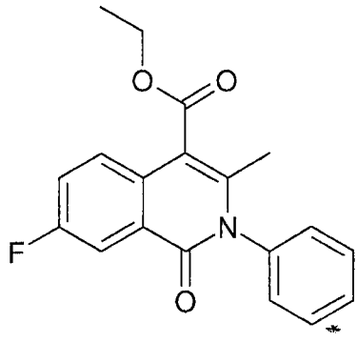
7-Bromo-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ethyl ester.

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).



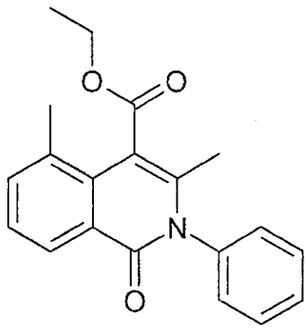
3,7-Dimethyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ethyl ester.

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.



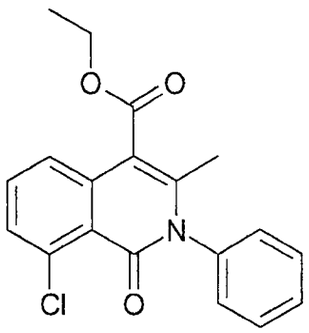
7-Fluoro-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ethyl ester.

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).



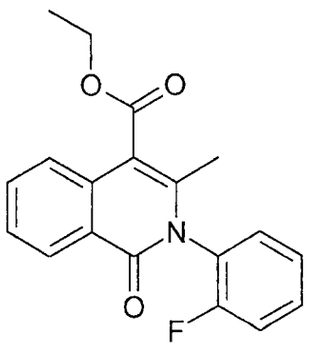
3,5-Dimethyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ethyl ester.

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



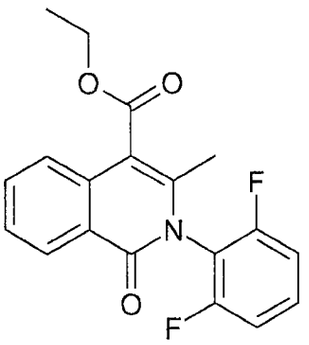
8-Chloro-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ethyl ester.

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



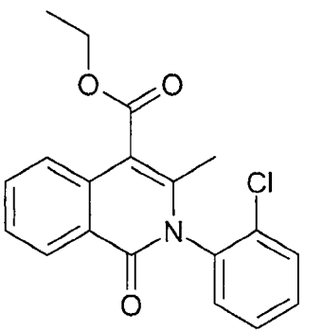
2-(2-Fluoro-phenyl)-3-methyl-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ethyl ester.

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



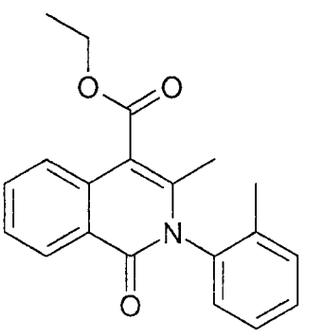
2-(2,6-Difluoro-phenyl)-3-methyl-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ethyl ester.

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



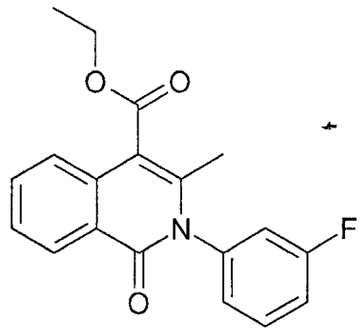
2-(2-Chloro-phenyl)-3-methyl-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ethyl ester.

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



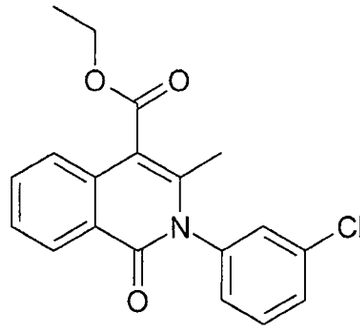
3-Methyl-1-oxo-2-o-tolyl-1,2-dihydro-isoquinoline-4-carboxylic acid ethyl ester.

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



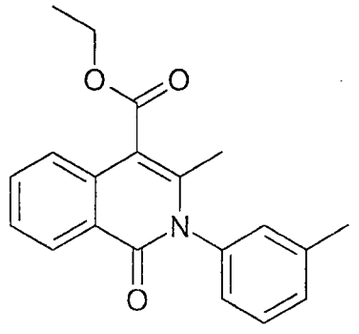
2-(3-Fluoro-phenyl)-3-methyl-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ethyl ester.

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



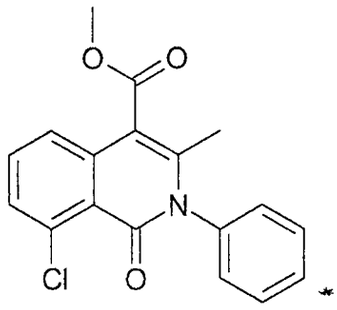
2-(3-Chloro-phenyl)-3-methyl-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ethyl ester.

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



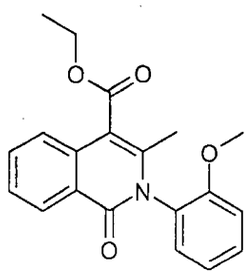
3-Methyl-1-oxo-2-m-tolyl-1,2-dihydro-isoquinoline-4-carboxylic acid ethyl ester.

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



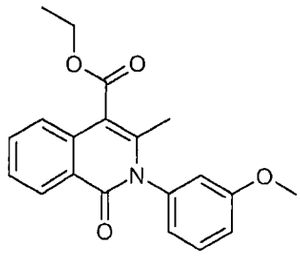
8-Chloro-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid methyl ester.

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).



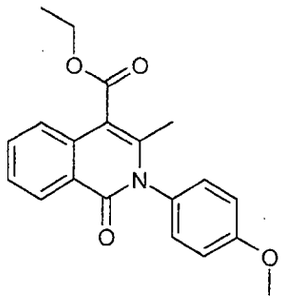
2-(2-Methoxy-phenyl)-3-methyl-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ethyl ester.

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



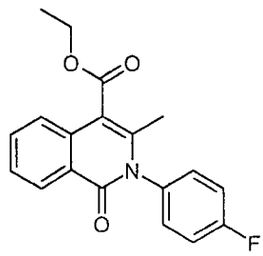
2-(3-Methoxy-phenyl)-3-methyl-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ethyl ester.

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



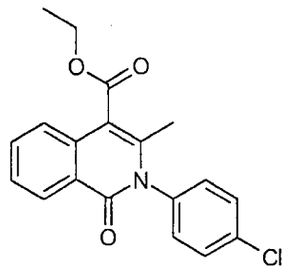
2-(4-Methoxy-phenyl)-3-methyl-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ethyl ester.

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



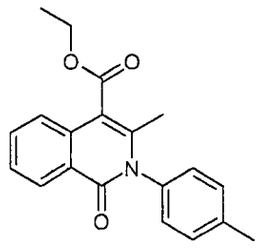
2-(4-Fluoro-phenyl)-3-methyl-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ethyl ester.

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



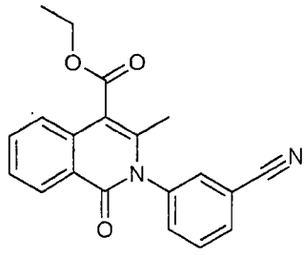
2-(4-Chloro-phenyl)-3-methyl-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ethyl ester.

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



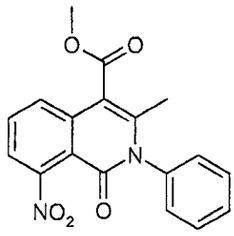
3-Methyl-1-oxo-2-p-tolyl-1,2-dihydro-isoquinoline-4-carboxylic acid ethyl ester.

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



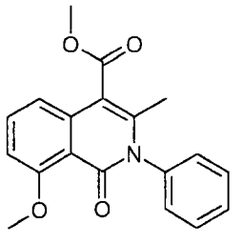
2-(3-Cyano-phenyl)-3-methyl-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ethyl ester.

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



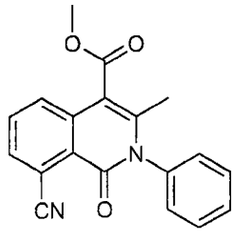
3-Methyl-8-nitro-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid methyl ester.

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



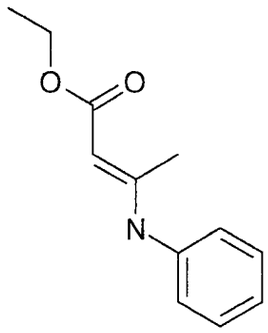
8-Methoxy-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid methyl ester.

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.

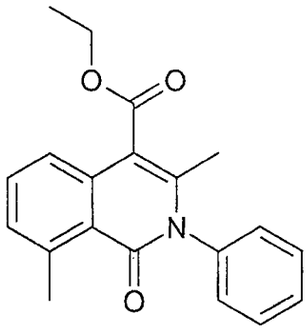
A suspension of 3-methyl-8-nitro-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid methyl ester (320 mg, 0.95 mmol) and Zn (898 mg, 13.8 mmol) in THF (4.5 ml) and 2M aq. HCl (4.5 ml) was stirred for 10 min, filtered and partitioned between ethyl acetate (3x150 ml) and sat. aq. $NaHCO_3$ (100 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).

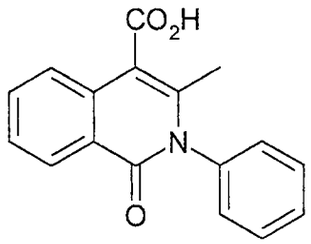
^{1}H NMR (500 MHz, DMSO-d_6): 1.19 (t, 3H), 2.01 (s, 3H), 4.06 (q, 2H), 4.7 (s, 1H), 7.17 (overlapping t, 1H), 7.18 (overlapping d, 2H), 7.36 (t, 2H), 10.36 (s, 1H).



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),

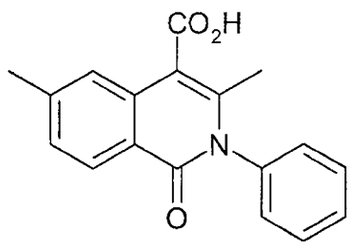
water (2 x 10 ml) and sat. aq. $NaHCO_3$ solution (30 ml), absorbed on SiO_2 (3 g) and flash chromatographed on SiO_2 (50 g, gradient heptane – 30% ethyl acetate in heptane) to give 217 mg of yellow oil. Yield 22%. LC-MS (m/z) 322.2 (MH^+); t_R = 1.62. ^1H NMR (500 MHz, DMSO-d_6): 1.32 (t, 3H), 1.91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

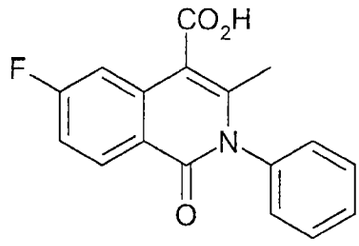
3-Methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ethyl ester (4.2 g, 13.7 mmol) was dissolved in 100 ml of hot methanol and a solution of NaOH (6 g) in water (20 ml) was added. The reaction mixture was heated at reflux for 2 hrs, diluted with water (200 ml) and stirred overnight at 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:



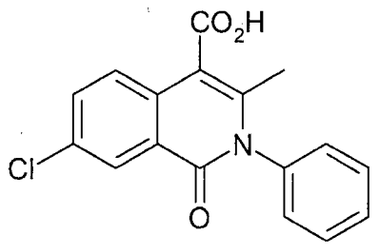
3,6-Dimethyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid.

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).



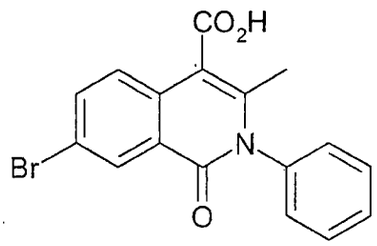
6-Fluoro-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid.

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).

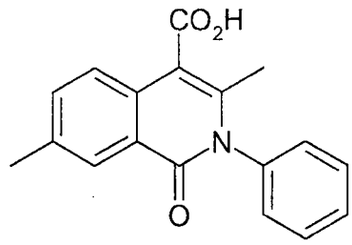


7-Chloro-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid.

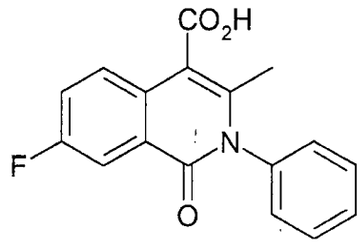
The crude product was used in the next step without crystallization. LC-MS (m/z) 314.2 (MH^+); t_R = 1.13. ^1H NMR (500 MHz, DMSO-d_6): ^1H NMR (500 MHz, DMSO-d_6): 2.03 (s, 3H), 7.38 (d, 2H), 7.51 (t, 1H), 7.57 (t, 2H), 7.79 (d, 1H), 7.86 (dd, 1H), 8.15(d, 1H), 13.55 (b, 1H).



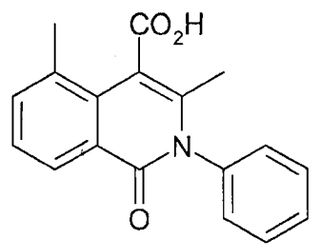
7-Bromo-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid.
LC-MS (m/z) 358.1 (MH^+, ^{79}Br); t_R = 1.2. ^1H NMR (500 MHz, DMSO-d_6): 2.02 (s, 3H), 7.38 (d, 2H), 7.51 (t, 1H), 7.57 (t, 2H), 7.72 (d, 1H), 7.97 (dd, 1H), 8.29 (d, 1H), 13.55 (b, 1H).



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).

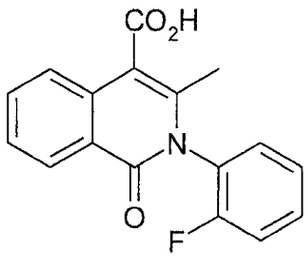


7-Fluoro-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid.
LC-MS (m/z) 298.2 (MH^+); t_R = 1.01. ^1H NMR (500 MHz, DMSO-d_6): 2.02 (s, 3H), 7.37 (d, 2H), 7.51 (t, 1H), 7.57 (t, 2H), 7.71 (dt, 1H), 7.83 (dd, 1H), 7.88 (dd, 1H), 13.54 (br, 1H).



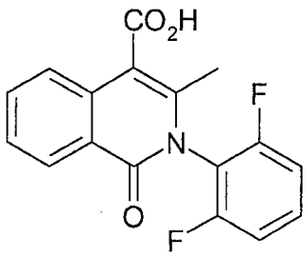
3,5-Dimethyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid.

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).



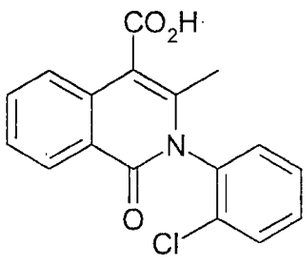
2-(2-Fluoro-phenyl)-3-methyl-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid.

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



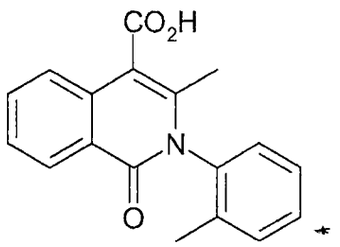
2-(2,6-Difluoro-phenyl)-3-methyl-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid.

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



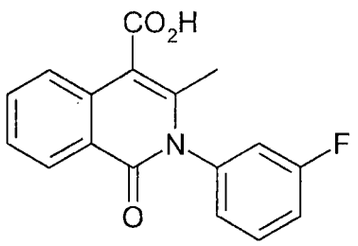
2-(2-Chloro-phenyl)-3-methyl-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid.

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



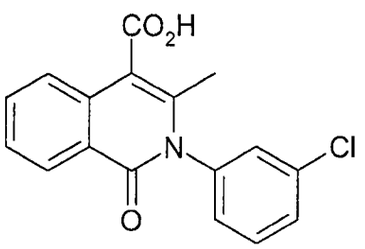
3-Methyl-1-oxo-2-o-tolyl-1,2-dihydro-isoquinoline-4-carboxylic acid.

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



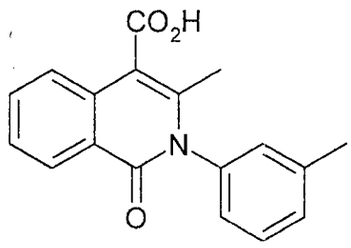
2-(3-Fluoro-phenyl)-3-methyl-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid.

LC-MS (m/z) 298.4 (MH^+); t_R = 0.96. ^1H 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).



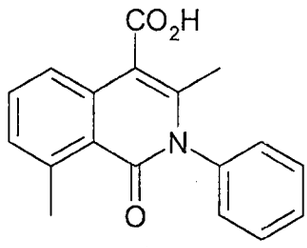
2-(3-Chloro-phenyl)-3-methyl-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid.

LC-MS (m/z) 314.2 (MH^+); t_R = 1.09. ^1H 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).



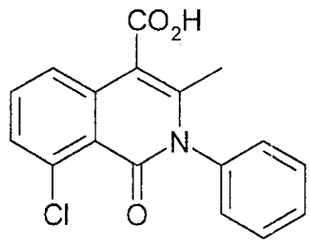
3-Methyl-1-oxo-2-m-tolyl-1,2-dihydro-isoquinoline-4-carboxylic acid.

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).



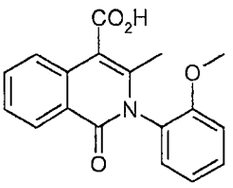
3,8-Dimethyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid.

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).



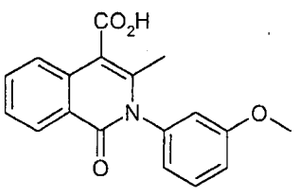
8-Chloro-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid.

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.



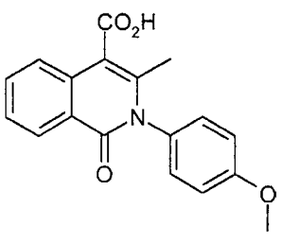
2-(2-Methoxy-phenyl)-3-methyl-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid.

The title compound was used in the next step without purification. LC-MS (m/z) 310.3 (MH^+); t_R = 0.87.



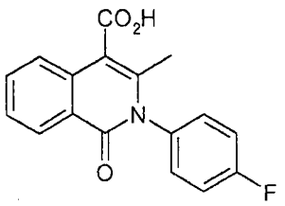
2-(3-Methoxy-phenyl)-3-methyl-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid.

The title compound was used in the next step without purification. LC-MS (m/z) 310.4 (MH^+); t_R = 0.9.



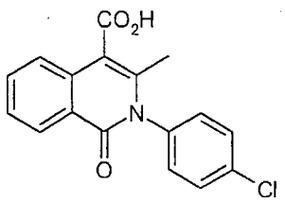
2-(4-Methoxy-phenyl)-3-methyl-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid.

The title compound was used in the next step without purification. LC-MS (m/z) 310.4 (MH^+); t_R = 0.89.



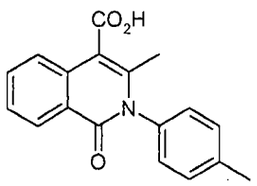
2-(4-Fluoro-phenyl)-3-methyl-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid.

The title compound was used in the next step without purification. LC-MS (m/z) 298.2 (MH^+); t_R = 0.9.



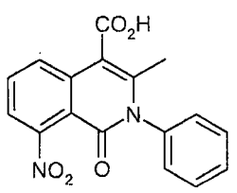
2-(4-Chloro-phenyl)-3-methyl-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid.

The title compound was used in the next step without purification. LC-MS (m/z) 314.2 (MH^+); t_R = 1.53.



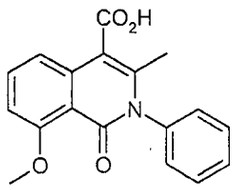
3-Methyl-1-oxo-2-p-tolyl-1,2-dihydro-isoquinoline-4-carboxylic acid.

The title compound was used in the next step without purification. LC-MS (m/z) 293.9 (MH^+); t_R = 0.99.



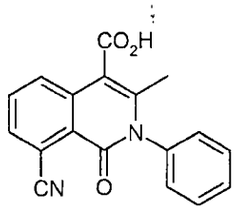
3-Methyl-8-nitro-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid.

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.

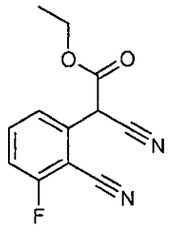
The title compound was used in the next step without purification. LC-MS (m/z) 310.6 (MH^+); t_R = 0.73.



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.

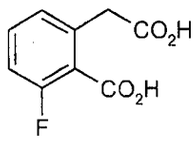
Synthesis of homophthalic anhydrides of the general formula XVIII:



Cyano-(2-cyano-3-fluoro-phenyl)-acetic acid ethyl ester.

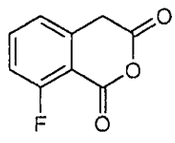
A mixture of cyanoacetic acid ethyl ester (26.7 mL, 251 mmol), 2,6-difluorobenzonitrile (33.2 g, 239 mmol) and potassium carbonate (82.5 g, 597 mmol) in dimethyl sulfoxide (120 mL) was stirred at +55°C for 16 hours and poured into ice-water mixture (ca. 400 mL). It was acidified with conc. aq. HCl with 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.

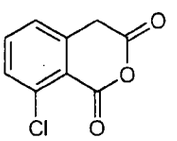
A mixture of 62% sulfuric acid (2:1 conc. H_2SO_4 in water, 400 ml) and cyano-(2-cyano-3-fluoro-phenyl)-acetic acid ethyl ester (52.0 g, 224 mmol) was stirred at +150°C overnight (16 hours). The reaction mixture was poured into ice (ca. 500 g) and neutralised with 10.8 N aq. NaOH (500 mL) with cooling. 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).



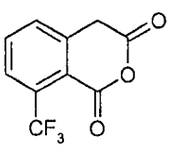
8-Fluoro-isochroman-1,3-dione.

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).

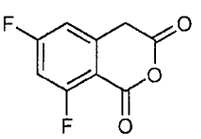
The following homophthalic anhydrides were obtained analogously by the described above 3-step procedure from corresponding fluorobenzonitriles and ethyl cyanoacetate:



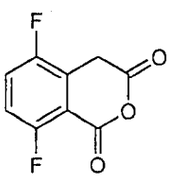
8-Chloro-isochroman-1,3-dione.



8-Trifluoromethyl-isochroman-1,3-dione.

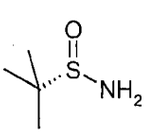


6,8-Difluoro-isochroman-1,3-dione.



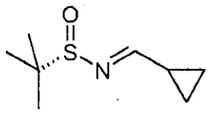
5,8-Difluoro-isochroman-1,3-dione.

Synthesis of chiral and racemic amines of the general formula XI:



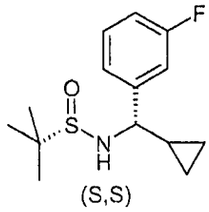
(S)-(–)-2-Methyl-2-propanesulfinamide.

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.

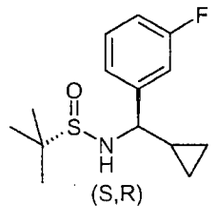


(S)-2-Methyl-2-propanesulfinic acid 1-cyclopropyl-methylideneamide.

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,S)



(S,R)

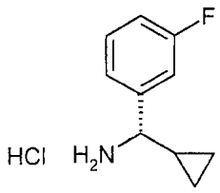
(S)-2-Methyl-2-propanesulfinic acid [(S)-cyclopropyl-(3-fluoro-phenyl)-methyl]-amide and *(S)-2-Methyl-2-propanesulfinic acid [(R)-cyclopropyl-(3-fluoro-phenyl)-methyl]-amide.*

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%).

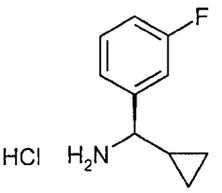
Procedure B: Alternatively, to a suspension of Mg (13.4 g, 0.55 mol) in 50 mL of anhydrous THF at 50°C a solution of 1-bromo-3-fluorobenzene (89.0 g, 0.50 mol) was added dropwise. The mixture was stirred for 2 hours at +50°C and then it was added dropwise to a solution of (S)-2-methyl-2-propanesulfinic 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

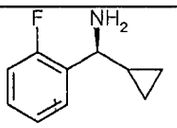
(CD_3OD, 400 MHz, TMS=0): 7.44-7.39 (m, 1H), 7.25-7.19 (m, 2H), 7.12-7.07 (m, 1H), 3.56 (d, J = 10.0 Hz, 1H), 1.37-1.28 (m, 1H), 0.78-0.75 (m, 1H), 0.61-0.55 (m, 2H), 0.39-0.36 (m, 1H).

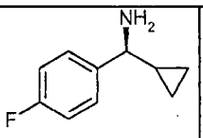
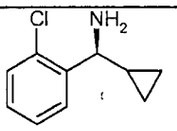
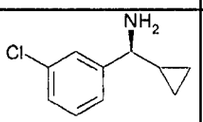
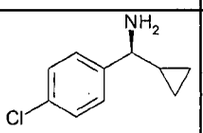
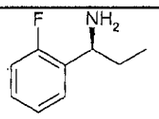
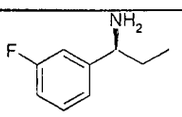


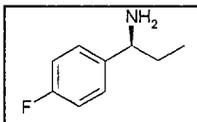
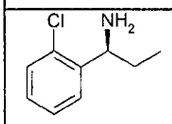
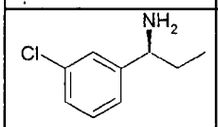
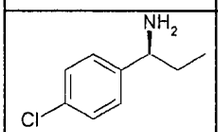
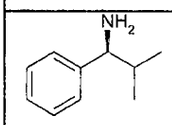
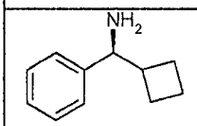
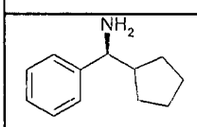
(R)-(–)-C-[C-Cyclopropyl-C-(3-fluoro-phenyl)]-methylamine hydrochloride.

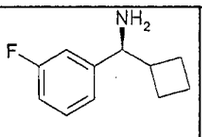
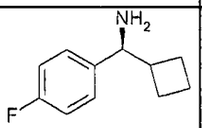
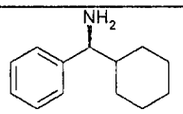
The title compound was prepared according to the above identical procedure from (S)-2-methyl-2-propanesulfinic acid [(R)-cyclopropyl-(3-fluoro-phenyl)-methyl]-amide (0.16g, 0.6 mmol) to give 0.116 g of the title compound as a white solid. $[\alpha]^{20}_{,D}$ = – 49.18 (c = 10 mg/mL, CH_3OH), ee 100%. ^1H NMR (CD_3OD, 400 MHz, TMS=0): identical with (S)-enantiomer.

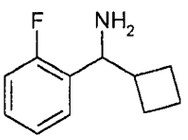
The following enantiomerically pure amine hydrochlorides were obtained analogously in three-step procedure starting from condensation of the corresponding aldehyde with chiral auxiliary, stereoselctive Grignard addition where the mixture of diastereoisomers was resolved either by recrystallisation or 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**	**$[\alpha]^{20}_{,D}$ (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).

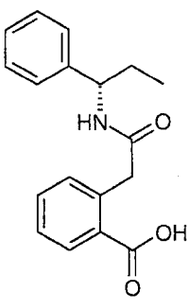


C-Cyclobutyl-C-(2-fluoro-phenyl)-methylamine.

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:

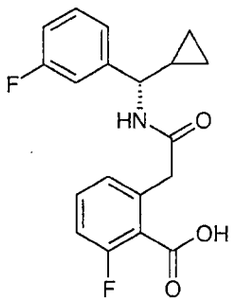


2-[((S)-1-Phenyl-propylcarbamoyl)-methyl]-benzoic acid.

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).

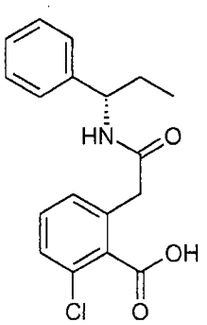
The following compounds were obtained analogously from corresponding homophthalic anhydrides of general formula and amines of the general formula XVIII and XI, respectively. The reactions were usually run at room temperature and the products were isolated by extraction or filtration and used in the next steps without

further purification.



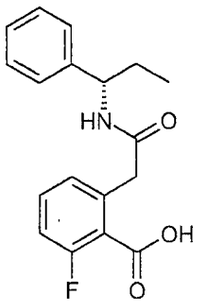
2-({[(S)-Cyclopropyl-(3-fluoro-phenyl)-methyl]-carbamoyl}-methyl)-6-fluoro-benzoic acid.

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).



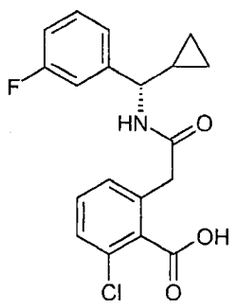
2-Chloro-6-[((S)-1-phenyl-propylcarbamoyl)-methyl]-benzoic acid.

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).

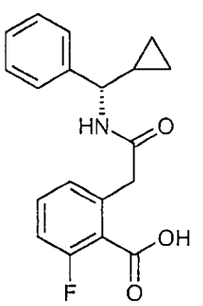


2-Fluoro-6-[((S)-1-phenyl-propylcarbamoyl)-methyl]-benzoic acid.

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).

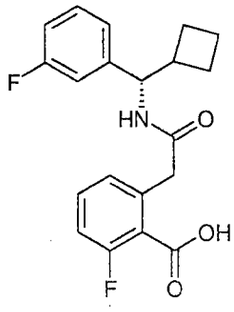


2-Chloro-6-({[(S)-cyclopropyl-(3-fluoro-phenyl)-methyl]-carbamoyl}-methyl)-benzoic acid.



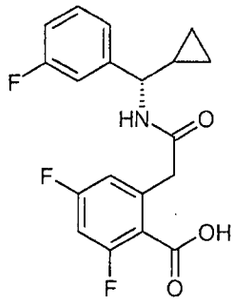
2-{[((S)-Cyclopropyl-phenyl-methyl)-carbamoyl]-methyl}-6-fluoro-benzoic acid.

LC-MS (m/z) 328.4 (MH^+); t_R = 1.12.

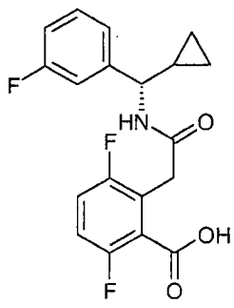


2-({[(S)-Cyclobutyl-(3-fluoro-phenyl)-methyl]-carbamoyl}-methyl)-6-fluoro-benzoic acid.

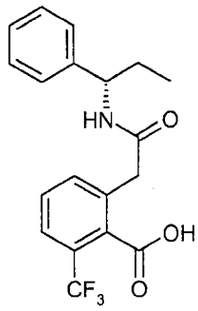
LC-MS (m/z) 360.2 (MH^+); t_R = 1.31.



2-({[(S)-Cyclopropyl-(3-fluoro-phenyl)-methyl]-carbamoyl}-methyl)-4,6-difluoro-benzoic acid.



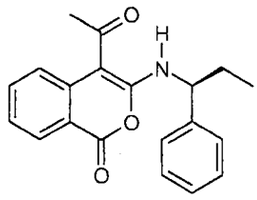
2-({[(S)-Cyclopropyl-(3-fluoro-phenyl)-methyl]-carbamoyl}-methyl)-3,6-difluoro-benzoic acid.



2-[((S)-1-Phenyl-propylcarbamoyl)-methyl]-6-trifluoromethyl-benzoic acid.

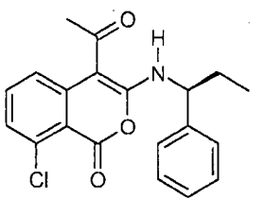
LC-MS (m/z) 366.4 (MH^+); t_R = 1.24.

Synthesis of compounds of the general formula XXIII:



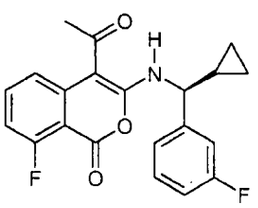
4-Acetyl-3-((S)-1-phenyl-propylamino)-isochromen-1-one.

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, C<u>H</u>-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, Me<u>CO</u>).



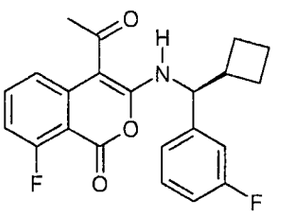
4-Acetyl-8-chloro-3-((S)-1-phenyl-propylamino)-isochromen-1-one.

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).



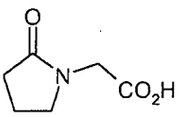
4-Acetyl-3-{[(S)-cyclopropyl-(3-fluoro-phenyl)-methyl]-amino}-8-fluoro-isochromen-1-one.

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).



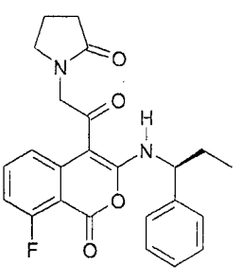
4-Acetyl-3-{[(S)-cyclobutyl-(3-fluoro-phenyl)-methyl]-amino}-8-fluoro-isochromen-1-one.

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).

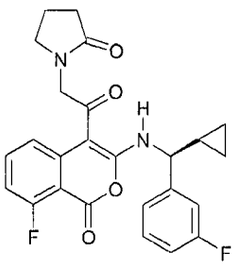


1-{2-[8-Fluoro-1-oxo-3-((S)-1-phenyl-propylamino)-1H-isochromen-4-yl]-2-oxo-ethyl}-pyrrolidin-2-one.

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

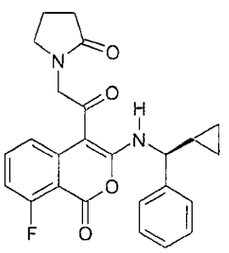
added with gas evolution observed. After stirring at r.t. for 1 hour, 2-fluoro-6-[((S)-1-phenyl-propylcarbamoyl)-methyl]-benzoic acid (1.56 g, 4.95 mmol), triethylamine (2.1 ml, 14.9 mmol) and DMAP (85 mg, 0.1 eq.) were added and stirred at r.t. overnight. It was partitioned between mixture of 0.2 M 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).



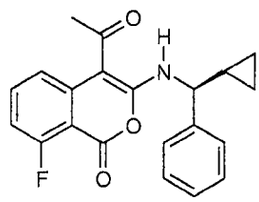
1-[2-(3-{[(S)-Cyclopropyl-(3-fluoro-phenyl)-methyl]-amino}-8-fluoro-1-oxo-1H-isochromen-4-yl)-2-oxo-ethyl]-pyrrolidin-2-one.

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.

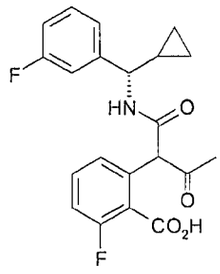
The title compound was prepared analogously. LC-MS (m/z) 435.3 (MH^+); t_R = 1.43.



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).

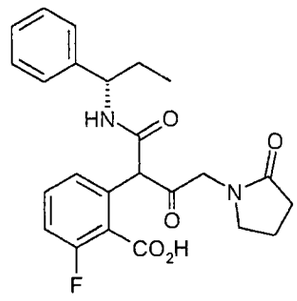
Hydrolysis of compounds of the general formula XXIII into compounds of the general formula XXV:



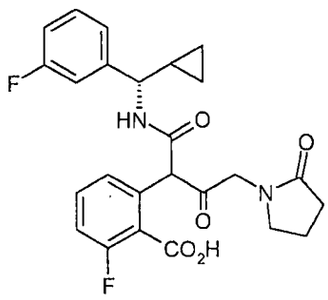
2-(1-{[(S)-Cyclopropyl-(3-fluoro-phenyl)-methyl]-carbamoyl}-2-oxo-propyl)-6-fluoro-benzoic acid.

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:

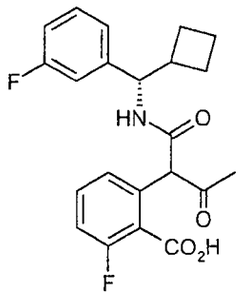


2-Fluoro-6-[2-oxo-3-(2-oxo-pyrrolidin-1-yl)-1-((S)-1-phenyl-propylcarbamoyl)-propyl]-benzoic acid.



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.

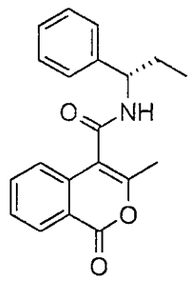


2-(1-{[(S)-Cyclobutyl-(3-fluoro-phenyl)-methyl]-carbamoyl}-2-oxo-propyl)-6-fluoro-benzoic acid.

LC-MS (m/z) 402.2 (MH^+); t_R = 1.36.

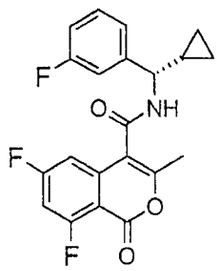
Synthesis of compounds of the general formula XXIV and XXV: Compounds of general formula XXIV obtained analogously as described above for compounds of

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.



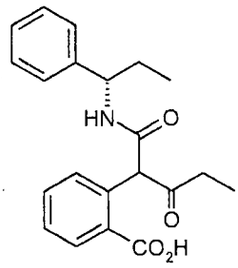
3-Methyl-1-oxo-1H-isochromene-4-carboxylic acid ((S)-1-phenyl-propyl)-amide.

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.

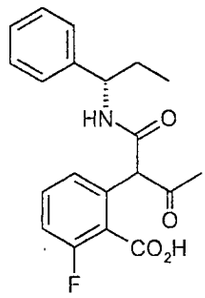
The title compound was purified by flash chromatography on SiO_2. LC-MS (m/z) 388.4 (MH^+); t_R = 1.39.



2-[2-Oxo-1-((S)-1-phenyl-propylcarbamoyl)-butyl]-benzoic acid.

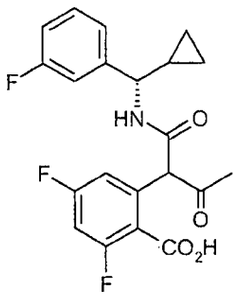
A sealed mixture of 2-[((S)-1-phenyl-propylcarbamoyl)-methyl]-benzoic acid (409 mg, 1.38 mmol), propionic anhydride (10 ml) and 4-N,N-dimethylaminopyridine (15 mg) was heated under microwave irradiation at 150°C for 20 min and partitioned between 1M HCl (50 ml) and ethyl acetate (100 ml). The organic 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:



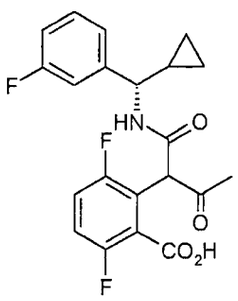
2-Fluoro-6-[2-oxo-1-((S)-1-phenyl-propylcarbamoyl)-propyl]-benzoic acid.

LC-MS (m/z) 358.4 (MH^+); t_R = 1.17.



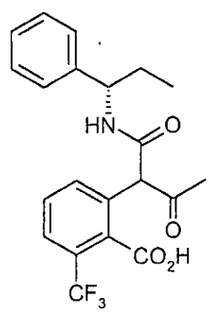
2-(1-{[(S)-Cyclopropyl-(3-fluoro-phenyl)-methyl]-carbamoyl}-2-oxo-propyl)-4,6-difluoro-benzoic acid.

LC-MS (m/z) 406.7 (MH^+); t_R = 1.3.



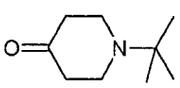
2-(1-{[(S)-Cyclopropyl-(3-fluoro-phenyl)-methyl]-carbamoyl}-2-oxo-propyl)-3,6-difluoro-benzoic acid.

LC-MS (m/z) 406.0 (MH^+); t_R = 0.72 (method B).



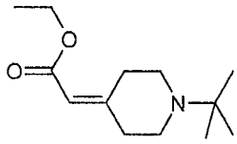
2-[2-Oxo-1-((S)-1-phenyl-propylcarbamoyl)-propyl]-6-trifluoromethyl-benzoic acid.

The title compound was used in the next step directly.



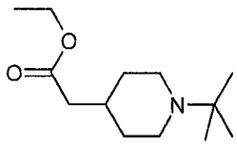
1-tert-Butyl-piperidin-4-one.

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.



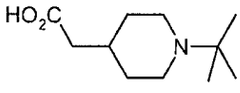
(1-tert-Butyl-piperidin-4-ylidene)-acetic acid ethyl ester.

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.

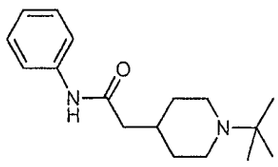
To a solution of (1-tert-butyl-piperidin-4-ylidene)-acetic acid ethyl ester (5.1 g, 22.7 mmol) in ethanol (50 mL) 10% Pd/C (0.6 g) was added and the mixture was stirred under the hydrogen atmosphere (42 psi) at ambient temperature for 14 hours. The catalyst was removed by filtration, and the filtrate 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).

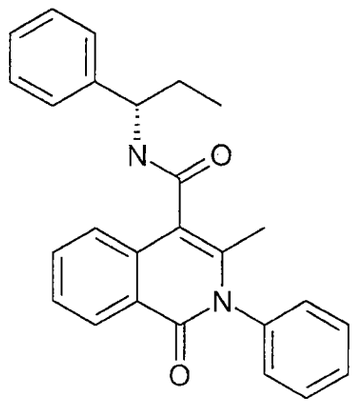


2-(1-tert-Butyl-piperidin-4-yl)-N-phenyl-acetamide.

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

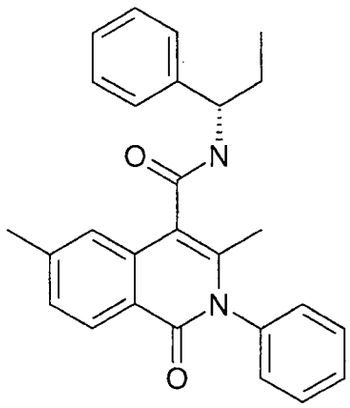


1a *3-Methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide.*

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

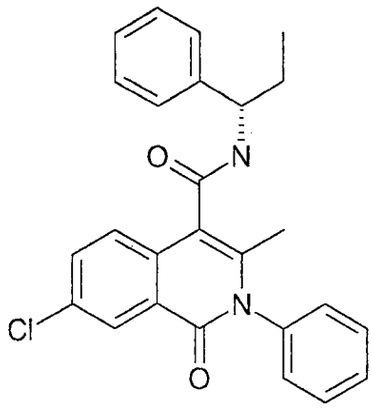
at reflux for 5 min. Volatiles were removed in vacuo to give 228 mg of the corresponding acid chloride as a pale brown solid. A portion of the acid chloride (110 mg, 0.37 mmol) was dissolved in 1,2-dichloroethane (2 ml) and (S)-(–)-1-phenylpropylamine (150 µL, 1.1 mmol) was added. The obtained suspension 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. ^1H 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:



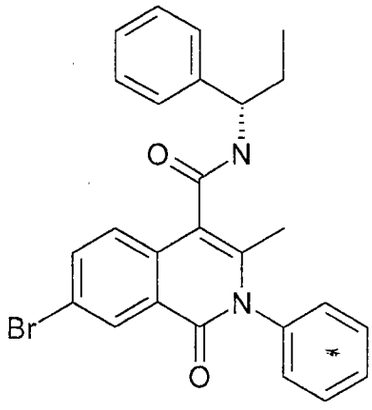
1b *3,6-Dimethyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide.*

LC-MS (m/z) 411.3 (MH^+); t_R = 0.8 (method B).



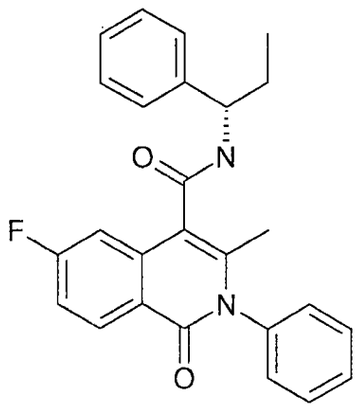
1c *7-Chloro-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide.*

LC-MS (m/z) 431.3 (MH^+); t_R = 0.86 (method B).



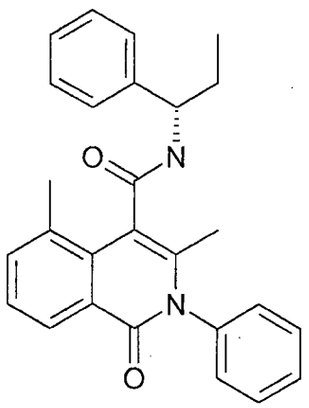
1d *7-Bromo-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide.*

LC-MS (m/z) 475.1 (MH^+, ^{79}Br); t_R = 0.87 (method B).



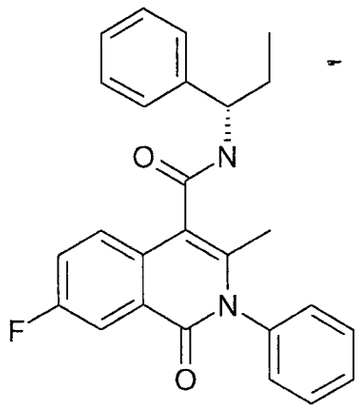
1e 6-Fluoro-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide.

LC-MS (m/z) 415.5 (MH^+); t_R = 0.80 (method B).



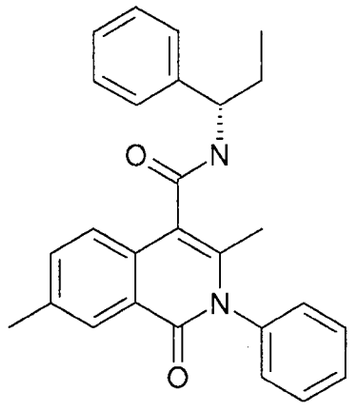
1f 3,5-Dimethyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide.

LC-MS (m/z) 411.3 (MH^+); t_R = 0.84 (method B).



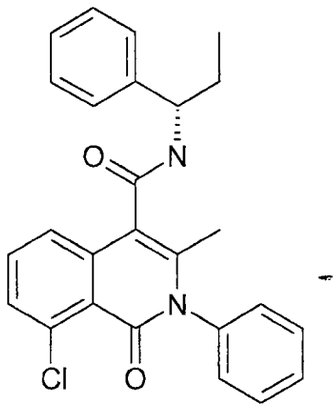
1g *7-Fluoro-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide.*

LC-MS (m/z) 415.4 (MH^+); t_R = 1.49.



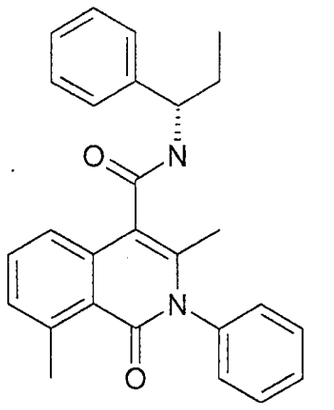
1h *3,7-Dimethyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide.*

LC-MS (m/z) 411.4 (MH^+); t_R = 1.5.



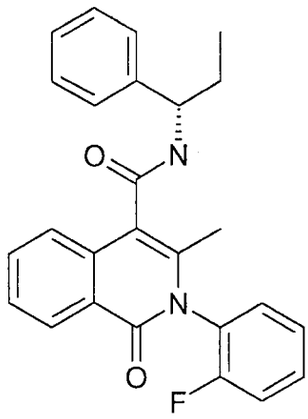
1i 8-Chloro-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide.

LC-MS (m/z) 431.4 (MH^+); t_R = 1.54.



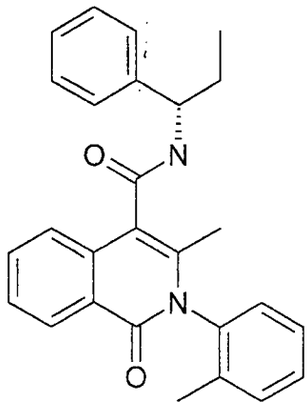
1j 3,8-Dimethyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide.

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).



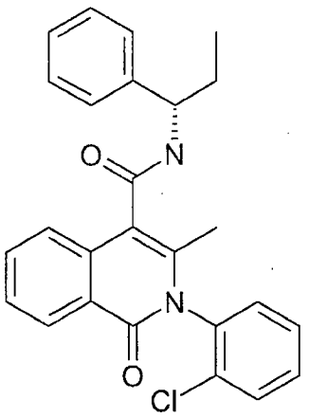
1k *2-(2-Fluoro-phenyl)-3-methyl-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide.*

LC-MS (m/z) 415.5 (MH^+); t_R = 1.49.



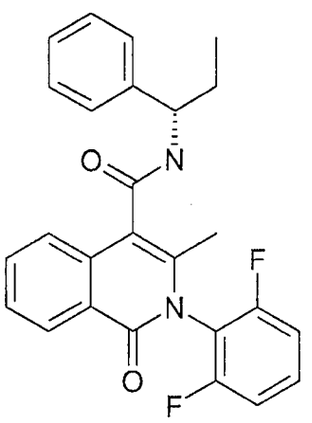
1l *3-Methyl-1-oxo-2-o-tolyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide.*

LC-MS (m/z) 411.5 (MH^+); t_R = 1.5.



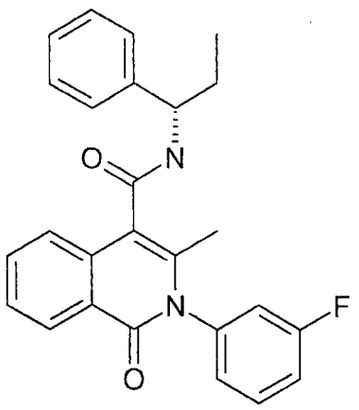
1m *2-(2-Chloro-phenyl)-3-methyl-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide.*

LC-MS (m/z) 431.2 (MH^+); t_R = 1.51.



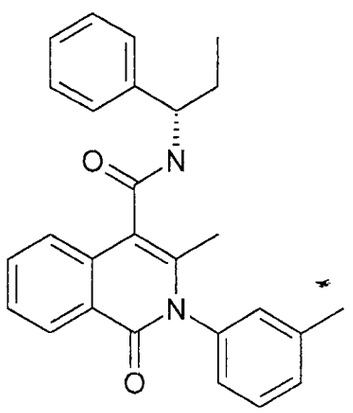
1n *2-(2,6-Difluoro-phenyl)-3-methyl-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide.*

LC-MS (m/z) 433.4 (MH^+); t_R = 1.54.



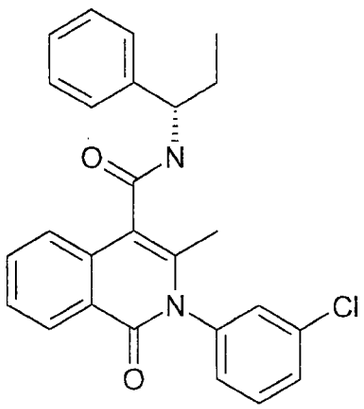
1o *2-(3-Fluoro-phenyl)-3-methyl-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide.*

LC-MS (m/z) 415.1 (MH^+); t_R = 1.48.



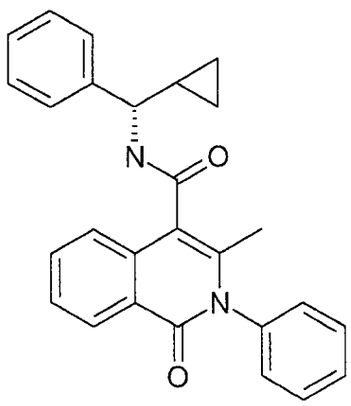
1p *3-Methyl-1-oxo-2-m-tolyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide.*

LC-MS (m/z) 411.5 (MH^+); t_R = 1.53.



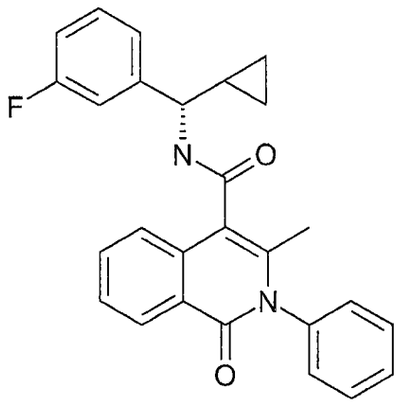
1q *2-(3-Chloro-phenyl)-3-methyl-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide.*

LC-MS (m/z) 431.2 (MH^+); t_R = 1.57.



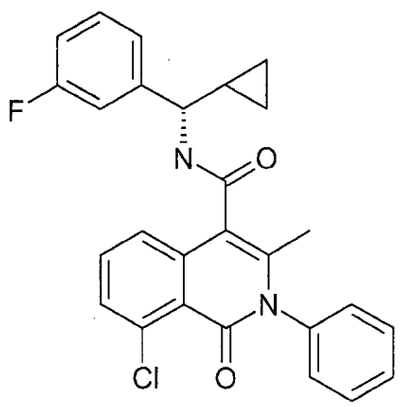
1r *3-Methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-cyclopropyl-phenyl-methyl)-amide.*

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).



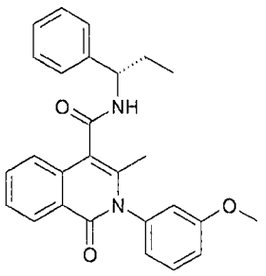
1s 3-Methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-cyclopropyl-(3-fluoro-phenyl)-methyl]-amide.

LC-MS (m/z) 427.1 (MH^+); t_R = 1.48. ^1H 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).



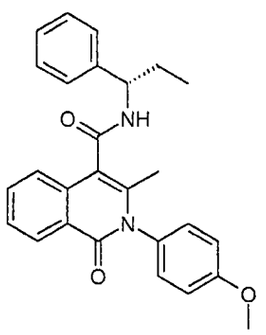
1t 8-Chloro-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-cyclopropyl-(3-fluoro-phenyl)-methyl]-amide.

LC-MS (m/z) 461.6 (MH^+); t_R = 1.51. ^1H 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).



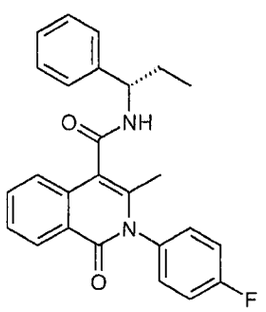
1aa 2-(3-Methoxy-phenyl)-3-methyl-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide.

LC-MS (m/z) 426.7 (MH^+); t_R = 1.43.



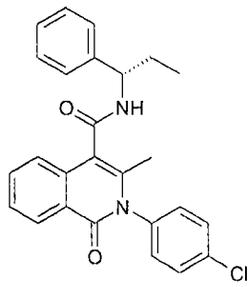
1ab 2-(4-Methoxy-phenyl)-3-methyl-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide.

LC-MS (m/z) 427.0 (MH^+); t_R = 1.43.



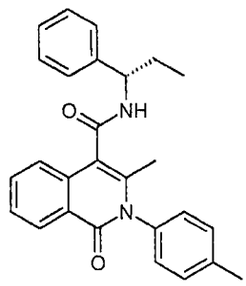
1ac 2-(4-Fluoro-phenyl)-3-methyl-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide.

LC-MS (m/z) 415.0 (MH^+); t_R = 1.43.



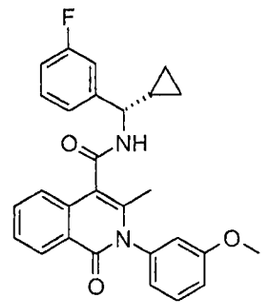
1ad 2-(4-Chloro-phenyl)-3-methyl-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide.

LC-MS (m/z) 431.1 (MH^+); t_R = 1.54.



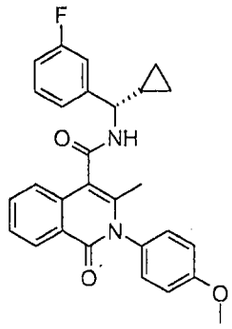
1ae 3-Methyl-1-oxo-2-p-tolyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide.

LC-MS (m/z) 411.2 (MH^+); t_R = 1.51.



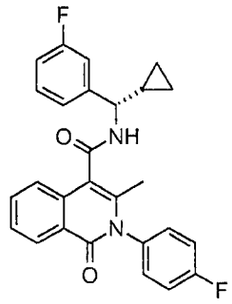
1af 2-(3-Methoxy-phenyl)-3-methyl-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-cyclopropyl-(3-fluoro-phenyl)-methyl]-amide.

LC-MS (m/z) 457.0 (MH^+); t_R = 1.47.



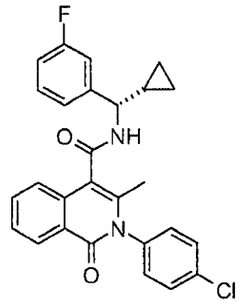
1ag 2-(4-Methoxy-phenyl)-3-methyl-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-cyclopropyl-(3-fluoro-phenyl)-methyl]-amide.

LC-MS (m/z) 457.1 (MH^+); t_R = 1.46.



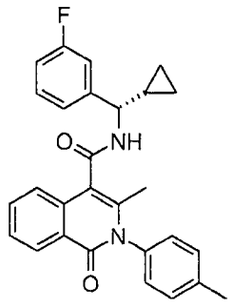
1ah 2-(4-Fluoro-phenyl)-3-methyl-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-cyclopropyl-(3-fluoro-phenyl)-methyl]-amide.

LC-MS (m/z) 445.6 (MH^+); t_R = 1.48.



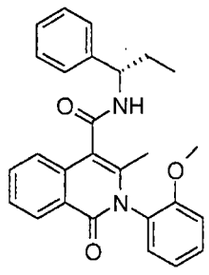
1ai 2-(4-Chloro-phenyl)-3-methyl-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-cyclopropyl-(3-fluoro-phenyl)-methyl]-amide.

LC-MS (m/z) 461.3 (MH^+); t_R = 1.57.



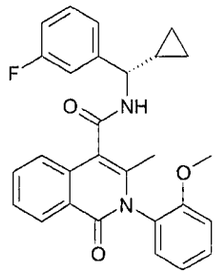
1aj 3-Methyl-1-oxo-2-p-tolyl-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-cyclopropyl-(3-fluoro-phenyl)-methyl]-amide.

LC-MS (m/z) 440.9 (MH^+); t_R = 1.54.



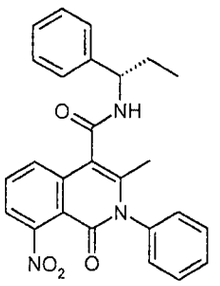
1ak 2-(2-Methoxy-phenyl)-3-methyl-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide.

LC-MS (m/z) 427.0 (MH^+); t_R = 1.39.



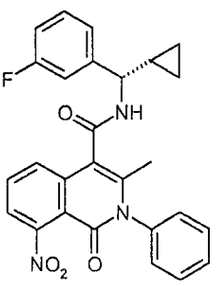
1al 2-(2-Methoxy-phenyl)-3-methyl-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-cyclopropyl-(3-fluoro-phenyl)-methyl]-amide.

LC-MS (m/z) 457.4 (MH^+); t_R = 1.43.



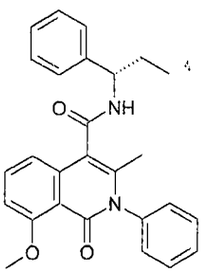
1am *3-Methyl-8-nitro-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide.*

LC-MS (m/z) 442.4 (MH^+); t_R = 1.46.



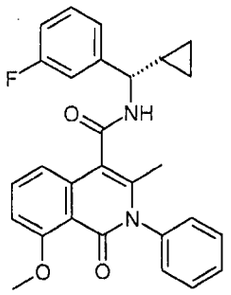
1an *3-Methyl-8-nitro-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-cyclopropyl-(3-fluoro-phenyl)-methyl]-amide.*

LC-MS (m/z) 442.4 (MH^+); t_R = 1.46.



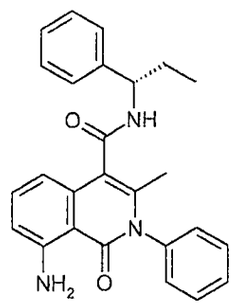
1ao *8-Methoxy-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide.*

LC-MS (m/z) 427.1 (MH^+); t_R = 1.32.



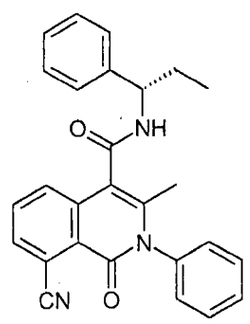
1ap *8-Methoxy-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-cyclopropyl-(3-fluoro-phenyl)-methyl]-amide.*

LC-MS (m/z) 457.4 (MH^+); t_R = 1.36.



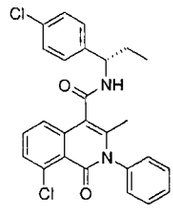
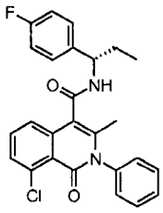
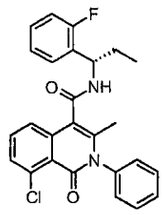
1aq *8-Amino-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide.*

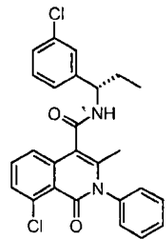
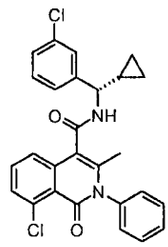
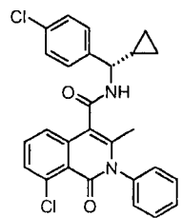
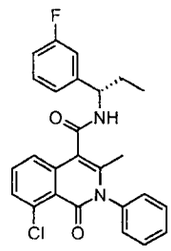
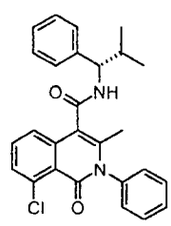
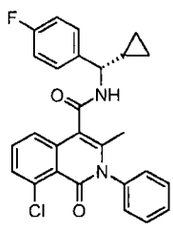
To a stirred solution of 3-methyl-8-nitro-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide (**1am,** 10 mg, 0.023 mmol) in tetrahydrofurane (0.15 ml) 2M aq. HCl (0.12 ml, 0.25 mmol) and Zn powder (45 mg, 0.69 mmol) was added. After 30 min the mixture was filtered 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.

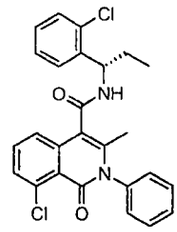
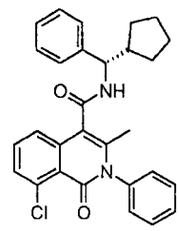
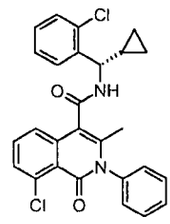
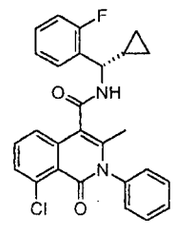
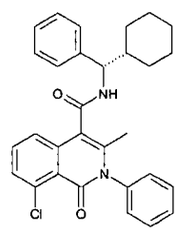
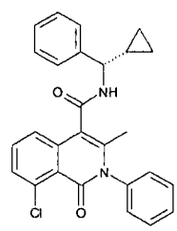


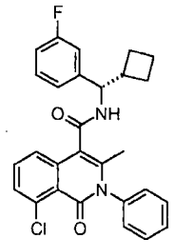
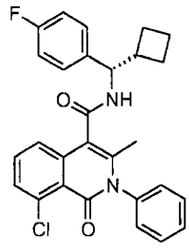
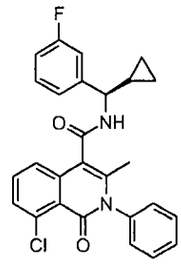
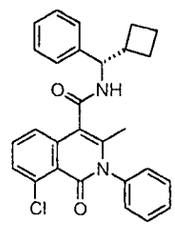
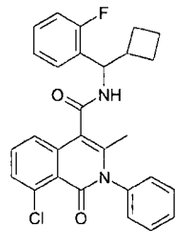
1ar 8-Cyano-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide.
LC-MS (m/z) 422.1 (MH^+); t_R = 1.37.

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.

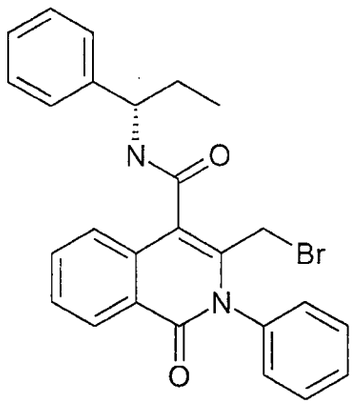
	Chemical name	**structure**	**t_R (min)**	**MW**	**m/z (MH^+)**
1as	*8-Chloro-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-1-(4-chloro-phenyl)-propyl]-amide*		1.63	465.4	465.4
1at	*8-Chloro-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-1-(4-fluoro-phenyl)-propyl]-amide*		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

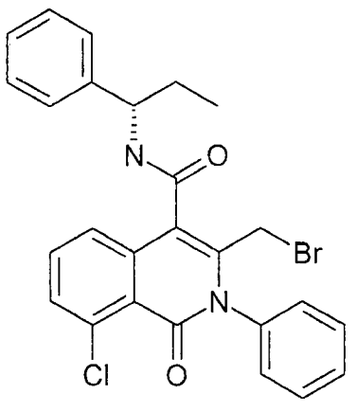
Example 2: Preparation of intermediates



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

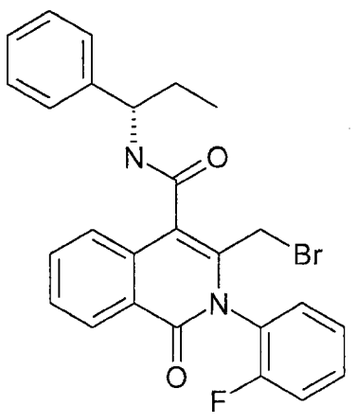
To a suspension of $CaCO_3$ (500 mg, 5 mmol) and 3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide (115 mg, 0.29 mmol) in 1,2-dichloroethane (5 ml) bromine (600 mg, 3.75 mmol) was added. The obtained mixture was sonicated at +33°C for 2 hours, diluted with 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:



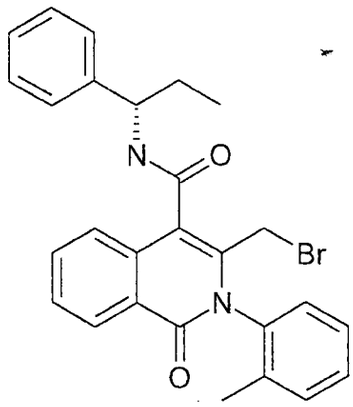
3-Bromomethyl-8-chloro-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide.

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.



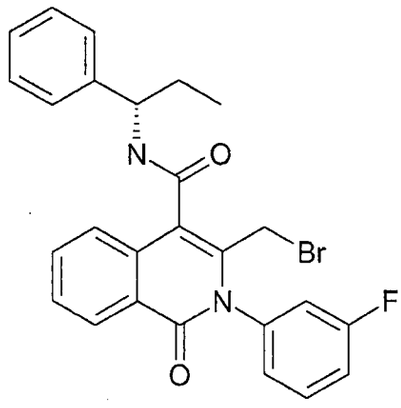
3-Bromomethyl-2-(2-fluoro-phenyl)-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide.

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.



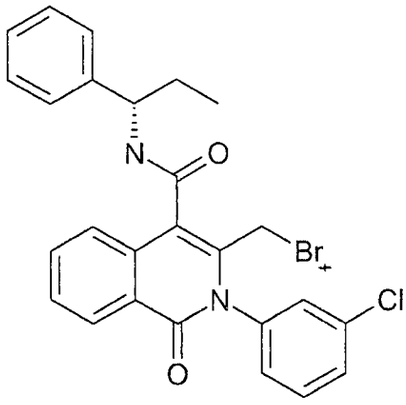
3-Bromomethyl-1-oxo-2-o-tolyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide.

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.



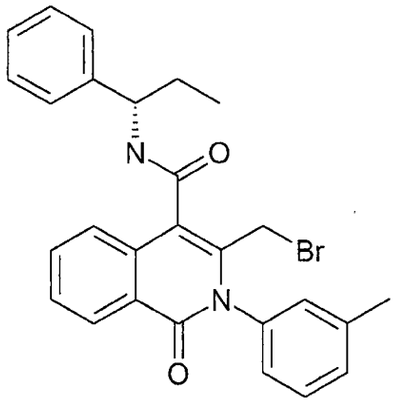
3-Bromomethyl-2-(3-fluoro-phenyl)-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide.

LC-MS (m/z) 493.5 (MH^+, ^{79}Br); t_R = 0.80 (method B).



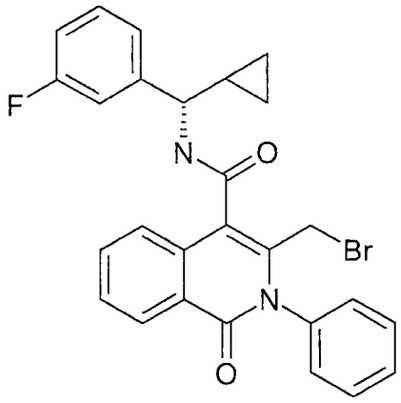
3-Bromomethyl-2-(3-chloro-phenyl)-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide.

LC-MS (m/z) 511.5 (MH^+, ^{81}Br); t_R = 0.84 (method B).



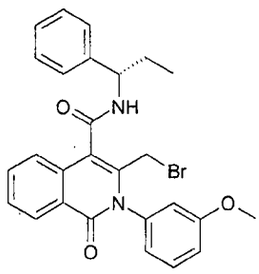
3-Bromomethyl-1-oxo-2-m-tolyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide.

LC-MS (m/z) 489.2 (MH^+, ^{79}Br); t_R = 0.86 (method B).



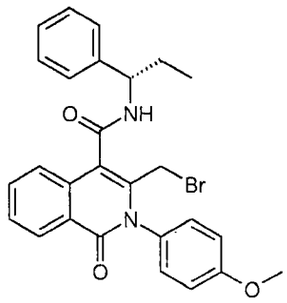
3-Bromomethyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-cyclopropyl-(3-fluoro-phenyl)-methyl]-amide.

LC-MS (m/z) 505.1 (MH^+); t_R = 1.62.



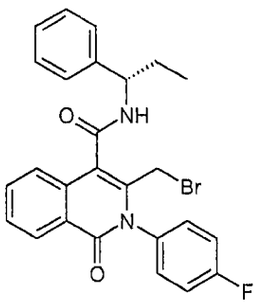
3-Bromomethyl-2-(3-methoxy-phenyl)-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide.

The product was purified by flash chromatography on SiO_2 (gradient heptane - ethyl acetate) and used in the next step directly.



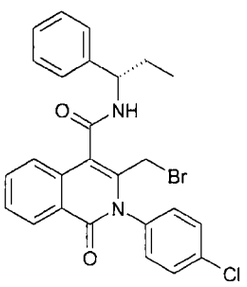
3-Bromomethyl-2-(4-methoxy-phenyl)-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide.

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.



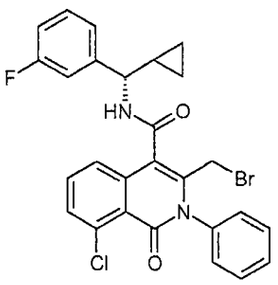
3-Bromomethyl-2-(4-fluoro-phenyl)-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide.

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.



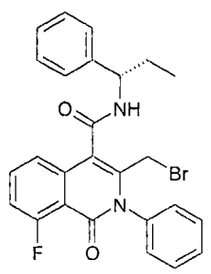
3-Bromomethyl-2-(4-chloro-phenyl)-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide.

LC-MS (m/z) 509.2 & 511.1 (MH^+); t_R = 1.63.



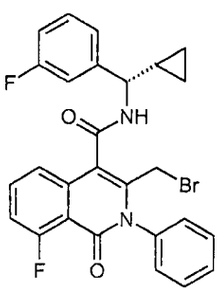
3-Bromomethyl-8-chloro-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-cyclopropyl-(3-fluoro-phenyl)-methyl]-amide.

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.

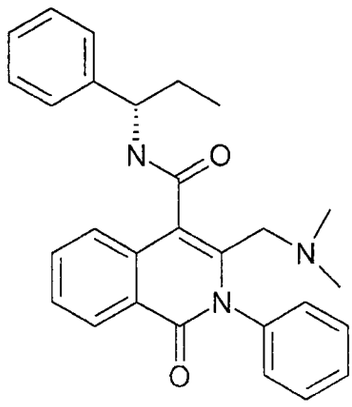
LC-MS (m/z) 493.3 & 495.2 (MH^+); t_R = 1.52.



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

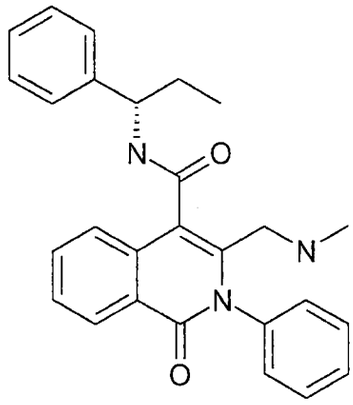
LC-MS (m/z) 523.5 & 525.6 (MH^+); t_R = 1.56.

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

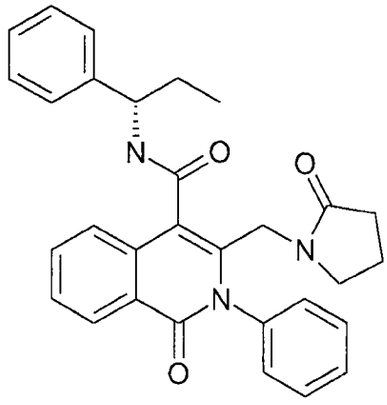
	amide			
2kr	3-(4-Methyl-pyrazol-1-ylmethyl)-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	1.65	476.6	477.3
2ks	1-Oxo-2-phenyl-3-[1,2,3]triazol-1-ylmethyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide	1.23	463.5	464.4
2kt	2-(3-Methoxy-phenyl)-1-oxo-3-(4-pyridin-4-ylmethyl-piperazin-1-ylmethyl)-1,2-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

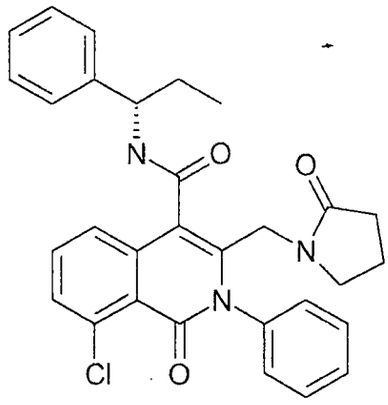


3a 1-Oxo-3-(2-oxo-pyrrolidin-1-ylmethyl)-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide.

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,

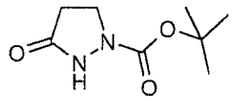
1,2-dichloroethane then gradient 50% to 100% ethyl acetate in heptane) to give 17 mg of white solid. Yield 56%. LC-MS (m/z) 480.5 (MH^+); t_R = 1.21.

The following compound was obtained analogously:

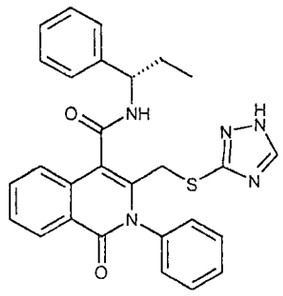


3b 8-Chloro-1-oxo-3-(2-oxo-pyrrolidin-1-ylmethyl)-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide.
LC-MS (m/z) 514.7 (MH^+); t_R = 1.33.

Synthesis of intermediates:

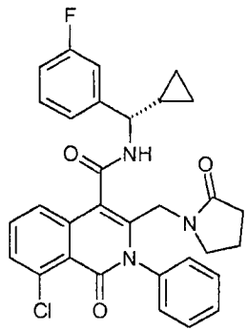


3-Oxo-pyrazolidine-1-carboxylic acid tert-butyl ester.
To a mixture of 3-pyrazolidinone hydrochloride (55.3 mg, 0.45 mmol), Na_2CO_3 (133 mg, 1.24 mol), water (0.5 ml) and dioxane (0.054 ml) BOC-anhydride (101 mg, 0.46 mmol) in dioxane (0.16 ml) was added and stirred at r.t. overnight. It was filtered, 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).



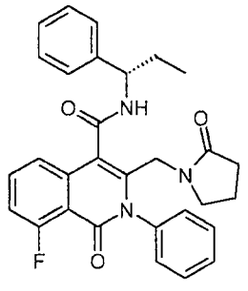
3c 1-Oxo-2-phenyl-3-(1H-[1,2,4]triazol-3-ylsulfanylmethyl)-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide.

LC-MS (m/z) 496.6 (MH^+); t_R = 0.64 (method B).



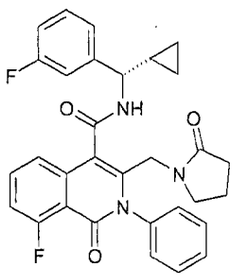
***3d** 8-Chloro-1-oxo-3-(2-oxo-pyrrolidin-1-ylmethyl)-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-cyclopropyl-(3-fluoro-phenyl)-methyl]-amide.*

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).

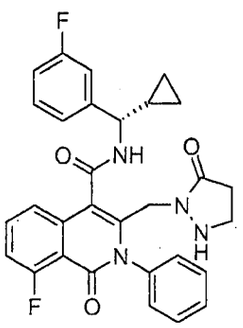


***3e** 8-Fluoro-1-oxo-3-(2-oxo-pyrrolidin-1-ylmethyl)-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide.*

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).

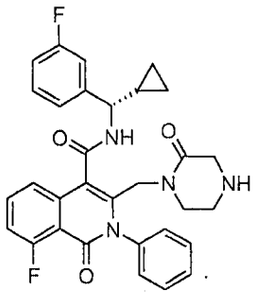


3f 8-Fluoro-1-oxo-3-(2-oxo-pyrrolidin-1-ylmethyl)-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-cyclopropyl-(3-fluoro-phenyl)-methyl]-amide. LC-MS (m/z) 528.7 (MH^+); t_R = 1.29, t_R = 0.7 (method B). ^1H NMR (250 MHz, 80°C, DMSO-d_6): 0.37-0.62 (m, 4H), 1.25 (m, 1H), 1.71 (quintet, J=7.5 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).



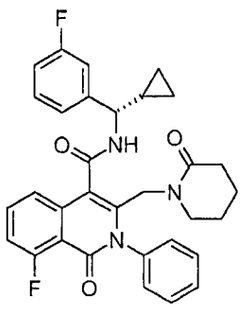
3g 8-Fluoro-1-oxo-3-(5-oxo-pyrazolidin-1-ylmethyl)-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-cyclopropyl-(3-fluoro-phenyl)-methyl]-amide. 3-Oxo-pyrazolidine-1-carboxylic acid tert-butyl ester was used in the coupling reaction promoted by NaH. The BOC-group in the obtained intermediate 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.*

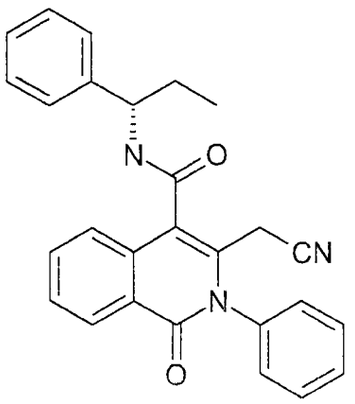
The title compound was prepared analogously from 2-oxo-4-(tert-butoxycarbonyl)piperazine followed by BOC group removal. LC-MS (m/z) 543.6 (MH^+); t_R = 0.84.



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.*

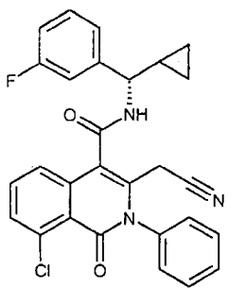
The title compound was prepared analogously from 2-piperidone. LC-MS (m/z) 542.5 (MH^+); t_R = 1.35.

Example 4



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

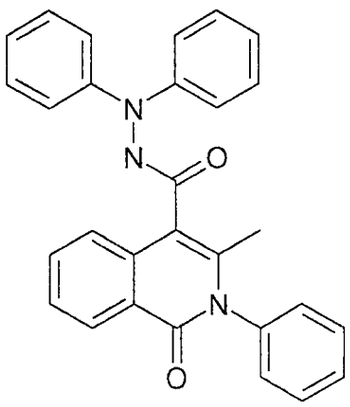
To a solution of 3-bromomethyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide (83 mg, 0.174 mmol) in THF (1.5 ml, anhydrous) and DMF (1.5 ml, anhydrous) sodium cyanide (83 mg, excess) was added. After 5 min the obtained suspension was poured into water (50 ml) followed 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.

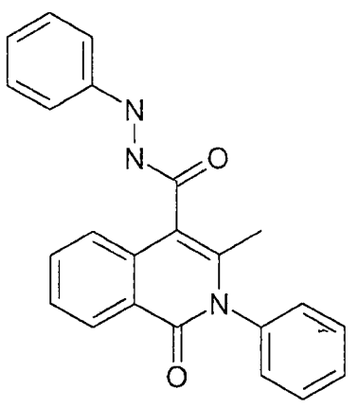
LC-MS (m/z) 486.5 (MH^+); t_R = 1.81.

Example 5



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

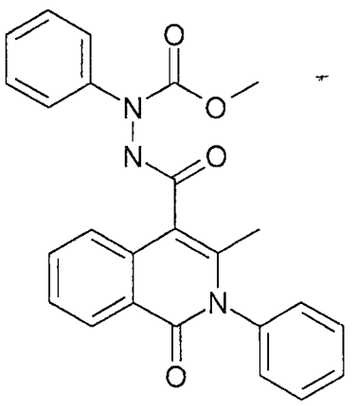
A mixture of 3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carbonyl chloride (the synthesis is described above in example **1a**) (25 mg, 0.08 mmol) and 1,1-diphenylhydrazine hydrochloride (56 mg, 0.25 mmol) in 1,2-dichloroethane (1 ml) was heated under microwave irradiation for 20 min at 140°C. 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),

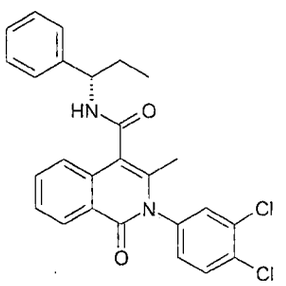
7.33 (br, 2H), 7.5-7.62 (m, 5H), 7.83 (t, 1H), 8.11 (br, 1H), 8.24 (d, 1H), 10.33 (s, 1H).



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.

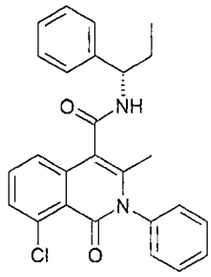
Example 6



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

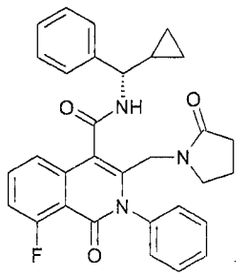
A mixture of 4-acetyl-3-((S)-1-phenyl-propylamino)-isochromen-1-one (60 mg) and 3,4-dichloroaniline (250 mg) in acetonitrile (0.5 ml) were heated under microwave irradiation at 160°C for 15 min. The reaction mixture was partitioned between 2M HCl (3 ml) and ethyl acetate (3 ml). The organic solution 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:



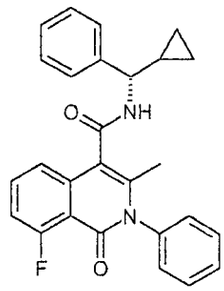
8-Chloro-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide (1i).

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.*

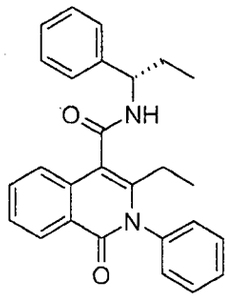
LC-MS (m/z) 510.3 (MH^+); t_R = 1.25.



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.

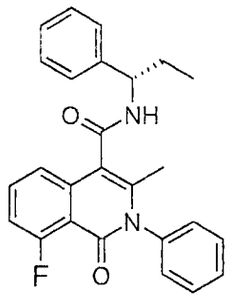
Example 7



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

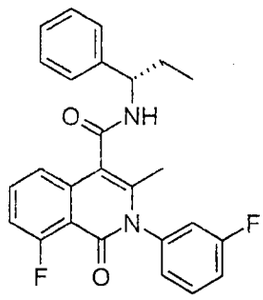
A sealed mixture of 2-[2-oxo-1-((S)-1-phenyl-propylcarbamoyl)-butyl]-benzoic acid (82 mg, 0.2 mmol) and aniline (0.3 ml, 3.3 mmol) in acetonitrile (0.3 ml) was heated under microwave irradiation at +160°C for 10 min. The mixture was partitioned between ethyl acetate (20 ml) and 3M aq. HCl (2 x 8 ml), 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:



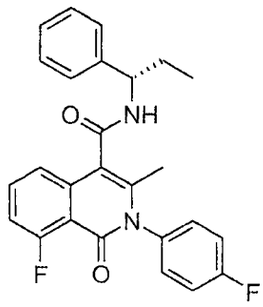
7b *8-Fluoro-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide.*

LC-MS (m/z) 415.5 (MH^+); t_R = 1.39.



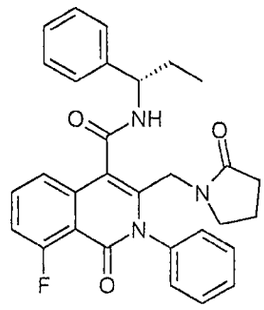
7c 8-Fluoro-2-(3-fluoro-phenyl)-3-methyl-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide.

LC-MS (m/z) 433.5 (MH^+); t_R = 1.41.



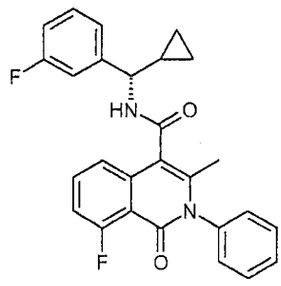
7d 8-Fluoro-2-(4-fluoro-phenyl)-3-methyl-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide.

LC-MS (m/z) 433.6 (MH^+); t_R = 1.4.



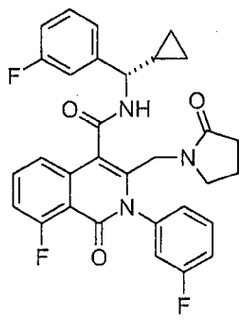
8-Fluoro-1-oxo-3-(2-oxo-pyrrolidin-1-ylmethyl)-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide (3e).

The title compound and its alternative method of preparation was described above in the example 3.



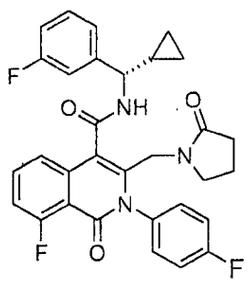
***7e** 8-Fluoro-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-cyclopropyl-(3-fluoro-phenyl)-methyl]-amide.*

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).



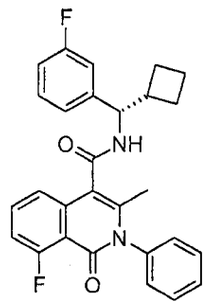
7f 8-Fluoro-2-(3-fluoro-phenyl)-1-oxo-3-(2-oxo-pyrrolidin-1-ylmethyl)-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-cyclopropyl-(3-fluoro-phenyl)-methyl]-amide.

The title product was isolated by preparative TLC on silica gel. LC-MS (m/z) 546.4 (MH^+); t_R = 0.71 (method B).



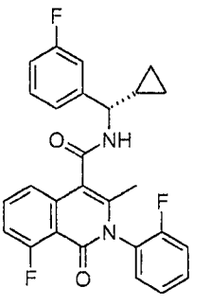
7g 8-Fluoro-2-(4-fluoro-phenyl)-1-oxo-3-(2-oxo-pyrrolidin-1-ylmethyl)-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-cyclopropyl-(3-fluoro-phenyl)-methyl]-amide.

The title product was isolated by preparative TLC on silica gel. LC-MS (m/z) 546.3 (MH^+); t_R = 0.71 (method B).



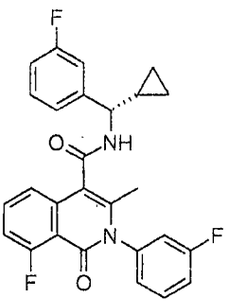
***7h** 8-Fluoro-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-cyclobutyl-(3-fluoro-phenyl)-methyl]-amide.*

LC-MS (m/z) 459.4 (MH^+); t_R = 1.54.



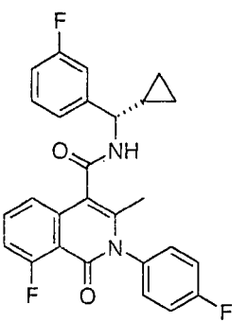
7i 8-Fluoro-2-(2-fluoro-phenyl)-3-methyl-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-cyclopropyl-(3-fluoro-phenyl)-methyl]-amide.

LC-MS (m/z) 463.3 (MH^+); t_R = 1.46.



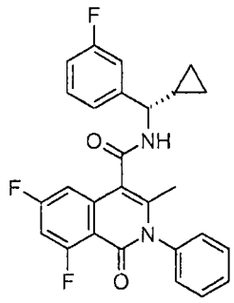
7j 8-Fluoro-2-(3-fluoro-phenyl)-3-methyl-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-cyclopropyl-(3-fluoro-phenyl)-methyl]-amide.

LC-MS (m/z) 463.3 (MH^+); t_R = 1.46.



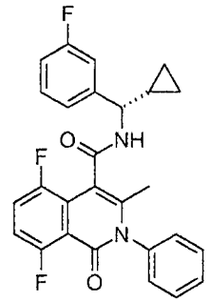
7k 8-Fluoro-2-(4-fluoro-phenyl)-3-methyl-1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-cyclopropyl-(3-fluoro-phenyl)-methyl]-amide.

LC-MS (m/z) 463.4 (MH^+); t_R = 1.45.



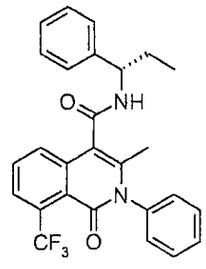
7l 6,8-Difluoro-3-methyl-1-oxo-2-phenyl-1,2-dihydro-isoquinoline-4-carboxylic acid [(S)-cyclopropyl-(3-fluoro-phenyl)-methyl]-amide.

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.

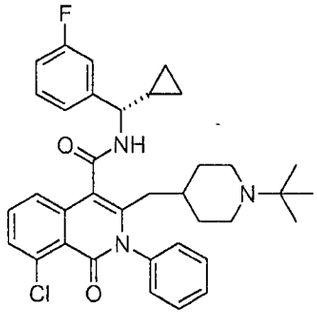
LC-MS (m/z) 463.4 (MH^+); t_R = 1.39.



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	X16320G0025
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 34°C, 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.

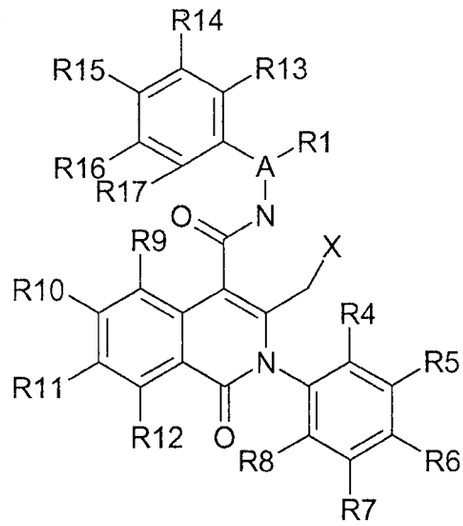
All isoquinolinones of the present invention characterized in the NK3 receptor efficacy and potency assay have been antagonists without any observed significant agonist activity at relevant doses. The table shows affinity data (obtained as described in Example 9) and potency data obtained with the compounds 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;

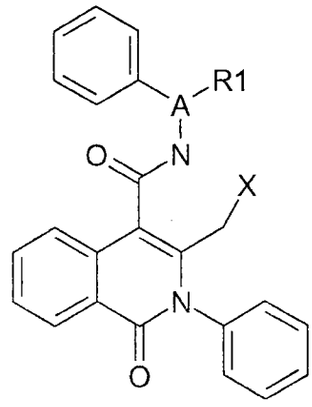
and pharmaceutically acceptable salts thereof.

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),

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-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;

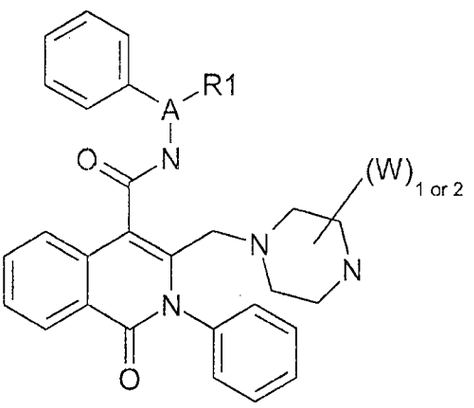
wherein a and b independently represent an integer selected from 0, 1, 2 and 3;

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.

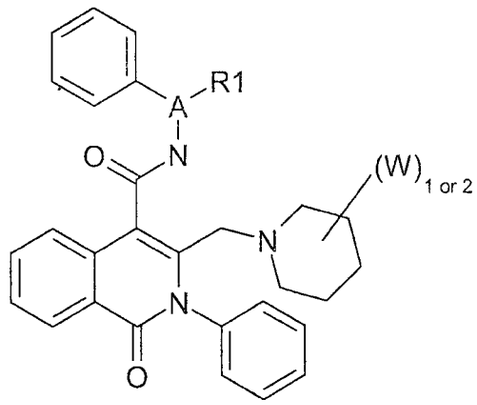
38. A compound according to claim 22, wherein Y represents a bond, C(O), -C(O)-O-, C(O)-NH-, -O-, or $S(O)_2$; a+b is 0, 1, 2, 3 or 4; and wherein Z represents hydrogen, C_{1-6}alkyl, NR^2R^3 or cyano.

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;

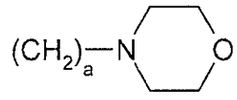
wherein R^2 and R^3 independently represent hydrogen, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, haloC_{1-6}alkyl or phenyl;

and pharmaceutically acceptable salts thereof.

43. A compound according to claim 42, wherein A represent CH, and R^1 represents C_{1-6}alkyl.

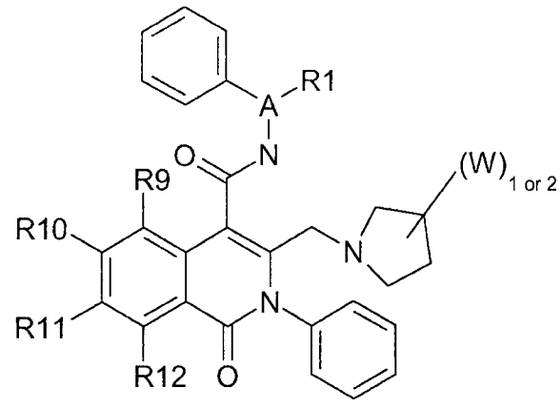
44. A compound according to claim 43, wherein R^1 represents ethyl or cyclopropyl.

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;

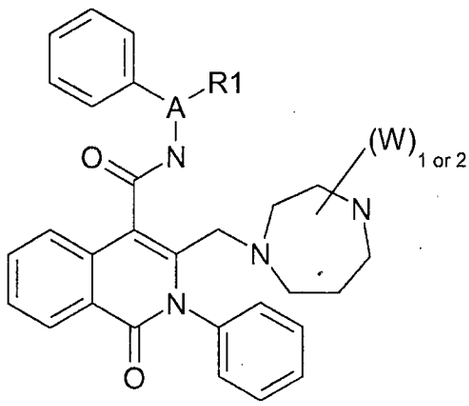
wherein each R^1 independently represents hydrogen, C_{1-6}alkyl, -C(O)-C_{1-6}alkyl, C(O)-O-C_{1-6}alkyl, or phenyl, wherein said phenyl, or C_{1-6}alkyl is optionally substituted with one or more substituents selected from halogen, hydroxyl, haloC_{1-6}alkyl, nitro, C_{1-6}alkoxy, and NR^2R^3;

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;

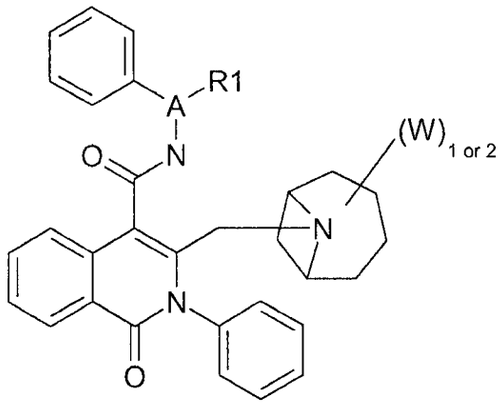
wherein R^2 and R^3 independently represent hydrogen, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, haloC_{1-6}alkyl or phenyl;

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;

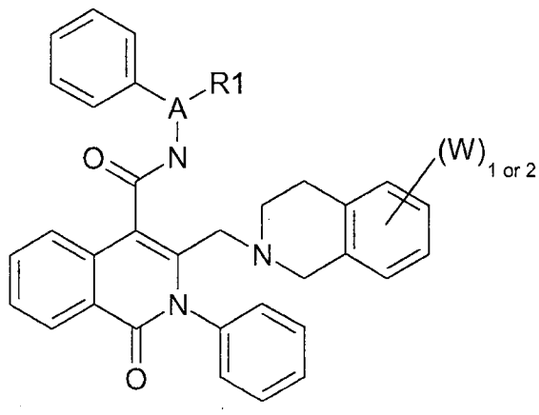
wherein R^2 and R^3 independently represent hydrogen, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, haloC_{1-6}alkyl or phenyl;

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;

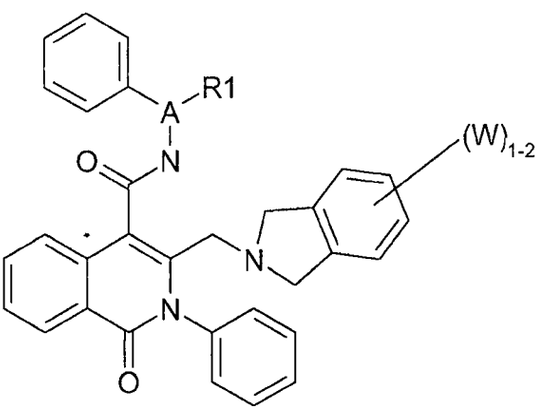
wherein R^2 and R^3 independently represent hydrogen, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, haloC_{1-6}alkyl or phenyl;

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;

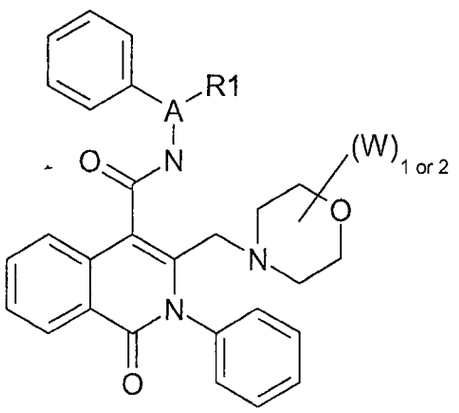
wherein R^2 and R^3 independently represent hydrogen, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, haloC_{1-6}alkyl or phenyl;

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;

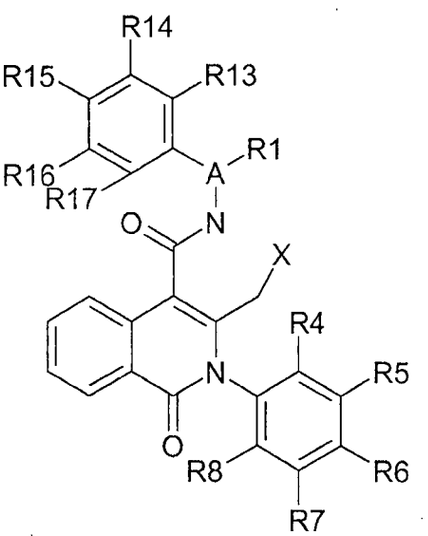
wherein R^2 and R^3 independently represent hydrogen, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, haloC_{1-6}alkyl or phenyl;

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;

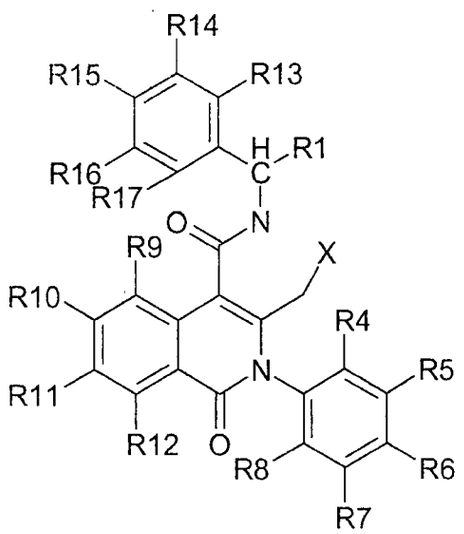
wherein R^2 and R^3 independently represent hydrogen, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, haloC_{1-6}alkyl or phenyl;

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 sclected 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;

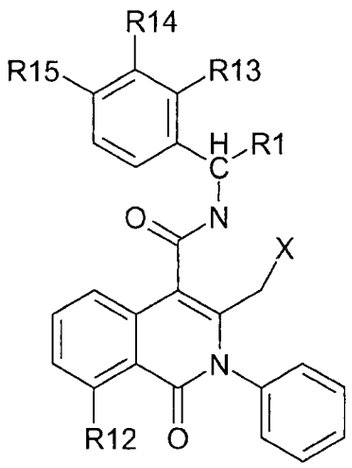
wherein each of R^4-R^8 independently represents hydrogen or halogen;

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;

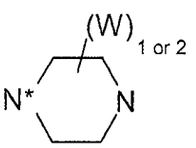
wherein R^{12} represents halogen;

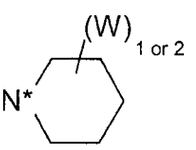
R^{13}-R^{15} each independently represents hydrogen or halogen;

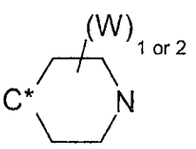
and pharmaceutically acceptable salts thereof.

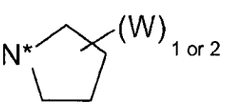
69. The compound according to any of claims 67-68, wherein R^1 represents methyl, ethyl, cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl.

70. The compound according to claim 69, wherein X represents



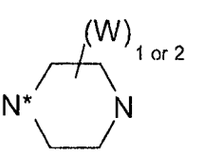
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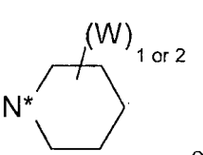
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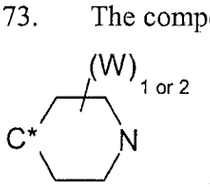
$-NR^2R^3$, or hydrogen

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.

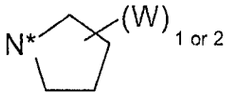
73. The compound according to claim 70, wherein X represents 

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 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).

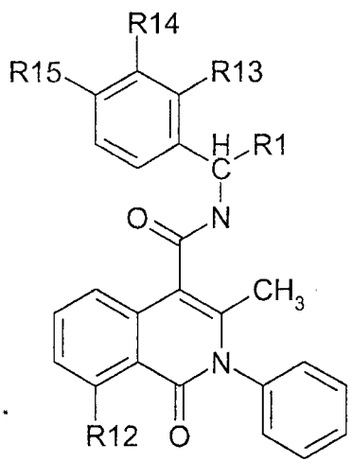
76. The compound according to claim 70, wherein X represents $-NR^2R^3$.

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''



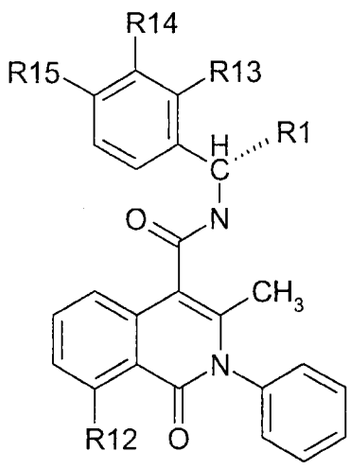
[Ik'']

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'''



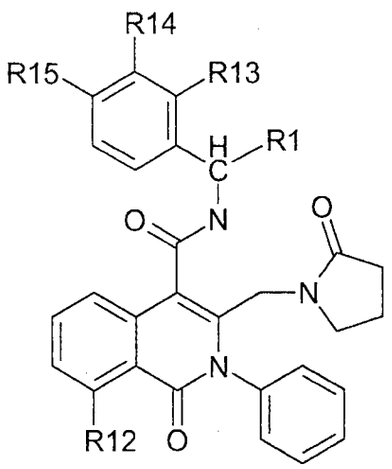
[Ik'"]

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']

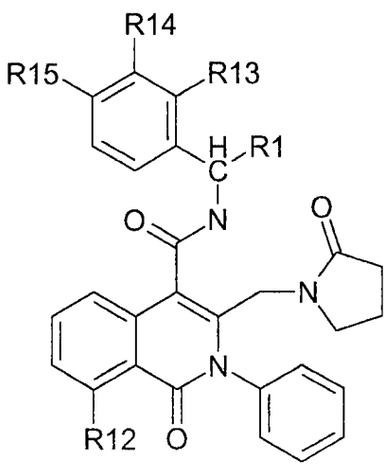
wherein R^1 represents ethyl or cyclopropyl;

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''



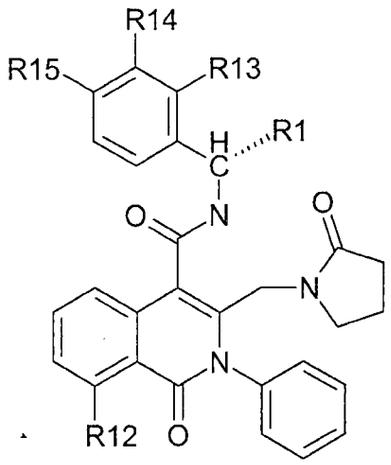
[Id'']

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.

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Derivados de isoquinolinona como antagonistas del NK3

Campo de la Invención

La presente invención se refiere a compuestos útiles en terapia, en particular en el tratamiento de psicosis, a composiciones que contienen dichos compuestos, y a métodos para tratar enfermedades que comprenden la administración de dichos compuestos.

Antecedentes de la Invención

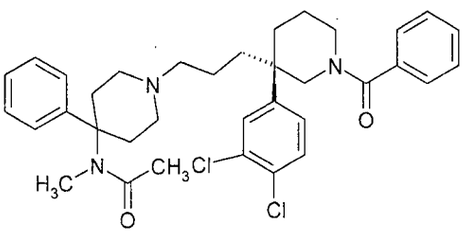
Los fármacos antisicóticos actualmente aprobados comparten la característica común de reducir la señalización de dopamina en el cerebro. Esto se obtiene por, o bien un efecto antagonista o parcial agonista sobre el receptor de dopamina D2. Los antisicóticos de primera generación (también denominados "típicos") a menudo están asociados con efectos colaterales extra piramidales por lo que el uso de estos agentes ha disminuido. La segunda generación o antisicóticos "atípicos" además de la afinidad al receptor D2 tienen afinidad con el receptor de serotonina 2A (5-HT_{2A}). Algunos antisicóticos atípicos además tienen afinidad para los receptores 5-HT_{2C}, 5-$HT_{6,}$ o 5-HT_7. Los antisicóticos atípicos dan lugar a menores efectos colaterales extra-piramidales, pero aún se encuentran obstaculizados por el aumento de peso y los efectos QT_C. Ejemplos de atípicos son clozapina, olanzapina y risperidona.

Recientemente, los receptores de neuroquinina han sido sugeridos como blancos para enfermedades del SNC [Albert, *Expert Opin. Ther. Patents*, 14, 1421-1433, 2004]. Las neuroquininas (o taquiquininas) son una familia de neuropéptidos, los cuales incluyen la sustancia P (SP), la neuroquinina A (NKA), y la neuroquinina B (NKB). Los efectos biológicos de estas sustancias se producen esencialmente por unión a y activación de los tres receptores de neuroquinina NK1, NK2 y NK3. Si bien probablemente existe algo de reactividad cruzada, la SP tiene la afinidad más alta y se cree que es el ligando endógeno para NK1, y de igual modo para NKA y NK2, y para NKB y NK3.

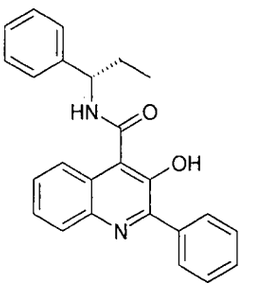
El NK3 se expresa esencialmente en forma central en regiones que incluyen regiones corticales, tales como frontal, parietal y córtex cingulado; núcleo de la amígdala, tal como el núcleo basal, central y lateral; el hipocampo; y las estructuras mesencéfalas, tales como el área tegmental ventral, la substantia nigra pars compacta, y el núcleo del rafé dorsal [Spooren et al, *Nature Reviews*, 4, 9675 a 975, 2005]. El

receptor NK3 se expresa en neuronas dopaminérgicas, y Spooren et al han sugerido que los efectos antisicóticos de los antagonistas del NK3 están mediados por una inhibición del tono dopaminérgico, particularmente en el receptor D2 combinado con una reducción del tono serotoninérgico, particularmente en el receptor 5-HT_{2A}.

Dos antagonistas del NK3 estructuralmente distintos, a saber talnetant y osanetant, han sido probados clínicamente para efectos antisicóticos, y en particular antiesquizofrénicos.



Osanetant



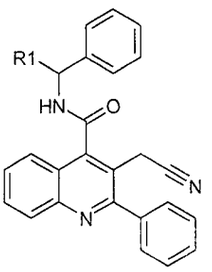
Talnetant

Osanetant demostró ser superior al placebo en ensayos clínicos, en particular sobre síntomas positivos de psicosis, es decir, delirios, alucinaciones, y paranoia [*Am.J.Psychiatry*, 161, 2004, 975 a 984]. De manera similar, se ha demostrado en ensayos clínicos que talnetant mejora el comportamiento cognitivo de los esquizofrénicos [*Curr. Opinion. Invest. Drug*, 6, 717-721, 2005]. Sin embargo, ambos compuestos se han visto obstaculizados por propiedades farmacocinéticas y farmacodinámicas deficientes que incluyen escasa solubilidad, una escasa biodisponibilidad, aclaramiento relativamente alto, y una escasa penetración de la barrera hematoencefálica [*Nature reviews*, 4, 9675 a 975, 2005]. Estos resultados dan soporte a la noción de que el receptor NK3 es un blanco promisorio para el tratamiento de por ej., psicosis, enfatizando no obstante la necesidad de identificar compuestos con propiedades farmacocinéticas y farmacodinámicas adecuadas.

La WO95/32948 divulga una gama de derivados de quinolina, que incluyen el talnetant como antagonistas del NK3.

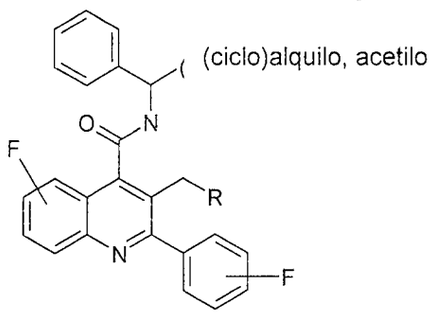
Recientemente, la WO 2006/130080 revela compuestos que tienen la estructura de núcleo

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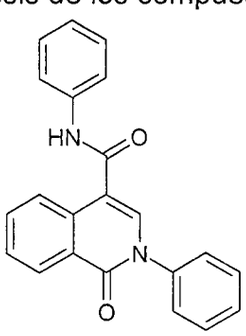
cuyos compuestos se dicen que son antagonistas del NK3; y las WO 2006/050991 y WO 2006/050992 divulgan otros derivados de quinolincarboxamidas, cuyos derivados se dice que son antagonistas del NK3.

La WO 2005/014575 divulga compuestos de la fórmula



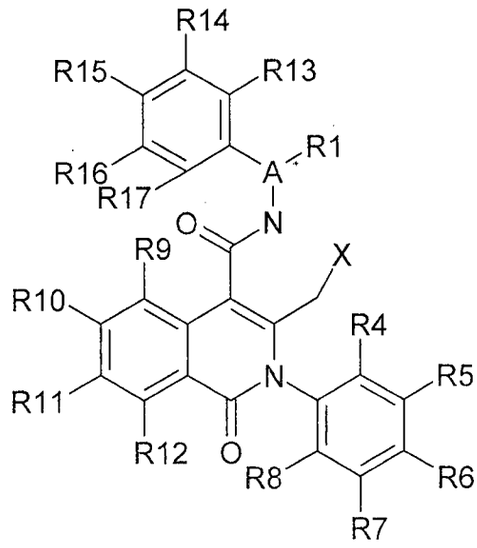
en donde R representa heterociclos que contienen N, es decir pirazolilo, triazolilo y tetrazolilo.

Finalmente, *Ind. J. Chem. Parte B*, 18B, 304-306, 1979 divulga un estudio sobre la síntesis de los compuestos con la siguiente estructura de núcleo



Resumen de la Invención

Sorprendentemente, los actuales inventores han hallado que ciertos derivados de isoquinolina son potentes antagonistas del NK3, los cuales pueden ser utilizados como tales en el tratamiento de por ej., psicosis. En consecuencia, en una realización, la invención se refiere a compuestos de la fórmula I



[I]

en donde A representa N, CH o CR^1;

en donde cada R^1 independientemente representa hidrógeno, alquilo C_{1-6}, alquenilo C_{2-6}, alquinilo C_{2-6}, -C(O)-alquilo C_{1-6}, -C(O)-alquenilo C_{2-6}, -C(O)-alquinilo C_{2-6}, -C(O)-O-alquilo C_{1-6}, -C(O)-O-alquenilo C_{2-6}, -C(O)-O-alquinilo C_{2-6} o fenilo, en donde dicho fenilo, alquilo C_{1-6}, alquenilo C_{2-6} o alquinilo C_{2-6} está opcionalmente sustituido con uno o más sustituyentes seleccionados entre halógeno, hidroxilo, haloalquilo C_{1-6}, nitro, alcoxi C_{1-6}, y NR^2R^3;

en donde X representa hidrógeno, alquilo C_{1-6}, alquenilo C_{2-6}, alquinilo C_{2-6}, ciano, $-OR^2$, $-O-C(O)R^2$, $-OC(O)NR^2R^3$, $-C(O)-NR^2R^3$, $-N(R^2)C(O)R^3$, $-N(R^2)-C(O)NR^2R^3$ o NR^2R^3, o X representa una parte monocíclica, bicíclica o tricíclica que tiene 4 a 16 átomos constitutivos del anillo uno de los cuales es nitrógeno, y en donde uno, dos o tres átomos constitutivos del anillo , adicionalmente, pueden ser heteroátomos seleccionados entre N, O y S, y en donde dicha parte monocíclica, bicíclica o tricíclica puede estar opcionalmente sustituida con uno o más sustituyentes W, en donde W se selecciona entre hidrógeno, hidroxi, halógeno, ciano, (=O), $-O-(CH_2)_c-O-$, en donde c es 2 o 3 (espiro), $(CH_2)_d$, en donde d es 5 o 6 (espiro), alquilo C_{1-6}, alquenilo C_{2-6}, alquinilo C_{2-6}, alcoxi C_{1-6}, -C(O)-alquilo C_{1-6}, -C(O)-alquenilo C_{2-6}, -C(O)-alquinilo C_{2-6}, -C(O)-O-alquilo C_{1-6}, -C(O)-O-alquenilo C_{2-6}, -C(O)-O-alquinilo C_{2-6}, -O-C(O)-alquilo C_{1-6}, -O-C(O)-alquenilo C_{2-6}, -O-C(O)-alquinilo C_{2-6}, -C(O)H, COOH; o en donde W representa una parte de la fórmula $-(CH_2)_a-Y-(CH_2)_b-Z$;

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en donde a y b independientemente representan un número entero seleccionado entre 0, 1, 2 y 3;

en donde Y representa un enlace, C(O), O, S, -O-C(O), -C(O)-O-, -NR^2-, -NR^2-C(O)-, -C(O)-NH-, o $S(O)_2$;

en donde Z representa hidrógeno, alquilo C_{1-6}, NR^2R^3, ciano o una parte monocíclica o bicíclica fusionada que comprende 4 a 12 átomos constitutivos del anillo de los cuales opcionalmente uno, dos o tres son heteroátomos seleccionados entre N, O, y S, y en donde dicha parte monocíclica o bicíclica fusionada está opcionalmente sustituida con uno o más sustituyentes seleccionados del grupo integrado por halógeno, ciano, alquilo C_{1-6}, hidroxilo, y alcoxi C_{1-6}, pirazinilo, fenilo, piridilo, y fenilo sustituido con halógeno;

en donde cada uno entre R^4-R^8, R^9-R^{12}, y R^{13}-R^{17} independientemente representa hidrógeno, alquilo C_{1-6}, alquenilo C_{2-6}, alquinilo C_{2-6}, halógeno, NR^2R^3, hidroxi, ciano, nitro, alcoxi C_{1-6}, halo-alquilo C_{1-6} o hidroxi-alquilo C_{1-6};

en donde R^2 y R^3 independientemente representan hidrógeno, alquilo C_{1-6}, alquenilo C_{2-6}, alquinilo C_{2-6}, hidroxi-alquilo C_{1-6}, halo-alquilo C_{1-6} o fenilo;

y sus sales aceptables para uso farmacéutico.

En una realización, la invención se refiere a compuestos de la fórmula I y sus sales farmacéuticamente aceptables para uso en terapias.

En una realización, la invención se refiere a composiciones farmacéuticas que comprenden compuestos de la fórmula I y sus sales aceptables para uso farmacéutico.

En una realización, la invención se refiere a métodos de tratamiento, dichos métodos comprenden la administración de cantidades terapéuticamente eficaces de un compuesto de la fórmula I y sus sales aceptables para uso farmacéutico a un paciente que necesita del mismo.

En una realización, la invención se refiere al uso de un compuesto de la fórmula I y sus sales aceptables para uso farmacéutico en la producción de un medicamento.

En una realización, la invención se refiere a compuestos de la fórmula I y sus sales farmacéuticamente aceptables para uso en el tratamiento de enfermedades.

Definiciones

En el presente contexto, "alquilo" indica un hidrocarburo saturado lineal, ramificado y/o cíclico. En particular "alquilo C_{1-6}" indica un hidrocarburo tal que tiene 1,

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2, 3, 4, 5, o 6 átomos de carbono. Ejemplos de alquilo C_{1-6} incluyen metilo, etilo, propilo, butilo, pentilo, hexilo, ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, 2-metil-propilo, ter-butilo, y ciclopropilmetilo.

En el presente contexto, "alquenilo" indica un hidrocarburo lineal, ramificado y/o cíclico que comprende al menos un enlace doble carbono-carbono. En particular "alquenilo C_{2-6}" indica un hidrocarburo tal que tiene 2, 3, 4, 5, o 6 átomos de carbono. Ejemplos de alquenilo C_{2-6} incluyen etenilo, 1-propenilo, 2-propenilo, 1-butenilo, 2-butenilo, 3-butenilo, y ciclohexenilo.

En el presente contexto, "alquinilo" indica un hidrocarburo lineal, ramificado y/o cíclico que comprende al menos un enlace triple carbono-carbono y opcionalmente además uno o más enlaces dobles carbono-carbono. En particular "alquinilo C_{2-6}" indica un hidrocarburo tal que tiene 2, 3, 4, 5, o 6 átomos de carbono. Ejemplos de alquinilo C_{2-6} incluyen etinilo, 1-propinilo, 2-propinilo, 1-butinilo, 2-butinilo, 3-butinilo y 5-but-1-en-3-inilo.

En el presente contexto "halógeno" indica miembros del 7º grupo del sistema periódico, es decir: flúor, cloro, bromo, y yodo.

En el presente contexto, "alcoxi" indica una parte de fórmula –OR', en donde R' indica alquilo como se definió anteriormente. En particular "alcoxi C_{1-6}" indica tal parte en donde la parte alquilo tiene 1, 2, 3, 4, 5, o 6 átomos de carbono.

En el presente contexto, haloalquilo indica un alquilo como se definió anteriormente sustituido con uno o más halógenos. En particular, halo-alquilo C_{1-6} indica una parte en donde la parte alquilo tiene 1, 2, 3, 4, 5 o 6 átomos de carbono. Un ejemplo de haloalquilo es trifluorometilo.

En el presente contexto, sales aceptables para uso farmacéutico incluyen sales de adición de ácido aceptables para uso farmacéutico, sales metálicas aceptables para uso farmacéutico, sales de amonio y amonio alquilado. Las sales de adición de ácido incluyen sales de ácidos inorgánicos como así también ácidos orgánicos.

Ejemplos de ácidos inorgánicos adecuados incluyen clorhídrico, bromhídrico, yodhídrico, fosfórico, sulfúrico, sulfámico, nítricos y similares.

Ejemplos de ácidos orgánicos adecuados incluyen ácidos fórmico, acético, tricloroacético, trifluoroacético, propiónico, benzoico, cinámico, cítrico, fumárico, glicólico, itacónico, láctico, metansulfónico, maleico, málico, malónico, mandélico,

oxálico, pícrico, pirúvico, salicílico, succínico, metansulfónico, etansulfónico, tartárico, ascórbico, pamoico, bismetilen salicílico, etandisulfónico, glucónico, citracónico, aspártico, esteárico, palmítico, EDTA, glicólico, p-aminobenzoico, glutámico, bencensulfónico, p-toluensulfónico, ácidos acéticos de teofilina, como así también las 8-haloteofilinas, por ejemplo 8-bromoteofilina y similares. Otros ejemplos de sales de adición de ácido orgánico e inorgánico aceptable para uso farmacéutico incluyen las sales aceptables para uso farmacéutico mencionadas en J. Pharm. Sci. 1977, 66,2, el cual se incorpora a la presente como referencia.

Ejemplos de sales metálicas incluyen sales de litio, sodio, potasio, magnesio y similares.

Ejemplos de sales de amonio y amonio alquilado incluyen sales de amonio, sales de metil-, dimetil-, trimetil-, etil-, hidroxietil-, dietil-, n-butil-, sec-butil-, ter-butil-, tetrametilamonio y similares.

En el presente contexto, "átomos constitutivos del anillo" pretende indicar los átomos que constituyen un anillo, y los átomos constitutivos de los anillos se seleccionan entre C, N, O y S. Como ejemplo, benceno y tolueno ambos tienen 6 carbonos como átomos constitutivos del anillo mientras que la piridina tiene 5 carbonos y 1 nitrógeno como átomos constitutivos del anillo.

En el presente contexto, una "parte monocíclica" indica una estructura con forma anillada que comprende sólo un anillo. De manera similar una "parte bicíclica" indica una estructura formada por dos anillos unidos. Los dos anillos pueden estar unidos por dos átomos constitutivos del anillo adyacentes en cada anillo en cuya caso dicha parte bicíclica se dice que está fusionada. El Naftaleno es un ejemplo de una parte anillada bicíclica fusionada. En forma alternativa, los dos anillos se unen en un solo átomo constitutivo de anillo en cuyo caso dicha parte bicíclica se dice que es espiro. Un ejemplo de una parte anillada bicíclica en forma espiro es 1,4-dioxa-8-aza-espiro[4.5]decano. En forma alternativa, los dos anillos pueden estar unidos por dos átomos constitutivos del anillo que no son adyacentes en cada anillo en cuyo caso dicha parte anillada bicíclica se dice que está enjaulada. Un ejemplo de una parte bicíclica enjaulada es 3-aza-biciclo[3.2.2]nonano. Una "parte tricíclica" indica una estructura compuesta de tres anillos unidos. Como se mencionó para las partes bicíclicas

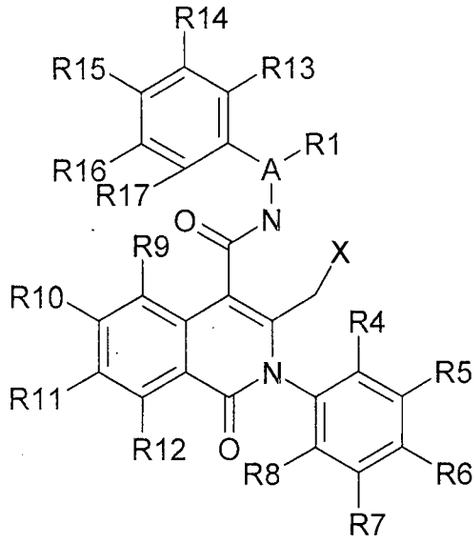
anteriores, las partes tricíclicas pueden ser fusionadas, espiro o enjauladas, o en verdad, un combinación de las mismas.

En el presente contexto, el término "cantidad eficaz para uso terapéutico" de un compuesto significa una cantidad suficiente para curar, mejorar o parcialmente detener las manifestaciones clínicas de una enfermedad dada y sus complicaciones en una intervención terapéutica que comprende la administración de dicho compuesto. Una cantidad adecuada para obtener esto se define como "cantidad eficaz para uso terapéutico". Las cantidades efectivas para cada fin dependerán de la severidad de la enfermedad o lesión como así también del peso y el estado general del sujeto. Se entenderá que determinar una dosificación apropiada se puede lograr utilizando experimentación de rutina, construyendo una matriz de valores y ensayando diferentes puntos en la matriz, lo cual está dentro de las capacidades ordinarias de un profesional capacitado.

En el presente contexto, el término "tratamiento" y "tratar" significan el manejo y cuidado de un paciente con el propósito de combatir una afección, tal como una enfermedad o un trastorno. El término intenta incluir el espectro total de los tratamientos para una afección dada de la cual está sufriendo el paciente, tal como la administración del compuesto activo para aliviar los síntomas o complicaciones, para retardar el avance de la enfermedad, el trastorno o el condición, para mejorar y aliviar los síntomas y complicaciones, y/o curar o eliminar la enfermedad, trastorno o condición, así como también prevenir la condición, en donde la prevención se entiende como el manejo y el cuidado de un paciente con el propósito de combatir la enfermedad, condición, o trastorno e incluye la administración de los compuestos para prevenir el inicio de los síntomas o complicaciones. No obstante, los tratamientos profilácticos (preventivos) y terapéuticos (curativos) son dos aspectos separados de la invención. El paciente a ser tratado es preferentemente un mamífero, en particular, un ser humano.

Descripción detallada de la invención

Los compuestos de la presente invención se definen mediante la fórmula I a continuación:



[I]

en donde A representa N, CH o CR^1;

en donde cada R^1 independientemente representa hidrógeno, alquilo C_{1-6}, alquenilo C_{2-6}, alquinilo C_{2-6}, -C(O)-alquilo C_{1-6}, -C(O)-alquenilo C_{2-6}, -C(O)-alquinilo C_{2-6}, -C(O)-O-alquilo C_{1-6}, -C(O)-O-alquenilo C_{2-6}, -C(O)-O-alquinilo C_{2-6} o fenilo, en donde dicho fenilo, alquilo C_{1-6}, alquenilo C_{2-6} o alquinilo C_{2-6} está opcionalmente sustituido con uno o más sustituyentes seleccionados entre halógeno, hidroxilo, halo-alquilo C_{1-6}, nitro, alcoxi C_{1-6}, y NR^2R^3;

en donde X representa hidrógeno, alquilo C_{1-6}, alquenilo C_{2-6}, alquinilo C_{2-6}, ciano, $-OR^2$, $-O-C(O)R^2$, $-OC(O)NR^2R^3$, $-C(O)-NR^2R^3$, $-N(R^2)C(O)R^3$, $-N(R^2)-C(O)NR^2R^3$ o NR^2R^3, o X representa una parte monocíclica, bicíclica o tricíclica que tiene 4 a 16 átomos constitutivos del anillo uno de los cuales es nitrógeno, y en donde uno, dos o tres átomos constitutivos del anillo, adicionalmente, pueden ser heteroátomos seleccionados entre N, O y S, y en donde dicha parte monocíclica, bicíclica o tricíclica puede estar opcionalmente sustituida con uno o más sustituyentes W, en donde W se selecciona entre hidrógeno, hidroxi, halógeno, ciano, (=O), $-O-(CH_2)_c-O-$, en donde c es 2 o 3 (espiro), $(CH_2)_d$, en donde d es 5 o 6 (espiro), alquilo C_{1-6}, alquenilo C_{2-6}, alquinilo C_{2-6}, alcoxi C_{1-6}, -C(O)-alquilo C_{1-6}, -C(O)-alquenilo C_{2-6}, -C(O)-alquinilo C_{2-6}, -C(O)-O-alquilo C_{1-6}, -C(O)-O-alquenilo C_{2-6}, -C(O)-O-alquinilo C_{2-6}, -O-C(O)-alquilo C_{1-6}, -O-C(O)-alquenilo C_{2-6}, -O-C(O)-alquinilo C_{2-6}, -C(O)H, COOH; o en donde W representa una parte de la fórmula $-(CH_2)_a-Y-(CH_2)_b-Z$;

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en donde a y b independientemente representan un número entero seleccionado entre 0, 1, 2 y 3;

en donde Y representa un enlace, C(O), O, S, -O-C(O), -C(O)-O-, $-NR^2-$, $-NR^2-$C(O)-, -C(O)-NH-, o $S(O)_2$;

en donde Z representa hidrógeno, alquilo C_{1-6}, NR^2R^3, ciano o una parte monocíclica o bicíclica fusionada que comprende 4 a 12 átomos constitutivos del anillo de los cuales opcionalmente uno, dos o tres son heteroátomos seleccionados entre N, O, y S, y en donde dicha parte monocíclica o bicíclica fusionada está opcionalmente sustituida con uno o más sustituyentes seleccionados del grupo integrado por halógeno, ciano, alquilo C_{1-6}, hidroxilo, y alcoxi C_{1-6}, pirazinilo, fenilo, piridilo, y fenilo sustituido con halógeno;

en donde cada uno entre R^4-R^8, R^9-R^{12}, y R^{13}-R^{17} independientemente representa hidrógeno, alquilo C_{1-6}, alquenilo C_{2-6}, alquinilo C_{2-6}, halógeno, NR^2R^3, hidroxi, ciano, nitro, alcoxi C_{1-6}, halo-alquilo C_{1-6} o hidroxi-alquilo C_{1-6};

en donde R^2 y R^3 independientemente representan hidrógeno, alquilo C_{1-6}, alquenilo C_{2-6}, alquinilo C_{2-6}, hidroxi-alquilo C_{1-6}, halo-alquilo C_{1-6} o fenilo;

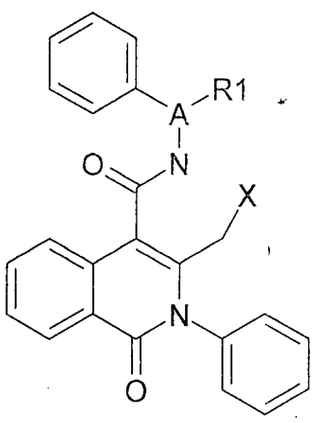
y sus sales aceptables para uso farmacéutico.

En una realización, R^4-R^8 representan hidrógeno.

En una realización, R^9-R^{12} representan hidrógeno.

En una realización, R^{13}-R^{17} representan hidrógeno.

En una realización, los compuestos de la presente invención se definen mediante la fórmula I_a



[Ia]

en donde A representa N, CH o CR^1;

en donde cada R^1 independientemente representa hidrógeno, alquilo C_{1-6}, -C(O)-alquilo C_{1-6}, -C(O)-O-alquilo C_{1-6}, o fenilo, en donde dicho fenilo o alquilo C_{1-6}, está opcionalmente sustituido con uno o más sustituyentes seleccionados entre halógeno, hidroxilo, halo-alquilo C_{1-6}, nitro, alcoxi C_{1-6}, y NR^2R^3;

en donde X representa hidrógeno, alquilo C_{1-6}, ciano, $-OR^2$, $-O-C(O)R^2$, $-OC(O)NR^2R^3$, $-C(O)-NR^2R^3$, $-N(R^2)C(O)R^3$, $-N(R^2)-C(O)NR^2R^3$ o NR^2R^3, o X representa una parte monocíclica, bicíclica o tricíclica que tiene 4 a 16 átomos constitutivos del anillo uno de los cuales es nitrógeno, y en donde uno, dos o tres átomos constitutivos del anillo, adicionalmente, pueden ser heteroátomos seleccionados entre N, O y S, y en donde dicha parte monocíclica, bicíclica o tricíclica puede estar opcionalmente sustituida con uno o más sustituyentes W, en donde W se selecciona entre hidrógeno, hidroxi, halógeno, ciano, (=O), $-O-(CH_2)_c-O-$, en donde c es 2 o 3 (espiro), $(CH_2)_d$, en donde d es 5 o 6 (espiro), alquilo C_{1-6}, alcoxi C_{1-6}, -C(O)-alquilo C_{1-6}, -C(O)-O-alquilo C_{1-6}, -O-C(O)-alquilo C_{1-6}, -C(O)H, COOH; o en donde W representa una parte de la fórmula $-(CH_2)_a-Y-(CH_2)_b-Z$;

en donde a y b independientemente representan un número entero seleccionado entre 0, 1, 2 y 3;

en donde Y representa un enlace, C(O), O, S, -O-C(O), -C(O)-O-, $-NR^2-$, $-NR^2-C(O)-$, -C(O)-NH-, o $S(O)_2$;

en donde Z representa hidrógeno, alquilo C_{1-6}, NR^2R^3, ciano o una parte monocíclica o bicíclica fusionada que comprende 4 a 12 átomos constitutivos del anillo de los cuales opcionalmente uno, dos o tres son heteroátomos seleccionados entre N, O, y S, y en donde dicha parte monocíclica o bicíclica fusionada está opcionalmente sustituida con uno o más sustituyentes seleccionados del grupo integrado por halógeno, ciano, alquilo C_{1-6}, hidroxilo, y alcoxi C_{1-6}, pirazinilo, fenilo, piridilo, y fenilo sustituido con halógeno;

en donde cada uno entre R^4-R^8, R^9-R^{12}, y R^{13}-R^{17} independientemente representa hidrógeno, alquilo C_{1-6}, alquenilo C_{2-6}, alquinilo C_{2-6}, halógeno, NR^2R^3, hidroxi, ciano, nitro, alcoxi C_{1-6}, halo-alquilo C_{1-6}o hidroxi-alquilo C_{1-6};

en donde R^2 y R^3 independientemente representan hidrógeno, alquilo C_{1-6}, alquenilo C_{2-6}, alquinilo C_{2-6}, hidroxi-alquilo C_{1-6}, halo-alquilo C_{1-6} o fenilo; y sus sales

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aceptables para uso farmacéutico. En particular, A representa CH y R^1 representa alquilo C_{1-6}, tal como etilo o ciclopropilo.

En una realización en donde los compuestos de la presente invención se definen mediante la fórmula I_a, X representa hidrógeno, alquilo C_{1-6}, ciano, $-OR^2$, $-O-C(O)R^2$, $-OC(O)NR^2R^3$, $-C(O)-NR^2R^3-$, $-N(R^2)C(O)R^3$, $-N(R^2)-C(O)NR^2R^3$ o NR^2R^3, en donde R^2 y R^3 independientemente representan hidrógeno, alquilo C_{1-6}, hidroxi-alquilo C_{1-6}, halo-alquilo C_{1-6} o fenilo. En particular, X representa hidrógeno, metilo, o NR^2R^3, en donde R^2 y R^3 independientemente representan hidrógeno, alquilo C_{1-6}, o hidroxi-alquilo C_{1-6}, y se hace particular mención de R^2 y R^3 que representan independientemente hidrógeno, ciclopropilmetilo, metilo, etilo o ciclopropilo.

En una realización en donde los compuestos de la presente invención se definen mediante la fórmula I_a, X representa una parte monocíclica, bicíclica o tricíclica que tiene 4 a 16 átomos constitutivos del anillo uno de los cuales es nitrógeno, y en donde uno, dos o tres átomos constitutivos del anillo, adicionalmente, pueden ser heteroátomos seleccionados entre N, O y S, y en donde dicha parte monocíclica, bicíclica o tricíclica puede estar opcionalmente sustituida con uno o más sustituyentes W, en donde W se selecciona entre hidrógeno, hidroxi, halógeno, ciano, (=O), $-O-(CH_2)_c-O-$, en donde c es 2 o 3 (espiro), $(CH_2)_d$, en donde d es 5 o 6 (espiro), alquilo C_{1-6}, alcoxi C_{1-6}, -C(O)-alquilo C_{1-6}, -C(O)-O-alquilo C_{1-6}, -O-C(O)-alquilo C_{1-6}, -O-C(O)-, -C(O)H, COOH; o en donde W representa una parte de la fórmula $-(CH_2)_a-Y-(CH_2)_b-Z$;

en donde a y b independientemente representan un número entero seleccionado entre 0, 1, 2 y 3;

en donde Y representa un enlace, C(O), O, S, -O-C(O), -C(O)-O-, $-NR^2-$, $-NR^2-C(O)-$, -C(O)-NH-, o $S(O)_2$;

en donde Z representa hidrógeno, alquilo C_{1-6}, NR^2R^3, ciano o una parte monocíclica o bicíclica fusionada que comprende 4 a 12 átomos constitutivos del anillo de los cuales opcionalmente uno, dos o tres son heteroátomos seleccionados entre N, O, y S, y en donde dicha parte monocíclica o bicíclica fusionada está opcionalmente sustituida con uno o más sustituyentes seleccionados del grupo integrado por halógeno, ciano, alquilo C_{1-6}, hidroxilo, y alcoxi C_{1-6}, pirazinilo, fenilo, piridilo, y fenilo sustituido con halógeno;

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en donde R^2 y R^3 independientemente representan hidrógeno, alquilo C_{1-6}, hidroxi-alquilo C_{1-6}, halo-alquilo C_{1-6} o fenilo.

En una realización en donde los compuestos de la presente invención se definen mediante la fórmula I_a, X representa una parte monocíclica que tiene 5 átomos constitutivos del anillo uno de los cuales es nitrógeno, y en donde uno, dos o tres átomos constitutivos del anillo, adicionalmente, pueden ser heteroátomos seleccionados entre N, O y S, y en donde dicha parte monocíclica puede estar opcionalmente sustituida con uno o más sustituyentes W, en donde W se selecciona entre hidrógeno, hidroxi, halógeno, ciano, (=O), -O-$(CH_2)_c$-O-, en donde c es 2 o 3 (espiro), $(CH_2)_d$, en donde d es 5 o 6 (espiro), alquilo C_{1-6}, alcoxi C_{1-6}, -C(O)-alquilo C_{1-6}, -C(O)-O-alquilo C_{1-6}, -O-C(O)-alquilo C_{1-6}, -O-C(O)-, -C(O)H, COOH; o en donde W representa una parte de la fórmula –$(CH_2)_a$-Y-$(CH_2)_b$-Z;

en donde a y b independientemente representan un número entero seleccionado entre 0, 1, 2 y 3;

en donde Y representa un enlace, C(O), O, S, -O-C(O), -C(O)-O-, -NR^2-, -NR^2-C(O)-, -C(O)-NH-, o $S(O)_2$;

en donde Z representa hidrógeno, alquilo C_{1-6}, NR^2R^3, ciano o una parte monocíclica o bicíclica fusionada que comprende 4 a 12 átomos constitutivos del anillo de los cuales opcionalmente uno, dos o tres son heteroátomos seleccionados entre N, O, y S, y en donde dicha parte monocíclica o bicíclica fusionada está opcionalmente sustituida con uno o más sustituyentes seleccionados del grupo integrado por halógeno, ciano, alquilo C_{1-6}, hidroxilo, y alcoxi C_{1-6}, pirazinilo, fenilo, piridilo, y fenilo sustituido con halógeno;

en donde R^2 y R^3 independientemente representan hidrógeno, alquilo C_{1-6}, hidroxi-alquilo C_{1-6}, halo-alquilo C_{1-6} o fenilo. Ejemplos de dicha parte monocíclica que tiene 5 átomos constitutivos del anillo incluyen pirrol, 2H-pirrol, pirazol, isotiazol, pirrolidina, pirrolina, tetrazol, imidazolidina, imidazolina, pirazolidina y pirazolina.

En una realización en donde los compuestos de la presente invención se definen mediante la fórmula I_a, X representa una parte monocíclica que tiene 6 átomos constitutivos del anillo uno de los cuales es nitrógeno, y en donde uno, dos o tres átomos constitutivos del anillo, adicionalmente, pueden ser heteroátomos seleccionados entre N, O y S, y en donde dicha parte monocíclica puede estar opcionalmente

sustituida con uno o más sustituyentes W, en donde W se selecciona entre hidrógeno, hidroxi, halógeno, ciano, (=O), -O-$(CH_2)_c$-O-, en donde c es 2 o 3 (espiro), $(CH_2)_d$, en donde d es 5 o 6 (espiro), alquilo C_{1-6}, alcoxi C_{1-6}, -C(O)-alquilo C_{1-6}, -C(O)-O-alquilo C_{1-6}, -O-C(O)-alquilo C_{1-6}, -O-C(O)-, -C(O)H, COOH; o en donde W representa una parte de la fórmula $-(CH_2)_a$-Y-$(CH_2)_b$-Z;

en donde a y b independientemente representan un número entero seleccionado entre 0, 1, 2 y 3;

en donde Y representa un enlace, C(O), O, S, -O-C(O), -C(O)-O-, $-NR^2$-, $-NR^2$-C(O)-, -C(O)-NH-, o $S(O)_2$;

en donde Z representa hidrógeno, alquilo C_{1-6}, NR^2R^3, ciano o una parte monocíclica o bicíclica fusionada que comprende 4 a 12 átomos constitutivos del anillo de los cuales opcionalmente uno, dos o tres son heteroátomos seleccionados entre N, O, y S, y en donde dicha parte monocíclica o bicíclica fusionada está opcionalmente sustituida con uno o más sustituyentes seleccionados del grupo integrado por halógeno, ciano, alquilo C_{1-6}, hidroxilo, y alcoxi C_{1-6}, pirazinilo, fenilo, piridilo, y fenilo sustituido con halógeno;

en donde R^2 y R^3 independientemente representan hidrógeno, alquilo C_{1-6}, hidroxi-alquilo C_{1-6}, halo-alquilo C_{1-6} o fenilo. Ejemplos de dicha parte monocíclica que tiene 6 átomos constitutivos del anillo incluyen piridina, pirazina, pirimidina, piridazina, piperidina, piperazina dihidropiridina, tetrahidropiridina, y morfolina.

En una realización, en donde los compuestos de la presente invención se definen mediante la fórmula I_a, X representa una parte monocíclica que tiene 7 átomos constitutivos del anillo uno de los cuales es nitrógeno, y en donde uno, dos o tres átomos constitutivos del anillo, adicionalmente, pueden ser heteroátomos seleccionados entre N, O y S, y en donde dicha parte monocíclica puede estar opcionalmente sustituida con uno o más sustituyentes W, en donde W se selecciona entre hidrógeno, hidroxi, halógeno, ciano, (=O), -O-$(CH_2)_c$-O-, en donde c es 2 o 3 (espiro), $(CH_2)_d$, en donde d es 5 o 6 (espiro), alquilo C_{1-6}, alquenilo C_{2-6}, alquinilo C_{2-6}, alcoxi C_{1-6}, -C(O)-alquilo C_{1-6}, -C(O)-O-alquilo C_{1-6}, -O-C(O)-alquilo C_{1-6}, -C(O)H, COOH; o en donde W representa una parte de la fórmula $-(CH_2)_a$-Y-$(CH_2)_b$-Z;

en donde a y b independientemente representan un número entero seleccionado entre 0, 1, 2 y 3;

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en donde Y representa un enlace, C(O), O, S, -O-C(O), -C(O)-O-, -NR^2-, -NR^2-C(O)-, -C(O)-NH-, o $S(O)_2$;

en donde Z representa hidrógeno, alquilo C_{1-6}, NR^2R^3, ciano o una parte monocíclica o bicíclica fusionada que comprende 4 a 12 átomos constitutivos del anillo de los cuales opcionalmente uno, dos o tres son heteroátomos seleccionados entre N, O, y S, y en donde dicha parte monocíclica o bicíclica fusionada está opcionalmente sustituida con uno o más sustituyentes seleccionados del grupo integrado por halógeno, ciano, alquilo C_{1-6}, hidroxilo, y alcoxi C_{1-6}, pirazinilo, fenilo, piridilo, y fenilo sustituido con halógeno;

en donde R^2 y R^3 independientemente representan hidrógeno, alquilo C_{1-6}, hidroxi-alquilo C_{1-6}, halo-alquilo C_{1-6} o fenilo. Ejemplos de tal parte monocíclica que tiene 7 átomos constitutivos del anillo incluyen azepan, [1,4]diazepan y 2,3,4,5-tetrahidro-1H-[1,4]diazepan.

En una realización en donde compuestos de la presente invención se definen mediante la fórmula I_a, X representa una parte monocíclica o bicíclico que tiene 8 átomos constitutivos del anillo uno de los cuales es nitrógeno, y en donde uno, dos o tres átomos constitutivos del anillo, adicionalmente, pueden ser heteroátomos seleccionados entre N, O y S, y en donde dicha parte cíclica o bicíclica puede estar opcionalmente sustituida con uno o más sustituyentes W, en donde W se selecciona entre hidrógeno, hidroxi, halógeno, ciano, (=O), -O-$(CH_2)_c$-O-, en donde c es 2 o 3 (espiro), $(CH_2)_d$, en donde d es 5 o 6 (espiro), alquilo C_{1-6}, alcoxi C_{1-6}, -C(O)-alquilo C_{1-6}, -C(O)-O-alquilo C_{1-6}, -O-C(O)-alquilo C_{1-6}, -C(O)H, COOH; o en donde W representa una parte de la fórmula –$(CH_2)_a$-Y-$(CH_2)_b$-Z;

en donde a y b independientemente representan un número entero seleccionado entre 0, 1, 2 y 3;

en donde Y representa un enlace, C(O), O, S, -O-C(O), -C(O)-O-, -NR^2-, -NR^2-C(O)-, -C(O)-NH-, o $S(O)_2$;

en donde Z representa hidrógeno, alquilo C_{1-6}, NR^2R^3, ciano o una parte monocíclica o bicíclica fusionada que comprende 4 a 12 átomos constitutivos del anillo de los cuales opcionalmente uno, dos o tres son heteroátomos seleccionados entre N, O, y S, y en donde dicha parte monocíclica o bicíclica fusionada está opcionalmente sustituida con uno o más sustituyentes seleccionados del grupo integrado por halógeno,

ciano, alquilo C_{1-6}, hidroxilo, y alcoxi C_{1-6}, pirazinilo, fenilo, piridilo, y fenilo sustituido con halógeno;

en donde R^2 y R^3 independientemente representan hidrógeno, alquilo C_{1-6}, hidroxi-alquilo C_{1-6}, halo alquilo C_{1-6} o fenilo. Ejemplos de tal parte monocíclica o bicíclica que tiene 8 átomos constitutivos del anillo incluyen quinuclidina, 8-aza-biciclo[3.2.1]octano y 2-aza-biciclo[2.2.2]octano.

En una realización en donde los compuestos de la presente invención se definen mediante la fórmula I_a, X representa una parte monocíclica o bicíclica que tiene 9 átomos constitutivos del anillo uno de los cuales es nitrógeno, y en donde uno, dos o tres átomos constitutivos del anillo, adicionalmente, pueden ser heteroátomos seleccionados entre N, O y S, y en donde dicha parte monocíclica o bicíclica puede estar opcionalmente sustituida con uno o más sustituyentes W, en donde W se selecciona entre hidrógeno, hidroxi, halógeno, ciano, (=O), -O-$(CH_2)_c$-O-, en donde c es 2 o 3 (espiro), $(CH_2)_d$, en donde d es 5 o 6 (espiro), alquilo C_{1-6}, alcoxi C_{1-6}, -C(O)-alquilo C_{1-6}, -C(O)-O-alquilo C_{1-6}, -O-C(O)-alquilo C_{1-6}, -C(O)H, COOH; o en donde W representa una parte de la fórmula –$(CH_2)_a$-Y-$(CH_2)_b$-Z;

en donde a y b independientemente representan un número entero seleccionado entre 0, 1, 2 y 3;

en donde Y representa un enlace, C(O), O, S, -O-C(O), -C(O)-O-, -NR^2-, -NR^2-C(O)-, -C(O)-NH-, o $S(O)_2$;

en donde Z representa hidrógeno, alquilo C_{1-6}, NR^2R^3, ciano o una parte monocíclica o bicíclica fusionada que comprende 4 a 12 átomos constitutivos del anillo de los cuales opcionalmente uno, dos o tres son heteroátomos seleccionados entre N, O, y S, y en donde dicha parte monocíclica o bicíclica fusionada está opcionalmente sustituida con uno o más sustituyentes seleccionados del grupo integrado por halógeno, ciano, alquilo C_{1-6}, hidroxilo, y alcoxi C_{1-6}, pirazinilo, fenilo, piridilo, y fenilo sustituido con halógeno;

en donde R^2 y R^3 independientemente representan hidrógeno, alquilo C_{1-6}, alquenilo C_{2-6}, alquinilo C_{2-6}, hidroxi-alquilo C_{1-6}, halo-alquilo C_{1-6} o fenilo. Ejemplos de tal parte monocíclica o bicíclica que tiene 9 átomos constitutivos del anillo incluyen indolizina, isoindol, 3H-indol, indol, 1H-indazol, purina, indolina, e isoindolina.

En una realización en donde los compuestos de la presente invención se definen mediante la fórmula I_a, X representa una parte monocíclica o bicíclica que tiene 10 átomos constitutivos del anillo uno de los cuales es nitrógeno, y en donde uno, dos o tres átomos constitutivos del anillo, adicionalmente, pueden ser heteroátomos seleccionados entre N, O y S, y en donde dicha parte monocíclica o bicíclica puede estar opcionalmente sustituida con uno o más sustituyentes W, en donde W se selecciona entre hidrógeno, hidroxi, halógeno, ciano, (=O), -O-$(CH_2)_c$-O-, en donde c es 2 o 3 (espiro), $(CH_2)_d$, en donde d es 5 o 6 (espiro), alquilo C_{1-6}, alcoxi C_{1-6}, -C(O)-alquilo C_{1-6}, -C(O)-O-alquilo C_{1-6}, -O-C(O)-alquilo C_{1-6}, -C(O)H, COOH; o en donde W representa una parte de la fórmula $-(CH_2)_a$-Y-$(CH_2)_b$-Z;

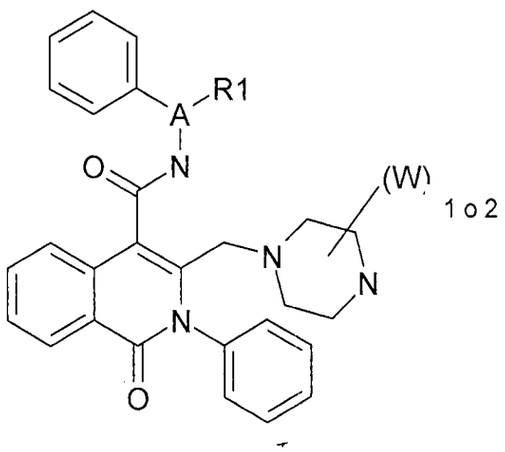
en donde a y b independientemente representan un número entero seleccionado entre 0, 1, 2 y 3;

en donde Y representa un enlace, C(O), O, S, -O-C(O), -C(O)-O-, -NR^2-, -NR^2-C(O)-, -C(O)-NH-, o $S(O)_2$;

en donde Z representa hidrógeno, alquilo C_{1-6}, NR^2R^3, ciano o una parte monocíclica o bicíclica fusionada que comprende 4 a 12 átomos constitutivos del anillo de los cuales opcionalmente uno, dos o tres son heteroátomos seleccionados entre N, O, y S, y en donde dicha parte monocíclica o bicíclica fusionada está opcionalmente sustituida con uno o más sustituyentes seleccionados del grupo integrado por halógeno, ciano, alquilo C_{1-6}, hidroxilo, y alcoxi C_{1-6}, pirazinilo, fenilo, piridilo, y fenilo sustituido con halógeno;

en donde R^2 y R^3 independientemente representan hidrógeno, alquilo C_{1-6}, hidroxi-alquilo C_{1-6}, halo-alquilo C_{1-6} o fenilo. Ejemplos de tal parte monocíclica o bicíclica que tiene 10 átomos constitutivos del anillo incluyen 4H-quinolizina, isoquinolina, quinolina, ftalazina, naftiridina, quinoxalina, cinnolina, pterridina, 1,2,3,4-tetrahidro-isoquinolona, 1,4,8-triaza-espiro[4.5]decano y 1,2,3,4-tetrahidro-quinolina.

En una realización, los compuestos de la presente invención se definen mediante la fórmula I_b



[Ib]

en donde A representa N, CH o CR^1;

en donde cada R^1 independientemente representa hidrógeno, alquilo C_{1-6}, -C(O)-alquilo C_{1-6}, C(O)-O-alquilo C_{1-6}, o fenilo, en donde dicho fenilo, o alquilo C_{1-6} está opcionalmente sustituido con uno o más sustituyentes seleccionados entre halógeno, hidroxilo, halo-alquilo C_{1-6}, nitro, alcoxi C_{1-6}, y NR^2R^3;

en donde W se selecciona entre hidrógeno, hidroxi, halógeno, ciano, (=O), -O-$(CH_2)_c$-O-, en donde c es 2 o 3 (espiro), $(CH_2)_d$, en donde d es 5 o 6 (espiro), alquilo C_{1-6}, alcoxi C_{1-6}, -C(O)-alquilo C_{1-6}, -C(O)-O-alquilo C_{1-6}, -O-C(O)-alquilo C_{1-6}, -C(O)H, COOH; o en donde W representa una parte de la fórmula $–(CH_2)_a$-Y-$(CH_2)_b$-Z;

en donde a y b independientemente representan un número entero seleccionado entre 0, 1, 2 y 3;

en donde Y representa un enlace, C(O), O, S, -O-C(O), -C(O)-O-, $-NR^2$-, $-NR^2$-C(O)-, -C(O)-NH-, o $S(O)_2$;

en donde Z representa hidrógeno, alquilo C_{1-6}, NR^2R^3, ciano o una parte monocíclica o bicíclica fusionada que comprende 4 a 12 átomos constitutivos del anillo de los cuales opcionalmente uno, dos o tres son heteroátomos seleccionados entre N, O, y S, y en donde dicha parte monocíclica o bicíclica fusionada está opcionalmente sustituida con uno o más sustituyentes seleccionados del grupo integrado por halógeno, ciano, alquilo C_{1-6}, hidroxilo, y alcoxi C_{1-6}, pirazinilo, fenilo, piridilo, y fenilo sustituido con halógeno;

en donde R^2 y R^3 independientemente representan hidrógeno, alquilo C_{1-6}, hidroxi-alquilo C_{1-6}, halo-alquilo C_{1-6} o fenilo; y sus sales aceptables para uso

farmacéutico. En particular, A representa CH, y R^1 representa alquilo C_{1-6}, tal como etilo o ciclopropilo.

En una realización en donde los compuestos de la presente invención se definen mediante la fórmula I_b, W representa una parte de la fórmula $-(CH_2)_a-Y-(CH_2)_b-Z$;

en donde a y b independientemente representan un número entero seleccionado entre 0, 1, 2 y 3;

en donde Y representa un enlace, C(O), O, S, -O-C(O), -C(O)-O-, $-NR^2-$, $-NR^2-$C(O)-, -C(O)-NH-, o $S(O)_2$;

en donde Z representa hidrógeno, alquilo C_{1-6}, NR^2R^3, ciano o una parte monocíclica o bicíclica fusionada que comprende 4 a 12 átomos constitutivos del anillo de los cuales opcionalmente uno, dos o tres son heteroátomos seleccionados entre N, O, y S, y en donde dicha parte monocíclica o bicíclica fusionada está opcionalmente sustituida con uno o más sustituyentes seleccionados del grupo integrado por halógeno, ciano, alquilo C_{1-6}, hidroxilo, y alcoxi C_{1-6}, pirazinilo, fenilo, piridilo, y fenilo sustituido con halógeno;

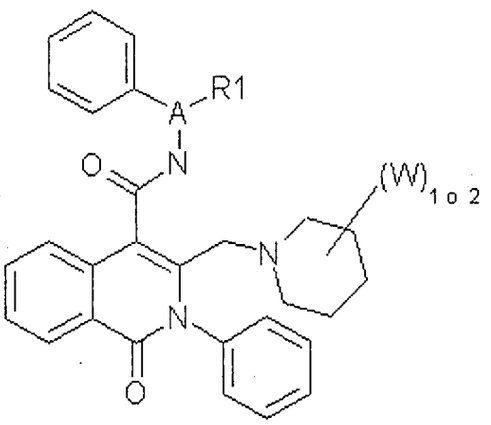
en donde R^2 y R^3 independientemente representan hidrógeno, alquilo C_{1-6}, hidroxi-alquilo C_{1-6}, halo-alquilo C_{1-6} o fenilo. En otra realización, Y representa un enlace, C(O) o $S(O)_2$; en donde a+b es 0, 1, 2, 3, o 4; y en donde Z representa una parte monocíclica o bicíclica fusionada que comprende 5 a 12 átomos constitutivos del anillo de carbono y opcionalmente uno, dos o tres heteroátomos seleccionados entre N, O, y S, y en donde dicha parte cíclica o bicíclica está opcionalmente sustituida con uno o más sustituyentes seleccionados del grupo integrado por halógeno, ciano, alquilo C_{1-6}, hidroxilo, y alcoxi C_{1-6}, fenilo, pirazinilo, piridilo, y fenilo sustituido con halógeno. Se hace particular mención de la realización, en donde Y representa un enlace o C(O), y a+b es 0, 1, 2, o 3. En particular, Z comprende 5 a 9 átomos constitutivos del anillo, tales como por ej. 5, 6, o 9 átomos constitutivos del anillo. Ejemplos de Z con 5 átomos constitutivos del anillo incluyen pirrolida y ciclopentilo; ejemplos de Z con 6 átomos constitutivos del anillo incluyen fenilo, pirimidinilo, morfolinilo y piridilo; ejemplos de Z con 9 átomos constitutivos del anillo incluyen furo [3.2-c]piridilo. Un ejemplo particular de Z es morfolinilo, por ej. unido al resto de la parte W mediante el nitrógeno, y opcionalmente sustituida con uno o más sustituyentes seleccionados del grupo integrado por halógeno, ciano, alquilo C_{1-6}, hidroxilo, y alcoxi C_{1-6}, fenilo, pirazinilo,

piridilo, y fenilo sustituido con halógeno. Otro ejemplo particular de Z es piperidilo, por ej. unido al resto de la parte W por el nitrógeno, y opcionalmente sustituido con uno o más sustituyentes seleccionados del grupo integrado por halógeno, ciano, alquilo C_{1-6}, hidroxilo, y alcoxi C_{1-6}, fenilo, pirazinilo, piridilo, y fenilo sustituido con halógeno. Otro ejemplo particular de Z es piridilo, por ej. unido al resto de la parte W por el nitrógeno. Otro ejemplo particular de Z es piridilo, por ej. unido al resto de la parte W en la posición 2, 3 o 4, y opcionalmente sustituida con uno o más sustituyentes seleccionados del grupo integrado por halógeno, ciano, alquilo C_{1-6}, hidroxilo, y alcoxi C_{1-6}, pirazinilo, fenilo, piridilo, y fenilo sustituido con halógeno. Otro ejemplo particular de Z es fenilo, opcionalmente sustituido con uno o más sustituyentes seleccionados del grupo integrado por halógeno, ciano, alquilo C_{1-6}, hidroxilo, y alcoxi C_{1-6}, fenilo, pirazinilo, piridilo, y fenilo sustituido con halógeno. Otro ejemplo particular de Z es pirrolidinilo, opcionalmente sustituido con uno o más sustituyentes seleccionados del grupo integrado por halógeno, ciano, alquilo C_{1-6}, hidroxilo, y alcoxi C_{1-6}, pirazinilo, fenilo, piridilo, y fenilo sustituido con halógeno. Otro ejemplo particular de Z es indolilo, por ej. unido al resto de la parte W en la posición 4, 5, 6 o 7, y opcionalmente sustituida con uno o más sustituyentes seleccionados del grupo integrado por halógeno, ciano, alquilo C_{1-6}, hidroxilo, y alcoxi C_{1-6}, fenilo, pirazinilo, piridilo, y fenilo sustituido con halógeno. Otros ejemplos particulares de Z incluyen ciclopentilo, furopiridilo, tetrahidrofuranilo, benzo[1.4]oxazinilo, benzo[1.4]dioxinilo, benzo[1.2.5]tiadiazol, y quinazolinilo.

En una realización en donde los compuestos de la presente invención se definen mediante la fórmula I_b, Y representa un enlace, C(O), -C(O)-O-, C(O)-NH-, -O-, o $S(O)_2$; a+b es 0, 1, 2, 3 o 4; y en donde Z representa hidrógeno, alquilo C_{1-6}, tales como metilo, iso-propilo, iso-butilo, o ter-butilo, NR^2R^3 o ciano.

En una realización en donde los compuestos de la presente invención se definen mediante la fórmula I_b, A representa CH; R^1 representa alquilo C_{1-6}, tal como etilo o ciclopropilo, W se selecciona entre hidrógeno, hidroxi, halógeno, ciano, (=O), -O-$(CH_2)_c$-O-, en donde c es 2 o 3 (espiro), $(CH_2)_d$, en donde d es 5 o 6 (espiro), C_{1-6}alquilo, C_{1-6}alcoxi, -C(O)-C_{1-6}alquilo, -C(O)-O-C_{1-6}alquilo, -O-C(O)-C_{1-6}alquilo, -C(O)H, COOH.

En una realización los compuestos de la presente invención se definen mediante la fórmula I_c



[Ic]

en donde A representa N, CH o CR^1;

en donde cada R^1 independientemente representa hidrógeno, alquilo C_{1-6}, -C(O)-alquilo C_{1-6}, C(O)-O-alquilo C_{1-6}, o fenilo, en donde dicho fenilo, o alquilo C_{1-6} está opcionalmente sustituido con uno o más sustituyentes seleccionados entre halógeno, hidroxilo, halo-alquilo C_{1-6}, nitro, alcoxi C_{1-6}, y NR^2R^3;

en donde W se selecciona entre hidrógeno, hidroxi, halógeno, ciano, (=O), -O-$(CH_2)_c$-O-, en donde c es 2 o 3 (espiro), $(CH_2)_d$, en donde d es 5 o 6 (espiro), alquilo C_{1-6}, alcoxi C_{1-6}, -C(O)-alquilo C_{1-6}, -C(O)-O-alquilo C_{1-6}, -O-C(O)-alquilo C_{1-6}, -C(O)H, COOH; o en donde W representa una parte de la fórmula $–(CH_2)_a$-Y-$(CH_2)_b$-Z;

en donde a y b independientemente representan un número entero seleccionado entre 0, 1, 2 y 3;

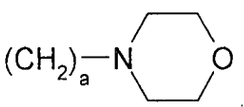
en donde Y representa un enlace, C(O), O, S, -O-C(O), -C(O)-O-, $-NR^2$-, $-NR^2$-C(O)-, -C(O)-NH-, o $S(O)_2$;

en donde Z representa hidrógeno, alquilo C_{1-6}, NR^2R^3, ciano o una parte monocíclica o bicíclica fusionada que comprende 4 a 12 átomos constitutivos del anillo de los cuales opcionalmente uno, dos o tres son heteroátomos seleccionados entre N, O, y S, y en donde dicha parte monocíclica o bicíclica fusionada está opcionalmente sustituida con uno o más sustituyentes seleccionados del grupo integrado por halógeno, ciano, alquilo C_{1-6}, hidroxilo, y alcoxi C_{1-6}, pirazinilo, fenilo, piridilo, y fenilo sustituido con halógeno;

en donde R^2 y R^3 independientemente representan hidrógeno, alquilo C_{1-6}, hidroxi-alquilo C_{1-6}, halo-alquilo C_{1-6} o fenilo; y sus sales aceptables para uso

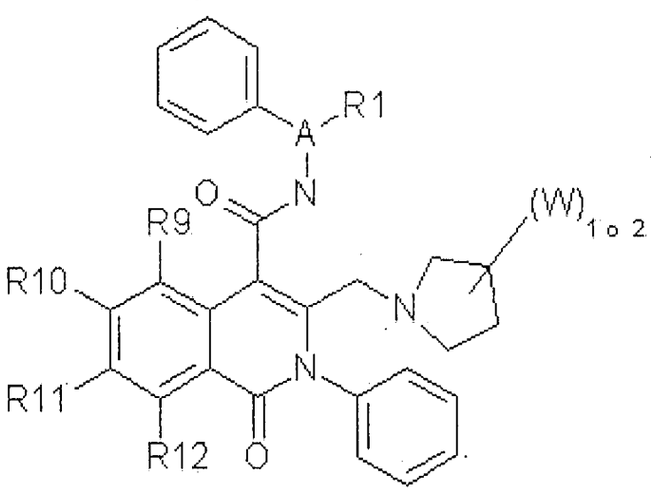
farmacéutico. En particular, A representan CH, y R^1 representa alquilo C_{1-6}, tales como etilo o ciclopropilo.

En una realización en donde los compuestos de la presente invención se definen mediante la fórmula I_c, W independientemente representa hidrógeno, hidroxilo, fenilo, fenilo sustituido con alcoxi C_{1-6}, piperidilo, piridilo, $-O-(CH_2)_c-O-$, en donde c es 2 o 3 (espiro), $N(CH_3)_2$, alquilo C_{1-6}, $-(CH_2)_a-C(O)-O-(CH_2)_b-H$, en donde a+b es 1, 2, o 3, o



; en donde a representa 1, 2, o 3.

En una realización, los compuestos de la presente invención se definen mediante la fórmula I_d



[Id]

en donde A representa N, CH o CR^1;

en donde cada R^1 independientemente representa hidrógeno, alquilo C_{1-6}, -C(O)-alquilo C_{1-6}, C(O)-O-alquilo C_{1-6}, o fenilo, en donde dicho fenilo, o alquilo C_{1-6} está opcionalmente sustituido con uno o más sustituyentes seleccionados entre halógeno, hidroxilo, halo-alquilo C_{1-6}, nitro, alcoxi C_{1-6}, y NR^2R^3;

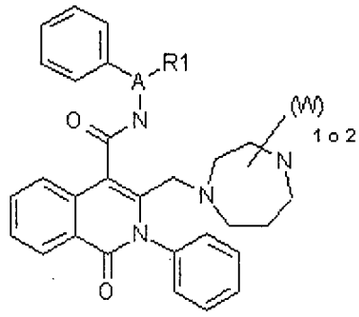
en donde W se selecciona entre hidrógeno, hidroxi, halógeno, ciano, (=O), $-O-(CH_2)_c-O-$, en donde c es 2 o 3 (espiro), $(CH_2)_d$, en donde d es 5 o 6 (espiro), alquilo C_{1-6}, alcoxi C_{1-6}, -C(O)-alquilo C_{1-6}, -C(O)-O-alquilo C_{1-6}, -O-C(O)-alquilo C_{1-6}, -C(O)H, COOH;

en donde R^2 y R^3 independientemente representan hidrógeno, alquilo C_{1-6}, hidroxi-alquilo C_{1-6}, halo-alquilo C_{1-6} o fenilo; en donde R^9-R^{12} independientemente representan hidrógeno o halógeno; y sus sales aceptables para uso farmacéutico. En

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particular, A es CH; R^1 representa alquilo C_{1-6}, tal como etilo o ciclopropilo; y cada uno de R^9-R^{12} independientemente representa hidrógeno o halógeno.

En una realización, los compuestos de la presente invención se definen según la fórmula I_e



[Ie]

en donde A representa N, CH o CR^1;

en donde cada R^1 independientemente representa hidrógeno, alquilo C_{1-6}, -C(O)-alquilo C_{1-6}, C(O)-O-alquilo C_{1-6}, o fenilo, en donde dicho fenilo, o alquilo C_{1-6} está opcionalmente sustituido con uno o más sustituyentes seleccionados entre halógeno, hidroxilo, halo-alquilo C_{1-6}, nitro, alcoxi C_{1-6}, y NR^2R^3;

en donde W se selecciona entre hidrógeno, hidroxi, halógeno, ciano, (=O), -O-$(CH_2)_c$-O-, en donde c es 2 o 3 (espiro), $(CH_2)_d$, en donde d es 5 o 6 (espiro), alquilo C_{1-6}, alcoxi C_{1-6}, -C(O)-alquilo C_{1-6}, -C(O)-O-alquilo C_{1-6}, -O-C(O)-alquilo C_{1-6}, -C(O)H, COOH; o en donde W representa una parte de la fórmula $-(CH_2)_a$-Y-$(CH_2)_b$-Z;

en donde *a* y b independientemente representan un número entero seleccionado entre 0, 1, 2 y 3;

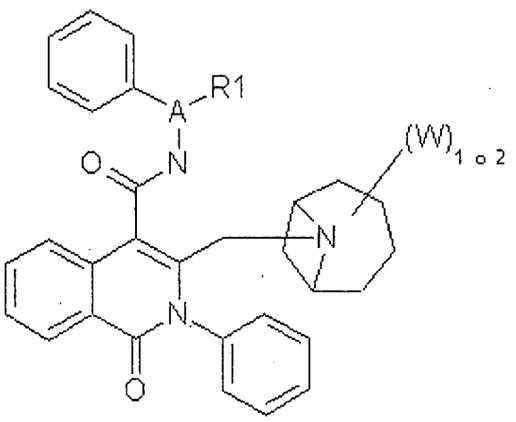
en donde Y representa un enlace, C(O), O, S, -O-C(O), -C(O)-O-, NR^2, -NR^2-C(O)-, -C(O)-NH-, o $S(O)_2$;

en donde Z representa hidrógeno, alquilo C_{1-6}, NR^2R^3, ciano o una parte monocíclica o bicíclica fusionada que comprende 4 a 12 átomos constitutivos del anillo de los cuales opcionalmente uno, dos o tres son heteroátomos seleccionados entre N, O, y S, y en donde dicha parte monocíclica o bicíclica fusionada está opcionalmente sustituida con uno o más sustituyentes seleccionados del grupo integrado por halógeno, ciano, alquilo C_{1-6}, hidroxilo, y alcoxi C_{1-6}, pirazinilo, fenilo, piridilo, y fenilo sustituido con halógeno;

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en donde R^2 y R^3 independientemente representan hidrógeno, alquilo C_{1-6}, hidroxi-alquilo C_{1-6}, halo-alquilo C_{1-6} o fenilo; y sus sales aceptables para uso farmacéutico. En particular, A es CH, y R^1 representa alquilo C_{1-6}, tal como etilo o ciclopropilo. En particular, Z comprende 5 a 9 átomos constitutivos del anillo, tales como por ej. 5, 6, o 9 átomos constitutivos del anillo. Ejemplos de Z con 5 átomos constitutivos del anillo incluyen pirrolida y ciclopentilo; ejemplos de Z con 6 átomos constitutivos del anillo incluyen fenilo, pirimidinilo, morfolinilo y piridilo; ejemplos de Z con 9 átomos constitutivos del anillo incluyen furo [3.2-c]piridilo.

En una realización, los compuestos de la presente invención se definen mediante la fórmula I_f



[If]

en donde A representa N, CH o CR^1;

en donde cada R^1 independientemente representa hidrógeno, alquilo C_{1-6}, -C(O)-alquilo C_{1-6}, C(O)-O-alquilo C_{1-6}, o fenilo, en donde dicho fenilo, o alquilo C_{1-6} está opcionalmente sustituido con uno o más sustituyentes seleccionados entre halógeno, hidroxilo, halo-alquilo C_{1-6}, nitro, alcoxi C_{1-6}, y NR^2R^3;

en donde W se selecciona entre hidrógeno, hidroxi, halógeno, ciano, (=O), -O-$(CH_2)_c$-O-, en donde c es 2 o 3 (espiro), $(CH_2)_d$, en donde d es 5 o 6 (espiro), alquilo C_{1-6}, alcoxi C_{1-6}, -C(O)-alquilo C_{1-6}, -C(O)-O-alquilo C_{1-6}, -O-C(O)-alquilo C_{1-6}, -C(O)H, COOH; o en donde W representa una parte de la fórmula $-(CH_2)_a$-Y-$(CH_2)_b$-Z;

en donde a y b independientemente representan un número entero seleccionado entre 0, 1, 2 y 3;

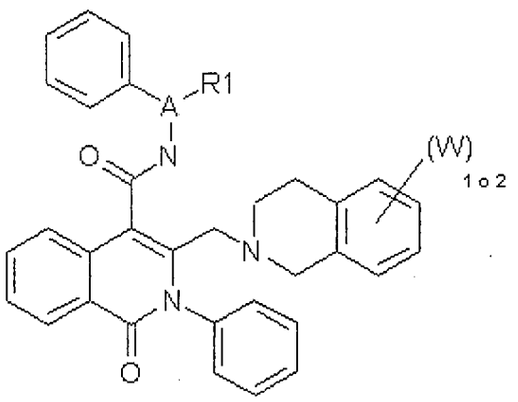
en donde Y representa un enlace, C(O), O, S, -O-C(O), -C(O)-O-, NR^2, -NR^2-C(O)-, -C(O)-NH-, o $S(O)_2$;

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en donde Z representa hidrógeno, alquilo C_{1-6}, NR^2R^3, ciano o una parte monocíclica o bicíclica fusionada que comprende 4 a 12 átomos constitutivos del anillo de los cuales opcionalmente uno, dos o tres son heteroátomos seleccionados entre N, O, y S, y en donde dicha parte monocíclica o bicíclica fusionada está opcionalmente sustituida con uno o más sustituyentes seleccionados del grupo integrado por halógeno, ciano, alquilo C_{1-6}, hidroxilo, y alcoxi C_{1-6}, pirazinilo, fenilo, piridilo, y fenilo sustituido con halógeno;

en donde R^2 y R^3 -independientemente representan hidrógeno, alquilo C_{1-6}, hidroxi-alquilo C_{1-6}, halo-alquilo C_{1-6} o fenilo; y sus sales aceptables para uso farmacéutico. En particular, A es CH, y R^1 representa alquilo C_{1-6}, tales como etilo o ciclopropilo. En particular, Z comprende 5 a 9 átomos constitutivos del anillo, tales como por ej. 5, 6, o 9 átomos constitutivos del anillo. Ejemplos de Z con 5 átomos constitutivos del anillo incluyen pirrolida y ciclopentilo; ejemplos de Z con 6 átomos constitutivos del anillo incluyen fenilo, pirimidinilo, morfolinilo y piridilo; ejemplos de Z con 9 átomos constitutivos del anillo incluyen furo [3.2-c]piridilo.

En una realización, los compuestos de la presente invención se definen mediante la fórmula I_g



[Ig] en

donde A representa N, CH o CR^1;

en donde cada R^1 independientemente representa hidrógeno, alquilo C_{1-6}, -C(O)-alquilo C_{1-6}, C(O)-O-alquilo C_{1-6}, o fenilo, en donde dicho fenilo, o C_{1-6}alquilo está opcionalmente sustituido con uno o más sustituyentes seleccionados entre halógeno, hidroxilo, halo-alquilo C_{1-6}, nitro, alcoxi C_{1-6}, y NR^2R^3;

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en donde W se selecciona entre hidrógeno, hidroxi, halógeno, ciano, (=O), -O-$(CH_2)_c$-O-, en donde c es 2 o 3 (espiro), $(CH_2)_d$, en donde d es 5 o 6 (espiro), alquilo C_{1-6}, alcoxi C_{1-6}, -C(O)-alquilo C_{1-6}, -C(O)-O-alquilo C_{1-6}, -O-C(O)-alquilo C_{1-6}, -N(R^2)-C(O)-R^3, -C(O)H, COOH; o en donde W representa una parte de la fórmula –$(CH_2)_a$-Y-$(CH_2)_b$-Z;

en donde a y b independientemente representan un número entero seleccionado entre 0, 1, 2 y 3;

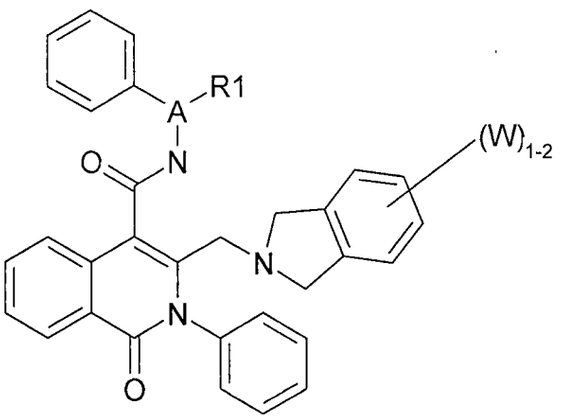
en donde Y representa un enlace, C(O), O, S, -O-C(O), -C(O)-O-, NR^2, -NR^2-C(O)-, -C(O)-NH-, o $S(O)_2$;

en donde Z representa hidrógeno, alquilo C_{1-6}, NR^2R^3, ciano o una parte monocíclica o bicíclica fusionada que comprende 4 a 12 átomos constitutivos del anillo de los cuales opcionalmente uno, dos o tres son heteroátomos seleccionados entre N, O, y S, y en donde dicha parte monocíclica o bicíclica fusionada está opcionalmente sustituida con uno o más sustituyentes seleccionados del grupo integrado por halógeno, ciano, alquilo C_{1-6}, hidroxilo, y alcoxi C_{1-6}, pirazinilo, fenilo, piridilo, y fenilo sustituido con halógeno;

en donde R^2 y R^3 independientemente representan hidrógeno, alquilo C_{1-6}, hidroxi-alquilo C_{1-6}, halo-alquilo C_{1-6} o fenilo; y sus sales aceptables para uso farmacéutico. En particular, A es CH, y R^1 representa alquilo C_{1-6}, tal como etilo o ciclopropilo. En particular, Z comprende 5 a 9 átomos constitutivos del anillo, tales como por ej. 5, 6, o 9 átomos constitutivos del anillo. Ejemplos de Z con 5 átomos constitutivos del anillo incluyen pirrolida y ciclopentilo; ejemplos de Z con 6 átomos constitutivos del anillo incluyen fenilo, pirimidinilo, morfolinilo y piridilo; ejemplos de Z con 9 átomos constitutivos del anillo incluyen furo [3.2-c]piridilo.

En una realización, los compuestos de la presente invención se definen mediante la fórmula I_h

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$[I_h]$

en donde A representa N, CH o CR^1;

en donde cada R^1 independientemente representa hidrógeno, alquilo C_{1-6}, -C(O)-alquilo C_{1-6}, C(O)-O-alquilo C_{1-6}, o fenilo, en donde dicho fenilo, o alquilo C_{1-6} está opcionalmente sustituido con uno o más sustituyentes seleccionados entre halógeno, hidroxilo, halo-alquilo C_{1-6}, nitro, alcoxi C_{1-6}, y NR^2R^3;

en donde W se selecciona entre hidrógeno, hidroxi, halógeno, ciano, (=O), -O-$(CH_2)_c$-O-, en donde c es 2 o 3 (espiro), $(CH_2)_d$, en donde d es 5 o 6 (espiro), alquilo C_{1-6}, alcoxi C_{1-6}, -C(O)-alquilo C_{1-6}, -C(O)-O-alquilo C_{1-6}, -O-C(O)-alquilo C_{1-6}, -C(O)H, COOH; o en donde W representa una parte de la fórmula $-(CH_2)_a$-Y-$(CH_2)_b$-Z;

en donde a y b independientemente representan un número entero seleccionado entre 0, 1, 2 y 3;

en donde Y representa un enlace, C(O), O, S, -O-C(O), -C(O)-O-, NR^2, -NR^2-C(O)-, -C(O)-NH-, o $S(O)_2$;

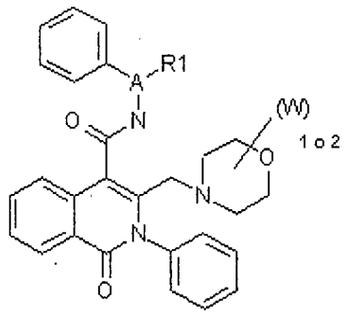
en donde Z representa hidrógeno, alquilo C_{1-6}, NR^2R^3, ciano o una parte monocíclica o bicíclica fusionada que comprende 4 a 12 átomos constitutivos del anillo de los cuales opcionalmente uno, dos o tres son heteroátomos seleccionados entre N, O, y S, y en donde dicha parte monocíclica o bicíclica fusionada está opcionalmente sustituida con uno o más sustituyentes seleccionados del grupo integrado por halógeno, ciano, alquilo C_{1-6}, hidroxilo, y alcoxi C_{1-6}, pirazinilo, fenilo, piridilo, y fenilo sustituido con halógeno;

en donde R^2 y R^3 independientemente representan hidrógeno, alquilo C_{1-6}, hidroxi-alquilo C_{1-6}, halo-alquilo C_{1-6} o fenilo; y sus sales aceptables para uso farmacéutico. En particular, A es CH, y R^1 representa C_{1-6}alquilo, tales como etilo o ciclopropilo. En particular, Z comprende 5 a 9 átomos constitutivos del anillo, tales como

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por ej. 5, 6, o 9 átomos constitutivos del anillo. Ejemplos de Z con 5 átomos constitutivos del anillo incluyen pirrolida y ciclopentilo; ejemplos de Z con 6 átomos constitutivos del anillo incluyen fenilo, pirimidinilo, morfolinilo y piridilo; ejemplos de Z con 9 átomos constitutivos del anillo incluyen furo [3.2-c]piridilo.

En una realización, los compuestos de la presente invención se definen mediante la fórmula I_i



[Ii]

en donde A representa N, CH o CR^1;

en donde cada R^1 independientemente representa hidrógeno, alquilo C_{1-6}, -C(O)-alquilo C_{1-6}, C(O)-O-alquilo C_{1-6}, o fenilo, en donde dicho fenilo, o alquilo C_{1-6} está opcionalmente sustituido con uno o más sustituyentes seleccionados entre halógeno, hidroxilo, halo-alquilo C_{1-6}, nitro, alcoxi C_{1-6}, y NR^2R^3;

en donde W se selecciona entre hidrógeno, hidroxi, halógeno, ciano, (=O), -O-$(CH_2)_c$-O-, en donde c es 2 o 3 (espiro), $(CH_2)_d$, en donde d es 5 o 6 (espiro), alquilo C_{1-6}, alcoxi C_{1-6}, -C(O)-alquilo C_{1-6}, -C(O)-O-alquilo C_{1-6}, -O-C(O)-alquilo C_{1-6}, -C(O)H, COOH; o en donde X representa una parte de la fórmula $-(CH_2)_a$-Y-$(CH_2)_b$-Z;

en donde a y b independientemente representan un número entero seleccionado entre 0, 1, 2 y 3;

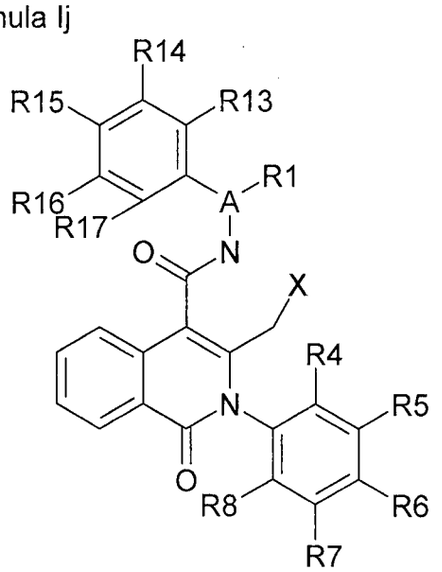
en donde Y representa un enlace, C(O), O, S, -O-C(O), -C(O)-O-, NR^2, -NR^2-C(O)-, -C(O)-NH-, o $S(O)_2$;

en donde Z representa hidrógeno, alquilo C_{1-6}, NR^2R^3, ciano o una parte monocíclica o bicíclica fusionada que comprende 4 a 12 átomos constitutivos del anillo de los cuales opcionalmente uno, dos o tres son heteroátomos seleccionados entre N, O, y S, y en donde dicha parte monocíclica o bicíclica fusionada está opcionalmente sustituida con uno o más sustituyentes seleccionados del grupo integrado por halógeno,

ciano, alquilo C_{1-6}, hidroxilo, y alcoxi C_{1-6}, pirazinilo, fenilo, piridilo, y fenilo sustituido con halógeno;

en donde R^2 y R^3 independientemente representan hidrógeno, alquilo C_{1-6}, hidroxi-alquilo C_{1-6}, halo-alquilo C_{1-6} o fenilo; y sus sales aceptables para uso farmacéutico. En particular, A es CH, y R^1 representa C_{1-6}alquilo, tales como etilo o ciclopropilo. En particular, Z comprende 5 a 9 átomos constitutivos del anillo, tales como por ej. 5, 6, o 9 átomos constitutivos del anillo. Ejemplos de Z con 5 átomos constitutivos del anillo incluyen pirrolida y ciclopentilo; ejemplos de Z con 6 átomos constitutivos del anillo incluyen fenilo, pirimidinilo, morfolinilo y piridilo; ejemplos de Z con 9 átomos constitutivos del anillo incluyen furo [3.2-c]piridilo.

En una realización, los compuestos de la presente invención se definen mediante la fórmula Ij



[Ij]

en donde A representa N, CH o CR^1;

en donde cada R^1 independientemente representa hidrógeno, alquilo C_{1-6}, -C(O)-alquilo C_{1-6}, -C(O)-O-alquilo C_{1-6}, o fenilo, en donde dicho fenilo o alquilo C_{1-6} está opcionalmente sustituido con uno o más sustituyentes seleccionados entre halógeno, hidroxilo, halo-alquilo C_{1-6}, nitro, alcoxi C_{1-6}, y NR^2R^3;

en donde X representa hidrógeno, alquilo C_{1-6}, ciano, $-OR^2$, $-O-C(O)R^2$, $-OC(O)NR^2R^3$, $-C(O)-NR^2R^3$, $-N(R^2)C(O)R^3$, $-N(R^2)-C(O)NR^2R^3$ o NR^2R^3, o X representa una parte monocíclica, bicíclica o tricíclica que tiene 4 a 16 átomos constitutivos del anillo uno de los cuales es nitrógeno, y en donde uno, dos o tres átomos constitutivos del anillo, adicionalmente, pueden ser heteroátomos seleccionados entre N, O y S, y en

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donde dicha parte monocíclica, bicíclica o tricíclica puede estar opcionalmente sustituida con uno o más sustituyentes W, en donde W se selecciona entre hidrógeno, hidroxi, halógeno, ciano, (=O), -O-$(CH_2)_c$-O-, en donde c es 2 o 3 (espiro), $(CH_2)_d$, en donde d es 5 o 6 (espiro), alquilo C_{1-6}, alcoxi C_{1-6}, -C(O)-alquilo C_{1-6}, -C(O)-O-alquilo C_{1-6}, -O-C(O)-alquilo C_{1-6}, -C(O)H, COOH; o en donde W representa una parte de la fórmula $-(CH_2)_a$-Y-$(CH_2)_b$-Z;

en donde a y b independientemente representan un número entero seleccionado entre 0, 1, 2 y 3;

en donde Y representa un enlace, C(O), O, S, -O-C(O), -C(O)-O-, $-NR^2$-, $-NR^2$-C(O)-, -C(O)-NH-, o $S(O)_2$;

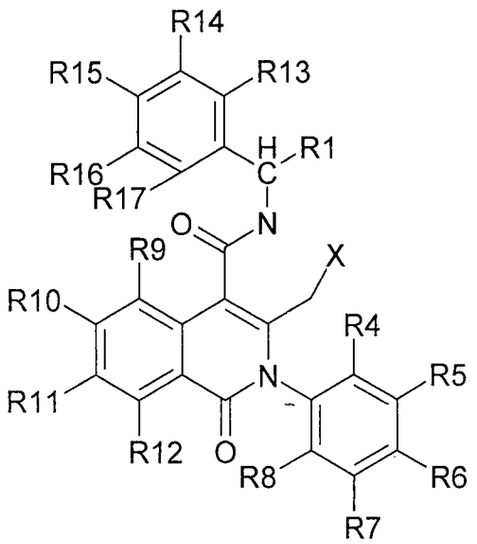
en donde Z representa hidrógeno, alquilo C_{1-6}, NR^2R^3, ciano o una parte monocíclica o bicíclica fusionada que comprende 4 a 12 átomos constitutivos del anillo de los cuales opcionalmente uno, dos o tres son heteroátomos seleccionados entre N, O, y S, y en donde dicha parte monocíclica o bicíclica fusionada está opcionalmente sustituida con uno o más sustituyentes seleccionados del grupo integrado por halógeno, ciano, alquilo C_{1-6}, hidroxilo, y alcoxi C_{1-6}, fenilo, piridilo, y fenilo sustituido con halógeno;

en donde uno entre R^4-R^8 representa halógeno y el otro representan hidrógeno; en donde uno entre R^{13}-R^{17} representa halógeno y el otro representan hidrógeno;

en donde R^2 y R^3 independientemente representan hidrógeno, alquilo C_{1-6}, hidroxi-alquilo C_{1-6}, halo-alquilo C_{1-6} o fenilo; y sus sales aceptables para uso farmacéutico. En particular, A representa CH; R^1 representa alquilo C_{1-6}, tales como etilo o ciclopropilo; R^{14} representa halógeno; y R^5 o R^8 representa halógeno. Se hace particular mención de la realización en donde X representa piperazinilo o 1-piperidilo sustituido con uno o dos sustituyentes W, en donde dicho W es una parte de la fórmula $-(CH_2)_a$-Y-$(CH_2)_b$-Z, en donde a y b independientemente representan 0, 1, 2 o 3; Y representa un enlace, O, $-NR^2$-C(O)-; y en donde Z representa hidrógeno, alquilo C_{1-6}, piperidilo, morfolinilo, piridilo, fenilo, fenilo sustituido con alcoxi C_{1-6}, o pirrolidinilo.

En una realización, los compuestos de la invención se definen mediante la fórmula I_k

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[Ik]

en donde R^1 representa hidrógeno, alquilo C_{1-6}, alquenilo C_{2-6} o alquinilo C_{2-6};

en donde X representa hidrógeno, alquilo C_{1-6}, alquenilo C_{2-6}, alquinilo C_{2-6} o NR^2R^3, o X representa una parte monocíclica o bicíclica que tiene 5 a 9 átomos constitutivos del anillo uno de los cuales es nitrógeno, y en donde uno, dos o tres átomos constitutivos del anillo, adicionalmente, pueden ser heteroátomos seleccionados entre N, O y S, y en donde dicha una parte monocíclica o bicíclica puede estar opcionalmente sustituida con uno o más sustituyentes W, en donde W se selecciona entre hidrógeno, halógeno, hidroxi, (=O), alquilo C_{1-6}, alquenilo C_{2-6}, alquinilo C_{2-6}, C_{1-6}alcoxi, o en donde W representa una parte de la fórmula $-(CH_2)_a$-Y-$(CH_2)_b$-Z;

en donde a y b independientemente representan un número entero seleccionado entre 0, 1, 2 y 3;

en donde Y representa un enlace, y en donde Z representa una parte monocíclica que comprende 5 a 6 átomos constitutivos del anillo de los cuales opcionalmente uno, dos o tres son heteroátomos seleccionados entre N, O, y S, y en donde dicha parte monocíclica está opcionalmente sustituida con uno o más sustituyentes seleccionados del grupo integrado por halógeno, alquilo C_{1-6}, hidroxilo, y alcoxi C_{1-6};

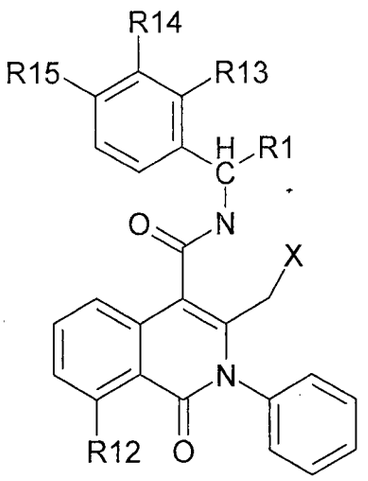
en donde cada uno entre R^4-R^8 independientemente representa hidrógeno o halógeno;

en donde cada uno entre R^9-R^{12} independientemente representa hidrógeno o halógeno siempre que al menos uno de R^9-R^{12} represente halógeno;

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en donde cada uno entre R^{13}-R^{17} independientemente representa hidrógeno o halógeno;

en donde R^2 y R^3 independientemente representan hidrógeno, alquilo C_{1-6}, alquenilo C_{2-6}, alquinilo C_{2-6}; y sus sales aceptables para uso farmacéutico. En particular, los compuestos definidos por la fórmula I_k además pueden estar definidos por la fórmula I_k'



[Ik']

en donde R^1 se selecciona de alquilo C_{1-6};

en donde X se selecciona entre hidrógeno, alquilo C_{1-6} o NR^2R^3, o X representa una parte monocíclica o bicíclica que tiene 5 a 9 átomos constitutivos del anillo uno de los cuales es nitrógeno, y en donde uno de los átomos constitutivos del anillo, adicionalmente, pueden ser heteroátomos seleccionados de N, y en donde dicha parte monocíclica o bicíclica puede estar opcionalmente sustituida con uno o más sustituyentes W, en donde W se selecciona entre hidrógeno, hidroxi, (=O), alquilo C_{1-6} o en donde W representa una parte de la fórmula $-(CH_2)_a$-Y-$(CH_2)_b$-Z;

en donde a y b independientemente representan un número entero seleccionado entre 0, 1, 2 y 3;

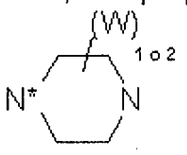
en donde Y representa un enlace, y en donde Z representa una parte monocíclica que comprende 5 a 6 átomos constitutivos del anillo de los cuales opcionalmente uno es un heteroátomo seleccionado entre N, O, y S, y en donde dicha parte monocíclica está opcionalmente sustituida con uno o más sustituyentes seleccionados del grupo integrado por halógeno, alquilo C_{1-6}, hidroxilo, y alcoxi C_{1-6};

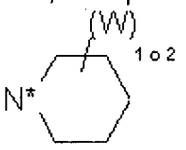
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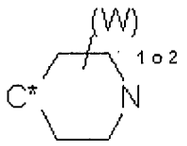
en donde R^{12} representa halógeno;

R^{13}-R^{15} cada uno independientemente representa hidrógeno o halógeno;

y sus sales aceptables para uso farmacéutico. En particular, R^1 representa metilo, etilo, ciclopropilo, ciclobutilo, ciclopentilo o ciclohexilo, y X representa



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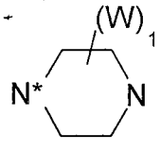
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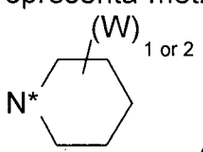

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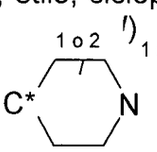
$-NR^2R^3$, o Hidrógeno

* indica el punto de unión

En una realización, en donde los compuestos de la invención se definen mediante la fórmula I_k' y R^1 representa metilo, etilo, ciclopropilo, ciclobutilo, ciclopentilo o ciclohexilo, X representa 

1 o 2 , y en donde W representa hidrógeno, (=O), alquilo C_{1-6}, o $-(CH_2)_a$-Y-$(CH_2)_b$-Z. En particular, W representa hidrógeno, metilo, ciclopropilmetilo, isopropilo, isobutilo, ter-butilo, (=O), o $-(CH_2)_a$-Y-$(CH_2)_a$-Z, en donde a+b es 2 y Z se selecciona de 4-morfolinilo, fenilo, 1-piperidina o 1-pirrolidinilo.

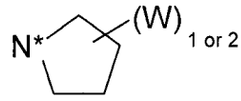
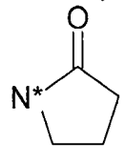
En una realización, en donde los compuestos de la invención se definen mediante la fórmula I_k' y R^1 representa metilo, etilo, ciclopropilo, ciclobutilo, ciclopentilo o ciclohexilo, X representa 

o 

1 o 2 , en donde W representa hidrógeno, hidroxilo, alquilo C_{1-6} o $-(CH_2)_a$-Y-$(CH_2)_a$-Z. En particular, W representa hidrógeno, hidroxilo, ter-butilo, o a+b es 0 o 2 y Z representa 4-morfolinilo, fenilo, opcionalmente sustituido con C_{1-6}alcoxi, o 4-piperidilo.

En una realización, en donde los compuestos de la invención se definen mediante la fórmula I_k' y R^1 representa metilo, etilo, ciclopropilo, ciclobutilo, ciclopentilo
1 o 2

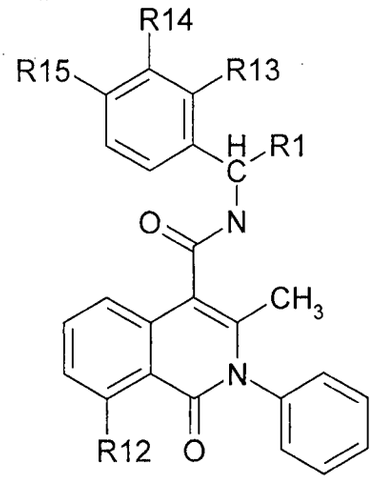
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o ciclohexilo, X representan  , y W representa (=O), y en particular, X representa  .

En una realización, en donde los compuestos de la invención se definen mediante la fórmula I_k' y R^1 representa metilo, etilo, ciclopropilo, ciclobutilo, ciclopentilo o ciclohexilo, X representa $-NR^2R^3$. En particular, R^2 y R^3 independientemente representa hidrógeno o alquilo C_{1-6}, y especial mención se hace de los compuestos en donde R^2 representa hidrógeno, y R^3 representa ciclopropilo, isobutilo o ter-butilo.

En una realización, en donde los compuestos de la invención se definen mediante la fórmula I_k' y R^1 representa metilo, etilo, ciclopropilo, ciclobutilo, ciclopentilo o ciclohexilo, X es hidrógeno.

En una realización, los compuestos de la invención se definen mediante la fórmula I_k"



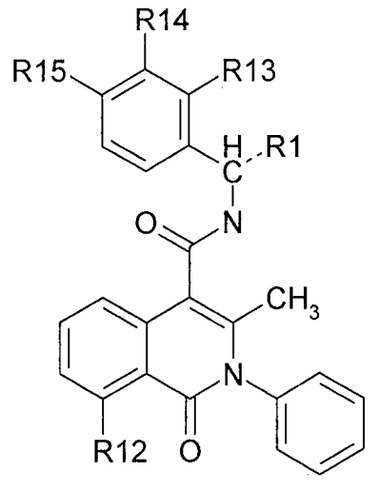
[Ik"]

en donde R^1 representa etilo, ciclopropilo o ciclobutilo;

en donde R^{12} representa flúor o cloro; y

R^{13}, R^{14} y R^{15} cada uno individualmente representa hidrógeno, flúor o cloro, en donde dos entre R^{13}, R^{14} y R^{15} representan hidrógeno, y sus sales aceptables para uso farmacéutico. En particular, dicho compuesto es esencialmente los enantiómeros S como se describe en la fórmula I_k"'

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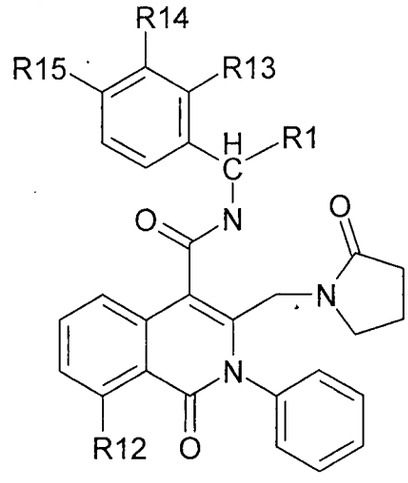
[Ik'"]

en donde R^1 representa etilo o ciclopropilo;

en donde R^{12} representa flúor o cloro; y

R^{13}, R^{14} y R^{15} cada uno individualmente representa hidrógeno, flúor o cloro, en donde dos entre R^{13}, R^{14} y R^{15} representan hidrógeno.

En una realización, los compuestos de la invención se definen mediante la fórmula I_d'



[Id']

en donde R^1 representa etilo o ciclopropilo;

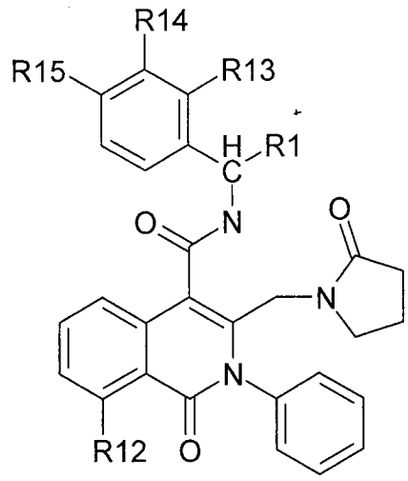
R^{12} representa halógeno;

R^{13}, R^{14} y R15 cada uno independientemente representa hidrógeno, o halógeno;

y sus sales aceptables para uso farmacéutico.

En una realización, los compuestos de la invención se definen mediante la fórmula I_d''

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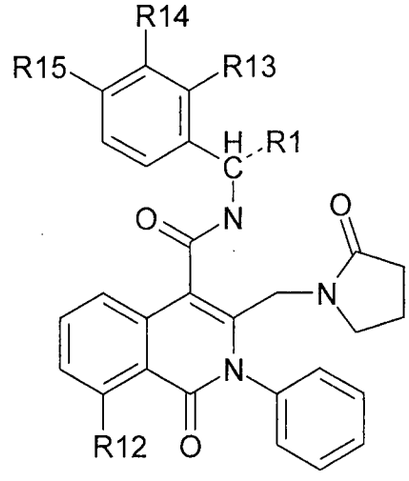
[Id"]

en donde R^1 representa etilo o ciclopropilo;

R^{12} representa cloro o flúor;

R^{12}, R^{14} y R^{15} cada uno independientemente representa hidrógeno, cloro o flúor, en donde dos entre R^{12}, R^{14} y R^{15} representan hidrógeno;

y sus sales aceptables para uso farmacéutico. En particular, dicho compuesto es esencialmente el enantiómero S como se describe en la fórmula Id"'



[Id""]

en donde R^1 representa etilo o ciclopropilo;

R^{12} representa cloro o flúor;

R^{12}, R^{14} y R^{15} cada uno independientemente representa hidrógeno, cloro o flúor, en donde dos entre R^{12}, R^{14} y R^{15} representan hidrógeno;

y sus sales aceptables para uso farmacéutico.

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En una realización los compuestos de la presente invención se seleccionan de la lista a continuación. Por conveniencia, el número indicado en negrita en frente del nombre del compuesto se refiere al número de ejemplo correspondiente.

1a ((S)-1-fenil-propil)-amida del ácido 3-metil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

1b ((S)-1-fenil-propil)-amida del ácido 3,6-dimetil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

1c ((S)-1-fenil-propil)-amida del ácido 7-cloro-3-metil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

1d ((S)-1-fenil-propil)-amida del ácido 7-bromo-3-metil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

1e ((S)-1-fenil-propil)-amida del ácido 6-fluoro-3-metil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

1f ((S)-1-fenil-propil)-amida del ácido 3,5-dimetil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

1g ((S)-1-fenil-propil)-amida del ácido 7-fluoro-3-metil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

1h ((S)-1-fenil-propil)-amida del ácido 3,7-dimetil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

1i ((S)-1-fenil-propil)-amida del ácido 8-cloro-3-metil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

1r ((S)-ciclopropil-fenil-metil)-amida del ácido 3-metil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

1s [(S)-ciclopropil-(3-fluoro-fenil)-metil]-amida del ácido 3-metil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

1j ((S)-1-fenil-propil)-amida del ácido 3,8-dimetil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

1k ((S)-1-fenil-propil)-amida del ácido 2-(2-fluoro-fenil)-3-metil-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico

1l ((S)-1-fenil-propil)-amida del ácido 3-metil-1-oxo-2-o-tolil-1,2-dihidro-isoquinolin-4-carboxílico

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1m ((S)-1-fenil-propil)-amida del ácido 2-(2-cloro-fenil)-3-metil-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico

1n ((S)-1-fenil-propil)-amida del ácido 2-(2,6-difluoro-fenil)-3-metil-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico

1o ((S)-1-fenil-propil)-amida del ácido 2-(3-fluoro-fenil)-3-metil-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico

1p ((S)-1-fenil-propil)-amida del ácido 3-metil-1-oxo-2-m-tolil-1,2-dihidro-isoquinolin-4-carboxílico

1q ((S)-1-fenil-propil)-amida del ácido 2-(3-cloro-fenil)-3-metil-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico

1t [(S)-ciclopropil-(3-fluoro-fenil)-metil]-amida del ácido 8-cloro-3-metil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2a ((S)-1-fenil-propil)-amida del ácido 3-dimetilaminometil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2b ((S)-1-fenil-propil)-amida del ácido 3-metilaminometil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2c ((S)-1-fenil-propil)-amida del ácido 3-etilaminometil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2d ((S)-1-fenil-propil)-amida del ácido 3-ciclopropilaminometil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2e ((S)-1-fenil-propil)-amida del ácido 3-[(ciclopropilmetil-amino)-metil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2f ((S)-1-fenil-propil)-amida del ácido 3-(3,6-dihidro-2H-piridin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2g ((S)-1-fenil-propil)-amida del ácido 3-[4-(2-metoxi-fenil)-piperazin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2h ((S)-1-fenil-propil)-amida del ácido 3-[4-(4-fluoro-fenil)-piperazin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2i ((S)-1-fenil-propil)-amida del ácido 3-(4-formil-piperazin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2j Etil éster del ácido 4-[1-oxo-2-fenil-4-(1-fenil-propilcarbamoil)-1,2-dihidro-isoquinolin-3-ilmetil]-piperazin-1-carboxílico

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2k ((S)-1-fenil-propil)-amida del ácido 3-(4-metil-piperazin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2l ((S)-1-fenil-propil)-amida del ácido 1-oxo-2-fenil-3-(1,3,4,9-tetrahidro-beta-carbolin-2-ilmetil)-1,2-dihidro-isoquinolin-4-carboxílico

2m ((S)-1-fenil-propil)-amida del ácido 1-oxo-2-fenil-3-piperazin-1-ilmetil-1,2-dihidro-isoquinolin-4-carboxílico

2n ((S)-1-fenil-propil)-amida del ácido 3-(3-metil-piperazin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2o ((S)-1-fenil-propil)-amida del ácido 3-(3,5-dimetil-piperazin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2p ((S)-1-fenil-propil)-amida del ácido 3-(4-bencil-piperazin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2q ((S)-1-fenil-propil)-amida del ácido 1-oxo-3-[4-(2-oxo-2-pirrolidin-1-il-etil)-piperazin-1-ilmetil]-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2r ((S)-1-fenil-propil)-amida del ácido 3-morfolin-4-ilmetil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2s ((S)-1-fenil-propil)-amida del ácido 3-(2,6-dimetil-morfolin-4-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2t ((S)-1-fenil-propil)-amida del ácido 1-oxo-2-fenil-3-tiomorfolin-4-ilmetil-1,2-dihidro-isoquinolin-4-carboxílico

2u ((S)-1-fenil-propil)-amida del ácido 3-(1,4-dioxa-8-aza-espiro[4.5]dec-8-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2v ((S)-1-fenil-propil)-amida del ácido 1-oxo-2-fenil-3-piperidin-1-ilmetil-1,2-dihidro-isoquinolin-4-carboxílico

2w ((S)-1-fenil-propil)-amida del ácido 3-(2-metil-piperidin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2x ((S)-1-fenil-propil)-amida del ácido 3-(2,6-dimetil-piperidin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2y ((S)-1-fenil-propil)-amida del ácido 3-(2-hidroximetil-piperidin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2z Etil éster del ácido 1-[1-oxo-2-fenil-4-(1-fenil-propilcarbamoil)-1,2-dihidro-isoquinolin-3-ilmetil]-piperidin-3-carboxílico

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2aa ((S)-1-fenil-propil)-amida del ácido 3-(3-metil-piperidin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2ab ((S)-1-fenil-propil)-amida del ácido 3-(4-hidroxi-piperidin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2ac ((S)-1-fenil-propil)-amida del ácido 1-oxo-2-fenil-3-(4-fenil-piperidin-1-ilmetil)-1,2-dihidro-isoquinolin-4-carboxílico

2ad etil éster del ácido 1-[1-oxo-2-fenil-4-(1-fenil-propilcarbamoil)-1,2-dihidro-isoquinolin-3-ilmetil]-piperidin-4-carboxílico

2ae ((S)-1-fenil-propil)-amida del ácido 3-(4-metil-piperidin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2af ((S)-1-fenil-propil)-amida del ácido 1-oxo-2-fenil-3-(4-piridin-2-il-piperazin-1-ilmetil)-1,2-dihidro-isoquinolin-4-carboxílico

2ag ((S)-1-fenil-propil)-amida del ácido 3-(octahidro-quinolin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2ah ((S)-1-fenil-propil)-amida del ácido 3-azepan-1-ilmetil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2ai ((S)-1-fenil-propil)-amida del ácido 3-(3-hidroxi-piperidin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2aj ((S)-1-fenil-propil)-amida del ácido 3-[4-(2,4-dimetil-fenil)-piperazin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2ak ((S)-1-fenil-propil)-amida del ácido 3-[4-(3,4-dimetil-fenil)-piperazin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2al ((S)-1-fenil-propil)-amida del ácido 3-(4-dimetilamino-piperidin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2am ((S)-1-fenil-propil)-amida del ácido 3-[4-(2,5-dimetil-fenil)-piperazin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2an ((S)-1-fenil-propil)-amida del ácido 3-[4-(2-fluoro-fenil)-piperazin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2ao ((S)-1-fenil-propil)-amida del ácido 3-[4-(3-metoxi-fenil)-piperazin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2ap ((S)-1-fenil-propil)-amida del ácido 1-oxo-2-fenil-3-(4-m-tolil-piperazin-1-ilmetil)-1,2-dihidro-isoquinolin-4-carboxílico

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2aq ((S)-1-fenil-propil)-amida del ácido 3-[4-(4-metoxi-fenil)-piperazin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2ar ((S)-1-fenil-propil)-amida del ácido 1-oxo-3-(4-fenetil-piperazin-1-ilmetil)-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2as ((S)-1-fenil-propil)-amida del ácido 1-oxo-2-fenil-3-(4-pirimidin-2-il-piperazin-1-ilmetil)-1,2-dihidro-isoquinolin-4-carboxílico

2at ((S)-1-fenil-propil)-amida del ácido 3-[4-(2-ciano-fenil)-piperazin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2au ((S)-1-fenil-propil)-amida del ácido 3-[4-(4-cloro-fenil)-piperazin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2av ((S)-1-fenil-propil)-amida del ácido 3-((1S,3R,5R)-3-hidroxi-8-aza-biciclo[3.2.1]oct-8-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2aw ((S)-1-fenil-propil)-amida del ácido 3-(4-acetil-piperazin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2ax ((S)-1-fenil-propil)-amida del ácido 3-(4-metil-[1,4]diazepan-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2ay ((S)-1-fenil-propil)-amida del ácido 3-(4-etil-piperazin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2az ((S)-1-fenil-propil)-amida del ácido 3-((2S,6R)-2,6-dimetil-morfolin-4-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2ba ((S)-1-fenil-propil)-amida del ácido 3-[4-(2,4-difluoro-fenil)-piperazin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2bb ((S)-1-fenil-propil)-amida del ácido 3-[4-(3-dimetilamino-propil)-piperazin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2bc ((S)-1-fenil-propil)-amida del ácido 3-(4-isopropil-piperazin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2bd ((S)-1-fenil-propil)-amida del ácido 3-(3-aza-biciclo[3.2.2]non-3-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2be ((S)-1-fenil-propil)-amida del ácido 3-(4-ciclopentil-piperazin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2bf ((S)-1-fenil-propil)-amida del ácido 3-[1,4']bipiperidinil-1'-ilmetil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

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2bg ((S)-1-fenil-propil)-amida del ácido 3-(3,4-dihidro-1H-isoquinolin-2-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2bh ((S)-1-fenil-propil)-amida del ácido 3-[4-(2-dimetilamino-etil)-piperazin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2bi ((S)-1-fenil-propil)-amida del ácido 3-(4-hidroximetil-piperidin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2bj ((S)-1-fenil-propil)-amida del ácido 1-oxo-2-fenil-3-[4-(tetrahidro-furan-2-carbonil)-piperazin-1-ilmetil]-1,2-dihidro-isoquinolin-4-carboxílico

2bk ((S)-1-fenil-propil)-amida del ácido 3-(4-isobutil-piperazin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2bl ((S)-1-fenil-propil)-amida del ácido 3-[4-(2-metoxi-etil)-piperazin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2bm ((S)-1-fenil-propil)-amida del ácido 3-[4-(2-morfolin-4-il-etil)-piperazin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2bn ((S)-1-fenil-propil)-amida del ácido 3-(1,3-dihidro-isoindol-2-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2bo ((S)-1-fenil-propil)-amida del ácido 3-[4-(1-metil-piperidin-4-il)-piperazin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2bp ((S)-1-fenil-propil)-amida del ácido 1-oxo-2-fenil-3-[4-(2-piperidin-1-il-etil)-piperazin-1-ilmetil]-1,2-dihidro-isoquinolin-4-carboxílico

2bq ((S)-1-fenil-propil)-amida del ácido 1-oxo-2-fenil-3-[4-(2-pirrolidin-1-il-etil)-piperazin-1-ilmetil]-1,2-dihidro-isoquinolin-4-carboxílico

2br ((S)-1-fenil-propil)-amida del ácido 3-(4-dimetilcarbamoilmetil-piperazin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2bs ((S)-1-fenil-propil)-amida del ácido 3-(octahidro-pirido[1,2-a]pirazin-2-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2bt ((S)-1-fenil-propil)-amida del ácido 3-(4-formil-[1,4]diazepan-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2bu ((S)-1-fenil-propil)-amida del ácido 3-[4-(4-ciano-fenil)-piperazin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2bv ((S)-1-fenil-propil)-amida del ácido 1-oxo-2-fenil-3-(4-piridin-4-ilmetil-piperazin-1-ilmetil)-1,2-dihidro-isoquinolin-4-carboxílico

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2bw ((S)-1-fenil-propil)-amida del ácido 1-oxo-2-fenil-3-[4-(3-pirrolidin-1-il-propil)-piperazin-1-ilmetil]-1,2-dihidro-isoquinolin-4-carboxílico

2bx ((S)-1-fenil-propil)-amida del ácido 1-oxo-2-fenil-3-(4-piridin-2-ilmetil-piperazin-1-ilmetil)-1,2-dihidro-isoquinolin-4-carboxílico

2by ((S)-1-fenil-propil)-amida del ácido 3-(4-etansulfonil-piperazin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2bz ((S)-1-fenil-propil)-amida del ácido 3-(4-sec-butil-piperazin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2ca ((S)-1-fenil-propil)-amida del ácido 3-[4-(1-etil-propil)-piperazin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2cb ((S)-1-fenil-propil)-amida del ácido 3-[4-(2-ciano-etil)-piperazin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2cc ((S)-1-fenil-propil)-amida del ácido 3-(4-metansulfonil-piperazin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2cd Etil éster del ácido {1-[1-oxo-2-fenil-4-(1-fenil-propilcarbamoil)-1,2-dihidro-isoquinolin-3-ilmetil]-piperidin-4-il}-acético

2ce ((S)-1-fenil-propil)-amida del ácido 3-[4-(3-fluoro-fenil)-piperazin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2cf ((S)-1-fenil-propil)-amida del ácido 1-oxo-2-fenil-3-((S)-3-fenil-piperidin-1-ilmetil)-1,2-dihidro-isoquinolin-4-carboxílico

2cg ((S)-1-fenil-propil)-amida del ácido 1-oxo-2-fenil-3-[4-(pirrolidin-1-carbonil)-piperazin-1-ilmetil]-1,2-dihidro-isoquinolin-4-carboxílico

2ch ((S)-1-fenil-propil)-amida del ácido 3-[4-(morfolin-4-carbonil)-piperazin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2ci ((S)-1-fenil-propil)-amida del ácido 3-(4-metoxi-piperidin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2cj ((S)-1-fenil-propil)-amida del ácido 3-(4'-hidroxi-3',4',5',6'-tetrahidro-2'H-[3,4']bipiridinil-1'-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2ck ((S)-1-fenil-propil)-amida del ácido 3-(4-hidroxi-3,4,5,6-tetrahidro-2H-[4,4']bipiridinil-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2cl ((S)-1-fenil-propil)-amida del ácido 3-(3H-espiro[isobenzofuran-1,4'-piperidin]-1'-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

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2cm ((S)-1-fenil-propil)-amida del ácido 3-(4-hidroxi-4-metil-piperidin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2cn ((S)-1-fenil-propil)-amida del ácido 3-(hexahidro-espiro[benzo[1,3]dioxol-2,4'-piperidin]-1'-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2co ((S)-1-fenil-propil)-amida del ácido 1-oxo-2-fenil-3-(3,4,5,6-tetrahidro-2H-[4,4']bipiridinil-1-ilmetil)-1,2-dihidro-isoquinolin-4-carboxílico

2cp ((S)-1-fenil-propil)-amida del ácido 3-[4-(2-dimetilamino-etil)-piperidin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2cq ((S)-1-fenil-propil)-amida del ácido 3-(4-dimetilosulfamoil-piperazin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2cr ((S)-1-fenil-propil)-amida del ácido 3-(1,1-dioxo-tiomorfolin-4-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2cs ((S)-1-fenil-propil)-amida del ácido 1-oxo-2-fenil-3-(2-piridin-2-ilmetil-piperidin-1-ilmetil)-1,2-dihidro-isoquinolin-4-carboxílico

2ct ((S)-1-fenil-propil)-amida del ácido 3-(2-morfolin-4-ilmetil-piperidin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2cu ((S)-1-fenil-propil)-amida del ácido 3-(4-furo[3,2-c]piridin-4-il-piperazin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2cv ((S)-1-fenil-propil)-amida del ácido 3-(4-ciclopropilmetil-piperazin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2cw ((S)-1-fenil-propil)-amida del ácido 3-[4-(2-morfolin-4-il-etil)-piperidin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2cx ((S)-1-fenil-propil)-amida del ácido 1-oxo-2-fenil-3-(4-pirimidin-2-il-[1,4]diazepan-1-ilmetil)-1,2-dihidro-isoquinolin-4-carboxílico

2cy ((S)-1-fenil-propil)-amida del ácido 3-(4-metil-6,7-dihidro-4H-tieno[3,2-c]piridin-5-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2cz ((S)-1-fenil-propil)-amida del ácido 3-[1,4]diazepan-1-ilmetil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2da ((S)-1-fenil-propil)-amida del ácido 3-((2S,5R)-2,5-dimetil-piperazin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2db ((S)-1-fenil-propil)-amida del ácido 3-((S)-3-metil-piperazin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

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2dc ((S)-1-fenil-propil)-amida del ácido 3-((R)-3-metil-piperazin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2dd ((S)-1-fenil-propil)-amida del ácido 3-[3-(3-cloro-fenil)-piperazin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2de ((S)-1-fenil-propil)-amida del ácido 3-[4-(1H-Indol-4-il)-piperazin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2df ((S)-1-fenil-propil)-amida del ácido 1-oxo-3-(3-oxo-piperazin-1-ilmetil)-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2dg ((S)-1-fenil-propil)-amida del ácido 3-[4-(1H-Indol-5-il)-piperazin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2dh ((S)-1-fenil-propil)-amida del ácido 3-(6,9-diaza-espiro[4.5]dec 9-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2di ((S)-1-fenil-propil)-amida del ácido 3-(1,4-diaza-espiro[5.5]undec-4-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2dj ((S)-1-fenil-propil)-amida del ácido 3-(3-isopropil-piperazin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2dk ((S)-1-fenil-propil)-amida del ácido 3-(3,3-dimetil-piperazin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2dl ((S)-1-fenil-propil)-amida del ácido 3-[3-(4-fluoro-fenil)-piperazin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2dm ((S)-1-fenil-propil)-amida del ácido 1-oxo-2-fenil-3-(3-p-tolil-piperazin-1-ilmetil)-1,2-dihidro-isoquinolin-4-carboxílico

2dn Ter-butil éster del ácido 4-[1-oxo-2-fenil-4-(1-fenil-propilcarbamoil)-1,2-dihidro-isoquinolin-3-ilmetil]-piperazin-1-carboxílico

2do ((S)-1-fenil-propil)-amida del ácido 3-(4-metilcarbamoilmetil-piperazin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2dp ((S)-1-fenil-propil)-amida del ácido 8-cloro-3-dimetilaminometil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2dr ((S)-1-fenil-propil)-amida del ácido 3-ciclopentilaminometil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2ds ((S)-1-fenil-propil)-amida del ácido 3-ciclohexilaminometil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

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2dt ((S)-1-fenil-propil)-amida del ácido 3-{[(2-hidroxi-etil)-metil-amino]-metil}-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2du ((S)-1-fenil-propil)-amida del ácido 3-imidazol-1-ilmetil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2dv ((S)-1-fenil-propil)-amida del ácido 3-(2-metil-imidazol-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2dw ((S)-1-fenil-propil)-amida del ácido 3-(4-metil-imidazol-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2dx ((S)-1-fenil-propil)-amida del ácido 3-(2,5-dihidro-pirrol-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2dy ((S)-1-fenil-propil)-amida del ácido 3-(2,5-dimetil-2,5-dihidro-pirrol-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2dz ((S)-1-fenil-propil)-amida del ácido 1-oxo-2-fenil-3-pirrolidin-1-ilmetil-1,2-dihidro-isoquinolin-4-carboxílico

2ea ((S)-1-fenil-propil)-amida del ácido 1-oxo-2-fenil-3-(tiazol-2-ilaminometil)-1,2-dihidro-isoquinolin-4-carboxílico

2eb ((S)-1-fenil-propil)-amida del ácido 1-oxo-2-fenil-3-(pirimidin-4-ilaminometil)-1,2-dihidro-isoquinolin-4-carboxílico

2ec ((S)-1-fenil-propil)-amida del ácido 3-(ter-butilamino-metil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2ed ((S)-1-fenil-propil)-amida del ácido 3-[(2-hidroxi-1,1-dimetil-etilamino)-metil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2ee ((S)-1-fenil-propil)-amida del ácido 3-(isopropilamino-metil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2ef ((S)-1-fenil-propil)-amida del ácido 3-[(2-hidroxi-1-metil-etilamino)-metil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2eg ((S)-1-fenil-propil)-amida del ácido 3-[(1-hidroximetil-propilamino)-metil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2eh ((S)-1-fenil-propil)-amida del ácido 3-[(2,2-dimetil-propilamino)-metil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2ei ((S)-1-fenil-propil)-amida del ácido 1-oxo-2-fenil-3-prop-2-inilaminometil-1,2-dihidro-isoquinolin-4-carboxílico

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2ej ((S)-1-fenil-propil)-amida del ácido 3-aliloaminometil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2ek ((S)-1-fenil-propil)-amida del ácido 3-[(metil-prop-2-inil-amino)-metil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2el ((S)-1-fenil-propil)-amida del ácido 3-dialiloaminometil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2em ((S)-1-fenil-propil)-amida del ácido 3-dietilaminometil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2en ((S)-1-fenil-propil)-amida del ácido 3-[(isopropil-metil-amino)-metil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2eo ((S)-1-fenil-propil)-amida del ácido 3-[((S)-2-hidroxi-1-metil-etilamino)-metil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2ep ((S)-1-fenil-propil)-amida del ácido 3-[((R)-2-hidroxi-1-metil-etilamino)-metil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2eq ((S)-1-fenil-propil)-amida del ácido 3-{[(2-metoxi-etil)-metil-amino]-metil}-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2er ((S)-1-fenil-propil)-amida del ácido 3-((R)-3-hidroxi-pirrolidin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2es ((S)-1-fenil-propil)-amida del ácido 3-((S)-3-hidroxi-pirrolidin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2et ((S)-1-fenil-propil)-amida del ácido 3-[(ciclopentil-metil-amino)-metil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2eu ((S)-1-fenil-propil)-amida del ácido 3-{[(2-hidroxi-1-metil-etil)-metil-amino]-metil}-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2ev ((S)-1-fenil-propil)-amida del ácido 3-{[etil-(2-hidroxi-etil)-amino]-metil}-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2ew ((S)-1-fenil-propil)-amida del ácido 3-[(etil-metil-amino)-metil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2ex ((S)-1-fenil-propil)-amida del ácido 3-ciclobutilaminometil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2ey ((S)-1-fenil-propil)-amida del ácido 3-azetidin-1-ilmetil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

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2ez ((S)-1-fenil-propil)-amida del ácido 3-(4-ter-butil-piperazin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2fa ((S)-1-fenil-propil)-amida del ácido 3-[4-(2-hidroxi-etil)-piperazin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2fb ((S)-1-fenil-propil)-amida del ácido 3-{4-[2-(2-hidroxi-etoxi)-etil]-piperazin-1-ilmetil}-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2fc ((S)-1-fenil-propil)-amida del ácido 3-[4-(3-cloro-5-trifluorometil-piridin-2-il)-piperazin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2fd ((S)-1-fenil-propil)-amida del ácido 3-[4-(3,5-dicloro-piridin-4-il)-piperazin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2fe Bencil éster del ácido 4-[1-oxo-2-fenil-4-((S)-1-fenil-propilcarbamoil)-1,2-dihidro-isoquinolin-3-ilmetil]-piperazin-1-carboxílico

2ff ((S)-1-fenil-propil)-amida del ácido 3-[4-(3-morfolin-4-il-propil)-piperazin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2fg ((S)-1-fenil-propil)-amida del ácido 1-oxo-2-fenil-3-[4-(3-piperidin-1-il-propil)-piperazin-1-ilmetil]-1,2-dihidro-isoquinolin-4-carboxílico

2fh ((S)-1-fenil-propil)-amida del ácido 3-[4-(4,6-dimetoxi-pirimidin-2-ilmetil)-piperazin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2fi ((S)-1-fenil-propil)-amida del ácido 3-[4-(3-hidroxi-propil)-piperazin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2fj ((S)-1-fenil-propil)-amida del ácido 3-[4-(2,3-dihidroxi-propil)-piperazin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2fk Ter-butil éster del ácido (2-oxo-2-{4-[1-oxo-2-fenil-4-(1-fenil-propilcarbamoil)-1,2-dihidro-isoquinolin-3-ilmetil]-piperazin-1-il}-etil)-carbámico

2fl ((S)-1-fenil-propil)-amida del ácido 3-[4-(1H-indazol-5-il)-piperazin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2fm ((S)-1-fenil-propil)-amida del ácido 1-oxo-2-fenil-3-(4-quinolin-6-il-piperazin-1-ilmetil)-1,2-dihidro-isoquinolin-4-carboxílico

2fn ((S)-1-fenil-propil)-amida del ácido 3-[4-(6,7-dimetoxi-quinazolin-4-il)-piperazin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2fo Ter-butil éster del ácido 4-{4-[1-oxo-2-fenil-4-(1-fenil-propilcarbamoil)-1,2-dihidro-isoquinolin-3-ilmetil]-piperazin-1-il}-piperidin-1-carboxílico

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2fp ((S)-1-fenil-propil)-amida del ácido 3-{4-[2-(4-cloro-fenoxi)-etil]-piperazin-1-ilmetil}-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2fq Ter-butil éster del ácido {4-[1-oxo-2-fenil-4-(1-fenil-propilcarbamoil)-1,2-dihidro-isoquinolin-3-ilmetil]-piperazin-1-il}-acético

2fr ((S)-1-fenil-propil)-amida del ácido 1-oxo-2-fenil-3-[4-(3,3,3-trifluoro-2-hidroxi-propil)-piperazin-1-ilmetil]-1,2-dihidro-isoquinolin-4-carboxílico

2fs ((S)-1-fenil-propil)-amida del ácido 3-[4-(2-hidroxi-propil)-piperazin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2fu ((S)-1-fenil-propil)-amida del ácido 3-[4-(4-amino-6,7-dimetoxi-quinazolin-2-il)-piperazin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2fv ter-butil éster del ácido (2-{4-[1-oxo-2-fenil-4-(1-fenil-propilcarbamoil)-1,2-dihidro-isoquinolin-3-ilmetil]-piperazin-1-il}-etil)-carbámico

2fw ((S)-1-fenil-propil)-amida del ácido 1-oxo-3-{4-[2-(2-oxo-imidazolidin-1-il)-etil]-piperazin-1-ilmetil}-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2fx ((S)-1-fenil-propil)-amida del ácido 3-{4-[(4,6-dimetoxi-pirimidin-2-il)-fenil-metil]-piperazin-1-ilmetil}-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2fy ((S)-1-fenil-propil)-amida del ácido 3-(4-benzo[1,2,5]tiadiazol-4-il-piperazin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2fz ((S)-1-fenil-propil)-amida del ácido 3-[4-(2,3-dihidro-benzo[1,4]dioxin-5-il)-piperazin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2ga ((S)-1-fenil-propil)-amida del ácido 3-[4-(4-metil-quinolin-2-il)-piperazin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2gb ((S)-1-fenil-propil)-amida del ácido 1-oxo-2-fenil-3-[4-(piridin-2-ilcarbamoilmetil)-piperazin-1-ilmetil]-1,2-dihidro-isoquinolin-4-carboxílico

2gc ((S)-1-fenil-propil)-amida del ácido 3-[4-(6-cloro-3-oxo-3,4-dihidro-2H-benzo[1,4]oxazin-8-il)-piperazin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2gd ((S)-1-fenil-propil)-amida del ácido 3-(4-carbamoilmetil-piperazin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2ge ((S)-1-fenil-propil)-amida del ácido 3-(4-hidroxi-4-fenil-piperidin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

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2gf ((S)-1-fenil-propil)-amida del ácido 3-[4-(4-cloro-fenil)-4-hidroxi-piperidin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2gg Ácido 1-[1-oxo-2-fenil-4-(1-fenil-propilcarbamoil)-1,2-dihidro-isoquinolin-3-ilmetil]-piperidin-4-carboxílico

2gh ((S)-1-fenil-propil)-amida del ácido 3-(4-ciano-4-fenil-piperidin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2gi ((S)-1-fenil-propil)-amida del ácido 3-(4-bencil-4-hidroxi-piperidin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2gj Etil éster del ácido 1-[1-oxo-2-fenil-4-(1-fenil-propilcarbamoil)-1,2-dihidro-isoquinolin-3-ilmetil]-4-fenil-piperidin-4-carboxílico

2gk ((S)-1-fenil-propil)-amida del ácido 1-oxo-2-fenil-3-[4-(fenil-propionil-amino)-piperidin-1-ilmetil]-1,2-dihidro-isoquinolin-4-carboxílico

2gl Ter-butil éster del ácido metil-{1-[1-oxo-2-fenil-4-(1-fenil-propilcarbamoil)-1,2-dihidro-isoquinolin-3-ilmetil]-piperidin-4-il}-carbámico

2gm ((S)-1-fenil-propil)-amida del ácido 1-oxo-2-fenil-3-[4-(2-pirrolidin-1-il-etil)-piperidin-1-ilmetil]-1,2-dihidro-isoquinolin-4-carboxílico

2gn ((S)-1-fenil-propil)-amida del ácido 3-{4-[5-(4-fluoro-fenil)-[1,3,4]oxadiazol-2-il]-piperidin-1-ilmetil}-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2go ((S)-1-fenil-propil)-amida del ácido 1-oxo-2-fenil-3-[4-(3-piridin-4-il-[1,2,4]oxadiazol-5-il)-piperidin-1-ilmetil]-1,2-dihidro-isoquinolin-4-carboxílico

2gp ((S)-1-fenil-propil)-amida del ácido 1-oxo-2-fenil-3-[4-(3-pirazin-2-il-[1,2,4]oxadiazol-5-il)-piperidin-1-ilmetil]-1,2-dihidro-isoquinolin-4-carboxílico

2gq ((S)-1-fenil-propil)-amida del ácido 1-oxo-2-fenil-3-[4-(3-piridin-4-il-[1,2,4]oxadiazol-5-il)-piperidin-1-ilmetil]-1,2-dihidro-isoquinolin-4-carboxílico

2gr ((S)-1-fenil-propil)-amida del ácido 3-(4'-hidroxi-3',4',5',6'-tetrahidro-2'H-[2,4']bipiridinil-1'-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2gs ((S)-1-fenil-propil)-amida del ácido 3-(espiro[isocroman-1,4'-piperidin]-1'-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2gt ((S)-1-fenil-propil)-amida del ácido 3-[4-hidroxi-4-(3-metoxi-fenil)-piperidin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2gu ((S)-1-fenil-propil)-amida del ácido 3-[4-(3-cloro-fenil)-4-hidroxi-piperidin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

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2gv ((S)-1-fenil-propil)-amida del ácido 3-(6-cloro-3H-espiro[isobenzofuran-1,4'-piperidin]-1'-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2gw ((S)-1-fenil-propil)-amida del ácido 3-(4-{[4-cloro-3-(4-fluoro-fenil)-indan-1-il]-metil-amino}-piperidin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2gx ((S)-1-fenil-propil)-amida del ácido 3-(1-acetil-espiro[indolin-3,4'-piperidin]-1'-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2gy ((S)-1-fenil-propil)-amida del ácido 3-(1-acetil-5-fluoro-espiro[indolin-3,4'-piperidin]-1'-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2gz ((S)-1-fenil-propil)-amida del ácido 1-oxo-3-(4-oxo-1-fenil-1,3,8-triaza-espiro[4.5]dec-8-ilmetil)-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2ha ((S)-1-fenil-propil)-amida del ácido 3-(4-acetilamino-piperidin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2hb ((S)-1-fenil-propil)-amida del ácido 1-oxo-3-(1-oxo-2,8-diaza-espiro[4.5]dec-8-ilmetil)-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2hc ((S)-1-fenil-propil)-amida del ácido 3-[4-hidroxi-4-(3-trifluorometil-fenil)-piperidin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2hd ((S)-1-fenil-propil)-amida del ácido 1-oxo-2-fenil-3-(4-trifluorometil-piperidin-1-ilmetil)-1,2-dihidro-isoquinolin-4-carboxílico

2he ((S)-1-fenil-propil)-amida del ácido 3-[4-(4-metil-piperazin-1-carbonil)-piperidin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2hf ((S)-1-fenil-propil)-amida del ácido 3-(5-isopropil-3H-espiro[isobenzofuran-1,4'-piperidin]-1'-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2hg ((S)-1-fenil-propil)-amida del ácido 3-[4-(acetil-metil-amino)-4-fenil-piperidin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2hh Ter-butil éster del ácido 4-{1-[1-oxo-2-fenil-4-(1-fenil-propilcarbamoil)-1,2-dihidro-isoquinolin-3-ilmetil]-piperidin-4-il}-piperazin-1-carboxílico

2hi Ter-butil éster del ácido (2-{1-[1-oxo-2-fenil-4-(1-fenil-propilcarbamoil)-1,2-dihidro-isoquinolin-3-ilmetil]-piperidin-4-il}-etil)-carbámico

2hj ((S)-1-fenil-propil)-amida del ácido 3-(4-metilamino-4-fenil-piperidin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2hk ((S)-1-fenil-propil)-amida del ácido 3-(4-acetilamino-4-fenil-piperidin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

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2hl ((S)-1-fenil-propil)-amida del ácido 3-[4-acetilamino-4-(3-fluoro-fenil)-piperidin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2hm ((S)-1-fenil-propil)-amida del ácido 1-oxo-3-[4-(4-oxo-piperidin-1-carbonil)-piperidin-1-ilmetil]-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2hn ((S)-1-fenil-propil)-amida del ácido 3-[4,4']bipiperidinil-1-ilmetil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2ho Ter-butil éster del ácido {1-[1-oxo-2-fenil-4-(1-fenil-propilcarbamoil)-1,2-dihidro-isoquinolin-3-ilmetil]-piperidin-4-il}-carbámico

2hp [Ciclopropil-(3-fluoro-fenil)-metil]-amida del ácido 3-[1,4']bipiperidinil-1'-ilmetil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2hq [Ciclopropil-(3-fluoro-fenil)-metil]-amida del ácido 1-oxo-3-(4-fenetil-piperazin-1-ilmetil)-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2hr [Ciclopropil-(3-fluoro-fenil)-metil]-amida del ácido 3-(4-isopropil-piperazin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2hs [Ciclopropil-(3-fluoro-fenil)-metil]-amida del ácido 3-[4-(2-morfolin-4-il-etil)-piperazin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2ht [Ciclopropil-(3-fluoro-fenil)-metil]-amida del ácido 3-[4-(1-metil-piperidin-4-il)-piperazin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2hu [Ciclopropil-(3-fluoro-fenil)-metil]-amida del ácido 1-oxo-2-fenil-3-[4-(2-piperidin-1-il-etil)-piperazin-1-ilmetil]-1,2-dihidro-isoquinolin-4-carboxílico

2hv [Ciclopropil-(3-fluoro-fenil)-metil]-amida del ácido 1-oxo-2-fenil-3-[4-(2-pirrolidin-1-il-etil)-piperazin-1-ilmetil]-1,2-dihidro-isoquinolin-4-carboxílico

2hw [Ciclopropil-(3-fluoro-fenil)-metil]-amida del ácido 1-oxo-2-fenil-3-(4-piridin-4-ilmetil-piperazin-1-ilmetil)-1,2-dihidro-isoquinolin-4-carboxílico

2hx [Ciclopropil-(3-fluoro-fenil)-metil]-amida del ácido 3-(4-hidroxi-3,4,5,6-tetrahidro-2H-[4,4']bipiridinil-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2hy [Ciclopropil-(3-fluoro-fenil)-metil]-amida del ácido 3-[4-(2-morfolin-4-il-etil)-piperidin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2hz [Ciclopropil-(3-fluoro-fenil)-metil]-amida del ácido 3-[4-hidroxi-4-(3-metoxi-fenil)-piperidin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2ia [Ciclopropil-(3-fluoro-fenil)-metil]-amida del ácido 3-[4-(acetil-metil-amino)-4-fenil-piperidin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

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2ib ((S)-1-fenil-propil)-amida del ácido 2-(2-fluoro-fenil)-1-oxo-3-(4-fenetil-piperazin-1-ilmetil)-1,2-dihidro-isoquinolin-4-carboxílico

2ic ((S)-1-fenil-propil)-amida del ácido 2-(2-fluoro-fenil)-3-(4-isopropil-piperazin-1-ilmetil)-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico

2id ((S)-1-fenil-propil)-amida del ácido 3-[1,4']bipiperidinil-1'-ilmetil-2-(2-fluoro-fenil)-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico

2ie ((S)-1-fenil-propil)-amida del ácido 2-(2-fluoro-fenil)-3-[4-(2-morfolin-4-il-etil)-piperazin-1-ilmetil]-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico

2if ((S)-1-fenil-propil)-amida del ácido 2-(2-fluoro-fenil)-3-[4-(1-metil-piperidin-4-il)-piperazin-1-ilmetil]-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico

2ig ((S)-1-fenil-propil)-amida del ácido 2-(2-fluoro-fenil)-1-oxo-3-[4-(2-piperidin-1-il-etil)-piperazin-1-ilmetil]-1,2-dihidro-isoquinolin-4-carboxílico

2ih ((S)-1-fenil-propil)-amida del ácido 2-(2-fluoro-fenil)-1-oxo-3-[4-(2-pirrolidin-1-il-etil)-piperazin-1-ilmetil]-1,2-dihidro-isoquinolin-4-carboxílico

2ii ((S)-1-fenil-propil)-amida del ácido 2-(2-fluoro-fenil)-1-oxo-3-(4-piridin-4-ilmetil-piperazin-1-ilmetil)-1,2-dihidro-isoquinolin-4-carboxílico

2ij ((S)-1-fenil-propil)-amida del ácido 2-(2-fluoro-fenil)-3-(4-hidroxi-3,4,5,6-tetrahidro-2H-[4,4']bipiridinil-1-ilmetil)-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico

2ik ((S)-1-fenil-propil)-amida del ácido 2-(2-fluoro-fenil)-3-[4-(2-morfolin-4-il-etil)-piperidin-1-ilmetil]-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico

2il ((S)-1-fenil-propil)-amida del ácido 2-(2-fluoro-fenil)-3-[4-hidroxi-4-(3-metoxi-fenil)-piperidin-1-ilmetil]-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico

2im ((S)-1-fenil-propil)-amida del ácido 3-[4-(2-morfolin-4-il-etil)-piperazin-1-ilmetil]-1-oxo-2-o-tolil-1,2-dihidro-isoquinolin-4-carboxílico

2in ((S)-1-fenil-propil)-amida del ácido 1-oxo-3-[4-(2-piperidin-1-il-etil)-piperazin-1-ilmetil]-2-o-tolil-1,2-dihidro-isoquinolin-4-carboxílico

2io ((S)-1-fenil-propil)-amida del ácido 1-oxo-3-(4-piridin-4-ilmetil-piperazin-1-ilmetil)-2-o-tolil-1,2-dihidro-isoquinolin-4-carboxílico

2ip ((S)-1-fenil-propil)-amida del ácido 2-(3-fluoro-fenil)-1-oxo-3-(4-fenetil-piperazin-1-ilmetil)-1,2-dihidro-isoquinolin-4-carboxílico

2iq ((S)-1-fenil-propil)-amida del ácido 2-(3-fluoro-fenil)-3-(4-isopropil-piperazin-1-ilmetil)-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico

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2ir ((S)-1-fenil-propil)-amida del ácido 3-[1,4']bipiperidinil-1'-ilmetil-2-(3-fluoro-fenil)-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico

2is ((S)-1-fenil-propil)-amida del ácido 2-(3-fluoro-fenil)-3-[4-(2-morfolin-4-il-etil)-piperazin-1-ilmetil]-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico

2it ((S)-1-fenil-propil)-amida del ácido 2-(3-fluoro-fenil)-3-[4-(1-metil-piperidin-4-il)-piperazin-1-ilmetil]-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico

2iu ((S)-1-fenil-propil)-amida del ácido 2-(3-fluoro-fenil)-1-oxo-3-[4-(2-piperidin-1-il-etil)-piperazin-1-ilmetil]-1,2-dihidro-isoquinolin-4-carboxílico

2iv ((S)-1-fenil-propil)-amida del ácido 2-(3-fluoro-fenil)-1-oxo-3-[4-(2-pirrolidin-1-il-etil)-piperazin-1-ilmetil]-1,2-dihidro-isoquinolin-4-carboxílico

2iw ((S)-1-fenil-propil)-amida del ácido 2-(3-fluoro-fenil)-1-oxo-3-(4-piridin-4-ilmetil-piperazin-1-ilmetil)-1,2-dihidro-isoquinolin-4-carboxílico

2ix ((S)-1-fenil-propil)-amida del ácido 2-(3-fluoro-fenil)-3-[4-(2-morfolin-4-il-etil)-piperidin-1-ilmetil]-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico

2iy ((S)-1-fenil-propil)-amida del ácido 2-(3-fluoro-fenil)-3-[4-hidroxi-4-(3-metoxi-fenil)-piperidin-1-ilmetil]-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico

2iz ((S)-1-fenil-propil)-amida del ácido 3-[4-(acetil-metil-amino)-4-fenil-piperidin-1-ilmetil]-2-(3-fluoro-fenil)-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico

2ja ((S)-1-fenil-propil)-amida del ácido 2-(3-cloro-fenil)-1-oxo-3-(4-fenetil-piperazin-1-ilmetil)-1,2-dihidro-isoquinolin-4-carboxílico

2jb ((S)-1-fenil-propil)-amida del ácido 2-(3-cloro-fenil)-3-(4-isopropil-piperazin-1-ilmetil)-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico

2jc ((S)-1-fenil-propil)-amida del ácido 3-[1,4']bipiperidinil-1'-ilmetil-2-(3-cloro-fenil)-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico

2jd ((S)-1-fenil-propil)-amida del ácido 2-(3-cloro-fenil)-3-[4-(2-morfolin-4-il-etil)-piperazin-1-ilmetil]-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico

2je ((S)-1-fenil-propil)-amida del ácido 2-(3-cloro-fenil)-3-[4-(1-metil-piperidin-4-il)-piperazin-1-ilmetil]-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico

2jf ((S)-1-fenil-propil)-amida del ácido 2-(3-cloro-fenil)-1-oxo-3-[4-(2-piperidin-1-il-etil)-piperazin-1-ilmetil]-1,2-dihidro-isoquinolin-4-carboxílico

2jg ((S)-1-fenil-propil)-amida del ácido 2-(3-cloro-fenil)-1-oxo-3-[4-(2-pirrolidin-1-il-etil)-piperazin-1-ilmetil]-1,2-dihidro-isoquinolin-4-carboxílico

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2jh ((S)-1-fenil-propil)-amida del ácido 2-(3-cloro-fenil)-1-oxo-3-(4-piridin-4-ilmetil-piperazin-1-ilmetil)-1,2-dihidro-isoquinolin-4-carboxílico

2ji ((S)-1-fenil-propil)-amida del ácido 2-(3-cloro-fenil)-3-[4-(2-morfolin-4-il-etil)-piperidin-1-ilmetil]-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico

2jj ((S)-1-fenil-propil)-amida del ácido 2-(3-cloro-fenil)-3-[4-hidroxi-4-(3-metoxi-fenil)-piperidin-1-ilmetil]-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico

2jk ((S)-1-fenil-propil)-amida del ácido 3-[4-(acetil-metil-amino)-4-fenil-piperidin-1-ilmetil]-2-(3-cloro-fenil)-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico

2jl ((S)-1-fenil-propil)-amida del ácido 1-oxo-3-(4-fenetil-piperazin-1-ilmetil)-2-m-tolil-1,2-dihidro-isoquinolin-4-carboxílico

2jm ((S)-1-fenil-propil)-amida del ácido 3-[1,4']bipiperidinil-1'-ilmetil-1-oxo-2-m-tolil-1,2-dihidro-isoquinolin-4-carboxílico

2jn ((S)-1-fenil-propil)-amida del ácido 3-[4-(2-morfolin-4-il-etil)-piperazin-1-ilmetil]-1-oxo-2-m-tolil-1,2-dihidro-isoquinolin-4-carboxílico

2jo ((S)-1-fenil-propil)-amida del ácido 3-[4-(1-metil-piperidin-4-il)-piperazin-1-ilmetil]-1-oxo-2-m-tolil-1,2-dihidro-isoquinolin-4-carboxílico

2jp ((S)-1-fenil-propil)-amida del ácido 1-oxo-3-[4-(2-piperidin-1-il-etil)-piperazin-1-ilmetil]-2-m-tolil-1,2-dihidro-isoquinolin-4-carboxílico

2jq ((S)-1-fenil-propil)-amida del ácido 1-oxo-3-[4-(2-pirrolidin-1-il-etil)-piperazin-1-ilmetil]-2-m-tolil-1,2-dihidro-isoquinolin-4-carboxílico

2jr ((S)-1-fenil-propil)-amida del ácido 1-oxo-3-(4-piridin-4-ilmetil-piperazin-1-ilmetil)-2-m-tolil-1,2-dihidro-isoquinolin-4-carboxílico

2js ((S)-1-fenil-propil)-amida del ácido 3-[4-(2-morfolin-4-il-etil)-piperidin-1-ilmetil]-1-oxo-2-m-tolil-1,2-dihidro-isoquinolin-4-carboxílico

2jt ((S)-1-fenil-propil)-amida del ácido 3-[4-hidroxi-4-(3-metoxi-fenil)-piperidin-1-ilmetil]-1-oxo-2-m-tolil-1,2-dihidro-isoquinolin-4-carboxílico

2ju ((S)-1-fenil-propil)-amida del ácido 3-[4-(acetil-metil-amino)-4-fenil-piperidin-1-ilmetil]-1-oxo-2-m-tolil-1,2-dihidro-isoquinolin-4-carboxílico

3a ((S)-1-fenil-propil)-amida del ácido 1-oxo-3-(2-oxo-pirrolidin-1-ilmetil)-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

3b ((S)-1-fenil-propil)-amida del ácido 8-cloro-1-oxo-3-(2-oxo-pirrolidin-1-ilmetil)-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

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4a ((S)-1-fenil-propil)-amida del ácido 3-cianometil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

5a N,N-difenil-hidrazida del ácido 3-metil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

5b Metil éster del ácido N'-(3-metil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carbonil)-N-fenil-hidrazincarboxílico

1aa ((S)-1-fenil-propil)-amida del ácido 2-(3-metoxi-fenil)-3-metil-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico

1ab ((S)-1-fenil-propil)-amida del ácido 2-(4-metoxi-fenil)-3-metil-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico

1ac ((S)-1-fenil-propil)-amida del ácido 2-(4-fluoro-fenil)-3-metil-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico

1ad ((S)-1-fenil-propil)-amida del ácido 2-(4-cloro-fenil)-3-metil-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico

1ae ((S)-1-fenil-propil)-amida del ácido 3-metil-1-oxo-2-p-tolil-1,2-dihidro-isoquinolin-4-carboxílico

1af [(S)-ciclopropil-(3-fluoro-fenil)-metil]-amida del ácido 2-(3-metoxi-fenil)-3-metil-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico

1ag [(S)-ciclopropil-(3-fluoro-fenil)-metil]-amida del ácido 2-(4-metoxi-fenil)-3-metil-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico

1ah [(S)-ciclopropil-(3-fluoro-fenil)-metil]-amida del ácido 2-(4-fluoro-fenil)-3-metil-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico

1ai [(S)-ciclopropil-(3-fluoro-fenil)-metil]-amida del ácido 2-(4-cloro-fenil)-3-metil-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico

1aj [(S)-ciclopropil-(3-fluoro-fenil)-metil]-amida del ácido 3-metil-1-oxo-2-p-tolil-1,2-dihidro-isoquinolin-4-carboxílico

1ak ((S)-1-fenil-propil)-amida del ácido 2-(2-metoxi-fenil)-3-metil-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico

1al [(S)-ciclopropil-(3-fluoro-fenil)-metil]-amida del ácido 2-(2-metoxi-fenil)-3-metil-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico

1am ((S)-1-fenil-propil)-amida del ácido 3-metil-8-nitro-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

1an [(S)-ciclopropil-(3-fluoro-fenil)-metil]-amida del ácido 3-metil-8-nitro-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

1ao ((S)-1-fenil-propil)-amida del ácido 8-metoxi-3-metil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

1ap [(S)-ciclopropil-(3-fluoro-fenil)-metil]-amida del ácido 8-metoxi-3-metil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

1aq ((S)-1-fenil-propil)-amida del ácido 8-amino-3-metil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

1ar ((S)-1-fenil-propil)-amida del ácido 8-ciano-3-metil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

1as [(S)-1-(4-cloro-fenil)-propil]-amida del ácido 8-cloro-3-metil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

1at [(S)-1-(4-fluoro-fenil)-propil]-amida del ácido 8-cloro-3-metil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

1au [(S)-1-(2-fluoro-fenil)-propil]-amida del ácido 8-cloro-3-metil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

1av [(S)-1-(3-cloro-fenil)-propil]-amida del ácido 8-cloro-3-metil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

1aw [(S)-(3-cloro-fenil)-ciclopropil-metil]-amida del ácido 8 -cloro-3-metil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

1ax [(S)-(4-cloro-fenil)-ciclopropil-metil]-amida del ácido 8-cloro-3-metil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

1ay [(S)-1-(3-fluoro-fenil)-propil]-amida del ácido 8-cloro-3-metil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

1az ((S)-2-metil-1-fenil-propil)-amida del ácido 8-cloro-3-metil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

1ba [(S)-ciclopropil-(4-fluoro-fenil)-metil]-amida del ácido 8-cloro-3-metil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

1bb [(S)-1-(2-cloro-fenil)-propil]-amida del ácido 8-cloro-3-metil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

1bc ((S)-ciclopentil-fenil-metil)-amida del ácido 8-cloro-3-metil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

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1bd [(S)-(2-cloro-fenil)-ciclopropil-metil]-amida del ácido 8-cloro-3-metil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

1be [(S)-ciclopropil-(2-fluoro-fenil)-metil]-amida del ácido 8-cloro-3-metil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

1bf ((S)-ciclohexil-fenil-metil)-amida del ácido 8-cloro-3-metil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

1bg ((S)-ciclopropil-fenil-metil)-amida del ácido 8-cloro-3-metil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

1bh [(S)-ciclobutil-(3-fluoro-fenil)-metil]-amida del ácido 8-cloro-3-metil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

1bi [(S)-ciclobutil-(4-fluoro-fenil)-metil]-amida del ácido 8-cloro-3-metil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

1bl [(R)-ciclopropil-(3-fluoro-fenil)-metil]-amida del ácido 8-cloro-3-metil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

1bn ((S)ciclobutil-fenil-metil)-amida del ácido 8-cloro-3-metil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

1bo [Ciclobutil-(2-fluoro-fenil)-metil]-amida del ácido 8-cloro-3-metil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2ka [(S)-ciclopropil-(3-fluoro-fenil)-metil]-amida del ácido 3-(4-ter-butil-piperazin-1-ilmetil)-8-cloro-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2kb ((S)-1-fenil-propil)-amida del ácido 8-cloro-3-(4-isopropil-piperazin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2kc ((S)-1-fenil-propil)-amida del ácido 8-cloro-3-(4-isobutil-piperazin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2kd ((S)-1-fenil-propil)-amida del ácido 8-cloro-3-(octahidro-pirido[1,2-a]pirazin-2-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2ke ((S)-1-fenil-propil)-amida del ácido 8-cloro-3-(4-hidroxi-3,4,5,6-tetrahidro-2H-[4,4']bipiridinil-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2kf ((S)-1-fenil-propil)-amida del ácido 8-cloro-3-(4-ciclopropilmetil-piperazin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2kg ((S)-1-fenil-propil)-amida del ácido 8-cloro-3-[4-(2-morfolin-4-il-etil)-piperidin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2kh ((S)-1-fenil-propil)-amida del ácido 8-cloro-3-[1,4]diazepan-1-ilmetil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2ki ((S)-1-fenil-propil)-amida del ácido 8-cloro-3-((S)-3-metil-piperazin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2kj ((S)-1-fenil-propil)-amida del ácido 8-cloro-3-imidazol-1-ilmetil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2kk ((S)-1-fenil-propil)-amida del ácido 8-cloro-3-(4-metil-imidazol-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2kl ((S)-1-fenil-propil)-amida del ácido 3-(ter-butilamino-metil)-8-cloro-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2km ((S)-1-fenil-propil)-amida del ácido 8-cloro-3-(isopropilamino-metil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2kn ((S)-1-fenil-propil)-amida del ácido 8-cloro-3-[4-hidroxi-4-(3-metoxi-fenil)-piperidin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2ko ((S)-1-fenil-propil)-amida del ácido 3-(4-ter-butil-piperazin-1-ilmetil)-8-cloro-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2kp ((S)-1-fenil-propil)-amida del ácido 3-benzoimidazol-1-ilmetil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2kq ((S)-1-fenil-propil)-amida del ácido 1-oxo-2-fenil-3-pirazol-1-ilmetil-1,2-dihidro-isoquinolin-4-carboxílico

2kr ((S)-1-fenil-propil)-amida del ácido 3-(4-metil-pirazol-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2ks ((S)-1-fenil-propil)-amida del ácido 1-oxo-2-fenil-3-[1,2,3]triazol-1-ilmetil-1,2-dihidro-isoquinolin-4-carboxílico

2kt ((S)-1-fenil-propil)-amida del ácido 2-(3-metoxi-fenil)-1-oxo-3-(4-piridin-4-ilmetil-piperazin-1-ilmetil)-1,2-dihidro-isoquinolin-4-carboxílico

2ku ((S)-1-fenil-propil)-amida del ácido 2-(4-metoxi-fenil)-3-[4-(2-morfolin-4-il-etil)-piperazin-1-ilmetil]-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico

2kv ((S)-1-fenil-propil)-amida del ácido 2-(4-fluoro-fenil)-1-oxo-3-(4-fenetil-piperazin-1-ilmetil)-1,2-dihidro-isoquinolin-4-carboxílico

2kw ((S)-1-fenil-propil)-amida del ácido 2-(4-fluoro-fenil)-3-(4-isopropil-piperazin-1-ilmetil)-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico

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2kx ((S)-1-fenil-propil)-amida del ácido 3-[1,4']bipiperidinil-1'-ilmetil-2-(4-fluoro-fenil)-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico

2ky ((S)-1-fenil-propil)-amida del ácido 2-(4-fluoro-fenil)-3-[4-(2-morfolin-4-il-etil)-piperazin-1-ilmetil]-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico

2kz ((S)-1-fenil-propil)-amida del ácido 2-(4-fluoro-fenil)-3-[4-(1-metil-piperidin-4-il)-piperazin-1-ilmetil]-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico

2la ((S)-1-fenil-propil)-amida del ácido 2-(4-fluoro-fenil)-1-oxo-3-[4-(2-pirrolidin-1-il-etil)-piperazin-1-ilmetil]-1,2-dihidro-isoquinolin-4-carboxílico

2lb ((S)-1-fenil-propil)-amida del ácido 2-(4-fluoro-fenil)-3-[4-hidroxi-4-(3-metoxi-fenil)-piperidin-1-ilmetil]-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico

2lc ((S)-1-fenil-propil)-amida del ácido 2-(4-cloro-fenil)-1-oxo-3-(4-fenetil-piperazin-1-ilmetil)-1,2-dihidro-isoquinolin-4-carboxílico

2ld ((S)-1-fenil-propil)-amida del ácido 2-(4-cloro-fenil)-3-(4-isopropil-piperazin-1-ilmetil)-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico

2le ((S)-1-fenil-propil)-amida del ácido 3-[1,4']bipiperidinil-1'-ilmetil-2-(4-cloro-fenil)-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico

2lf ((S)-1-fenil-propil)-amida del ácido 2-(4-cloro-fenil)-3-[4-(2-morfolin-4-il-etil)-piperazin-1-ilmetil]-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico

2lg ((S)-1-fenil-propil)-amida del ácido 2-(4-cloro-fenil)-3-[4-(1-metil-piperidin-4-il)-piperazin-1-ilmetil]-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico

2lh ((S)-1-fenil-propil)-amida del ácido 2-(4-cloro-fenil)-1-oxo-3-[4-(2-piperidin-1-il-etil)-piperazin-1-ilmetil]-1,2-dihidro-isoquinolin-4-carboxílico

2li ((S)-1-fenil-propil)-amida del ácido 2-(4-cloro-fenil)-1-oxo-3-[4-(2-pirrolidin-1-il-etil)-piperazin-1-ilmetil]-1,2-dihidro-isoquinolin-4-carboxílico

2lj ((S)-1-fenil-propil)-amida del ácido 3-(4-ter-butil-piperazin-1-ilmetil)-8-fluoro-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2lk ((S)-1-fenil-propil)-amida del ácido 8-cloro-3-ciclopropilaminometil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2ll [(S)-ciclopropil-(3-fluoro-fenil)-metil]-amida del ácido 3-(4-ter-butil-piperazin-1-ilmetil)-8-fluoro-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2lm [(S)-ciclopropil-(3-fluoro-fenil)-metil]-amida del ácido 8-fluoro-1-oxo-2-fenil-3-piperazin-1-ilmetil-1,2-dihidro-isoquinolin-4-carboxílico

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2ln [(S)-ciclopropil-(3-fluoro-fenil)-metil]-amida del ácido 8-fluoro-1-oxo-3-(3-oxo-pirazolidin-1-ilmetil)-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2lo [(S)-ciclopropil-(3-fluoro-fenil)-metil]-amida del ácido 8-fluoro-1-oxo-3-(3-oxo-piperazin-1-ilmetil)-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

3c ((S)-1-fenil-propil)-amida del ácido 1-oxo-2-fenil-3-(1H-[1,2,4]triazol-3-ilsulfanilmetil)-1,2-dihidro-isoquinolin-4-carboxílico

3d [(S)-ciclopropil-(3-fluoro-fenil)-metil]-amida del ácido 8-cloro-1-oxo-3-(2-oxo-pirrolidin-1-ilmetil)-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

3e ((S)-1-fenil-propil)-amida del ácido 8-fluoro-1-oxo-3-(2-oxo-pirrolidin-1-ilmetil)-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

3f [(S)-ciclopropil-(3-fluoro-fenil)-metil]-amida del ácido 8-fluoro-1-oxo-3-(2-oxo-pirrolidin-1-ilmetil)-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

3g [(S)-ciclopropil-(3-fluoro-fenil)-metil]-amida del ácido 8-fluoro-1-oxo-3-(5-oxo-pirazolidin-1-ilmetil)-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

3h [(S)-ciclopropil-(3-fluoro-fenil)-metil]-amida del ácido 8-fluoro-1-oxo-3-(2-oxo-piperazin-1-ilmetil)-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

3i [(S)-ciclopropil-(3-fluoro-fenil)-metil]-amida del ácido 8-fluoro-1-oxo-3-(2-oxo-piperidin-1-ilmetil)-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

4b [(S)-ciclopropil-(3-fluoro-fenil)-metil]-amida del ácido 8-cloro-3-cianometil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

6a ((S)-1-fenil-propil)-amida del ácido 2-(3,4-dicloro-fenil)-3-metil-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico

6b ((S)-ciclopropil-fenil-metil)-amida del ácido 8-fluoro-1-oxo-3-(2-oxo-pirrolidin-1-ilmetil)-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

6c ((S)-ciclopropil-fenil-metil)-amida del ácido 8-fluoro-3-metil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

7a ((S)-1-fenil-propil)-amida del ácido 3-etil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

7b ((S)-1-fenil-propil)-amida del ácido 8-fluoro-3-metil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

7c ((S)-1-fenil-propil)-amida del ácido 8-fluoro-2-(3-fluoro-fenil)-3-metil-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico

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7d ((S)-1-fenil-propil)-amida del ácido 8-fluoro-2-(4-fluoro-fenil)-3-metil-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico

7e [(S)-ciclopropil-(3-fluoro-fenil)-metil]-amida del ácido 8-fluoro-3-metil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

7f [(S)-ciclopropil-(3-fluoro-fenil)-metil]-amida del ácido 8-fluoro-2-(3-fluoro-fenil)-1-oxo-3-(2-oxo-pirrolidin-1-ilmetil)-1,2-dihidro-isoquinolin-4-carboxílico

7g [(S)-ciclopropil-(3-fluoro-fenil)-metil]-amida del ácido 8-fluoro-2-(4-fluoro-fenil)-1-oxo-3-(2-oxo-pirrolidin-1-ilmetil)-1,2-dihidro-isoquinolin-4-carboxílico

7h [(S)-ciclobutil-(3-fluoro-fenil)-metil]-amida del ácido 8-fluoro-3-metil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

7i [(S)-ciclopropil-(3-fluoro-fenil)-metil]-amida del ácido 8-fluoro-2-(2-fluoro-fenil)-3-metil-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico

7j [(S)-ciclopropil-(3-fluoro-fenil)-metil]-amida del ácido 8-fluoro-2-(3-fluoro-fenil)-3-metil-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico

7k [(S)-ciclopropil-(3-fluoro-fenil)-metil]-amida del ácido 8-fluoro-2-(4-fluoro-fenil)-3-metil-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico

7l [(S)-ciclopropil-(3-fluoro-fenil)-metil]-amida del ácido 6,8-difluoro-3-metil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

7m [(S)-ciclopropil-(3-fluoro-fenil)-metil]-amida del ácido 5,8-difluoro-3-metil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

7n ((S)-1-fenil-propil)-amida del ácido 3-metil-1-oxo-2-fenil-8-trifluorometil-1,2-dihidro-isoquinolin-4-carboxílico

8a [(S)-ciclopropil-(3-fluoro-fenil)-metil]-amida del ácido 3-(1-ter-butil-piperidin-4-ilmetil)-8-cloro-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

y sus sales aceptables para uso farmacéutico.

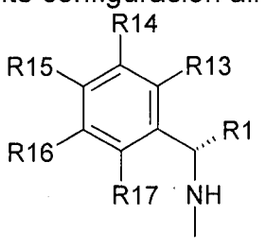
Además, los compuestos de esta invención pueden existir en forma no solvatada como así también en forma solvatada con solventes aceptable para uso farmacéutico tales como agua, etanol y similares. En general, las formas solvatadas se consideran equivalentes a las formas no solvatadas para los fines de esta invención.

Los compuestos de la presente invención pueden tener uno o más centros asimétricos y se pretende que cualquier isómero óptico (es decir enantiómeros o diastereómeros), como isómeros ópticos separados, puros o parcialmente purificados y

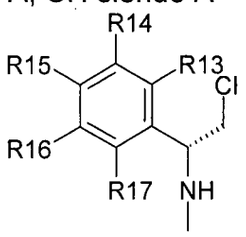
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cualquiera de sus mezclas que incluyen mezclas racémicas, es decir una mezcla de estereoisómeros, estén incluidos dentro del alcance de la invención. En particular, cuando A representa CH o CR^1, A puede ser un centro óptico que da lugar a dos isómeros ópticos, una forma R y una forma S. En una realización, los compuestos de la presente invención tienen la forma S.

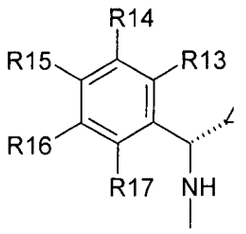
En una realización particular, los compuestos de la presente invención tienen la siguiente configuración alrededor de A, CH siendo A



por ej.



o



En este contexto, se entiende que cuando se especifica la forma enantiomérica, entonces el compuesto está en un exceso enantiomérico, es decir, esencialmente en forma pura. En consecuencia, una realización de la invención se refiere a un compuesto de la invención que tiene un exceso enantiomérico de al menos 60%, al menos 70%, al menos 80%, al menos 85%, al menos 90%, al menos 96%, preferentemente al menos 98%.

Las formas racémicas se pueden resolver en las antípodas ópticas mediante métodos conocidos, por ejemplo por separación de sales diastereoméricas de las mismas con un ácido ópticamente activo, y liberando el compuesto amina ópticamente activo mediante tratamiento con una base. Otro método para resolver racematos en de las antípodas ópticas se basa en la cromatografía de una matriz ópticamente activa. Los compuestos de la presente invención además se pueden resolver mediante la formación de derivados diastereoméricos. Se pueden utilizar métodos adicionales para la resolución de isómeros ópticos, conocidos por los expertos en la técnica. Dicho métodos incluyen los mencionados en J. Jaques, A. Collet y S. Wilen en "Enantiomers, Racemates, and Resolutions", John Wiley and Sons, New York (1981). Los compuestos ópticamente activos además se pueden preparar a partir de materiales de partida ópticamente activos.

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Además, cuando un enlace doble o un sistema anular total o parcialmente saturado está presente en la molécula, se pueden formar isómeros geométricos. Se pretende que cualquier isómero geométrico, ya sean isómeros geométricos separados, puros o parcialmente purificados o sus mezclas se incluyen dentro del alcance de la invención. De igual modo, las moléculas que tienen un enlace con rotación restringida pueden formar isómeros geométricos. Estos además están incluidos dentro del alcance de la presente invención.

Más aún, algunos de los compuestos de la presente invención pueden existir en diferentes formas tautoméricas y se pretende que cualquier forma tautomérica que los compuestos puedan formar se incluya dentro del alcance de la presente invención.

Los antagonistas del receptor NK3 han estado implicados en varias enfermedades además de psicosis y esquizofrenia mencionadas anteriormente. Langlois et al en *J. Pharm. Exp. Ther.*, 299, 712-717, 2001, concluye que los antagonistas del NK3 puede ser aplicables en enfermedades del SNC en general, y en ansiedad y depresión en particular. Yip et al en *Br. J. Phar.*, 122, 715-722, 1997 además implican a los antagonistas del NK3 en diversas funciones cerebrales, tales como procesamiento cortical, aprendizaje y memoria, regulación neuroendocrina y del comportamiento. Estudios adicionales han demostrado que los receptores NKB y NK3 están involucrados en el dolor, y que los antagonistas del NK3 tienen un efecto antinociceptivo y analgésico [Fioramonti, *Neurogastronumber enterol. Motyl.*,15, 363-369, 2003]. Mazelin et al en *Life Sci.*, 63, 293-304, 1998 muestran que los antagonistas del NK3 tienen efecto en la inflamación intestinal y concluye que dichos antagonistas se pueden utilizar en la síndrome del colon irritable (IBS). Además, se ha demostrado que los antagonistas del NK3 en modelos *in vivo* son útiles en el tratamiento de enfermedades relacionadas con las vías respiratorias, tales como asma, hipersensibilidad de las vías respiratorias, tos, y broncorrestricción [Daoui, *Am. J. Respir. Crit. Care Med.*, 158, 42-48, 1998]. Maubach et al en *Neurosci.*, 83, 1047-1062, 1998 muestran que el senktide agonista del NKB y del NK3 aumentan la frecuencia y duración de las descargas epileptiformes, y de este modo por inferencia que los antagonistas del NK3 tienen un potencial anticonvulsivo. Finalmente, Kemel et al en *J.Neurosci.*, 22, 1929-1936, 2002, sugiere el uso de antagonistas del NK3 en el tratamiento de la enfermedad de Parkinson.

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En consecuencia, los estudios clínicos, pre-clínicos, *in vivo* y *in vitro* respaldan que los antagonistas del receptor NK3 son de relevancia para el tratamiento o prevención de varios trastornos que incluyen psicosis, esquizofrenia, depresión, ansiedad, deterioro cognitivo, obesidad, enfermedad de Alzheimer, enfermedad de Parkinson, dolor, convulsiones, tos, asma, hipersensibilidad de las vías respiratorias, hipersensibilidad microvascular, broncoconstricción, inflamación intestinal, y síndrome del colon irritable.

La esquizofrenia está clasificada en de subgrupos. El tipo paranoide se caracteriza por delirios y alucinaciones y ausencia de trastorno del pensamiento, comportamiento desordenado, y abatimiento afectivo. El tipo desorganizado, el cual también se denomina "esquizofrenia hebefrénica" en el ICD, en el cual el trastorno del pensamiento, y el abatimiento afectivo están presentes en forma conjunta. El tipo catatónico, en el cual los trastornos sicomotores prominentes son evidentes, y los síntomas pueden incluir estupor catatónico y flexibilidad cérea. El tipo indiferenciado en el cual los síntomas sicóticos están presentes, pero no han sido reunidos los criterios para la paranoia de tipo desorganizado o catatónico. Los síntomas de la esquizofrenia normalmente se manifiestan en tres amplias categorías, es decir síntomas positivos, negativos y cognitivos. Los síntomas positivos son aquellos, que representan un "exceso" de experiencias normales, tales como alucinaciones y delirios. Los síntomas negativos son aquellos en donde el paciente sufre de una falta de experiencias normales, tales como anhedonía y falta de interacción social. Los síntomas cognitivos se refieren al deterioro cognitivo en esquizofrénicos, tales como falta de atención sostenida y déficit en la toma de decisiones. Los actuales antisicóticos son bastante eficientes en el tratamiento de síntomas positivos pero no muy buenos para los síntomas negativos y cognitivos. Por el contrario, los antagonistas del NK3 han demostrado clínicamente que mejoran tanto los síntomas positivos como los negativos en esquizofrénicos. [*Am.J.Psychiatry*, 161, 975 a 984, 204], y de acuerdo con la descripción anterior además se esperan que tengan un efecto sobre los síntomas cognitivos.

El deterioro cognitivo incluye una disminución en las funciones o dominios cognitivos, por ej., memoria para el trabajo, atención y vigilancia, aprendizaje y memoria verbales, aprendizaje y memoria visuales , razonamiento y solución de problemas por

ej., función ejecutiva, velocidad del procesamiento y/o percepción social. En particular, el deterioro cognitivo puede indicar déficit en la atención, el pensamiento desordenado, el pensamiento lento, dificultad en el entendimiento, baja concentración, desequilibrio en la solución de problemas, poca memoria, dificultades para expresar pensamientos y/o dificultades en la integración de pensamientos, sentimientos y comportamiento, o dificultades en la eliminación de pensamientos irrelevantes.

En una realización, la presente invención se refiere a los compuestos de la presente invención para uso en terapias.

En una realización, la presente invención se refiere a un método para tratar una enfermedad seleccionada entre psicosis; esquizofrenia; trastorno esquizoide; trastorno afectivo esquizoide; trastorno delirante; trastorno sicótico breve; trastorno sicótico compartido; trastorno sicótico debido a una condición médica general; trastorno sicótico inducido por sustancia o fármaco (cocaína, alcohol, anfetamina etc.); trastorno esquizoide de la personalidad; trastorno tipo esquizoide de la personalidad; psicosis o esquizofrenia asociada con depresión mayor, trastorno bipolar, enfermedad de Alzheimer o enfermedad de Parkinson; depresión mayor; trastorno de ansiedad general; trastorno bipolar (tratamiento de mantenimiento, prevención de reaparición y estabilización); manía; hipomanía; deterioro cognitivo; ADHD; obesidad; reducción del apetito; enfermedad de Alzheimer; enfermedad de Parkinson; dolor; convulsiones; tos; asma; hipersensibilidad de las vías respiratorias; hipersensibilidad microvascular; broncoconstricción; enfermedad pulmonar obstructiva crónica; incontinencia urinaria; inflamación intestinal; y síndrome del colon irritable; el método que comprende la administración de una cantidad eficaz para uso terapéutico de un compuesto de la presente invención a un paciente que necesita del mismo.

En una realización, la presente invención se refiere a un método para el tratamiento de esquizofrenia, el método que comprende la administración de una cantidad eficaz para uso terapéutico de un compuesto de la presente invención a un paciente que necesita del mismo. En particular, dicho tratamiento incluye el tratamiento de los síntomas positivos, negativos y/o cognitivos de esquizofrenia.

En una realización, la presente invención se refiere a un método para tratar deterioro cognitivo, el método que comprende la administración de una cantidad eficaz para uso terapéutico de un compuesto de la presente invención a un paciente que

necesita del mismo. En particular, dicho deterioro cognitivo se manifiesta como una disminución en la memoria para el trabajo, atención y vigilancia, aprendizaje y memoria verbales, aprendizaje y memoria visuales, razonamiento y solución de problemas por ej., función ejecutiva, velocidad del procesamiento y/o percepción social.

El efecto antisicótico de los antisicóticos típicos y atípicos, en particular de los antagonistas del D2 es ejercido mediante una inhibición de los receptores pos-sinápticos D2. Los auto-receptores D2 pre-sinápticos, sin embargo, además están afectados por la administración de estos compuestos que dan lugar a un aumento en la velocidad de activación de la neurona dopaminérgica, lo cual, en realidad, contrarresta los efectos antisicóticos. La velocidad de activación aumentada continúa hasta que el efecto de los auto-receptores presinápticos se bloquea (el bloqueo de despolarización), típicamente después de aproximadamente 3 semanas de tratamiento crónico con antisicóticos típicos o atípicos. Este modelo explica el retardo de hasta 3 semanas de efecto clínico normalmente visto cuando se inicia el tratamiento con antagonista del D2. Los antagonistas del NK3 parecen inhibir el aumento en la activación de la neurona dopaminérgica mediado por los autorreceptores D2 presinápticos traídos por los antagonistas del D2, por lo que la administración combinada de antagonistas del NK3 y antagonistas del D2 se espera que dé lugar a un inicio más rápido del efecto clínico. Además, los antagonistas del D2 se sabe que aumentan los niveles de prolactina, lo que da lugar a efectos colaterales serios, tales como la osteoporosis. Se sabe que los agonistas del NK3 dan lugar a un aumento en la prolactina de lo cual se puede deducir que un agonista del NK3 disminuirá, es decir normalizará, un nivel aumentado de prolactina. De este modo, un uso combinado de antagonistas del NK3 y antagonistas del D2 pueden dirigir algunos de los aspectos de seguridad asociados con la administración de los antagonistas del D2. De manera similar, los antagonistas del NK3 pueden ser administrados juntos con antagonistas/agonistas inversos/moduladores negativos/agonistas parciales de uno o más de los receptores específicos: receptor D2 de dopamina, receptor D3 de dopamina, receptor D4 de dopamina, PDE10 fosfodiesterasa, receptor 5-HT_{1A} de serotonina, receptor 5-HT_{2A} de serotonina, receptor 5-HT_6 de serotonina, receptor alfa 2 adrenérgico, receptor tipo 1 canabinoide, receptor H3 de histamina, ciclooxigenasas, canales de sodio o transportador de glicina GlyT1; o con agonistas/moduladores positivos/agonistas parciales de uno o más de los

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específicos receptor 5-HT_{2C} de serotonina, Canales KCNQ, Receptor NMDA, Receptor AMPA, receptor alfa-7 nicotínico, receptor M1 muscarínico, receptor M4 muscarínico, receptor metabotrópico del glutamato mGluR2, receptor metabotrópico del glutamato mGluR5, receptor D1 de dopamina o receptor D5 de dopamina.

Dicha administración combinada de compuestos de la presente invención y otros compuestos antisicóticos, tales como antagonistas del D2, agonistas parciales del D2, antagonistas del PDE10, 5-HT_{2A} antagonistas, 5-HT_6 antagonistas o antagonistas del KCNQ4 puede ser secuencial o concomitante. Ejemplos de antagonistas del D2 o agonistas parciales incluyen haloperidol, clorpromazina, sulpirid, risperidona, ziprasidon, olanzapina, quetiapina, y clozapina.

En una realización, el compuesto de la presente invención se administra en una cantidad desde aproximadamente 0,001 de mg/kg de peso corporal hasta aproximadamente 100 mg/kg de peso corporal por día. En particular, las dosificaciones diarias pueden estar en el rango de 0,01 mg/kg de peso corporal hasta aproximadamente 50 mg/kg de peso corporal por día. Las dosificaciones exactas dependerán de la frecuencia y el modo de administración, el sexo, la edad, el peso, y el estado general del sujeto a ser tratado, la naturaleza y la severidad de la condición a ser tratada, cualquier enfermedad concomitante a ser tratada, el efecto deseado del tratamiento y otros factores conocidos por los expertos en la técnica.

Una dosificación típica para adultos estará en el rango de 1-1000 mg/día de un compuesto de la presente invención, tal como 1-500 mg/día.

En una realización, la presente invención se refiere al uso de los compuestos de la presente invención en la producción de un medicamento para el tratamiento de una enfermedad seleccionada de psicosis; esquizofrenia; trastorno esquizoide; trastorno afectivo esquizoide; trastorno delirante; trastorno sicótico breve; trastorno sicótico compartido; trastorno sicótico debido a una condición médica general; trastorno sicótico inducido por sustancia o fármaco (cocaína, alcohol, anfetamina etc.); trastorno esquizoide de la personalidad; trastorno tipo esquizoide de la personalidad; psicosis o esquizofrenia asociada con depresión mayor, trastorno bipolar, enfermedad de Alzheimer o enfermedad de Parkinson; depresión mayor; trastorno de ansiedad general; trastorno bipolar (tratamiento de mantenimiento, prevención de reaparición y estabilización); manía; hipomanía; deterioro cognitivo; ADHD; obesidad; reducción del

apetito; enfermedad de Alzheimer; enfermedad de Parkinson; dolor; convulsiones; tos; asma; hipersensibilidad de las vías respiratorias; hipersensibilidad microvascular; broncoconstricción; enfermedad pulmonar obstructiva crónica; incontinencia urinaria; inflamación intestinal; y síndrome del colon irritable.

En una realización, la presente invención se refiere al uso de un compuesto de la presente invención en la producción de un medicamento para el tratamiento de esquizofrenia. En particular, dicho tratamiento incluye el tratamiento de los síntomas positivos, negativos y/o cognitivos de esquizofrenia.

En una realización, la presente invención se refiere al uso de un compuesto de la presente invención en la producción de un medicamento para el tratamiento de deterioro cognitivo. En particular, dicho deterioro cognitivo se manifiesta como una disminución en la memoria para el trabajo, atención y vigilancia, aprendizaje y memoria verbales, aprendizaje y memoria visuales, razonamiento y solución de problemas por ej., función ejecutiva, velocidad del procesamiento y/o percepción social. .

En una realización, la presente invención se refiere a un compuesto de la presente invención para uso en el tratamiento de una enfermedad seleccionada entre psicosis; esquizofrenia; trastorno esquizoide; trastorno afectivo esquizoide; trastorno delirante; trastorno sicótico breve; trastorno sicótico compartido; trastorno sicótico debido a una condición médica general; trastorno sicótico inducido por sustancia o fármaco (cocaína, alcohol, anfetamina etc.); trastorno esquizoide de la personalidad; trastorno tipo esquizoide de la personalidad; psicosis o esquizofrenia asociada con depresión mayor, trastorno bipolar, enfermedad de Alzheimer o enfermedad de Parkinson; depresión mayor; trastorno de ansiedad general; trastorno bipolar (tratamiento de mantenimiento, prevención de reaparición y estabilización); manía; hipomanía; deterioro cognitivo; ADHD; obesidad; reducción del apetito; enfermedad de Alzheimer; enfermedad de Parkinson; dolor; convulsiones; tos; asma; hipersensibilidad de las vías respiratorias; hipersensibilidad microvascular; broncoconstricción; enfermedad pulmonar obstructiva crónica; incontinencia urinaria; inflamación intestinal; y enfermedad del intestino irritable.

En una realización, la presente invención se refiere a un compuesto de la presente invención para uso en el tratamiento de esquizofrenia. En particular, dicho

tratamiento incluye el tratamiento de los síntomas positivos, negativos y/o cognitivos de esquizofrenia.

En una realización, la presente invención se refiere a un compuesto de la presente invención para uso en el tratamiento de deterioro cognitivo. En particular, dicho deterioro cognitivo se manifiesta como una disminución en la memoria para el trabajo, atención y vigilancia, aprendizaje y memoria verbales, aprendizaje y memoria visuales, razonamiento y solución de problemas por ej., función ejecutiva, velocidad del procesamiento y/o cognición social.

Los compuestos de la presente invención pueden ser administrados solos en forma de un compuesto puro o en combinación con vehículos o excipientes aceptables para uso farmacéutico, ya sea en dosis únicas o múltiples. Las composiciones farmacéuticas de acuerdo con la invención se pueden formular con vehículos o excipientes aceptables para uso farmacéutico como así también cualquier otro adyuvante y excipiente de acuerdo con técnicas convencionales tales como las divulgadas en Remington: The Science and Practice of Pharmacy, 19º Edición, Gennaro, Ed., Mack Publishing Co., Easton, PA, 1995.

Las composiciones farmacéuticas se pueden formular específicamente para la administración por cualquier vía adecuada tal como la vía oral, rectal, nasal, pulmonar, tópica (que incluye bucal y sublingual), transdérmica, intracisternal, intraperitoneal, vaginal y parenteral (que incluye subcutánea, intramuscular, intratecal, intravenosa e intradérmica), siendo la vía oral la preferida. Se apreciará que la vía preferida dependerá del estado general y la edad del sujeto a ser tratado, la naturaleza de la condición a ser tratada y el principio activo elegido.

Las composiciones farmacéuticas para administración oral incluyen formas de dosificación sólidas tales como cápsulas, comprimidos, grageas, píldoras, sellos, polvos, y gránulos. En donde sea apropiado, se pueden preparar con recubrimientos.

Las formas de dosificación líquidas para administración oral incluyen soluciones, emulsiones, suspensiones, jarabes y elixires.

Las composiciones farmacéuticas para administración parenteral incluyen soluciones acuosas estériles e inyectables no acuosas, dispersiones, suspensiones o emulsiones como así también polvos estériles a ser reconstituidos en soluciones inyectables estériles o dispersiones antes del uso.

Otras formas de administración adecuadas incluyen supositorios, atomizadores, ungüentos, cremas, geles, inhalantes, parches dérmicos, implantes, etc.

En forma conveniente, los compuestos de la invención se administran en una dosificación unitaria que contiene dichos compuestos en una cantidad de aproximadamente 0,1 a 500 mg, tales como 10 mg, 50 mg 100 mg, 150 mg, 200 mg o 250 mg de un compuesto de la presente invención.

Para las vías parenterales tales como intravenosa, intratecal, intramuscular y de administración similar, típicamente las dosis están en el orden de aproximadamente la mitad de la dosis empleada para administración oral.

Para la administración parenteral, se pueden emplear soluciones del compuesto de la invención en solución acuosa estéril, propilenglicol acuoso, vitamina E acuosa o aceite de sésamo o maní. Dichas soluciones acuosas deben estar tamponadas en forma adecuada si fuera necesario y el diluyente líquido volverse isotónico primero con suficiente solución salina o glucosa. Las soluciones acuosas son particularmente adecuadas para administración intravenosa, intramuscular, subcutánea e intraperitoneal. El medio estéril acuoso empleado está disponible con facilidad mediante técnicas estándares conocidas por los expertos en la técnica.

Los vehículos farmacéuticos adecuados incluyen diluyentes o rellenos sólidos inertes, solución acuosa estéril y varios solventes orgánicos. Ejemplos de vehículos sólidos son lactosa, terra alba, sacarosa, ciclodextrina, talco, gelatina, agar, pectina, acacia, estearato de magnesio, ácido esteárico, y éteres celulósicos de alquilos inferiores. Ejemplos de vehículos líquidos son jarabe, aceite de maní, aceite de oliva, fosfolípidos, ácidos grasos, aminas de ácido graso, polioxietileno y agua. Las composiciones farmacéuticas formadas por la combinación del compuesto de la invención y los vehículos farmacéuticos aceptables se administran fácilmente en una variedad de formas de dosificación adecuadas para las vías de administración divulgadas.

Las formulaciones de la presente invención adecuadas para administración oral se pueden presentar como unidades discretas tales como cápsulas, o comprimidos, cada uno contiene una cantidad predeterminada del principio activo, y el cual puede incluir un excipiente adecuado. Más aún, las formulaciones disponibles por vía oral

pueden estar en la forma de un polvo o gránulos, una solución o suspensión en un líquido acuoso o no acuoso, o una emulsión líquida de aceite en agua o agua en aceite.

Si un vehículo sólido se utiliza para administración oral, la preparación puede ser un comprimido, por ejemplo colocado en una cápsula de gelatina dura en forma de polvo o pellet o en la forma de una pastilla o sello. La cantidad de vehículos sólido puede variar pero usualmente será de aproximadamente 25 mg hasta aproximadamente 1 g.

Si se utiliza un vehículo líquido, la preparación puede estar en la forma de un jarabe, emulsión, cápsula de gelatina blanda o líquido inyectable estéril tales como una suspensión o solución líquida acuosa o no acuosa.

Los comprimidos se pueden preparar mezclando el principio activo con adyuvantes y/o diluyentes comunes seguido de la compresión de la mezcla en una máquina de tableteado convencional. Ejemplo de adyuvantes o diluyentes comprenden: almidón de maíz, almidón de papa, talco, estearato de magnesio, gelatina, lactosa, gomas, y similares. Cualquier otro adyuvante o aditivos usualmente utilizados a tales fines tales como colorantes, saborizantes, conservantes, etc. se pueden utilizar siempre que sean compatibles con los principios activos.

En una realización, la invención se refiere a una composición farmacéutica que comprende un compuesto de la presente invención junto con un segundo agente antisicótico. En una realización, dicho segundo agente antisicótico se selecciona de antagonistas/agonistas inversos/moduladores negativos/ agonistas parciales de los receptores específicos: receptor D2 de dopamina, receptor D3 de dopamina, receptor D4 de dopamina, PDE10 fosfodiesterasa, receptor 5-HT_{1A} de serotonina, receptor 5-HT_{2A} de serotonina, receptor 5-HT_6 de serotonina, receptor alfa 2 adrenérgico, receptor tipo 1 canabinoide, receptor H3 de histamina, ciclooxigenasas, canales de sodio o transportador de glicina GlyT1; o de agonistas/moduladores positivos/ agonistas parciales de los receptores específicos: receptor 5-HT_{2C} de serotonina, canales KCNQ, receptor NMDA, receptor AMPA, receptor alfa-7 nicotínico, receptor M1 muscarínico, receptor M4 muscarínico, receptor metabotrópico del glutamato mGluR2, receptor metabotrópico del glutamato mGluR5, receptor D1 de dopamina o receptor D5 de dopamina. En una realización, dicho segundo agente antisicótico se selecciona de antisicóticos típicos, antisicóticos atípicos, antagonistas D2, agonistas D2 parciales,

antagonistas PDE10, antagonistas 5-HT_{2A}, antagonistas 5-HT_6 y antagonistas KCNQ4, y en particular antisicóticos atípicos, antagonistas D2, agonistas D2 parciales. Ejemplos particulares de dichos antisicóticos incluyen haloperidol, clorpromazina, sulpirid, risperidona, ziprasidon, olanzapina, quetiapina, y clozapina.

En una realización, la invención se refiere a un kit farmacéutico que comprende un recipiente que incluye un compuesto de la presente invención y un recipiente separado que incluye un fármaco antisicótico. Antisicóticos típicos, antisicóticos atípicos, antagonistas D2, agonistas D2 parciales, antagonistas PDE10, antagonistas 5-HT_{2A}, antagonistas 5-HT_6 y antagonistas KCNQ4, y en particular antisicóticos atípicos, antagonistas D2, agonistas D2 parciales. Ejemplos particulares de tales antisicóticos incluyen haloperidol, clorpromazina, sulpirid, risperidona, ziprasidon, olanzapina, quetiapina, y clozapina.

Todas las referencias, que incluyen publicaciones, solicitudes de patente, y patentes, mencionadas en la presente se incorporan a la presente como referencia en su totalidad y en el mismo grado como si cada referencia fuese indicada en forma individual y específica para ser incorporada como referencia y fuera establecida en su totalidad en la presente (hasta el máximo alcance permitido por la ley), sin considerar cualquier incorporación provista en forma separada de documentos particulares efectuada en cualquier lugar en la presente.

El uso del término “un” y “una” y “la/el” y referentes similares en el contexto de descripción de la invención debe ser considerados como que cubren tanto el singular como el plural, a menos que se indique lo contrario en la presente, o se contradiga claramente en el contexto. Por ejemplo, la frase "el compuesto" debe ser considerada como que se refiere a varios "compuestos" de la invención o un aspecto particular descrito, a menos que se indique lo contrario.

A menos que se indique lo contrario, todos los valores exactos suministrados en la presente son representativos de los valores aproximados correspondientes (por ej., todos los valores ejemplares exactos proporcionados con respecto a un factor o medición particular se pueden considerar como que además proveen una medición aproximada correspondiente, modificada por "aproximadamente," en donde sea apropiado).

La descripción en la presente de cualquier aspecto o aspecto de la invención que utiliza términos tales como "que comprende", "que tiene," "que incluye," o "que contiene" con referencia a un elemento o elementos provee soporte a un aspecto similar o aspecto de la invención que "consiste de", "consiste esencialmente de ", o "comprende sustancialmente" ese elemento o elementos particulares, a menos que se exprese de otro modo o que claramente se contradiga por el contexto (por ej., una composición descripta en la presente como que comprende un elemento particular debe entenderse que además describe una composición que consiste de elemento, a menos que se establezca lo contrario o claramente se contradiga por el contexto).

VÍAS DE SÍNTESIS

Los compuestos de la presente invención de la fórmula general I, en donde R^1-R^{17}, A, y X son como se definieron anteriormente, se pueden preparar por los métodos delineados en los siguientes esquemas de reacción y ejemplos. En los métodos descritos es posible hacer uso de variantes o modificaciones, las cuales son conocidas por los expertos en la técnica o podrían ser evidentes a los mismos. Más aún, otros métodos para preparar compuestos de la invención serán fácilmente evidentes para los expertos a la luz de los siguientes esquemas de reacción y ejemplos

En los compuestos intermedios de las fórmulas generales I – XX, R1-R17, A, y X son como se definieron en la fórmula I.

Para los compuestos, que pueden encontrarse como una mezcla o equilibrio entre dos o más tautómeros, sólo un tautómero está representado en los esquemas, aunque pueda no ser el tautómero más estable. Para los compuestos, que pueden encontrase en formas enantioméricas, estereoisoméricas o geométricas, se especifica su configuración geométrica; de otro modo la estructura representa una mezcla de estereoisómeros. Dichos compuestos incluyen, pero sin limitación, 1,3-cetoésteres o enaminas de la fórmula general IV y VII, los cuales pueden existir en equilibrio entre formas ceto o enol y éste último puede además existir en formas Z y E isoméricas como bien saben los expertos en la técnica. Dichos compuestos además incluyen compuestos de la presente invención de la fórmula general I, los cuales pueden existir como una mezcla de atropisómeros debido a una rotación restringida alrededor de los enlaces carbono-carbono similar al atropisomerismo en los compuestos biarilo orto, orto'-disustituido también conocidos para los expertos en la técnica.

Los materiales iniciales de las formulas generales III, VI, y XI se obtienen o bien de fuentes comerciales como se sintetiza en la Tabla 2 o se pueden preparar fácilmente mediante métodos estándar o sus modificaciones descritas en la literatura.

Los ácidos 2-bromobenzoicos de la fórmula general II se acoplan con ceto-ésteres de la fórmula general III en presencia de una base fuerte tal como hidruro de sodio y cobre o sales de cobre tal como bromuro de cobre (I) en un solvente adecuado tal como 1,4-dioxano, acetonitrilo o un exceso de los ceto-ésteres anteriores a temperatura adecuada tal como reflujo o a 70ºC con la formación de compuestos de la fórmula general IV. Dicha reacción de arilación es bien conocida en general como reacción de acoplamiento tipo Ullmann catalizada con cobre (revisión: S.V. Ley, A.W. Thomas *Angew. Chem. Int. Ed.* **2003**, *42*, 5400). Además, en este caso particular cuando la reacción de acoplamiento involucra compuestos de metileno activado tales como compuestos de la fórmula general IV en presencia de cobre o sales de cobre la reacción es conocida como reacción de Hurtley (W.R.H. Hurtley *J. Chem. Soc.* **1929**, 1870).

Los compuestos de la fórmula general IV obtenidos luego se hacen reaccionar con anilinas de la fórmula general VI con o sin solvente apropiado en las condiciones de calentamiento con la formación de isoquinolonas de la fórmula general VIII mediante la formación intermedia de enaminas de la fórmula general VII los cuales usualmente no se separan de la mezcla de reacción. En forma alternativa, las enaminas de la fórmula general VII se pueden obtener a partir de anilinas de la fórmula general VI en presencia del agente deshidratado apropiado tal como tetraetoxisilano en condiciones de calentamiento o a temperatura ambiente en presencia de una cantidad catalítica de ácido tal como ácido acético. Luego, la reacción de ciclización con la formación de isoquinolonas de la fórmula general VIII se puede llevar a cabo en las condiciones de calentamiento como se mencionó anteriormente o a temperatura ambiente en presencia de un reactivo de acoplamiento apropiado tal como EDC/HOBT.

Más aún, las isoquinolinonas de la fórmula general VIII se pueden obtener directamente de los ácidos 2-bromobenzoico de partida de la fórmula general II y de las enaminas deprotonadasdesprotonizadas de la fórmula general V en un procedimiento de un recipiente modificado que involucra la reacción de Hurtley realizada a 70°C con la formación de los compuestos de la fórmula general VII y la subsiguiente ciclización

realizada a temperatura más elevada. Las enaminas de la fórmula general V están fácilmente disponibles a partir de cetoésteres III y anilinas VI en las condiciones descritas anteriormente para la preparación de enaminas de la fórmula general VII.

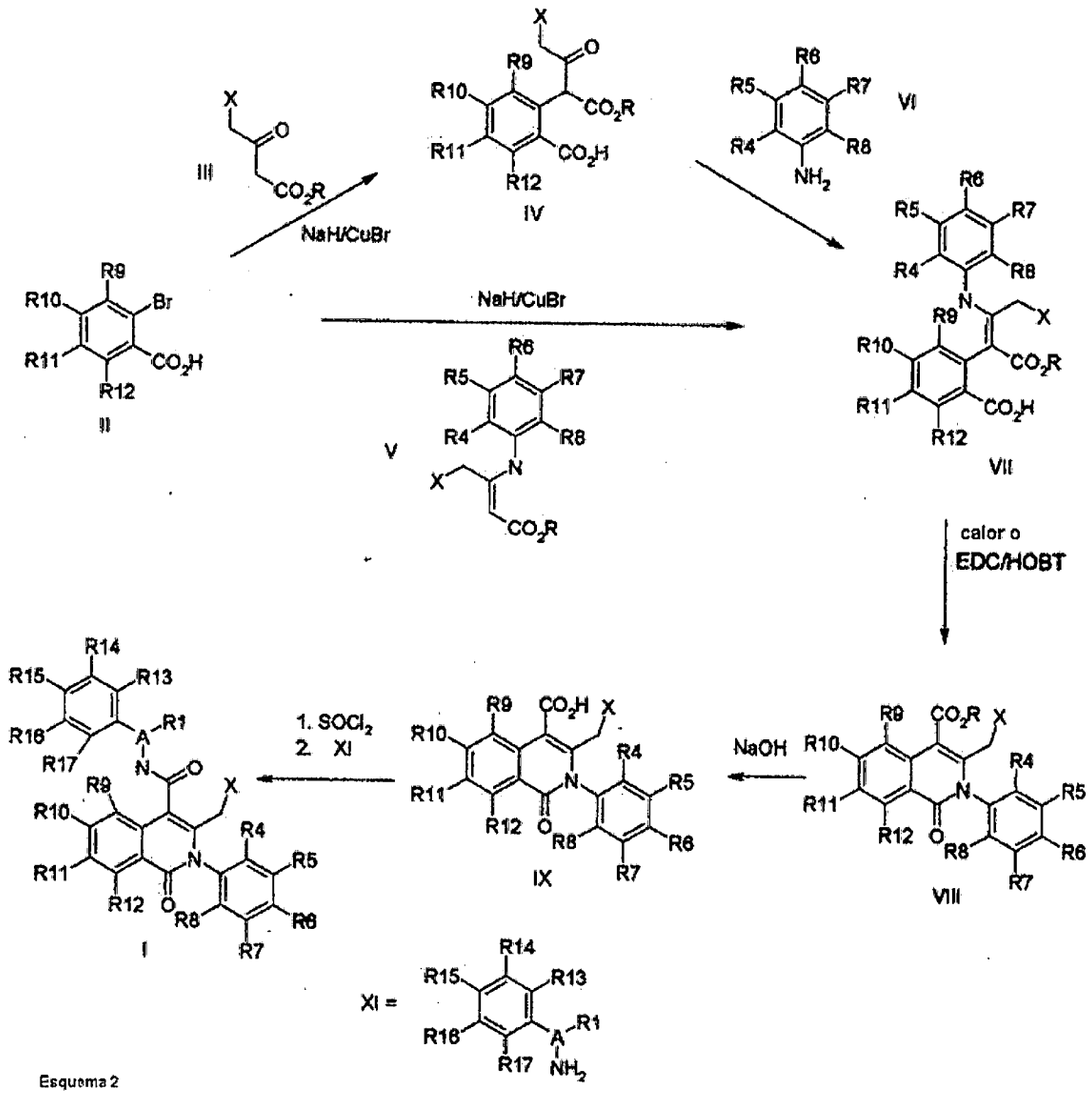
Los compuestos de la fórmula general VIII se hidrolizan fácilmente a los ácidos de la fórmula general IX en condiciones para la hidrólisis de éster bien conocidas para los químicos expertos en la técnica. Finalmente, el subsiguiente acoplamiento con aminas (A = C) o hidracinas (A = N) de la fórmula general XI conduce a la formación de los compuestos de la invención de la fórmula general I. Tales condiciones de acoplamiento usualmente realizadas mediante la activación del ácido con un reactivo de activación o acoplamiento apropiado tal como, pero sin limitación, cloruro de tionilo con la formación del correspondiente cloruro de acilo. Las hidracinas de la fórmula general I en donde R1 = H se pueden convertir en hidrazidas disustituidas de la misma fórmula general en donde R1 no es hidrógeno mediante reacciones de acilación, alquilación o arilación con los reactivos de acilación o alquilación apropiados tales como, pero sin limitación, cloruros de ácido, cloruros de carbamoílo, cloroformiatos o alquilhalogenuros.

Los compuestos de la fórmula general I en donde X es hidrógeno se pueden convertir en los compuestos de la fórmula general XII por la reacción de bromación regioselectivo (sic) en presencia del reactivo para bromación tal como el bromo. Luego el átomo de bromo se puede sustituir por varios nucleófilos de la fórmula general X-H o X^- con la formación de los compuestos de la invención de la fórmula general I. Los expertos en la técnica apreciarán fácilmente que muchos nucleófilos de nitrógeno, carbono y azufre tales como, pero sin limitación, aminas, aminas aromáticas, amidas, heterociclos, alcoholes, fenoles, cianuros o tioles están disponibles en el comercio o son de fácil acceso en la forma neutral o en la forma aniónica desprotonizada requerida para dicha transformación.

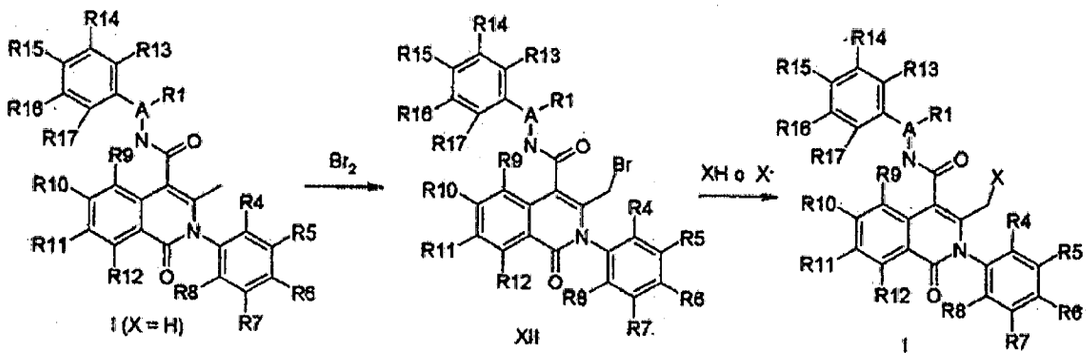
Si fuera necesario, otra derivación o transformación se puede llevar a cabo en los sustituyentes R4-R12 y X utilizando métodos estándar de síntesis orgánica conocidos por las personas con experiencia normal en la técnica.

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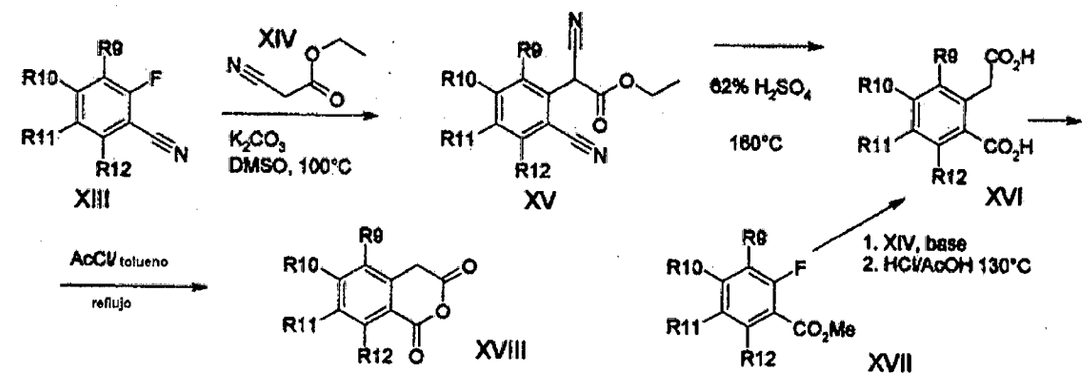
Esquema 1



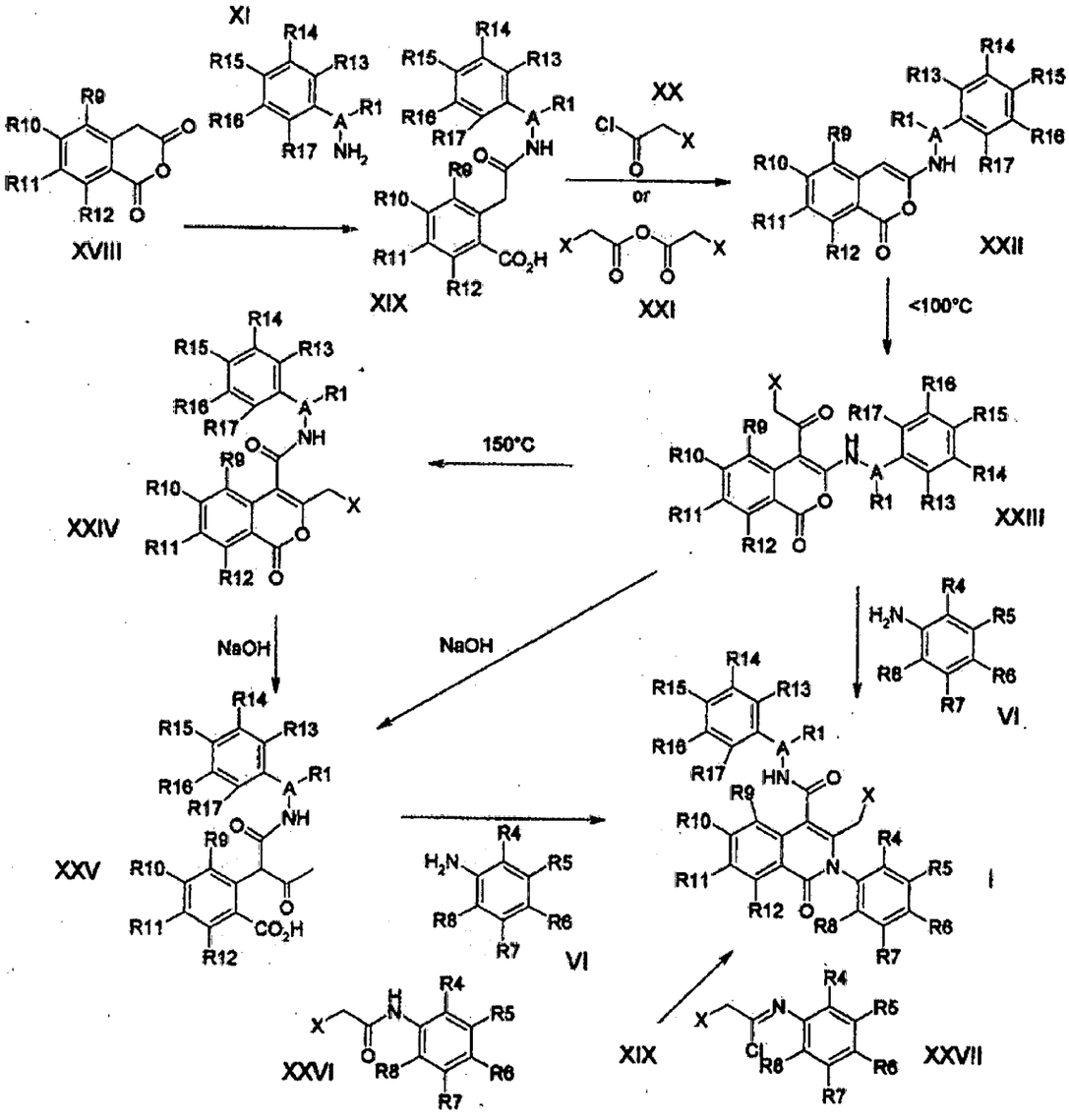
Esquema 2



Esquema 3. Síntesis de anhídridos homoftálicos



Esquema 4



En forma alternativa, los compuestos de la fórmula general I se pueden preparar a partir de anhídridos homoftálicos sustituidos de la fórmula general XVIII como se muestra en el Esquema 4. Los anhídridos homoftálicos están disponibles en el comercio o bien se pueden preparar como se muestra en el Esquema 3 a partir de los

correspondientes fluorobenzonitrilos o fluorobenzoatos de la fórmula general XIII y XVII, respectivamente. Éstos experimentan la reacción de sustitución nucleofílica aromática con cianoacetato XIV de etilo en presencia de una base tal como carbonato de potasio o carbonato de cesio en condiciones de calentamiento en solvente apropiado tal como dimetilsulfóxido. Los productos de acoplamiento se hidrolizan en presencia de los ácidos fuertes tales como ácidos sulfúrico o clorhídrico en agua en condiciones de calentamiento con la formación de diácidos de la fórmula general XVI. Finalmente, los diácidos se convierten en los anhídridos homoftálicos de la fórmula general XVIII en presencia del agente de deshidratación tal como, pero sin limitación, cloruro de acetilo sin un solvente o en el solvente apropiado tal como tolueno en condiciones de calentamiento tal como reflujo.

Los anhídridos homoftálicos de la fórmula general XVIII se pueden convertir regioselectivamente en amidas de ácidos de la fórmula general XIX a temperatura ambiente o en condiciones de calentamiento en el solvente apropiado tal como acetonitrilo. Luego se tratan con los anhídridos de ácido apropiados o cloruros de ácido de la fórmula general XX y XXI, respectivamente, en ausencia o presencia de una base tal como trietilamina y DMAP en el solvente apropiado, usualmente en acetonitrilo, a temperatura ambiente o en condiciones de calentamiento suaves (T < +100°C). Esta transformación primero provee intermedios ceteno-aminales de la fórmula general XXII, los cuales experimentan además la reacción de acilación con la formación de los compuestos de la fórmula general XXIII. El posterior calentamiento a temperatura más elevada tal como a +150°C conduce al reordenamiento con la formación de amidas de la fórmula general XIV. Ambos compuestos de la fórmula general XXIII y XXIV se pueden hidrolizar fácilmente a temperatura ambiente con una base apropiada tal como hidróxido de sodio en metanol acuoso o tetrahidrofurano acuoso en forma de solvente. Los ceto-ácidos obtenidos de la fórmula general XXV o los ceteno-aminales de la fórmula general XXIII se convierten en los compuestos finales de la invención de la fórmula general I por condensación con anilinas de la fórmula general VI en las mismas condiciones que las descritas anteriormente para la condensación de ceto-ácidos de la fórmula general IV.

En forma alternativa, las amidas de los ácidos de la fórmula general XIX se pueden convertir directamente en los compuestos de la invención de la fórmula general

I por condensación con los cloruros de imidoílo apropiados de la fórmula general XXVII los cuales están disponibles fácilmente a partir de la correspondiente amida de la fórmula general XXVI, los cuales se preparan fácilmente mediante el acoplamiento bien conocido entre la anilina de la fórmula general VI y los correspondientes carboxílicos o sus anhídridos o cloruros de acilo de la fórmula general XX y XXI, respectivamente.

Ejemplos

LC-MS analítica, método A (utilizado en la mayoría de los casos a menos que se indique lo contrario): los datos se obtuvieron en un sistema de LC/MS analítico Sciex API 150EX equipado con un espectrómetro de masa de cuadripolo simple Applied Biosystems API150EX y fuentes iónicas de fotoionización a presión atmosférica (APPI), bombas Shimadzu LC10ADvp LC (3X), detector de arreglo de fotodiodos Shimadzu SPD-M20A, SEDERE Sedex 85 - detector de dispersión de luz por evaporación a baja temperatura (ELSD), controlador de sistema Shimadzu CBM-20A, toma muestras automático Gilson 215 y desgasificador controlado por Analyst Software Gilson 864. Columna: 30 X 4,6 mm Waters Symmetry C18 columna con 3,5 µm de tamaño de partícula; Volumen de inyección: 15 µl; Temperatura de columna: 60°C; Sistema de solvente: A = agua/ácido trifluoroacético (100:0,05) y B = agua/acetonitrilo/ácido trifluoroacético (5:95:0,035); Método: elución de gradiente lineal con 10% B a 100% B en 2,4 minutos luego con 10% B en 0,4 minutos y con un caudal de 3,3 ml/minuto. Los tiempos de retención (Tr) se expresa en minutos sobre la base del trazado en UV a 254 nm.

LC-MS analítica, método B: los datos se obtuvieron sobre un sistema LC/MS analítico Sciex API300 equipado con espectrómetro de masa de triple cuadripolo Applied Biosystems API300 con fuentes iónicas de fotoionización a presión atmosférica (APPI), bombas Shimadzu LC10ADvp LC (3X), detector de arreglo de fotodiodos Shimadzu SPD-M20A, Polymer Labs PL-ELS 2100 - detector de dispersión de luz por evaporación a baja temperatura (ELSD), controlador de sistema Shimadzu SCL10A VP, muestreador automático Gilson 215 y desgasificador controlado por Analyst Software Gilson 864. Columna: Symmetry C18 3,5 µm, 4,6 x 30 mm 30 X 4,6 mm; volumen de inyección: 5 µl; temperatura de columna: 60°C; sistema de solvente: A = agua/ácido trifluoroacético (100:0,05) y B = agua/acetonitrilo/ácido trifluoroacético (5:95:0,035);

Método: elución de gradiente lineal con 10% B a 100% B en 1,45 minutos luego con 10% B en 0,55 minutos y con un caudal de 5,5 ml/minuto:

Tiempo, min.	%B
0,00	10,0
1,45	100,0
1,55	10,0
2,0	10,0

Los tiempos de retención (T_r) se expresan en minutos sobre la base del trazado en UV a 254 nm.

La purificación por LC-MS preparativa se llevó a cabo sobre el mismo sistema Sciex API 150EX equipado con bombas Gilson 333 y 334, bomba Shimadzu LC10ADvp, detector Gilson UV/VIS 155 UV, muestreador automático Gilson 233XL, fracción Gilson FC204, interfaz de sistema Gilson 506C, desgasificador Gilson 864, separador de flujo DIY (aprox. 1:1000), y separador de flujo LC Packings Accurate (1:10.000 @ 140 ml/min). La EM y el recolector de fracciones se controlaron por un software Masschrom (Macintosh PC), el sistema de LC se controló por software Unipoint. Para una pequeña escala (<20 mg) las fracciones de purificación se recolectaron en recipientes de 4 ml utilizando Symmetry C18 5 µm, columna 10 x 50 mm, volumen de inyección de 0-300 µL, caudal de 5,7 ml/min y duración de 8 min. Gradiente:

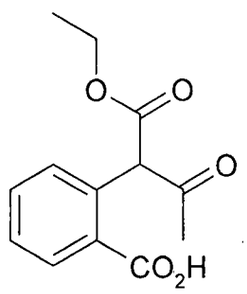
Time, min.	%B
0,00	10,0-50,0 (variable, dependiendo de la muestra)
7,00	100,0
7,10	10,0-50,0
8,00	10,0-50,0

Los espectros de ^{1}H RMN se registraron a 500,13 MHz en un instrumento Bruker Avance DRX-500 a T=303,3 K. La temperatura variable de los espectros ^{1}H RMN se registró a 250 MHz en un instrumento Bruker Avance DPX-250. El dimetilsulfóxido deuterado (DMSO-d_6, 99,8% D) se utilizó como solvente a menos que se especifique de

otro modo. El tetrametilsilano se utilizó como estándar de referencia interno. Los valores de desplazamiento químico se expresan en valores en ppm con relación al tetrametilsilano. Las siguientes abreviaturas o sus combinaciones se utilizaron para multiplicidad de señales de RMN: s = singulete, d = doblete, t = triplete, q = cuarteto, qui = quinteto, h = hepteto, dd = doble doblete, ddd = doble doble doblete, dt = doble triplete, dq = doble cuarteto, tt = triplete de tripletes, m = multiplete y br = amplio o singulete amplio

Los experimentos con microondas se realizaron en recipientes o reactores sellados para proceso utilizando un Emrys Synthesizer o Emrys Optimizer EXP de Personal Chemistry o un instrumento Milestone Microsynth de Milestone. Antes de sellar el recipiente del proceso se le hizo una descarga de argón. Cuando la reacción se calentó en un instrumento de microondas, se enfrió hasta 25°C antes del próximo paso del proceso.

Preparación de intermedios



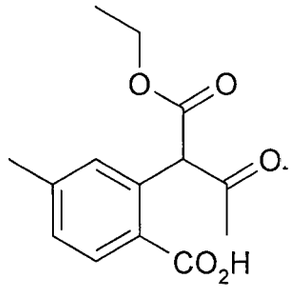
Ácido 2-(1-etoxicarbonil-2-oxo-propil)-benzoico.

A una mezcla agitada en frío (baño hielo/agua) de ácido 2-bromobenzoico (20,1g, 0,1 mol) y acetoacetato de etilo (13,01 g, 0,1 mol) en 1,4-dioxano (200 ml) hidruro de sodio (8 g, 0,2 mol, dispersión al 60% en aceite mineral) se agregó en pequeñas porciones. Después de la adición el baño frío se eliminó y la mezcla de reacción se dejó agitar a temperatura ambiente durante 10 minutos. Se agregó bromuro de cobre (I) (15,2 g, 0,106 mol) en porciones y la mezcla obtenida se calentó a reflujo durante 1 hora. Se dejó enfriar y se agitó durante la noche a temperatura ambiente. La suspensión verde obtenida se enfrió con acetato de etilo (200 ml) y con hielo (300 g) y se acidificó con HCl concentrado (50 ml). La fase orgánica se lavó con HCl 2 M acuoso (2x100 ml) y salmuera, se secó (Na_2SO_4) y se evaporó al vacío. El aceite mineral

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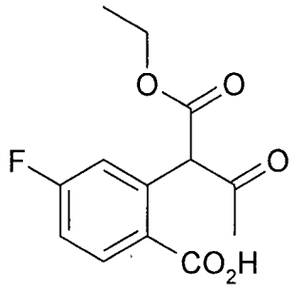
restante se eliminó por decantación después de agitar con heptano (3x100 ml) y evaporación. Rendimiento alrededor de 20g, aceite de amarillo pálido. El producto crudo se utilizó en el próximo paso sin purificación posterior. LC-MS (m/z) 205 ([M-CO_2]$^+$); t_R = 0,91. ^{1}H RMN (500 MHz, DMSO-d_6): mezcla de al menos 3 tautómeros.

Los siguientes compuestos se prepararon en forma análoga a partir de los correspondientes ácidos 2-bromobenzoicos y se utilizaron en el próximo paso sin purificación posterior y caracterización a menos que se especifique lo contrario:

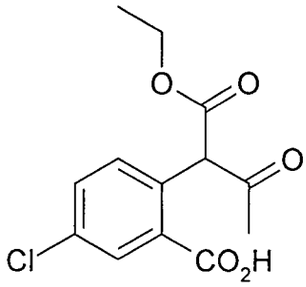


Ácido 2-(1-etoxicarbonil-2-oxo-propil)-4-metil-benzoico.

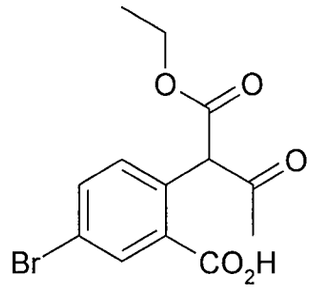
LC-MS (m/z) 247,2 ([MH-H_2O]$^+$); T_R = 1,05.



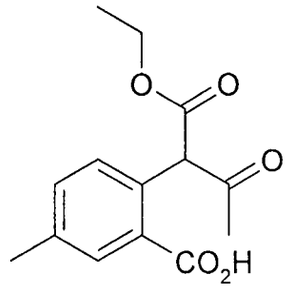
Ácido 2-(1-etoxicarbonil-2-oxo-propil)-4-fluoro-benzoico.



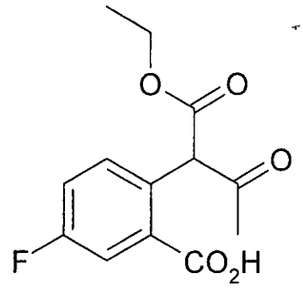
Ácido 5-cloro-2-(1-etoxicarbonil-2-oxo-propil)-benzoico.



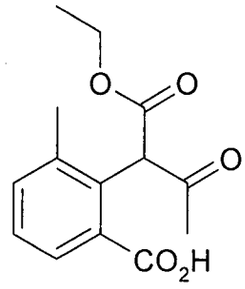
Ácido 5-bromo-2-(1-etoxicarbonil-2-oxo-propil)-benzoico.



Ácido 2-(1-etoxicarbonil-2-oxo-propil)-5-metil-benzoico.

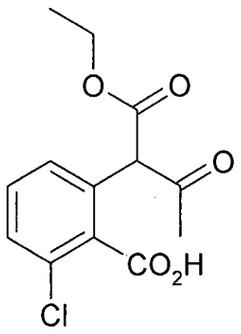


Ácido 2-(1-etoxicarbonil-2-oxo-propil)-5-fluoro-benzoico.

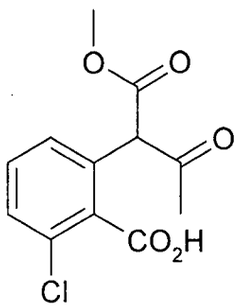


Ácido 2-(1-etoxicarbonil-2-oxo-propil)-3-metil-benzoico.

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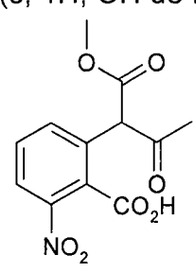


Ácido 2-cloro-6-(1-etoxicarbonil-2-oxo-propil)-benzoico.

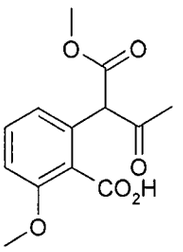


Ácido 2-cloro-6-(1-metoxicarbonil-2-oxo-propil)-benzoico.

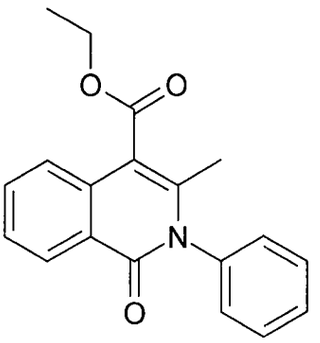
A una mezcla agitada de ácido 2-bromo-6-clorobenzoico (20 g, 85 mmol), acetoacetato de metilo (310 ml, exceso), y bromuro de cobre (I) 12,2 g, 85 mmol) se agregó hidruro de sodio (8,5 g, 212 mmol, 60% en aceite) en porciones y luego se calentó a 70°C durante 16 horas. La mezcla resultante se diluyó con agua (600 ml) y se extrajo con éter dietílico (3 x 500 ml). La fase acuosa se acidificó con HCl 2M y se extrajo con acetato de etilo (2 x 800 ml). La solución orgánica combinada se lavó con salmuera (100 ml), se secó (Na_2SO_4) y se evaporó. El aceite obtenido se trató con una mezcla caliente de acetato de etilo (20 ml) y heptano (200 ml) y se decantó, dos veces, se secó al vacío para dar 8 g de sólido de amarillo-marrón, rendimiento 34%. ^{1}H RMN (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 de forma enol), 13,4 (br, 1H, CO_2H).



Ácido 2-(1-metoxicarbonil-2-oxo-propil)-6-nitro-benzoico.



Ácido 2-metoxi-6-(1-metoxicarbonil-2-oxo-propil)-benzoico.

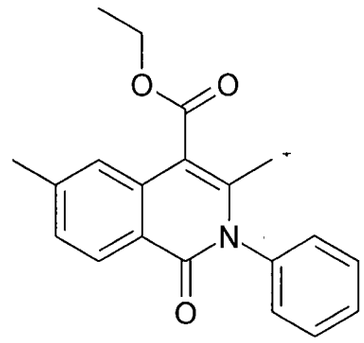


Etil éster del ácido 3-metil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico.

Una mezcla de ácido 2-(1-etoxicarbonil-2-oxo-propil)-benzoico (7,6 g, 30,4 mmol) y anilina (10 ml, 108 mmol) se limpió con argón, se selló en el recipiente de proceso Emrys y se calentó a 150°C durante 15 min bajo irradiación de microondas. Los volátiles se eliminaron al vacío y el residuo obtenido se dividió por partición entre acetato de etilo (100 ml) y HCl 2M (100 ml). La capa orgánica se lavó con salmuera (2 x 20 ml), se secó (Na_2SO_4) y se evaporó para dar 8,7 g de aceite marrón que se solidificó. El producto crudo obtenido fue de alrededor de 90% de pureza de acuerdo con ^{1}H RMN y puede ser usado en el próximo paso sin purificación posterior. En forma alternativa, el producto crudo se disolvió en acetato de etilo caliente (20 ml), precipitó con heptano (60 ml), se dejó enfriar, se filtró y se lavó con éter dietílico para dar 4,2 g de un sólido cristalino de marrón pálido, rendimiento 45%. LC-MS (m/z) 308,2 (MH^+); t_R = 1,43. ^{1}H RMN (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 (m traslapado), 3H), 7,62 (d, 1H), 7,8 (t, 1H), 8,22 (d, 1H).

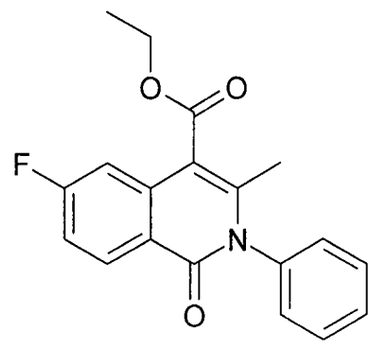
Los siguientes compuestos se prepararon en forma análoga a partir de los correspondientes ácidos 2-(1-etoxicarbonil-2-oxo-propil)-4-metilbenzoico crudos y las correspondientes anilinas.

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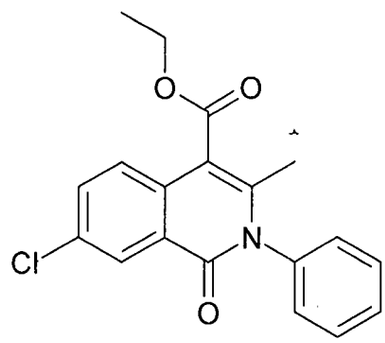
Etil éster del ácido 3,6-dimetil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico.

El producto crudo se utilizó en el próximo paso sin cristalización. LC-MS (m/z) 322,1 (MH^+); t_R = 1,53. ^1H RMN (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).



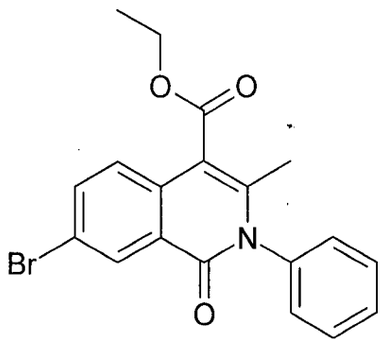
Etil éster del ácido 6-fluoro-3-metil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico.

El producto crudo se utilizó en el próximo paso sin cristalización. LC-MS (m/z) 326,3 (MH^+); t_R = 1,54. ^1H RMN (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).



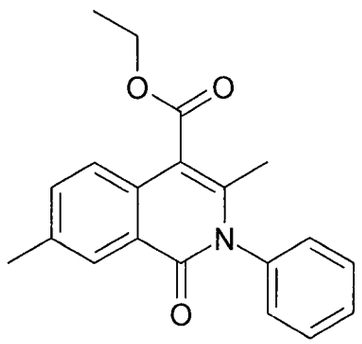
Etil éster del ácido 7-cloro-3-metil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico.

El producto crudo se utilizó en el próximo paso sin cristalización. LC-MS (m/z) 342,0 (MH^+); t_R = 1,67. ^1H RMN (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).



Etil éster del ácido 7-bromo-3-metil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico.

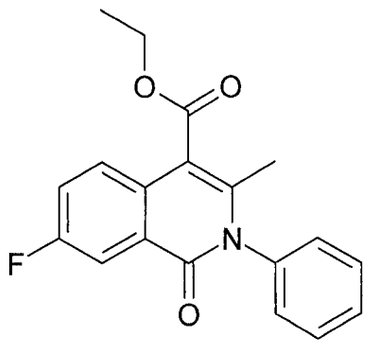
El producto crudo se utilizó en el próximo paso sin cristalización. LC-MS (m/z) 386,1 (MH^+, ^{79}Br); t_R = 1,71. ^1H RMN (500 MHz, DMSO-d_6): 1,33 (t, 3H), 1,98 (s, 3H), 4,4 (q, 2H), 7,39 (d, 2H), 7,51 (t, 1H), 7,57 (t, 2H), 7,62 (d, 1H), 7,96 (dd, 1H), 8,29 (d, 1H).



Etil éster del ácido 3,7-dimetil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico.

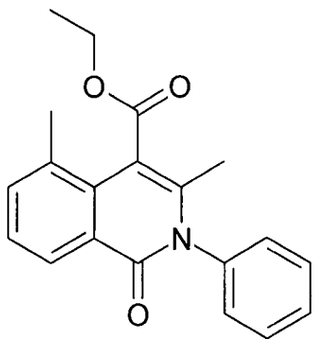
El producto crudo en forma de un aceite marrón se utilizó en el próximo paso sin purificación. LC-MS (m/z) 322,2 (MH^+); t_R = 1,59.

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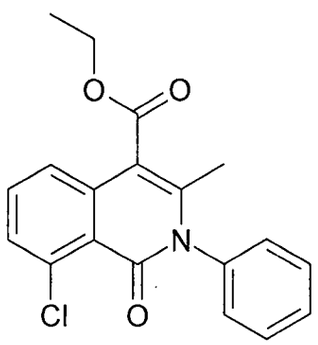
Etil éster del ácido 7-fluoro-3-metil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico.

El producto crudo en forma de un aceite marrón se utilizó en el próximo paso sin purificación. LC-MS (m/z) 326,1 (MH^+); t_R = 0,79 (método B).



Etil éster del ácido 3,5-dimetil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico.

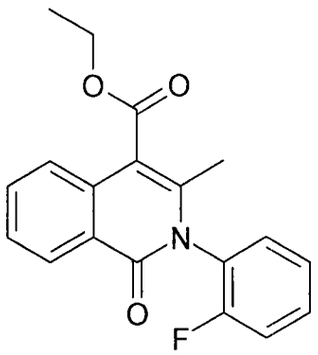
El producto crudo se utilizó en el próximo paso sin purificación. LC-MS (m/z) 322,1 (MH^+); t_R = 1,63.



Etil éster del ácido 8-cloro-3-metil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico.

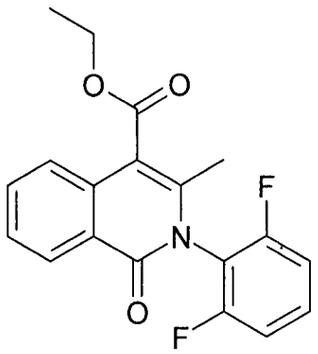
El producto crudo se utilizó en el próximo paso sin purificación. LC-MS (m/z) 342,0 (MH^+); t_R = 1,55.

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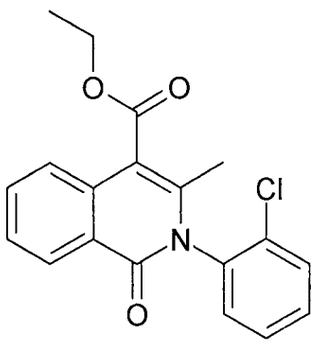
Etil éster del ácido 2-(2-fluoro-fenil)-3-metil-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico.

LC-MS (m/z) 326,5 (MH^+); t_R = 1,46.



Etil éster del ácido 2-(2,6-difluoro-fenil)-3-metil-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico.

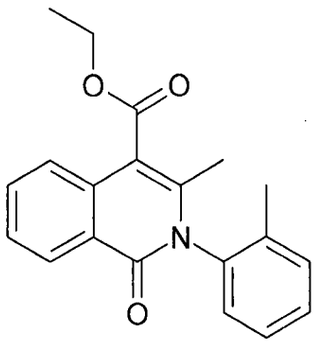
El producto crudo se utilizó en el próximo paso sin purificación y caracterización.



Etil éster del ácido 2-(2-cloro-fenil)-3-metil-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico

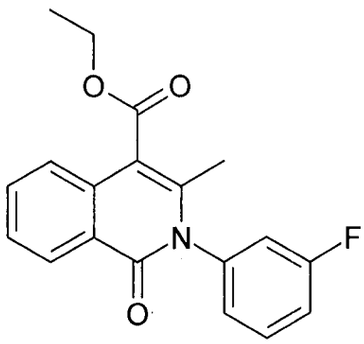
El producto crudo se utilizó en el próximo paso sin purificación y caracterización.

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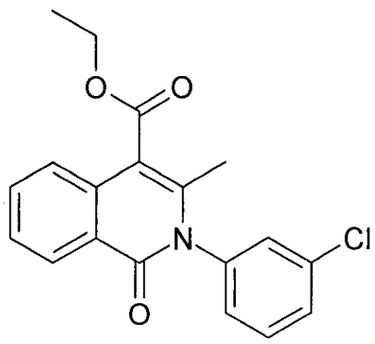
Etil éster del ácido 3-metil-1-oxo-2-o-tolil-1,2-dihidro-isoquinolin-4-carboxílico

El producto crudo se utilizó en el próximo paso sin purificación y caracterización.



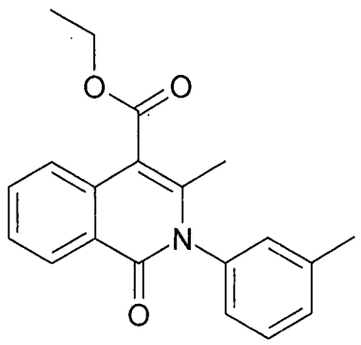
Etil éster del ácido 2-(3-fluoro-fenil)-3-metil-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico

LC-MS (m/z) 326,3 (MH^+); t_R = 1,47.



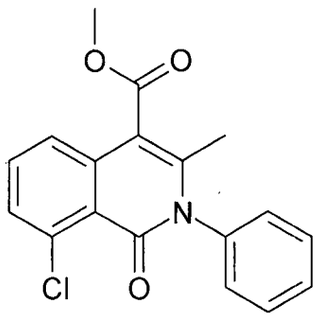
Etil éster del ácido 2-(3-cloro-fenil)-3-metil-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico

LC-MS (m/z) 342,1 (MH^+); t_R = 1,61.



Etil éster del ácido 3-metil-1-oxo-2-m-tolil-1,2-dihidro-isoquinolin-4-carboxílico

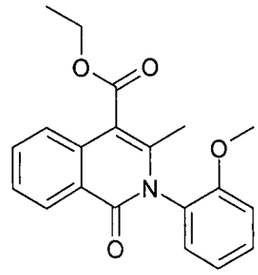
LC-MS (m/z) 322,1 (MH^+); t_R = 1,57.



Metil éster del ácido 8-cloro-3-metil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

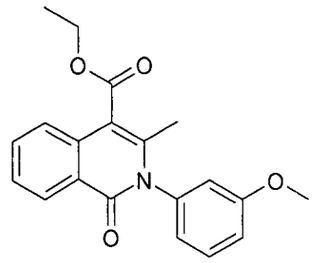
Una mezcla del ácido 2-cloro-6-(1-metoxicarbonil-2-oxo-propil)-benzoico (4 g, 15 mmol), anilina (1,369 ml, 15 mmol) y tetraetoxisilano (6,65 ml, 30 mmol) en metanol (20 ml) se selló y se calentó bajo irradiación de microondas a +150°C durante 20 min. La solución obtenida se diluyó con agua (150 ml) se extrajo con acetato de etilo (2x300 ml). La solución orgánica combinada se secó ($MgSO_4$) y se evaporó. La enamina cruda obtenida (ácido 2-cloro-6-(1-metoxicarbonil-2-fenilamino-propenil)-benzoico) se disolvió en dimetilformamida (80 ml) seguido por la adición de clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (EDC, 4,3 g, 22,5 mmol) y 1-hidroxibenzotriazol (HOBT, 3,04 g, 22,5 mmol). Se agitó durante 16 horas y se dividió por partición entre agua (250 ml), éter dietílico (250 ml) y acetato de etilo (150 ml). La fase orgánica se lavó con NaOH 0,5 M (2x100 ml), salmuera (2x200 ml), se secó ($MgSO_4$) y se evaporó para dar 4,25 g de aceite marrón, el cual se utilizó en el próximo paso sin purificación posterior. Rendimiento 87%. LC-MS (m/z) 328,0 (MH^+); t_R = 1,36. ^1H RMN (500 MHz, $CDCl_3$): 2,02 (s, 3H), 3,98 (s, 3H), 7,23 (d, 2H), 7,44-7,55 (m, 6H).

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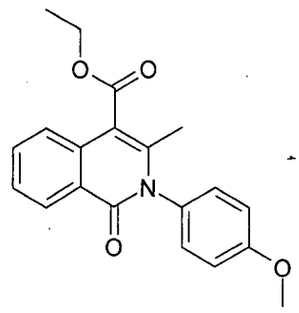
Etil éster del ácido 2-(2-metoxi-fenil)-3-metil-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico

El compuesto del título se utilizó en el próximo paso sin purificación. LC-MS (m/z) 338,3 (MH^+); t_R = 1,38.



Etil éster del ácido 2-(3-metoxi-fenil)-3-metil-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico

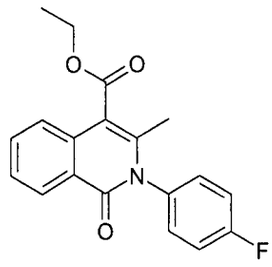
El compuesto del título se utilizó en el próximo paso sin purificación. LC-MS (m/z) 338,5 (MH^+); t_R = 1,41.



Etil éster del ácido 2-(4-metoxi-fenil)-3-metil-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico

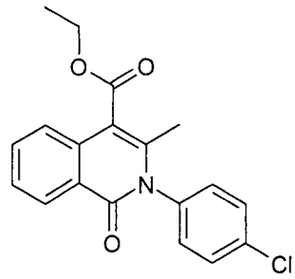
El compuesto del título se utilizó en el próximo paso sin purificación. LC-MS (m/z) 338,5 (MH^+); t_R = 1,4.

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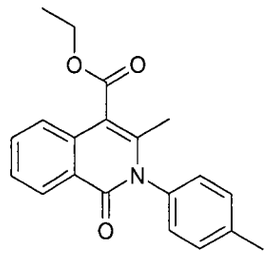
Etil éster del ácido 2-(4-fluoro-fenil)-3-metil-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico

El compuesto del título se utilizó en el próximo paso sin purificación. LC-MS (m/z) 326,2 (MH^+); t_R = 1,41.



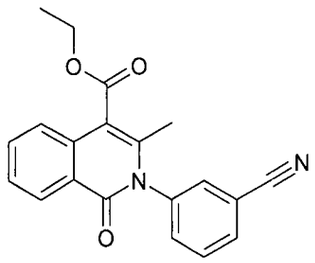
Etil éster del ácido 2-(4-cloro-fenil)-3-metil-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico

El compuesto del título se utilizó en el próximo paso sin purificación. LC-MS (m/z) 342,2 (MH^+); t_R = 1,53.



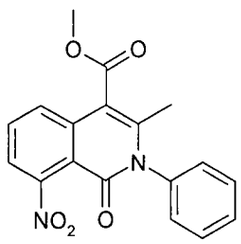
Etil éster del ácido 3-metil-1-oxo-2-p-tolil-1,2-dihidro-isoquinolin-4-carboxílico

El compuesto del título se utilizó en el próximo paso sin purificación. LC-MS (m/z) 321,7 (MH^+); t_R = 1,51.



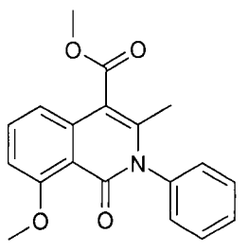
Etil éster del ácido 2-(3-ciano-fenil)-3-metil-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico

El compuesto del título se utilizó en el próximo paso sin purificación. LC-MS (m/z) 333,0 (MH^+); t_R = 1,3.



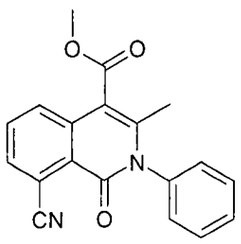
Metil éster del ácido 3-metil-8-nitro-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

El compuesto del título se utilizó en el próximo paso sin purificación. LC-MS (m/z) 339,3 (MH^+); t_R = 1,26.



Metil éster del ácido 8-metoxi-3-metil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

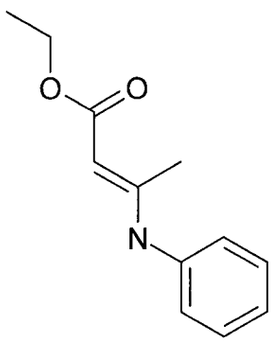
El compuesto del título se utilizó en el próximo paso sin purificación. LC-MS (m/z) 324,3 (MH^+); t_R = 1,12.



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Metil éster del ácido 8-ciano-3-metil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

Una suspensión de metil éster del ácido 3-metil-8-nitro-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico (320 mg, 0,95 mmol) y Zn (898 mg, 13,8 mmol) en THF (4,5 ml) y HCl acuoso 2M (4,5 ml) se agitó durante 10 minutos, se filtró y se dividió por partición entre acetato de etilo (3x150 ml) y $NaHCO_3$ ac. sat. (100 ml). La solución orgánica combinada se secó ($MgSO_4$) y se evaporó para dar metil éster del ácido 8-amino-3-metil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico en forma de un aceite oscuro (200 mg, 0,645 mmol, 69% de rendimiento. LC-MS (m/z) 309,4 (MH^+); t_R = 1,2. Se disolvió en HCl ac. conc. (0,4 ml) y H_2O (3,25 ml). A la solución obtenida se agregó $NaNO_2$ (46,3 mg, 0,645 mmol, en 0,12 ml H_2O) gota a gota a 0°C. Después de 15 min se neutralizó (pH = 6-7) con $NaHCO_3$ ac. sat. para dar solución de sal de diazonio. A una solución de KCN (202 mg, 3 mmol) en agua (0,4 ml) se agregó gota a gota solución de $CuSO_4x5H_2O$ (197 mg, 0,774 mmol) en agua (0,8 ml) a 0°C. Después de terminar la adición se agregó benceno (2 ml) y la mezcla se calentó hasta +60°C. A esta mezcla se agregó gota a gota la solución de sal de diazonio durante 15 min, luego se mantuvo a 70°C durante 85 min. Se dejó enfriar hasta temperatura ambiente, se diluyó con acetato de etilo (10 ml) y se filtró vía tapón de celite. La capa orgánica se lavó con salmuera (10 ml), se secó ($MgSO_4$) y se evaporó para dar 97,9 mg del compuesto del título (48% de rendimiento). LC-MS (m/z) 319,2 (MH^+); t_R = 1,15.

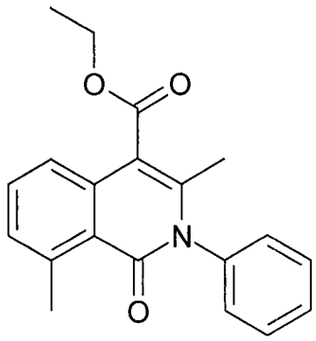


Etil éster del ácido 3-fenilamino-but-2-enoico

El compuesto se preparó de acuerdo con el procedimiento descrito (Q. Dai, W. Yang, y X. Zhang *Org. Letters* **2005**, 5343).

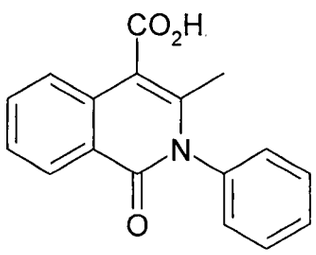
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^{1}H RMN (500 MHz, DMSO-d_6): 1,19 (t, 3H), 2,01 (s, 3H), 4,06 (q, 2H), 4,7 (s, 1H), 7,17 (t traslapado, 1H), 7,18 (d traslapado, 2H), 7,36 (t, 2H), 10,36 (s, 1H).



Etil éster del ácido 3,8-dimetil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

A una solución fría (baño de hielo/agua) de ácido 2-bromo-6-metil-benzoico (650 mg, 3,023 mmol) y etil éster del ácido 3-fenilamino-but-2-enoico (750 mg, 3,65 mmol) en acetonitrilo (10 ml), se agregó en porciones hidruro de sodio (267 mg, 6,67 mmol, dispersión al 60% en aceite mineral). El baño frío se eliminó y la mezcla se sometió a tratamiento sónico a temperatura ambiente hasta que cesó la evolución de gas (10 min). Se agregó bromuro de cobre (I) (957 mg, 6,67 mmol) y la suspensión obtenida se limpió con argón, se selló y se calentó bajo irradiación de microondas a +80°C durante 30 min. LC-MS indicó una conversión total en ácido 2-(1-etoxicarbonil-2-fenilamino-propenil)-6-metil-benzoico (LC-MS (m/z) 340,4 (MH^+); t_R = 1,59. La suspensión obtenida se calentó a +160°C bajo irradiación de microondas durante 30 min. Se diluyó con acetato de etilo (50 ml) y se filtró. La solución orgánica obtenida se lavó con HCl 1M (3 x 50 ml), agua (2 x 10 ml) y solución de $NaHCO_3$ ac. sat. (30 ml), adsorbida sobre SiO_2 (3 g) y se sometió a cromatografía flash (cromatografía rápida con columna corta) sobre SiO_2 (50 g, gradiente heptano –acetato de etilo al 30% en heptano) para dar 217 mg de aceite amarillo. Rendimiento 22%. LC-MS (m/z) 322,2 (MH^+); t_R = 1,62. ^{1}H RMN (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 (m traslapado, 3H), 7,49 (m, 1H), 7,55 (t, 2H), 7,61 (t, 1H).

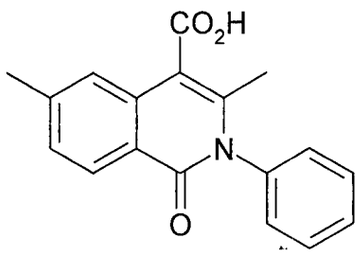


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Ácido 3-metil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico.

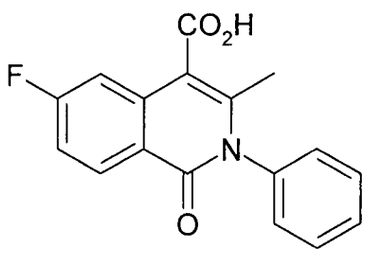
Se disolvió etil éster del ácido 3-metil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico (4,2 g, 13,7 mmol) en 100 ml de metanol caliente y se agregó una solución de NaOH (6 g) en agua (20 ml). La mezcla de reacción se calentó a reflujo durante 2 hrs, se diluyó con agua (200 ml) y se agitó durante la noche a temperatura ambiente. Los volátiles orgánicos se eliminaron a presión reducida y la solución acuosa obtenida se extrajo con acetato de etilo (2 x 50 ml). La solución acuosa se vertió en hielo/HCl 2M (150 ml). La suspensión obtenida se sometió a tratamiento sónico, y el producto se separó por filtración, se lavó con agua y se secó al vacío para dar 2,9 g de un sólido incoloro, rendimiento 76%. LC-MS (m/z) 280,2 (MH^+); t_R = 0,9. ^{1}H RMN (500 MHz, DMSO-d_6): 2,01 (s, 3H), 7,36 (d, 2H), 7,50 (t, 1H), 7,56 (q (m traslapado), 3H), 7,72 (d, 1H), 7,81 (t, 1H), 8,22 (d, 1H), 13,5 (br, 1H).

Los siguientes ácidos se prepararon en forma análoga a partir de los correspondientes ésteres de etilo:



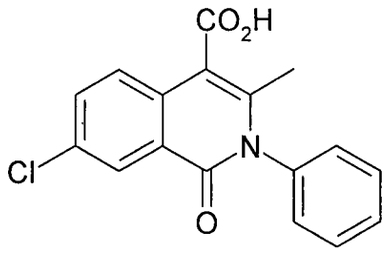
Ácido 3,6-dimetil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico.

LC-MS (m/z) 293,9 (MH^+); t_R = 0,99. ^{1}H RMN (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).



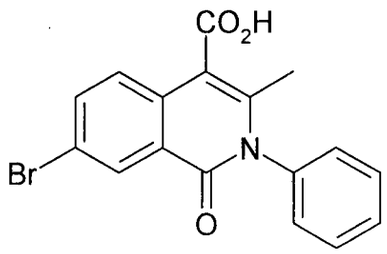
Ácido 6-fluoro-3-metil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico.

LC-MS (m/z) 298,4 (MH^+); t_R = 0,99. ^{1}H RMN (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).



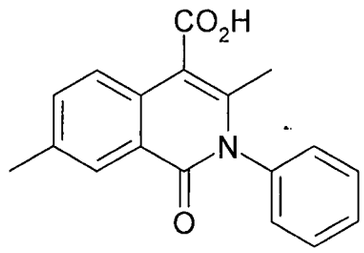
Ácido 7-cloro-3-metil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico.

El producto crudo se utilizó en el próximo paso sin cristalización. LC-MS (m/z) 314,2 (MH^+); t_R = 1,13. ^1H RMN (500 MHz, DMSO-d_6): ^1H RMN (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).



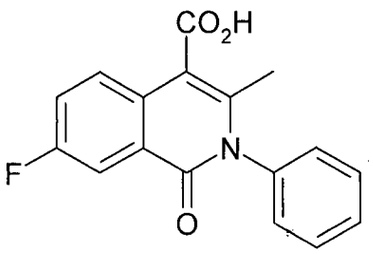
Ácido 7-bromo-3-metil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico.

LC-MS (m/z) 358,1 (MH^+, ^{79}Br); t_R = 1,2. ^1H RMN (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).



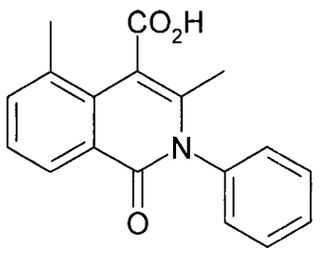
Ácido 3,7-dimetil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico.

LC-MS (m/z) 293,9 (MH^+); t_R = 1,02. ^1H RMN (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).



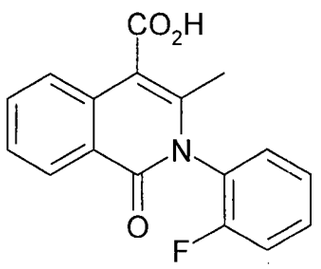
Ácido 7-fluoro-3-metil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico.

LC-MS (m/z) 298,2 (MH^+); t_R = 1,01. ^1H RMN (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).



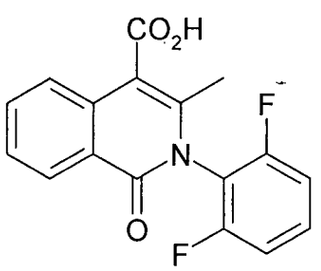
Ácido 3,5-dimetil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico.

LC-MS (m/z) 294,1 (MH^+); t_R = 1,09. ^1H RMN (500 MHz, DMSO-d_6): 1,95 (s, 3H), 2,74 (s, 3H), 7,27-7,64 (m, 8H), 13,35 (b, 1H).



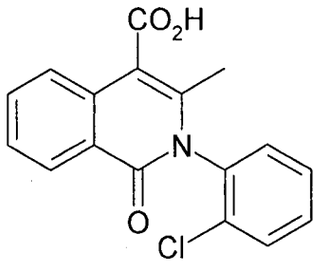
Ácido 2-(2-fluoro-fenil)-3-metil-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico.

LC-MS (m/z) 298,4 (MH^+); t_R = 0,83.



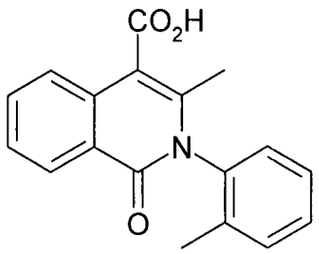
Ácido 2-(2,6-difluoro-fenil)-3-metil-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico.

LC-MS (m/z) 316,2 (MH^+); t_R = 1,03.



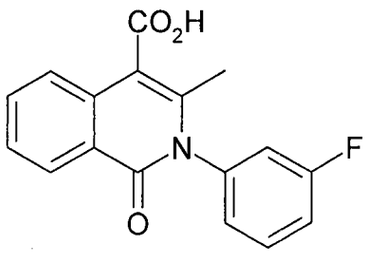
Ácido 2-(2-cloro-fenil)-3-metil-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico.

LC-MS (m/z) 314,2 (MH^+); t_R = 1,0.



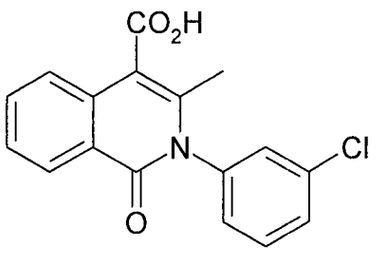
Ácido 3-metil-1-oxo-2-o-tolil-1,2-dihidro-isoquinolin-4-carboxílico.

LC-MS (m/z) 294,1 (MH^+); t_R = 0,99.



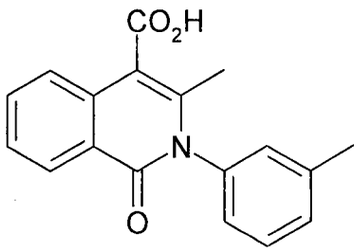
Ácido 2-(3-fluoro-fenil)-3-metil-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico.

LC-MS (m/z) 298,4 (MH^+); t_R = 0,96. ^{1}H RMN (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).



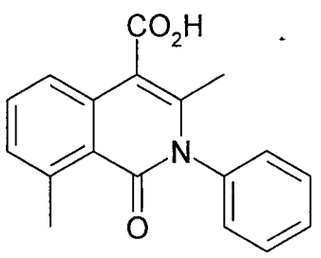
Ácido 2-(3-cloro-fenil)-3-metil-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico.

LC-MS (m/z) 314,2 (MH^+); t_R = 1,09. ^{1}H RMN (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).



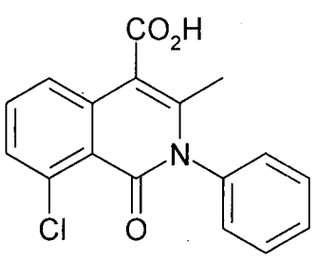
Ácido 3-metil-1-oxo-2-m-tolil-1,2-dihidro-isoquinolin-4-carboxílico.

LC-MS (m/z) 293,9 (MH^+); t_R = 1,03. ^1H RMN (250 MHz, DMSO-d_6): 2,02 (s, 3H), 2,38 (s, 3H), 7,14 (d traslapado, 1H), 7,16 (s traslapado, 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).



Ácido 3,8-dimetil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico.

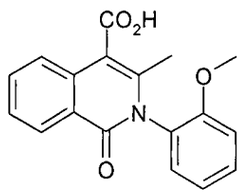
Una solución de etil éster del ácido 3,8-dimetil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico (200 mg, 0,62 mmol) en DMSO (3 ml) y NaOH 1N acuoso (2 ml, 2 mmol) se calentó bajo irradiación de microondas a +120°C durante 20 min y se diluyó con agua (30 ml). Las impurezas sin carga se extrajeron con éter dietílico (30 ml) y la solución acuosa se vertió en hielo (50 g) con HCl acuoso 2M (10 ml). El precipitado obtenido se filtró, se lavó con agua y se secó al vacío para dar 75 mg de sólido amarillo. Rendimiento 41%. LC-MS (m/z) 293,9 (MH^+); t_R = 1,09. ^1H RMN (500 MHz, DMSO-d_6): 1,95 (s, 3H), 2,74 (s, 3H), 7,3 (d, 1H), 7,32 (d, 2H), 7,48 (dos m traslapadas, 2H), 7,55 (t, 2H), 7,62 (t, 1H), 13,42 (b, 1H).



Ácido 8-cloro-3-metil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico.

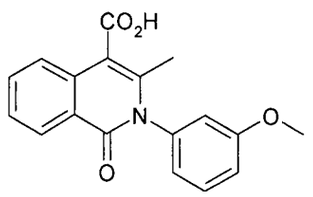
380

El compuesto del título se preparó en forma análoga por hidrólisis del correspondiente metil o etil éster a 100°C. LC-MS (m/z) 314,1 (MH^+); t_R = 1,03.



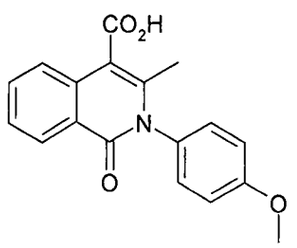
Ácido 2-(2-metoxi-fenil)-3-metil-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico.

El compuesto del título se utilizó en el próximo paso sin purificación. LC-MS (m/z) 310,3 (MH^+); t_R = 0,87.



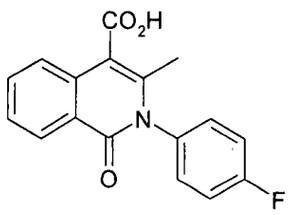
Ácido 2-(3-metoxi-fenil)-3-metil-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico.

El compuesto del título se utilizó en el próximo paso sin purificación. LC-MS (m/z) 310,4 (MH^+); t_R = 0,9.



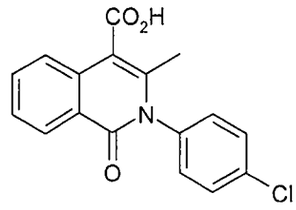
Ácido 2-(4-metoxi-fenil)-3-metil-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico.

El compuesto del título se utilizó en el próximo paso sin purificación. LC-MS (m/z) 310,4 (MH^+); t_R = 0,89.



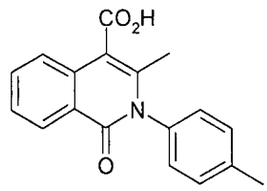
Ácido 2-(4-fluoro-fenil)-3-metil-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico.

El compuesto del título se utilizó en el próximo paso sin purificación. LC-MS (m/z) 298,2 (MH^+); t_R = 0,9.



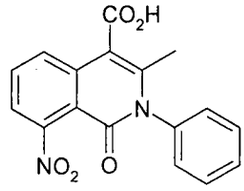
Ácido 2-(4-cloro-fenil)-3-metil-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico.

El compuesto del título se utilizó en el próximo paso sin purificación. LC-MS (m/z) 314,2 (MH^+); t_R = 1,53.



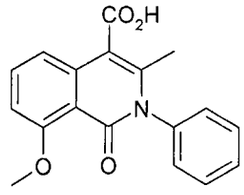
Ácido 3-metil-1-oxo-2-p-tolil-1,2-dihidro-isoquinolin-4-carboxílico.

El compuesto del título se utilizó en el próximo paso sin purificación. LC-MS (m/z) 293,9 (MH^+); t_R = 0,99.



Ácido 3-metil-8-nitro-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico.

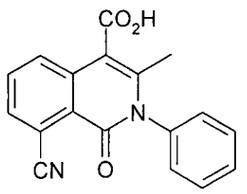
El compuesto del título se utilizó en el próximo paso sin purificación. LC-MS (m/z) 325,5 (MH^+); t_R = 0,94.



Ácido 8-metoxi-3-metil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico.

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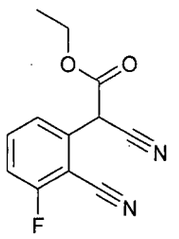
El compuesto del título se utilizó en el próximo paso sin purificación. LC-MS (m/z) 310,6 (MH^+); t_R = 0,73.



Ácido 8-ciano-3-metil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico.

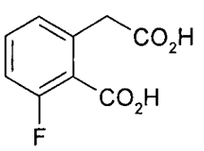
LC-MS (m/z) 305,0 (MH^+); t_R = 0,82.

Síntesis de anhídridos homoftálicos de la fórmula general XVIII:



Etil éster del ácido ciano-(2-ciano-3-fluoro-fenil)-acético

Una mezcla de etil éster del ácido cianoacético (26,7 ml, 251 mmol), 2,6-difluorobenzonitrilo (33,2 g, 239 mmol) y carbonato de potasio (82,5 g, 597 mmol) en dimetilsulfóxido (120 ml) se agitó a +55°C durante 16 horas y se vertió en una mezcla de hielo-agua (ca. 400 ml). Se acidificó con HCl ac. conc. con precaución (evolución de CO_2) y se extrajo con acetato de etilo (600 ml). La fase orgánica se lavó con salmuera (100 ml) y se evaporó para dar 55,1 g de un sólido amarillo pálido que se utilizó en el próximo paso sin purificación posterior. ^1H RMN (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).

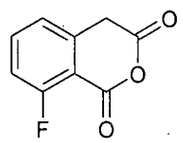


Ácido *2-carboximetil-6-fluoro-benzoico.*

Una mezcla de ácido sulfúrico al 62% (2:1, H_2SO_4 conc. en agua, 400 ml) y etil éster del ácido ciano-(2-ciano-3-fluoro-fenil)-acético (52,0 g, 224 mmol) se agitó a +150°C durante la noche (16 horas). La mezcla de reacción se vertió en hielo (ca. 500 g) y se neutralizó con NaOH acuoso 10,8 N (500 ml) con enfriamiento. La mezcla se

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extrajo con acetato de etilo (3 x ml500ml) y la solución orgánica combinada se lavó con salmuera, se secó sobre $MgSO_4$ y se evaporó para dar 40,28 g del producto crudo que se utilizó en el próximo paso sin purificación posterior. La muestra para análisis se preparó por recristalización a partir de tolueno - acetato de etilo. ^{1}H RMN (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 (solapado t (dd no resuelto), 1H), 7,45 (dd, J=7,9 Hz, J=13,9 Hz, 1H), 12,95 (br, CO_2H).

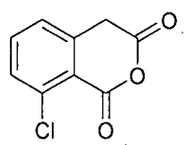


8-fluoro-isocroman-1,3-diona.

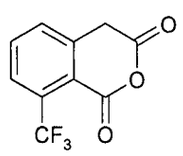
Se calentó ácido 2-carboximetil-6-fluoro-benzoico (130 mg, 0,65 mmol) en cloruro de acetilo (2 ml) bajo irradiación de microondas a 150°C durante 10 minutos luego se concentró al vacío para dar el producto del título (120 mg, 100% de rendimiento). El compuesto es hidroscópico (sic) y lentamente se descompone al diácido inicial en solventes húmedos o bajo atmósfera humedecida.

^{1}H RMN (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).

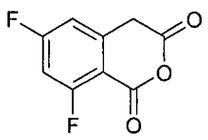
Los siguientes anhídridos homoftálicos se obtuvieron en forma análoga mediante el procedimiento de tres pasos descrito anteriormente a partir de los correspondientes fluorobenzonitrilos y cianoacetato de etilo:



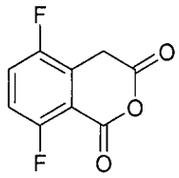
8-cloro-isocroman-1,3-diona.



8-trifluorometil-isocroman-1,3-diona.

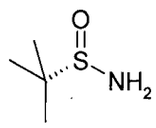


6,8-difluoro-isocroman-1,3-diona.



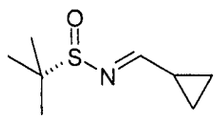
5,8-difluoro-isocroman-1,3-diona.

Síntesis de aminas quirales y racémicas de la fórmula general XI:



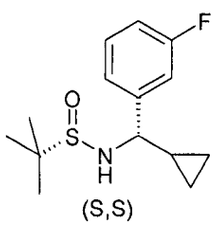
(S)-(–)-2-metil-2-propanosulfinamida.

El auxiliar quiral del título se preparó de acuerdo con un procedimiento descrito para el enantiómero (R)-(+) de D. J. Weix y J. A. Ellman *Organic Syntheses* **2005**, *82*, 157.

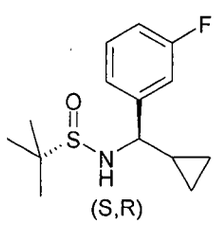


1-ciclopropil-metilidenamida del ácido (S)-2-metil-2-propansulfínico.

El compuesto del título se preparó de acuerdo con un procedimiento general descrito por G. Liu, D. A. Cogan, T. D. Owens, T. P. Tang, y J. A. Ellman *J. Org. Chem.* **1999**, *64*, 1278: Una mezcla de ciclopropancarboxaldehído (35,0 g, 0,5 mol), 1-ciclopropil-metilidenamida del ácido 2-metil-2-propansulfínico (30 g, 0,25 mol) y $CuSO_4$ anhidro (120 g, 0,75 mol) en CH_2Cl_2 (1500 ml) se agitó a temperatura ambiente durante la noche. La mezcla de reacción se filtró y se evaporó para dar el compuesto del título (39 g, rendimiento 95%), el cual se utilizó en el próximo paso sin purificación posterior.



(S,S)



(S,R)

[(S)-ciclopropil-(3-fluoro-fenil)-metil]-amida del ácido (S)-2-metil-2-propansulfínico y [(R)-ciclopropil-(3-fluoro-fenil)-metil]-amida del ácido (S)-2-metil-2-propansulfínico.

Los compuestos del título se obtuvieron de acuerdo con un procedimiento general descrito para la adición 1,2-estereoselectiva de reactivos organometálicos a iminas de sulfinilo de D. A. Cogan, G. Liu, J. A. Ellman, *Tetrahedron* **1999**, *55*, 8883.

Procedimiento A: A un cloruro de litio anhidro (1,7 g, 40 mmol) se agregó THF (20 ml) bajo nitrógeno seguido de un lento agregado de *i*-PrMgCl (22 ml, 2 M in THF) y la mezcla obtenida se agitó a temperatura ambiente durante la noche. La solución de *i*-PrMgCl·LiCl obtenida se agregó gota a gota a una solución agitada de 1-bromo-3-fluorobenceno (5,6 g, 33 mmol) en THF (25 ml) a 0°C y se continuó la agitación durante 2 horas. El reactivo De Grignard obtenido se agregó a una solución de 1-ciclopropil-metilidenamida del ácido (S)-2-metil-2-propansulfínico (2,5 g, 14 mmol) en CH_2Cl_2 (60 ml) a -48°C. La mezcla se agitó a -48°C durante 5 horas y luego a temperatura ambiente durante la noche. La mezcla de reacción se enfrió rápidamente por la adición de NH_4Cl ac. sat. (50 ml) se extrajo con CH_2Cl_2 (3x100 ml). La solución orgánica combinada se secó (Na_2SO_4) y se evaporó para dar una mezcla crudo, la cual se purificó por cromatografía de columna sobre gel de sílice (EtOAc/éter de petróleo = 1/10). La mezcla obtenida de diastereoisómeros se resolvió por SFC para dar el isómero (S, S) del título como producto principal (1,5 g, rendimiento 37,5%) y el isómero (S, R) del título (0,16 g, rendimiento: 4,0%).

Procedimiento B: En forma alternativa, a una suspensión de Mg (13,4 g, 0,55 mol) en 50 ml de THF anhidro a 50°C se agregó gota a gota una solución de 1-bromo-3-fluorobenceno (89,0 g, 0,50 mol). La mezcla se agitó durante 2 horas a +50°C y luego se agregó gota a gota a una solución de 1-ciclopropil-metilidenamida del ácido (S)-2-metil-2-propansulfínico (78,0 g, 0,46 mol) en 100 ml de THF a 50-60°C y se agitó durante 2 horas. Se en frió rápidamente con NH_4Cl ac. sat. (100 ml), agua (300 ml), se filtró, y tanto el sólido como el filtrado se extrajeron con acetato de etilo caliente (600 ml) y se evaporó al vacío. El residuo se cristalizó a partir de una mezcla de acetato de etilo y éter de petróleo (1:1, 200 ml) a -20°C para dar 80 g del isómero (S, S) del título en forma de un polvo blanco, 66% de rendimiento, de 100% de acuerdo con HPLC quiral. ^1H RMN ($CDCl_3$, 400 MHz, TMS=0 ppm): 7,34-7,28 (m, 1H), 7,16-7,12 (m, 2H), 7,00-

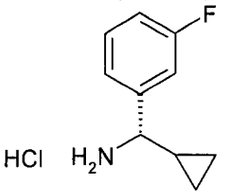
Organizacion y
Digitalizacion CSA Ltda

PATENTE DE INVENCIÓN

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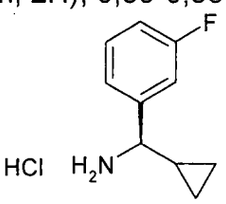
3/3

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).



Clorhidrato de (S)-(+)-C-[C-ciclopropil-C-(3-fluoro-fenil)]-metilamina

A una solución saturada de HCl en dioxano anhidro (400 ml) se agregó [(S)-ciclopropil-(3-fluoro-fenil)-metil]-amida del ácido (S)-2-metil-2-propansulfínico (80 g, 0,3 mol) a 0ºC. Después de agitar a temperatura ambiente durante 1 hora, la mezcla de reacción se evaporó al vacío. El residuo se lavó con éter anhidro (2x100 ml) y se secó al vacío para dar 56 g del compuesto del título en forma de un sólido blanco, rendimiento 93%, ee 100% de acuerdo con HPLC quiral. $[\alpha]_D^{20}$ = + 52,69 (c = 10 mg/ml, CH_3OH). ^1H RMN (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).

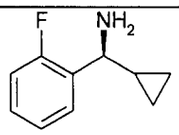
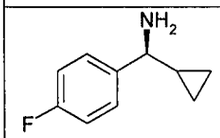
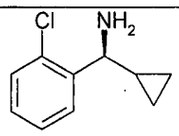
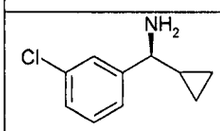
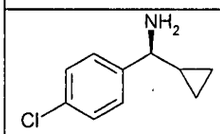
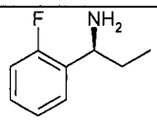
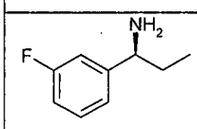
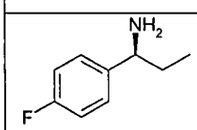
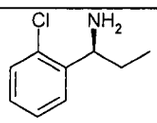


Clorhidrato de (R)-(–)-C-[C-ciclopropil-C-(3-fluoro-fenil)]-metilamina.

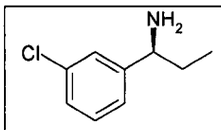
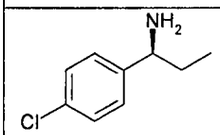
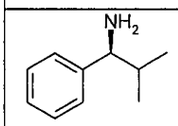
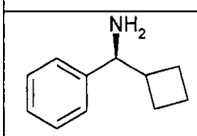
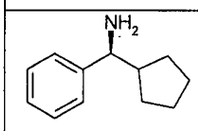
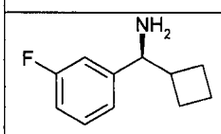
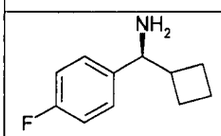
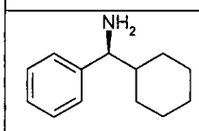
El compuesto del título se preparó de acuerdo con el procedimiento idéntico anterior a partir de [(R)-ciclopropil-(3-fluoro-fenil)-metil]-amida del ácido (S)-2-metil-2-propansulfínico (0,16g, 0,6 mmol) para dar 0,116 g del compuesto del título en forma de un sólido blanco. $[\alpha]_D^{20}$ = – 49,18 (c = 10 mg/ml, CH_3OH), ee 100%. ^1H RMN (CD_3OD, 400 MHz, TMS=0): idéntico con el enantiómero (S).

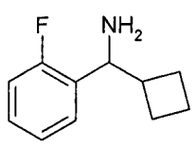
Los siguientes clorhidratos de amina enantioméricamente puros se obtuvieron en forma análoga en el procedimiento de tres pasos a partir de la condensación del correspondiente aldehído con el auxiliar quiral, la adición estereoselectiva de Grignard en donde la mezcla de diastereómeros se resolvió ya sea por recristalización o por cromatografía (SFC o columna) y el principal diastereoisómero (S, S) se convirtió finalmente a una amina quiral con HCl.

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Estructura (sal HCl)	Nombre químico	$[\alpha]_D^{20}$, (10mg/ml) MeOH	ee HPLC quiral	^{1}H RMN (CD_3OD, 400 MHz)
	*C-[(S)-C-ciclopropil-C-(2-fluoro-fenil)]-metilamina*	+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-ciclopropil-C-(4-fluoro-fenil)]-metilamina*	+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-cloro-fenil)-C-ciclopropil]-metilamina*	+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-cloro-fenil)-C-ciclopropil]-metilamina*	+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-cloro-fenil)-C-ciclopropil]-metilamina*	+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-fenil)-propilamina*	–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-fenil)-propilamina*	+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-fenil)-propilamina*	+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-cloro-fenil)-propilamina*	–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).

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	*(S)-1-(3-cloro-fenil)-propilamina*	+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-cloro-fenil)-propilamina*	+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-metil-1-fenil-propilamina*	+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-ciclobutil-C-fenil)-metilamina*	+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-ciclopentil-C-fenil)-metilamina*	+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-ciclobutil-C-(3-fluoro-fenil)]-metilamina*	+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-ciclobutil-C-(4-fluoro-fenil)]-metilamina*	+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-ciclohexil-C-fenil)-metilamina*	+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).



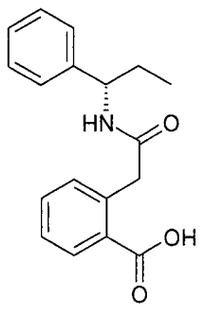
C-ciclobutil-C-(2-fluoro-fenil)-metilamina.

Una tercera parte de una solución de bromuro de ciclobutilo (5,0 g, 41,3 mmol) en tetrahidrofurano anhidro (24 ml) se agitó con magnesio (1,11 g, 46,3 mmol) bajo reflujo. La solución restante se agregó gota a gota durante un período de 15 minutos, y la agitación a reflujo continuó durante 30 min. A la solución obtenida se agregó gota a

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gota 2-fluorobenzonitrilo (1,2 g) in THF (15 ml) a 0°C. La mezcla se agitó durante 5,5 h a 0ºC seguido del agregado de metanol (30 ml) y borohidruro de sodio (1,13 g). La mezcla de reacción se agitó durante 16 horas a temperatura ambiente y se concentró. El residuo se dividió por partición entre cloroformo (3x100 ml) y agua, y el pH se ajustó hasta 1. La mezcla se extrajo con cloroformo. La fase acuosa se ajustó hasta pH=10, se extrajo con cloroformo (3 x 100 ml). Las capas orgánicas combinadas se secaron, se evaporaron y se purificaron por cromatografía de columna sobre gel de sílice (acetato de etilo/éter de petróleo = 1/1) para dar la amina del título (0,45 g, rendimiento: 7,9%) ^{1}H RMN (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).

Síntesis de amidas de ácidos de la fórmula general XIX:

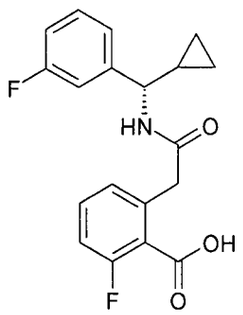


Ácido 2-[((S)-1-Fenil-propilcarbamoil)-metil]-benzoico.

Una mezcla de anhídrido homoftálico (810 mg, 5 mmol) y (S)-(–)-1-fenilpropilamina (676 mg, 5 mmol) en acetonitrilo (15 ml) se calentó bajo irradiación de microondas a +150°C durante 15 min. El precipitado de blanco se recolectó por filtración, se lavó con heptano y se secó al vacío para dar el compuesto del título puro con 72% de rendimiento (1,065g). En forma alternativa, a una solución agitada de anhídrido homoftálico (16,214 g, 0,1 mol) en acetonitrilo (100 ml) (S)-(–)-1-fenilpropilamina (13,83 g, 0,102 mol) se agregó gota a gota (reacción exotérmica) y la mezcla de reacción obtenida se sometió a reflujo durante 5 min. Se dejó enfriar y el producto se aisló por filtración como se hizo anteriormente para dar 23,4 g de sólido incoloro, 79% de rendimiento. LC-MS (m/z) 298,5 (MH^+); t_R = 1,11. ^{1}H RMN (500 MHz, DMSO-d_6): 0,84 (t, J=7,3 Hz, 3H), 1,67 (quinteto, J=7,3 Hz, 2H), 3,85 (d del sistema AB, J=15,1 Hz, 1H), 3,95 (d del sistema AB, J=15,1 Hz, 1H), 4,66 (q, J=7,6 Hz, 1H), 7,2 (m no resuelto, 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).

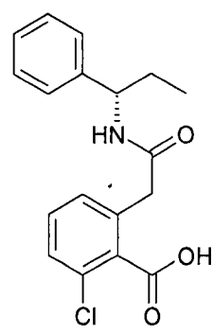
Los siguientes compuestos se obtuvieron en forma análoga a partir de los

correspondientes anhídridos homoftálicos de fórmula general y aminas de la fórmula general XVIII y XI, respectivamente. Las reacciones se corrieron usualmente a temperatura ambiente y los productos se aislaron por extracción o filtración y se utilizaron en los próximos pasos sin purificación posterior.



Ácido 2-({[(S)-ciclopropil-(3-fluoro-fenil)-metil]-carbamoil}-metil)-6-fluoro-benzoico.

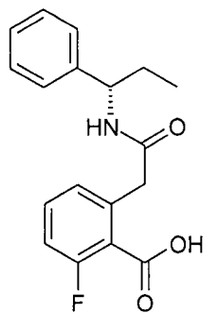
LC-MS (m/z) 346,2 (MH^+); t_R = 1,14. ^1H RMN (500 MHz, DMSO-d_6): 0,35 (m, 1H), 0,39 (m, 1H), 0,5 (m, 2H), 1,12 (m, 1H), 3,68 & 3,74 (dos d del sistema AB, J= 15,2 Hz, 2H, CH_2), 4,25 (t, J= 8,5 Hz, 1H), 7,05 (dt, J=2,2, 8,05 Hz, 1H), 7,13 (d, J= 8,1 Hz, 1H), 7,16-7,21 (m, 2H), 7,35 (m, 1H), 7,42 (m, 1H), 8,66 (d, J= 8,2 Hz, 1H, NH), 13,44 (br., CO_2H).



Ácido 2-cloro-6-[((S)-1-fenil-propilcarbamoil)-metil]-benzoico.

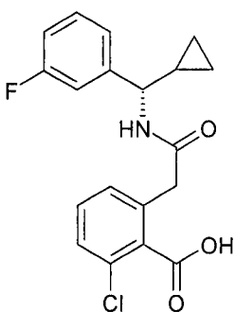
LC-MS (m/z) 332,2 (MH^+); t_R = 1,19. ^1H RMN (500 MHz, DMSO-d_6): 0,84 (t, J=7,3 Hz, 3H), 1,68 (quinteto, J=7,3 Hz, 2H), 3,54 & 3,61 (dos d del Sistema AB, J=15,3 Hz, 2H, CH_2), 4,67 (q, J=7,5 Hz, 1H), 7,19-7,4 (m, 8H), 8,48 (d, J=8,3 Hz, 1H, NH), 13,64 (br., CO_2H).

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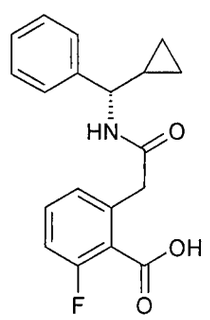


Ácido 2-fluoro-6-[((S)-1-fenil-propilcarbamoil)-metil]-benzoico.

LC-MS (m/z) 316,3 (MH^+); t_R = 1,13. ^1H RMN (500 MHz, $CDCl_3$): 0,79 (t, J= 7,4 Hz, 3H), 1,76 (d del quinteto, 2H, diastereotópico CH_2 de 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 (m traslapada, 3H), 7,24-7,28 (m traslapada, 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).

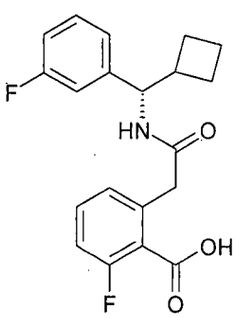


Ácido 2-cloro-6-({[(S)-ciclopropil-(3-fluoro-fenil)-metil]-carbamoil}-metil)-benzoico.



Ácido 2-{[((S)-ciclopropil-fenil-metil)-carbamoil]-metil}-6-fluoro-benzoico.

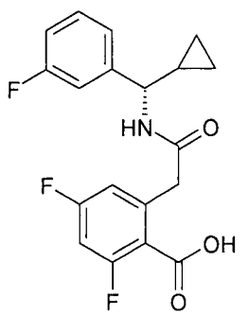
LC-MS (m/z) 328,4 (MH^+); t_R = 1,12.



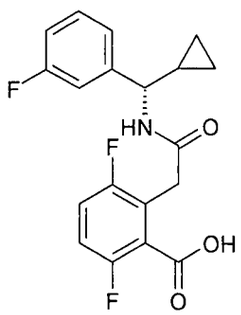
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Ácido 2-({[(S)-ciclobutil-(3-fluoro-fenil)-metil]-carbamoil}-metil)-6-fluoro-benzoico.

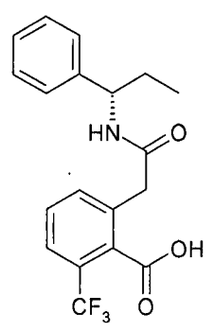
LC-MS (m/z) 360,2 (MH^+); t_R = 1,31.



Ácido 2-({[(S)-ciclopropil-(3-fluoro-fenil)-metil]-carbamoil}-metil)-4,6-difluoro-benzoico.



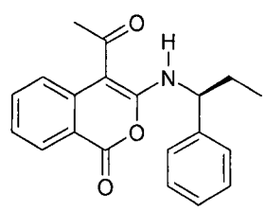
Ácido 2-({[(S)-ciclopropil-(3-fluoro-fenil)-metil]-carbamoil}-metil)-3,6-difluoro-benzoico.



Ácido 2-[((S)-1-fenil-propilcarbamoil)-metil]-6-trifluorometil-benzoico.

LC-MS (m/z) 366,4 (MH^+); t_R = 1,24.

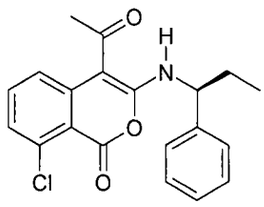
Síntesis de compuestos de la fórmula general XXIII:



4-acetil-3-((S)-1-fenil-propilamino)-isocromen-1-ona.

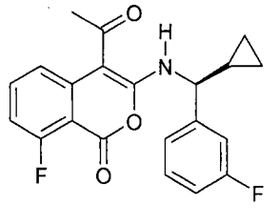
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Una mezcla de ácido 2-[((S)-1-fenil-propilcarbamoil)-metil]-benzoico (10 g), anhídrido acético (50 ml), y N,N-dimetilaminopiridina (100 mg) se calentó a reflujo suave (T_{max} = +124°C) durante 7 min y se evaporó al vacío a +50°C para dar el compuesto del título en forma de un sólido de amarillo-marrón (11,1 g, pureza 98% por RMN). LC-MS (m/z) 322,3 (MH^+); t_R = 1,72. ^{1}H RMN (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 (m no resuelto, 1H), 7,36-7,41 (m no resuelto., 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 RMN (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-acetil-8-cloro-3-((S)-1-fenil-propilamino)-isocromen-1-ona.

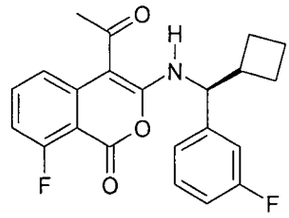
Se calentaron ácido 2-cloro-6-[((S)-1-fenil-propilcarbamoil)-metil]-benzoico (11,4 g) y anhídrido acético (50 ml) a 103°C durante 60 min y se evaporaron para dar 12,45 g de aceite marrón (pureza aproximada a 95% de acuerdo con ^{1}H RMN). LC-MS (m/z) 355,2 (MH^+); t_R = 1,82. La muestra analíticamente pura se preparó por recristalización (9 g a partir de 30 ml de MeCN caliente) para dar el compuesto del título (4,41 g) en forma de un sólido amarillo pálido después de enfriar (baño de hielo seco – EtOH) y filtración. LC-MS (m/z) 355,2 (MH^+); t_R = 1,82. ^{1}H RMN (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 (m no resuelto), J= 4,3 Hz, 4H), 7,59-7,66 (m, 2H), 11,11 (d, J=7,8 Hz, 1H, NH).



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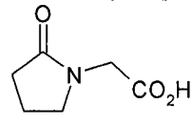
4-acetil-3-{[(S)-ciclopropil-(3-fluoro-fenil)-metil]-amino}-8-fluoro-isocromen-1-ona.

Una mezcla de ácido 2-({[(S)-ciclopropil-(3-fluoro-fenil)-metil]-carbamoil}-metil)-6-fluoro-benzoico (12,92 g, 37,41 mmol) y anhídrido acético (100 ml, 1 mol) se agitó a +65°C durante 20 horas y se evaporó al vacío (65°C, 10 mbar, 2 horas) para dar el compuesto del título como un aceite marrón espeso, el cual se utilizó en el próximo paso sin purificación (14,30 g, rendimiento 103,5%, 95% de pureza, de acuerdo con ^{1}H RMN). LC-MS (m/z) 370,1 (MH^+); t_R = 1,65. ^{1}H RMN (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 (dd no resuelto), 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).



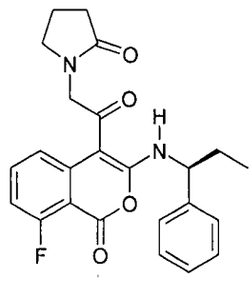
4-acetil-3-{[(S)-ciclobutil-(3-fluoro-fenil)-metil]-amino}-8-fluoro-isocromen-1-ona.

LC-MS (m/z) 384,4 (MH^+); t_R = 1,82.



Ácido (2-oxo-pirrolidin-1-il)-acético.

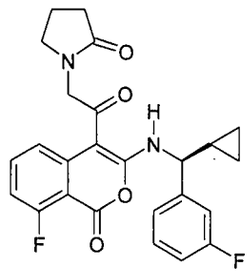
Una mezcla de 2-pirrolidona (2,66 ml, 34 mmol) y NaH (60% en aceite, 1,25 g, 31,3 mmol) en THF (75 ml) se agitó hasta que cesó la evolución de gas (30 min). Se agregó 2-bromoacetato de ter-butilo (4,45 ml, 30 mmol) y se agitó a temperatura ambiente durante la noche luego se dividió por partición entre agua (200 ml) y acetato de etilo (200 ml) para dar el intermedio ter-butil éster del ácido 2-(oxo-pirrolidin-1-il)-acético (5,8 g). Este disolvió en ácido acético (40 ml) y HCl ac. conc. (6 ml), se observó evolución de gas. Después de agitar a temperatura ambiente durante 2 horas se evaporó y se recristalizó a partir de tolueno/etanol para dar 2,58 g del compuesto del título (60% de rendimiento). ^{1}H RMN (500 MHz, DMSO-d_6): 1,95 (quinteto, J= 7,7 Hz, 2H), 2,24 (t, J= 8,1 Hz, 2H), 3,38 (m, traslapado con H_2O (3,35 ppm), 2H), 3,91 (s, 2H), 12,77 (br., 1H).



1-{2-[8-fluoro-1-oxo-3-((S)-1-fenil-propilamino)-1H-isocromen-4-il]-2-oxo-etil}-pirrolidin-2-ona.

A una solución de ácido 2-oxo-pirrolidin-1-il-acético (1,56 g, 10,9 mmol) en 1,2-dicloroetano (40 ml) se agregaron cloruro de oxalilo (0,95 ml, 10,9 mmol) y DMF (1 gota) con evolución de gas. Después de agitar a temperatura ambiente durante 1 hora, se agregaron ácido 2-fluoro-6-[((S)-1-fenil-propilcarbamoil)-metil]-benzoico (1,56 g, 4,95 mmol), trietilamina (2,1 ml, 14,9 mmol) y DMAP (85 mg, 0,1 eq.) y se agitó a temperatura ambiente durante la noche. Se dividió por partición entre mezcla de HCl ac. 0,2 M (100 ml) – salmuera (100 ml) y acetato de etilo (250 ml), se lavó con agua y se evaporó para dar 1,89 g del compuesto crudo del título que se utilizó en el próximo paso sin purificación posterior.

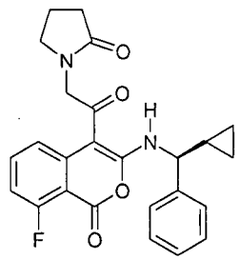
^{1}H RMN (500 MHz, DMSO-d_6, resonancias seleccionadas): 4,51 & 4,58 (dos d del Sistema AB, J=16,3 Hz, N-CH_2-CO), 4,99 (q, J= 7,5 Hz, 1H, C<u>H</u>-NH), 11,31 (d, J= 7,9 Hz, 1H, NH).



1-[2-(3-{[(S)-ciclopropil-(3-fluoro-fenil)-metil]-amino}-8-fluoro-1-oxo-1H-isocromen-4-il)-2-oxo-etil]-pirrolidin-2-ona.

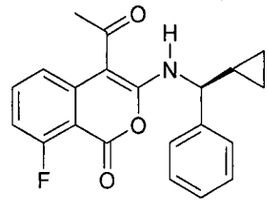
El compuesto del título se preparó en forma análoga y se purificó por cromatografía flash sobre SiO_2. LC-MS (m/z) 453,3 (MH^+); t_R = 1,48.

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1-(2-{3-[((S)-ciclopropil-fenil-metil)-amino]-8-fluoro-1-oxo-1H-isocromen-4-il}-2-oxo-etil)-pirrolidin-2-ona.

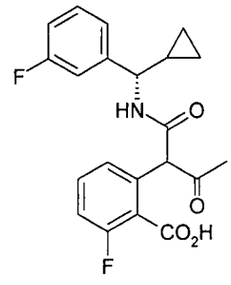
El compuesto del título se preparó en forma análoga. LC-MS (m/z) 435,3 (MH^+); t_R = 1,43.



4-acetil-3-[((S)-ciclopropil-fenil-metil)-amino]-8-fluoro-isocromen-1-ona.

LC-MS (m/z) 352,6 (MH^+); t_R = 1,62. ^1H RMN (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 (dd no resuelto), 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).

La hidrólisis de compuestos de la fórmula general XXIII a compuestos de la fórmula general XXV:



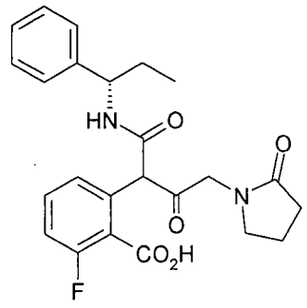
Ácido 2-(1-{[(S)-ciclopropil-(3-fluoro-fenil)-metil]-carbamoil}-2-oxo-propil)-6-fluoro-benzoico.

Se disolvió 4-acetil-3-{[(S)-ciclopropil-(3-fluoro-fenil)-metil]-amino}-8-fluoro-2-benzopiran-1-ona (14,30 g, 38,72 mmol) en una mezcla de tetrahidrofurano (50 ml) y metanol (50 ml) y se colocó en un baño de hielo/agua con agitación. Se agregó NaOH (1 M en H_2O, 100 ml) y se continuó la agitación durante 1 hora. El baño frío se eliminó y la mezcla se dejó calentar hasta temperatura ambiente (20°C) durante 1 hora. La mezcla de reacción se vertió en una mezcla de hielo-agua (200 g + 200 ml), seguido por

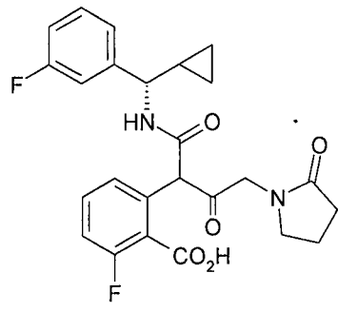
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la adición lenta de HCl 2 M ac. (200 ml) y se extrajo con acetato de etilo (200 ml), se lavó con NaCl ac. sat., se secó (Na_2SO_4), se filtró y se evaporó para dar el compuesto del título (14,65 g, rendimiento 97,7%) en forma de una espuma marrón pálido. El producto crudo se utilizó en el próximo paso sin purificación posterior. LC-MS (m/z) 388,3 (MH^+); t_R = 1,2. ^1H RMN (500 MHz, DMSO-d_6): una mezcla de tautómeros y diastereoisómeros.

Los siguientes compuestos se prepararon en forma análoga:

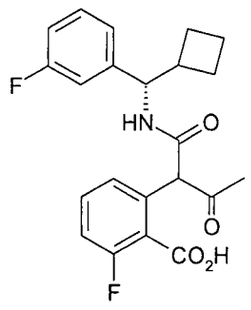


Ácido 2-fluoro-6-[2-oxo-3-(2-oxo-pirrolidin-1-il)-1-((S)-1-fenil-propil-carbamoil)-propil]-benzoico.



Ácido 2-[1-{[(S)-ciclopropil-(3-fluoro-fenil)-metil]-carbamoil}-2-oxo-3-(2-oxo-pirrolidin-1-il)-propil]-6-fluoro-benzoico.

LC-MS (m/z) 471,4 (MH^+); t_R = 1,17.

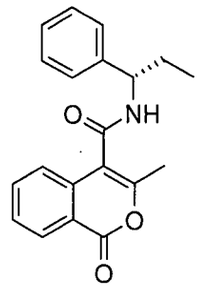


Ácido 2-(1-{[(S)-ciclobutil-(3-fluoro-fenil)-metil]-carbamoil}-2-oxo-propil)-6-fluoro-benzoico.

LC-MS (m/z) 402,2 (MH^+); t_R = 1,36.

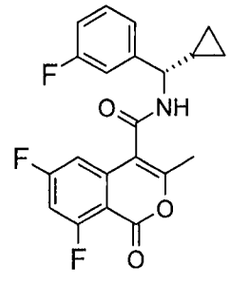
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Síntesis de compuestos de la fórmula general XXIV y XXV: Compuestos de general fórmula XXIV obtenidos en forma análoga a la descrita anteriormente para los compuestos de fórmula general XXIII pero a una temperatura superior (150°C, 15 min) y se hidrolizaron usualmente a compuestos de la fórmula general XXV sin aislamiento y caracterización, por eso sólo se dan a continuación dos ejemplos de compuestos XXIV.



((S)-1-fenil-propil)-amida del ácido 3-metil-1-oxo-1H-isocromen-4-carboxílico.

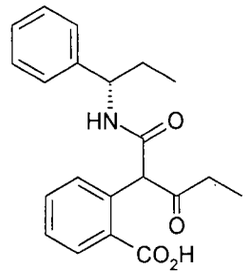
El compuesto del título se purificó por cromatografía flash sobre SiO_2. LC-MS (m/z) 322,1 (MH^+); t_R = 1,27. ^1H RMN (500 MHz, $CDCl_3$): 1,03 (t, J=7,3 Hz, 3H), 1,91-2,06 (m complejo, 2H, CH_2), 2,19 (s, 3H), 5,11 (q, J=7,8 Hz, 1H), 7,06 (br. d, J=8,3 Hz, 1H, NH), 7,22-7,33 (m, 3H), 7,36-7,43 (m, 4H), 7,54 (t, J= 7,6 Hz, 1H), 7,95 (d, J= 7,8 Hz, 1H). ^1H RMN (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).



[(S)-ciclopropil-(3-fluoro-fenil)-metil]-amida del ácido 6,8-difluoro-3-metil-1-oxo-1H-isocromen-4-carboxílico

El compuesto del título se purificó por cromatografía flash sobre SiO_2. LC-MS (m/z) 388,4 (MH^+); t_R = 1,39.

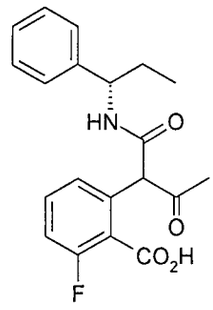
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Ácido 2-[2-oxo-1-((S)-1-fenil-propilcarbamoil)-butil]-benzoico.

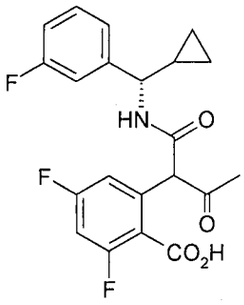
Una mezcla sellada de ácido 2-[((S)-1-fenil-propilcarbamoil)-metil]-benzoico (409 mg, 1,38 mmol), anhídrido propiónico (10 ml) y 4-N,N-dimetilaminopiridina (15 mg) se calentó bajo irradiación de microondas a 150°C durante 20 min y se dividió por partición entre HCl 1M (50 ml) y acetato de etilo (100 ml). La capa orgánica se lavó con $NaHCO_3$ ac. sat. (2x50 ml) y salmuera y se concentró al vacío. Al residuo obtenido se agregó metanol (25 ml) tetrahidrofurano (25 ml) y NaOH ac. 2M (50 ml) y se agitó a temperatura ambiente durante 1 hora. Los volátiles orgánicos se eliminaron al vacío y el pH se ajustó hasta 1 con HCl ac. 3M. El producto crudo del título (495 mg) se separó por extracción con acetato de etilo (150 ml) y se utilizó en el próximo paso sin purificación posterior. ^1H RMN (500 MHz, DMSO-d_6): una mezcla de tautómeros y diastereoisómeros.

Los siguientes compuestos se obtuvieron en forma análoga:



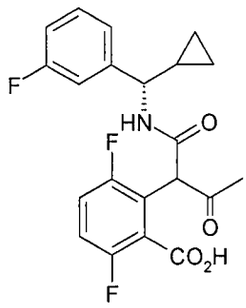
Ácido 2-fluoro-6-[2-oxo-1-((S)-1-fenil-propilcarbamoil)-propil]-benzoico.

LC-MS (m/z) 358,4 (MH^+); t_R = 1,17.



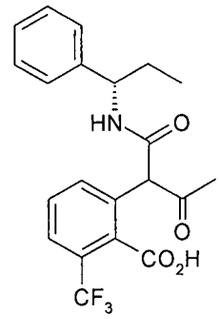
Ácido 2-(1-{[(S)-ciclopropil-(3-fluoro-fenil)-metil]-carbamoil}-2-oxo-propil)-4,6-difluoro-benzoico.

LC-MS (m/z) 406,7 (MH^+); t_R = 1,3.



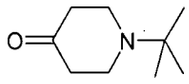
Ácido 2-(1-{[(S)-ciclopropil-(3-fluoro-fenil)-metil]-carbamoil}-2-oxo-propil)-3,6-difluoro-benzoico.

LC-MS (m/z) 406,0 (MH^+); t_R = 0,72 (método B).



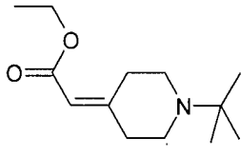
Ácido2-[2-oxo-1-((S)-1-fenil-propilcarbamoil)-propil]-6-trifluorometil-benzoico.

El compuesto del título se utilizó en el próximo paso directamente.



1-ter-butil-piperidin-4-ona.

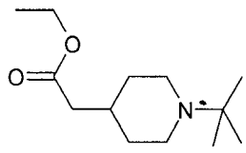
El compuesto del título se preparó de acuerdo con el procedimiento descrito: J. S. Amato, J. Y. L. Chung, R. J. Cvetovich, X. Gong, M. McLaughlin, R. A. Reamer *J. Org. Chem.* **2005**, *70*, 1930.



Etil éster del ácido (1-ter-butil-piperidin-4-iliden)-acético

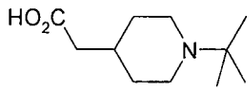
Una mezcla de 1-ter-butil-piperidin-4-ona (4,59 g, 23,6 mmol) y (trifenilfosforiliden)acetato de etilo (10,3 g, 23,6 mmol) en tolueno (100 ml) se agitó a reflujo durante 24 horas bajo nitrógeno y se evaporó al vacío. El residuo se purificó por cromatografía de columna sobre gel de sílice (éter de petróleo/trietilamina = 100/1) para dar 5,1 g del compuesto del título en forma de un aceite amarillo pálido, 76,5% de rendimiento.

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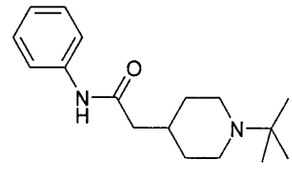
Etil éster del ácido (1-ter-butil-piperidin-4-il)-acético

A una solución de etil éster del ácido (1-ter-butil-piperidin-4-iliden)-acético (5,1 g, 22,7 mmol) en etanol (50 ml) se agregó 10% Pd/C (0,6 g) y la mezcla se agitó bajo atmósfera de hidrógeno (42 psi) a temperatura ambiente durante 14 horas. El catalizador se eliminó por filtración, y el filtrado se concentró para dar el compuesto del título (4,03 g, rendimiento 78%), el cual se utilizó en el próximo paso directamente.



Ácido (1-ter-butil-piperidin-4-il)-acético.

A una solución de NaOH en agua/etanol (v/v = 40/10, 50 ml) se agregó etil éster del ácido (1-ter-butil-piperidin-4-il)-acético (4,03 g, 17,8 mmol) y la mezcla se agitó a temperatura ambiente durante la noche. Se agregó HCl ac. 1 N para ajustar el pH a 5. Los volátiles se evaporaron al vacío, el residuo se diluyó con metanol (30 ml), y las sales inorgánicas insolubles se eliminaron por filtración. El filtrado se concentró y se purificó por cromatografía de columna sobre gel de sílice (CH_2Cl_2/MeOH = 20/1 a 5/1) para dar 0,7 g del compuesto del título en forma de un polvo gris claro. ^{1}H RMN (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-ter-butil-piperidin-4-il)-N-fenil-acetamida.

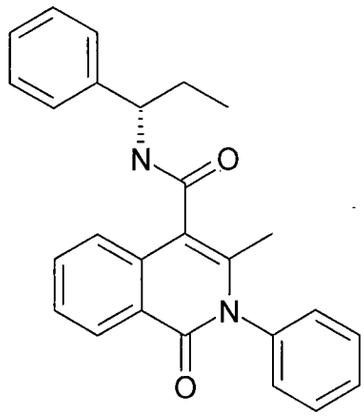
A una mezcla de ácido (1-ter-butil-piperidin-4-il)-acético (672 mg, 3,37 mmol), anilina (0,32 ml, 3,5 mmol), y HOBt (568 mg, 4,2 mmol) en DMF (20 ml), se agregó EDC (805 mg, 4,2 mmol). Se agitó a temperatura ambiente durante 2 horas y se dividió por partición entre agua (200 ml) y acetato de etilo (200 ml). La fase orgánica se lavó con NaOH 0,5 N ac. (2x50 ml) y salmuera (3x50 ml), se secó ($MgSO_4$) y se concentró al vacío. El residuo se purificó por cromatografía flash sobre (SiO_2, gradiente heptano - acetato de etilo) para dar 250 mg del compuesto del título. ^{1}H RMN (500 MHz, DMSO-

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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).

Compuestos de la invención

Ejemplo 1

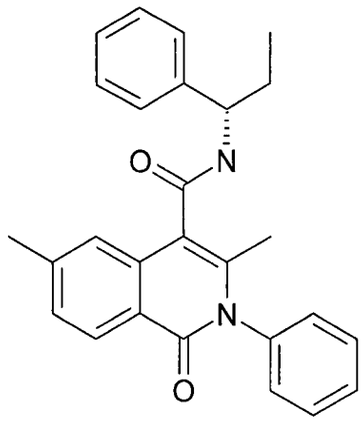


1a *((S)-1-fenil-propil)-amida del ácido 3-metil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico*

Una solución de ácido 3-metil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico (212 mg, 0,76 mmol) en $SOCl_2$ (1,5 ml) y dimetilformamida (ca. 5 µl) se calentó a reflujo durante 5 min. Los volátiles se eliminaron al vacío para dar 228 mg del correspondiente cloruro de acilo en forma de un sólido marrón pálido. Una porción del cloruro de acilo (110 mg, 0,37 mmol) se disolvió en 1,2-dicloroetano (2 ml) y se agregó (S)-(–)-1-fenilpropilamina (150 µl, 1,1 mmol). La suspensión obtenida se agitó durante 5 min, se diluyó con 1,2-dicloroetano (10 ml), se lavó con HCl 1M acuoso (3 x 5 ml) y agua (5 ml). La fase orgánica se vertió en SiO_2 (5 g), eluyó con 1,2-dicloroetano (50 ml) y el producto se eluyó con acetato de etilo – heptano 1:1 para dar 140 mg de sólido cristalino incoloro. Rendimiento 95%. En forma alternativa, en otra corrida la mezcla de reacción se dividió por partición entre HCl 2M y heptano (10 ml) y el producto se separó por filtración a partir del sistema bifásico obtenido.

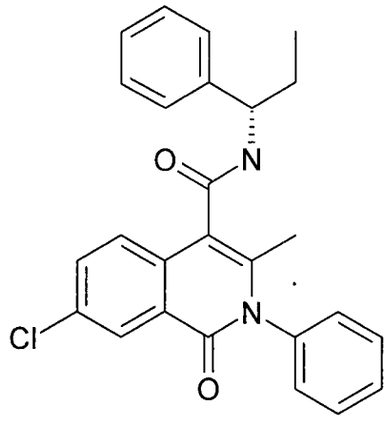
LC-MS (m/z) 397,1 (MH^+); t_R = 1,44. ^{1}H RMN (500 MHz, $CDCl_3$): 1,0 (t, 3H), 1,93 (m, 5H), 5,16 (q, 1H), 6,7 (d, 1H), 7,07 (d, 2H), 7,31 (m, 1H), 7,36 (d, 4H), 7,4-7,5 (m, 5H), 7,63 (t no resuelto, 1H), 8,31 (d, 1H).

Los siguientes compuestos se obtuvieron en forma análoga a partir del ácido y la amina correspondiente y se purificaron por LC-MS preparativa:



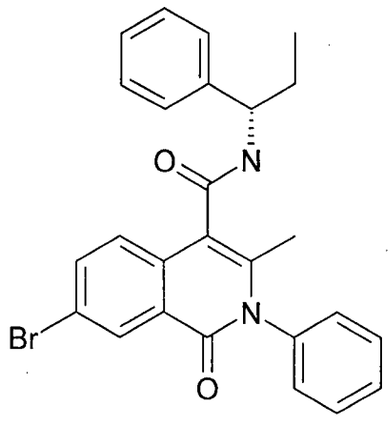
1b *((S)-1-fenil-propil)-amida del ácido 3,6-dimetil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico.*

LC-MS (m/z) 411,3 (MH^+); t_R = 0,8 (método B).



1c *((S)-1-fenil-propil)-amida del ácido 7-cloro-3-metil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico.*

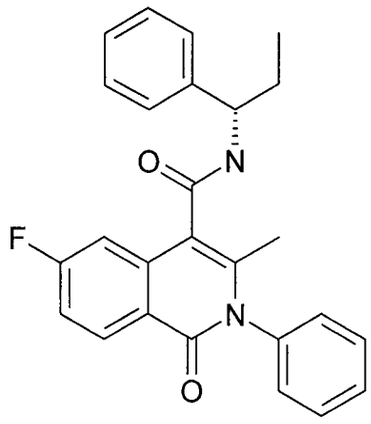
LC-MS (m/z) 431,3 (MH^+); t_R = 0,86 (método B).



1d *((S)-1-fenil-propil)-amida del ácido 7-bromo-3-metil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico.*

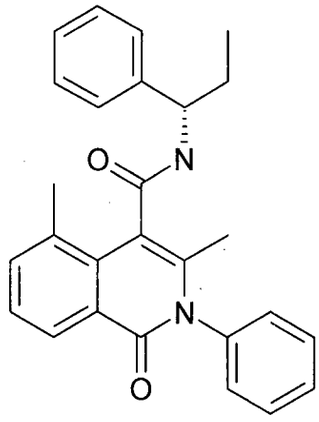
LC-MS (m/z) 475,1 (MH^+, ^{79}Br); t_R = 0,87 (método B).

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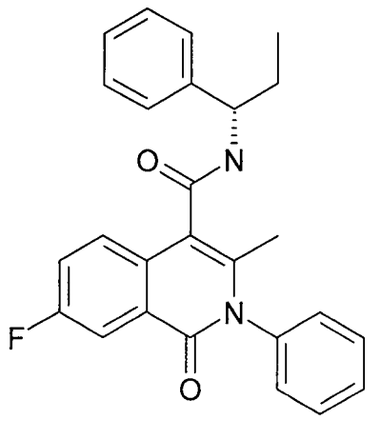
1e *((S)-1-fenil-propil)-amida del ácido 6-fluoro-3-metil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico.*

LC-MS (m/z) 415,5 (MH^+); t_R = 0,80 (método B).



1f *((S)-1-fenil-propil)-amida del ácido 3,5-dimetil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico.*

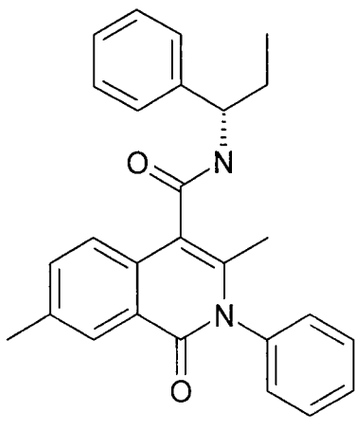
LC-MS (m/z) 411,3 (MH^+); t_R = 0,84 (método B).



1g *((S)-1-fenil-propil)-amida del ácido 7-fluoro-3-metil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico.*

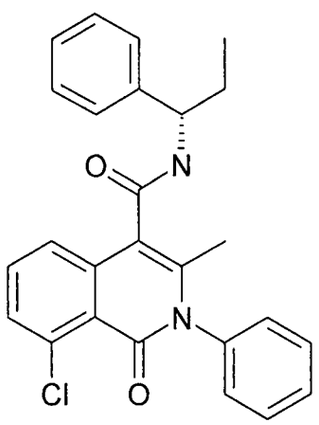
405

LC-MS (m/z) 415,4 (MH^+); t_R = 1,49.



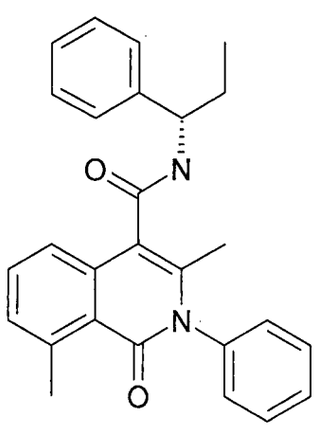
1h *((S)-1-fenil-propil)-amida del ácido 3,7-dimetil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico.*

LC-MS (m/z) 411,4 (MH^+); t_R = 1,5.



1i *((S)-1-fenil-propil)-amida del ácido 8-cloro-3-metil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico.*

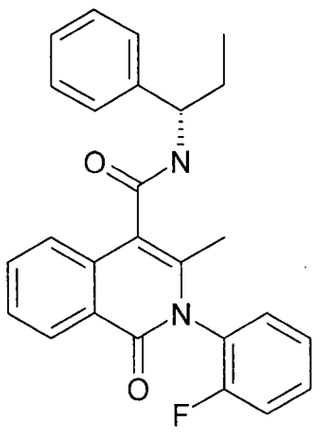
LC-MS (m/z) 431,4 (MH^+); t_R = 1,54.



406

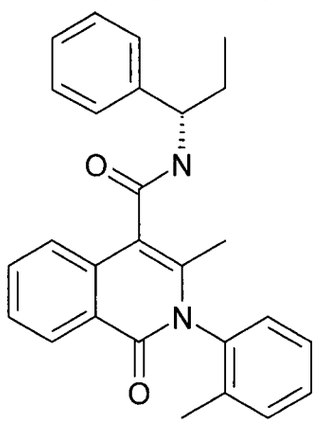
1j *((S)-1-fenil-propil)-amida del ácido 3,8-dimetil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico.*

LC-MS (m/z) 411,4 (MH^+); t_R = 1,5. ^1H RMN (250 MHz, DMSO-d_6, T=343K): 0,91 (t, 3H), 1,78 (traslapado s, 3H), 1,79 (traslapado 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).



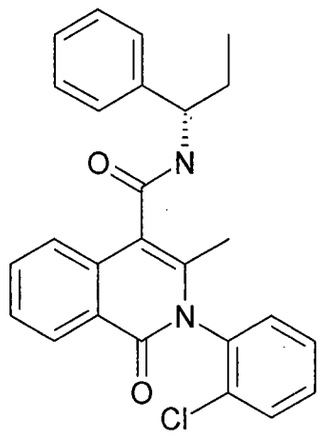
1k *((S)-1-fenil-propil)-amida del ácido 2-(2-fluoro-fenil)-3-metil-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico.*

LC-MS (m/z) 415,5 (MH^+); t_R = 1,49.



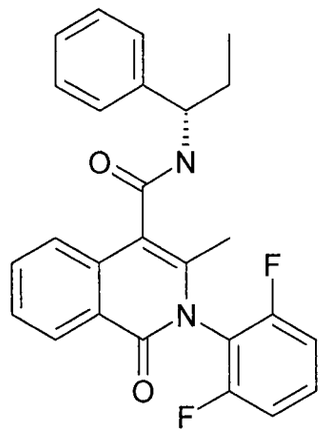
1l *((S)-1-fenil-propil)-amida del ácido 3-metil-1-oxo-2-o-tolil-1,2-dihidro-isoquinolin-4-carboxílico.*

LC-MS (m/z) 411,5 (MH^+); t_R = 1,5.



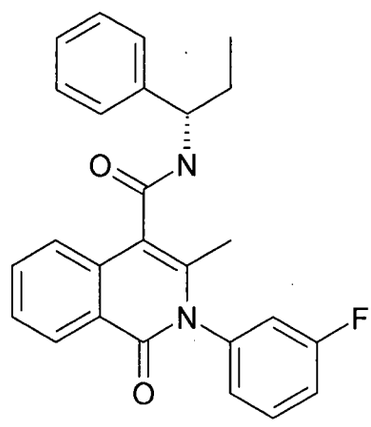
1m *((S)-1-fenil-propil)-amida del ácido 2-(2-cloro-fenil)-3-metil-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico.*

LC-MS (m/z) 431,2 (MH^+); t_R = 1,51.



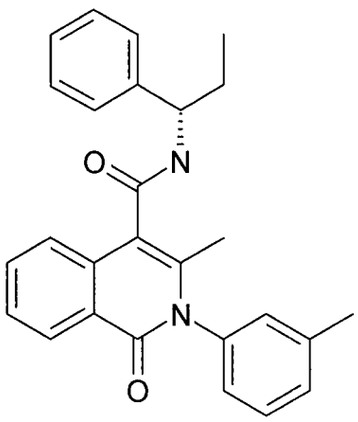
1n *((S)-1-fenil-propil)-amida del ácido 2-(2,6-difluoro-fenil)-3-metil-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico.*

LC-MS (m/z) 433,4 (MH^+); t_R = 1,54.



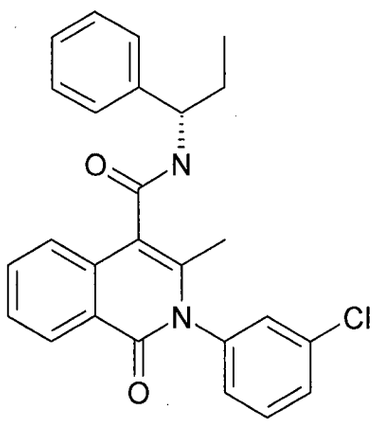
1o *((S)-1-fenil-propil)-amida del ácido 2-(3-fluoro-fenil)-3-metil-1-oxo-1,2-dihidro-isoquinolin-4- carboxílico*

LC-MS (m/z) 415,1 (MH^+); t_R = 1,48.



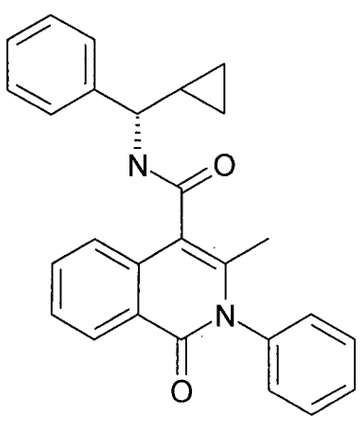
1p *((S)-1-fenil-propil)-amida del ácido 3-metil-1-oxo-2-m-tolil-1,2-dihidro-isoquinolin-4-carboxílico.*

LC-MS (m/z) 411,5 (MH^+); t_R = 1,53.



1q *((S)-1-fenil-propil)-amida del ácido 2-(3-cloro-fenil)-3-metil-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico.*

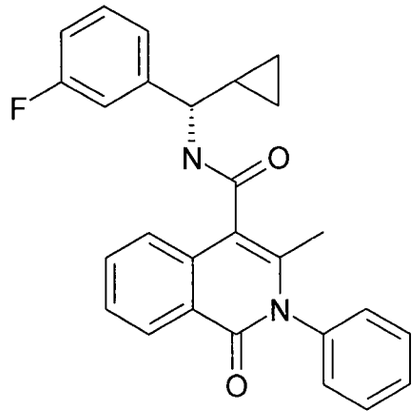
LC-MS (m/z) 431,2 (MH^+); t_R = 1,57.



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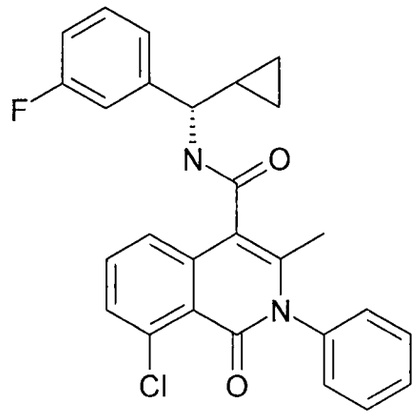
1r *((S)-ciclopropil-fenil-metil)-amida del ácido 3-metil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico.*

LC-MS (m/z) 409,4 (MH^+); t_R = 1,43. ^1H RMN (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 *[(S)-ciclopropil-(3-fluoro-fenil)-metil]-amida del ácido 3-metil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico.*

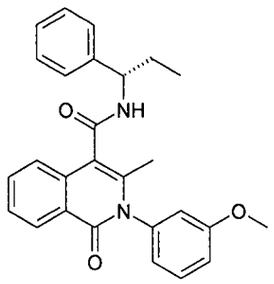
LC-MS (m/z) 427,1 (MH^+); t_R = 1,48. ^1H RMN (250 MHz, DMSO-d_6, T=343K): 0,48 (m, 2H), 0,57 (m, 2H), 1,24 (m, 1H), 1,89 (s, 3H), 4,51 (t, 1H), 7,05 (m, 1H), 7,21-7,31 (m, 4H), 7,33-7,6 (m, 6H), 7,7 (dt, 1H), 8,21 (dd, 1H), 8,94 (d, 1H).



1t *[(S)-ciclopropil-(3-fluoro-fenil)-metil]-amida del ácido 8-cloro-3-metil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico.*

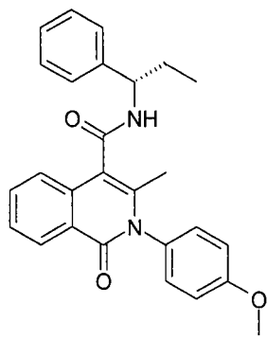
LC-MS (m/z) 461,6 (MH^+); t_R = 1,51. ^1H RMN (250 MHz, DMSO-d_6, T=343K): 0,48 (m, 2H), 0,58 (m, 2H), 1,27 (m, 1H), 1,87 (s, 3H), 4,5 (t, 1H), 7,06 (m, 1H), 7,21-7,32 (m, 4H), 7,32-7,45 (m, 2H), 7,45-7,66 (m, 5H), 8,95 (d, 1H).

410



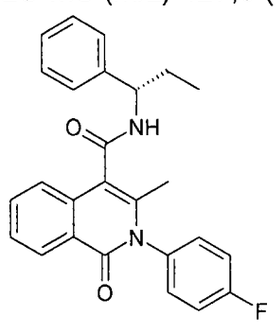
1aa ((S)-1-fenil-propil)-amida del ácido2-(3-metoxi-fenil)-3-metil-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico

LC-MS (m/z) 426,7 (MH^+); t_R = 1,43.



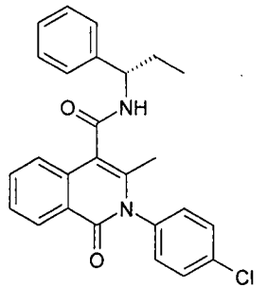
1ab ((S)-1-fenil-propil)-amida del ácido 2-(4-metoxi-fenil)-3-metil-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico

LC-MS (m/z) 427,0 (MH^+); t_R = 1,43.



1ac ((S)-1-fenil-propil)-amida del ácido 2-(4-fluoro-fenil)-3-metil-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico.

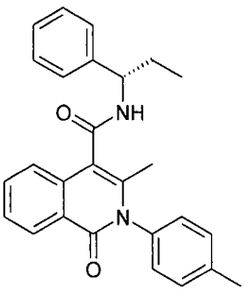
LC-MS (m/z) 415,0 (MH^+); t_R = 1,43.



1ad ((S)-1-fenil-propil)-amida del ácido 2-(4-cloro-fenil)-3-metil-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico.

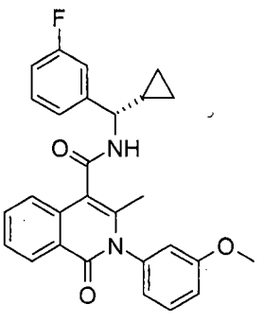
411

LC-MS (m/z) 431,1 (MH^+); t_R = 1,54.



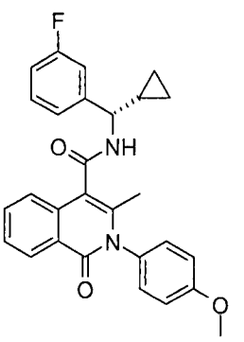
1ae ((S)-1-fenil-propil)-amida del ácido 3-metil-1-oxo-2-p-tolil-1,2-dihidro-isoquinolin-4-carboxílico.

LC-MS (m/z) 411,2 (MH^+); t_R = 1,51.



1af [(S)-ciclopropil-(3-fluoro-fenil)-metil]-amida del ácido 2-(3-metoxi-fenil)-3-metil-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico.

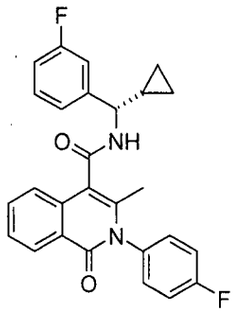
LC-MS (m/z) 457,0 (MH^+); t_R = 1,47.



1ag [(S)-ciclopropil-(3-fluoro-fenil)-metil]-amida del ácido 2-(4-metoxi-fenil)-3-metil-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico.

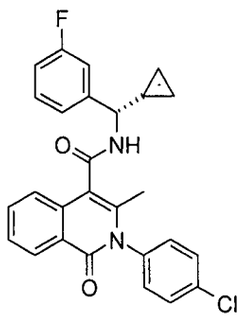
LC-MS (m/z) 457,1 (MH^+); t_R = 1,46.

412



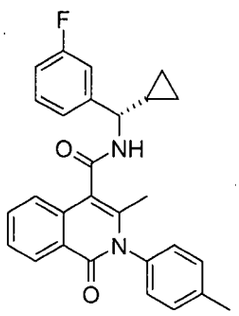
1ah [(S)-ciclopropil-(3-fluoro-fenil)-metil]-amida del ácido 2-(4-fluoro-fenil)-3-metil-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico.

LC-MS (m/z) 445,6 (MH^+); t_R = 1,48.



1ai [(S)-ciclopropil-(3-fluoro-fenil)-metil]-amida del ácido 2-(4-cloro-fenil)-3-metil-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico.

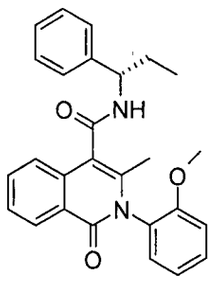
LC-MS (m/z) 461,3 (MH^+); t_R = 1,57.



1aj [(S)-ciclopropil-(3-fluoro-fenil)-metil]-amida del ácido 3-metil-1-oxo-2-p-tolil-1,2-dihidro-isoquinolin-4-carboxílico.

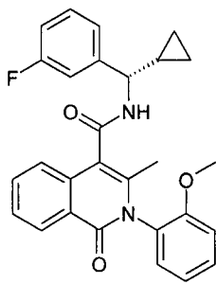
LC-MS (m/z) 440,9 (MH^+); t_R = 1,54.

413



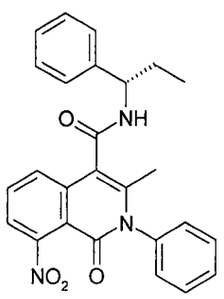
1ak ((S)-1-fenil-propil)-amida del ácido 2-(2-metoxi-fenil)-3-metil-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico.

LC-MS (m/z) 427,0 (MH^+); t_R = 1,39.



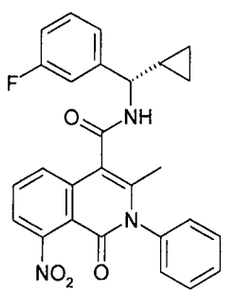
1al [(S)-ciclopropil-(3-fluoro-fenil)-metil]-amida del ácido 2-(2-metoxi-fenil)-3-metil-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico.

LC-MS (m/z) 457,4 (MH^+); t_R = 1,43.



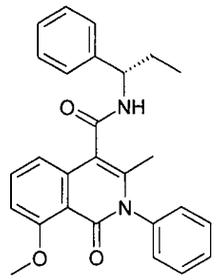
1am *((S)-1-fenil-propil)-amida del ácido 3-metil-8-nitro-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico.*

LC-MS (m/z) 442,4 (MH^+); t_R = 1,46.



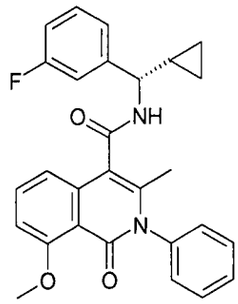
1an *[(S)-ciclopropil-(3-fluoro-fenil)-metil]-amida del ácido 3-metil-8-nitro-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico.*

LC-MS (m/z) 442,4 (MH^+); t_R = 1,46.



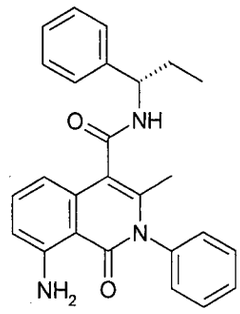
1ao *((S)-1-fenil-propil)-amida del ácido 8-metoxi-3-metil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico.*

LC-MS (m/z) 427,1 (MH^+); t_R = 1,32.



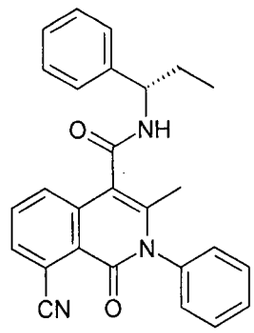
1ap *[(S)-ciclopropil-(3-fluoro-fenil)-metil]-amida del ácido 8-metoxi-3-metil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico.*

LC-MS (m/z) 457,4 (MH^+); t_R = 1,36.



1aq *((S)-1-fenil-propil)-amida del ácido 8-amino-3-metil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico.*

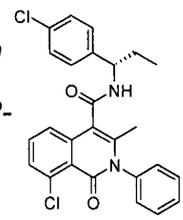
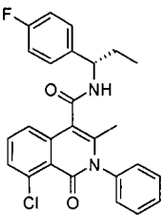
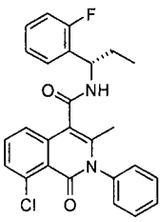
A una solución agitada de ((S)-1-fenil-propil)-amida del ácido 3-metil-8-nitro-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico (**1am,** 10 mg, 0,023 mmol) en tetrahidrofurano (0,15 ml) se agregó HCl acuoso 2M (0,12 ml, 0,25 mmol) y Zn en polvo(45 mg, 0,69 mmol). Después de 30 min la mezcla se filtró y se dividió por partición entre acetato de etilo (4 ml) y $NaHCO_3$ ac.sat. (2 ml), luego salmuera (sic) (3 ml). La solución orgánica se secó ($MgSO_4$) y se evaporó para dar 5,9 mg del compuesto del título (70% de rendimiento). LC-MS (m/z) 412,4 (MH^+); t_R = 1,37.

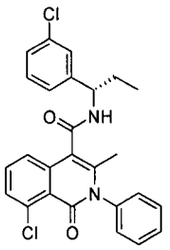
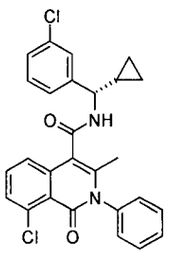
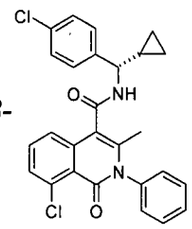
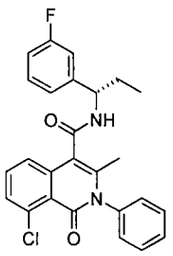
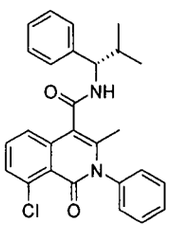
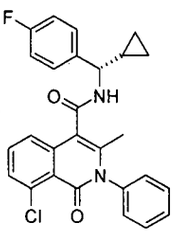
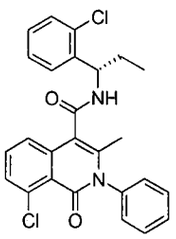


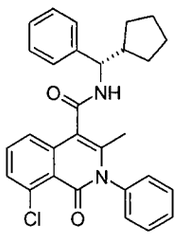
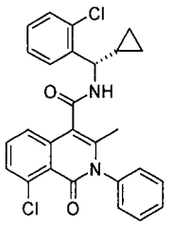
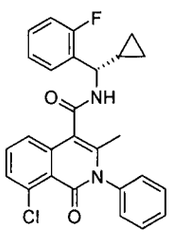
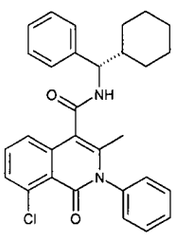
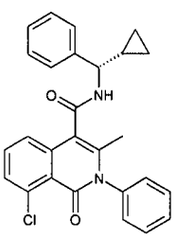
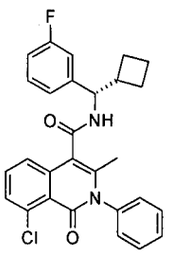
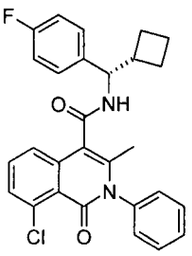
1ar *((S)-1-fenil-propil)-amida del ácido 8-ciano-3-metil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico.*

LC-MS (m/z) 422,1 (MH^+); t_R = 1,37.

Los siguientes compuestos se obtuvieron de acuerdo con el procedimiento general: el ácido correspondiente de la fórmula general IX (0,04 mmol) y la amina de la fórmula general XI (0,06 mmol) en DMF (0,5 ml), se agitó en presencia de Et_3N (3 eq.), EDC (1,5 eq.), y HOBT (1,5 eq.) a temperatura ambiente durante la noche seguido de la separación por partición entre acetato de etilo (2 ml) y NaOH 0,5 M (1 ml) y cromatografía flash sobre SiO_2.

	Nombre químico	**Estructura**	**t_R (min)**	**PM**	**m/z (MH^+)**
1as	*[(S)-1-(4-cloro-fenil)-propil]-amida del ácido 8-cloro-3-metil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico*		1,63	465,4	465,4
1at	*[(S)-1-(4-fluoro-fenil)-propil]-amida del ácido 8-cloro-3-metil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico*		1,52	448,9	449,3
1au	*[(S)-1-(2-fluoro-fenil)-propil]-amida del ácido 8-cloro-3-metil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico*		1,52	448,9	449,4

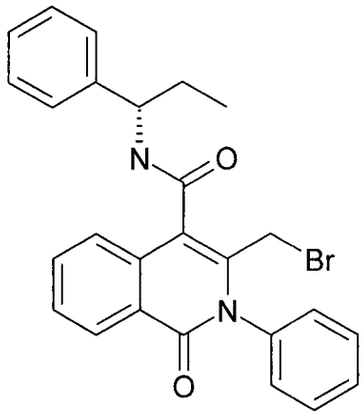
1av	*[(S)-1-(3-cloro-fenil)-propil]-amida del ácido 8-cloro-3-metil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico*		1,62	465,4	465,3
1aw	*[(S)-(3-cloro-fenil)-ciclopropil-metil]-amida del ácido 8-cloro-3-metil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico*		1,64	477,4	477,3
1ax	*[(S)-(4-cloro-fenil)-ciclopropil-metil]-amida del ácido 8-cloro-3-metil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico*		1,64	477,4	477,4
1ay	*[(S)-1-(3-fluoro-fenil)-propil]-amida del ácido 8-cloro-3-metil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico*		1,53	448,9	449,3
1az	*((S)-2-metil-1-fenil-propil)-amida del ácido 8-cloro-3-metil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico*		1,59	444,96	445,7
1ba	*[(S)-ciclopropil-(4-fluoro-fenil)-metil]-amida del ácido 8-cloro-3-metil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico*		1,53	460,9	461,5
1bb	*[(S)-1-(2-cloro-fenil)-propil]-amida del ácido 8-cloro-3-metil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico*		1,61	465,4	465,3

1bc	*((S)-ciclopentil-fenil-metil)-amida del ácido 8-cloro-3-metil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico*		1,72	470,99	471,8
1bd	*[(S)-(2-cloro-fenil)-ciclopropil-metil]-amida del ácido 8-cloro-3-metil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico*		1,6	477,4	477,2
1be	*[(S)-ciclopropil-(2-fluoro-fenil)-metil]-amida del ácido 8-cloro-3-metil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico*		1,6	460,9	461,6
1bf	*((S)-ciclohexil-fenil-metil)-amida del ácido 8-cloro-3-metil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico*		1,8	485,0	485,4
1bg	*((S)-ciclopropil-fenil-metil)-amida del ácido 8-cloro-3-metil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico*		1,5	442,9	443,5
1bh	*[(S)-ciclobutil-(3-fluoro-fenil)-metil]-amida del ácido 8-cloro-3-metil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico*		1,65	474,96	475,5
1bi	*[(S)-ciclobutil-(4-fluoro-fenil)-metil]-amida del ácido 8-cloro-3-metil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico*		1,64	474,96	475,5

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1bl	*[(R)-ciclopropil-(3-fluoro-fenil)-metil]-amida del ácido 8-cloro-3-metil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico*	1,52	460,9	461,5
1bn	*((S)ciclobutil-fenil-metil)-amida del ácido 8-cloro-3-metil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico*	1,61	456,97	457,3
1bo	*[ciclobutil-(2-fluoro-fenil)-metil]-amida del ácido 8-cloro-3-metil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico*	1,64	474,96	475,4

Ejemplo 2: Preparación de los intermedios

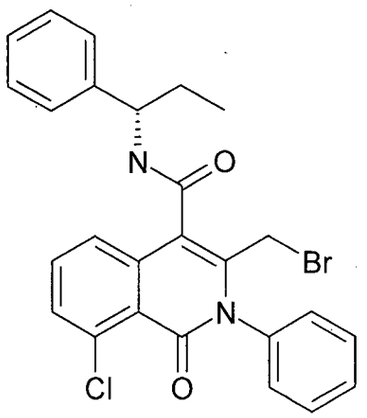


((S)-1-fenil-propil)-amida del ácido 3-bromometil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico.

A una suspensión de $CaCO_3$ (500 mg, 5 mmol) y ((S)-1-fenil-propil)-amida del ácido 3-metil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico (115 mg, 0,29 mmol) en 1,2-dicloroetano (5 ml) se agregó bromo (600 mg, 3,75 mmol). La mezcla obtenida se sometió a tratamiento sónico a +33°C durante 2 horas, se diluyó con 1,2-dicloroetano (20 ml) y se vertió en columna de gel de sílice (5 g). El exceso de bromo se eluyó con 1,2-dicloroetano y el producto se eluyó con acetato de etilo – heptano 1:1 para dar 135 mg de sólido marrón. Se disolvió en acetato de etilo (0,5 ml) y precipitó con heptano (20 ml) para dar 100 mg de sólido de amarillo-marrón. Rendimiento 72%. LC-MS (m/z) 475,2 (MH^+, ^{79}Br); t_R = 1,59. ^1H RMN (500 MHz, DMSO-d_6, una mezcla de dos

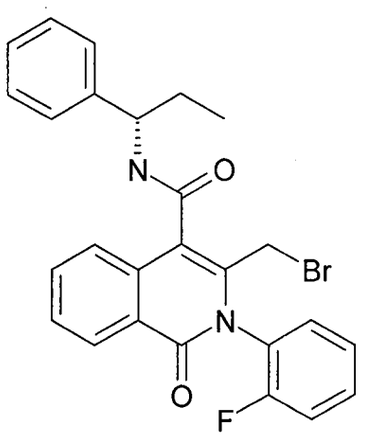
rotámeros interconvertidores): 0,95 (br, 3H, CH_3), 1,74 y 1,82 (dos m no resuelto, 2 x 1H, CH_2), 4,0 (m no resuelto, 1H, CH_2Br), 4,21 y 4,35 (dos m no resuelto, 2 x 0,5H, CH_2Br), 4,97 (q, 1H, CH), 7,1 (br, 0,5H), 7,24 (br, 0,5H), 7,28-7,21 (br m, 11,5H), 7,89 (br, 0,5H), 8,25 (br, 1H), 9,28 (d, 1H, NH).

Los siguientes compuestos se obtuvieron en forma análoga:



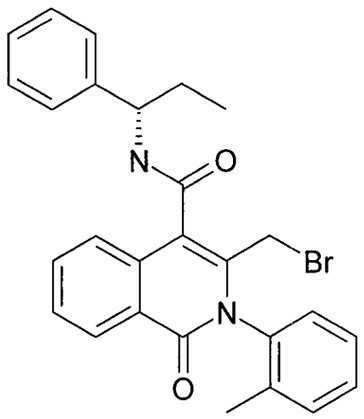
((S)-1-fenil-propil)-amida del ácido 3-bromometil-8-cloro-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico.

El producto crudo se utilizó en el próximo paso sin purificación posterior. LC-MS (m/z) 511,3 (MH^+, ^{79}Br); t_R = 1,68.



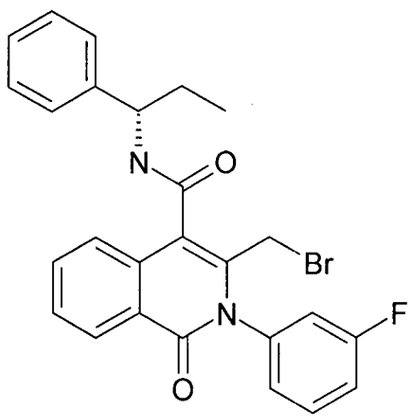
((S)-1-fenil-propil)-amida del ácido 3-bromometil-2-(2-fluoro-fenil)-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico.

El producto crudo se utilizó en el próximo paso sin purificación posterior. LC-MS (m/z) 493,3 (MH^+, ^{79}Br); t_R = 1,62.



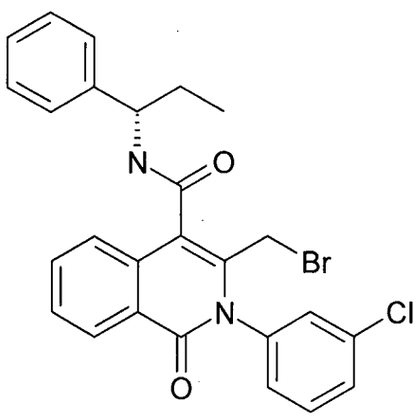
((S)-1-fenil-propil)-amida del ácido 3-bromometil-1-oxo-2-o-tolil-1,2-dihidro-isoquinolin-4-carboxílico.

El producto crudo se utilizó en el próximo paso sin purificación posterior. LC-MS (m/z) 489,3 (MH^+, ^{79}Br); t_R = 1,65.



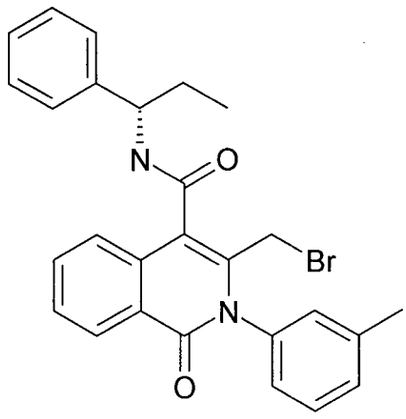
((S)-1-fenil-propil)-amida del ácido 3-bromometil-2-(3-fluoro-fenil)-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico.

LC-MS (m/z) 493,5 (MH^+, ^{79}Br); t_R = 0,80 (método B).



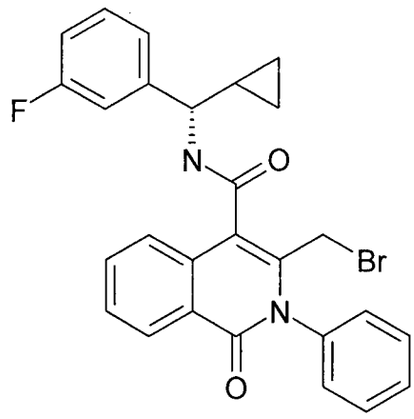
((S)-1-fenil-propil)-amida del ácido 3-bromometil-2-(3-cloro-fenil)-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico.

LC-MS (m/z) 511,5 (MH^+, ^{81}Br); t_R = 0,84 (método B).



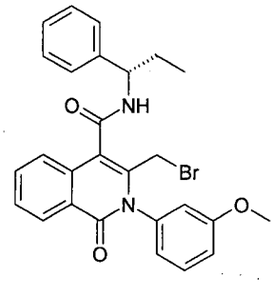
((S)-1-fenil-propil)-amida del ácido 3-bromometil-1-oxo-2-m-tolil-1,2-dihidro-isoquinolin-4-carboxílico.

LC-MS (m/z) 489,2 (MH^+, ^{79}Br); t_R = 0,86 (método B).



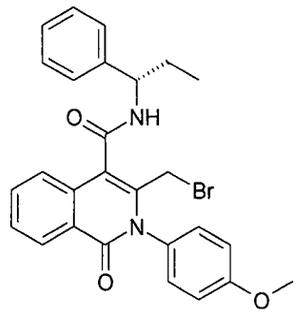
[(S)-ciclopropil-(3-fluoro-fenil)-metil]-amida del ácido 3-bromometil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico.

LC-MS (m/z) 505,1 (MH^+); t_R = 1,62.



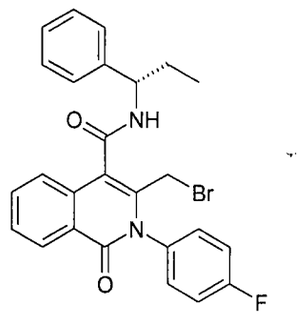
((S)-1-fenil-propil)-amida del ácido 3-bromometil-2-(3-metoxi-fenil)-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico.

El producto se purificó por cromatografía flash sobre SiO_2 (gradiente heptano - acetato de etilo) y se utilizó en el próximo paso directamente.



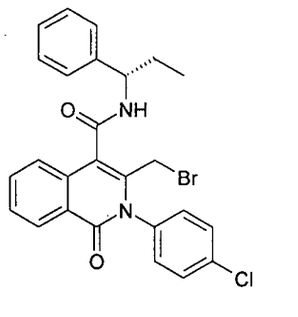
((S)-1-fenil-propil)-amida del ácido 3-bromometil-2-(4-metoxi-fenil)-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico.

El producto se purificó por cromatografía flash sobre SiO_2 (gradiente heptano - acetato de etilo). LC-MS (m/z) 505,1 & 507,2 (MH^+); t_R = 1,52.



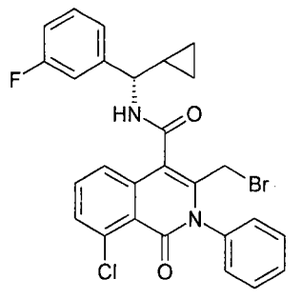
((S)-1-fenil-propil)-amida del ácido 3-bromometil-2-(4-fluoro-fenil)-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico.

El producto se purificó por cromatografía flash sobre SiO_2 (gradiente heptano - acetato de etilo). LC-MS (m/z) 493,3 & 495,3 (MH^+); t_R = 1,54.



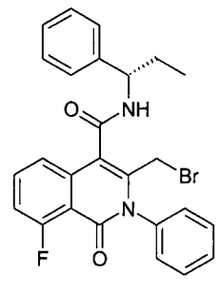
((S)-1-fenil-propil)-amida del ácido 3-bromometil-2-(4-cloro-fenil)-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico.

LC-MS (m/z) 509,2 & 511,1 (MH^+); t_R = 1,63.



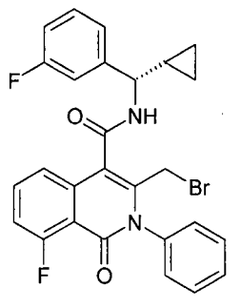
[(S)-ciclopropil-(3-fluoro-fenil)-metil]-amida del ácido 3-bromometil-8-cloro-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico.

LC-MS (m/z) 539,1 & 541,4 (MH^+); t_R = 1,69.



((S)-1-fenil-propil)-amida del ácido 3-bromometil-8-fluoro-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico.

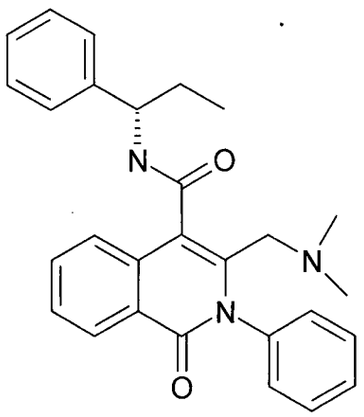
LC-MS (m/z) 493,3 & 495,2 (MH^+); t_R = 1,52.



[(S)-ciclopropil-(3-fluoro-fenil)-metil]-amida del ácido 3-bromometil-8-fluoro-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico.

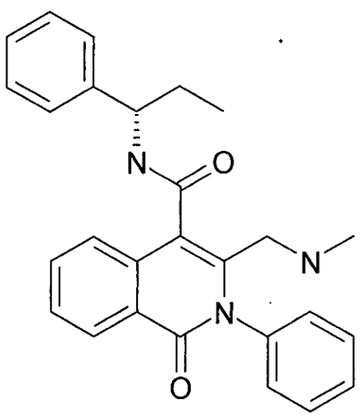
LC-MS (m/z) 523,5 & 525,6 (MH^+); t_R = 1,56.

Compuestos de la invención



2a *((S)-1-fenil-propil)-amida del ácido 3-dimetilaminometil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico.*

Una mezcla de ((S)-1-fenil-propil)-amida del ácido 3-bromometil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico (70 mg, 0,147 mmol) y dimetilamina (1 ml de de solución al 33% en exceso de etanol abs.,) se mantuvo a 50°C durante 10 minutos y luego se evaporó al vacío. El residuo se disolvió en metanol y se pasó a través de columna de intercambio de cationes SCX (1 g, forma RSO_3H). Las impurezas sin carga (neutras) se eluyeron con metanol y el producto se eluyó con NH_3 4M en metanol para dar 53 mg de sólido tipo vidrio incoloro. Posteriormente es purificó por cromatografía flash sobre SiO_2 (5 g, gradiente 1,2-dicloroetano –de acetato de etilo al 10%en 1,2-dicloroetano) para dar 45 mg de sólido incoloro. Rendimiento 70%. LC-MS (m/z) 440,1 (MH^+); t_R = 0,88. ^1H RMN (250 MHz, DMSO-d_6, T = 333 K): 0,92 (t, 2H), 1,83 (dos m traslapado, 2H), 1,66 (s, 6H), 2,96 y 3,08 (dos d de 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 *((S)-1-fenil-propil)-amida del ácido 3-metilaminometil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico.*

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Una mezcla de ((S)-1-fenil-propil)-amida del ácido 3-bromometil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico (4,7 mg, 0,01 mmol) y metilamina (1 ml de solución 2M en tetrahidrofurano, exceso) se mantuvo a temperatura ambiente durante 20 min y luego se evaporó al vacío. El producto se utilizó para ensayo biológico sin purificación posterior. LC-MS (m/z) 426,3 (MH^+); t_R = 0,85.

Los siguientes derivados de 3-aminometilo se prepararon en forma análoga a partir de los correspondientes derivados de 3-bromometilo y 1,2 - 5 equivalentes molares de amina primaria o secundaria alifática o aromática apropiada en tetrahidrofurano como solvente a temperatura ambiente. Las reacciones se monitorearon por LC-MS. En varios casos se utilizaron tiempos de reacción más largos o la mezcla de reacción se calentó hasta 50°C y/o se agregó diisopropiletilamina (2 eq.) como base. Después de la evaporación de la mezcla de reacción los compuestos fueron de una pureza suficiente según se detectó por LC-MS analítica; de otro modo, posteriormente se realizó la purificación por columna SCX o por LC-MS preparativa.

Listado de compuestos del ejemplo 2

	Nombre químico	**t_R (min)**	**PM**	**m/z (MH+)**
2c	((S)-1-fenil-propil)-amida del ácido 3-etilaminometil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	0,45 (método B)	439,6	440,6
2d	((S)-1-fenil-propil)-amida del ácido 3-ciclopropilaminometil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	0,49 (método B)	451,6	452,1
2e	((S)-1-fenil-propil)-amida del ácido 3-[(ciclopropilmetil-amino)-metil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	0,51 (método B)	465,6	466,4
2f	((S)-1-fenil-propil)-amida del ácido 3-(3,6-dihidro-2H-piridin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	0,99	477,6	478,1
2g	((S)-1-fenil-propil)-amida del ácido 3-[4-(2-	1,14	586,7	587,5

	metoxi-fenil)-piperazin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico			
2h	((S)-1-fenil-propil)-amida del ácido 3-[4-(4-fluoro-fenil)-piperazin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	1,35	574,7	575,6
2i	((S)-1-fenil-propil)-amida del ácido 3-(4-formil-piperazin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	1,12	508,6	509,3
2j	etil éster del ácido 4-[1-oxo-2-fenil-4-(1-fenil-propilcarbamoil)-1,2-dihidro-isoquinolin-3-ilmetil]-piperazin-1-carboxílico	1,33	552,7	553,7
2k	((S)-1-fenil-propil)-amida del ácido 3-(4-metil-piperazin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	0,87	494,6	495,7
2l	((S)-1-fenil-propil)-amida del ácido 1-oxo-2-fenil-3-(1,3,4,9-tetrahidro-beta-carbolin-2-ilmetil)-1,2-dihidro-isoquinolin-4-carboxílico	1,27	566,7	567,7
2m	((S)-1-fenil-propil)-amida del ácido 1-oxo-2-fenil-3-piperazin-1-ilmetil-1,2-dihidro-isoquinolin-4-carboxílico	0,86	480,6	481,2
2n	((S)-1-fenil-propil)-amida del ácido 3-(3-metil-piperazin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	0,88	494,6	495,7
2o	((S)-1-fenil-propil)-amida del ácido 3-(3,5-dimetil-piperazin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	0,9	508,7	509,3
2p	((S)-1-fenil-propil)-amida del ácido 3-(4-bencil-piperazin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	1,02	570,7	571,5
2q	((S)-1-fenil-propil)-amida del ácido 1-oxo-3-[4-(2-oxo-2-pirrolidin-1-il-etil)-piperazin-1-ilmetil]-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	0,92	591,8	592,4

2r	((S)-1-fenil-propil)-amida del ácido 3-morfolin-4-ilmetil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	1,08	481,6	482,2
2s	((S)-1-fenil-propil)-amida del ácido 3-(2,6-dimetil-morfolin-4-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	1,21	509,6	510,2
2t	((S)-1-fenil-propil)-amida del ácido 1-oxo-2-fenil-3-tiomorfolin-4-ilmetil-1,2-dihidro-isoquinolin-4-carboxílico	1,22	497,7	498,8
2u	((S)-1-fenil-propil)-amida del ácido 3-(1,4-dioxa-8-aza-espiro[4,5]dec-8-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	1,01	537,7	538,4
2v	((S)-1-fenil-propil)-amida del ácido 1-oxo-2-fenil-3-piperidin-1-ilmetil-1,2-dihidro-isoquinolin-4-carboxílico	1	479,6	480,3
2w	((S)-1-fenil-propil)-amida del ácido 3-(2-metil-piperidin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	1,07	493,6	494,4
2x	((S)-1-fenil-propil)-amida del ácido 3-(2,6-dimetil-piperidin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	1,09	507,7	508,4
2y	((S)-1-fenil-propil)-amida del ácido 3-(2-hidroximetil-piperidin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	0,93	509,6	510,3
2z	etil éster del ácido 1-[1-oxo-2-fenil-4-(1-fenil-propilcarbamoil)-1,2-dihidro-isoquinolin-3-ilmetil]-piperidin-3-carboxílico	1,14	551,7	552,4
2aa	((S)-1-fenil-propil)-amida del ácido 3-(3-metil-piperidin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	1,09	493,6	494,5
2ab	((S)-1-fenil-propil)-amida del ácido 3-(4-hidroxi-piperidin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-	0,83	495,6	496,5

	isoquinolin-4-carboxílico			
2ac	((S)-1-fenil-propil)-amida del ácido 1-oxo-2-fenil-3-(4-fenil-piperidin-1-ilmetil)-1,2-dihidro-isoquinolin-4-carboxílico	1,27	555,7	556,5
2ad	etil éster del ácido 1-[1-oxo-2-fenil-4-(1-fenil-propilcarbamoil)-1,2-dihidro-isoquinolin-3-ilmetil]-piperidin-4-carboxílico	1,11	551,7	552,5
2ae	((S)-1-fenil-propil)-amida del ácido 3-(4-metil-piperidin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	1,1	493,6	494,6
2af	((S)-1-fenil-propil)-amida del ácido 1-oxo-2-fenil-3-(4-piridin-2-il-piperazin-1-ilmetil)-1,2-dihidro-isoquinolin-4-carboxílico	0,97	557,7	558,4
2ag	((S)-1-fenil-propil)-amida del ácido 3-(octahidro-quinolin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	1,18	533,7	534,4
2ah	((S)-1-fenil-propil)-amida del ácido 3-azepan-1-ilmetil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	1,08	493,6	494,6
2ai	((S)-1-fenil-propil)-amida del ácido 3-(3-hidroxi-piperidin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	0,88	495,6	496,5
2aj	((S)-1-fenil-propil)-amida del ácido 3-[4-(2,4-dimetil-fenil)-piperazin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	1,45	584,8	585,5
2ak	((S)-1-fenil-propil)-amida del ácido 3-[4-(3,4-dimetil-fenil)-piperazin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	1,29	584,8	585,6
2al	((S)-1-fenil-propil)-amida del ácido 3-(4-dimetilamino-piperidin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	0,81	522,7	523,5
2am	((S)-1-fenil-propil)-amida del ácido 3-[4-(2,5-	1,47	584,8	585,6

	dimetil-fenil)-piperazin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico			
2an	((S)-1-fenil-propil)-amida del ácido 3-[4-(2-fluoro-fenil)-piperazin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	1,42	574,7	575,4
2ao	((S)-1-fenil-propil)-amida del ácido 3-[4-(3-metoxi-fenil)-piperazin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	1,32	586,7	587,3
2ap	((S)-1-fenil-propil)-amida del ácido 1-oxo-2-fenil-3-(4-m-tolil-piperazin-1-ilmetil)-1,2-dihidro-isoquinolin-4-carboxílico	1,33	570,7	571,7
2aq	((S)-1-fenil-propil)-amida del ácido 3-[4-(4-metoxi-fenil)-piperazin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	1,11	586,7	587,6
2ar	((S)-1-fenil-propil)-amida del ácido 1-oxo-3-(4-fenetil-piperazin-1-ilmetil)-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	1,09	584,8	585,5
2as	((S)-1-fenil-propil)-amida del ácido 1-oxo-2-fenil-3-(4-pirimidin-2-il-piperazin-1-ilmetil)-1,2-dihidro-isoquinolin-4-carboxílico	1,18	558,7	559,3
2at	((S)-1-fenil-propil)-amida del ácido 3-[4-(2-ciano-fenil)-piperazin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	1,43	581,7	582,7
2au	((S)-1-fenil-propil)-amida del ácido 3-[4-(4-cloro-fenil)-piperazin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	1,54	591,2	591,3
2av	((S)-1-fenil-propil)-amida del ácido 3-((1S,3R,5R)-3-hidroxi-8-aza-biciclo[3,2,1]oct-8-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	0,88	521,7	522,7
2aw	((S)-1-fenil-propil)-amida del ácido 3-(4-acetil-piperazin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-	1,07	522,6	523,5

	isoquinolin-4-carboxílico			
2ax	((S)-1-fenil-propil)-amida del ácido 3-(4-metil-[1,4]diazepan-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	0,89	508,7	509,2
2ay	((S)-1-fenil-propil)-amida del ácido 3-(4-etil-piperazin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	0,89	508,7	509,2
2az	((S)-1-fenil-propil)-amida del ácido 3-((2S,6R)-2,6-dimetil-morfolin-4-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	1,21	509,6	510,2
2ba	((S)-1-fenil-propil)-amida del ácido 3-[4-(2,4-difluoro-fenil)-piperazin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	1,48	592,7	593,6
2bb	((S)-1-fenil-propil)-amida del ácido 3-[4-(3-dimetilamino-propil)-piperazin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	0,76	565,8	566,7
2bc	((S)-1-fenil-propil)-amida del ácido 3-(4-isopropil-piperazin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	0,91	522,7	523,5
2bd	((S)-1-fenil-propil)-amida del ácido 3-(3-aza-biciclo[3,2,2]non-3-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	1,21	519,7	520,4
2be	((S)-1-fenil-propil)-amida del ácido 3-(4-ciclopentil-piperazin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	0,98	548,7	549,6
2bf	((S)-1-fenil-propil)-amida del ácido 3-[1,4']bipiperidinil-1'-ilmetil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	0,86	562,8	563,2
2bg	((S)-1-fenil-propil)-amida del ácido 3-(3,4-dihidro-1H-isoquinolin-2-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	1,22	527,7	528,7
2bh	((S)-1-fenil-propil)-amida del ácido 3-[4-(2-	0,74	551,7	552,5

	dimetilamino-etil)-piperazin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico			
2bi	((S)-1-fenil-propil)-amida del ácido 3-(4-hidroximetil-piperidin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	0,86	509,6	510,3
2bj	((S)-1-fenil-propil)-amida del ácido 1-oxo-2-fenil-3-[4-(tetrahidro-furan-2-carbonil)-piperazin-1-ilmetil]-1,2-dihidro-isoquinolin-4-carboxílico	1,16	578,7	579,9
2bk	((S)-1-fenil-propil)-amida del ácido 3-(4-isobutil-piperazin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	0,98	536,7	537,4
2bl	((S)-1-fenil-propil)-amida del ácido 3-[4-(2-metoxi-etil)-piperazin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	0,91	538,7	539,6
2bm	((S)-1-fenil-propil)-amida del ácido 3-[4-(2-morfolin-4-il-etil)-piperazin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	0,75	593,8	594,7
2bn	((S)-1-fenil-propil)-amida del ácido 3-(1,3-dihidro-isoindol-2-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	1,16	513,6	514,8
2bo	((S)-1-fenil-propil)-amida del ácido 3-[4-(1-metil-piperidin-4-il)-piperazin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	0,72	577,8	578,5
2bp	((S)-1-fenil-propil)-amida del ácido 1-oxo-2-fenil-3-[4-(2-piperidin-1-il-etil)-piperazin-1-ilmetil]-1,2-dihidro-isoquinolin-4-carboxílico	0,75	591,8	592,5
2bq	((S)-1-fenil-propil)-amida del ácido 1-oxo-2-fenil-3-[4-(2-pirrolidin-1-il-etil)-piperazin-1-ilmetil]-1,2-dihidro-isoquinolin-4-carboxílico	0,74	577,8	578,4
2br	((S)-1-fenil-propil)-amida del ácido 3-(4-dimetilcarbamoilmetil-piperazin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	0,89	565,7	566,6

2bs	((S)-1-fenil-propil)-amida del ácido 3-(octahidro-pirido[1,2-a]pirazin-2-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	0,93	534,7	535,4
2bt	((S)-1-fenil-propil)-amida del ácido 3-(4-formil-[1,4]diazepan-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	0,94	522,6	523,6
2bu	((S)-1-fenil-propil)-amida del ácido 3-[4-(4-ciano-fenil)-piperazin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	1,46	581,7	582,6
2bv	((S)-1-fenil-propil)-amida del ácido 1-oxo-2-fenil-3-(4-piridin-4-ilmetil-piperazin-1-ilmetil)-1,2-dihidro-isoquinolin-4-carboxílico	0,77	571,7	572,4
2bw	((S)-1-fenil-propil)-amida del ácido 1-oxo-2-fenil-3-[4-(3-pirrolidin-1-il-propil)-piperazin-1-ilmetil]-1,2-dihidro-isoquinolin-4-carboxílico	0,75	591,8	592,6
2bx	((S)-1-fenil-propil)-amida del ácido 1-oxo-2-fenil-3-(4-piridin-2-ilmetil-piperazin-1-ilmetil)-1,2-dihidro-isoquinolin-4-carboxílico	0,93	571,7	572,5
2by	((S)-1-fenil-propil)-amida del ácido 3-(4-etansulfonil-piperazin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	1,38	572,7	573,7
2bz	((S)-1-fenil-propil)-amida del ácido 3-(4-sec-butil-piperazin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	0,96	536,7	537,4
2ca	((S)-1-fenil-propil)-amida del ácido 3-[4-(1-etil-propil)-piperazin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	1,01	550,7	551,8
2cb	((S)-1-fenil-propil)-amida del ácido 3-[4-(2-ciano-etil)-piperazin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	0,9	533,7	534,4
2cc	((S)-1-fenil-propil)-amida del ácido 3-(4-metansulfonil-piperazin-1-ilmetil)-1-oxo-2-fenil-	1,31	558,7	559,2

	1,2-dihidro-isoquinolin-4-carboxílico			
2cd	etil éster del ácido {1-[1-oxo-2-fenil-4-(1-fenil-propilcarbamoil)-1,2-dihidro-isoquinolin-3-ilmetil]-piperidin-4-il}-acético	1,12	565,7	566,7
2ce	((S)-1-fenil-propil)-amida del ácido 3-[4-(3-fluoro-fenil)-piperazin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	1,48	574,7	575,5
2cf	((S)-1-fenil-propil)-amida del ácido 1-oxo-2-fenil-3-((S)-3-fenil-piperidin-1-ilmetil)-1,2-dihidro-isoquinolin-4-carboxílico	1,27	555,7	556,5
2cg	((S)-1-fenil-propil)-amida del ácido 1-oxo-2-fenil-3-[4-(pirrolidin-1-carbonil)-piperazin-1-ilmetil]-1,2-dihidro-isoquinolin-4-carboxílico	1,11	577,7	578,6
2ch	((S)-1-fenil-propil)-amida del ácido 3-[4-(morfolin-4-carbonil)-piperazin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	1,04	593,7	594,7
2ci	((S)-1-fenil-propil)-amida del ácido 3-(4-metoxi-piperidin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	0,98	509,6	510,2
2cj	((S)-1-fenil-propil)-amida del ácido 3-(4'-hidroxi-3',4',5',6'-tetrahidro-2'H-[3,4']bipiridinil-1'-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	0,71	572,7	573,8
2ck	((S)-1-fenil-propil)-amida del ácido 3-(4-hidroxi-3,4,5,6-tetrahidro-2H-[4,4']bipiridinil-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	0,71	572,7	573,8
2cl	((S)-1-fenil-propil)-amida del ácido 3-(3H-espiro[isobenzofuran-1,4'-piperidin]-1'-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	1,25	583,7	584,5
2cm	((S)-1-fenil-propil)-amida del ácido 3-(4-hidroxi-4-metil-piperidin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	0,91	509,6	510,1
2cn	((S)-1-fenil-propil)-amida del ácido 3-(hexahidro-	1,27	591,7	592,5

	espiro[benzo[1,3]dioxol-2,4'-piperidin]-1'-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico			
2co	((S)-1-fenil-propil)-amida del ácido 1-oxo-2-fenil-3-(3,4,5,6-tetrahidro-2H-[4,4']bipiridinil-1-ilmetil)-1,2-dihidro-isoquinolin-4-carboxílico	0,71	556,7	557,4
2cp	((S)-1-fenil-propil)-amida del ácido 3-[4-(2-dimetilamino-etil)-piperidin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	0,68	550,7	551,4
2cq	((S)-1-fenil-propil)-amida del ácido 3-(4-dimetilosulfamoil-piperazin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	1,43	587,7	588,3
2cr	((S)-1-fenil-propil)-amida del ácido 3-(1,1-dioxo-tiomorfolin-4-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	1,29	529,7	530,3
2cs	((S)-1-fenil-propil)-amida del ácido 1-oxo-2-fenil-3-(2-piridin-2-ilmetil-piperidin-1-ilmetil)-1,2-dihidro-isoquinolin-4-carboxílico	1,05	570,7	571,6
2ct	((S)-1-fenil-propil)-amida del ácido 3-(2-morfolin-4-ilmetil-piperidin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	1,08	578,8	579,8
2cu	((S)-1-fenil-propil)-amida del ácido 3-(4-Furo[3,2-c]piridin-4-il-piperazin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	1,01	597,7	598,5
2cv	((S)-1-fenil-propil)-amida del ácido 3-(4-ciclopropilmetil-piperazin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	0,95	534,7	535,3
2cw	((S)-1-fenil-propil)-amida del ácido 3-[4-(2-morfolin-4-il-etil)-piperidin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	0,69	592,8	593,5
2cx	((S)-1-fenil-propil)-amida del ácido 1-oxo-2-fenil-3-(4-pirimidin-2-il-[1,4]diazepan-1-ilmetil)-1,2-dihidro-isoquinolin-4-carboxílico	1,05	572,7	573,5

2cy	((S)-1-fenil-propil)-amida del ácido 3-(4-metil-6,7-dihidro-4H-tieno[3,2-c]piridin-5-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	1,23	547,7	548,5
2cz	((S)-1-fenil-propil)-amida del ácido 3-[1,4]diazepan-1-ilmetil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	0,89	494,6	495,7
2da	((S)-1-fenil-propil)-amida del ácido 3-((2S,5R)-2,5-dimetil-piperazin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	0,92	508,7	509,2
2db	((S)-1-fenil-propil)-amida del ácido 3-((S)-3-metil-piperazin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	0,88	494,6	495,7
2dc	((S)-1-fenil-propil)-amida del ácido 3-((R)-3-metil-piperazin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	0,88	494,6	495,7
2dd	((S)-1-fenil-propil)-amida del ácido 3-[3-(3-cloro-fenil)-piperazin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	1,11	591,2	591,4
2de	((S)-1-fenil-propil)-amida del ácido 3-[4-(1H-Indol-4-il)-piperazin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	1,1	595,7	596,6
2df	((S)-1-fenil-propil)-amida del ácido 1-oxo-3-(3-oxo-piperazin-1-ilmetil)-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	1,09	494,6	495,7
2dg	((S)-1-fenil-propil)-amida del ácido 3-[4-(1H-Indol-5-il)-piperazin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	1,04	595,7	596,7
2dh	((S)-1-fenil-propil)-amida del ácido 3-(6,9-diaza-espiro[4,5]dec- 9-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	0,97	534,7	535,3
2di	((S)-1-fenil-propil)-amida del ácido 3-(1,4-diaza-espiro[5,5]undec-4-ilmetil)-1-oxo-2-fenil-1,2-	1,01	548,7	549,7

	dihidro-isoquinolin-4-carboxílico			
2dj	((S)-1-fenil-propil)-amida del ácido 3-(3-isopropil-piperazin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	0,96	522,7	523,5
2dk	((S)-1-fenil-propil)-amida del ácido 3-(3,3-dimetil-piperazin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	0,9	508,7	509,2
2dl	((S)-1-fenil-propil)-amida del ácido 3-[3-(4-fluoro-fenil)-piperazin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	1,05	574,7	575,4
2dm	((S)-1-fenil-propil)-amida del ácido 1-oxo-2-fenil-3-(3-p-tolil-piperazin-1-ilmetil)-1,2-dihidro-isoquinolin-4-carboxílico	1,08	570,7	571,7
2dn	ter-butil éster del ácido 4-[1-oxo-2-fenil-4-(1-fenil-propilcarbamoil)-1,2-dihidro-isoquinolin-3-ilmetil]-piperazin-1-carboxílico	1,49	580,7	581,9
2do	((S)-1-fenil-propil)-amida del ácido 3-(4-metilcarbamoilmetil-piperazin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	0,86	551,7	552,9
2dp	((S)-1-fenil-propil)-amida del ácido 8-cloro-3-dimetilaminometil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	0,95	474,0	474,6
2dr	((S)-1-fenil-propil)-amida del ácido 3-ciclopentilaminometil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	1,03	479,6	480,4
2ds	((S)-1-fenil-propil)-amida del ácido 3-ciclohexilaminometil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	1,1	493,6	494,4
2dt	((S)-1-fenil-propil)-amida del ácido 3-{[(2-hidroxi-etil)-metil-amino]-metil}-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	0,84	469,6	470,6
2du	((S)-1-fenil-propil)-amida del ácido 3-imidazol-1-	0,86	462,6	463,4

	ilmetil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico			
2dv	((S)-1-fenil-propil)-amida del ácido 3-(2-metil-imidazol-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	0,88	476,6	477,3
2dw	((S)-1-fenil-propil)-amida del ácido 3-(4-metil-imidazol-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	0,89	476,6	477,3
2dx	((S)-1-fenil-propil)-amida del ácido 3-(2,5-dihidro-pirrol-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	0,92	463,6	464,5
2dy	((S)-1-fenil-propil)-amida del ácido 3-(2,5-dimetil-2,5-dihidro-pirrol-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	1,06	491,6	492,4
2dz	((S)-1-fenil-propil)-amida del ácido 1-oxo-2-fenil-3-pirrolidin-1-ilmetil-1,2-dihidro-isoquinolin-4-carboxílico	0,92	465,6	466,3
2ea	((S)-1-fenil-propil)-amida del ácido 1-oxo-2-fenil-3-(tiazol-2-ilaminometil)-1,2-dihidro-isoquinolin-4-carboxílico	0,88	494,6	495,6
2eb	((S)-1-fenil-propil)-amida del ácido 1-oxo-2-fenil-3-(pirimidin-4-ilaminometil)-1,2-dihidro-isoquinolin-4-carboxílico	0,85	489,6	490,4
2ec	((S)-1-fenil-propil)-amida del ácido 3-(ter-butilamino-metil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	1	467,6	468,7
2ed	((S)-1-fenil-propil)-amida del ácido 3-[(2-hidroxi-1,1-dimetil-etilamino)-metil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	0,91	483,6	484,3
2ee	((S)-1-fenil-propil)-amida del ácido 3-(isopropilamino-metil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	0,93	453,6	454,3

2ef	((S)-1-fenil-propil)-amida del ácido 3-[(2-hidroxi-1-metil-etilamino)-metil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	0,86	469,6	470,5
2eg	((S)-1-fenil-propil)-amida del ácido 3-[(1-hidroximetil-propilamino)-metil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	0,92	483,6	484,4
2eh	((S)-1-fenil-propil)-amida del ácido 3-[(2,2-dimetil-propilamino)-metil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	1,13	481,6	482,2
2ei	((S)-1-fenil-propil)-amida del ácido 1-oxo-2-fenil-3-prop-2-inilaminometil-1,2-dihidro-isoquinolin-4-carboxílico	0,95	449,6	450,2
2ej	((S)-1-fenil-propil)-amida del ácido 3-aliloaminometil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	0,94	451,6	452,4
2ek	((S)-1-fenil-propil)-amida del ácido 3-[(metil-prop-2-inil-amino)-metil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	1,22	463,6	464,5
2el	((S)-1-fenil-propil)-amida del ácido 3-dialiloaminometil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	1,19	491,6	492,4
2em	((S)-1-fenil-propil)-amida del ácido 3-dietilaminometil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	0,98	467,6	468,5
2en	((S)-1-fenil-propil)-amida del ácido 3-[(isopropil-metil-amino)-metil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	0,96	467,6	468,7
2eo	((S)-1-fenil-propil)-amida del ácido 3-[((S)-2-hidroxi-1-metil-etilamino)-metil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	0,86	469,6	470,5
2ep	((S)-1-fenil-propil)-amida del ácido 3-[((R)-2-hidroxi-1-metil-etilamino)-metil]-1-oxo-2-fenil-1,2-	0,87	469,6	470,5

	dihidro-isoquinolin-4-carboxílico			
2eq	((S)-1-fenil-propil)-amida del ácido 3-{[(2-metoxi-etil)-metil-amino]-metil}-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	0,96	483,6	484,4
2er	((S)-1-fenil-propil)-amida del ácido 3-((R)-3-hidroxi-pirrolidin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	0,85	481,6	482,3
2es	((S)-1-fenil-propil)-amida del ácido 3-((S)-3-hidroxi-pirrolidin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	0,84	481,6	482,3
2et	((S)-1-fenil-propil)-amida del ácido 3-[(ciclopentil-metil-amino)-metil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	1,09	493,6	494,5
2eu	((S)-1-fenil-propil)-amida del ácido 3-{[(2-hidroxi-1-metil-etil)-metil-amino]-metil}-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	0,89	483,6	484,4
2ev	((S)-1-fenil-propil)-amida del ácido 3-{[etil-(2-hidroxi-etil)-amino]-metil}-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	0,89	483,6	484,4
2ew	((S)-1-fenil-propil)-amida del ácido 3-[(etil-metil-amino)-metil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	0,92	453,6	454,4
2ex	((S)-1-fenil-propil)-amida del ácido 3-ciclobutilaminometil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	0,98	465,6	466,4
2ey	((S)-1-fenil-propil)-amida del ácido 3-azetidin-1-ilmetil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	0,86	451,6	452,3
2ez	((S)-1-fenil-propil)-amida del ácido 3-(4-ter-butil-piperazin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	0,91	536,7	537,3
2fa	((S)-1-fenil-propil)-amida del ácido 3-[4-(2-	0,86	524,7	525,6

	hidroxi-etil)-piperazin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico			
2fb	((S)-1-fenil-propil)-amida del ácido 3-{4-[2-(2-hidroxi-etoxi)-etil]-piperazin-1-ilmetil}-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	0,86	568,7	569,6
2fc	((S)-1-fenil-propil)-amida del ácido 3-[4-(3-cloro-5-trifluorometil-piridin-2-il)-piperazin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	1,77	660,1	660,8
2fd	((S)-1-fenil-propil)-amida del ácido 3-[4-(3,5-dicloro-piridin-4-il)-piperazin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	1,45	626,6	626,5
2fe	bencil éster del ácido 4-[1-oxo-2-fenil-4-((S)-1-fenil-propilcarbamoil)-1,2-dihidro-isoquinolin-3-ilmetil]-piperazin-1-carboxílico	1,57	614,7	615,4
2ff	((S)-1-fenil-propil)-amida del ácido 3-[4-(3-morfolin-4-il-propil)-piperazin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	0,74	607,8	609,0
2fg	((S)-1-fenil-propil)-amida del ácido 1-oxo-2-fenil-3-[4-(3-piperidin-1-il-propil)-piperazin-1-ilmetil]-1,2-dihidro-isoquinolin-4-carboxílico	0,76	605,8	607,1
2fh	((S)-1-fenil-propil)-amida del ácido 3-[4-(4,6-dimetoxi-pirimidin-2-ilmetil)-piperazin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	1,05	632,8	633,9
2fi	((S)-1-fenil-propil)-amida del ácido 3-[4-(3-hidroxi-propil)-piperazin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	0,86	538,7	539,4
2fj	((S)-1-fenil-propil)-amida del ácido 3-[4-(2,3-dihidroxi-propil)-piperazin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	0,84	554,7	555,7
2fk	ter-butil éster del ácido (2-oxo-2-{4-[1-oxo-2-fenil-4-(1-fenil-propilcarbamoil)-1,2-dihidro-isoquinolin-3-ilmetil]-piperazin-1-il}-etil)-	1,39	637,8	638,5

	carbámico			
2fl	((S)-1-fenil-propil)-amida del ácido 3-[4-(1H-indazol-5-il)-piperazin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	0,99	596,7	597,7
2fm	((S)-1-fenil-propil)-amida del ácido 1-oxo-2-fenil-3-(4-quinolin-6-il-piperazin-1-ilmetil)-1,2-dihidro-isoquinolin-4-carboxílico	0,95	607,8	608,7
2fn	((S)-1-fenil-propil)-amida del ácido 3-[4-(6,7-dimetoxi-quinazolin-4-il)-piperazin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	1,06	668,8	669,3
2fo	ter-butil éster del ácido 4-{4-[1-oxo-2-fenil-4-(1-fenil-propilcarbamoil)-1,2-dihidro-isoquinolin-3-ilmetil]-piperazin-1-il}-piperidin-1-carboxílico	1,09	663,9	664,8
2fp	((S)-1-fenil-propil)-amida del ácido 3-{4-[2-(4-cloro-fenoxi)-etil]-piperazin-1-ilmetil}-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	1,19	635,2	635,9
2fq	ter-butil éster del ácido {4-[1-oxo-2-fenil-4-(1-fenil-propilcarbamoil)-1,2-dihidro-isoquinolin-3-ilmetil]-piperazin-1-il}-acético	1,08	594,8	595,9
2fr	((S)-1-fenil-propil)-amida del ácido 1-oxo-2-fenil-3-[4-(3,3,3-trifluoro-2-hidroxi-propil)-piperazin-1-ilmetil]-1,2-dihidro-isoquinolin-4-carboxílico	0,96	592,7	593,6
2fs	((S)-1-fenil-propil)-amida del ácido 3-[4-(2-hidroxi-propil)-piperazin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	0,86	538,7	539,5
2fu	((S)-1-fenil-propil)-amida del ácido 3-[4-(4-amino-6,7-dimetoxi-quinazolin-2-il)-piperazin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	1,03	683,8	684,7
2fv	ter-butil éster del ácido (2-{4-[1-oxo-2-fenil-4-(1-fenil-propilcarbamoil)-1,2-dihidro-isoquinolin-3-ilmetil]-piperazin-1-il}-etil)-carbámico	1,06	623,8	624,5

2fw	((S)-1-fenil-propil)-amida del ácido 1-oxo-3-{4-[2-(2-oxo-imidazolidin-1-il)-etil]-piperazin-1-ilmetil}-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	0,85	592,7	593,7
2fx	((S)-1-fenil-propil)-amida del ácido 3-{4-[(4,6-dimetoxi-pirimidin-2-il)-fenil-metil]-piperazin-1-ilmetil}-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	1,21	708,9	709,4
2fy	((S)-1-fenil-propil)-amida del ácido 3-(4-benzo[1,2,5]tiadiazol-4-il-piperazin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	1,48	614,8	615,4
2fz	((S)-1-fenil-propil)-amida del ácido 3-[4-(2,3-dihidro-benzo[1,4]dioxin-5-il)-piperazin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	1,2	614,7	615,3
2ga	((S)-1-fenil-propil)-amida del ácido 3-[4-(4-metil-quinolin-2-il)-piperazin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	1,15	621,8	622,7
2gb	((S)-1-fenil-propil)-amida del ácido 1-oxo-2-fenil-3-[4-(piridin-2-ilcarbamoilmetil)-piperazin-1-ilmetil]-1,2-dihidro-isoquinolin-4-carboxílico	0,93	614,7	615,4
2gc	((S)-1-fenil-propil)-amida del ácido 3-[4-(6-cloro-3-oxo-3,4-dihidro-2H-benzo[1,4]oxazin-8-il)-piperazin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	1,21	662,2	662,8
2gd	((S)-1-fenil-propil)-amida del ácido 3-(4-carbamoilmetil-piperazin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	0,85	537,7	538,5
2ge	((S)-1-fenil-propil)-amida del ácido 3-(4-hidroxi-4-fenil-piperidin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	1,12	571,7	572,6
2gf	((S)-1-fenil-propil)-amida del ácido 3-[4-(4-cloro-fenil)-4-hidroxi-piperidin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	1,23	606,2	606,8

2gg	Ácido 1-[1-oxo-2-fenil-4-(1-fenil-propilcarbamoil)-1,2-dihidro-isoquinolin-3-ilmetil]-piperidin-4-carboxílico	0,9	523,6	524,5
2gh	((S)-1-fenil-propil)-amida del ácido 3-(4-ciano-4-fenil-piperidin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	1,59	580,7	581,9
2gi	((S)-1-fenil-propil)-amida del ácido 3-(4-bencil-4-hidroxi-piperidin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	1,16	585,7	586,0
2gj	etil éster del ácido 1-[1-oxo-2-fenil-4-(1-fenil-propilcarbamoil)-1,2-dihidro-isoquinolin-3-ilmetil]-4-fenil-piperidin-4-carboxílico	1,35	627,8	628,5
2gk	((S)-1-fenil-propil)-amida del ácido 1-oxo-2-fenil-3-[4-(fenil-propionil-amino)-piperidin-1-ilmetil]-1,2-dihidro-isoquinolin-4-carboxílico	1,17	626,8	627,6
2gl	ter-butil éster del ácido metil-{1-[1-oxo-2-fenil-4-(1-fenil-propilcarbamoil)-1,2-dihidro-isoquinolin-3-ilmetil]-piperidin-4-il}-carbámico	1,25	608,8	609,8
2gm	((S)-1-fenil-propil)-amida del ácido 1-oxo-2-fenil-3-[4-(2-pirrolidin-1-il-etil)-piperidin-1-ilmetil]-1,2-dihidro-isoquinolin-4-carboxílico	0,72	576,8	577,5
2gn	((S)-1-fenil-propil)-amida del ácido 3-{4-[5-(4-fluoro-fenil)-[1,3,4]oxadiazol-2-il]-piperidin-1-ilmetil}-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	1,22	641,7	642,3
2go	((S)-1-fenil-propil)-amida del ácido 1-oxo-2-fenil-3-[4-(3-piridin-4-il-[1,2,4]oxadiazol-5-il)-piperidin-1-ilmetil]-1,2-dihidro-isoquinolin-4-carboxílico	0,96	624,7	625,5
2gp	((S)-1-fenil-propil)-amida del ácido 1-oxo-2-fenil-3-[4-(3-pirazin-2-il-[1,2,4]oxadiazol-5-il)-piperidin-1-ilmetil]-1,2-dihidro-isoquinolin-4-carboxílico	1,04	625,7	626,5
2gq	((S)-1-fenil-propil)-amida del ácido 1-oxo-2-fenil-	1,04	624,7	625,5

	3-[4-(3-piridin-4-il-[1,2,4]oxadiazol-5-il)-piperidin-1-ilmetil]-1,2-dihidro-isoquinolin-4-carboxílico			
2gr	((S)-1-fenil-propil)-amida del ácido 3-(4'-hidroxi-3',4',5',6'-tetrahidro-2'H-[2,4']bipiridinil-1'-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	0,83	572,7	573,5
2gs	((S)-1-fenil-propil)-amida del ácido 3-(espiro[isocroman-1,4'-piperidin]-1'-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	1,24	597,8	598,6
2gt	((S)-1-fenil-propil)-amida del ácido 3-[4-hidroxi-4-(3-metoxi-fenil)-piperidin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	1,13	601,7	602,4
2gu	((S)-1-fenil-propil)-amida del ácido 3-[4-(3-cloro-fenil)-4-hidroxi-piperidin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	1,23	606,2	606,8
2gv	((S)-1-fenil-propil)-amida del ácido 3-(6-cloro-3H-espiro[isobenzofuran-1,4'-piperidin]-1'-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	1,36	618,2	618,4
2gw	((S)-1-fenil-propil)-amida del ácido 3-(4-{[4-cloro-3-(4-fluoro-fenil)-indan-1-il]-metil-amino}-piperidin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	1,36	753,4	753,4
2gx	((S)-1-fenil-propil)-amida del ácido 3-(1-acetil-espiro[indolin-3,4'-piperidin]-1'-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	1,15	624,8	625,6
2gy	((S)-1-fenil-propil)-amida del ácido 3-(1-acetil-5-fluoro-espiro[indolin-3,4'-piperidin]-1'-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	1,2	642,8	643,4
2gz	((S)-1-fenil-propil)-amida del ácido 1-oxo-3-(4-oxo-1-fenil-1,3,8-triaza-espiro[4,5]dec-8-ilmetil)-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	1,15	625,8	626,6
2ha	((S)-1-fenil-propil)-amida del ácido 3-(4-acetilamino-piperidin-1-ilmetil)-1-oxo-2-fenil-1,2-	0,83	536,7	537,4

	dihidro-isoquinolin-4-carboxílico			
2hb	((S)-1-fenil-propil)-amida del ácido 1-oxo-3-(1-oxo-2,8-diaza-espiro[4,5]dec-8-ilmetil)-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	0,85	548,7	549,7
2hc	((S)-1-fenil-propil)-amida del ácido 3-[4-hidroxi-4-(3-trifluorometil-fenil)-piperidin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	1,29	639,7	640,3
2hd	((S)-1-fenil-propil)-amida del ácido 1-oxo-2-fenil-3-(4-trifluorometil-piperidin-1-ilmetil)-1,2-dihidro-isoquinolin-4-carboxílico	1,3	547,6	548,4
2he	((S)-1-fenil-propil)-amida del ácido 3-[4-(4-metil-piperazin-1-carbonil)-piperidin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	0,7	605,8	607,0
2hf	((S)-1-fenil-propil)-amida del ácido 3-(5-isopropil-3H-espiro[isobenzofuran-1,4'-piperidin]-1'-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	1,48	625,8	626,6
2hg	((S)-1-fenil-propil)-amida del ácido 3-[4-(acetil-metil-amino)-4-fenil-piperidin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	1,13	626,8	627,7
2hh	ter-butil éster del ácido 4-{1-[1-oxo-2-fenil-4-(1-fenil-propilcarbamoil)-1,2-dihidro-isoquinolin-3-ilmetil]-piperidin-4-il}-piperazin-1-carboxílico	1,03	663,9	664,7
2hi	ter-butil éster del ácido (2-{1-[1-oxo-2-fenil-4-(1-fenil-propilcarbamoil)-1,2-dihidro-isoquinolin-3-ilmetil]-piperidin-4-il}-etil)-carbámico	1,19	622,8	623,5
2hj	((S)-1-fenil-propil)-amida del ácido 3-(4-metilamino-4-fenil-piperidin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	1,01	584,8	585,5
2hk	((S)-1-fenil-propil)-amida del ácido 3-(4-acetilamino-4-fenil-piperidin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	1,06	612,8	613,3

2hl	((S)-1-fenil-propil)-amida del ácido 3-[4-acetilamino-4-(3-fluoro-fenil)-piperidin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	1,06	630,8	631,5
2hm	((S)-1-fenil-propil)-amida del ácido 1-oxo-3-[4-(4-oxo-piperidin-1-carbonil)-piperidin-1-ilmetil]-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	0,89	604,7	605,3
2hn	((S)-1-fenil-propil)-amida del ácido 3-[4,4']bipiperidinil-1-ilmetil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	0,7	562,8	563,2
2ho	ter-butil éster del ácido {1-[1-oxo-2-fenil-4-(1-fenil-propilcarbamoil)-1,2-dihidro-isoquinolin-3-ilmetil]-piperidin-4-il}-carbámico	1,15	594,8	595,8
2hp	[ciclopropil-(3-fluoro-fenil)-metil]-amida del ácido 3-[1,4']bipiperidinil-1'-ilmetil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	0,95	592,8	593,5
2hq	[ciclopropil-(3-fluoro-fenil)-metil]-amida del ácido 1-oxo-3-(4-fenetil-piperazin-1-ilmetil)-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	1,15	614,8	615,5
2hr	[ciclopropil-(3-fluoro-fenil)-metil]-amida del ácido 3-(4-isopropil-piperazin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	0,97	552,7	553,8
2hs	[ciclopropil-(3-fluoro-fenil)-metil]-amida del ácido 3-[4-(2-morfolin-4-il-etil)-piperazin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	0,81	623,8	624,6
2ht	[ciclopropil-(3-fluoro-fenil)-metil]-amida del ácido 3-[4-(1-metil-piperidin-4-il)-piperazin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	0,78	607,8	608,9
2hu	[ciclopropil-(3-fluoro-fenil)-metil]-amida del ácido 1-oxo-2-fenil-3-[4-(2-piperidin-1-il-etil)-piperazin-1-ilmetil]-1,2-dihidro-isoquinolin-4-carboxílico	0,82	621,8	622,6
2hv	[ciclopropil-(3-fluoro-fenil)-metil]-amida del ácido 1-oxo-2-fenil-3-[4-(2-pirrolidin-1-il-etil)-piperazin-	0,8	607,8	608,8

	1-ilmetil]-1,2-dihidro-isoquinolin-4-carboxílico			
2hw	[ciclopropil-(3-fluoro-fenil)-metil]-amida del ácido 1-oxo-2-fenil-3-(4-piridin-4-ilmetil-piperazin-1-ilmetil)-1,2-dihidro-isoquinolin-4-carboxílico	0,84	601,7	602,6
2hx	[ciclopropil-(3-fluoro-fenil)-metil]-amida del ácido 3-(4-hidroxi-3,4,5,6-tetrahidro-2H-[4,4']bipiridinil-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	0,77	602,7	603,7
2hy	[ciclopropil-(3-fluoro-fenil)-metil]-amida del ácido 3-[4-(2-morfolin-4-il-etil)-piperidin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	0,75	622,8	623,7
2hz	[ciclopropil-(3-fluoro-fenil)-metil]-amida del ácido 3-[4-hidroxi-4-(3-metoxi-fenil)-piperidin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	1,17	631,7	632,6
2ia	[ciclopropil-(3-fluoro-fenil)-metil]-amida del ácido 3-[4-(acetil-metil-amino)-4-fenil-piperidin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	1,18	656,8	657,8
2ib	((S)-1-fenil-propil)-amida del ácido 2-(2-fluoro-fenil)-1-oxo-3-(4-fenetil-piperazin-1-ilmetil)-1,2-dihidro-isoquinolin-4-carboxílico	1,12	602,8	603,8
2ic	((S)-1-fenil-propil)-amida del ácido 2-(2-fluoro-fenil)-3-(4-isopropil-piperazin-1-ilmetil)-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico	0,96	540,7	541,7
2id	((S)-1-fenil-propil)-amida del ácido 3-[1,4']bipiperidinil-1'-ilmetil-2-(2-fluoro-fenil)-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico	1	580,7	581,7
2ie	((S)-1-fenil-propil)-amida del ácido 2-(2-fluoro-fenil)-3-[4-(2-morfolin-4-il-etil)-piperazin-1-ilmetil]-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico	0,82	611,8	612,5
2if	((S)-1-fenil-propil)-amida del ácido 2-(2-fluoro-fenil)-3-[4-(1-metil-piperidin-4-il)-piperazin-1-	0,76	595,8	596,8

	ilmetil]-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico			
2ig	((S)-1-fenil-propil)-amida del ácido 2-(2-fluoro-fenil)-1-oxo-3-[4-(2-piperidin-1-il-etil)-piperazin-1-ilmetil]-1,2-dihidro-isoquinolin-4-carboxílico	0,81	609,8	610,5
2ih	((S)-1-fenil-propil)-amida del ácido 2-(2-fluoro-fenil)-1-oxo-3-[4-(2-pirrolidin-1-il-etil)-piperazin-1-ilmetil]-1,2-dihidro-isoquinolin-4-carboxílico	0,8	595,8	596,7
2ii	((S)-1-fenil-propil)-amida del ácido 2-(2-fluoro-fenil)-1-oxo-3-(4-piridin-4-ilmetil-piperazin-1-ilmetil)-1,2-dihidro-isoquinolin-4-carboxílico	0,84	589,7	590,4
2ij	((S)-1-fenil-propil)-amida del ácido 2-(2-fluoro-fenil)-3-(4-hidroxi-3,4,5,6-tetrahidro-2H-[4,4']bipiridinil-1-ilmetil)-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico	0,85	590,7	591,3
2ik	((S)-1-fenil-propil)-amida del ácido 2-(2-fluoro-fenil)-3-[4-(2-morfolin-4-il-etil)-piperidin-1-ilmetil]-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico	0,76	610,8	611,7
2il	((S)-1-fenil-propil)-amida del ácido 2-(2-fluoro-fenil)-3-[4-hidroxi-4-(3-metoxi-fenil)-piperidin-1-ilmetil]-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico	1,21	619,7	620,3
2im	((S)-1-fenil-propil)-amida del ácido 3-[4-(2-morfolin-4-il-etil)-piperazin-1-ilmetil]-1-oxo-2-o-tolil-1,2-dihidro-isoquinolin-4-carboxílico	0,82	607,8	608,8
2in	((S)-1-fenil-propil)-amida del ácido 1-oxo-3-[4-(2-piperidin-1-il-etil)-piperazin-1-ilmetil]-2-o-tolil-1,2-dihidro-isoquinolin-4-carboxílico	0,81	605,8	606,9
2io	((S)-1-fenil-propil)-amida del ácido 1-oxo-3-(4-piridin-4-ilmetil-piperazin-1-ilmetil)-2-o-tolil-1,2-dihidro-isoquinolin-4-carboxílico	0,84	585,7	586,4
2ip	((S)-1-fenil-propil)-amida del ácido 2-(3-fluoro-	1,13	602,8	603,8

	fenil)-1-oxo-3-(4-fenetil-piperazin-1-ilmetil)-1,2-dihidro-isoquinolin-4-carboxílico			
2iq	((S)-1-fenil-propil)-amida del ácido 2-(3-fluoro-fenil)-3-(4-isopropil-piperazin-1-ilmetil)-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico	0,96	540,7	541,3
2ir	((S)-1-fenil-propil)-amida del ácido 3-[1,4']bipiperidinil-1'-ilmetil-2-(3-fluoro-fenil)-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico	0,98	580,7	581,8
2is	((S)-1-fenil-propil)-amida del ácido 2-(3-fluoro-fenil)-3-[4-(2-morfolin-4-il-etil)-piperazin-1-ilmetil]-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico	0,81	611,8	612,6
2it	((S)-1-fenil-propil)-amida del ácido 2-(3-fluoro-fenil)-3-[4-(1-metil-piperidin-4-il)-piperazin-1-ilmetil]-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico	0,75	595,8	596,8
2iu	((S)-1-fenil-propil)-amida del ácido 2-(3-fluoro-fenil)-1-oxo-3-[4-(2-piperidin-1-il-etil)-piperazin-1-ilmetil]-1,2-dihidro-isoquinolin-4-carboxílico	0,8	609,8	610,7
2iv	((S)-1-fenil-propil)-amida del ácido 2-(3-fluoro-fenil)-1-oxo-3-[4-(2-pirrolidin-1-il-etil)-piperazin-1-ilmetil]-1,2-dihidro-isoquinolin-4-carboxílico	0,79	595,8	596,8
2iw	((S)-1-fenil-propil)-amida del ácido 2-(3-fluoro-fenil)-1-oxo-3-(4-piridin-4-ilmetil-piperazin-1-ilmetil)-1,2-dihidro-isoquinolin-4-carboxílico	0,83	589,7	590,2
2ix	((S)-1-fenil-propil)-amida del ácido 2-(3-fluoro-fenil)-3-[4-(2-morfolin-4-il-etil)-piperidin-1-ilmetil]-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico	0,73	610,8	611,6
2iy	((S)-1-fenil-propil)-amida del ácido 2-(3-fluoro-fenil)-3-[4-hidroxi-4-(3-metoxi-fenil)-piperidin-1-ilmetil]-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico	1,18	619,7	620,7
2iz	((S)-1-fenil-propil)-amida del ácido 3-[4-(acetil-	1,2	644,8	645,7

	metil-amino)-4-fenil-piperidin-1-ilmetil]-2-(3-fluoro-fenil)-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico			
2ja	((S)-1-fenil-propil)-amida del ácido 2-(3-cloro-fenil)-1-oxo-3-(4-fenetil-piperazin-1-ilmetil)-1,2-dihidro-isoquinolin-4-carboxílico	1,17	619,2	619,4
2jb	((S)-1-fenil-propil)-amida del ácido 2-(3-cloro-fenil)-3-(4-isopropil-piperazin-1-ilmetil)-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico	1	557,1	557,5
2jc	((S)-1-fenil-propil)-amida del ácido 3-[1,4']bipiperidinil-1'-ilmetil-2-(3-cloro-fenil)-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico	1,04	597,2	597,8
2jd	((S)-1-fenil-propil)-amida del ácido 2-(3-cloro-fenil)-3-[4-(2-morfolin-4-il-etil)-piperazin-1-ilmetil]-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico	0,86	628,2	628,6
2je	((S)-1-fenil-propil)-amida del ácido 2-(3-cloro-fenil)-3-[4-(1-metil-piperidin-4-il)-piperazin-1-ilmetil]-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico	0,79	612,2	612,2
2jf	((S)-1-fenil-propil)-amida del ácido 2-(3-cloro-fenil)-1-oxo-3-[4-(2-piperidin-1-il-etil)-piperazin-1-ilmetil]-1,2-dihidro-isoquinolin-4-carboxílico	0,84	626,2	626,7
2jg	((S)-1-fenil-propil)-amida del ácido 2-(3-cloro-fenil)-1-oxo-3-[4-(2-pirrolidin-1-il-etil)-piperazin-1-ilmetil]-1,2-dihidro-isoquinolin-4-carboxílico	0,83	612,2	612,4
2jh	((S)-1-fenil-propil)-amida del ácido 2-(3-cloro-fenil)-1-oxo-3-(4-piridin-4-ilmetil-piperazin-1-ilmetil)-1,2-dihidro-isoquinolin-4-carboxílico	0,88	606,2	606,1
2ji	((S)-1-fenil-propil)-amida del ácido 2-(3-cloro-fenil)-3-[4-(2-morfolin-4-il-etil)-piperidin-1-ilmetil]-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico	0,78	627,2	627,4
2jj	((S)-1-fenil-propil)-amida del ácido 2-(3-cloro-	1,23	636,2	636,7

	fenil)-3-[4-hidroxi-4-(3-metoxi-fenil)-piperidin-1-ilmetil]-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico			
2jk	((S)-1-fenil-propil)-amida del ácido 3-[4-(acetil-metil-amino)-4-fenil-piperidin-1-ilmetil]-2-(3-cloro-fenil)-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico	1,26	661,2	662,0
2jl	((S)-1-fenil-propil)-amida del ácido 1-oxo-3-(4-fenetil-piperazin-1-ilmetil)-2-m-tolil-1,2-dihidro-isoquinolin-4-carboxílico	1,15	598,8	599,6
2jm	((S)-1-fenil-propil)-amida del ácido 3-[1,4']bipiperidinil-1'-ilmetil-1-oxo-2-m-tolil-1,2-dihidro-isoquinolin-4-carboxílico	0,96	576,8	577,5
2jn	((S)-1-fenil-propil)-amida del ácido 3-[4-(2-morfolin-4-il-etil)-piperazin-1-ilmetil]-1-oxo-2-m-tolil-1,2-dihidro-isoquinolin-4-carboxílico	0,83	607,8	609,0
2jo	((S)-1-fenil-propil)-amida del ácido 3-[4-(1-metil-piperidin-4-il)-piperazin-1-ilmetil]-1-oxo-2-m-tolil-1,2-dihidro-isoquinolin-4-carboxílico	0,78	591,8	592,6
2jp	((S)-1-fenil-propil)-amida del ácido 1-oxo-3-[4-(2-piperidin-1-il-etil)-piperazin-1-ilmetil]-2-m-tolil-1,2-dihidro-isoquinolin-4-carboxílico	0,83	605,8	607,1
2jq	((S)-1-fenil-propil)-amida del ácido 1-oxo-3-[4-(2-pirrolidin-1-il-etil)-piperazin-1-ilmetil]-2-m-tolil-1,2-dihidro-isoquinolin-4-carboxílico	0,81	591,8	592,6
2jr	((S)-1-fenil-propil)-amida del ácido 1-oxo-3-(4-piridin-4-ilmetil-piperazin-1-ilmetil)-2-m-tolil-1,2-dihidro-isoquinolin-4-carboxílico	0,85	585,7	586,0
2js	((S)-1-fenil-propil)-amida del ácido 3-[4-(2-morfolin-4-il-etil)-piperidin-1-ilmetil]-1-oxo-2-m-tolil-1,2-dihidro-isoquinolin-4-carboxílico	0,73	606,8	608,1
2jt	((S)-1-fenil-propil)-amida del ácido 3-[4-hidroxi-4-(3-metoxi-fenil)-piperidin-1-ilmetil]-1-oxo-2-m-	1,18	615,8	616,3

tolil-1,2-dihidro-isoquinolin-4-carboxílico

2ju	((S)-1-fenil-propil)-amida del ácido 3-[4-(acetil-metil-amino)-4-fenil-piperidin-1-ilmetil]-1-oxo-2-m-tolil-1,2-dihidro-isoquinolin-4-carboxílico	1,19	640,8	641,7

Listado de compuestos del ejemplo **2**, continuación

	Nombre químico	**t_R (min)**	**PM**	**m/z (MH+)**
2ka	[(S)-ciclopropil-(3-fluoro-fenil)-metil]-amida del ácido 3-(4-ter-butil-piperazin-1-ilmetil)-8-cloro-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	1,06	601,2	601,5
2kb	((S)-1-fenil-propil)-amida del ácido 8-cloro-3-(4-isopropil-piperazin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	1,01	557,1	557,5
2kc	((S)-1-fenil-propil)-amida del ácido 8-cloro-3-(4-isobutil-piperazin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	1,07	571,2	571,7
2kd	((S)-1-fenil-propil)-amida del ácido 8-cloro-3-(octahidro-pirido[1,2-a]pirazin-2-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	1,03	569,1	569,6
2ke	((S)-1-fenil-propil)-amida del ácido 8-cloro-3-(4-hidroxi-3,4,5,6-tetrahidro-2H-[4,4']bipiridinil-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	0,8	607,2	607,9
2kf	((S)-1-fenil-propil)-amida del ácido 8-cloro-3-(4-ciclopropilmetil-piperazin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	1,04	569,1	569,8
2kg	((S)-1-fenil-propil)-amida del ácido 8-cloro-3-[4-(2-morfolin-4-il-etil)-piperidin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	0,75	627,2	627,4
2kh	((S)-1-fenil-propil)-amida del ácido 8-cloro-3-[1,4]diazepan-1-ilmetil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	0,98	529,1	529,3

2ki	((S)-1-fenil-propil)-amida del ácido 8-cloro-3-((S)-3-metil-piperazin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	0,98	529,1	529,2
2kj	((S)-1-fenil-propil)-amida del ácido 8-cloro-3-imidazol-1-ilmetil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	0,92	497,0	497,4
2kk	((S)-1-fenil-propil)-amida del ácido 8-cloro-3-(4-metil-imidazol-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	0,97	511,0	511,3
2kl	((S)-1-fenil-propil)-amida del ácido 3-(ter-butilamino-metil)-8-cloro-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	1,06	502,1	502,5
2km	((S)-1-fenil-propil)-amida del ácido 8-cloro-3-(isopropilamino-metil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	1	488,0	488,6
2kn	((S)-1-fenil-propil)-amida del ácido 8-cloro-3-[4-hidroxi-4-(3-metoxi-fenil)-piperidin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	1,2	636,2	636,8
2ko	((S)-1-fenil-propil)-amida del ácido 3-(4-ter-butil-piperazin-1-ilmetil)-8-cloro-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	1,03	571,2	571,4
2kp	((S)-1-fenil-propil)-amida del ácido 3-benzoimidazol-1-ilmetil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	1,02	512,6	513,3
2kq	((S)-1-fenil-propil)-amida del ácido 1-oxo-2-fenil-3-pirazol-1-ilmetil-1,2-dihidro-isoquinolin-4-carboxílico	1,54	462,6	463,4
2kr	((S)-1-fenil-propil)-amida del ácido 3-(4-metil-pirazol-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	1,65	476,6	477,3
2ks	((S)-1-fenil-propil)-amida del ácido 1-oxo-2-fenil-3-[1,2,3]triazol-1-ilmetil-1,2-dihidro-isoquinolin-4-carboxílico	1,23	463,5	464,4

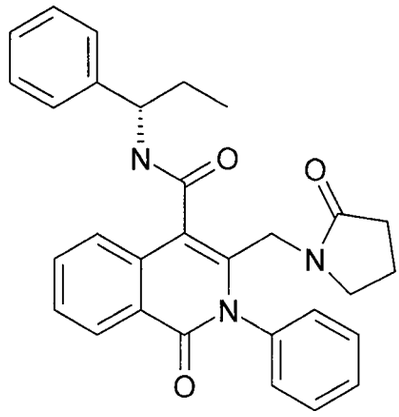
2kt	((S)-1-fenil-propil)-amida del ácido 2-(3-metoxi-fenil)-1-oxo-3-(4-piridin-4-ilmetil-piperazin-1-ilmetil)-1,2-dihidro-isoquinolin-4-carboxílico	0,82	601,7	602,7
2ku	((S)-1-fenil-propil)-amida del ácido 2-(4-metoxi-fenil)-3-[4-(2-morfolin-4-il-etil)-piperazin-1-ilmetil]-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico	0,8	623,8	624,5
2kv	((S)-1-fenil-propil)-amida del ácido 2-(4-fluoro-fenil)-1-oxo-3-(4-fenetil-piperazin-1-ilmetil)-1,2-dihidro-isoquinolin-4-carboxílico	1,13	602,8	603,8
2kw	((S)-1-fenil-propil)-amida del ácido 2-(4-fluoro-fenil)-3-(4-isopropil-piperazin-1-ilmetil)-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico	0,95	540,7	541,7
2kx	((S)-1-fenil-propil)-amida del ácido 3-[1,4']bipiperidinil-1'-ilmetil-2-(4-fluoro-fenil)-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico	0,98	580,7	581,9
2ky	((S)-1-fenil-propil)-amida del ácido 2-(4-fluoro-fenil)-3-[4-(2-morfolin-4-il-etil)-piperazin-1-ilmetil]-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico	0,79	611,8	612,6
2kz	((S)-1-fenil-propil)-amida del ácido 2-(4-fluoro-fenil)-3-[4-(1-metil-piperidin-4-il)-piperazin-1-ilmetil]-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico	0,74	595,8	596,8
2la	((S)-1-fenil-propil)-amida del ácido 2-(4-fluoro-fenil)-1-oxo-3-[4-(2-pirrolidin-1-il-etil)-piperazin-1-ilmetil]-1,2-dihidro-isoquinolin-4-carboxílico	0,78	595,8	596,7
2lb	((S)-1-fenil-propil)-amida del ácido 2-(4-fluoro-fenil)-3-[4-hidroxi-4-(3-metoxi-fenil)-piperidin-1-ilmetil]-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico	1,18	619,7	620,4
2lc	((S)-1-fenil-propil)-amida del ácido 2-(4-cloro-fenil)-1-oxo-3-(4-fenetil-piperazin-1-ilmetil)-1,2-dihidro-isoquinolin-4-carboxílico	1,17	619,2	619,3
2ld	((S)-1-fenil-propil)-amida del ácido 2-(4-cloro-fenil)-3-(4-isopropil-piperazin-1-ilmetil)-1-oxo-1,2-dihidro-	0,99	557,1	557,4

	isoquinolin-4-carboxílico			
2le	((S)-1-fenil-propil)-amida del ácido 3-[1,4']bipiperidinil-1'-ilmetil-2-(4-cloro-fenil)-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico	1,04	597,2	597,8
2lf	((S)-1-fenil-propil)-amida del ácido 2-(4-cloro-fenil)-3-[4-(2-morfolin-4-il-etil)-piperazin-1-ilmetil]-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico	0,85	628,2	628,6
2lg	((S)-1-fenil-propil)-amida del ácido 2-(4-cloro-fenil)-3-[4-(1-metil-piperidin-4-il)-piperazin-1-ilmetil]-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico	0,77	612,2	612,3
2lh	((S)-1-fenil-propil)-amida del ácido 2-(4-cloro-fenil)-1-oxo-3-[4-(2-piperidin-1-il-etil)-piperazin-1-ilmetil]-1,2-dihidro-isoquinolin-4-carboxílico	0,84	626,2	626,8
2li	((S)-1-fenil-propil)-amida del ácido 2-(4-cloro-fenil)-1-oxo-3-[4-(2-pirrolidin-1-il-etil)-piperazin-1-ilmetil]-1,2-dihidro-isoquinolin-4-carboxílico	0,81	612,2	612,6
2lj	((S)-1-fenil-propil)-amida del ácido 3-(4-ter-butil-piperazin-1-ilmetil)-8-fluoro-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	0,96	554,7	555,7
2lk	((S)-1-fenil-propil)-amida del ácido 8-cloro-3-ciclopropilaminometil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	0,61 (método B)	486,0	486,4
2ll	[(S)-ciclopropil-(3-fluoro-fenil)-metil]-amida del ácido 3-(4-ter-butil-piperazin-1-ilmetil)-8-fluoro-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	0,98	584,7	585,5
2lm	[(S)-ciclopropil-(3-fluoro-fenil)-metil]-amida del ácido 8-fluoro-1-oxo-2-fenil-3-piperazin-1-ilmetil-1,2-dihidro-isoquinolin-4-carboxílico (*)	0,89	528,6	529,4
2ln	[(S)-ciclopropil-(3-fluoro-fenil)-metil]-amida del ácido 8-fluoro-1-oxo-3-(3-oxo-pirazolidin-1-ilmetil)-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico	1,14	528,6	528,8
2lo	[(S)-ciclopropil-(3-fluoro-fenil)-metil]-amida del ácido	1,13	542,6	543,5

8-fluoro-1-oxo-3-(3-oxo-piperazin-1-ilmetil)-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

(*): se utilizó 1-(ter-butoxicarbonil)piperazina como amina y el grupo BOC se eliminó en el próximo paso por HCl 2M in éter dietílico y metanol (1:1) a temperatura ambiente

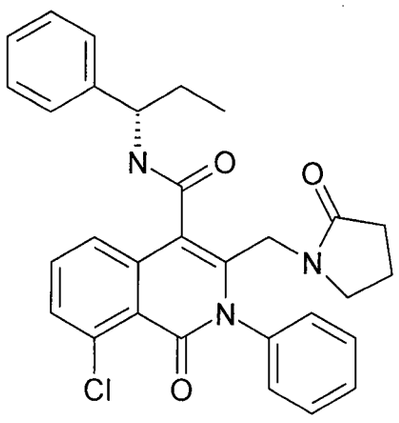
Ejemplo 3



3a *((S)-1-fenil-propil)-amida del ácido 1-oxo-3-(2-oxo-pirrolidin-1-ilmetil)-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico.*

A una solución de 2-pirrolidinona (0,1 ml) en tetrahidrofurano (2 ml) se agregó hidruro de sodio (20 mg, dispersión al 60% en aceite mineral). La mezcla de reacción se agitó a temperatura ambiente hasta que cesó la evolución de gas, luego se agregó ((S)-1-fenil-propil)-amida del ácido 3-bromometil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico (30 mg). Después de 30 min se agregó ácido acético (0,05 ml) y los volátiles se eliminaron al vacío. El producto se purificó por cromatografía flash sobre SiO_2 (5 g, 1,2-dicloroetano luego gradiente 50% a 100% acetato de etilo en heptano) para dar 17 mg de sólido blanco. Rendimiento 56%. LC-MS (m/z) 480,5 (MH^+); t_R = 1,21.

El siguiente compuesto se obtuvo en forma análoga:

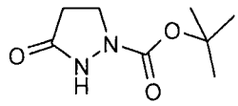


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3b *((S)-1-fenil-propil)-amida del ácido 8-cloro-1-oxo-3-(2-oxo-pirrolidin-1-ilmetil)-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico.*

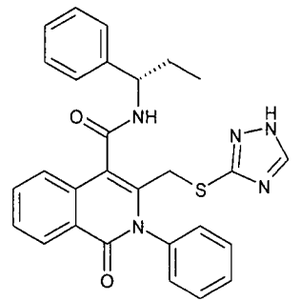
LC-MS (m/z) 514,7 (MH^+); t_R = 1,33.

Síntesis de intermedios:



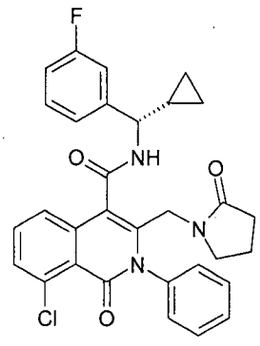
Ter-butil éster del ácido 3-oxo-pirazolidin-1-carboxílico.

A una mezcla de clorhidrato de 3-pirazolidinona (55,3 mg, 0,45 mmol), Na_2CO_3 (133 mg, 1,24 mol), agua (0,5 ml) y dioxano (0,054 ml) se agregó BOC-anhídrido (101 mg, 0,46 mmol) en dioxano (0,16 ml) y se agitó a temperatura ambiente durante la noche. Se filtró, se evaporó y se utilizó en el próximo paso sin purificación posterior. ^1H RMN (500 MHz, DMSO-d_6): 1,4 (s, 9H), 2,32 (t, J=9 Hz, 2H), 3,6 (t, J=9 Hz, 2H).



3c *((S)-1-fenil-propil)-amida del ácido 1-oxo-2-fenil-3-(1H-[1,2,4]triazol-3-ilsulfanilmetil)-1,2-dihidro-isoquinolin-4-carboxílico.*

LC-MS (m/z) 496,6 (MH^+); t_R = 0,64 (método B).

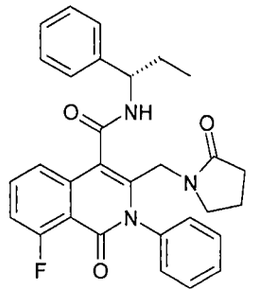


3d *[(S)-ciclopropil-(3-fluoro-fenil)-metil]-amida del ácido 8-cloro-1-oxo-3-(2-oxo-pirrolidin-1-ilmetil)-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico.*

LC-MS (m/z) 544,3 (MH^+); t_R = 1,39. ^1H RMN (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-

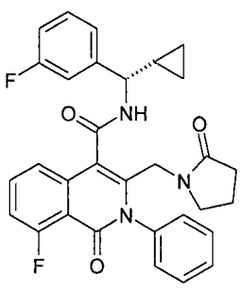
458

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).



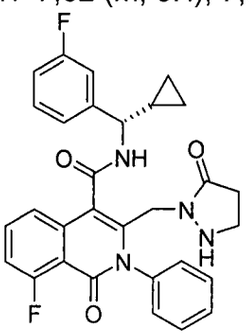
3e *((S)-1-fenil-propil)-amida del ácido 8-fluoro-1-oxo-3-(2-oxo-pirrolidin-1-ilmetil)-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico.*

LC-MS (m/z) 498,8 (MH^+); t_R = 1,23, t_R = 0,68 (método B). ^{1}H RMN (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 (señal de H_2Otraslapado), 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 *[(S)-ciclopropil-(3-fluoro-fenil)-metil]-amida del ácido 8-fluoro-1-oxo-3-(2-oxo-pirrolidin-1-ilmetil)-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico.*

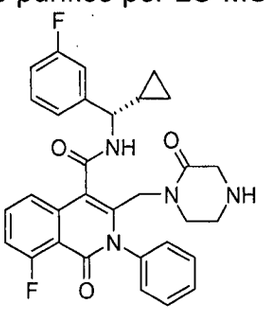
LC-MS (m/z) 528,7 (MH^+); t_R = 1,29, t_R = 0,7 (método B). ^{1}H RMN (250 MHz, 80°C, DMSO-d_6): 0,37-0,62 (m, 4H), 1,25 (m, 1H), 1,71 (quinteto, J=7,5 Hz, 2H), 1,94 (t, J=7,9 Hz, 2H), 2,85 (br, 2H), 2,94 (H_2O), 4,05 (br, 2H), 4,5 (t, J=8,6 Hz, 1H), 7,04 (m, 1H), 7,17-7,32 (m, 5H), 7,32-7,52 (m, 5H), 7,7 (m, 1H), 8,97 (d, J=8,1 Hz, 1H, NH).



3g *[(S)-ciclopropil-(3-fluoro-fenil)-metil]-amida del ácido 8-fluoro-1-oxo-3-(5-oxo-pirazolidin-1-ilmetil)-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico.*

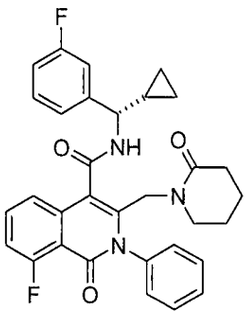
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Se utilizó ter-butil éster del ácido 3-oxo-pirazolidin-1-carboxílico en la reacción de acoplamiento promovida por el NaH. El grupo BOC en el intermedio obtenido ter-butil éster del ácido 2-(4-{[(S)-ciclopropil-(3-fluoro-fenil)-metil]-carbamoil}-8-fluoro-1-oxo-2-fenil-1,2-dihidro-isoquinolin-3-ilmetil)-3-oxo-irazolidin-1-carboxílico se eliminó con HCl 2M en éter etílico – metanol (1:1) a temperatura ambiente, 30 min y el compuesto del título se purificó por LC-MS preparativa. LC-MS (m/z) 529,3 (MH^+); t_R = 1,15.



3h *[(S)-ciclopropil-(3-fluoro-fenil)-metil]-amida del ácido 8-fluoro-1-oxo-3-(2-oxo-piperazin-1-ilmetil)-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico.*

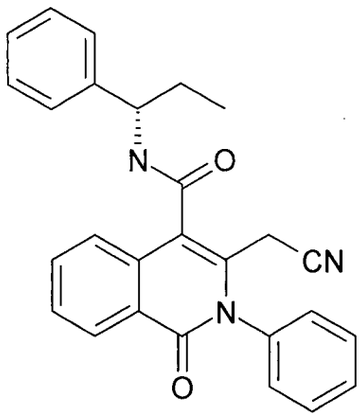
El compuesto del título se preparó en forma análoga a partir de 2-oxo-4-(ter-butoxicarbonil)piperazina seguido de la eliminación del grupo BOC. LC-MS (m/z) 543,6 (MH^+); t_R = 0,84.



3i *[(S)-ciclopropil-(3-fluoro-fenil)-metil]-amida del ácido 8-fluoro-1-oxo-3-(2-oxo-piperidin-1-ilmetil)-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico.*

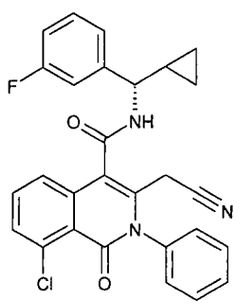
El compuesto del título se preparó en forma análoga a partir de 2-piperidona. LC-MS (m/z) 542,5 (MH^+); t_R = 1,35.

Ejemplo 4



4a *((S)-1-fenil-propil)-amida del ácido 3-cianometil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico.*

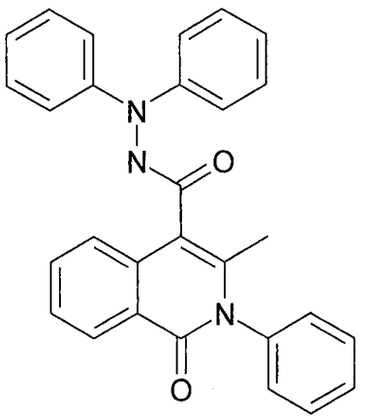
A una solución de ((S)-1-fenil-propil)-amida del ácido 3-bromometil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico (83 mg, 0,174 mmol) en THF (1,5 ml, anhidro) y DMF (1,5 ml, anhidro) se agregó cianuro de sodio (83 mg, exceso). Después de 5 min la suspensión obtenida se vertió en agua (50 ml) seguido del agregado de heptano (20 ml). El producto crudo se separó por filtración y se purificó por cromatografía flash sobre SiO_2 (5g, EA-heptano 1:1) para dar 50 mg de sólido incoloro, rendimiento 68%. LC-MS (m/z) 422,4 (MH^+); t_R = 1,39. ^1H RMN (250 MHz, DMSO-d_6, T = 343 K): 0,94 (t, 3H), 1,78 y 1,85 (dos qui traslapado de ABX_4, 2H, CH_2 de Et), 3,45 y 3,54 (dos d de 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 *[(S)-ciclopropil-(3-fluoro-fenil)-metil]-amida del ácido 8-cloro-3-cianometil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico.*

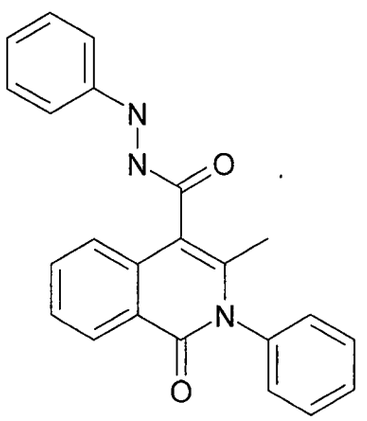
LC-MS (m/z) 486,5 (MH^+); t_R = 1,81.

Ejemplo 5



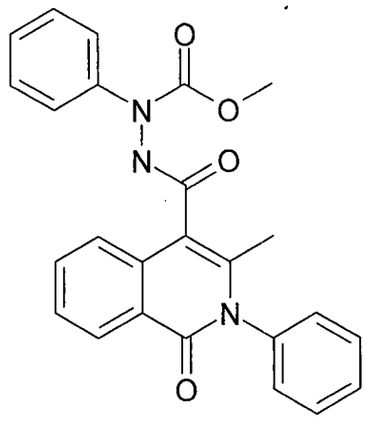
5a *N',N'-difenil-hidrazida del ácido 3-metil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico.*

Una mezcla de cloruro de 3-metil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carbonilo (la síntesis como se describió anteriormente en el ejemplo **1a**) (25 mg, 0,08 mmol) y clorhidrato de 1,1-difenilhidrazina (56 mg, 0,25 mmol) en 1,2-dicloroetano (1 ml) se calentó bajo irradiación de microondas durante 20 min a 140°C. Los volátiles se eliminaron al vacío y el producto se purificó por LC-MS preparativa para dar 14 mg de sólido incoloro. LC-MS (m/z) 446,7 (MH^+); t_R = 1,58.



N'-fenil-hidrazida del ácido 3-metil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico. [740-170]

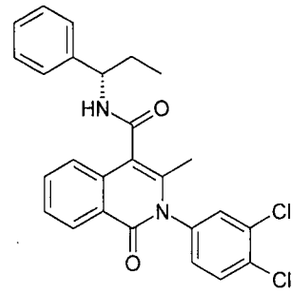
El compuesto del título se preparó en forma análoga. LC-MS (m/z) 370,2 (MH^+); t_R = 1,15. ^{1}H RMN (500 MHz, DMSO-d_6): 2,01 (s, 3H), 6,76 (t, 1H), 6,83 (d, 2H), 7,2 (t, 2H), 7,33 (br, 2H), 7,5-7,62 (m, 5H), 7,83 (t, 1H), 8,11 (br, 1H), 8,24 (d, 1H), 10,33 (s, 1H).



5b *Metil éster del ácido N'-(3-metil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carbonil)-N-fenil-hidrazincarboxílico*

Una mezcla de N'-fenil-hidrazida del ácido 3-metil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico (**5a**, 490 mg, 1,3 mmol) y cloroformiato de metilo (0,6 ml, 8 mmol) en 1,2-dicloroetano (10 ml) se calentó bajo irradiación de microondas durante 10 minutos a 100°C. Los volátiles se eliminaron al vacío y el producto se purificó por cromatografía flash (SiO_2, gradiente heptano –acetato de etilo/heptano 1:1) para dar 190 mg de sólido. LC-MS (m/z) 428,8 (MH^+); t_R = 1,22.

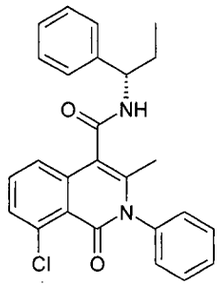
Ejemplo 6



6a *((S)-1-fenil-propil)-amida del ácido 2-(3,4-dicloro-fenil)-3-metil-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico.*

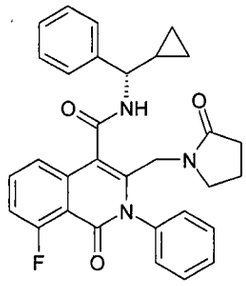
Una mezcla de 4-acetil-3-((S)-1-fenil-propilamino)-isocromen-1-ona (60 mg) y 3,4-dicloroanilina (250 mg) en acetonitrilo (0,5 ml) se calentó bajo irradiación de microondas a 160°C durante 15 min. La mezcla de reacción se dividió por partición entre HCl 2M (3 ml) y acetato de etilo (3 ml). La solución orgánica se absorbió sobre SiO_2 (600 mg) y se sometió a cromatografía flash sobre SiO_2 (20g) con gradiente heptano - acetato de etilo para dar 22 mg del compuesto del título en forma de un sólido blanco. LC-MS (m/z) 465,4 & 467,4 (MH^+); t_R = 1,63.

Los siguientes compuestos se obtuvieron en forma análoga a partir de los correspondientes compuestos de la fórmula general XXIII y las anilinas apropiadas de la fórmula general VI:



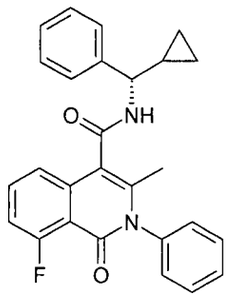
((S)-1-fenil-propil)-amida del ácido 8-cloro-3-metil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico (1i).

El compuesto del título y su método de preparación alternativo se describieron en el ejemplo 1i.



6b *((S)-ciclopropil-fenil-metil)-amida del ácido 8-fluoro-1-oxo-3-(2-oxo-pirrolidin-1-ilmetil)-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico.*

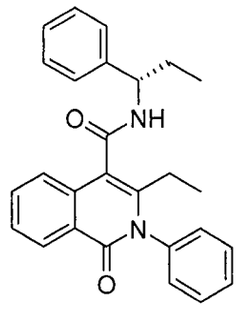
LC-MS (m/z) 510,3 (MH^+); t_R = 1,25.



6c *((S)-ciclopropil-fenil-metil)-amida del ácido 8-fluoro-3-metil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico.*

LC-MS (m/z) 427,3 (MH^+); t_R = 1,39.

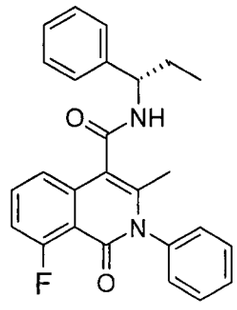
Ejemplo 7



7a *((S)-1-fenil-propil)-amida del ácido 3-etil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico.*

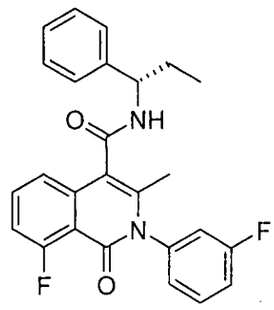
Una mezcla sellada de ácido 2-[2-oxo-1-((S)-1-fenil-propilcarbamoil)-butil]-benzoico (82 mg, 0,2 mmol) y anilina (0,3 ml, 3,3 mmol) en acetonitrilo (0,3 ml) se calentó bajo irradiación de microondas a +160°C durante 10 minutos. La mezcla se dividió por partición entre acetato de etilo (20 ml) y HCl 3M ac. (2 x 8 ml), $NaHCO_3$ ac. sat. (2 x 10 ml) y salmuera, ($MgSO_4$) seco y se evaporó. El residuo se purificó por cromatografía flash (SiO_2, gradiente heptano – acetato de etilo) para dar 32 mg del compuesto del título. LC-MS (m/z) 411,5 (MH^+); t_R = 1,48. ^1H RMN (500 MHz, DMSO-d_6): una mezcla de dos atropisómeros.

Los siguientes compuestos se obtuvieron en forma análoga por condensación de compuestos de la fórmula general XXV con la anilina apropiada de la fórmula general VI:



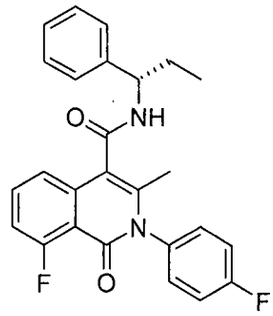
7b *((S)-1-fenil-propil)-amida del ácido 8-fluoro-3-metil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico.*

LC-MS (m/z) 415,5 (MH^+); t_R = 1,39.



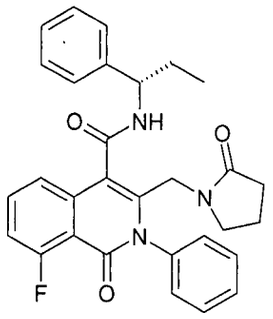
7c *((S)-1-fenil-propil)-amida del ácido 8-fluoro-2-(3-fluoro-fenil)-3-metil-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico.*

LC-MS (m/z) 433,5 (MH^+); t_R = 1,41.



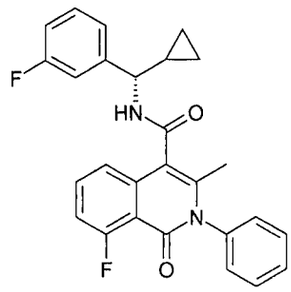
7d *((S)-1-fenil-propil)-amida del ácido 8-fluoro-2-(4-fluoro-fenil)-3-metil-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico.*

LC-MS (m/z) 433,6 (MH^+); t_R = 1,4.



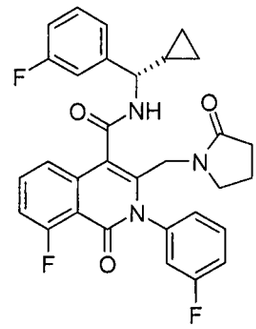
((S)-1-fenil-propil)-amida del ácido 8-fluoro-1-oxo-3-(2-oxo-pirrolidin-1-ilmetil)-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico (3e).

El compuesto del título y su método de preparación alternativo se describieron anteriormente en el ejemplo 3.



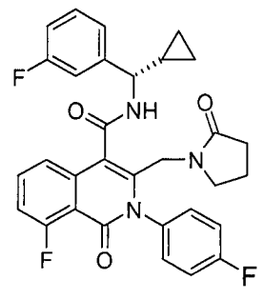
7e *[(S)-ciclopropil-(3-fluoro-fenil)-metil]-amida del ácido 8-fluoro-3-metil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico.*

LC-MS (m/z) 445,6 (MH^+); t_R = 1,44. ^1H RMN (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).



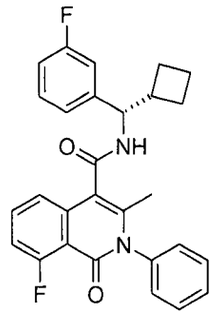
7f *[(S)-ciclopropil-(3-fluoro-fenil)-metil]-amida del ácido 8-fluoro-2-(3-fluoro-fenil)-1-oxo-3-(2-oxo-pirrolidin-1-ilmetil)-1,2-dihidro-isoquinolin-4-carboxílico.*

El producto del título se aisló por TLC preparativa sobre gel de sílice. LC-MS (m/z) 546,4 (MH^+); t_R = 0,71 (método B).



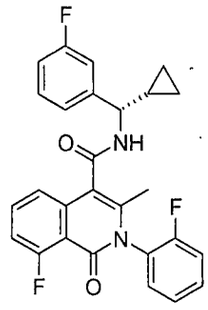
7g *[(S)-ciclopropil-(3-fluoro-fenil)-metil]-amida del ácido 8-fluoro-2-(4-fluoro-fenil)-1-oxo-3-(2-oxo-pirrolidin-1-ilmetil)-1,2-dihidro-isoquinolin-4-carboxílico.*

El producto del título se aisló por TLC preparativa sobre gel de sílice. LC-MS (m/z) 546,3 (MH^+); t_R = 0,71 (método B).



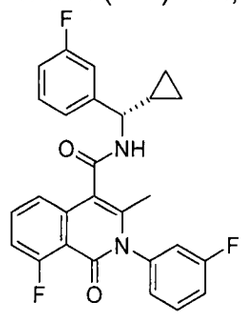
7h *[(S)-ciclobutil-(3-fluoro-fenil)-metil]-amida del ácido 8-fluoro-3-metil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico.*

LC-MS (m/z) 459,4 (MH^+); t_R = 1,54.



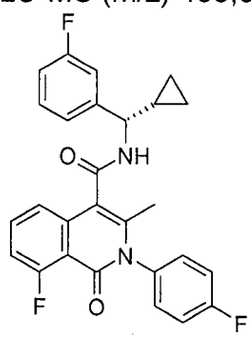
7i *[(S)-ciclopropil-(3-fluoro-fenil)-metil]-amida del ácido 8-fluoro-2-(2-fluoro-fenil)-3-metil-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico.*

LC-MS (m/z) 463,3 (MH^+); t_R = 1,46.



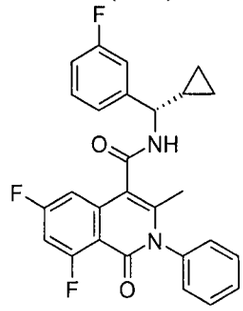
7j *[(S)-ciclopropil-(3-fluoro-fenil)-metil]-amida del ácido 8-fluoro-2-(3-fluoro-fenil)-3-metil-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico.*

LC-MS (m/z) 463,3 (MH^+); t_R = 1,46.



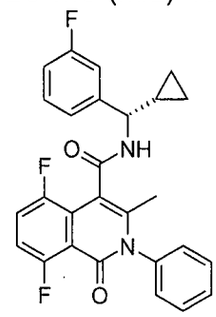
7k *[(S)-ciclopropil-(3-fluoro-fenil)-metil]-amida del ácido 8-fluoro-2-(4-fluoro-fenil)-3-metil-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico.*

LC-MS (m/z) 463,4 (MH^+); t_R = 1,45.



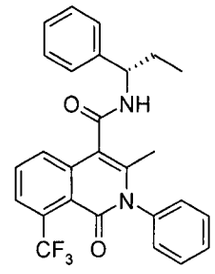
7l *[(S)-ciclopropil-(3-fluoro-fenil)-metil]-amida del ácido 6,8-difluoro-3-metil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico.*

LC-MS (m/z) 463,2 (MH^+); t_R = 0,82 (método B).



7m *[(S)-ciclopropil-(3-fluoro-fenil)-metil]-amida del ácido 5,8-difluoro-3-metil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico.*

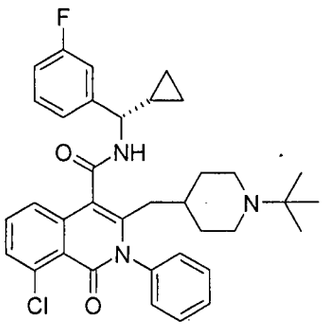
LC-MS (m/z) 463,4 (MH^+); t_R = 1,39.



7n ((S)-1-fenil-propil)-amida del ácido 3-metil-1-oxo-2-fenil-8-trifluorometil-1,2-dihidro-isoquinolin-4-carboxílico.

LC-MS (m/z) 465,3 (MH^+); t_R = 1,57.

Ejemplo 8



8a *[(S)-ciclopropil-(3-fluoro-fenil)-metil]-amida del ácido 3-(1-ter-butil-piperidin-4-ilmetil)-8-cloro-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico.*

A una mezcla fría (baño helado) de 2-(1-ter-butil-piperidin-4-il)-N-fenil-acetamida (250 mg, 0,91 mmol) y 2,6-dimetilpiridina (0,139 ml, 1,2 mmol) en 1,2-dicloroetano (8 ml) se agregó cloruro de oxalilo (0,07 ml, 0,8 mmol) y se agitó a 0°C durante 15 min. Se agregó ácido 2-cloro-6-({[(S)-ciclopropil-(3-fluoro-fenil)-metil]-carbamoil}-metil)-benzoico (70 mg, 0,2 mmol) y la mezcla de reacción se agitó en un recipiente sellado a 90°C durante 15 horas. Se dividió por partición entre NaOH ac. 0,5 M (40 ml) y acetato de etilo (200 ml), la fase orgánica se lavó con agua, se secó y se evaporó. El residuo se purificó por cromatografía flash (SiO_2, acetato de etilo – metanol) para dar 19 mg del compuesto del título. LC-MS (m/z) 600,6 (MH^+); t_R = 1,1. ^1H RMN (500 MHz, temperatura ambiente, DMSO-d_6): señales amplias, una mezcla de dos atropisómeros.

Reactivos utilizados para la preparación de los compuestos.

Nombre	**Proveedor**	**CAS no.**	**Cat. no.**
acetoacetato de etilo	Aldrich	141- 97 -9	E 964-1
acetoacetato de metilo	Aldrich	105-45-3	53,736-5
Hidruro de sodio, dispersión al 60% en aceite mineral	Aldrich	7646-69-7	45,291-2
Bromuro de cobre (I)	Aldrich	7787-70-4	21,286-5
ácido 2-bromobenzoico	Janssen Chimica	88-65-3	41066/1
Ácido 2-bromo-4-metilbenzoico	Matrix Scientific	7697-27-0	001816
Ácido 2-bromo-6-metilbenzoico	Matrix Scientific	90259-31-7	001819
Ácido 2,5-dibromobenzoico	ABCR	610-71 9	AV15077
Ácido 2-bromo-4-fluorobenzoico	fluorochem	1006-41-3	005470

Ácido 2-bromo-5-clorobenzoico	ABCR	21739 93-5	AV10103
Ácido 2-bromo-5-fluorobenzoico	Aldrich	394-28-5	56,349-8
Ácido 2-bromo-3-metilbenzoico	fluorochem	53663-39-1	112800
Ácido 2-bromo-5-metilbenzoico	fluorochem	6967-82-4	B2947-E
Ácido 2-bromo-6-clorobenzoico	fluorochem	93224-85-2	19332
Anilina	Aldrich	62-53-3	13,293-4
2-fluoroanilina	Lancaster	348-54- 9	1236
2,6-difluoroanilina	Aldrich	5509-65 - 9	196614
2-cloroanilina	Aldrich	95-51-2	23300
o-Toluidina	Aldrich	95-53-4	18,542-6
3-fluoroanilina	Flrochem	372-19-0	1438
3-cloroanilina	Fluka	108-42- 9	23330
m-Toluidina	Aldrich	108-44-1	511218
(S)-(-)-1-fenilpropilamina	Lancaster	3789-59-1	X16320G00 25
C-((S)-*C*-ciclopropil-*C*-fenil)-metilamina	El compuesto se preparó de acuerdo con un procedimiento descrito en la patente WO 2005/014575		
C-[(S)-*C*-ciclopropil-*C*-(3-fluoro-fenil)]-metilamina	El compuesto se preparó de acuerdo con un procedimiento descrito en la patente WO 2005/014575		
Tetraetoxisilano	Aldrich	78-10-4	236209
Clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (EDC)	Aldrich	25952-53-8	16,146-2
1-hidroxibenzotriazol (HOBT)	ABCR	2592- 95-2	AV21700
dimetilamina, solución al 33% en etanol abs.	Fluka	124-40-3	38950
metilamina, solución 2M en THF	Aldrich	74-89-5	42,646-6
2-pirrolidona	Aldrich	616-45-5	240338
clorhidrato de 1,1-difenilhidrazina	Aldrich	530-47-2	11,459-6
Fenilhidrazina	Aldrich	100-63-0	P2,625-2

Cloroformiato de metilo	Aldrich	79-22-1	M35304
Cianuro de sodio	Aldrich	143-33- 9	380970

Reactivos utilizados para la preparación de los compuestos, continuación.

Nombre	**Proveedor**	**CAS no.**	**Cat. no.**
Anhídrido homoftálico	ABCR	703-59-3	AV15538
ciclopropancarboxaldehído	Aldrich	1489-69-6	27,221-3
1-bromo-3-fluorobenceno	Aldrich	1073-06-9	B67007
(S)-3-amino-3-fenilpropanonitrilo	Netchem	-	331516
3,4-dicloroanilina	Aldrich	95-76-1	56042
Ácido 2-bromo-6-nitrobenzoico	Ref. 1	38876-67-4	-
Ácido 2-bromo-6-metoxibenzoico	Ref. 2	31786-45-5	-
2-bromoacetato de ter-butilo	Aldrich	5292-43-3	12,426-0
acetato de etil (trifenilofosforiliden)	Aldrich	1099-45-2	C510-6
1-(ter-butoxicarbonil)piperazina	Lancaster	57260-71-6	13363
clorhidrato de 3-pirazolidinona	Acros	1752-88-1	335490050
2-oxo-4-(ter-butoxicarbonil)piperazina	Aldrich	76003-29-7	64,105-7
2-Piperidona	Aldrich	675-20-7	V20- 9

Ref. 1. El compuesto se preparó de acuerdo con un procedimiento descrito: S.C. Glossop *Síntesis* **2007**, *7,* 981.

Ref. 2. El compuesto se preparó de acuerdo con un procedimiento descrito: T. Sugaya, Y. Mimura, N. Kato, M. Ikuta, T. Mimura et al. *Síntesis* **1994**, 73.

Ejemplo 9 – Ensayo de unión al receptor NK3

Preparación de las membranas: las células BHK que expresan en forma estable el receptor NK3 humano se sembraron en placas de recolección en MEM Dulbeccos que contiene GlutaMax (862 mg/l), piruvato de sodio 1mM, 10% de suero bovino fetal, 1% de Pen/Strep, 1 mg/ml de G418 y se desarrollaron a 34 °C en una atmósfera humedecida que contiene 10% de CO_2. Para aumentar la expresión del

receptor, se agregaron al medio 10 µM de trichotatin A 24 horas antes de la recolección de las células a una confluencia de aprox. 90%. Antes de la recolección, las células se lavaron dos veces con PBS sin Mg^{2+} o Ca^{2+} y a continuación se disgregaron en 10 ml de PBS por placa de recolección. La suspensión de células se centrifugó a 1500XG durante tres minutos antes de la resuspensión en 15 mM buffer Tris-HCl pH 7,5 que contiene $MgCl_2$, 2 mM; EDTA, 0,3 mM y EGTA, 1 mM (buffer A). La suspensión de células se homogenizó y a continuación se centrifugó a 40000xG durante 30 minutos. El pellet de membranas se resuspendió en buffer A que contiene 250 mM de sacarosa, se fraccionó en alícuotas y se almacenó a – 80 °C.

Descripción del ensayo de afinidad: El ensayo se llevó a cabo en la forma de un ensayo de unión competitiva basado en SPA en un buffer de ensayo Tris, 50 mM, pH 7,4 que contiene NaCl, 120 mM, $MnCl_2$,3 mM, 40 µg/ml de bacitracin, 2 µg/ml de quimostatina, 1 µg/ml de fosforamidon y 4 µg/ml de leupeptina. Se mezclaron aprox. 0,02 nM de ^{125}I-NKB con los compuestos de ensayo antes de agregar 4 µg de la preparación de membrana del NK3 homogenizada y 0,025 mg de perlas de SPA en un volumen total de 60 µl. A continuación la placa de ensayo se colocó bajo agitación y se incubó durante 90 minutos a temperatura ambiente. La placa se centrifugó 10 minutos a 500xG y se realizó el recuento en un conteo máximo de 5 minutos por celda.

La unión total, la cual contenía menos de 5% del radioligando agregado, se definió utilizando un buffer de ensayo mientras que la unión no específica se definió en presencia de 1 µM de osanetant. La unión no específica constituyó aprox. 5 % de la unión total.

Los puntos de los datos se expresaron en porcentaje de unión específica del ^{125}I-NKB y los valores IC_{50} (concentración que causa 50 por ciento de inhibición de unión específica del ^{125}I-NKB) se determinaron por análisis de regresión no lineal utilizando un ajuste de curva sigmoidal de pendiente variable. La constante de disociación (K_i) se calculó a partir de la ecuación de Cheng Prusoff ($K_i = IC_{50}/(1+(L/K_D))$), en donde la concentración del radioligando libre L se aproximó a la concentración del ^{125}I-NKB agregado en el ensayo (aprox. 0,02 nM). A partir de tres ensayos de saturación independientes, cada uno realizado con determinaciones duplicadas, se determinó que la K_D del ^{125}I-NKB fue 0,7 nM. Bmax fue aprox. 2 pmol/mg.

Los compuestos de la presente invención en general tienen valores de K_i de 500 nM o inferiores. Muchos compuestos, en realidad, tienen valores de K_i por debajo de 100 nM y por debajo, hasta valores de un solo dígito.

La tabla a continuación muestra la K_i para el receptor NK3

Compuesto	K_i nM
Ej 2a	180
Ej 2bm	8,2
Ej 2hs	5,3
Ej 2hz	3
Ej 3a	72
Ej 5a	55

Ver además la tabla en el Ejemplo 10 para más datos de afinidad para los compuestos de la presente invención.

Ejemplo 10 Ensayo para potencia y eficacia del receptor NK3

Células BHK que expresan en forma estable el receptor NK3 humano se sembraron en 100 µl de medio en placas de 96 celdas de base transparente y pared negra (Costar) pretendiendo una confluencia de 95-100% en el día del ensayo. El ensayo se realizó con el equipo para Ensayo de calcio FLIPR Calcium 4 (Molecular Devices). El día del ensayo, se eliminó el medio y las células se lavaron una vez con el buffer HBSS (buffer Hanks BSS, pH 7,4 que contiene Hepes20 mM) antes de agregar a las células 100 µl de una solución de del reactivo para el ensayo de calcio disuelto en el buffer HBSS que contiene 2,5 mM de probinicid. Las placas se incubaron durante 60 min a 34°C, 10% de CO_2 antes del uso en el FLIPR para examen de fluorescencia.

Una placa representativa se examinó con respecto a una curva de respuesta a las dosis con NKB en una configuración en la cual a las celdas se les agregó inicialmente buffer HBSS y 15 minutos más tarde las diversas concentraciones de NKB a fin de determinar la EC_{50} y la EC_{85} de NKB. Todas las placas de compuestos utilizadas para NKB se cubrieron previamente con una solución al 1% de BSA y a continuación se lavaron tres veces con H_2O. Se diluyó NKB en buffer HBSS que contiene 0,1% de BSA.

Para la evaluación de eficacia y potencia de los compuestos, estos se diluyeron en buffer HBSS antes del ensayo. Para el ensayo de actividad agonista, se agregaron 25 µl de la solución de compuesto diluido y la placa se analizó durante 5 minutos en el FLIPR. Para ensayo de la actividad antagonista, la placa se incubó durante otros 45 minutos antes de agregar 25 µl de la concentración EC_{85} de NKB (aprox. 4 nM) como se describió anteriormente. Las placas se analizaron a continuación durante 5 minutos antes de terminarse el ensayo. Se determinó el máximo incremento en fluorescencia por encima del fondo subsiguiente a cada adición de ligando. El valor IC_{50} se calculó utilizando el ajuste de curva sigmoidal de pendiente variable, y el valor de cIC_{50} se determinó utilizando la ecuación ($cIC_{50} = IC_{50}/ (1+(EC_{85}/EC_{50}))$), en donde EC_{85} y EC_{50} para NKB se determinaron como se describió anteriormente.

Todas las isoquinolinonas de la presente invención, caracterizadas en el ensayo de potencia y eficacia del receptor NK3, han sido antagonistas sin que se haya observado alguna actividad agonista significativa a dosis relevantes. La tabla muestra los datos de afinidad (obtenidos como se describió en el Ejemplo 9) y los datos de potencia obtenidos con los compuestos de la invención. Las diferencias menores entre los valores tabulados en el Ejemplo 9 y 10 sólo reflejan que más de un lote ha sido ensayado y/o que un lote ha sido ensayado más de una vez.

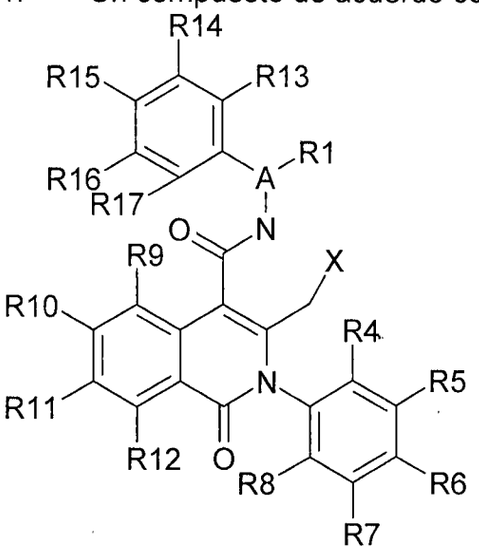
	Afinidad		**Potencia**
Ejemplo No	**K_i/nM**		**cIC_{50}/nM**
2e	330		470
1i	41		130
3a	88		270
2r	320		420
2s	200		340
2u	90		96
2ah	290		360
2bg	160		220
2bm	8,8		14
2bn	160		300

	Afinidad		Potencia
Ejemplo No	K_i/nM		cIC_{50}/nM
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

	Afinidad		Potencia
Ejemplo No	**K_i/nM**		**cIC_{50}/nM**
1bn	23		23
6c	23		24
1bl	470		

REIVINDICACIONES

1. Un compuesto de acuerdo con la fórmula I



[I]

en donde A representa N, CH o CR^1;

en donde cada R^1 independientemente representa hidrógeno, alquilo C_{1-6}, alquenilo C_{2-6}, alquinilo C_{2-6}, -C(O)-alquilo C_{1-6}, -C(O)-alquenilo C_{2-6}, -C(O)-alquinilo C_{2-6}, -C(O)-O-alquilo C_{1-6}, -C(O)-O-alquenilo C_{2-6}, -C(O)-O-alquinilo C_{2-6} o fenilo, en donde dicho fenilo, alquilo C_{1-6}, alquenilo C_{2-6} o alquinilo C_{2-6} está opcionalmente sustituido con uno o más sustituyentes seleccionados entre halógeno, hidroxilo, halo-alquilo C_{1-6}, nitro, alcoxi C_{1-6}, y NR^2R^3;

en donde X representa hidrógeno, alquilo C_{1-6}, alquenilo C_{2-6}, alquinilo C_{2-6}, ciano, $-OR^2$, $-O-C(O)R^2$, $-OC(O)NR^2R^3$, $-C(O)-NR^2R^3$, $-N(R^2)C(O)R^3$, $-N(R^2)-C(O)NR^2R^3$ o NR^2R^3, o X representa una parte monocíclica, bicíclica o tricíclica que tiene 4 a 16 átomos constitutivos del anillo uno de los cuales es nitrógeno, y en donde uno, dos o tres átomos constitutivos del anillo, adicionalmente, pueden ser heteroátomos seleccionados entre N, O y S, y en donde dicha parte monocíclica, bicíclica o tricíclica puede estar opcionalmente sustituida con uno o más sustituyentes W, en donde W se selecciona entre hidrógeno, hidroxi, halógeno, ciano, (=O), $-O-(CH_2)_c-O-$, en donde c es 2 o 3 (espiro), $(CH_2)_d$, en donde d es 5 o 6 (espiro), alquilo C_{1-6}, alquenilo C_{2-6}, alquinilo C_{2-6}, alcoxi C_{1-6}, -C(O)-alquilo C_{1-6}, -C(O)-alquenilo C_{2-6}, -C(O)-alquinilo C_{2-6}, -C(O)-O-alquilo C_{1-6}, -C(O)-O-alquenilo C_{2-6}, -C(O)-O-alquinilo C_{2-6}, -O-C(O)-alquilo C_{1-6}, -O-

C(O)-alquenilo C_{2-6}, -O-C(O)-alquinilo C_{2-6}, -C(O)H, COOH; o en donde W representa una parte de la fórmula $-(CH_2)_a$-Y-$(CH_2)_b$-Z;

en donde a y b independientemente representan un número entero seleccionado entre 0, 1, 2 y 3;

en donde Y representa un enlace, C(O), O, S, -O-C(O), -C(O)-O-, $-NR^2$-, $-NR^2$-C(O)-, -C(O)-NH-, o $S(O)_2$;

en donde Z representa hidrógeno, alquilo C_{1-6}, NR^2R^3, ciano o una parte monocíclica o bicíclica fusionada que comprende 4 a 12 átomos constitutivos del anillo de los cuales opcionalmente uno, dos o tres son heteroátomos seleccionados entre N, O, y S, y en donde dicha parte monocíclica o bicíclica fusionada está opcionalmente sustituida con uno o más sustituyentes seleccionados del grupo integrado por halógeno, ciano, alquilo C_{1-6}, hidroxilo, y alcoxi C_{1-6}, pirazinilo, fenilo, piridilo, y fenilo sustituido con halógeno;

en donde cada uno entre R^4-R^8, R^9-R^{12}, y R^{13}-R^{17} independientemente representan hidrógeno, alquilo C_{1-6}, alquenilo C_{2-6}, alquinilo C_{2-6}, halógeno, NR^2R^3, hidroxi, ciano, nitro, alcoxi C_{1-6}, halo-alquilo C_{1-6} o hidroxi-alquilo C_{1-6};

en donde R^2 y R^3 independientemente representan hidrógeno, alquilo C_{1-6}, alquenilo C_{2-6}, alquinilo C_{2-6}, hidroxi-alquilo C_{1-6}, halo-alquilo C_{1-6} o fenilo;

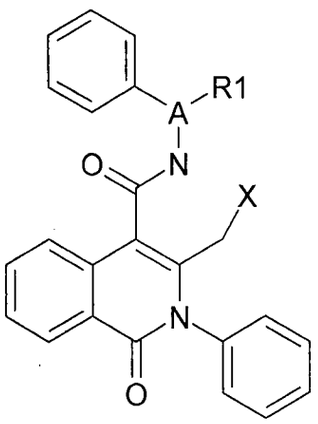
y sus sales aceptables para uso farmacéutico.

2. Un compuesto de acuerdo con la reivindicación 1, en donde R^4-R^8 representan hidrógeno.

3. Un compuesto de acuerdo con la reivindicación 1, en donde R^9-R^{12} representan hidrógeno.

4. Un compuesto de acuerdo con la reivindicación 1, en donde R^{13}-R^{17} representan hidrógeno.

5. Un compuesto de acuerdo con la reivindicación 1 de la fórmula I_a



[Ia]

en donde A representa N, CH o CR^1;

en donde cada R^1 independientemente representa hidrógeno, alquilo C_{1-6}, -C(O)-alquilo C_{1-6}, -C(O)-O-alquilo C_{1-6}, o fenilo, en donde dicho fenilo o alquilo C_{1-6}, está opcionalmente sustituido con uno o más sustituyentes seleccionados entre halógeno, hidroxilo, halo-alquilo C_{1-6}, nitro, alcoxi C_{1-6}, y NR^2R^3;

en donde X representa hidrógeno, alquilo C_{1-6}, ciano, $-OR^2$, $-O-C(O)R^2$, $-OC(O)NR^2R^3$, $-C(O)-NR^2R^3$, $-N(R^2)C(O)R^3$, $-N(R^2)-C(O)NR^2R^3$ o NR^2R^3, o X representa una parte monocíclica, bicíclica o tricíclica que tiene 4 a 16 átomos constitutivos del anillo uno de los cuales es nitrógeno, y en donde uno, dos o tres átomos constitutivos del anillo, adicionalmente, pueden ser heteroátomos seleccionados entre N, O y S; y en donde dicha parte monocíclica, bicíclica o tricíclica puede estar opcionalmente sustituida con uno o más sustituyentes W, en donde W se selecciona entre hidrógeno, hidroxi, halógeno, ciano, (=O), $-O-(CH_2)_c-O-$, en donde c es 2 o 3 (espiro), $(CH_2)_d$, en donde d es 5 o 6 (espiro), alquilo C_{1-6}, alcoxi C_{1-6}, -C(O)-alquilo C_{1-6}, -C(O)-O-alquilo C_{1-6}, -O-C(O)-alquilo C_{1-6}, -C(O)H, COOH; o en donde W representa una parte de la fórmula $-(CH_2)_a-Y-(CH_2)_b-Z$;

en donde a y b independientemente representan un número entero seleccionado entre 0, 1, 2 y 3;

en donde Y representa un enlace, C(O), O, S, -O-C(O), -C(O)-O-, $-NR^2-$, $-NR^2-C(O)-$, -C(O)-NH-, o $S(O)_2$;

en donde Z representa hidrógeno, alquilo C_{1-6}, NR^2R^3, ciano o una parte monocíclica o bicíclica fusionada que comprende 4 a 12 átomos constitutivos del anillo de los cuales opcionalmente uno, dos o tres son heteroátomos seleccionados entre N,

O, y S, y en donde dicha parte monocíclica o bicíclica fusionada está opcionalmente sustituida con uno o más sustituyentes seleccionados del grupo integrado por halógeno, ciano, alquilo C_{1-6}, hidroxilo, y alcoxi C_{1-6}, pirazinilo, fenilo, piridilo, y fenilo sustituido con halógeno;

en donde cada uno entre R^4-R^8, R^9-R^{12}, y R^{13}-R^{17} independientemente representan hidrógeno, alquilo C_{1-6}, alquenilo C_{2-6}, alquinilo C_{2-6}, halógeno, NR^2R^3, hidroxi, ciano, nitro, alcoxi C_{1-6}, halo-alquilo C_{1-6} o hidroxi-alquilo C_{1-6};

en donde R^2 y R^3 independientemente representan hidrógeno, alquilo C_{1-6}, alquenilo C_{2-6}, alquinilo C_{2-6}, hidroxi-alquilo C_{16-}, halo-alquilo C_{1-6} o fenilo;

y sus sales aceptables para uso farmacéutico.

6. Un compuesto de acuerdo con la reivindicación 5, en donde A representa CH.

7. Un compuesto de acuerdo con la reivindicación 6, en donde R^1 representa alquilo C_{1-6}.

8. Un compuesto de acuerdo con la reivindicación 7, en donde R^1 representa etilo o ciclopropilo.

9. Un compuesto de acuerdo con cualquiera de las reivindicaciones 5 a 8, en donde X representa hidrógeno, alquilo C_{1-6}, ciano, $-OR^2$, $-O-C(O)R^2$, $-OC(O)NR^2R^3$, $-C(O)-NR^2R^3-$, $-N(R^2)C(O)R^3$, $-N(R^2)-C(O)NR^2R^3$ o NR^2R^3, en donde R^2 y R^3 independientemente representan hidrógeno, alquilo C_{1-6}, hidroxi-alquilo C_{1-6}, halo-alquilo C_{1-6} o fenilo.

10. Un compuesto de acuerdo con la reivindicación 9, en donde X representa hidrógeno, metilo, o NR^2R^3, en donde R^2 y R^3 independientemente representan hidrógeno, alquilo C_{1-6}, o hidroxi-alquilo C_{1-6}.

11. Un compuesto de acuerdo con la reivindicación 10, en donde R^2 y R^3 independientemente representan hidrógeno, ciclopropilmetilo, metilo, etilo o ciclopropilo.

12. Un compuesto de acuerdo con cualquiera de las reivindicaciones 5 a 8, en donde X representa una parte monocíclica, bicíclica tricíclica que tiene 4 a 16 átomos constitutivos del anillo uno de los cuales es nitrógeno, y en donde uno, dos o tres átomos constitutivos del anillo, adicionalmente, pueden ser heteroátomos seleccionados entre N, O y S, y en donde dicha parte monocíclica, bicíclica o tricíclica puede estar opcionalmente sustituida con uno o más sustituyentes W, en donde W se selecciona entre hidrógeno, hidroxi, halógeno, ciano, (=O), $-O-(CH_2)_c-O-$, en donde c es 2 o 3

(espiro), $(CH_2)_d$, en donde d es 5 o 6 (espiro), alquilo C_{1-6}, alcoxi C_{1-6}, -C(O)-alquilo C_{1-6}, -C(O)-O-alquilo C_{1-6}, -O-C(O)-alquilo C_{1-6}, -O-C(O)-, -C(O)H, COOH; o en donde W representa una parte de la fórmula $-(CH_2)_a$-Y-$(CH_2)_b$-Z;

en donde a y b independientemente representan un número entero seleccionado entre 0, 1, 2 y 3;

en donde Y representa un enlace, C(O), O, S, -O-C(O), -C(O)-O-, $-NR^2$-, $-NR^2$-C(O)-, -C(O)-NH-, o $S(O)_2$;

en donde Z representa hidrógeno, alquilo C_{1-6}, NR^2R^3, ciano o una parte monocíclica o bicíclica fusionada que comprende 4 a 12 átomos constitutivos del anillo de los cuales opcionalmente uno, dos o tres son heteroátomos seleccionados entre N, O, y S, y en donde dicha parte monocíclica o bicíclica fusionada está opcionalmente sustituida con uno o más sustituyentes seleccionados del grupo integrado por halógeno, ciano, alquilo C_{1-6}, hidroxilo, y alcoxi C_{1-6}, pirazinilo, fenilo, piridilo, y fenilo sustituido con halógeno;

en donde R^2 y R^3 independientemente representan hidrógeno, alquilo C_{1-6}, hidroxi-alquilo C_{1-6}, halo-alquilo C_{1-6} o fenilo.

13. Un compuesto de acuerdo con la reivindicación 12, en donde X representa una parte monocíclica que tiene 5 átomos constitutivos del anillo uno de los cuales es nitrógeno, y en donde uno, dos o tres átomos constitutivos del anillo, adicionalmente, pueden ser heteroátomos seleccionados entre N, O y S, y en donde dicha parte monocíclica puede estar opcionalmente sustituida con uno o más sustituyentes W, en donde W se selecciona entre hidrógeno, hidroxi, halógeno, ciano, (=O), -O-$(CH_2)_c$-O-, en donde c es 2 o 3 (espiro), $(CH_2)_d$, en donde d es 5 o 6 (espiro), alquilo C_{1-6}, alcoxi C_{1-6}, -C(O)-alquilo C_{1-6}, -C(O)-O-alquilo C_{1-6}, -O-C(O)-alquilo C_{1-6}, -O-C(O)-, -C(O)H, COOH; o en donde W representa una parte de la fórmula $-(CH_2)_a$-Y-$(CH_2)_b$-Z;

en donde a y b independientemente representan un número entero seleccionado entre 0, 1, 2 y 3;

en donde Y representa un enlace, C(O), O, S, -O-C(O), -C(O)-O-, $-NR^2$-, $-NR^2$-C(O)-, -C(O)-NH-, o $S(O)_2$;

en donde Z representa hidrógeno, alquilo C_{1-6}, NR^2R^3, ciano o una parte monocíclica o bicíclica fusionada que comprende 4 a 12 átomos constitutivos del anillo de los cuales opcionalmente uno, dos o tres son heteroátomos seleccionados entre N,

O, y S, y en donde dicha parte monocíclica o bicíclica fusionada está opcionalmente sustituido con uno o más sustituyentes seleccionados del grupo integrado por halógeno, ciano, alquilo C_{1-6}, hidroxilo, y alcoxi C_{1-6}, pirazinilo, fenilo, piridilo, y fenilo sustituido con halógeno;

en donde R^2 y R^3 independientemente representan hidrógeno, alquilo C_{1-6}, hidroxi-alquilo C_{1-6}, halo-alquilo C_{1-6} o fenilo.

14. Un compuesto de acuerdo con la reivindicación 12, en donde X representa una parte monocíclica que tiene 6 átomos constitutivos del anillo uno de los cuales es nitrógeno, y en donde uno, dos o tres átomos constitutivos del anillo, adicionalmente, pueden ser heteroátomos seleccionados entre N, O y S, y en donde dicha parte monocíclica puede estar opcionalmente sustituida con uno o más sustituyentes W, en donde W se selecciona entre hidrógeno, hidroxi, halógeno, ciano, (=O), $-O-(CH_2)_c-O-$, en donde c es 2 o 3 (espiro), $(CH_2)_d$, en donde d es 5 o 6 (espiro), alquilo C_{1-6}, alcoxi C_{1-6}, -C(O)-alquilo C_{1-6}, -C(O)-O-alquilo C_{1-6}, -O-C(O)-alquilo C_{1-6}, -O-C(O)-, -C(O)H, COOH; o en donde W representa una parte de la fórmula $-(CH_2)_a-Y-(CH_2)_b-Z$;

en donde a y b independientemente representan un número entero seleccionado entre 0, 1, 2 y 3;

en donde Y representa un enlace, C(O), O, S, -O-C(O), -C(O)-O-, $-NR^2-$, $-NR^2-$C(O)-, -C(O)-NH-, o $S(O)_2$;

en donde Z representa hidrógeno, alquilo C_{1-6}, NR^2R^3, ciano o una parte monocíclica o bicíclica fusionada que comprende 4 a 12 átomos constitutivos del anillo de los cuales opcionalmente uno, dos o tres son heteroátomos seleccionados entre N, O, y S, y en donde dicha parte monocíclica o bicíclica fusionada está opcionalmente sustituida con uno o más sustituyentes seleccionados del grupo integrado por halógeno, ciano, alquilo C_{1-6}, hidroxilo, y alcoxi C_{1-6}, pirazinilo, fenilo, piridilo, y fenilo sustituido con halógeno;

en donde R^2 y R^3 independientemente representan hidrógeno, alquilo C_{1-6}, hidroxi-alquilo C_{1-6}, halo-alquilo C_{1-6} o fenilo.

15. Un compuesto de acuerdo con la reivindicación 12, en donde X representa una parte monocíclica que tiene 7 átomos constitutivos del anillo uno de los cuales es nitrógeno, y en donde uno, dos o tres átomos constitutivos del anillo, adicionalmente, pueden ser heteroátomos seleccionados entre N, O y S, y en donde dicha parte

monocíclica puede estar opcionalmente sustituida con uno o más sustituyentes W, en donde W se selecciona entre hidrógeno, hidroxi, halógeno, ciano, (=O), -O-$(CH_2)_c$-O-, en donde c es 2 o 3 (espiro), $(CH_2)_d$, en donde d es 5 o 6 (espiro), alquilo C_{1-6}, alquenilo C_{2-6}, alquinilo C_{2-6}, alcoxi C_{1-6}, -C(O)-alquilo C_{1-6}, -C(O)-O-alquilo C_{1-6}, -O-C(O)-alquilo C_{1-6}, -C(O)H, COOH; o en donde W representa una parte de la fórmula $-(CH_2)_a$-Y-$(CH_2)_b$-Z;

en donde a y b independientemente representan un número entero seleccionado entre 0, 1, 2 y 3;

en donde Y representa un enlace, C(O), O, S, -O-C(O), -C(O)-O-, $-NR^2$-, $-NR^2$-C(O)-, -C(O)-NH-, o $S(O)_2$;

en donde Z representa hidrógeno, alquilo C_{1-6}, NR^2R^3, ciano o una parte monocíclica o bicíclica fusionada que comprende 4 a 12 átomos constitutivos del anillo de los cuales opcionalmente uno, dos o tres son heteroátomos seleccionados entre N, O, y S, y en donde dicha parte monocíclica o bicíclica fusionada está opcionalmente sustituida con uno o más sustituyentes seleccionados del grupo integrado por halógeno, ciano, alquilo C_{1-6}, hidroxilo, y alcoxi C_{1-6}, pirazinilo, fenilo, piridilo, y fenilo sustituido con halógeno;

en donde R^2 y R^3 independientemente representan hidrógeno, alquilo C_{1-6}, hidroxi-alquilo C_{1-6}, halo-alquilo C_{1-6} o fenilo.

16. Un compuesto de acuerdo con la reivindicación 12, en donde X representa una parte monocíclica o bicíclica que tiene 8 átomos constitutivos del anillo uno de los cuales es nitrógeno, y en donde uno, dos o tres átomos constitutivos del anillo, adicionalmente, pueden ser heteroátomos seleccionados entre N, O y S, y en donde dicha parte cíclica o bicíclica puede estar opcionalmente sustituida con uno o más sustituyentes W, en donde W se selecciona entre hidrógeno, hidroxi, halógeno, ciano, (=O), -O-$(CH_2)_c$-O-, en donde c es 2 o 3 (espiro), $(CH_2)_d$, en donde d es 5 o 6 (espiro), alquilo C_{1-6}, alcoxi C_{1-6}, -C(O)-alquilo C_{1-6}, -C(O)-O-alquilo C_{1-6}, -O-C(O)-alquilo C_{1-6}, -C(O)H, COOH; o en donde W representa una parte de la fórmula $-(CH_2)_a$-Y-$(CH_2)_b$-Z;

en donde a y b independientemente representan un número entero seleccionado entre 0, 1, 2 y 3;

en donde Y representa un enlace, C(O), O, S, -O-C(O), -C(O)-O-, $-NR^2$-, $-NR^2$-C(O)-, -C(O)-NH-, o $S(O)_2$;

en donde Z representa hidrógeno, alquilo C_{1-6}, NR^2R^3, ciano o una parte monocíclica o bicíclica fusionada que comprende 4 a 12 átomos constitutivos del anillo de los cuales opcionalmente uno, dos o tres son heteroátomos seleccionados entre N, O; y S, y en donde dicha parte monocíclica o bicíclica fusionada está opcionalmente sustituida con uno o más sustituyentes seleccionados del grupo integrado por halógeno, ciano, alquilo C_{1-6}, hidroxilo, y alcoxi C_{1-6}, pirazinilo, fenilo, piridilo, y fenilo sustituido con halógeno;

en donde R^2 y R^3 independientemente representan hidrógeno, alquilo C_{1-6}, hidroxi-alquilo C_{1-6}, halo-alquilo C_{1-6} o fenilo.

17. Un compuesto de acuerdo con la reivindicación 12, en donde X representa una parte monocíclica o bicíclica que tiene 9 átomos constitutivos del anillo uno de los cuales es nitrógeno, y en donde uno, dos o tres átomos constitutivos del anillo, adicionalmente, pueden ser heteroátomos seleccionados entre N, O y S, y en donde dicha parte monocíclica o bicíclica puede estar opcionalmente sustituida con uno o más sustituyentes W, en donde W se selecciona entre hidrógeno, hidroxi, halógeno, ciano, (=O), $-O-(CH_2)_c-O-$, en donde c es 2 o 3 (espiro), $(CH_2)_d$, en donde d es 5 o 6 (espiro), alquilo C_{1-6}, alcoxi C_{1-6}, -C(O)-alquilo C_{1-6}, -C(O)-O-alquilo C_{1-6}, -O-C(O)-alquilo C_{1-6}, -C(O)H, COOH; o en donde W representa una parte de la fórmula $-(CH_2)_a-Y-(CH_2)_b-Z$;

en donde a y b independientemente representan un número entero seleccionado entre 0, 1, 2 y 3;

en donde Y representa un enlace, C(O), O, S, -O-C(O), -C(O)-O-, $-NR^2-$, $-NR^2-$C(O)-, -C(O)-NH-, o $S(O)_2$;

en donde Z representa hidrógeno, alquilo C_{1-6}, NR^2R^3, ciano o una parte monocíclica o bicíclica fusionada que comprende 4 a 12 átomos constitutivos del anillo de los cuales opcionalmente uno, dos o tres son heteroátomos seleccionados entre N, O, y S, y en donde dicha parte monocíclica o bicíclica fusionada está opcionalmente sustituida con uno o más sustituyentes seleccionados del grupo integrado por halógeno, ciano, alquilo C_{1-6}, hidroxilo, y alcoxi C_{1-6}, pirazinilo, fenilo, piridilo, y fenilo sustituido con halógeno;

en donde R^2 y R^3 independientemente representan hidrógeno, alquilo C_{1-6}, alquenilo C_{2-6}, alquinilo C_{2-6}, hidroxi-alquilo C_{1-6}, halo-alquilo C_{1-6} o fenilo.

18. Un compuesto de acuerdo con la reivindicación 12, en donde X representa una parte monocíclica o bicíclica que tiene 10 átomos constitutivos del anillo uno de los cuales es nitrógeno, y en donde uno, dos o tres átomos constitutivos del anillo, adicionalmente, pueden ser heteroátomos seleccionados entre N, O y S, y en donde dicha parte monocíclica o bicíclica puede estar opcionalmente sustituida con uno o más sustituyentes W, en donde W se selecciona entre hidrógeno, hidroxi, halógeno, ciano, (=O), -O-$(CH_2)_c$-O-, en donde c es 2 o 3 (espiro), $(CH_2)_d$, en donde d es 5 o 6 (espiro), alquilo C_{1-6}, alcoxi C_{1-6}, -C(O)-alquilo C_{1-6}, -C(O)-O-alquilo C_{1-6}, -O-C(O)-alquilo C_{1-6}, -C(O)H, COOH; o en donde W representa una parte de la fórmula $-(CH_2)_a$-Y-$(CH_2)_b$-Z;

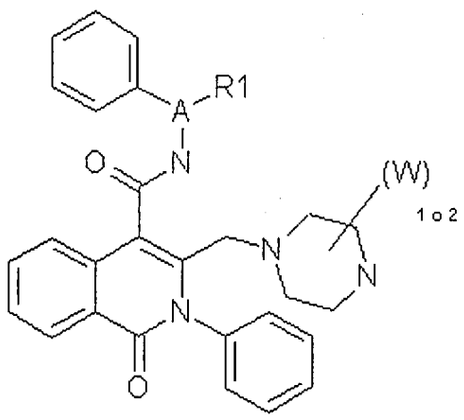
en donde a y b independientemente representan un número entero seleccionado entre 0, 1, 2 y 3;

en donde Y representa un enlace, C(O), O, S, -O-C(O), -C(O)-O-, -NR^2-, -NR^2-C(O)-, -C(O)-NH-, o $S(O)_2$;

en donde Z representa hidrógeno, alquilo C_{1-6}, NR^2R^3, ciano o una parte monocíclica o bicíclica fusionada que comprende 4 a 12 átomos constitutivos del anillo de los cuales opcionalmente uno, dos o tres son heteroátomos seleccionados entre N, O, y S, y en donde dicha parte monocíclica o bicíclica fusionada está opcionalmente sustituida con uno o más sustituyentes seleccionados del grupo integrado por halógeno, ciano, alquilo C_{1-6}, hidroxilo, y alcoxi C_{1-6}, pirazinilo, fenilo, piridilo, y fenilo sustituido con halógeno;

en donde R^2 y R^3 independientemente representan hidrógeno, alquilo C_{1-6}, hidroxi-alquilo C_{1-6}, halo-alquilo C_{1-6} o fenilo.

19. Un compuesto de acuerdo con la reivindicación 1 de la fórmula I_b



[Ib]

en donde A representa N, CH o CR^1;

en donde cada R^1 independientemente representa hidrógeno, alquilo C_{1-6}, -C(O)-alquilo C_{1-6}, C(O)-O-alquilo C_{1-6}, o fenilo, en donde dicho fenilo, o alquilo C_{1-6} está opcionalmente sustituido con uno o más sustituyentes seleccionados entre halógeno, hidroxilo, halo-alquilo C_{1-6}, nitro, alcoxi C_{1-6}, y NR^2R^3;

en donde W se selecciona entre hidrógeno, hidroxi, halógeno, ciano, (=O), -O-$(CH_2)_c$-O-, en donde c es 2 o 3 (espiro), $(CH_2)_d$, en donde d es 5 o 6 (espiro), alquilo C_{1-6}, alcoxi C_{1-6}, -C(O)-alquilo C_{1-6}, -C(O)-O-alquilo C_{1-6}, -O-C(O)-alquilo C_{1-6}, -C(O)H, COOH; o en donde W representa una parte de la fórmula $-(CH_2)_a$-Y-$(CH_2)_b$-Z;

en donde a y b independientemente representan un número entero seleccionado entre 0, 1, 2 y 3;

en donde Y representa un enlace, C(O), O, S, -O-C(O), -C(O)-O-, $-NR^2$-, $-NR^2$-C(O)-, -C(O)-NH-, o $S(O)_2$;

en donde Z representa hidrógeno, alquilo C_{1-6}, NR^2R^3, ciano o una parte monocíclica o bicíclica fusionada que comprende 4 a 12 átomos constitutivos del anillo de los cuales opcionalmente uno, dos o tres son heteroátomos seleccionados entre N, O, y S, y en donde dicha parte monocíclica o bicíclica fusionada está opcionalmente sustituida con uno o más sustituyentes seleccionados del grupo integrado por halógeno, ciano, alquilo C_{1-6}, hidroxilo, y alcoxi C_{1-6}, pirazinilo, fenilo, piridilo, y fenilo sustituido con halógeno;

en donde R^2 y R^3 independientemente representan hidrógeno, alquilo C_{1-6}, hidroxi-alquilo C_{1-6}, halo-alquilo C_{1-6} o fenilo;

y sus sales aceptables para uso farmacéutico.

20. Un compuesto de acuerdo con la reivindicación 19, en donde A representa CH, y R^1 representa alquilo C_{1-6}.

21. Un compuesto de acuerdo con la reivindicación 20, en donde R^1 representa etilo o ciclopropilo.

22. Un compuesto de acuerdo con cualquiera de las reivindicaciones 19 a 21, en donde W representa una parte de la fórmula $-(CH_2)_a$-Y-$(CH_2)_b$-Z;

en donde a y b independientemente representan un número entero seleccionado entre 0, 1, 2 y 3;

en donde Y representa un enlace, C(O), O, S, -O-C(O), -C(O)-O-, -NR^2-, -NR^2-C(O)-, -C(O)-NH-, o $S(O)_2$;

en donde Z representa hidrógeno, alquilo C_{1-6}, NR^2R^3, ciano o una parte monocíclica o bicíclica fusionada que comprende 4 a 12 átomos constitutivos del anillo de los cuales opcionalmente uno, dos o tres son heteroátomos seleccionados entre N, O, y S, y en donde dicha parte monocíclica o bicíclica fusionada está opcionalmente sustituida con uno o más sustituyentes seleccionados del grupo integrado por halógeno, ciano, alquilo C_{1-6}, hidroxilo, y alcoxi C_{1-6}, pirazinilo, fenilo, piridilo, y fenilo sustituido con halógeno;

en donde R^2 y R^3 independientemente representan hidrógeno, alquilo C_{1-6}, hidroxi-alquilo C_{1-6}, halo-alquilo C_{1-6} o fenilo.

23. Un compuesto de acuerdo con la reivindicación 22, en donde Y representa un enlace, C(O) o $S(O)_2$; en donde a+b es 0, 1, 2, 3, o 4; y en donde Z representa una parte monocíclica o bicíclica fusionada que comprende 4 a 12 átomos constitutivos del anillo de carbono y opcionalmente uno, dos o tres heteroátomos seleccionados entre N, O, y S, y en donde dicha parte cíclica o bicíclica está opcionalmente sustituida con uno o más sustituyentes seleccionados del grupo integrado por halógeno, ciano, alquilo C_{1-6}, hidroxilo, y alcoxi C_{1-6}, fenilo, pirazinilo, piridilo, y fenilo sustituido con halógeno.

24. Un compuesto de acuerdo con la reivindicación 23, en donde Y representa un enlace o C(O), y a+b es 0, 1, 2, o 3.

25. Un compuesto de acuerdo con cualquiera de las reivindicaciones 22 a 24, en donde Z representa morfolinilo opcionalmente sustituido con uno o más sustituyentes seleccionados del grupo integrado por halógeno, ciano, alquilo C_{1-6}, hidroxilo, y alcoxi C_{1-6}, fenilo, pirazinilo, piridilo, y fenilo sustituido con halógeno.

26. Un compuesto de acuerdo con la reivindicación 25, en donde dicho morfolinilo está unido al resto de la parte W por el nitrógeno

27. Un compuesto de acuerdo con cualquiera de las reivindicaciones 22 a 24, en donde Z representa piperidilo opcionalmente sustituido con uno o más sustituyentes seleccionados del grupo integrado por halógeno, ciano, alquilo C_{1-6}, hidroxilo, y alcoxi C_{1-6}, fenilo, pirazinilo, piridilo, y fenilo sustituido con halógeno.

28. Un compuesto de acuerdo con la reivindicación 27, en donde dicho piperidilo está unido al resto de la parte W por el nitrógeno.

29. Un compuesto de acuerdo con cualquiera de las reivindicaciones 22 a 24, en donde Z representa piridilo, opcionalmente sustituido con uno o más sustituyentes seleccionados del grupo integrado por halógeno, ciano, alquilo C_{1-6}, hidroxilo, y alcoxi C_{1-6}, pirazinilo, fenilo, piridilo, y fenilo sustituido con halógeno.

30. Un compuesto de acuerdo con la reivindicación 29, en donde dicho piridilo está unido al resto de la parte W en la posición 2, 3, o 4 del piridilo.

31. Un compuesto de acuerdo con cualquiera de las reivindicaciones 22 a 24, en donde Z representa fenilo, opcionalmente sustituido con uno o más sustituyentes seleccionados del grupo integrado por halógeno, ciano, alquilo C_{1-6}, hidroxilo, y alcoxi C_{1-6}, fenilo, pirazinilo, piridilo, y fenilo sustituido con halógeno.

32. Un compuesto de acuerdo con cualquiera de las reivindicaciones 22 a 24, en donde Z representa pirrolidinilo, opcionalmente sustituido con uno o más sustituyentes seleccionados del grupo integrado por halógeno, ciano, alquilo C_{1-6}, hidroxilo, y alcoxi C_{1-6}, pirazinilo, fenilo, piridilo, y fenilo sustituido con halógeno.

33. Un compuesto de acuerdo con cualquiera de las reivindicaciones 22 a 24, en donde Z representa indolilo, opcionalmente sustituido con uno o más sustituyentes seleccionados del grupo integrado por halógeno, ciano, alquilo C_{1-6}, hidroxilo, y alcoxi C_{1-6}, fenilo, pirazinilo, piridilo, y fenilo sustituido con halógeno.

34. Un compuesto de acuerdo con la reivindicación 33, en donde dicho indolinilo está unido al resto de la parte W en la posición 4, 5, 6 o 7 del grupo indolilo.

35. Un compuesto de acuerdo con cualquiera de las reivindicaciones 22 a 24, en donde Z representa ciclopentilo.

36. Un compuesto de acuerdo con cualquiera de las reivindicaciones 22 a 24, en donde Z representa furopiridilo.

37. Un compuesto de acuerdo con cualquiera de las reivindicaciones 22 a 24, en donde Z representa tetrahidrofuranilo.

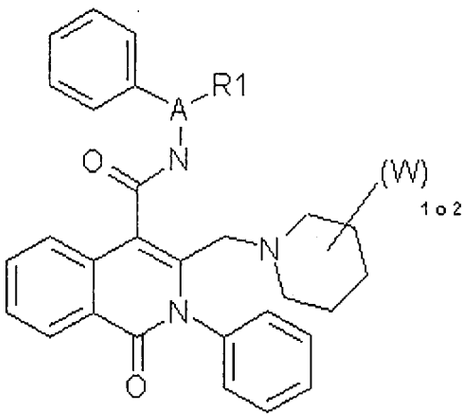
38. Un compuesto de acuerdo con la reivindicación 22, en donde Y representa un enlace, C(O), -C(O)-O-, C(O)-NH-, -O-, o $S(O)_2$; a+b es 0, 1, 2, 3 o 4; y en donde Z representa hidrógeno, alquilo C_{1-6}, NR^2R^3 o ciano.

39. Un compuesto de acuerdo con la reivindicación 38, en donde Y representa un enlace, C(O), -C(O)-O-, C(O)-NH-, -O-, o $S(O)_2$, a+b es 0, 1, 2 o 3, y en donde Z representa hidrógeno, metilo, etilo, $-N(CH_3)_2$, ciano, iso-propilo, iso-butilo, o ter-butilo.

40. Un compuesto de acuerdo con cualquiera de las reivindicaciones 19 a 21, en donde W se selecciona entre hidrógeno, hidroxi, halógeno, ciano, (=O), -O-$(CH_2)_c$-O-, en donde c es 2 o 3 (espiro), $(CH_2)_d$, en donde d es 5 o 6 (espiro), alquilo C_{1-6}, alcoxi C_{1-6}, -C(O)-alquilo C_{1-6}, -C(O)-O-alquilo C_{1-6}, -O-C(O)-alquilo C_{1-6}, -C(O)H, COOH.

41. Un compuesto de acuerdo con la reivindicación 40, en donde W se selecciona de -$(CH_2)_d$-, en donde d es 5 o 6 (espiro) y alquilo C_{1-6}.

42. Un compuesto de acuerdo con la reivindicación 1 de fórmula Ic



[Ic]

en donde A representa N, CH o CR^1;

en donde cada R^1 independientemente representa hidrógeno, alquilo C_{1-6}, -C(O)-alquilo C_{1-6}, C(O)-O-alquilo C_{1-6}, o fenilo, en donde dicho fenilo, o alquilo C_{1-6} está opcionalmente sustituido con uno o más sustituyentes seleccionados entre halógeno, hidroxilo, halo-alquilo C_{1-6}, nitro, alcoxi C_{1-6}, y NR^2R^3;

en donde W se selecciona entre hidrógeno, hidroxi, halógeno, ciano, (=O), -O-$(CH_2)_c$-O-, en donde c es 2 o 3 (espiro), $(CH_2)_d$, en donde d es 5 o 6 (espiro), alquilo C_{1-6}, alcoxi C_{1-6}, -C(O)-alquilo C_{1-6}, -C(O)-O-alquilo C_{1-6}, -O-C(O)-alquilo C_{1-6}, -C(O)H, COOH; o en donde W representa una parte de la fórmula –$(CH_2)_a$-Y-$(CH_2)_b$-Z;

en donde a y b independientemente representan un número entero seleccionado entre 0, 1, 2 y 3;

en donde Y representa un enlace, C(O), O, S, -O-C(O), -C(O)-O-, -NR^2-, -NR^2-C(O)-, -C(O)-NH-, o $S(O)_2$;

en donde Z representa hidrógeno, alquilo C_{1-6}, NR^2R^3, ciano o una parte monocíclica o bicíclica fusionada que comprende 4 a 12 átomos constitutivos del anillo

de los cuales opcionalmente uno, dos o tres son heteroátomos seleccionados entre N, O, y S, y en donde dicha parte monocíclica o bicíclica fusionada está opcionalmente sustituida con uno o más sustituyentes seleccionados del grupo integrado por halógeno, ciano, alquilo C_{1-6}, hidroxilo, y alcoxi C_{1-6}, pirazinilo, fenilo, piridilo, y fenilo sustituido con halógeno;

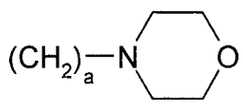
en donde R^2 y R^3 independientemente representan hidrógeno, alquilo C_{1-6}, hidroxi-alquilo C_{1-6}, halo-alquilo C_{1-6} o fenilo;

y sus sales aceptables para uso farmacéutico.

43. Un compuesto de acuerdo con la reivindicación 42, en donde A representa CH, y R^1 representa alquilo C_{1-6}.

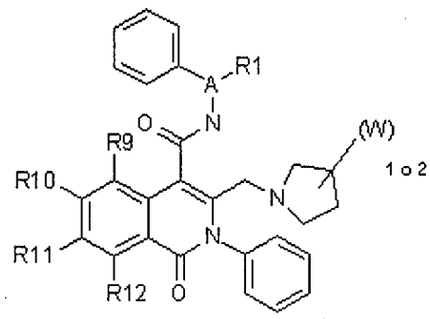
44. Un compuesto de acuerdo con la reivindicación 43, en donde R^1 representa etilo o ciclopropilo.

45. Un compuesto de acuerdo con cualquiera de las reivindicaciones 42 a 44, en donde W independientemente representa hidrógeno, hidroxilo, fenilo, fenilo sustituido con alcoxi C_{1-6}, piperidilo, piridilo, -O-$(CH_2)_c$-O-, en donde c es 2 o 3 (espiro), $N(CH_3)_2$, alquilo C_{1-6}, –$(CH_2)_a$-C(O)-O-$(CH_2)_b$-H, en donde a+b es 1, 2, o 3, o



, en donde a representa 1, 2, o 3.

46. Un compuesto de acuerdo con la reivindicación 1 de la fórmula I_d



[Id]

en donde A representa N, CH o CR^1;

en donde cada R^1 independientemente representa hidrógeno, alquilo C_{1-6}, -C(O)-alquilo C_{1-6}, C(O)-O-alquilo C_{1-6}, o fenilo, en donde dicho fenilo, o alquilo C_{1-6} está opcionalmente sustituido con uno o más sustituyentes seleccionados entre halógeno, hidroxilo, halo-alquilo C_{1-6}, nitro, alcoxi C_{1-6}, y NR^2R^3;

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en donde W se selecciona entre hidrógeno, hidroxi, halógeno, ciano, (=O), -O-$(CH_2)_c$-O-, en donde c es 2 o 3 (espiro), $(CH_2)_d$, en donde d es 5 o 6 (espiro), alquilo C_{1-6}, alcoxi C_{1-6}, -C(O)-alquilo C_{1-6}, -C(O)-O-alquilo C_{1-6}, -O-C(O)-alquilo C_{1-6}, -C(O)H, COOH;

en donde R^2 y R^3 independientemente representan hidrógeno, alquilo C_{1-6}, hidroxi-alquilo C_{1-6}, halo-alquilo C_{1-6} o fenilo;

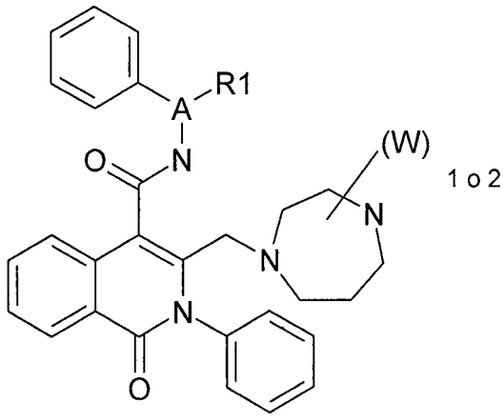
en donde R^9-R^{12} independientemente representan hidrógeno o halógeno;

y sus sales aceptables para uso farmacéutico.

47. Un compuesto de acuerdo con la reivindicación 46, en donde A es CH; R^1 representa alquilo C_{1-6}; y cada uno de R^9-R^{12} independientemente representan hidrógeno o halógeno.

48. Un compuesto de acuerdo con la reivindicación 47, en donde R^1 representa etilo o ciclopropilo; y cada uno de R^9-R^{12} representan hidrógeno.

49. Un compuesto de acuerdo con la reivindicación 1 de la fórmula I_e



[Ie]

en donde A representa N, CH o CR^1;

en donde cada R^1 independientemente representa hidrógeno, alquilo C_{1-6}, -C(O)-alquilo C_{1-6}, C(O)-O-alquilo C_{1-6}, o fenilo, en donde dicho fenilo, o alquilo C_{1-6} está opcionalmente sustituido con uno o más sustituyentes seleccionados entre halógeno, hidroxilo, halo-alquilo C_{1-6}, nitro, alcoxi C_{1-6}, y NR^2R^3;

en donde W se selecciona entre hidrógeno, hidroxi, halógeno, ciano, (=O), -O-$(CH_2)_c$-O-, en donde c es 2 o 3 (espiro), $(CH_2)_d$, en donde d es 5 o 6 (espiro), alquilo C_{1-6}, alcoxi C_{1-6}, -C(O)-alquilo C_{1-6}, -C(O)-O-alquilo C_{1-6}, -O-C(O)-alquilo C_{1-6}, -C(O)H, COOH; o en donde W representa una parte de la fórmula $-(CH_2)_a$-Y-$(CH_2)_b$-Z;

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en donde a y b independientemente representan un número entero seleccionado entre 0, 1, 2 y 3;

en donde Y representa un enlace, C(O), O, S, -O-C(O), -C(O)-O-, NR^2, -NR^2-C(O)-, -C(O)-NH-, o $S(O)_2$;

en donde Z representa hidrógeno, alquilo C_{1-6}, NR^2R^3, ciano o una parte monocíclica o bicíclica fusionada que comprende 4 a 12 átomos constitutivos del anillo de los cuales opcionalmente uno, dos o tres son heteroátomos seleccionados entre N, O, y S, y en donde dicha parte monocíclica o bicíclica fusionada está opcionalmente sustituida con uno o más sustituyentes seleccionados del grupo integrado por halógeno, ciano, alquilo C_{1-6}, hidroxilo, y alcoxi C_{1-6}, pirazinilo, fenilo, piridilo, y fenilo sustituido con halógeno;

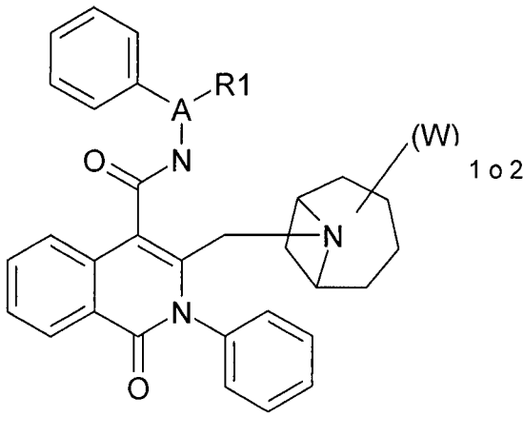
en donde R^2 y R^3 independientemente representan hidrógeno, alquilo C_{1-6}, hidroxi-alquilo C_{1-6}, halo-alquilo C_{1-6} o fenilo;

y sus sales aceptables para uso farmacéutico.

50. Un compuesto de acuerdo con la reivindicación 49, en donde A es CH, y R^1 representa alquilo C_{1-6}.

51. Un compuesto de acuerdo con la reivindicación 50, en donde R^1 representa etilo o ciclopropilo.

52. Un compuesto de acuerdo con la reivindicación 1 de la fórmula I_f



[If]

en donde A representa N, CH o CR^1;

en donde cada R^1 independientemente representa hidrógeno, alquilo C_{1-6}, -C(O)-alquilo C_{1-6}, C(O)-O-alquilo C_{1-6}, o fenilo, en donde dicho fenilo, o alquilo C_{1-6} está

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opcionalmente sustituido con uno o más sustituyentes seleccionados entre halógeno, hidroxilo, halo-alquilo C_{1-6}, nitro, alcoxi C_{1-6}, y NR^2R^3;

en donde W se selecciona entre hidrógeno, hidroxi, halógeno, ciano, (=O), -O-$(CH_2)_c$-O-, en donde c es 2 o 3 (espiro), $(CH_2)_d$, en donde d es 5 o 6 (espiro), alquilo C_{1-6}, alcoxi C_{1-6}, -C(O)-alquilo C_{1-6}, -C(O)-O-alquilo C_{1-6}, -O-C(O)-alquilo C_{1-6}, -C(O)H, COOH; o en donde W representa una parte de la fórmula $-(CH_2)_a$-Y-$(CH_2)_b$-Z;

en donde a y b independientemente representan un número entero seleccionado entre 0, 1, 2 y 3;

en donde Y representa un enlace, C(O), O, S, -O-C(O), -C(O)-O-, NR^2, -NR^2-C(O)-, -C(O)-NH-, o $S(O)_2$;

en donde Z representa hidrógeno, alquilo C_{1-6}, NR^2R^3, ciano o una parte monocíclica o bicíclica fusionada que comprende 4 a 12 átomos constitutivos del anillo de los cuales opcionalmente uno, dos o tres son heteroátomos seleccionados entre N, O, y S, y en donde dicha parte monocíclica o bicíclica fusionada está opcionalmente sustituida con uno o más sustituyentes seleccionados del grupo integrado por halógeno, ciano, alquilo C_{1-6}, hidroxilo, y alcoxi C_{1-6}, pirazinilo, fenilo, piridilo, y fenilo sustituido con halógeno;

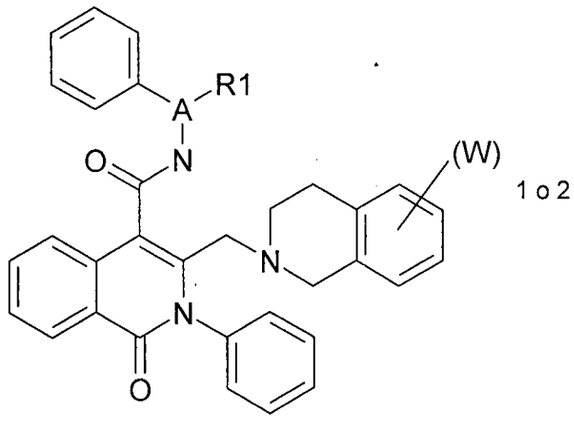
en donde R^2 y R^3 independientemente representan hidrógeno, alquilo C_{1-6}, hidroxi-alquilo C_{1-6}, halo-alquilo C_{1-6} o fenilo;

y sus sales aceptables para uso farmacéutico.

53. Un compuesto de acuerdo con la reivindicación 52, en donde A es CH, y R^1 representa alquilo C_{1-6}.

54. Un compuesto de acuerdo con la reivindicación 53, en donde R^1 representa etilo o ciclopropilo.

55. Un compuesto de acuerdo con la reivindicación 1 de la fórmula I_g



[Ig]

en donde A representa N, CH o CR^1;

en donde cada R^1 independientemente representa hidrógeno, alquilo C_{1-6}, -C(O)-alquilo C_{1-6}, C(O)-O-alquilo C_{1-6}, o fenilo, en donde dicho fenilo, o alquilo C_{1-6} está opcionalmente sustituido con uno o más sustituyentes seleccionados entre halógeno, hidroxilo, haloalquilo C_{1-6}, nitro, alcoxi C_{1-6}, y NR^2R^3;

en donde W se selecciona entre hidrógeno, hidroxi, halógeno, ciano, (=O), -O-$(CH_2)_c$-O-, en donde c es 2 o 3 (espiro), $(CH_2)_d$, en donde d es 5 o 6 (espiro), alquilo C_{1-6}, alcoxi C_{1-6}, -C(O)-alquilo C_{1-6}, -C(O)-O-alquilo C_{1-6}, -O-C(O)-alquilo C_{1-6}, $-N(R^2)$-C(O)-R^3, -C(O)H, COOH; o en donde W representa una parte de la fórmula $-(CH_2)_a$-Y-$(CH_2)_b$-Z;

en donde a y b independientemente representan un número entero seleccionado entre 0, 1, 2 y 3;

en donde Y representa un enlace, C(O), O, S, -O-C(O), -C(O)-O-, NR^2, $-NR^2$-C(O)-, -C(O)-NH-, o $S(O)_2$;

en donde Z representa hidrógeno, alquilo C_{1-6}, NR^2R^3, ciano o una parte monocíclica o bicíclica fusionada que comprende 4 a 12 átomos constitutivos del anillo de los cuales opcionalmente uno, dos o tres son heteroátomos seleccionados entre N, O, y S, y en donde dicha parte monocíclica o bicíclica fusionada está opcionalmente sustituida con uno o más sustituyentes seleccionados del grupo integrado por halógeno, ciano, alquilo C_{1-6}, hidroxilo, y alcoxi C_{1-6}, pirazinilo, fenilo, piridilo, y fenilo sustituido con halógeno;

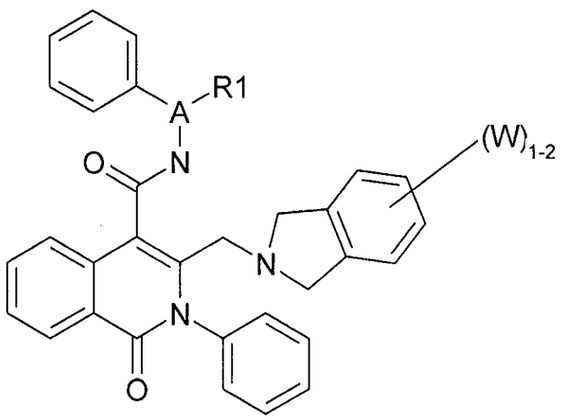
en donde R^2 y R^3 independientemente representan hidrógeno, alquilo C_{1-6}, hidroxi-alquilo C_{1-6}, halo-alquilo C_{1-6} o fenilo;

y sus sales aceptables para uso farmacéutico.

56. Un compuesto de acuerdo con la reivindicación 55, en donde A es CH, y R^1 representa alquilo C_{1-6}.

57. Un compuesto de acuerdo con la reivindicación 56, en donde R^1 representa etilo o ciclopropilo.

58. Un compuesto de acuerdo con la reivindicación 1 de fórmula I_h



$[I_h]$

en donde A representa N, CH o CR^1;

en donde cada R^1 independientemente representa hidrógeno, alquilo C_{1-6}, -C(O)-alquilo C_{1-6}, C(O)-O-alquilo C_{1-6}, o fenilo, en donde dicho fenilo, o alquilo C_{1-6} está opcionalmente sustituido con uno o más sustituyentes seleccionados entre halógeno, hidroxilo, halo-alquilo C_{1-6}, nitro, alcoxi C_{1-6}, y NR^2R^3;

en donde W se selecciona entre hidrógeno, hidroxi, halógeno, ciano, (=O), -O-$(CH_2)_c$-O-, en donde c es 2 o 3 (espiro), $(CH_2)_d$, en donde d es 5 o 6 (espiro), alquilo C_{1-6}, alcoxi C_{1-6}, -C(O)-alquilo C_{1-6}, -C(O)-O-alquilo C_{1-6}, -O-C(O)-alquilo C_{1-6}, -C(O)H, COOH; o en donde W representa una parte de la fórmula $-(CH_2)_a$-Y-$(CH_2)_b$-Z;

en donde a y b independientemente representan un número entero seleccionado entre 0, 1, 2 y 3;

en donde Y representa un enlace, C(O), O, S, -O-C(O), -C(O)-O-, NR^2, -NR^2-C(O)-, -C(O)-NH-, o $S(O)_2$;

en donde Z representa hidrógeno, alquilo C_{1-6}, NR^2R^3, ciano o una parte monocíclica o bicíclica fusionada que comprende 4 a 12 átomos constitutivos del anillo de los cuales opcionalmente uno, dos o tres son heteroátomos seleccionados entre N, O, y S, y en donde dicha parte monocíclica o bicíclica fusionada está opcionalmente sustituido con uno o más sustituyentes seleccionados del grupo integrado por halógeno,

ciano, alquilo C_{1-6}, hidroxilo, y alcoxi C_{1-6}, pirazinilo, fenilo, piridilo, y fenilo sustituido con halógeno;

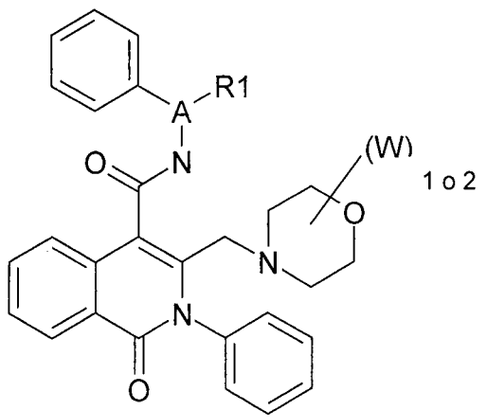
en donde R^2 y R^3 independientemente representan hidrógeno, alquilo C_{1-6}, hidroxi-alquilo C_{1-6}, halo-alquilo C_{1-6} o fenilo;

y sus sales aceptables para uso farmacéutico.

59. Un compuesto de acuerdo con la reivindicación 58, en donde A es CH, y R^1 representa alquilo C_{1-6}.

60. Un compuesto de acuerdo con la reivindicación 57, en donde R^1 representa etilo o ciclopropilo.

61. Un compuesto de acuerdo con la reivindicación 1 de fórmula I_i



[Ii]

en donde A representa N, CH o CR^1;

en donde cada R^1 independientemente representa hidrógeno, alquilo C_{1-6}, -C(O)-alquilo C_{1-6}, C(O)-O-alquilo C_{1-6}, o fenilo, en donde dicho fenilo, o alquilo C_{1-6} está opcionalmente sustituido con uno o más sustituyentes seleccionados entre halógeno, hidroxilo, halo-alquilo C_{1-6}, nitro, alcoxi C_{1-6}, y NR^2R^3;

en donde W se selecciona entre hidrógeno, hidroxi, halógeno, ciano, (=O), -O-$(CH_2)_c$-O-, en donde c es 2 o 3 (espiro), $(CH_2)_d$, en donde d es 5 o 6 (espiro), alquilo C_{1-6}, alcoxi C_{1-6}, -C(O)-alquilo C_{1-6}, -C(O)-O-alquilo C_{1-6}, -O-C(O)-alquilo C_{1-6}, -C(O)H, COOH; o en donde X representa una parte de la fórmula $-(CH_2)_a$-Y-$(CH_2)_b$-Z;

en donde a y b independientemente representan un número entero seleccionado entre 0, 1, 2 y 3;

en donde Y representa un enlace, C(O), O, S, -O-C(O), -C(O)-O-, NR^2, -NR^2-C(O)-, -C(O)-NH-, o $S(O)_2$;

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en donde Z representa hidrógeno, alquilo C_{1-6}, NR^2R^3, ciano o una parte monocíclica o bicíclica fusionada que comprende 4 a 12 átomos constitutivos del anillo de los cuales opcionalmente uno, dos o tres son heteroátomos seleccionados entre N, O, y S, y en donde dicha parte monocíclica o bicíclica fusionada está opcionalmente sustituida con uno o más sustituyentes seleccionados del grupo integrado por halógeno, ciano, alquilo C_{1-6}, hidroxilo, y alcoxi C_{1-6}, pirazinilo, fenilo, piridilo, y fenilo sustituido con halógeno;

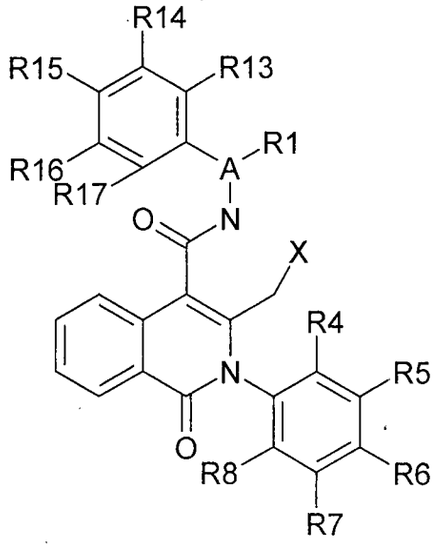
en donde R^2 y R^3 independientemente representan hidrógeno, alquilo C_{1-6}, hidroxi-alquilo C_{1-6}, halo-alquilo C_{1-6} o fenilo;

y sus sales aceptables para uso farmacéutico.

62. Un compuesto de acuerdo con la reivindicación 61, en donde A es CH, y R^1 representa alquilo C_{1-6}.

63. Un compuesto de acuerdo con la reivindicación 62, en donde R^1 representa etilo o ciclopropilo.

64. Un compuesto de acuerdo con la reivindicación 1 de fórmula Ij



[Ij]

en donde A representa N, CH o CR^1;

en donde cada R^1 independientemente representa hidrógeno, alquilo C_{1-6}, -C(O)-alquilo C_{1-6}, -C(O)-O-alquilo C_{1-6}, o fenilo, en donde dicho fenilo o alquilo C_{1-6} está opcionalmente sustituido con uno o más sustituyentes seleccionados entre halógeno, hidroxilo, halo-alquilo C_{1-6}, nitro, alcoxi C_{1-6}, y NR^2R^3;

en donde X representa hidrógeno, alquilo C_{1-6}, ciano, $-OR^2$, $-O-C(O)R^2$, $-OC(O)NR^2R^3$, $-C(O)-NR^2R^3$, $-N(R^2)C(O)R^3$, $-N(R^2)-C(O)NR^2R^3$ o NR^2R^3, o X representa

una parte monocíclica, bicíclica o tricíclica que tiene 4 a 16 átomos constitutivos del anillo uno de los cuales es nitrógeno, y en donde uno, dos o tres átomos constitutivos del anillo, adicionalmente, pueden ser heteroátomos seleccionados entre N, O y S, y en donde dicha parte monocíclica, bicíclica o tricíclica puede estar opcionalmente sustituida con uno o más sustituyentes W, en donde W se selecciona entre hidrógeno, hidroxi, halógeno, ciano, (=O), -O-$(CH_2)_c$-O-, en donde c es 2 o 3 (espiro), $(CH_2)_d$, en donde d es 5 o 6 (espiro), alquilo C_{1-6}, alcoxi C_{1-6}, -C(O)-alquilo C_{1-6}, -C(O)-O-alquilo C_{1-6}, -O-C(O)-alquilo C_{1-6}, -C(O)H, COOH; o en donde W representa una parte de la fórmula –$(CH_2)_a$-Y-$(CH_2)_b$-Z;

en donde a y b independientemente representan un número entero seleccionado entre 0, 1, 2 y 3;

en donde Y representa un enlace, C(O), O, S, -O-C(O), -C(O)-O-, -NR^2-, -NR^2-C(O)-, -C(O)-NH-, o $S(O)_2$;

en donde Z representa hidrógeno, alquilo C_{1-6}, NR^2R^3, ciano o una parte monocíclica o bicíclica fusionada que comprende 4 a 12 átomos constitutivos del anillo de los cuales opcionalmente uno, dos o tres son heteroátomos seleccionados entre N, O, y S, y en donde dicha parte monocíclica o bicíclica fusionada está opcionalmente sustituida con uno o más sustituyentes seleccionados del grupo integrado por halógeno, ciano, alquilo C_{1-6}, hidroxilo, y alcoxi C_{1-6}, fenilo, piridilo, y fenilo sustituido con halógeno;

en donde uno entre R^4-R^8 representa halógeno y el otro representa hidrógeno; en donde uno de R^{13}-R^{17} representa halógeno y el otro representa hidrógeno;

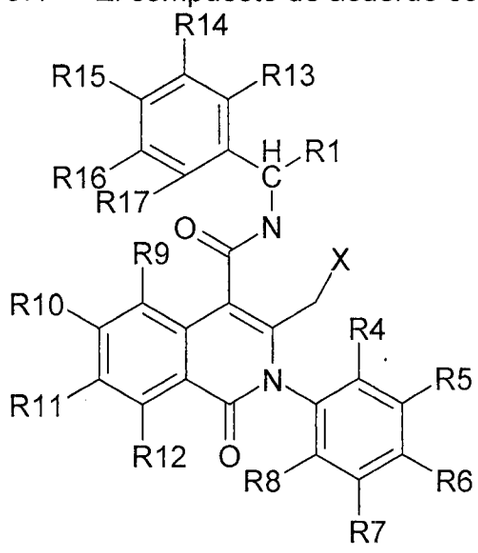
en donde R^2 y R^3 independientemente representan hidrógeno, alquilo C_{1-6}, hidroxi-alquilo C_{1-6}, halo-alquilo C_{1-6} o fenilo;

y sus sales aceptables para uso farmacéutico.

65. Un compuesto de acuerdo con la reivindicación 64 en donde A representa CH; R^1 representa etilo o ciclopropilo; R^{14} representa halógeno; y R^5 o R^8 representa halógeno.

66. Un compuesto de acuerdo con la reivindicación 65 en donde X representa piperazinilo o 1-piperidilo sustituido con uno o dos sustituyentes W, en donde dicho W es una parte de la fórmula –$(CH_2)_a$-Y-$(CH_2)_b$-Z, en donde a y b independientemente representan 0, 1, 2 o 3; Y representa un enlace, O, -NR^2-C(O)-; y en donde Z representa hidrógeno, alquilo C_{1-6}, piperidilo, morfolinilo, piridilo, fenilo, fenilo sustituido con alcoxi C_{1-6}, o pirrolidinilo.

67. El compuesto de acuerdo con la reivindicación 1 de la fórmula Ik



[Ik]

en donde R^1 representa hidrógeno, alquilo C_{1-6}, alquenilo C_{2-6} o alquinilo C_{2-6};

en donde X representa hidrógeno, alquilo C_{1-6}, alquenilo C_{2-6}, alquinilo C_{2-6} o NR^2R^3, o X representa una parte monocíclica o bicíclica que tiene 5 a 9 átomos constitutivos del anillo uno de los cuales es nitrógeno, y en donde uno, dos o tres átomos constitutivos del anillo, adicionalmente, pueden ser heteroátomos seleccionados entre N, O y S, y en donde dicha parte monocíclica o bicíclica puede estar opcionalmente sustituida con uno o más sustituyentes W, en donde W se selecciona entre hidrógeno, halógeno, hidroxi, (=O), alquilo C_{1-6}, alquenilo C_{2-6}, alquinilo C_{2-6}, alcoxi C_{1-6}, o en donde W representa una parte de la fórmula $-(CH_2)_a-Y-(CH_2)_b-Z$;

en donde a y b independientemente representan un número entero seleccionado entre 0, 1, 2 y 3;

en donde Y representa un enlace, y en donde Z representa una parte monocíclica que comprende 5 a 6 átomos constitutivos del anillo de los cuales opcionalmente uno, dos o tres son heteroátomos seleccionados entre N, O, y S, y en donde dicha parte monocíclica está opcionalmente sustituida con uno o más sustituyentes seleccionados del grupo integrado por halógeno, alquilo C_{1-6}, hidroxilo, y alcoxi C_{1-6};

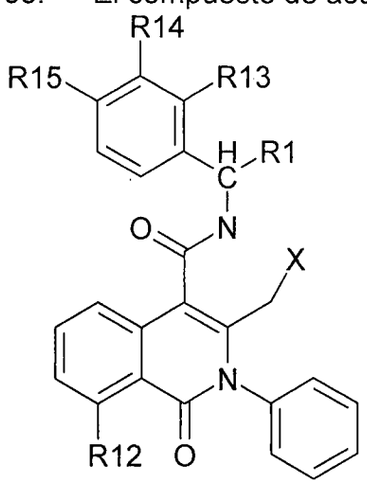
en donde cada uno entre R^4-R^8 independientemente representa hidrógeno o halógeno;

en donde cada uno entre R^9-R^{12} independientemente representa hidrógeno o halógeno siempre que al menos uno entre R^9-R^{12} represente halógeno;

en donde cada uno entre R^{13}-R^{17} independientemente representan hidrógeno o halógeno;

en donde R^2 y R^3 independientemente representan hidrógeno, alquilo C_{1-6}, alquenilo C_{2-6}, alquinilo C_{2-6}; y sus sales aceptables para uso farmacéutico.

68. El compuesto de acuerdo con la reivindicación 67 de fórmula Ik'



[Ik']

en donde R^1 se selecciona de alquilo C_{1-6};

en donde X se selecciona entre hidrógeno, alquilo C_{1-6} o NR^2R^3, o X representa una parte monocíclica o bicíclica que tiene 5 a 9 átomos constitutivos del anillo uno de los cuales es nitrógeno, y en donde uno de los átomos constitutivos del anillo, adicionalmente, pueden ser heteroátomos seleccionados de N (sic), y en donde dicha parte monocíclica o bicíclica puede estar opcionalmente sustituida con uno o más sustituyentes W, en donde W se selecciona entre hidrógeno, hidroxi, (=O), C_{1-6}alquilo o en donde W representa una parte de la fórmula $-(CH_2)_a$-Y-$(CH_2)_b$-Z;

en donde a y b independientemente representan un número entero seleccionado entre 0, 1, 2 y 3;

en donde Y representa un enlace, y en donde Z representa una parte monocíclica que comprende 5 a 6 átomos constitutivos del anillo de los cuales opcionalmente uno es un heteroátomo seleccionado entre N, O, y S, y en donde dicha parte monocíclica está opcionalmente sustituida con uno o más sustituyentes seleccionados del grupo integrado por halógeno, alquilo C_{1-6}, hidroxilo, y alcoxi C_{1-6};

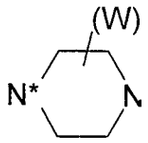
en donde R^{12} representa halógeno;

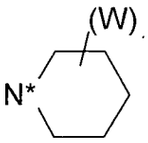
R^{13}-R^{15} cada uno independientemente representa hidrógeno o halógeno;

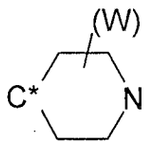
y sus sales aceptables para uso farmacéutico.

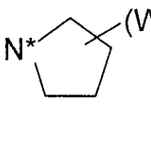
69. El compuesto de acuerdo con cualquiera de las reivindicaciones 67 a 68, en donde R^1 representa metilo, etilo, ciclopropilo, ciclobutilo, ciclopentilo o ciclohexilo.

70. El compuesto de acuerdo con la reivindicación 69, en donde X representa



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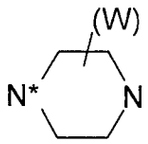
,


,


,

$-NR^2R^3$, o hidrógeno

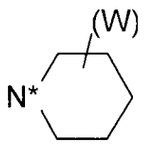
71. El compuesto de acuerdo con la reivindicación 70, en donde X representa

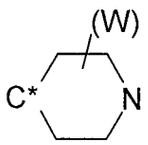


, y en donde W representa hidrógeno, (=O), alquilo C_{1-6}, o $-(CH_2)_a$-Y-$(CH_2)_b$-Z.

72. El compuesto de acuerdo con la reivindicación 71, en donde W representa hidrógeno, metilo, ciclopropilmetilo, isopropilo, isobutilo, ter-butilo, (=O), o $-(CH_2)_a$-Y-$(CH_2)_a$-Z, en donde a+b es 2 y Z se selecciona de 4-morfolinilo, fenilo, 1-piperidina o 1-pirrolidinilo.

73. El compuesto de acuerdo con la reivindicación 70, en donde X representa

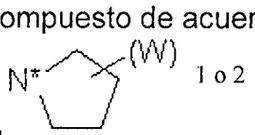


o


, en donde W representa hidrógeno, hidroxilo, alquilo C_{1-6}- o $-(CH_2)_a$-Y-$(CH_2)_a$-Z.

74. El compuesto de acuerdo con la reivindicación 73, en donde W representa hidrógeno, hidroxilo, ter-butilo, o a+b es 0 o 2 y Z representa 4-morfolinilo, fenilo, opcionalmente sustituido con alcoxi C_{1-6}, o 4-piperidilo.

75. El compuesto de acuerdo con la reivindicación 70, en donde X representa



, y W representa (=O).

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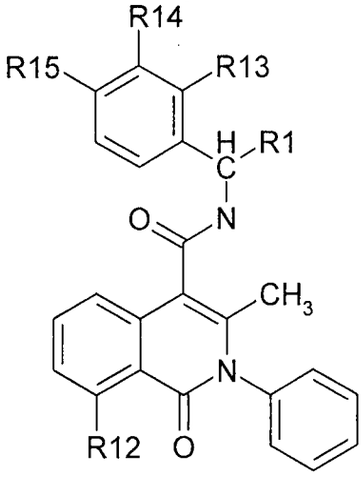
76. El compuesto de acuerdo con la reivindicación 70, en donde X representa – NR^2R^3.

77. El compuesto de acuerdo con la reivindicación 76, en donde R^2 y R^3 independientemente representan hidrógeno o alquilo C_{1-6}.

78. El compuesto de acuerdo con la reivindicación 77, en donde R^2 representa hidrógeno, y R^3 representa ciclopropilo, isobutilo o ter-butilo.

79. El compuesto de acuerdo con la reivindicación 70, en donde X es hidrógeno.

80. El compuesto de acuerdo con la reivindicación 1 de la fórmula Ik''



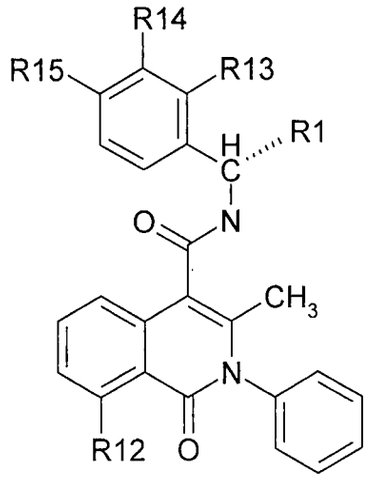
[Ik'']

en donde R^1 representa etilo, ciclopropilo o ciclobutilo;

en donde R^{12} representa flúor o cloro; y

R^{13}, R^{14} y R^{15} cada uno individualmente representan hidrógeno, flúor o cloro, en donde dos entre R^{13}, R^{14} y R^{15} representan hidrógeno.

81. El compuesto de acuerdo con la reivindicación 80, en donde dicho compuesto es esencialmente enantiómero S como se describe en la fórmula Ik'''



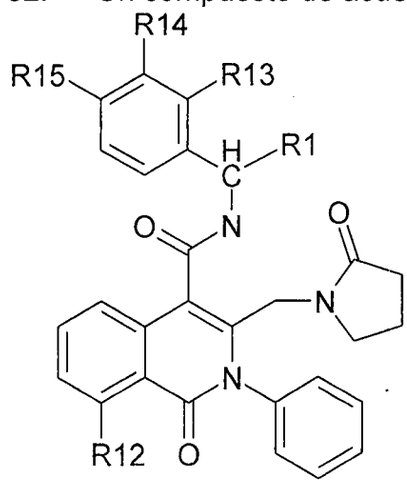
[Ik'"]

en donde R^1 representa etilo o ciclopropilo;

en donde R^{12} representa flúor o cloro; y

R^{13}, R^{14} y R^{15} cada uno individualmente representan hidrógeno, flúor o cloro, en donde dos entre R^{13}, R^{14} y R^{15} representan hidrógeno.

82. Un compuesto de acuerdo con la reivindicación 1 de la fórmula Id'



[Id']

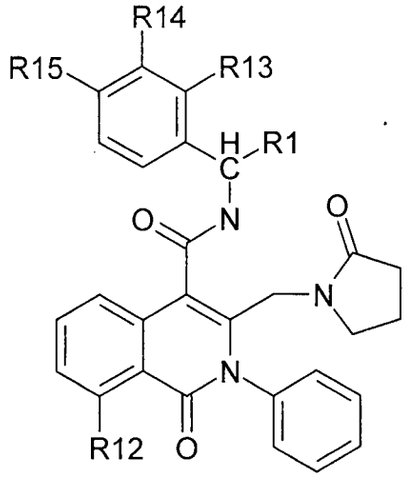
en donde R^1 representa etilo o ciclopropilo;

R^{12} representa halógeno;

R^{13}, R^{14} y R15 cada uno independientemente representa hidrógeno, o halógeno;

y sus sales aceptables para uso farmacéutico.

83. Un compuesto de acuerdo con la reivindicación 1 de la fórmula Id''



[Id"]

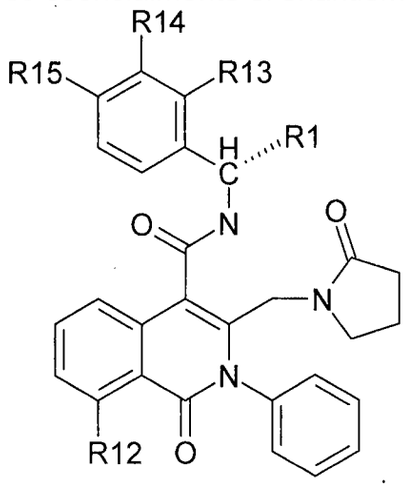
en donde R^1 representa etilo o ciclopropilo;

R^{12} representa cloro o flúor;

R^{12}, R^{14} y R^{15} cada uno independientemente representa hidrógeno, cloro o flúor, en donde dos entre R^{12}, R^{14} y R^{15} representan hidrógeno;

y sus sales aceptables para uso farmacéutico.

84. Un compuesto de acuerdo con la reivindicación 83, en donde dicho compuesto es esencialmente el enantiómero S como se describe en la fórmula Id'''



[Id''']

en donde R^1 representa etilo o ciclopropilo;

R^{12} representa cloro o flúor;

R^{12}, R^{14} y R^{15} cada uno independientemente representa hidrógeno, cloro o flúor, en donde dos entre R^{12}, R^{14} y R^{15} representan hidrógeno;

y sus sales aceptables para uso farmacéutico.

85. Un compuesto de acuerdo con la reivindicación 1 seleccionado entre

1a ((S)-1-fenil-propil)-amida del ácido 3-metil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

1b ((S)-1-fenil-propil)-amida del ácido 3,6-dimetil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

1c ((S)-1-fenil-propil)-amida del ácido 7-cloro-3-metil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

1d ((S)-1-fenil-propil)-amida del ácido 7-bromo-3-metil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

1e ((S)-1-fenil-propil)-amida del ácido 6-fluoro-3-metil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

1f ((S)-1-fenil-propil)-amida del ácido 3,5-dimetil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

1g ((S)-1-fenil-propil)-amida del ácido 7-fluoro-3-metil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

1h ((S)-1-fenil-propil)-amida del ácido 3,7-dimetil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

1i ((S)-1-fenil-propil)-amida del ácido 8-cloro-3-metil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

1r ((S)-ciclopropil-fenil-metil)-amida del ácido 3-metil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

1s [(S)-ciclopropil-(3-fluoro-fenil)-metil]-amida del ácido 3-metil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

1j ((S)-1-fenil-propil)-amida del ácido 3,8-dimetil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

1k ((S)-1-fenil-propil)-amida del ácido 2-(2-fluoro-fenil)-3-metil-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico

1l ((S)-1-fenil-propil)-amida del ácido 3-metil-1-oxo-2-o-tolil-1,2-dihidro-isoquinolin-4-carboxílico

1m ((S)-1-fenil-propil)-amida del ácido 2-(2-cloro-fenil)-3-metil-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico

1n ((S)-1-fenil-propil)-amida del ácido 2-(2,6-difluoro-fenil)-3-metil-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico

1o ((S)-1-fenil-propil)-amida del ácido 2-(3-fluoro-fenil)-3-metil-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico

1p ((S)-1-fenil-propil)-amida del ácido 3-metil-1-oxo-2-m-tolil-1,2-dihidro-isoquinolin-4-carboxílico

1q ((S)-1-fenil-propil)-amida del ácido 2-(3-cloro-fenil)-3-metil-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico

1t [(S)-ciclopropil-(3-fluoro-fenil)-metil]-amida del ácido 8-cloro-3-metil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2a ((S)-1-fenil-propil)-amida del ácido 3-dimetilaminometil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2b ((S)-1-fenil-propil)-amida del ácido 3-metilaminometil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2c ((S)-1-fenil-propil)-amida del ácido 3-etilaminometil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2d ((S)-1-fenil-propil)-amida del ácido 3-ciclopropilaminometil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2e ((S)-1-fenil-propil)-amida del ácido 3-[(ciclopropilmetil-amino)-metil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2f ((S)-1-fenil-propil)-amida del ácido 3-(3,6-dihidro-2H-piridin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2g ((S)-1-fenil-propil)-amida del ácido 3-[4-(2-metoxi-fenil)-piperazin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2h ((S)-1-fenil-propil)-amida del ácido 3-[4-(4-fluoro-fenil)-piperazin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2i ((S)-1-fenil-propil)-amida del ácido 3-(4-formil-piperazin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2j Etil éster del ácido 4-[1-oxo-2-fenil-4-(1-fenil-propilcarbamoil)-1,2-dihidro-isoquinolin-3-ilmetil]-piperazin-1-carboxílico

2k ((S)-1-fenil-propil)-amida del ácido 3-(4-metil-piperazin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2l ((S)-1-fenil-propil)-amida del ácido 1-oxo-2-fenil-3-(1,3,4,9-tetrahidro-beta-carbolin-2-ilmetil)-1,2-dihidro-isoquinolin-4-carboxílico

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2m ((S)-1-fenil-propil)-amida del ácido 1-oxo-2-fenil-3-piperazin-1-ilmetil-1,2-dihidro-isoquinolin-4-carboxílico

2n ((S)-1-fenil-propil)-amida del ácido 3-(3-metil-piperazin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2o ((S)-1-fenil-propil)-amida del ácido 3-(3,5-dimetil-piperazin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2p ((S)-1-fenil-propil)-amida del ácido 3-(4-bencil-piperazin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2q ((S)-1-fenil-propil)-amida del ácido 1-oxo-3-[4-(2-oxo-2-pirrolidin-1-il-etil)-piperazin-1-ilmetil]-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2r ((S)-1-fenil-propil)-amida del ácido 3-morfolin-4-ilmetil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2s ((S)-1-fenil-propil)-amida del ácido 3-(2,6-dimetil-morfolin-4-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2t ((S)-1-fenil-propil)-amida del ácido 1 -oxo-2-fenil-3-tiomorfolin-4-ilmetil-1,2-dihidro-isoquinolin-4-carboxílico

2u ((S)-1-fenil-propil)-amida del ácido 3-(1,4-dioxa-8-aza-espiro[4.5]dec-8-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2v ((S)-1-fenil-propil)-amida del ácido 1-oxo-2-fenil-3-piperidin-1-ilmetil-1,2-dihidro-isoquinolin-4-carboxílico

2w ((S)-1-fenil-propil)-amida del ácido 3-(2-metil-piperidin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2x ((S)-1-fenil-propil)-amida del ácido 3-(2,6-dimetil-piperidin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2y ((S)-1-fenil-propil)-amida del ácido 3-(2-hidroximetil-piperidin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2z Etil éster del ácido 1-[1-oxo-2-fenil-4-(1-fenil-propilcarbamoil)-1,2-dihidro-isoquinolin-3-ilmetil]-piperidin-3-carboxílico

2aa ((S)-1-fenil-propil)-amida del ácido 3-(3-metil-piperidin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2ab ((S)-1-fenil-propil)-amida del ácido 3-(4-hidroxi-piperidin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2ac ((S)-1-fenil-propil)-amida del ácido 1-oxo-2-fenil-3-(4-fenil-piperidin-1-ilmetil)-1,2-dihidro-isoquinolin-4-carboxílico

2ad Etil éster del ácido 1-[1-oxo-2-fenil-4-(1-fenil-propilcarbamoil)-1,2-dihidro-isoquinolin-3-ilmetil]-piperidin-4-carboxílico

2ae ((S)-1-fenil-propil)-amida del ácido 3-(4-metil-piperidin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2af ((S)-1-fenil-propil)-amida del ácido 1-oxo-2-fenil-3-(4-piridin-2-il-piperazin-1-ilmetil)-1,2-dihidro-isoquinolin-4-carboxílico

2ag ((S)-1-fenil-propil)-amida del ácido 3-(octahidro-quinolin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2ah ((S)-1-fenil-propil)-amida del ácido 3-azepan-1-ilmetil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2ai ((S)-1-fenil-propil)-amida del ácido 3-(3-hidroxi-piperidin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2aj ((S)-1-fenil-propil)-amida del ácido 3-[4-(2,4-dimetil-fenil)-piperazin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2ak ((S)-1-fenil-propil)-amida del ácido 3-[4-(3,4-dimetil-fenil)-piperazin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2al ((S)-1-fenil-propil)-amida del ácido 3-(4-dimetilamino-piperidin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2am ((S)-1-fenil-propil)-amida del ácido 3-[4-(2,5-dimetil-fenil)-piperazin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2an ((S)-1-fenil-propil)-amida del ácido 3-[4-(2-fluoro-fenil)-piperazin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2ao ((S)-1-fenil-propil)-amida del ácido 3-[4-(3-metoxi-fenil)-piperazin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2ap ((S)-1-fenil-propil)-amida del ácido 1-oxo-2-fenil-3-(4-m-tolil-piperazin-1-ilmetil)-1,2-dihidro-isoquinolin-4-carboxílico

2aq ((S)-1-fenil-propil)-amida del ácido 3-[4-(4-metoxi-fenil)-piperazin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2ar ((S)-1-fenil-propil)-amida del ácido 1-oxo-3-(4-fenetil-piperazin-1-ilmetil)-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2as ((S)-1-fenil-propil)-amida del ácido 1-oxo-2-fenil-3-(4-pirimidin-2-il-piperazin-1-ilmetil)-1,2-dihidro-isoquinolin-4-carboxílico

2at ((S)-1-fenil-propil)-amida del ácido 3-[4-(2-ciano-fenil)-piperazin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2au ((S)-1-fenil-propil)-amida del ácido 3-[4-(4-cloro-fenil)-piperazin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2av ((S)-1-fenil-propil)-amida del ácido 3-((1S,3R,5R)-3-hidroxi-8-aza-biciclo[3.2.1]oct-8-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2aw ((S)-1-fenil-propil)-amida del ácido 3-(4-acetil-piperazin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2ax ((S)-1-fenil-propil)-amida del ácido 3-(4-metil-[1,4]diazepan-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2ay ((S)-1-fenil-propil)-amida del ácido 3-(4-etil-piperazin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2az ((S)-1-fenil-propil)-amida del ácido 3-((2S,6R)-2,6-dimetil-morfolin-4-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2ba ((S)-1-fenil-propil)-amida del ácido 3-[4-(2,4-difluoro-fenil)-piperazin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2bb ((S)-1-fenil-propil)-amida del ácido 3-[4-(3-dimetilamino-propil)-piperazin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2bc ((S)-1-fenil-propil)-amida del ácido 3-(4-isopropil-piperazin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2bd ((S)-1-fenil-propil)-amida del ácido 3-(3-aza-biciclo[3.2.2]non-3-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2be ((S)-1-fenil-propil)-amida del ácido 3-(4-ciclopentil-piperazin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2bf ((S)-1-fenil-propil)-amida del ácido 3-[1,4']bipiperidinil-1'-ilmetil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2bg ((S)-1-fenil-propil)-amida del ácido 3-(3,4-dihidro-1H-isoquinolin-2-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2bh ((S)-1-fenil-propil)-amida del ácido 3-[4-(2-dimetilamino-etil)-piperazin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2bi ((S)-1-fenil-propil)-amida del ácido 3-(4-hidroximetil-piperidin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2bj ((S)-1-fenil-propil)-amida del ácido 1-oxo-2-fenil-3-[4-(tetrahidro-furan-2-carbonil)-piperazin-1-ilmetil]-1,2-dihidro-isoquinolin-4-carboxílico

2bk ((S)-1-fenil-propil)-amida del ácido 3-(4-isobutil-piperazin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2bl ((S)-1-fenil-propil)-amida del ácido 3-[4-(2-metoxi-etil)-piperazin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2bm ((S)-1-fenil-propil)-amida del ácido 3-[4-(2-morfolin-4-il-etil)-piperazin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2bn ((S)-1-fenil-propil)-amida del ácido 3-(1,3-dihidro-isoindol-2-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2bo ((S)-1-fenil-propil)-amida del ácido 3-[4-(1-metil-piperidin-4-il)-piperazin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2bp ((S)-1-fenil-propil)-amida del ácido 1-oxo-2-fenil-3-[4-(2-piperidin-1-il-etil)-piperazin-1-ilmetil]-1,2-dihidro-isoquinolin-4-carboxílico

2bq ((S)-1-fenil-propil)-amida del ácido 1-oxo-2-fenil-3-[4-(2-pirrolidin-1-il-etil)-piperazin-1-ilmetil]-1,2-dihidro-isoquinolin-4-carboxílico

2br ((S)-1-fenil-propil)-amida del ácido 3-(4-dimetilcarbamoilmetil-piperazin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2bs ((S)-1-fenil-propil)-amida del ácido 3-(octahidro-pirido[1,2-a]pirazin-2-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2bt ((S)-1-fenil-propil)-amida del ácido 3-(4-formil-[1,4]diazepan-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2bu ((S)-1-fenil-propil)-amida del ácido 3-[4-(4-ciano-fenil)-piperazin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2bv ((S)-1-fenil-propil)-amida del ácido 1-oxo-2-fenil-3-(4-piridin-4-ilmetil-piperazin-1-ilmetil)-1,2-dihidro-isoquinolin-4-carboxílico

2bw ((S)-1-fenil-propil)-amida del ácido 1-oxo-2-fenil-3-[4-(3-pirrolidin-1-il-propil)-piperazin-1-ilmetil]-1,2-dihidro-isoquinolin-4-carboxílico

2bx ((S)-1-fenil-propil)-amida del ácido 1-oxo-2-fenil-3-(4-piridin-2-ilmetil-piperazin-1-ilmetil)-1,2-dihidro-isoquinolin-4-carboxílico

2by ((S)-1-fenil-propil)-amida del ácido 3-(4-etansulfonil-piperazin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2bz ((S)-1-fenil-propil)-amida del ácido 3-(4-sec-butil-piperazin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2ca ((S)-1-fenil-propil)-amida del ácido 3-[4-(1-etil-propil)-piperazin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2cb ((S)-1-fenil-propil)-amida del ácido 3-[4-(2-ciano-etil)-piperazin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2cc ((S)-1-fenil-propil)-amida del ácido 3-(4-metansulfonil-piperazin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2cd Etil éster del ácido {1-[1-oxo-2-fenil-4-(1-fenil-propilcarbamoil)-1,2-dihidro-isoquinolin-3-ilmetil]-piperidin-4-il}-acético

2ce ((S)-1-fenil-propil)-amida del ácido 3-[4-(3-fluoro-fenil)-piperazin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2cf ((S)-1-fenil-propil)-amida del ácido 1-oxo-2-fenil-3-((S)-3-fenil-piperidin-1-ilmetil)-1,2-dihidro-isoquinolin-4-carboxílico

2cg ((S)-1-fenil-propil)-amida del ácido 1-oxo-2-fenil-3-[4-(pirrolidin-1-carbonil)-piperazin-1-ilmetil]-1,2-dihidro-isoquinolin-4-carboxílico

2ch ((S)-1-fenil-propil)-amida del ácido 3-[4-(morfolin-4-carbonil)-piperazin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2ci ((S)-1-fenil-propil)-amida del ácido 3-(4-metoxi-piperidin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2cj ((S)-1-fenil-propil)-amida del ácido 3-(4'-hidroxi-3',4',5',6'-tetrahidro-2'H-[3,4']bipiridinil-1'-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2ck ((S)-1-fenil-propil)-amida del ácido 3-(4-hidroxi-3,4,5,6-tetrahidro-2H-[4,4']bipiridinil-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2cl ((S)-1-fenil-propil)-amida del ácido 3-(3H-espiro[isobenzofuran-1,4'-piperidin]-1'-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2cm ((S)-1-fenil-propil)-amida del ácido 3-(4-hidroxi-4-metil-piperidin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2cn ((S)-1-fenil-propil)-amida del ácido 3-(hexahidro-espiro[benzo[1,3]dioxol-2,4'-piperidin]-1'-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

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2co ((S)-1-fenil-propil)-amida del ácido 1-oxo-2-fenil-3-(3,4,5,6-tetrahidro-2H-[4,4']bipiridinil-1-ilmetil)-1,2-dihidro-isoquinolin-4-carboxílico

2cp ((S)-1-fenil-propil)-amida del ácido 3-[4-(2-dimetilamino-etil)-piperidin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2cq ((S)-1-fenil-propil)-amida del ácido 3-(4-dimetilsulfamoil-piperazin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2cr ((S)-1-fenil-propil)-amida del ácido 3-(1,1-dioxo-tiomorfolin-4-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2cs ((S)-1-fenil-propil)-amida del ácido 1-oxo-2-fenil-3-(2-piridin-2-ilmetil-piperidin-1-ilmetil)-1,2-dihidro-isoquinolin-4-carboxílico

2ct ((S)-1-fenil-propil)-amida del ácido 3-(2-morfolin-4-ilmetil-piperidin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2cu ((S)-1-fenil-propil)-amida del ácido 3-(4-furo[3,2-c]piridin-4-il-piperazin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2cv ((S)-1-fenil-propil)-amida del ácido 3-(4-ciclopropilmetil-piperazin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2cw ((S)-1-fenil-propil)-amida del ácido 3-[4-(2-morfolin-4-il-etil)-piperidin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2cx ((S)-1-fenil-propil)-amida del ácido 1-oxo-2-fenil-3-(4-pirimidin-2-il-[1,4]diazepan-1-ilmetil)-1,2-dihidro-isoquinolin-4-carboxílico

2cy ((S)-1-fenil-propil)-amida del ácido 3-(4-metil-6,7-dihidro-4H-tieno[3,2-c]piridin-5-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2cz ((S)-1-fenil-propil)-amida del ácido 3-[1,4]diazepan-1-ilmetil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2da ((S)-1-fenil-propil)-amida del ácido 3-((2S,5R)-2,5-dimetil-piperazin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2db ((S)-1-fenil-propil)-amida del ácido 3-((S)-3-metil-piperazin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2dc ((S)-1-fenil-propil)-amida del ácido 3-((R)-3-metil-piperazin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2dd ((S)-1-fenil-propil)-amida del ácido 3-[3-(3-cloro-fenil)-piperazin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

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2de ((S)-1-fenil-propil)-amida del ácido 3-[4-(1H-indol-4-il)-piperazin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2df ((S)-1-fenil-propil)-amida del ácido 1-oxo-3-(3-oxo-piperazin-1-ilmetil)-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2dg ((S)-1-fenil-propil)-amida del ácido 3-[4-(1H-indol-5-il)-piperazin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2dh ((S)-1-fenil-propil)-amida del ácido 3-(6,9-diaza-espiro[4.5]dec 9-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2di ((S)-1-fenil-propil)-amida del ácido 3-(1,4-diaza-espiro[5.5]undec-4-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2dj ((S)-1-fenil-propil)-amida del ácido 3-(3-isopropil-piperazin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2dk ((S)-1-fenil-propil)-amida del ácido 3-(3,3-dimetil-piperazin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2dl ((S)-1-fenil-propil)-amida del ácido 3-[3-(4-fluoro-fenil)-piperazin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2dm ((S)-1-fenil-propil)-amida del ácido 1-oxo-2-fenil-3-(3-p-tolil-piperazin-1-ilmetil)-1,2-dihidro-isoquinolin-4-carboxílico

2dn Ter-butil éster del ácido 4-[1-oxo-2-fenil-4-(1-fenil-propilcarbamoil)-1,2-dihidro-isoquinolin-3-ilmetil]-piperazin-1-carboxílico

2do ((S)-1-fenil-propil)-amida del ácido 3-(4-metilcarbamoilmetil-piperazin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2dp ((S)-1-fenil-propil)-amida del ácido 8-cloro-3-dimetilaminometil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2dr ((S)-1-fenil-propil)-amida del ácido 3-ciclopentilaminometil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2ds ((S)-1-fenil-propil)-amida del ácido 3-ciclohexilaminometil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2dt ((S)-1-fenil-propil)-amida del ácido 3-{[(2-hidroxi-etil)-metil-amino]-metil}-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2du ((S)-1-fenil-propil)-amida del ácido 3-imidazol-1-ilmetil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

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2dv ((S)-1-fenil-propil)-amida del ácido 3-(2-metil-imidazol-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2dw ((S)-1-fenil-propil)-amida del ácido 3-(4-metil-imidazol-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2dx ((S)-1-fenil-propil)-amida del ácido 3-(2,5-dihidro-pirrol-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2dy ((S)-1-fenil-propil)-amida del ácido 3-(2,5-dimetil-2,5-dihidro-pirrol-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2dz ((S)-1-fenil-propil)-amida del ácido 1-oxo-2-fenil-3-pirrolidin-1-ilmetil-1,2-dihidro-isoquinolin-4-carboxílico

2ea ((S)-1-fenil-propil)-amida del ácido 1-oxo-2-fenil-3-(tiazol-2-ilaminometil)-1,2-dihidro-isoquinolin-4-carboxílico

2eb ((S)-1-fenil-propil)-amida del ácido 1-oxo-2-fenil-3-(pirimidin-4-ilaminometil)-1,2-dihidro-isoquinolin-4-carboxílico

2ec ((S)-1-fenil-propil)-amida del ácido 3-(ter-butilamino-metil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2ed ((S)-1-fenil-propil)-amida del ácido 3-[(2-hidroxi-1,1-dimetil-etilamino)-metil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2ee ((S)-1-fenil-propil)-amida del ácido 3-(isopropilamino-metil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2ef ((S)-1-fenil-propil)-amida del ácido 3-[(2-hidroxi-1-metil-etilamino)-metil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2eg ((S)-1-fenil-propil)-amida del ácido 3-[(1-hidroximetil-propilamino)-metil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2eh ((S)-1-fenil-propil)-amida del ácido 3-[(2,2-dimetil-propilamino)-metil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2ei ((S)-1-fenil-propil)-amida del ácido 1-oxo-2-fenil-3-prop-2-inilaminometil-1,2-dihidro-isoquinolin-4-carboxílico

2ej ((S)-1-fenil-propil)-amida del ácido 3-aliloaminometil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2ek ((S)-1-fenil-propil)-amida del ácido 3-[(metil-prop-2-inil-amino)-metil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2el ((S)-1-fenil-propil)-amida del ácido 3-dialiloaminometil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2em ((S)-1-fenil-propil)-amida del ácido 3-dietilaminometil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2en ((S)-1-fenil-propil)-amida del ácido 3-[(isopropil-metil-amino)-metil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2eo ((S)-1-fenil-propil)-amida del ácido 3-[((S)-2-hidroxi-1-metil-etilamino)-metil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2ep ((S)-1-fenil-propil)-amida del ácido 3-[((R)-2-hidroxi-1-metil-etilamino)-metil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2eq ((S)-1-fenil-propil)-amida del ácido 3-{[(2-metoxi-etil)-metil-amino]-metil}-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2er ((S)-1-fenil-propil)-amida del ácido 3-((R)-3-hidroxi-pirrolidin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2es ((S)-1-fenil-propil)-amida del ácido 3-((S)-3-hidroxi-pirrolidin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2et ((S)-1-fenil-propil)-amida del ácido 3-[(ciclopentil-metil-amino)-metil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2eu ((S)-1-fenil-propil)-amida del ácido 3-{[(2-hidroxi-1-metil-etil)-metil-amino]-metil}-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2ev ((S)-1-fenil-propil)-amida del ácido 3-{[etil-(2-hidroxi-etil)-amino]-metil}-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2ew ((S)-1-fenil-propil)-amida del ácido 3-[(etil-metil-amino)-metil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2ex ((S)-1-fenil-propil)-amida del ácido 3-ciclobutilaminometil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2ey ((S)-1-fenil-propil)-amida del ácido 3-azetidin-1-ilmetil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2ez ((S)-1-fenil-propil)-amida del ácido 3-(4-ter-butil-piperazin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2fa ((S)-1-fenil-propil)-amida del ácido 3-[4-(2-hidroxi-etil)-piperazin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2fb ((S)-1-fenil-propil)-amida del ácido 3-{4-[2-(2-hidroxi-etoxi)-etil]-piperazin-1-ilmetil}-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2fc ((S)-1-fenil-propil)-amida del ácido 3-[4-(3-cloro-5-trifluorometil-piridin-2-il)-piperazin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2fd ((S)-1-fenil-propil)-amida del ácido 3-[4-(3,5-dicloro-piridin-4-il)-piperazin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2fe Bencil éster del ácido 4-[1-oxo-2-fenil-4-((S)-1-fenil-propilcarbamoil)-1,2-dihidro-isoquinolin-3-ilmetil]-piperazin-1-carboxílico

2ff ((S)-1-fenil-propil)-amida del ácido 3-[4-(3-morfolin-4-il-propil)-piperazin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2fg ((S)-1-fenil-propil)-amida del ácido 1-oxo-2-fenil-3-[4-(3-piperidin-1-il-propil)-piperazin-1-ilmetil]-1,2-dihidro-isoquinolin-4-carboxílico

2fh 3((S)-1-fenil-propil)-amida del ácido -[4-(4,6-dimetoxi-pirimidin-2-ilmetil)-piperazin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2fi ((S)-1-fenil-propil)-amida del ácido 3-[4-(3-hidroxi-propil)-piperazin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2fj ((S)-1-fenil-propil)-amida del ácido 3-[4-(2,3-dihidroxi-propil)-piperazin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2fk Ter-butil éster del ácido (2-oxo-2-{4-[1-oxo-2-fenil-4-(1-fenil-propilcarbamoil)-1,2-dihidro-isoquinolin-3-ilmetil]-piperazin-1-il}-etil)-carbámico

2fl ((S)-1-fenil-propil)-amida del ácido 3-[4-(1H-indazol-5-il)-piperazin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2fm ((S)-1-fenil-propil)-amida del ácido 1-oxo-2-fenil-3-(4-quinolin-6-il-piperazin-1-ilmetil)-1,2-dihidro-isoquinolin-4-carboxílico

2fn ((S)-1-fenil-propil)-amida del ácido 3-[4-(6,7-dimetoxi-quinazolin-4-il)-piperazin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2fo Ter-butil éster del ácido 4-{4-[1-oxo-2-fenil-4-(1-fenil-propilcarbamoil)-1,2-dihidro-isoquinolin-3-ilmetil]-piperazin-1-il}-piperidin-1-carboxílico

2fp ((S)-1-fenil-propil)-amida del ácido 3-{4-[2-(4-cloro-fenoxi)-etil]-piperazin-1-ilmetil}-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2fq Ter-butil éster del ácido {4-[1-oxo-2-fenil-4-(1-fenil-propilcarbamoil)-1,2-dihidro-isoquinolin-3-ilmetil]-piperazin-1-il}-acético

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2fr ((S)-1-fenil-propil)-amida del ácido 1-oxo-2-fenil-3-[4-(3,3,3-trifluoro-2-hidroxi-propil)-piperazin-1-ilmetil]-1,2-dihidro-isoquinolin-4-carboxílico

2fs ((S)-1-fenil-propil)-amida del ácido 3-[4-(2-hidroxi-propil)-piperazin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2fu ((S)-1-fenil-propil)-amida del ácido 3-[4-(4-amino-6,7-dimetoxi-quinazolin-2-il)-piperazin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2fv Ter-butil éster del ácido (2-{4-[1-oxo-2-fenil-4-(1-fenil-propilcarbamoil)-1,2-dihidro-isoquinolin-3-ilmetil]-piperazin-1-il}-etil)-carbámico

2fw ((S)-1-fenil-propil)-amida del ácido 1-oxo-3-{4-[2-(2-oxo-imidazolidin-1-il)-etil]-piperazin-1-ilmetil}-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2fx ((S)-1-fenil-propil)-amida del ácido 3-{4-[(4,6-dimetoxi-pirimidin-2-il)-fenil-metil]-piperazin-1-ilmetil}-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2fy ((S)-1-fenil-propil)-amida del ácido 3-(4-benzo[1,2,5]tiadiazol-4-il-piperazin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2fz ((S)-1-fenil-propil)-amida del ácido 3-[4-(2,3-dihidro-benzo[1,4]dioxin-5-il)-piperazin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2ga ((S)-1-fenil-propil)-amida del ácido 3-[4-(4-metil-quinolin-2-il)-piperazin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2gb ((S)-1-fenil-propil)-amida del ácido 1-oxo-2-fenil-3-[4-(piridin-2-ilcarbamoilmetil)-piperazin-1-ilmetil]-1,2-dihidro-isoquinolin-4-carboxílico

2gc ((S)-1-fenil-propil)-amida del ácido 3-[4-(6-cloro-3-oxo-3,4-dihidro-2H-benzo[1,4]oxazin-8-il)-piperazin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2gd ((S)-1-fenil-propil)-amida del ácido 3-(4-carbamoilmetil-piperazin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2ge ((S)-1-fenil-propil)-amida del ácido 3-(4-hidroxi-4-fenil-piperidin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2gf ((S)-1-fenil-propil)-amida del ácido 3-[4-(4-cloro-fenil)-4-hidroxi-piperidin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2gg Ácido 1-[1-oxo-2-fenil-4-(1-fenil-propilcarbamoil)-1,2-dihidro-isoquinolin-3-ilmetil]-piperidin-4-carboxílico

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2gh ((S)-1-fenil-propil)-amida del ácido 3-(4-ciano-4-fenil-piperidin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2gi ((S)-1-fenil-propil)-amida del ácido 3-(4-bencil-4-hidroxi-piperidin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2gj Etil éster del ácido 1-[1-oxo-2-fenil-4-(1-fenil-propilcarbamoil)-1,2-dihidro-isoquinolin-3-ilmetil]-4-fenil-piperidin-4-carboxílico

2gk ((S)-1-fenil-propil)-amida del ácido 1-oxo-2-fenil-3-[4-(fenil-propionil-amino)-piperidin-1-ilmetil]-1,2-dihidro-isoquinolin-4-carboxílico

2gl Ter-butil éster del ácido metil-{1-[1-oxo-2-fenil-4-(1-fenil-propilcarbamoil)-1,2-dihidro-isoquinolin-3-ilmetil]-piperidin-4-il}-carbámico

2gm ((S)-1-fenil-propil)-amida del ácido 1-oxo-2-fenil-3-[4-(2-pirrolidin-1-il-etil)-piperidin-1-ilmetil]-1,2-dihidro-isoquinolin-4-carboxílico

2gn ((S)-1-fenil-propil)-amida del ácido 3-{4-[5-(4-fluoro-fenil)-[1,3,4]oxadiazol-2-il]-piperidin-1-ilmetil}-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2go ((S)-1-fenil-propil)-amida del ácido 1-oxo-2-fenil-3-[4-(3-piridin-4-il-[1,2,4]oxadiazol-5-il)-piperidin-1-ilmetil]-1,2-dihidro-isoquinolin-4-carboxílico

2gp ((S)-1-fenil-propil)-amida del ácido 1-oxo-2-fenil-3-[4-(3-pirazin-2-il-[1,2,4]oxadiazol-5-il)-piperidin-1-ilmetil]-1,2-dihidro-isoquinolin-4-carboxílico

2gq ((S)-1-fenil-propil)-amida del ácido 1-oxo-2-fenil-3-[4-(3-piridin-4-il-[1,2,4]oxadiazol-5-il)-piperidin-1-ilmetil]-1,2-dihidro-isoquinolin-4-carboxílico

2gr ((S)-1-fenil-propil)-amida del ácido 3-(4'-hidroxi-3',4',5',6'-tetrahidro-2'H-[2,4']bipiridinil-1'-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2gs ((S)-1-fenil-propil)-amida del ácido 3-(espiro[isocroman-1,4'-piperidin]-1'-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2gt ((S)-1-fenil-propil)-amida del ácido 3-[4-hidroxi-4-(3-metoxi-fenil)-piperidin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2gu ((S)-1-fenil-propil)-amida del ácido 3-[4-(3-cloro-fenil)-4-hidroxi-piperidin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2gv ((S)-1-fenil-propil)-amida del ácido 3-(6-cloro-3H-espiro[isobenzofuran-1,4'-piperidin]-1'-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2gw ((S)-1-fenil-propil)-amida del ácido 3-(4-{[4-cloro-3-(4-fluoro-fenil)-indan-1-il]-metil-amino}-piperidin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2gx ((S)-1-fenil-propil)-amida del ácido 3-(1-acetil-espiro[indolin-3,4'-piperidin]-1'-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2gy ((S)-1-fenil-propil)-amida del ácido 3-(1-acetil-5-fluoro-espiro[indolin-3,4'-piperidin]-1'-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2gz ((S)-1-fenil-propil)-amida del ácido 1-oxo-3-(4-oxo-1-fenil-1,3,8-triaza-espiro[4.5]dec-8-ilmetil)-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2ha ((S)-1-fenil-propil)-amida del ácido 3-(4-acetilamino-piperidin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2hb ((S)-1-fenil-propil)-amida del ácido 1-oxo-3-(1-oxo-2,8-diaza-espiro[4.5]dec-8-ilmetil)-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2hc ((S)-1-fenil-propil)-amida del ácido 3-[4-hidroxi-4-(3-trifluorometil-fenil)-piperidin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2hd ((S)-1-fenil-propil)-amida del ácido 1-oxo-2-fenil-3-(4-trifluorometil-piperidin-1-ilmetil)-1,2-dihidro-isoquinolin-4-carboxílico

2he ((S)-1-fenil-propil)-amida del ácido 3-[4-(4-metil-piperazin-1-carbonil)-piperidin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2hf ((S)-1-fenil-propil)-amida del ácido 3-(5-isopropil-3H-espiro[isobenzofuran-1,4'-piperidin]-1'-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2hg ((S)-1-fenil-propil)-amida del ácido 3-[4-(acetil-metil-amino)-4-fenil-piperidin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2hh Ter-butil éster del ácido 4-{1-[1-oxo-2-fenil-4-(1-fenil-propilcarbamoil)-1,2-dihidro-isoquinolin-3-ilmetil]-piperidin-4-il}-piperazin-1-carboxílico

2hi Ter-butil éster del ácido (2-{1-[1-oxo-2-fenil-4-(1-fenil-propilcarbamoil)-1,2-dihidro-isoquinolin-3-ilmetil]-piperidin-4-il}-etil)-carbámico

2hj ((S)-1-fenil-propil)-amida del ácido 3-(4-metilamino-4-fenil-piperidin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2hk ((S)-1-fenil-propil)-amida del ácido 3-(4-acetilamino-4-fenil-piperidin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2hl ((S)-1-fenil-propil)-amida del ácido 3-[4-acetilamino-4-(3-fluoro-fenil)-piperidin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2hm ((S)-1-fenil-propil)-amida del ácido 1-oxo-3-[4-(4-oxo-piperidin-1-carbonil)-piperidin-1-ilmetil]-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

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2hn ((S)-1-fenil-propil)-amida del ácido 3-[4,4']bipiperidinil-1-ilmetil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2ho Ter-butil éster del ácido {1-[1-oxo-2-fenil-4-(1-fenil-propilcarbamoil)-1,2-dihidro-isoquinolin-3-ilmetil]-piperidin-4-il}-carbámico

2hp [ciclopropil-(3-fluoro-fenil)-metil]-amida del ácido 3-[1,4']bipiperidinil-1'-ilmetil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2hq [Ciclopropil-(3-fluoro-fenil)-metil]-amida del ácido 1-oxo-3-(4-fenetil-piperazin-1-ilmetil)-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2hr [Ciclopropil-(3-fluoro-fenil)-metil]-amida del ácido 3-(4-isopropil-piperazin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2hs [Ciclopropil-(3-fluoro-fenil)-metil]-amida del ácido 3-[4-(2-morfolin-4-il-etil)-piperazin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2ht [Ciclopropil-(3-fluoro-fenil)-metil]-amida del ácido 3-[4-(1-metil-piperidin-4-il)-piperazin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2hu [Ciclopropil-(3-fluoro-fenil)-metil]-amida del ácido 1-oxo-2-fenil-3-[4-(2-piperidin-1-il-etil)-piperazin-1-ilmetil]-1,2-dihidro-isoquinolin-4-carboxílico

2hv [Ciclopropil-(3-fluoro-fenil)-metil]-amida del ácido 1-oxo-2-fenil-3-[4-(2-pirrolidin-1-il-etil)-piperazin-1-ilmetil]-1,2-dihidro-isoquinolin-4-carboxílico

2hw [Ciclopropil-(3-fluoro-fenil)-metil]-amida del ácido 1-oxo-2-fenil-3-(4-piridin-4-ilmetil-piperazin-1-ilmetil)-1,2-dihidro-isoquinolin-4-carboxílico

2hx [Ciclopropil-(3-fluoro-fenil)-metil]-amida del ácido 3-(4-hidroxi-3,4,5,6-tetrahidro-2H-[4,4']bipiridinil-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2hy [Ciclopropil-(3-fluoro-fenil)-metil]-amida del ácido 3-[4-(2-morfolin-4-il-etil)-piperidin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2hz [Ciclopropil-(3-fluoro-fenil)-metil]-amida del ácido 3-[4-hidroxi-4-(3-metoxi-fenil)-piperidin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2ia [Ciclopropil-(3-fluoro-fenil)-metil]-amida del ácido 3-[4-(acetil-metil-amino)-4-fenil-piperidin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2ib ((S)-1-fenil-propil)-amida del ácido 2-(2-fluoro-fenil)-1-oxo-3-(4-fenetil-piperazin-1-ilmetil)-1,2-dihidro-isoquinolin-4-carboxílico

2ic ((S)-1-fenil-propil)-amida del ácido 2-(2-fluoro-fenil)-3-(4-isopropil-piperazin-1-ilmetil)-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico

2id ((S)-1-fenil-propil)-amida del ácido 3-[1,4']bipiperidinil-1'-ilmetil-2-(2-fluoro-fenil)-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico

2ie ((S)-1-fenil-propil)-amida del ácido 2-(2-fluoro-fenil)-3-[4-(2-morfolin-4-il-etil)-piperazin-1-ilmetil]-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico

2if ((S)-1-fenil-propil)-amida del ácido 2-(2-fluoro-fenil)-3-[4-(1-metil-piperidin-4-il)-piperazin-1-ilmetil]-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico

2ig ((S)-1-fenil-propil)-amida del ácido 2-(2-fluoro-fenil)-1-oxo-3-[4-(2-piperidin-1-il-etil)-piperazin-1-ilmetil]-1,2-dihidro-isoquinolin-4-carboxílico

2ih ((S)-1-fenil-propil)-amida del ácido 2-(2-fluoro-fenil)-1-oxo-3-[4-(2-pirrolidin-1-il-etil)-piperazin-1-ilmetil]-1,2-dihidro-isoquinolin-4-carboxílico

2ii ((S)-1-fenil-propil)-amida del ácido 2-(2-fluoro-fenil)-1-oxo-3-(4-piridin-4-ilmetil-piperazin-1-ilmetil)-1,2-dihidro-isoquinolin-4-carboxílico

2ij ((S)-1-fenil-propil)-amida del ácido 2-(2-fluoro-fenil)-3-(4-hidroxi-3,4,5,6-tetrahidro-2H-[4,4']bipiridinil-1-ilmetil)-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico

2ik ((S)-1-fenil-propil)-amida del ácido 2-(2-fluoro-fenil)-3-[4-(2-morfolin-4-il-etil)-piperidin-1-ilmetil]-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico

2il ((S)-1-fenil-propil)-amida del ácido 2-(2-fluoro-fenil)-3-[4-hidroxi-4-(3-metoxi-fenil)-piperidin-1-ilmetil]-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico

2im ((S)-1-fenil-propil)-amida del ácido 3-[4-(2-morfolin-4-il-etil)-piperazin-1-ilmetil]-1-oxo-2-o-tolil-1,2-dihidro-isoquinolin-4-carboxílico

2in ((S)-1-fenil-propil)-amida del ácido 1-oxo-3-[4-(2-piperidin-1-il-etil)-piperazin-1-ilmetil]-2-o-tolil-1,2-dihidro-isoquinolin-4-carboxílico

2io ((S)-1-fenil-propil)-amida del ácido 1-oxo-3-(4-piridin-4-ilmetil-piperazin-1-ilmetil)-2-o-tolil-1,2-dihidro-isoquinolin-4-carboxílico

2ip ((S)-1-fenil-propil)-amida del ácido 2-(3-fluoro-fenil)-1-oxo-3-(4-fenetil-piperazin-1-ilmetil)-1,2-dihidro-isoquinolin-4-carboxílico

2iq ((S)-1-fenil-propil)-amida del ácido 2-(3-fluoro-fenil)-3-(4-isopropil-piperazin-1-ilmetil)-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico

2ir ((S)-1-fenil-propil)-amida del ácido 3-[1,4']bipiperidinil-1'-ilmetil-2-(3-fluoro-fenil)-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico

2is ((S)-1-fenil-propil)-amida del ácido 2-(3-fluoro-fenil)-3-[4-(2-morfolin-4-il-etil)-piperazin-1-ilmetil]-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico

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2it ((S)-1-fenil-propil)-amida del ácido 2-(3-fluoro-fenil)-3-[4-(1-metil-piperidin-4-il)-piperazin-1-ilmetil]-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico

2iu ((S)-1-fenil-propil)-amida del ácido 2-(3-fluoro-fenil)-1-oxo-3-[4-(2-piperidin-1-il-etil)-piperazin-1-ilmetil]-1,2-dihidro-isoquinolin-4-carboxílico

2iv ((S)-1-fenil-propil)-amida del ácido 2-(3-fluoro-fenil)-1-oxo-3-[4-(2-pirrolidin-1-il-etil)-piperazin-1-ilmetil]-1,2-dihidro-isoquinolin-4-carboxílico

2iw ((S)-1-fenil-propil)-amida del ácido 2-(3-fluoro-fenil)-1-oxo-3-(4-piridin-4-ilmetil-piperazin-1-ilmetil)-1,2-dihidro-isoquinolin-4-carboxílico

2ix ((S)-1-fenil-propil)-amida del ácido 2-(3-fluoro-fenil)-3-[4-(2-morfolin-4-il-etil)-piperidin-1-ilmetil]-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico

2iy ((S)-1-fenil-propil)-amida del ácido 2-(3-fluoro-fenil)-3-[4-hidroxi-4-(3-metoxi-fenil)-piperidin-1-ilmetil]-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico

2iz ((S)-1-fenil-propil)-amida del ácido 3-[4-(acetil-metil-amino)-4-fenil-piperidin-1-ilmetil]-2-(3-fluoro-fenil)-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico

2ja ((S)-1-fenil-propil)-amida del ácido 2-(3-cloro-fenil)-1-oxo-3-(4-fenetil-piperazin-1-ilmetil)-1,2-dihidro-isoquinolin-4-carboxílico

2jb ((S)-1-fenil-propil)-amida del ácido 2-(3-cloro-fenil)-3-(4-isopropil-piperazin-1-ilmetil)-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico

2jc ((S)-1-fenil-propil)-amida del ácido 3-[1,4']bipiperidinil-1'-ilmetil-2-(3-cloro-fenil)-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico

2jd 2((S)-1-fenil-propil)-amida del ácido -(3-cloro-fenil)-3-[4-(2-morfolin-4-il-etil)-piperazin-1-ilmetil]-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico

2je ((S)-1-fenil-propil)-amida del ácido 2-(3-cloro-fenil)-3-[4-(1-metil-piperidin-4-il)-piperazin-1-ilmetil]-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico

2jf ((S)-1-fenil-propil)-amida del ácido 2-(3-cloro-fenil)-1-oxo-3-[4-(2-piperidin-1-il-etil)-piperazin-1-ilmetil]-1,2-dihidro-isoquinolin-4-carboxílico

2jg ((S)-1-fenil-propil)-amida del ácido 2-(3-cloro-fenil)-1-oxo-3-[4-(2-pirrolidin-1-il-etil)-piperazin-1-ilmetil]-1,2-dihidro-isoquinolin-4-carboxílico

2jh ((S)-1-fenil-propil)-amida del ácido 2-(3-cloro-fenil)-1-oxo-3-(4-piridin-4-ilmetil-piperazin-1-ilmetil)-1,2-dihidro-isoquinolin-4-carboxílico

2ji ((S)-1-fenil-propil)-amida del ácido 2-(3-cloro-fenil)-3-[4-(2-morfolin-4-il-etil)-piperidin-1-ilmetil]-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico

2jj ((S)-1-fenil-propil)-amida del ácido 2-(3-cloro-fenil)-3-[4-hidroxi-4-(3-metoxi-fenil)-piperidin-1-ilmetil]-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico

2jk ((S)-1-fenil-propil)-amida del ácido 3-[4-(acetil-metil-amino)-4-fenil-piperidin-1-ilmetil]-2-(3-cloro-fenil)-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico

2jl ((S)-1-fenil-propil)-amida del ácido 1-oxo-3-(4-fenetil-piperazin-1-ilmetil)-2-m-tolil-1,2-dihidro-isoquinolin-4-carboxílico

2jm ((S)-1-fenil-propil)-amida del ácido 3-[1,4']bipiperidinil-1'-ilmetil-1-oxo-2-m-tolil-1,2-dihidro-isoquinolin-4-carboxílico

2jn ((S)-1-fenil-propil)-amida del ácido 3-[4-(2-morfolin-4-il-etil)-piperazin-1-ilmetil]-1-oxo-2-m-tolil-1,2-dihidro-isoquinolin-4-carboxílico

2jo ((S)-1-fenil-propil)-amida del ácido 3-[4-(1-metil-piperidin-4-il)-piperazin-1-ilmetil]-1-oxo-2-m-tolil-1,2-dihidro-isoquinolin-4-carboxílico

2jp ((S)-1-fenil-propil)-amida del ácido 1-oxo-3-[4-(2-piperidin-1-il-etil)-piperazin-1-ilmetil]-2-m-tolil-1,2-dihidro-isoquinolin-4-carboxílico

2jq ((S)-1-fenil-propil)-amida del ácido 1-oxo-3-[4-(2-pirrolidin-1-il-etil)-piperazin-1-ilmetil]-2-m-tolil-1,2-dihidro-isoquinolin-4-carboxílico

2jr ((S)-1-fenil-propil)-amida del ácido 1-oxo-3-(4-piridin-4-ilmetil-piperazin-1-ilmetil)-2-m-tolil-1,2-dihidro-isoquinolin-4-carboxílico

2js ((S)-1-fenil-propil)-amida del ácido 3-[4-(2-morfolin-4-il-etil)-piperidin-1-ilmetil]-1-oxo-2-m-tolil-1,2-dihidro-isoquinolin-4-carboxílico

2jt ((S)-1-fenil-propil)-amida del ácido 3-[4-hidroxi-4-(3-metoxi-fenil)-piperidin-1-ilmetil]-1-oxo-2-m-tolil-1,2-dihidro-isoquinolin-4-carboxílico

2ju ((S)-1-fenil-propil)-amida del ácido 3-[4-(acetil-metil-amino)-4-fenil-piperidin-1-ilmetil]-1-oxo-2-m-tolil-1,2-dihidro-isoquinolin-4-carboxílico

3a ((S)-1-fenil-propil)-amida del ácido 1-oxo-3-(2-oxo-pirrolidin-1-ilmetil)-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

3b ((S)-1-fenil-propil)-amida del ácido 8-cloro-1-oxo-3-(2-oxo-pirrolidin-1-ilmetil)-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

4a ((S)-1-fenil-propil)-amida del ácido 3-cianometil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

5a N,N-difenil-hidrazida del ácido 3-metil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

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5b Metil éster del ácido N'-(3-metil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carbonil)-N-fenil-hidrazincarboxílico

1aa ((S)-1-fenil-propil)-amida del ácido 2-(3-metoxi-fenil)-3-metil-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico

1ab ((S)-1-fenil-propil)-amida del ácido 2-(4-metoxi-fenil)-3-metil-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico

1ac ((S)-1-fenil-propil)-amida del ácido 2-(4-fluoro-fenil)-3-metil-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico

1ad ((S)-1-fenil-propil)-amida del ácido 2-(4-cloro-fenil)-3-metil-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico

1ae ((S)-1-fenil-propil)-amida del ácido 3-metil-1-oxo-2-p-tolil-1,2-dihidro-isoquinolin-4-carboxílico

1af [(S)-ciclopropil-(3-fluoro-fenil)-metil]-amida del ácido 2-(3-metoxi-fenil)-3-metil-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico

1ag [(S)-ciclopropil-(3-fluoro-fenil)-metil]-amida del ácido 2-(4-metoxi-fenil)-3-metil-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico

1ah [(S)-ciclopropil-(3-fluoro-fenil)-metil]-amida del ácido 2-(4-fluoro-fenil)-3-metil-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico

1ai [(S)-ciclopropil-(3-fluoro-fenil)-metil]-amida del ácido 2-(4-cloro-fenil)-3-metil-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico

1aj [(S)-ciclopropil-(3-fluoro-fenil)-metil]-amida del ácido 3-metil-1-oxo-2-p-tolil-1,2-dihidro-isoquinolin-4-carboxílico

1ak ((S)-1-fenil-propil)-amida del ácido 2-(2-metoxi-fenil)-3-metil-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico

1al [(S)-ciclopropil-(3-fluoro-fenil)-metil]-amida del ácido 2-(2-metoxi-fenil)-3-metil-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico

1am ((S)-1-fenil-propil)-amida del ácido 3-metil-8-nitro-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

1an [(S)-ciclopropil-(3-fluoro-fenil)-metil]-amida del ácido 3-metil-8-nitro-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

1ao ((S)-1-fenil-propil)-amida del ácido 8-metoxi-3-metil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

1ap [(S)-ciclopropil-(3-fluoro-fenil)-metil]-amida del ácido 8-metoxi-3-metil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

1aq ((S)-1-fenil-propil)-amida del ácido 8-amino-3-metil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

1ar ((S)-1-fenil-propil)-amida del ácido 8-ciano-3-metil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

1as [(S)-1-(4-cloro-fenil)-propil]-amida del ácido 8-cloro-3-metil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

1at [(S)-1-(4-fluoro-fenil)-propil]-amida del ácido 8-cloro-3-metil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

1au [(S)-1-(2-fluoro-fenil)-propil]-amida del ácido 8-cloro-3-metil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

1av [(S)-1-(3-cloro-fenil)-propil]-amida del ácido 8-cloro-3-metil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

1aw [(S)-(3-cloro-fenil)-ciclopropil-metil]-amida del ácido 8-cloro-3-metil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

1ax [(S)-(4-cloro-fenil)-ciclopropil-metil]-amida del ácido 8-cloro-3-metil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

1ay [(S)-1-(3-fluoro-fenil)-propil]-amida del ácido 8-cloro-3-metil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

1az ((S)-2-metil-1-fenil-propil)-amida del ácido 8-cloro-3-metil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

1ba [(S)-ciclopropil-(4-fluoro-fenil)-metil]-amida del ácido 8-cloro-3-metil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

1bb [(S)-1-(2-cloro-fenil)-propil]-amida del ácido 8-cloro-3-metil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

1bc ((S)-ciclopentil-fenil-metil)-amida del ácido 8-cloro-3-metil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

1bd [(S)-(2-cloro-fenil)-ciclopropil-metil]-amida del ácido 8-cloro-3-metil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

1be [(S)-ciclopropil-(2-fluoro-fenil)-metil]-amida del ácido 8-cloro-3-metil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

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1bf ((S)-ciclohexil-fenil-metil)-amida del ácido 8-cloro-3-metil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

1bg ((S)-ciclopropil-fenil-metil)-amida del ácido 8-cloro-3-metil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

1bh [(S)-ciclobutil-(3-fluoro-fenil)-metil]-amida del ácido 8-cloro-3-metil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

1bi [(S)-ciclobutil-(4-fluoro-fenil)-metil]-amida del ácido 8-cloro-3-metil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

1bl [(R)-ciclopropil-(3-fluoro-fenil)-metil]-amida del ácido 8-cloro-3-metil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

1bn ((S)ciclobutil-fenil-metil)-amida del ácido 8-cloro-3-metil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

1bo [Ciclobutil-(2-fluoro-fenil)-metil]-amida del ácido 8-cloro-3-metil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2ka [(S)-ciclopropil-(3-fluoro-fenil)-metil]-amida del ácido 3-(4-ter-butil-piperazin-1-ilmetil)-8-cloro-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2kb ((S)-1-fenil-propil)-amida del ácido 8-cloro-3-(4-isopropil-piperazin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2kc ((S)-1-fenil-propil)-amida del ácido 8-cloro-3-(4-isobutil-piperazin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2kd ((S)-1-fenil-propil)-amida del ácido 8-cloro-3-(octahidro-pirido[1,2-a]pirazin-2-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2ke ((S)-1-fenil-propil)-amida del ácido 8-cloro-3-(4-hidroxi-3,4,5,6-tetrahidro-2H-[4,4']bipiridinil-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2kf ((S)-1-fenil-propil)-amida del ácido 8-cloro-3-(4-ciclopropilmetil-piperazin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2kg ((S)-1-fenil-propil)-amida del ácido 8-cloro-3-[4-(2-morfolin-4-il-etil)-piperidin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2kh ((S)-1-fenil-propil)-amida del ácido 8-cloro-3-[1,4]diazepan-1-ilmetil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2ki ((S)-1-fenil-propil)-amida del ácido 8-cloro-3-((S)-3-metil-piperazin-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

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2kj ((S)-1-fenil-propil)-amida del ácido 8-cloro-3-imidazol-1-ilmetil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2kk ((S)-1-fenil-propil)-amida del ácido 8-cloro-3-(4-metil-imidazol-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2kl ((S)-1-fenil-propil)-amida del ácido 3-(ter-butilamino-metil)-8-cloro-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2km ((S)-1-fenil-propil)-amida del ácido 8-cloro-3-(isopropilamino-metil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2kn((S)-1-fenil-propil)-amida del ácido 8-cloro-3-[4-hidroxi-4-(3-metoxi-fenil)-piperidin-1-ilmetil]-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2ko ((S)-1-fenil-propil)-amida del ácido 3-(4-ter-butil-piperazin-1-ilmetil)-8-cloro-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2kp ((S)-1-fenil-propil)-amida del ácido 3-benzoimidazol-1-ilmetil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2kq ((S)-1-fenil-propil)-amida del ácido 1-oxo-2-fenil-3-pirazol-1-ilmetil-1,2-dihidro-isoquinolin-4-carboxílico

2kr ((S)-1-fenil-propil)-amida del ácido 3-(4-metil-pirazol-1-ilmetil)-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2ks ((S)-1-fenil-propil)-amida del ácido 1-oxo-2-fenil-3-[1,2,3]triazol-1-ilmetil-1,2-dihidro-isoquinolin-4-carboxílico

2kt ((S)-1-fenil-propil)-amida del ácido 2-(3-metoxi-fenil)-1-oxo-3-(4-piridin-4-ilmetil-piperazin-1-ilmetil)-1,2-dihidro-isoquinolin-4-carboxílico

2ku ((S)-1-fenil-propil)-amida del ácido 2-(4-metoxi-fenil)-3-[4-(2-morfolin-4-il-etil)-piperazin-1-ilmetil]-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico

2kv ((S)-1-fenil-propil)-amida del ácido 2-(4-fluoro-fenil)-1-oxo-3-(4-fenetil-piperazin-1-ilmetil)-1,2-dihidro-isoquinolin-4-carboxílico

2kw ((S)-1-fenil-propil)-amida del ácido 2-(4-fluoro-fenil)-3-(4-isopropil-piperazin-1-ilmetil)-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico

2kx ((S)-1-fenil-propil)-amida del ácido 3-[1,4']bipiperidinil-1'-ilmetil-2-(4-fluoro-fenil)-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico

2ky ((S)-1-fenil-propil)-amida del ácido 2-(4-fluoro-fenil)-3-[4-(2-morfolin-4-il-etil)-piperazin-1-ilmetil]-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico

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2kz ((S)-1-fenil-propil)-amida del ácido 2-(4-fluoro-fenil)-3-[4-(1-metil-piperidin-4-il)-piperazin-1-ilmetil]-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico

2la ((S)-1-fenil-propil)-amida del ácido 2-(4-fluoro-fenil)-1-oxo-3-[4-(2-pirrolidin-1-il-etil)-piperazin-1-ilmetil]-1,2-dihidro-isoquinolin-4-carboxílico

2lb ((S)-1-fenil-propil)-amida del ácido 2-(4-fluoro-fenil)-3-[4-hidroxi-4-(3-metoxi-fenil)-piperidin-1-ilmetil]-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico

2lc ((S)-1-fenil-propil)-amida del ácido 2-(4-cloro-fenil)-1-oxo-3-(4-fenetil-piperazin-1-ilmetil)-1,2-dihidro-isoquinolin-4-carboxílico

2ld ((S)-1-fenil-propil)-amida del ácido 2-(4-cloro-fenil)-3-(4-isopropil-piperazin-1-ilmetil)-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico

2le ((S)-1-fenil-propil)-amida del ácido 3-[1,4']bipiperidinil-1'-ilmetil-2-(4-cloro-fenil)-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico

2lf ((S)-1-fenil-propil)-amida del ácido 2-(4-cloro-fenil)-3-[4-(2-morfolin-4-il-etil)-piperazin-1-ilmetil]-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico

2lg ((S)-1-fenil-propil)-amida del ácido 2-(4-cloro-fenil)-3-[4-(1-metil-piperidin-4-il)-piperazin-1-ilmetil]-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico

2lh ((S)-1-fenil-propil)-amida del ácido 2-(4-cloro-fenil)-1-oxo-3-[4-(2-piperidin-1-il-etil)-piperazin-1-ilmetil]-1,2-dihidro-isoquinolin-4-carboxílico

2li ((S)-1-fenil-propil)-amida del ácido 2-(4-cloro-fenil)-1-oxo-3-[4-(2-pirrolidin-1-il-etil)-piperazin-1-ilmetil]-1,2-dihidro-isoquinolin-4-carboxílico

2lj ((S)-1-fenil-propil)-amida del ácido 3-(4-ter-butil-piperazin-1-ilmetil)-8-fluoro-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2lk ((S)-1-fenil-propil)-amida del ácido 8-cloro-3-ciclopropilaminometil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2ll [(S)-ciclopropil-(3-fluoro-fenil)-metil]-amida del ácido 3-(4-ter-butil-piperazin-1-ilmetil)-8-fluoro-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2lm [(S)-ciclopropil-(3-fluoro-fenil)-metil]-amida del ácido 8-fluoro-1-oxo-2-fenil-3-piperazin-1-ilmetil-1,2-dihidro-isoquinolin-4-carboxílico

2ln [(S)-ciclopropil-(3-fluoro-fenil)-metil]-amida del ácido 8-fluoro-1-oxo-3-(3-oxo-pirazolidin-1-ilmetil)-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

2lo [(S)-ciclopropil-(3-fluoro-fenil)-metil]-amida del ácido 8-fluoro-1-oxo-3-(3-oxo-piperazin-1-ilmetil)-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

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3c ((S)-1-fenil-propil)-amida del ácido 1-oxo-2-fenil-3-(1H-[1,2,4]triazol-3-ilsulfanilmetil)-1,2-dihidro-isoquinolin-4-carboxílico

3d [(S)-ciclopropil-(3-fluoro-fenil)-metil]-amida del ácido 8-cloro-1-oxo-3-(2-oxo-pirrolidin-1-ilmetil)-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

3e ((S)-1-fenil-propil)-amida del ácido 8-fluoro-1-oxo-3-(2-oxo-pirrolidin-1-ilmetil)-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

3f [(S)-ciclopropil-(3-fluoro-fenil)-metil]-amida del ácido 8-fluoro-1-oxo-3-(2-oxo-pirrolidin-1-ilmetil)-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

3g [(S)-ciclopropil-(3-fluoro-fenil)-metil]-amida del ácido 8-fluoro-1-oxo-3-(5-oxo-pirazolidin-1-ilmetil)-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

3h [(S)-ciclopropil-(3-fluoro-fenil)-metil]-amida del ácido 8-fluoro-1-oxo-3-(2-oxo-piperazin-1-ilmetil)-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

3i [(S)-ciclopropil-(3-fluoro-fenil)-metil]-amida del ácido 8-fluoro-1-oxo-3-(2-oxo-piperidin-1-ilmetil)-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

4b [(S)-ciclopropil-(3-fluoro-fenil)-metil]-amida del ácido 8-cloro-3-cianometil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

6a ((S)-1-fenil-propil)-amida del ácido 2-(3,4-dicloro-fenil)-3-metil-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico

6b ((S)-ciclopropil-fenil-metil)-amida del ácido 8-fluoro-1-oxo-3-(2-oxo-pirrolidin-1-ilmetil)-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

6c ((S)-ciclopropil-fenil-metil)-amida del ácido 8-fluoro-3-metil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

7a ((S)-1-fenil-propil)-amida del ácido 3-etil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

7b ((S)-1-fenil-propil)-amida del ácido 8-fluoro-3-metil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

7c ((S)-1-fenil-propil)-amida del ácido 8-fluoro-2-(3-fluoro-fenil)-3-metil-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico

7d ((S)-1-fenil-propil)-amida del ácido 8-fluoro-2-(4-fluoro-fenil)-3-metil-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico

7e [(S)-ciclopropil-(3-fluoro-fenil)-metil]-amida del ácido 8-fluoro-3-metil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

7f [(S)-ciclopropil-(3-fluoro-fenil)-metil]-amida del ácido 8-fluoro-2-(3-fluoro-fenil)-1-oxo-3-(2-oxo-pirrolidin-1-ilmetil)-1,2-dihidro-isoquinolin-4-carboxílico

7g [(S)-ciclopropil-(3-fluoro-fenil)-metil]-amida del ácido 8-fluoro-2-(4-fluoro-fenil)-1-oxo-3-(2-oxo-pirrolidin-1-ilmetil)-1,2-dihidro-isoquinolin-4-carboxílico

7h [(S)-ciclobutil-(3-fluoro-fenil)-metil]-amida del ácido 8-fluoro-3-metil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

7i [(S)-ciclopropil-(3-fluoro-fenil)-metil]-amida del ácido 8-fluoro-2-(2-fluoro-fenil)-3-metil-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico

7j [(S)-ciclopropil-(3-fluoro-fenil)-metil]-amida del ácido 8-fluoro-2-(3-fluoro-fenil)-3-metil-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico

7k [(S)-ciclopropil-(3-fluoro-fenil)-metil]-amida del ácido 8-fluoro-2-(4-fluoro-fenil)-3-metil-1-oxo-1,2-dihidro-isoquinolin-4-carboxílico

7l [(S)-ciclopropil-(3-fluoro-fenil)-metil]-amida del ácido 6,8-difluoro-3-metil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

7m [(S)-ciclopropil-(3-fluoro-fenil)-metil]-amida del ácido 5,8-difluoro-3-metil-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico

7n ((S)-1-fenil-propil)-amida del ácido 3-metil-1-oxo-2-fenil-8-trifluorometil-1,2-dihidro-isoquinolin-4-carboxílico

8a [(S)-ciclopropil-(3-fluoro-fenil)-metil]-amida del ácido 3-(1-ter-butil-piperidin-4-ilmetil)-8-cloro-1-oxo-2-fenil-1,2-dihidro-isoquinolin-4-carboxílico;

y las sales aceptables para uso farmacéutico de cualquiera de estos compuestos.

86. Un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 85 para uso en terapia.

87. Un método para el tratamiento de una enfermedad seleccionada entre psicosis; esquizofrenia; trastorno esquizoide; trastorno afectivo esquizoide; trastorno delirante; trastorno sicótico breve; trastorno sicótico compartido; trastorno sicótico debido a una condición médica general; trastorno sicótico inducido por sustancia o fármaco (cocaína, alcohol, anfetamina etc.); trastorno esquizoide de la personalidad; trastorno tipo esquizoide de la personalidad; sicosis o esquizofrenia asociada con depresión mayor, trastorno bipolar, enfermedad de Alzheimer o enfermedad de Parkinson; depresión mayor; trastorno de ansiedad general; trastorno bipolar (tratamiento de mantenimiento,

prevención de recurrencia y estabilización); manía; hipomanía; deterioro cognitivo; ADHD; obesidad; reducción del apetito; enfermedad de Alzheimer; enfermedad de Parkinson; dolor; convulsiones; tos; asma; hipersensibilidad de las vías respiratorias; hipersensibilidad microvascular; broncoconstricción; enfermedad pulmonar obstructiva crónica; incontinencia urinaria; inflamación intestinal; y enfermedad del colon irritable, dicho método comprende la administración de una cantidad terapéuticamente efectiva de un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 85 a un paciente que necesita del mismo.

88. El método de acuerdo con la reivindicación 87, en donde dicha enfermedad es esquizofrenia

89. El método de acuerdo con la reivindicación 88, en donde dicho tratamiento comprende el tratamiento de síntomas positivos, negativos y/o cognitivos de esquizofrenia.

90. El método de acuerdo con la reivindicación 88 u 89 el cual además comprende la administración concomitante o secuencial de una cantidad terapéuticamente efectiva de un compuesto seleccionado de la lista integrada por antagonistas D2, agonistas parciales D2, antagonistas PDE10, antagonistas 5-HT_{2A}, antagonistas 5-HT_6 y antagonistas KCNQ4.

91. Un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 85 para uso en el tratamiento de una enfermedad seleccionada entre sicosis; esquizofrenia; trastorno esquizoide; trastorno afectivo esquizoide; trastorno delirante; trastorno sicótico breve; trastorno sicótico compartido; trastorno sicótico debido a una condición médica general; trastorno sicótico inducido por sustancia o fármaco (cocaína, alcohol, anfetamina etc.); trastorno esquizoide de la personalidad; trastorno tipo esquizoide de la personalidad; sicosis o esquizofrenia asociada con depresión mayor, trastorno bipolar, enfermedad de Alzheimer o enfermedad de Parkinson; depresión mayor; trastorno de ansiedad general; trastorno bipolar (tratamiento de mantenimiento, prevención de recurrencia y estabilización); manía; hipomanía; deterioro cognitivo; ADHD; obesidad; reducción del apetito; enfermedad de Alzheimer; enfermedad de Parkinson; dolor; convulsiones; tos; asma; hipersensibilidad de las vías respiratorias; hipersensibilidad microvascular; broncoconstricción; enfermedad pulmonar obstructiva crónica; incontinencia urinaria; inflamación intestinal; y enfermedad del colon irritable.

92. El compuesto de acuerdo con la reivindicación 91, en donde dicha enfermedad es esquizofrenia.

93. El compuesto de acuerdo con la reivindicación 92, en donde dicha enfermedad consiste en los síntomas negativos, positivos y/o cognitivos de esquizofrenia.

94. El uso de un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 85 para la producción de un medicamento para el tratamiento de una enfermedad seleccionada entre sicosis; esquizofrenia; trastorno esquizoide; trastorno afectivo esquizoide; trastorno delirante; trastorno sicótico breve; trastorno sicótico compartido; trastorno sicótico debido a una condición médica general; trastorno sicótico inducido por sustancia o fármaco (cocaína, alcohol, anfetamina etc.); trastorno esquizoide de la personalidad; trastorno tipo esquizoide de la personalidad; sicosis o esquizofrenia asociada con depresión mayor, trastorno bipolar, enfermedad de Alzheimer o enfermedad de Parkinson; depresión mayor; trastorno de ansiedad general; trastorno bipolar (tratamiento de mantenimiento, prevención de recurrencia y estabilización); manía; hipomanía; deterioro cognitivo; ADHD; obesidad; reducción del apetito; enfermedad de Alzheimer; enfermedad de Parkinson; dolor; convulsiones; tos; asma; hipersensibilidad de las vías respiratorias; hipersensibilidad microvascular; broncoconstricción; enfermedad pulmonar obstructiva crónica; incontinencia urinaria; inflamación intestinal; y enfermedad del colon irritable.

95. El uso de acuerdo con la reivindicación 93, en donde dicha enfermedad es esquizofrenia.

96. El uso de acuerdo con la reivindicación 95, en donde dicha enfermedad consiste en los síntomas positivos, negativos y/o cognitivos de esquizofrenia.

97. El uso de acuerdo con la reivindicación 95 o 96 en donde dicha producción además comprende el uso de un compuesto seleccionado de la lista integrada por antagonistas D2, agonistas parciales D2, antagonistas PDE10, antagonistas 5-HT_{2A}, antagonistas 5-HT_6 y antagonistas KCNQ4.

98. Una composición farmacéutica que comprende un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 85 y uno o más vehículos o excipientes aceptables para uso farmacéutico.

99. Una composición de acuerdo con la reivindicación 98, dicha composición además comprende un compuesto seleccionado de la lista integrada por antagonistas D2,

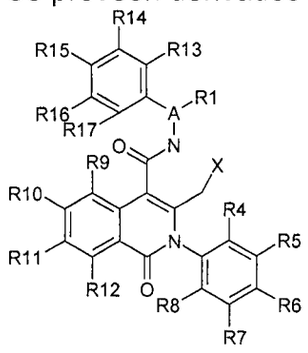
agonistas parciales D2, antagonistas PDE10, antagonistas 5-HT_{2A}, antagonistas 5-HT_6 y antagonistas KCNQ4.

100. Un kit que comprende un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 85 junto con un compuesto seleccionado de la lista integrada por antagonistas D2, agonistas parciales D2, antagonistas PDE10, antagonistas 5-HT_{2A}, antagonistas 5-HT_6 y antagonistas KCNQ4.

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RESUMEN

Se proveen derivados de isoquinolona de la fórmula general



[I]

Los compuestos son antagonistas del NK3 y útiles para el tratamiento de, por ej. sicosis y esquizofrenia.

135

INTERNATIONAL SEARCH REPORT

International application No
PCT/DK2008/050092

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D217/26 C07D401/06 C07D403/06 A61K31/472 A61K31/4725
A61P25/18

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K A61P

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 95/32948 A (SMITHKLINE BEECHAM FARMA [IT]; FARINA CARLO [IT]; GIARDINA GIUSEPPE AR) 7 December 1995 (1995-12-07) cited in the application claims	1-100
A	WO 2005/014575 A (SMITHKLINE BEECHAM CORP [US]; CHAN WAI NGOR [GB]; SMITH PAUL WILLIAM [) 17 February 2005 (2005-02-17) cited in the application claims	1-100
A	ALBERT, JEFFREY S. ET AL: "Neurokinin -3 receptor antagonists in schizophrenia" EXPERT OPINION ON THERAPEUTIC PATENTS 16(7), 925-937 CODEN: EOTPEG; ISSN: 1354-3776, 2006, XP002489687 the whole document	1-100

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
24 July 2008	05/08/2008

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

Form PCT/ISA/210 (second sheet) (April 2005)

536

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK2008/050092

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

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

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 87-90 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

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

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

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

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

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers allsearchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search reportcovers only those claims for which fees were paid, specifically claims Nos.:

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

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

[ ] The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

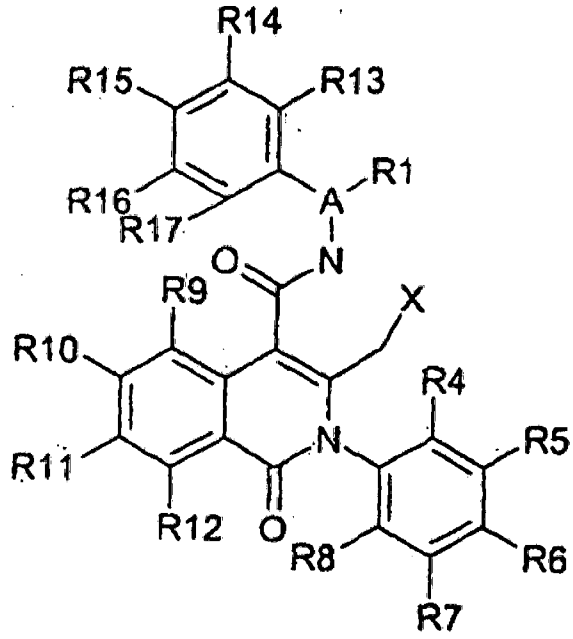
[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

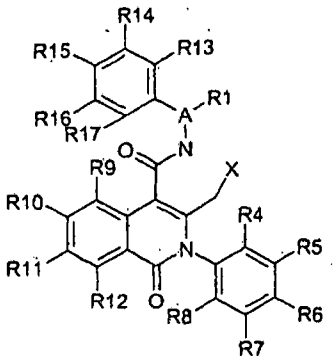
Information on patent family members

International application No
PCT/DK2008/050092

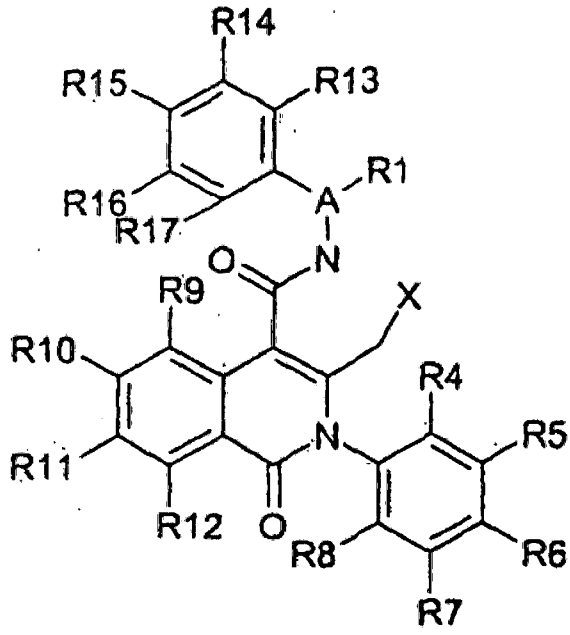
Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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R14
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[I]


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R12
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R8
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[I]

540

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 09-120188- -00000-0000

Fecha: 2009-10-26 16:57:44 Dep. 2020 NUECREACIONE
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 544

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

CERTIFICACION DE EXCEDENTE : 09 - 68,602
FECHA : SEPTIEMBRE 14 DE 2009

***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
CAVELIER ABOGADOS	CONSIGNACION	BANCO DE BOGOTA	062754387	17854546	14/09/2009	33,365,000.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-09 OTROS SERVICIOS DE PROPIEDAD I	99 OTROS SERVCIOS ADMINISTRATIVOS	1,000.00
		TOTAL : $	1,000.00

SON: MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

ESTA CERTIFICACION DE EXCEDENTE DE PAGO SOLO PODRA SER UTILIZADA COMO PARTE DE LA CANCELACION DE UNA TARIFA VIGENTE Y NO PODRA SER SUSTITUIDA POR NINGUN RECIBO.

C020:03003-841-094-7

341

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 09-120188- -00000-0000

Fecha: 2009-10-26 16:57:44 Dep. 2020 NUECREACIONE
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 544

NIT : 80017(

RECIBO OFICIAL DE CAJA : 09 - 75,150
FECHA : OCTUBRE 5 DE 2009

***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
CAVELIER ABOGADOS	CONSIGNACION	BANCO DE BOGOTA	062754387	130928173	05/10/2009	40,246,000.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	87 SOL RENOVACION REGISTRO CON RECAR	805,000.00
		TOTAL : $	805,000.00

SON: OCHOCIENTOS CINCO MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

Cole: 03003 - 841 - 0947.

542

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 09-120188- -00000-0000

Fecha: 2009-10-26 16:57:44 Dep. 2020 NUECREACIONE
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 544

RECIBO OFICIAL DE CAJA : 09 - 77,150
FECHA : OCTUBRE 13 DE 2009

***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
CAVELIER ABOGADOS	CONSIGNACION	BANCO DE BOGOTA	062754387	130928140	13/10/2009	15,516,000.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-08 PRORROGA DE TERMINOS	31 PRORROGA DE TERMINOS	81,000.00
		TOTAL : $	81,000.00

SON: OCHENTA Y UNO MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

Colo: 03003-841-0947.

543

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 09-120188- -00000-0000
Fecha: 2009-10-26 16:57:44 Dep. 2020 NUECREACIONE
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 544

RECIBO OFICIAL DE CAJA : 09 - 77,186
FECHA : OCTUBRE 13 DE 2009

***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
CAVELIER ABOGADOS	CONSIGNACION	BANCO DE BOGOTA	062754387	130928140	13/10/2009	15,516,000.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	3 PROC. REGISTRO DE MARCAS Y LEMAS	688,000.00
		TOTAL : $	688,000.00

SON: SEISCIENTOS OCHENTA Y OCHO MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

010-03003-841-094-7.

544

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 09-120188- -00000-0000

Fecha: 2009-10-26 16:57:44 Dep. 2020 NUECREACIONE
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 544

RECIBO OFICIAL DE CAJA : 09 - 78,692
FECHA : OCTUBRE 19 DE 2009

***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
CAVELIER ABOGADOS	CONSIGNACION	BANCO DE BOGOTA	062754387	130928162	19/10/2009	47,325,000.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-09 OTROS SERVICIOS DE PROPIEDAD I	*** TASA ANUAL C.RECARGO A#OS 17 a 30	1,090,000.00

****

TOTAL : $ 1,090,000.00

SON: UN MILLON NOVENTA MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

Cdo: 03003 - 841 - 0947 .

SAS

Industria y Comercio
SUPERINTENDENCIA

REQUISITOS MINIMOS PARA ADMISION A TRAMITE
PCT

PATENTE DE INVENCION [X] MODELO DE UTILIDAD [ ]

- Indicación de que se solicita la concesión de una patente [X]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [X]
- Descripción de la invención [X]
- Dibujos de ser estos pertinentes [ ]
- Comprobante de pago de las tasas establecidas [X]

COMPLETA [X] INCOMPLETA [ ]

DISEÑO INDUSTRIAL [ ]

- Indicación de que se solicita el registro de Diseño Industrial [ ]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- Representación gráfica y fotográfica del Diseño Industrial o muestra del material que incorpora el diseño [ ]
- Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

ESQUEMA DE TRAZADO [ ]

- Indicación de que se solicita el registro de un Esquema de Trazado [ ]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- Representación gráfica del esquema trazado [ ]
- Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

Firma Responsable

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Fech

No. 09-120188- -00000-0000

Fecha: 2009-10-26 16:57:44 Dep. 2020 NUECREACIONI
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 544

Carrera 13 No. 27-00 Piso 5, 7 y 10
Conmutador: 3 82 08 40
Fax: 350 52 20
E-mail: Info@sic.gov.co
www.sic.gov.co
Bogotá, D.C., Colombia

Industria y Comercio
SUPERINTENDENCIA

Bogotá,
2020

Doctor(a)
SUAREZ DE PAEZ LUZ CLEMENCIA

REFERENCIA	Radicación No.	9 120188
	Solicitud internacional	PCT/DK2008/050092
	Fecha inicio fase nacional	26/11/2009
	Trámite	11
	Evento	378
	Actuación	430
	Oficio No.	14355

Como resultado del examen de forma, realizado con fundamento en el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

1. La solicitud no contiene el poder debidamente otorgado, con el lleno de los requisitos exigidos por los artículos 63 y subsiguientes del Código de Procedimiento Civil. Adicionalmente, deberá presentar el documento que acredita la existencia y representación legal de la sociedad solicitante, cuando ésta fuere persona jurídica.

2. La solicitud no contiene la copia del documento en que consta la cesión del derecho a la patente del inventor al solicitante o a su causante, conforme a lo establecido por el artículo 26 literal k) de la Decisión 486 de la Comisión de la Comunidad Andina. Cuando se trate de documentos otorgados en el extranjero, estos deberán legalizarse de conformidad con lo dispuesto por los artículos 259 y 260 del Código de Procedimiento Civil. Cuando se trate de las declaraciones a que hace referencia la Regla 4.17 ii) del Tratado de Cooperación en Materia de Patentes PCT., el alcance de las tales declaraciones se determinará según indiquen claramente una cesión de derechos del inventor al solicitante o su causante, de conformidad con lo dispuesto en el numeral 5.2.15 del Capítulo Quinto, Título X de la Circular Única de Superintendencia de Industria y Comercio.

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Unica No.10 de 2001.

Continua en la página siguiente...

Industria y Comercio
SUPERINTENDENCIA

Radicación No.:9 120188

ALIX CARMENZA CESPEDES DE VERGEL
Directora de Nuevas Creaciones (c)

El anterior requerimiento fue notificado por fijación en lista de fecha 11 DIC. 2009
adpa11