

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
30 August 2007 (30.08.2007)

PCT

(10) International Publication Number
WO 2007/097697 A1

(51) International Patent Classification:

C07D 215/233 (2006.01) **A61P 25/24** (2006.01)
A61K 31/47 (2006.01) **A61P 25/28** (2006.01)
A61K 31/4709 (2006.01) **C07D 401/12** (2006.01)
A61P 25/22 (2006.01)

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(21) International Application Number:

PCT/SE2007/000164

(22) International Filing Date:

22 February 2007 (22.02.2007)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

60/775,967 23 February 2006 (23.02.2006) US

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(81) Designated States (unless otherwise indicated, for every kind of regional protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, 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.

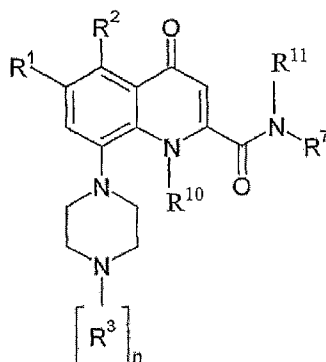
(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT,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

Published:

— with international search report

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

(54) Title: THERAPEUTIC QUINOLINE COMPOUNDS THAT ARE 5HT1B MODULATORS



(I)

(57) Abstract: The present invention provides compounds having formula (I): wherein the compounds are useful for the treatment of anxiety disorders, cognitive disorders, and/or mood disorders. The compounds are 5HT1B modulators.

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THERAPEUTIC QUINOLINE COMPOUNDS THAT ARE 5HT1B MODULATORS.**FIELD OF THE INVENTION**

The present invention is directed, in part, to novel quinolone compounds and
5 pharmaceutical compositions comprising the same, methods for their preparation, and
methods of using novel quinolone compounds in therapy.

BACKGROUND OF THE INVENTION

Serotonin (5-HT) has been implicated in many psychiatric disorders including but
10 not limited to depression, generalized anxiety, eating disorders, dementia, panic disorder, and
sleep disorders. Serotonin has also been implicated in gastrointestinal disorders,
cardiovascular regulation, motor disorders, endocrine disorders, vasospasm and sexual
dysfunction. Serotonin receptors have been subdivided into at least 14 subtypes, see Barnes
and Sharp, Neuropharmacology, 1999, 38, 1083-1152. These various subtypes are
15 responsible for serotonin's action in many pathophysiological conditions. The 5-HT1 family
of receptors has high affinity for serotonin and consists of five related receptors. This family
includes the 5-HT1B receptor subtypes. Compounds that interact with the 5-HT1 families are
known to have therapeutic potential in the above-mentioned disorders and diseases. In
particular, compounds that are 5HT1B antagonists have been known to be antidepressant and
20 anxiolytic agents.

Quinolone compounds and related compounds are reported in, for example,
Internationals Application Publications WO/2002/055012, WO/2002/055014,
WO/2003/037871, and WO/2003/037872.

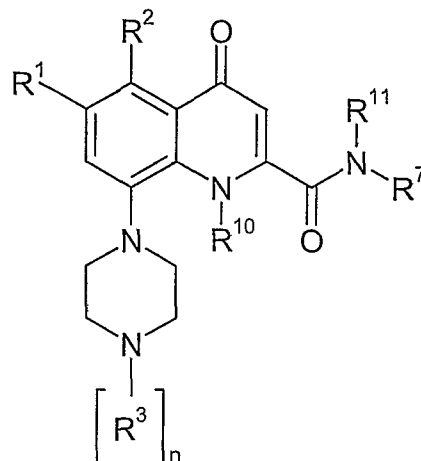
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SUMMARY OF THE INVENTION

The present invention provides compounds represented by formula (I):



I

5 wherein:

R^1 is hydrogen or halogen;

R^2 is selected from hydrogen, halogen, methyl, ethyl, propyl, isopropyl, $-OCH_3$, $-OCH_2CH_3$, $-O(CH_2)_2CH_3$, and $-OCH(CH_3)_2$;

provided that R^1 and R^2 are not both hydrogen, and when R^1 is halogen then R^2 is

10 hydrogen;

n is 1 or 2;

R^3 is methyl, provided that when n is 2 the nitrogen has a positive charge;

R^{10} is selected from hydrogen, methyl, ethyl, propyl, and isopropyl;

R^{11} is selected from hydrogen, methyl, ethyl, propyl, and isopropyl;

15 R^7 is selected from phenyl, pyridyl or indole and is substituted with one or two substituents selected from R^9 ;

R^9 is selected from $-OCH_3$, halogen, $-O(CH_2)_2OCH_3$, $-N(CH_2)_2OCH_3$, morpholino, pyran, piperidine- R^{12} , and piperazin- R^{12} , wherein R^{12} is selected from methyl, $-C(=O)N(CH_3)_2$, $-C(=O)OCH_3$, $-SO_2CH_3$, $-SO_2CH_2CH_3$, $-C(=O)CH_2CH_3$, and $-C(=O)CH_3$;

20

or a pharmaceutically acceptable salt.

In some embodiments, R^1 is halogen and R^2 is hydrogen; R^1 is fluorine and R^2 is hydrogen; R^2 is halogen and R^1 is hydrogen; or R^2 is fluorine and R^1 is hydrogen.

In some embodiments, R^2 is halogen, methyl, or $-OCH_3$.

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In some embodiments, n is 1; or n is 2.

In some embodiments, R¹⁰ is hydrogen or methyl.

In some embodiments, R¹¹ is hydrogen or methyl.

In some embodiments, R⁷ is phenyl or pyridyl.

- 5 In some embodiments, R⁹ is -OCH₃; -O(CH₂)₂OCH₃; -N(CH₂)₂OCH₃; morpholino; or piperazin-R¹². In some embodiments, R¹² is methyl; -C(=O)N(CH₃)₂; -C(=O)OCH₃; -SO₂CH₃; -SO₂CH₂CH₃; -C(=O)CH₂CH₃; or -C(=O)CH₃.

- In some embodiments, a compound is: 5-Methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-1,4-dihydro-quinoline-2-carboxylic acid (6-methoxy-pyridin-3-yl)-amide; 5-Methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-1,4-dihydro-quinoline-2-carboxylic acid [4-(4-dimethylcarbamoyl-piperazin-1-yl)-phenyl]-amide; 4-(5-[[5-Methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-1,4-dihydro-quinoline-2-carbonyl]-amino]-pyridin-2-yl)-piperazine-1-carboxylic acid methyl ester; 4-(4-[[5-Methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-1,4-dihydro-quinoline-2-carbonyl]amino]-phenyl)-piperazine-1-carboxylic acid methyl ester; 5-Methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-1,4-dihydro-quinoline-2-carboxylic acid [6-(2-methoxy-ethoxy)-pyridin-3-yl]-amide; 5-Methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-1,4-dihydro-quinoline-2-carboxylic acid [4-(4-methanesulfonyl-piperazin-1-yl)-phenyl]-amide; 5-Methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-1,4-dihydro-quinoline-2-carboxylic acid [4-(4-ethanesulfonyl-piperazin-1-yl)-phenyl]-amide; 5-Methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-1,4-dihydro-quinoline-2-carboxylic acid [6-(2-methoxy-ethylamino)-pyridin-3-yl]-amide; 5-Methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-1,4-dihydro-quinoline-2-carboxylic acid [6-(4-propionyl-piperazin-1-yl)-pyridin-3-yl]-amide; 5-Methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-1,4-dihydro-quinoline-2-carboxylic acid [6-(4-acetyl-piperazin-1-yl)-pyridin-3-yl]-amide; 5-Methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-1,4-dihydro-quinoline-2-carboxylic acid [4-(4-acetyl-piperazin-1-yl)-phenyl]-amide; 5-Methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-1,4-dihydro-quinoline-2-carboxylic acid [4-(4-propionyl-piperazin-1-yl)-phenyl]-amide; 5-Methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-1,4-dihydro-quinoline-2-carboxylic acid (6-morpholin-4-yl-pyridin-3-yl)-amide; 1,1-Dimethyl-4-[5-methyl-2-(4-morpholin-4-yl-phenylcarbamoyl)-4-oxo-1,4-dihydro-quinolin-8-yl]-piperazin-1-ium; 5-Fluoro-1-methyl-8-(4-methyl-piperazin-1-yl)-4-oxo-1,4-dihydro-quinoline-2-carboxylic acid methyl-(4-morpholin-4-yl-phenyl)-amide; 4-Hydroxy-5-methyl-8-(4-methyl-piperazin-1-yl)-quinoline-

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2-carboxylic acid (4-methoxy-phenyl)-amide; 4-Hydroxy-5-methoxy-8-(4-methyl-piperazin-1-yl)-quinoline-2-carboxylic acid (4-morpholin-4-yl-phenyl)-amide; 5-Fluoro-8-(4-methyl-piperazin-1-yl)-4-oxo-1,4-dihydro-quinoline-2-carboxylic acid (4-methoxy-phenyl)-amide; 5-Fluoro-8-(4-methyl-piperazin-1-yl)-4-oxo-1,4-dihydro-quinoline-2-carboxylic acid (6-methoxy-pyridin-3-yl)-amide; 5-Fluoro-8-(4-methyl-piperazin-1-yl)-4-oxo-1,4-dihydro-quinoline-2-carboxylic acid (4-morpholin-4-yl-phenyl)-amide; 4-Hydroxy-5-methyl-8-(4-methyl-piperazin-1-yl)-quinoline-2-carboxylic acid (6-methoxy-pyridin-3-yl)-amide; 4-Hydroxy-5-methyl-8-(4-methyl-piperazin-1-yl)-quinoline-2-carboxylic acid [4-(4-methyl-piperazin-1-yl)-phenyl]-amide; 4-Hydroxy-5-methyl-8-(4-methyl-piperazin-1-yl)-quinoline-2-carboxylic acid (4-morpholin-4-yl-phenyl)-amide; 6-Fluoro-8-(4-methyl-piperazin-1-yl)-4-oxo-1,4-dihydro-quinoline-2-carboxylic acid [4-(4-methyl-piperazin-1-yl)-phenyl]-amide; 6-Fluoro-8-(4-methyl-piperazin-1-yl)-4-oxo-1,4-dihydro-quinoline-2-carboxylic acid (6-methoxy-pyridin-3-yl)-amide; or 6-Fluoro-8-(4-methyl-piperazin-1-yl)-4-oxo-1,4-dihydro-quinoline-2-carboxylic acid (4-methoxy-phenyl)-amide.

15 In some embodiments, a composition comprising any of the compounds described herein and a pharmaceutically acceptable diluent or carrier is provided.

In some embodiments, use of any of the compounds described herein in the treatment of an anxiety disorder, cognitive disorder, or mood disorder is provided. In some embodiments, the anxiety disorder is selected from panic disorder, panic disorder without agoraphobia, panic disorder with agoraphobia, agoraphobia without history of panic disorder, specific phobia, social phobia, social anxiety disorder, obsessive-compulsive disorder, posttraumatic stress disorder, acute stress disorder, generalized anxiety disorder, and generalized anxiety disorder due to a general medical condition. In some embodiments, the cognitive disorder is selected from Alzheimer's disease, dementia, and dementia due to Alzheimer's disease, and dementia due to Parkinson's disease. In some embodiments, the mood disorder is a depressive disorder, such as, for example, major depressive disorder, dysthymic disorder, bipolar depression and/or bipolar mania, cyclothymic disorder, mood disorder due to a general medical condition, manic episode associated with bipolar disorder, and mixed episode associated with bipolar disorder. In some embodiments, the bipolar depression and/or bipolar mania is bipolar II, or bipolar I with or without manic, depressive or mixed episodes.

In some embodiments, methods of treating an animal suffering from an anxiety disorder, cognitive disorder, or mood disorder comprising administering to such animal an effective amount of any compound described herein or a pharmaceutically acceptable salt of the compound are provided.

- 5 In some embodiments, use of any one of the compounds described herein in the preparation of a medicament for the treatment of an anxiety disorder, a cognitive disorder, or a mood disorder is provided herein.

DESCRIPTION OF EMBODIMENTS

- As used herein, the term "halogen" refers to fluorine, chlorine, bromine and iodine
10 radicals.

As used herein, the term "animal" refers to any animal including but not limited to humans.

- As used herein, "anxiety disorder" includes, but is not limited to, panic disorder, panic disorder without agoraphobia, panic disorder with agoraphobia, agoraphobia without
15 history of panic disorder, specific phobia, social phobia, social anxiety disorder, obsessive-compulsive disorder, post-traumatic stress disorder, acute stress disorder, generalized anxiety disorder, and generalized anxiety disorder due to a general medical condition.

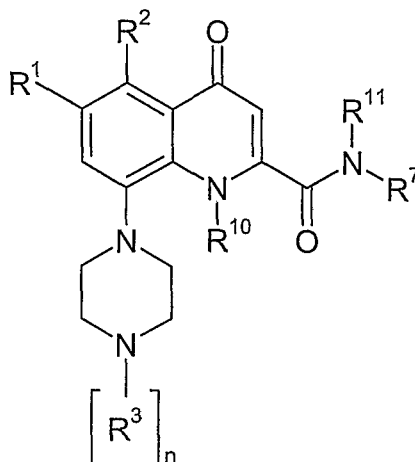
- As used herein, "cognitive disorder" includes, but is not limited to, Alzheimer's disease, dementia, and dementia due to Alzheimer's disease, and dementia due to Parkinson's
20 disease.

- As used herein, "mood disorder" includes depressive disorders such as, for example, major depressive disorder, dysthymic disorder, bipolar depression and/or bipolar mania, cyclothymic disorder, mood disorder due to a general medical condition, manic episode associated with bipolar disorder, and mixed episode associated with bipolar disorder.
25 Examples of bipolar depression and/or bipolar mania include, but are not limited to, bipolar II, or bipolar I with or without manic, depressive or mixed episodes.

- As used herein, the phrase "or any subset thereof" means any subset of the group described. For example, the phrase "X is selected from A, B, C, and D, or any subset thereof", X includes the following groups: 1) A, B, C, and D; 2) A, B, and C; 3) A, B, and D;
30 4) B, C, and D; 5) A and B; 6) A and C; 7) A and D; 8) B and C; 9) B and D; 10) C and D; 11) A; 12) B; 13) C; and 14) D.

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The present invention provides compounds represented by formula (I):



wherein:

R¹ is hydrogen or halogen;

5 R² is selected from hydrogen, halogen, methyl, ethyl, propyl, isopropyl, -OCH₃, -OCH₂CH₃, -O(CH₂)₂CH₃, and -OCH(CH₃)₂, or any subgroup thereof;

provided that R¹ and R² are not both hydrogen, and when R¹ is halogen then R² is hydrogen;

n is 1 or 2;

10 R³ is methyl, provided that when n is 2 the nitrogen has a positive charge;

R¹⁰ is selected from hydrogen, methyl, ethyl, propyl, and isopropyl, or any subgroup thereof;

R¹¹ is selected from hydrogen, methyl, ethyl, propyl, and isopropyl, or any subgroup thereof;

15 R⁷ is selected from phenyl, pyridyl or indole and is substituted with one or two substituents selected from R⁹;

R⁹ is selected from -OCH₃, halogen, -O(CH₂)₂OCH₃, -N(CH₂)₂OCH₃, morpholino, pyran, piperidine-R¹², and piperazin-R¹², or any subgroup thereof, wherein R¹² is selected from methyl, -C(=O)N(CH₃)₂, -C(=O)OCH₃, -SO₂CH₃, -SO₂CH₂CH₃, -C(=O)CH₂CH₃, and -C(=O)CH₃, or any subgroup thereof;

20

or a pharmaceutically acceptable salt.

In some embodiments, R¹ is hydrogen or halogen, such as F, Cl, Br, and I, or any subgroup thereof.

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In some embodiments, R^2 is selected from hydrogen, halogen, methyl, ethyl, propyl, isopropyl, $-OCH_3$, $-OCH_2CH_3$, $-O(CH_2)_2CH_3$, and $-OCH(CH_3)_2$, or any subgroup thereof. In other embodiments, R^2 is halogen, methyl, or $-OCH_3$, or any subgroup thereof. In other embodiments, R^2 is halogen. In other embodiments, R^2 is methyl. In other embodiments, R^2 is $-OCH_3$.

R^1 and R^2 are not both hydrogen. When R^1 is halogen, then R^2 is hydrogen.

In some embodiments, R^1 is halogen and R^2 is hydrogen. In other embodiments, R^1 is fluorine and R^2 is hydrogen. In yet other embodiments, R^2 is halogen and R^1 is hydrogen. In yet other embodiments, R^2 is fluorine and R^1 is hydrogen.

10 In some embodiments, n is 1 or 2.

In some embodiments, R^3 is methyl, provided that when n is 2, the nitrogen has a positive charge.

In some embodiments, R^{10} is selected from hydrogen, methyl, ethyl, propyl, and isopropyl, or any subgroup thereof. In some embodiments, R^{10} is hydrogen or methyl. In some embodiments, R^{10} is hydrogen. In other embodiments, R^{10} is methyl.

In some embodiments, R^{11} is selected from hydrogen, methyl, ethyl, propyl, and isopropyl, or any subgroup thereof. In some embodiments, R^{11} is hydrogen or methyl. In some embodiments, R^{11} is hydrogen. In other embodiments, R^{11} is methyl.

In some embodiments, R^7 is phenyl or pyridyl and is substituted with one substituent selected from R^9 .

In some embodiments, R^9 is selected from $-OCH_3$, $-O(CH_2)_2OCH_3$, $-N(CH_2)_2OCH_3$, morpholino, and piperazin- R^{12} , or any subgroup thereof, wherein R^{12} is selected from methyl, $-C(=O)N(CH_3)_2$, $-C(=O)OCH_3$, $-SO_2CH_3$, $-SO_2CH_2CH_3$, $-C(=O)CH_2CH_3$, and $-C(=O)CH_3$, or any subgroup thereof. In some embodiments, R^9 is $-OCH_3$. In other embodiments, R^9 is $-O(CH_2)_2OCH_3$. In other embodiments, R^9 is $-N(CH_2)_2OCH_3$. In other embodiments, R^9 is morpholino. In other embodiments, R^9 is piperazin- R^{12} .

In some embodiments, R^{12} is selected from methyl, $-C(=O)N(CH_3)_2$, $-C(=O)OCH_3$, $-SO_2CH_3$, $-SO_2CH_2CH_3$, $-C(=O)CH_2CH_3$, and $-C(=O)CH_3$, or any subgroup thereof. In some embodiments, R^{12} is methyl. In other embodiments, R^{12} is $-C(=O)N(CH_3)_2$. In other embodiments, R^{12} is $-C(=O)OCH_3$. In other embodiments, R^{12} is $-SO_2CH_3$. In other

embodiments, R^{12} is $-\text{SO}_2\text{CH}_2\text{CH}_3$. In other embodiments, R^{12} is $-\text{C}(=\text{O})\text{CH}_2\text{CH}_3$. In other embodiments, R^{12} is $-\text{C}(=\text{O})\text{CH}_3$.

In some embodiments, the compound is selected from: 5-Methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-1,4-dihydro-quinoline-2-carboxylic acid (6-methoxy-pyridin-3-yl)-
 5 amide; 5-Methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-1,4-dihydro-quinoline-2-carboxylic acid [4-(4-dimethylcarbamoyl-piperazin-1-yl)-phenyl]-amide; 4-(5-{[5-Methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-1,4-dihydro-quinoline-2-carbonyl]-amino}-pyridin-2-yl)-piperazine-1-carboxylic acid methyl ester; 4-(4-{[5-Methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-1,4-dihydro-quinoline-2-carbonyl]amino}-phenyl)-piperazine-1-carboxylic acid methyl
 10 ester; 5-Methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-1,4-dihydro-quinoline-2-carboxylic acid [6-(2-methoxy-ethoxy)-pyridin-3-yl]-amide; 5-Methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-1,4-dihydro-quinoline-2-carboxylic acid [4-(4-methanesulfonyl-piperazin-1-yl)-phenyl]-amide; 5-Methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-1,4-dihydro-quinoline-2-carboxylic acid [4-(4-ethanesulfonyl-piperazin-1-yl)-phenyl]-amide; 5-Methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-1,4-dihydro-quinoline-2-carboxylic acid [6-(2-methoxy-ethylamino)-pyridin-3-yl]-amide; 5-Methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-1,4-dihydro-quinoline-2-carboxylic acid [6-(4-propionyl-piperazin-1-yl)-pyridin-3-yl]-amide; 5-Methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-1,4-dihydro-quinoline-2-carboxylic acid [6-(4-acetyl-piperazin-1-yl)-pyridin-3-yl]-amide; 5-Methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-1,4-dihydro-quinoline-2-carboxylic acid [4-(4-acetyl-piperazin-1-yl)-phenyl]-amide; 5-Methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-1,4-dihydro-quinoline-2-carboxylic acid [4-(4-propionyl-piperazin-1-yl)-phenyl]-amide; 5-Methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-1,4-dihydro-quinoline-2-carboxylic acid (6-morpholin-4-yl-pyridin-3-yl)-amide; 1,1-Dimethyl-4-[5-methyl-2-(4-morpholin-4-yl-phenylcarbamoyl)-4-oxo-1,4-dihydro-quinolin-8-yl]-piperazin-1-ium; 5-Fluoro-1-methyl-8-(4-methyl-piperazin-1-yl)-4-oxo-1,4-dihydro-quinoline-2-carboxylic acid methyl-(4-morpholin-4-yl-phenyl)-amide; 4-Hydroxy-5-methyl-8-(4-methyl-piperazin-1-yl)-quinoline-2-carboxylic acid (4-methoxy-phenyl)-amide; 4-Hydroxy-5-methoxy-8-(4-methyl-piperazin-1-yl)-quinoline-2-carboxylic acid (4-morpholin-4-yl-phenyl)-amide; 5-Fluoro-8-(4-methyl-piperazin-1-yl)-4-oxo-1,4-dihydro-quinoline-2-carboxylic acid (4-methoxy-phenyl)-amide; 5-
 25 Fluoro-8-(4-methyl-piperazin-1-yl)-4-oxo-1,4-dihydro-quinoline-2-carboxylic acid (6-methoxy-pyridin-3-yl)-amide; 5-Fluoro-8-(4-methyl-piperazin-1-yl)-4-oxo-1,4-dihydro-

quinoline-2-carboxylic acid (4-morpholin-4-yl-phenyl)-amide; 4-Hydroxy-5-methyl-8-(4-methyl-piperazin-1-yl)-quinoline-2-carboxylic acid (6-methoxy-pyridin-3-yl)-amide; 4-Hydroxy-5-methyl-8-(4-methyl-piperazin-1-yl)-quinoline-2-carboxylic acid [4-(4-methyl-piperazin-1-yl)-phenyl]-amide; 4-Hydroxy-5-methyl-8-(4-methyl-piperazin-1-yl)-quinoline-2-carboxylic acid (4-morpholin-4-yl-phenyl)-amide; 6-Fluoro-8-(4-methyl-piperazin-1-yl)-4-oxo-1,4-dihydro-quinoline-2-carboxylic acid [4-(4-methyl-piperazin-1-yl)-phenyl]-amide; 6-Fluoro-8-(4-methyl-piperazin-1-yl)-4-oxo-1,4-dihydro-quinoline-2-carboxylic acid (6-methoxy-pyridin-3-yl)-amide; or 6-Fluoro-8-(4-methyl-piperazin-1-yl)-4-oxo-1,4-dihydro-quinoline-2-carboxylic acid (4-methoxy-phenyl)-amide, or any subgroup thereof.

10 The compounds provided herein are useful in the form as a free base, but may also be provided in the form of a pharmaceutically acceptable salt, and/or in the form of a pharmaceutically acceptable hydrate. For example, pharmaceutically acceptable salts of compounds of Formula I include those derived from mineral acids such as, for example: hydrochloric acid, nitric acid, phosphoric acid, sulfuric acid, hydrobromic acid, hydroiodic acid, nitrous acid, and phosphorous acid, or any subgroup thereof. Pharmaceutically acceptable salts may also be developed with organic acids including, but not limited to, aliphatic mono and dicarboxylates and aromatic acids, or any subgroup thereof. Other pharmaceutically acceptable salts of compounds of the present invention include, for example, hydrochloride, sulfate, pyrosulfate, bisulfate, bisulfite, nitrate, and phosphate, or any subgroup thereof.

20 It will be appreciated by those skilled in the art that certain compounds of the present invention contain for example asymmetrically substituted carbon and/or sulfur atoms, and accordingly may exist in and be isolated in, optically-active and racemic forms. Some compounds may exhibit polymorphism, thus it is to be understood that the present invention encompasses racemic, optically active, polymorphic or stereoisomeric forms, or mixtures thereof, which forms possess properties useful in the treatment of the disorders set forth below. Preparation of optically active forms is well known in the art how (for example by resolution of racemic forms by recrystallization techniques, synthesis from optically-active starting materials, chiral synthesis, or by chromatographic separation using a chiral stationary phase) and how to determine efficacy for the treatment of the disorder described above.

30 Processes for the manufacture of the compounds of Formula I are provided as

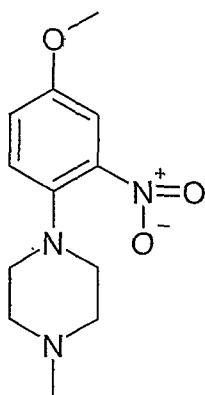
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further features of the invention. Many of the compounds described herein can be made by processes known in the chemical arts for the production of structurally analogous compounds. Accordingly, the compounds of this invention may be prepared by employing procedures known in the literature starting from known compounds or readily prepared

5 intermediates.

Compounds of the present invention are prepared via the synthetic route depicted in **METHOD A.**

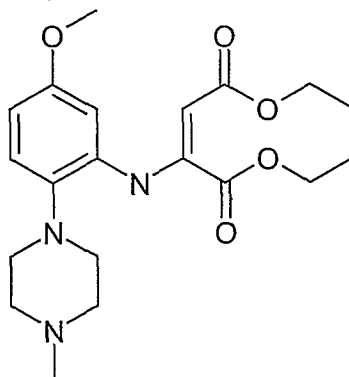
1-(4-Methoxy-2-nitro-phenyl)-4-methyl-piperazine



- 10 1-Chloro-4-methoxy-2-nitrobenzene (20 g, 107 mM) in N-methylpiperazine (30 mL, 267.5 mM) is heated to 120°C for 3 hours. The mixture is cooled, diluted with water, extracted with EtOAc, dried, and concentrated. The residue is taken up in EtOAc and treated with 4N HCl in dioxane (1.2 eq.) to generate the HCl salt. The product is collected by filtration, washed with additional EtOAc and dried overnight on a vacuum pump (18.5 g, 61%). LC/MS 1.23
- 15 min. 252 (M+H, 100%); ¹H-NMR (300 MHz, CDCl₃) δ 7.60 (s, 1H), 7.45 (d, J=11 Hz, 1H), 7.15 (d, J=11 Hz, 1H), 3.95 (s, 3H).

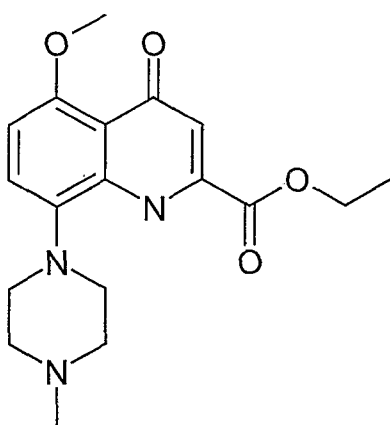
2-[5-Methoxy-2-(4-methyl-piperazin-1-yl)-phenylamino]-but-2-enedioic acid diethyl ester

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1-(4-Methoxy-2-nitro-phenyl)-4-methyl-piperazine hydrochloride (5 g, 17.4 mM) in MeOH treated with 10% Pd/C (0.5 g) and hydrogenated at 50 psi for 3 hours. The solution is filtered and the solvent removed at reduced pressure. The residue is dissolved in EtOH and treated
 5 with diethylacetylenedicarboxylate (2.96 mL, 17.4 mM) via syringe over 1 minute. After 1 hour, the solvent is removed at reduced pressure and the residue chromatographed (silica, 0 to 10% MeOH/DCM gradient) to give the product as a yellow oil (4.75 g, 70%). LC/MS 2.05 min. 392 (M+H, 100%); ¹H-NMR (300 MHz, CDCl₃) δ 8.52 (bs, 1H), 7.30 (d, J=8.6 Hz, 1 H), 6.70 (s, 1H), 6.49 (d, J=8.6 Hz, 1 H), 5.06 (s, 1H), 4.30 (m, 2H), 4.13 (m, 2H), 3.80 (s,
 10 3H), 3.13 (m, 2H), 2.72 (m, 2H), 2.34 (s, 3H), 1.29 (t, J=7.1 Hz, 3H), 1.18 (t, J=7.1 Hz, 3H).

5-Methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-1,4-dihydro-quinoline-2-carboxylic acid ethyl ester



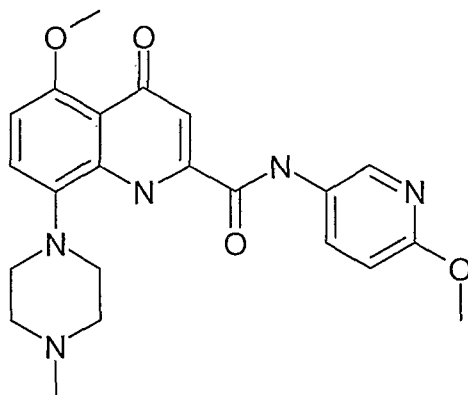
A three-neck flask equipped with a thermometer, Dean-Stark trap and septum is charged with
 15 Dowtherm (40 mL) and heated to reflux (245°C). A solution of 2-[5-Methoxy-2-(4-methyl-piperazin-1-yl)-phenylamino]-but-2-enedioic acid diethyl ester (5 g, 12.8 mM) in Dowtherm (5 mL) is added to the boiling reaction via syringe at such a rate as to keep the internal

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temperature above 240°C. The addition takes about 4 minutes. The reaction is allowed to reach reflux again and the heating source is removed. After cooling to room temperature the reaction mixture is diluted with DCM (10 mL) and applied directly to a silica gel column and chromatographed (0 to 10 % MeOH/DCM) to give the product as a brown solid.

- 5 Recrystallization from ethyl ether gives the product as a yellow solid (2.2 g, 50%). LC/MS 1.22 min. 346 (M+H, 100%); ¹H-NMR (300 MHz, CDCl₃) δ 10.68 (bs, 1H), 7.49 (d, J=8.6 Hz, 1 H), 6.60 (d, J=8.6 Hz, 1 H), 6.43 (s, 1H), 4.44 (q, J=7.1 Hz, 2H) 3.91 (s, 3H), 3.14 (m, 2H), 2.68 (m, 2H), 2.34 (s, 3H), 1.36 (t, J=7.1 Hz, 3H).

- 10 5-Methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-1,4-dihydro-quinoline-2-carboxylic acid (6-methoxy-pyridin-3-yl)-amide

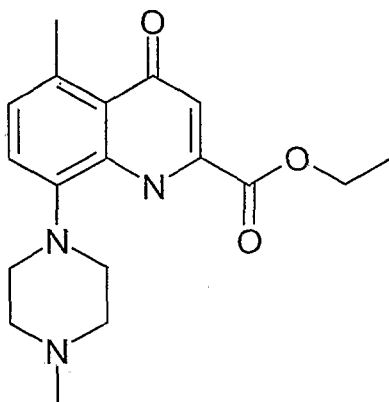


- 5-Methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-1,4-dihydro-quinoline-2-carboxylic acid ethyl ester (0.5g, 1.45 mM) is dissolved in EtOH and treated with 2N LiOH (0.83 mL, 1.67 mM) in one portion. The reaction mixture is heated to 50°C for 30 minutes. The reaction is cooled and the solvent evaporated at reduced pressure. Additional EtOH is added and the solvent removed at reduced pressure. The residue is triturated with AcN and the solid product collected by filtration. The solid is dried on a vacuum pump for several hours. The solid is suspended in DMF and treated with DIPEA (0.4 mL, 2.02 mM) and then HATU (0.66 g, 1.74 mM). The solid dissolves upon addition of HATU and the mixture turns deep red. After 30 minutes 2-amino-6-methoxypyridine (0.18 g, 1.45 mM), is added in one portion and the reaction mixture stirred for 3 hours. The product begins to precipitate after 1 hour. The reaction is diluted with AcN and the product filtered. The solid is rinsed with additional AcN and air-dried. The product is recrystallized from EtOH to give a yellow powder (0.3 g, 50%).

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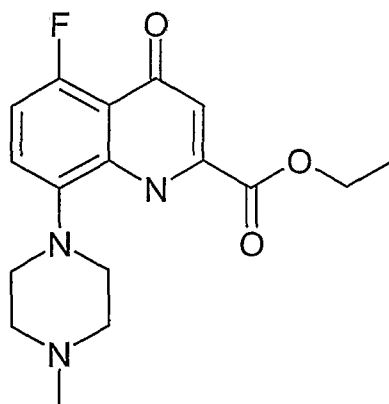
LC/MS 1.57 min. 424 (M+H, 100%); ¹H-NMR (300 MHz, DMSO-d₆) δ 10.09 (bs, 2H), 8.45 (s, 1H), 8.36 (d, J=8.0Hz, 1H), 7.52 (d, J=8.5Hz, 1H), 6.75 (s, 1H), 6.74 (d, J=8.0Hz, 1H), 6.62 (d, J=8.5Hz, 1H), 3.91 (s, 3H), 3.82 (s, 3H), 3.17 (m, 4H), 2.68 (m, 4H), 2.34 (s, 3H).

- 5 5-Methyl-8-(4-methyl-piperazin-1-yl)-4-oxo-1,4-dihydro-quinoline-2-carboxylic acid ethyl ester



- This compound is synthesized from 1-(4-methyl-2-nitrophenyl)-4-methyl-piperazine using the same synthetic procedures as described in method A. LC/MS 1.43 min. 330 (M+H, 100%); ¹H-NMR (300 MHz, DMSO-d₆) δ 10.68 (bs, 1H), 7.46 (d, J=8.6 Hz, 1 H), 6.93 (d, J=8.6 Hz, 1 H), 6.42 (s, 1H), 4.44 (q, J=7.1 Hz, 2H) 3.16 (s, 3H), (m, 4H), 2.68 (m, 4H), 2.60 (s, 3H), 2.34 (s, 3H), 1.36 (t, J=7.1 Hz, 2H).
- 10

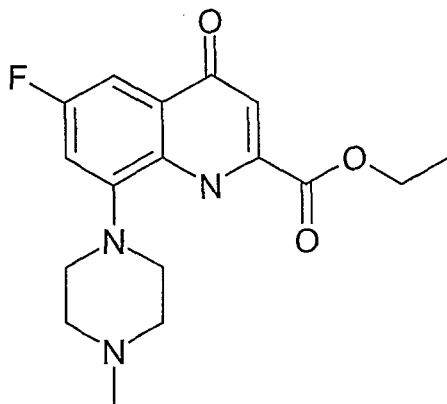
- 5-Fluoro-8-(4-methyl-piperazin-1-yl)-4-oxo-1,4-dihydro-quinoline-2-carboxylic acid ethyl ester
- 15 ester



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This compound is synthesized from 1-(4-fluoro-2-nitrophenyl)-4-methyl-piperazine using the same synthetic procedures as described in method A. LC/MS 1.47 min. 334 (M+H, 100%); ¹H-NMR (300 MHz, DMSO-d₆) δ 10.68 (bs, 1H), 7.75 (d, J=8.6 Hz, 1 H), 7.19 (d, J=8.6 Hz, 1 H), 6.50 (s, 1H), 4.44 (q, J=7.1 Hz, 2H), 3.15 (m, 4H), 2.68 (m, 4H), 2.34 (s, 3H), 1.36 (t, J=7.1 Hz, 2H).

6-Fluoro-8-(4-methyl-piperazin-1-yl)-4-oxo-1,4-dihydro-quinoline-2-carboxylic acid ethyl ester



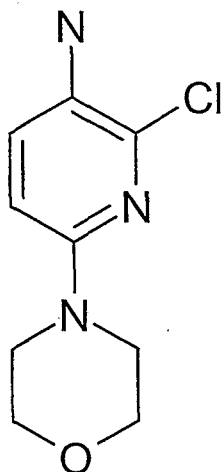
10 This compound is synthesized from 1-(5-fluoro-2-nitrophenyl)-4-methyl-piperazine using the same synthetic procedures as described in method A. LC/MS 1.41 min. 334 (M+H, 100%); ¹H-NMR (300 MHz, DMSO-d₆) δ 10.68 (bs, 1H), 7.32 (d, J=8.6 Hz, 1 H), 7.28 (m, 1H), 6.66 (s, 1H), 4.44 (q, J=7.1 Hz, 2H), 3.16 (m, 4H), 2.67 (m, 4H), 2.34 (s, 3H), 1.36 (t, J=7.1 Hz, 2H).

15

Aniline Synthesis

2-Chloro-6-morpholin-4-yl-pyridin-3-ylamine

-15-



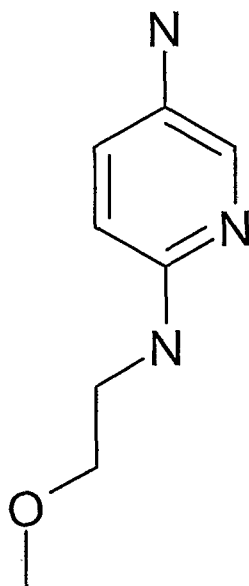
A solution of 2-chloro-4-nitropyridine (2.0 g, 12.6 mM) in EtOH is treated with morpholine (2.4 mL, 27.8 mM) in one portion. The reaction is heated to reflux and stirred for 1 hour.

Upon cooling, the product is filtered and collected as a yellow solid. The solid is suspended

5 in EtOH and treated with 4N HCl in dioxane. Then 10% Pd/C (0.2 g) is added and the reaction hydrogenated on a Parr Shaker at 50 psi for 2h. The reaction is then filtered and the solvent removed at reduced pressure to give the product as a tan solid (2.0 g, 75%). LC/MS 0.65 min. 214 (M+H, 100%); ¹H-NMR (300 MHz, DMSO-d₆) δ 7.10 (d, J=9.0 Hz, 1H), 6.60 (d, J=9.0 Hz, 1H), 5.44 (bs, 2H), 3.74 (m, 4H), 3.67 (m, 4H).

10

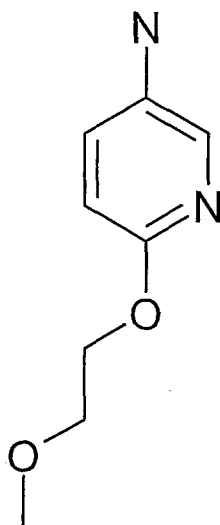
2-(Methoxyethylamino)-4-aminopyridine



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A solution of 2-chloro-4-nitropyridine (1.5 g, 9.5 mM) in EtOH is treated with 2-methoxyethylamine (2.1 mL, 23.5 mM) in one portion. The reaction is heated to reflux and stirred for 1 hour. Upon cooling, the product is filtered and collected as a yellow solid. The solid is suspended in EtOH, treated with 10% Pd/C (0.2 g) and the reaction hydrogenated on a Parr Shaker at 50 psi for 2 hours. The reaction is then filtered and the solvent removed at reduced pressure to give the product as a dark tan solid (1.8 g, 95%). LC/MS 0.41 min. 168 (M+H, 100%); ¹H-NMR (300 MHz, DMSO-d₆) δ7.60 (s, 1H), 6.93 (d, J=9.0 Hz, 1H), 6.37 (d, J=9.0 Hz, 1H), 5.72 (bs, 3H), 3.70 (t, J=13.0 Hz, 1H), 3.45 (t, J=13.0 Hz, 1H), 3.43 (s, 3H).

2-(Methoxyethoxy)-4-aminopyridine

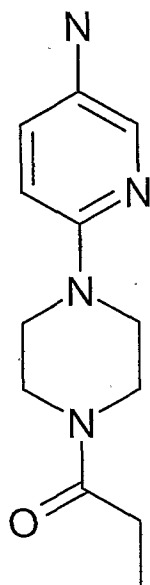


2-Methoxyethanol (5 ml) is treated with NaH (0.57 g, 14.3 mM) at room temperature in several portions over 10 minutes. The reaction is exothermic. After stirring at room

temperature for 20 minutes, 2-chloro-4-nitropyridine (1.5 g, 9.5 mM) is added in two portions. After stirring at room temperature for 20 minutes, the reaction is poured into water and the product is filtered off and air-dried. This solid is suspended in MeOH, treated with 10% Pd/C (0.2 g) and the reaction hydrogenated on a Parr Shaker at 50 psi for 2 hours. The reaction is then filtered and the solvent removed at reduced pressure to give the product as an off white solid (1.8 g, 95%). LC/MS 0.26 min. 169 (M+H, 100%); ¹H-NMR (300 MHz, DMSO-d₆) δ8.12 (s, 1H), 7.14 (d, J=8.6 Hz, 1H), 6.66 (d, J=8.6 Hz, 1H), 5.50 (bs, 1H), 4.47 (d, J=8.4 Hz, 1H), 3.74 (d, J=8.4 Hz, 1H), 3.44 (s, 3H).

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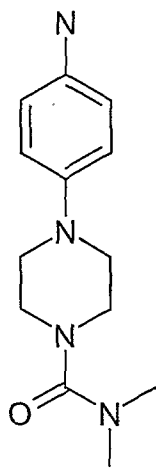
1-[4-(5-Amino-pyridin-2-yl)-piperazin-1-yl]-propan-1-one



A solution of 2-chloro-4-nitropyridine (1.5 g, 9.5 mM) in EtOH is treated with piperazine
5 (2.0 g, 23.5 mM) in one portion. The reaction is heated to reflux and stirred for 1 hour. Upon
cooling, the product is filtered and collected as a yellow solid. The solid is suspended in
DCM and treated with DIPEA (2.3 mL, 12.4 mM) followed by neat propionyl chloride (0.88
g, 12.4 mM). The reaction is stirred at room temperature for 12 hours. The reaction is
quenched with MeOH and the solvent removed at reduced pressure. The product is
10 recrystallized from EtOH. This solid is suspended in EtOH, treated with 10% Pd/C (0.2 g)
and the reaction hydrogenated on a Parr Shaker at 50 psi for 2 hours. The reaction is then
filtered and the solvent removed at reduced pressure to give the product as a gray solid (1.4 g,
90%). LC/MS 0.60 min. 235 (M+H, 100%); ¹H-NMR (300 MHz, DMSO-d₆) δ 7.56 (s, 1H),
6.98 (d, J=9.0 Hz, 1H), 6.86 (d, J=9.0 Hz, 1H), 5.51 (bs, 2H), 3.88 (m, 4H), 3.15 (m, 4H),
15 2.34 (q, J=7.4 Hz, 2H), 0.97 (t, J=7.4 Hz, 3H).

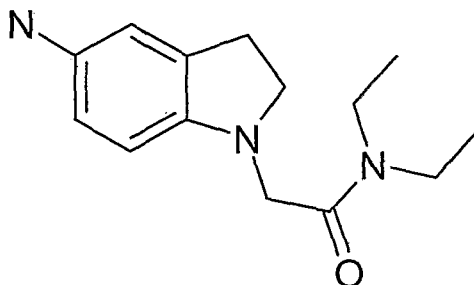
4-(4-Amino-phenyl)-piperazine-1-carboxylic acid dimethylamide

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A solution of 4-fluoronitrobenzene (2.7 mL, 25 mM) in EtOH is treated with piperazine (4.7 g, 55 mM) in one portion. The reaction is heated to reflux and stirred for 1 hour. Upon cooling, the product is filtered and collected as a yellow solid. The solid is suspended in
5 DCM and treated with DIPEA (1.7 mL, 9.4 mM) followed by neat N,N-dimethylcarbamoylchloride (0.71 mL, 7.9 mM). The reaction is stirred at reflux for 1 hour. The reaction is quenched with MeOH and the solvent removed at reduced pressure. The product is recrystallized from EtOH. This solid is suspended in EtOH, treated with 10% Pd/C (0.2 g) and the reaction hydrogenated on a Parr Shaker at 50 psi for 2 hours. The reaction is
10 then filtered and the solvent removed at reduced pressure to give the product as a gray solid (0.8 g, 13%). LC/MS 0.46 min. 249 (M+H, 100%); ¹H-NMR (300 MHz, DMSO-d₆) δ 7.03 (d, J=9.0 Hz, 2H), 6.60 (d, J=9.0 Hz, 2H), 3.75 (m, 4H), 3.72 (bs, 2H), 3.24 (m, 4H), 2.83 (s, 3H), 2.73 (s, 3H).

15 2-(5-Amino-2,3-dihydro-indol-1-yl)-N,N-diethyl-acetamide

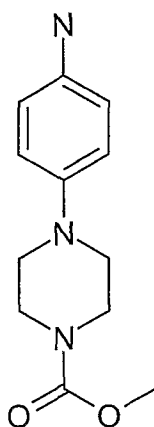


A solution of 5-nitro-2,3-dihydro-1H-indole (1.0 g, 6.1 mM) in DMF is treated with CsCO₃ (3.0 g, 9.1 mM) and 2-Chloro-N,N-diethyl-acetamide (1.1 g, 7.3 mM) and heated to 80°C for

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16 hours. The solution is cooled, poured into water, extracted with EtOAc, the organic layer separated, dried (MgSO₄) and the solvent removed at reduced pressure. The residue is recrystallized from EtOH. This solid is suspended in EtOH, treated with 10% Pd/C (0.2 g) and the reaction hydrogenated on a Parr Shaker at 50 psi for 2 hours. The reaction is then
5 filtered and the solvent removed at reduced pressure to give the product as a gray solid (0.8 g, 13%). LC/MS 0.46 min. 249 (M+H, 100%); ¹H-NMR (300 MHz, DMSO-d₆) δ 6.56 (m, 1H), 6.51 (m, 1H), 6.45 (s, 1H), 3.80 (bs, 2H), 3.62 (s, 2H), 3.30 (m, 2H), 3.26 (m, 4H), 2.91 (m, 2H), 1.21 (s, 3H), 1.20 (s, 3H).

10 4-(4-Amino-phenyl)-piperazine-1-carboxylic acid methyl ester



A solution of 4-fluoronitrobenzene (2.7 mL, 25 mM) in EtOH is treated with piperazine (4.7 g, 55 mM) in one portion. The reaction is heated to reflux and stirred for 1 hour. Upon cooling, the product is filtered and collected as a yellow solid. The solid is suspended in
15 DCM and treated with DIPEA (1.7 mL, 9.4 mM) followed by neat methyl chloroformate (0.62 mL, 7.9 mM). The reaction is stirred at reflux for 1 hour. The reaction is quenched with MeOH and the solvent removed at reduced pressure. The product is recrystallized from EtOH. This solid is suspended in EtOH, treated with 10% Pd/C (0.2 g) and the reaction hydrogenated on a Parr Shaker at 50 psi for 2 hours. The reaction is then filtered and the
20 solvent removed at reduced pressure to give the product as a gray solid (0.8 g, 13%). LC/MS

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0.49 min. 236 (M+H, 100%); ¹H-NMR (300 MHz, DMSO-d₆) δ 7.03 (d, J=9.0 Hz, 2H), 6.60 (d, J=9.0 Hz, 2H), 3.75 (m, 4H), 3.72 (bs, 2H), 3.56 (s, 3H), 3.24 (m, 4H).

The present invention also provides compositions comprising any one or more of the compounds described herein and a pharmaceutically acceptable diluent or carrier. Suitable
5 compositions are pharmaceutical compositions.

Compounds of Formula I have been found by the inventors to be useful as 5-HT_{1B} modulators, including as antagonists. The present invention also provides for use of any one or more of the compounds described herein in the treatment of an anxiety disorder, cognitive disorder, or mood disorder as defined herein. In some embodiments, the use is in the
10 treatment of an anxiety disorder. In other embodiments, the use is in the treatment of a cognitive disorder. In other embodiments, the use is in the treatment of a mood disorder.

The present invention also provides methods of treating an animal including a human suffering from an anxiety disorder, cognitive disorder, or mood disorder comprising administering to such animal an effective amount of any of the compounds described herein
15 or a pharmaceutically acceptable salt of the compound. The treatment of these disorders comprises administering to a warm-blooded animal, such as a mammal, or a human, an effective amount of a compound of Formula I, or a pharmaceutically acceptable salt of the compound.

The present invention also provides for use of any one of the compounds described
20 herein in the preparation of a medicament for the treatment of an anxiety disorder, a cognitive disorder, or a mood disorder.

The present invention also relates to combination therapies for the treatment of anxiety disorder(s), cognitive disorder(s), and/or mood disorder(s), wherein a compound of formula (I) or a pharmaceutically acceptable salt, solvate or *in vivo* hydrolysable ester
25 thereof, or a pharmaceutical composition or formulation comprising a compound of formula (I) is administered concurrently, simultaneously, sequentially or separately with another pharmaceutically active compound or compounds selected from the following: (i) antidepressants such as amitriptyline, amoxapine, bupropion, citalopram, clomipramine, desipramine, doxepin, duloxetine, elzasonan, escitalopram, fluvoxamine, fluoxetine, gepirone,
30 imipramine, ipsapirone, maprotiline, mirtazapine, nortriptyline, nefazodone, paroxetine, phenelzine, protriptyline, reboxetine, sertraline, sibutramine, thionisoxetine,

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tranylcypromaine, trazodone, trimipramine, venlafaxine and equivalents and pharmaceutically active isomer(s) and metabolite(s) thereof; (ii) atypical antipsychotics including for example quetiapine and lithium and pharmaceutically active isomer(s) and metabolite(s) thereof; (iii) antipsychotics including for example amisulpride, aripiprazole, 5 asenapine, benzisoxidil, bifeprunox, carbamazepine, clozapine, chlorpromazine, debenzapine, divalproex, duloxetine, eszopiclone, haloperidol, iloperidone, lamotrigine, loxapine, mesoridazine, olanzapine, paliperidone, perlapine, perphenazine, phenothiazine, phenylbutylpiperidine, pimozide, prochlorperazine, risperidone, sertindole, sulpiride, suproclonidine, suriclone, thioridazine, trifluoperazine, trimetozine, valproate, valproic acid, 10 zopiclone, zotepine, ziprasidone and equivalents and pharmaceutically active isomer(s) and metabolite(s) thereof; (iv) anxiolytics including for example alnespirone, azapirone, benzodiazepines, barbiturates such as adinazolam, alprazolam, balezepam, bentazepam, bromazepam, brotizolam, buspirone, clonazepam, clorazepate, chlordiazepoxide, cyprazepam, diazepam, diphenhydramine, estazolam, fenobam, 15 flunitrazepam, flurazepam, fosazepam, lorazepam, lormetazepam, meprobamate, midazolam, nitrazepam, oxazepam, prazepam, quazepam, reclazepam, tracazolate, trepipam, temazepam, triazolam, uldazepam, zolazepam and equivalents and pharmaceutically active isomer(s) and metabolite(s) thereof; (v) anticonvulsants including for example carbamazepine, topiramate, valproate, lamotrigine, gabapentin and equivalents and pharmaceutically active isomer(s) and 20 metabolite(s) thereof; (vi) Alzheimer's therapies including for example donepezil, memantine, tacrine and equivalents and pharmaceutically active isomer(s) and metabolite(s) thereof; (vii) Parkinson's therapies including for example deprenyl, L-dopa, Requip, Mirapex, MAOB inhibitors such as selegine and rasagiline, comP inhibitors such as Tasmar, A-2 inhibitors, dopamine reuptake inhibitors, NMDA antagonists, Nicotine agonists, 25 Dopamine agonists and inhibitors of neuronal nitric oxide synthase and equivalents and pharmaceutically active isomer(s) and metabolite(s) thereof; (viii) migraine therapies including for example almotriptan, amantadine, bromocriptine, butalbital, cabergoline, dichloralphenazone, eletriptan, frovatriptan, lisuride, naratriptan, pergolide, pramipexole, rizatriptan, ropinirole, sumatriptan, zolmitriptan, zomitriptan, and equivalents and 30 pharmaceutically active isomer(s) and metabolite(s) thereof; (ix) stroke therapies including for example abciximab, activase, (NXY-059), citicoline, crobenetine,

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desmoteplase, repinotan, traxoprodil and equivalents and pharmaceutically active isomer(s) and metabolite(s) thereof; (x) urinary incontinence therapies including for example darifenacin, falvoxate, oxybutynin, propiverine, robalzotan, solifenacin, trypium, tolterodine and equivalents thereof; (xi) neuropathic pain therapies including for example gabapentin, 5 lidoderm, pregablin and equivalents thereof; (xii) nociceptive pain therapies such as celecoxib, etoricoxib, lumiracoxib, rofecoxib, valdecoxib, diclofenac, loxoprofen, naproxen, paracetamol and equivalents thereof; (xiii) insomnia therapies including for example allobarbitol, alonimid, amobarbital, benzocetamine, butobarbital, capuride, chloral, cloperidone, clorethate, dexclamol, eszopiclone, ethchlorvynol, etomidate, glutethimide, 10 halazepam, hydroxyzine, mecloqualone, melatonin, mephobarbital, methaqualone, midazolam, nisobamate, pentobarbital, phenobarbital, propofol, roletamide, triclofos, secobarbital, zaleplon, zolpidem and equivalents thereof.

Such combination products employ the compounds of the present invention within the dosage range described herein and the other pharmaceutically active compound or 15 compounds within approved dosage ranges and/or the dosage described in the publication reference.

All compounds described herein demonstrate binding affinities (observed K_i values), in an assay described below, of less than about 10 μ M. Further, some compounds of the present invention not only demonstrate 5HT_{1B} antagonist activity by reversing 5HT_{1B} 20 agonist-induced hypothermia in the guinea pig, some of these compounds are considered to be orally active.

The compounds described herein may be provided or delivered in a form suitable for oral use, for example in a tablet, lozenge, hard and soft capsule, aqueous solution, oily solution, emulsion, and suspension. The compounds may be also be provided for topical 25 administration, for example, as a cream, ointment, gel, spray, or aqueous solutions, oily solutions, emulsions or suspensions. The compounds described herein may also be provided in a form suitable for nasal administration for example, as a nasal spray, nasal drops, or dry powder. The compositions may also be administered to the vagina or rectum in the form of a suppository. The compounds described herein may also be administered parentally, for 30 example by intravenous, intravesicular, subcutaneous, or intramuscular injection or infusion.

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The compounds may be administered by insufflation (for example as a finely divided powder). The compounds may also be administered transdermally or sublingually.

The compositions of the invention may accordingly be obtained by conventional procedures using conventional pharmaceutical excipients, well known in the art. Thus,
5 compositions intended for oral use may contain, for example, one or more coloring, sweetening, flavoring and/or preservative agents.

The amount of active ingredient that is combined with one or more excipients to produce a single dosage form will necessarily vary depending upon the host treated and the particular route of administration. The size of the dose for therapeutic or prophylactic
10 purposes of a compound of the Formula I will naturally vary according to the nature and severity of the conditions, the age and sex of the animal or patient and the route of administration, according to well known principles of medicine. Various assays and *in vivo* tests are known for determining the utility of the compounds in the disorders noted above and specifically as modulators of 5HT1B and 5HT1D.

15 A utility of the compounds for example to treat depression may be shown via a learned helplessness test in guinea pigs, which is used extensively as correlative to antidepressant activity in humans. The learned helplessness test may be carried out as follows: Seventy male Hartley guinea pigs, each weighing about 350-425 gm are fed *ad lib*, and are housed under a 12-hour light/dark cycle. The procedure consists of two phases: The
20 induction phase and the avoidance-training phase. In the induction phase, subjects are placed into standard shuttle cages (20 L X 16 W X 21 centimeters H) which are fitted with a grid floor. Electrical stimulation (1.25 mA, 10 sec duration) is delivered to the floor of the cage every 90-sec during 1 hour daily sessions. Subjects have no opportunity to escape or to avoid shocks. Induction is conducted for 2 consecutive days.

25 In avoidance training, testing may also be conducted in the shuttle cages, except that the subjects are not returned to the same chamber in which induction had occurred. Additionally, all cages are fitted with a partition with an arch in the center of the cage, through which animals can pass between the left and right halves of the cage. The procedure employed is a standard shuttle avoidance procedure in which a compound, conditioned
30 stimulus (a 10-second presentation of a tone and turning on of a lamp on the side of the cage that the guinea pig is occupying) serves to indicate presentation of electrical current to the

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floor of the cage. Shock is presented for a 5 second period, 5 seconds after initiation of the conditioned stimulus. Entry into the opposite side of the shuttle cage via the arched partition prior to shock onset results in the end of the trial (avoidance response). If shock is delivered, entry into the opposite side of the cage results in termination of the shock and CS (escape).

- 5 Reversal of learned helplessness in the induction subjects correlates to antidepressant activity of the test compound.

Avoidance training, 45-minute in duration, is conducted on 2 consecutive days, beginning 48 hours after the final induction session. Seventy subjects are assigned to 1 of 6 groups of 11-12 animals. The groups are as follows:

- 10 1) No induction group. The subjects are placed into the shuttle cages but are not given inescapable shock, the animals are subsequently trained in the avoidance procedure and the vehicle is administered;
- 2) Induction vehicle control group;
- 3) Imipramine 17.8 mg/kg;
- 15 4) 0.3 mg/kg compounds;
- 5) 1 mg/kg compounds; and
- 6) 5 mg/kg compounds.

Groups 2-6 are given induction and avoidance training sessions. Injections are administered immediately following induction sessions and 1 hour prior to avoidance training sessions. A
20 second injection is administered 7-8 hours following the first injection, for a total of 9 injections administered over 5 days. No injections are administered following the final avoidance training session.

Compounds of the present invention may be administered in a volume of 1 mL/kg bwt. Imipramine is dissolved in DI water. The compounds are dissolved in DI water, to
25 which is added a few drops of lactic acid (pH 5.5). The vehicle control is DI water prepared with lactic acid to the same pH as the-treated groups.

The primary dependent variable is escape failure during avoidance training. 2-way analysis of variance (ANOVA) is used to assess overall treatment effect, with Dunn's post hoc analysis used to compare the vehicle-treated group with the drug-treated groups. The no-
30 induction group is used to gauge whether learned helplessness is established, by comparison to the vehicle treated group.

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An alternative method for determining the utility of the compounds of the present invention is to investigate the in vivo activity of the compounds using a guinea pig hypothermia test (J. Med. Chem., 41: 1218-1235 (1998)).

Assays that may be used to measure for example affinity of compounds of the present invention for 5HT1B receptors are described in J. Med. Chem 41:1218-1235, 1228 (1998) and J. Med. Chem 42:4981-5001, (1999). These assays may be used with some modifications: Frozen membrane preparations of a stably transfected chinese hamster ovary (CHO) cell line expressing 5-HT1B receptors and 5-HT1D receptors are thawed rapidly, briefly vortexed, and diluted in assay buffer (AB) containing 50 mM Tris-HCl, 4 mM MgCl₂, 4 mM CaCl₂, 1 mM EDTA, and adjusted to pH 7.4 with NaOH. Final protein concentrations are - 0.185 mg/ml for 5-HT1B, and 0.4 mg/ml for 5-HT1D membranes. Test compounds are evaluated in competition assays using [³H]-GR125743 (Amersham). The ligand concentration in both assays is 0.27nM. K_d for [³H]-GR125743 may vary from 0.15 nM to 0.25 nM. The 5-HT1B and 5-HT1D assays are performed simultaneously on one 96-well assay plate, one drug/compound per plate. Ten serial dilutions (1 μM to 4 pM, final concentration) of compound are prepared in DMSO from 10 mM stock solutions. Incubation mixtures are prepared in quadruplicate in 96-deep well assay plates (Matrix 1 ml). Final assay volumes per well are 10 μl compound/nonspecific; 100 μl membranes; 100 μl [³H]-GR125743; and 790 μl AB. Specific binding is defined by using 10 μM Methiothepine. The assay plates are shaken for 5 minutes, and then incubated for an additional 55 minutes. Then the assay plates are filtered through Beckman GF/B filters (soaked > 2 hours in PEI) using a Packard Filtermate 196. Filters are washed 2x with 1 ml ice-cold wash buffer (5 mM Tris-HCl - pH7.4 with NaOH). After the filters are dried, 35 μl of Microscint20 is added to each well. The plates are then counted on a Packard TopCount to determine CPM's per well. K_i values are determined for each test compound utilizing the graphic and analytical software package, GraphPad Prism. Compounds are then ranked in order of potency, and selectivity for 5-HT1B over 5-HT1D receptors. K_i values for compounds of the present invention range from 1nM-10 μM.

A method that may be used to determine a compound's affinity for 5-HT1B and 5HT1D receptors is a guinea pig cortical test. This assay is described in detail by Roberts, et al, Br. J. Pharmacol., 1996, 117, 384-388, which is incorporated by reference herein. The test

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is carried out as follows: Guinea pigs are decapitated and the cortici is dissected out, weighed and homogenized in 50 mM Tris-HCl, pH 7.7 with an Ultra-Turrax followed by centrifugation for 10 min at 48000 x g and 5°C. The pellet is resuspended and recentrifuged. The final pellet is suspended in 0.32 M sucrose buffer to a concentration of 0.5g original wet weight per mL and stored frozen at -70°C. The radioligand binding assay is carried out as follows: [³H]GR125743 saturation studies are tested in duplicate with 3-4 mg w.w. per tube in 5 mL buffer (50 mM Tris, 4 mM CaCl₂, 4 mM MgCl₂ and 1 mM EDTA at pH 7.7), and a concentration range of 0.012 to 2 nM (10-12 concentrations) for the radioligand. Non-specific binding is determined in the presence of 10 mM methiothepin. In competition experiments 4-8 mg w.w. per tube and a radioligand concentration of 0.2 nM are used with 10-12 concentrations of the competing drug. The assays are run for 2-4 hours at 30°C and terminated by rapid filtration through Whatman GF/B filters (pretreated with 0.1% polyethyleneimine) using a Brandel cell harvester. Bovine serum albumin (0.1%) is added to the washing buffer to reduce non-specific binding. Data from the experiments may be analyzed using the iterative non-linear curve-fitting program LIGAND. The K_d values obtained from the saturation studies are used in the calculation of the K_i values by the LIGAND program. The K_d value of [³H]GR125743 may result in a measurement of 46 ± 4 pM and the B_{max} in a measurement of 4.9 ± 0.2 pmol/g w.w. K_d values for compounds of the present invention range from 1nM-10 μM.

A GTPγS binding assay may used to determine whether a compound is a 5HT1B or 5HT1D agonist or antagonist. One assay available measures agonist stimulated GTP binding for example as set forth by Lazareno, S. (1999) *Methods in Molecular Biology* 106: 231-245. Membrane preparations of a stably transfected CHO cell line expressing human 5-HT1B receptors are purchased for example from Unisyn, Hopkinton, MA. Frozen membranes are thawed, briefly sonicated, and diluted to 167 μg/ml protein in assay buffer containing 20 mM HEPES, 100 mM NaCl, 1mM MgCl₂ and 1 μM GDP, pH adjusted to 7.4 with NaOH. Diluted membranes are briefly homogenized with a Polytron and allowed to equilibrate at room temperature for at least 15 minutes before use. Serial dilutions (10 μM to 1 pM, final concentration) of test compounds are prepared in buffer with and without 100 nM 5-HT (final concentration) from 10 mM DMSO stock solutions. Incubation mixtures are prepared in quadruplicate in 96-well, deep-well plates and consisted of 180 μL of membranes (30 μg

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protein) and 40 μ L of compound with or without 5-HT. After an incubation period of 15 minutes at room temperature, 20 μ L of [^{35} S]GTP γ S (NEN; 100 pM final concentration) is added to begin the assay. Mixtures are shaken for 2 minutes and incubated at room temperature for an additional 28 minutes. The reaction is stopped by rapid filtration through Beckman GF/B glass fiber filters using a 96-well Packard cell harvester. Filters are washed four times with 1 mL ice-cold water. The filter plates are nominally dried and 30 μ L of scintillation cocktail (MicroScint 40, Packard) is added to each well. CPMs for each well is determined using a TopCount Scintillation Counter (Packard). Maximum stimulation of [^{35} S]GTP γ S binding is defined in the presence of 100nM 5-HT. Basal [^{35} S]GTP γ S binding is defined in buffer alone. IC₅₀ values are defined as the concentration of compound at which 50% of the 100nM 5-HT response [is] obtained. Maximal intrinsic activity (IA) of a compound is defined as the percent maximal 5-HT-induced stimulation by 10 μ M compound in the absence of 5-HT. As an inter-assay standard, a concentration response curve of 5-HT (1 μ M to 1 pM final) in the absence of compounds is included in each assay and an EC₅₀ is determined. EC₅₀ values for compounds of the present invention range from 10nM-10 μ M.

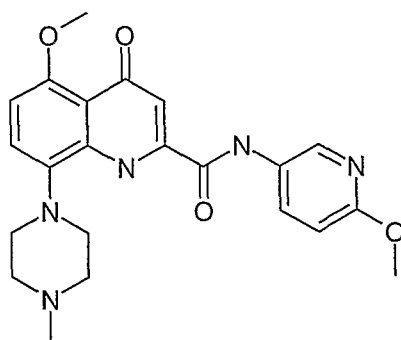
In order that the invention disclosed herein may be more efficiently understood, examples are provided below. It should be understood that these examples are for illustrative purposes only and are not to be construed as limiting the invention in any manner. Throughout these examples, molecular cloning reactions, and other standard recombinant DNA techniques, were carried out according to methods described in Maniatis et al., Molecular Cloning - A Laboratory Manual, 2nd ed., Cold Spring Harbor Press (1989), using commercially available reagents, except where otherwise noted.

Compounds of the present invention include, but are not limited to, those disclosed in the following Examples. All examples can be synthesized according to Method A starting from the appropriate quinolone ester core and the corresponding amine partner.

EXAMPLES

Example 1: 5-Methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-1,4-dihydro-quinoline-2-carboxylic acid (6-methoxy-pyridin-3-yl)-amide

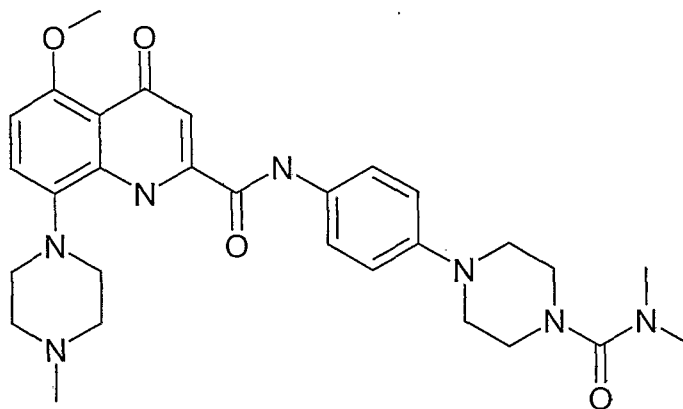
-28-



LC/MS 1.57 min. 424 (M+H, 100%); ¹H-NMR (300 MHz, DMSO-d₆) δ 10.09 (bs, 2H), 8.45 (s, 1H), 8.36 (d, J=8.0Hz, 1H), 7.52 (d, J=8.5Hz, 1H), 6.75 (s, 1H), 6.74 (d, J=8.0Hz, 1H), 6.62 (d, J=8.5Hz, 1H), 3.91 (s, 3H), 3.82 (s, 3H), 3.17 (m, 4H), 2.68 (m, 4H), 2.34 (s, 3H).

5

Example 2: 5-Methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-1,4-dihydro-quinoline-2-carboxylic acid [4-(4-dimethylcarbamoyl-piperazin-1-yl)-phenyl]-amide

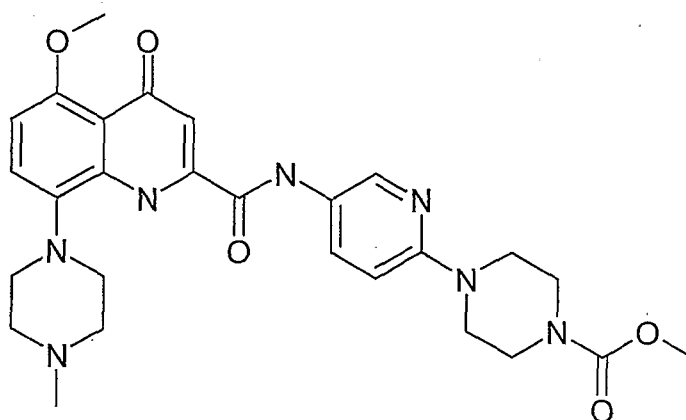


LC/MS 1.65 min. 548 (M+H, 100%); ¹H-NMR (300 MHz, DMSO-d₆) δ 9.89 (bs, 2H), 7.59 (d, J=9.3Hz, 2H), 7.52 (d, J=8.5Hz, 1H), 6.91 (d, J=9.3Hz, 2H), 6.62 (d, J=8.5Hz, 1H), 6.62 (s, 1H), 3.91 (s, 3H), 3.75 (m, 4H), 3.27 (m, 4H), 3.17 (m, 4H), 2.83 (s, 3H), 2.73 (s, 3H), 2.68 (m, 4H), 2.34 (s, 3H).

Example 3: 4-(5-{[5-Methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-1,4-dihydro-quinoline-2-carbonyl]-amino}-pyridin-2-yl)-piperazine-1-carboxylic acid methyl ester

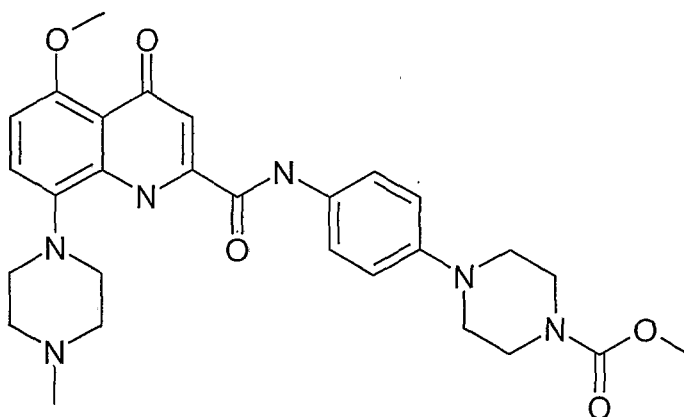
15

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LC/MS 1.53 min. 536 (M+H, 100%); ¹H-NMR (300 MHz, DMSO-d₆) δ 10.09 (bs, 2H), 8.70 (s, 1H), 8.16 (d, J=8.2Hz, 1H), 7.52 (d, J=8.5Hz, 1H), 6.98 (d, J=8.2Hz, 1H), 6.75 (s, 1H), 6.62 (d, J=8.2Hz, 1H), 3.91 (s, 3H), 3.67 (m, 4H), 3.56 (s, 3H), 3.17 (m, 4H), 2.85 (m, 4H), 2.68 (m, 4H), 2.34 (s, 3H).

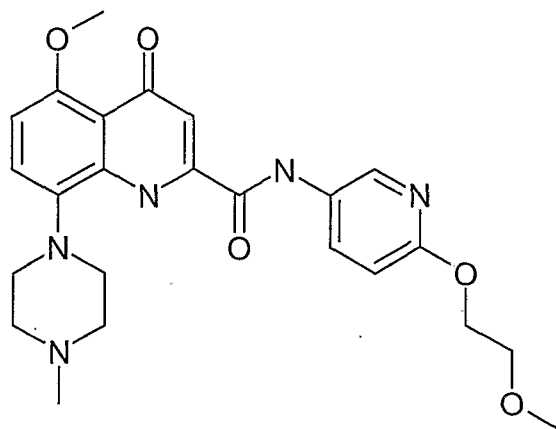
Example 4: 4-(4-{[5-Methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-1,4-dihydro-quinoline-2-carbonyl]amino}-phenyl)-piperazine-1-carboxylic acid methyl ester



LC/MS 1.62 min. 535 (M+H, 100%); ¹H-NMR (300 MHz, DMSO-d₆) δ 9.89 (bs, 2H), 7.59 (d, J=9.3Hz, 2H), 7.52 (d, J=8.5Hz, 1H), 6.89 (d, J=9.3Hz, 2H), 6.62 (d, J=8.5Hz, 1H), 6.61 (s, 1H), 3.91 (s, 3H), 3.62 (m, 4H), 3.56 (s, 3H), 3.45 (m, 4H), 3.23 (m, 4H), 3.17 (m, 4H), 3.03 (m, 4H), 2.68 (m, 4H), 2.34 (s, 3H).

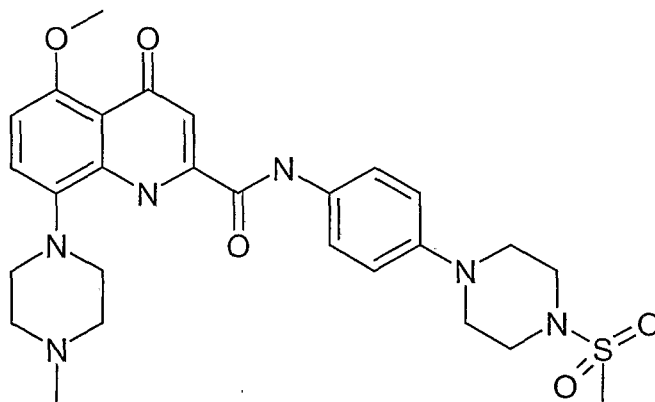
Example 5: 5-Methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-1,4-dihydro-quinoline-2-carboxylic acid [6-(2-methoxy-ethoxy)-pyridin-3-yl]-amide

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LC/MS 1.59 min. 468 (M+H, 100%); ¹H-NMR (300 MHz, DMSO-d₆) δ 10.09 (bs, 2H), 8.45 (s, 1H), 8.36 (d, J=8.0Hz, 1H), 7.52 (d, J=8.5Hz, 1H), 6.77 (d, J=8.0Hz, 1H), 6.75 (s, 1H), 6.62 (d, J=8.0Hz, 1H), 4.47 (m, 2H), 3.91 (s, 3H), 3.71 (m, 2H), 3.44 (s, 3H), 3.17 (m, 4H), 2.68 (m, 4H), 2.34 (s, 3H).

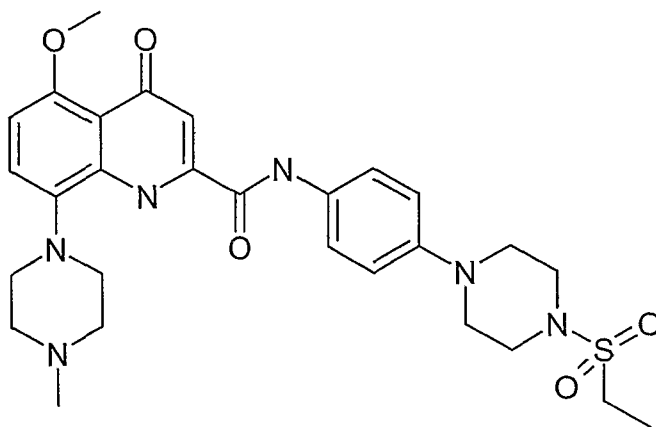
Example 6: 5-Methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-1,4-dihydro-quinoline-2-carboxylic acid [4-(4-methanesulfonyl-piperazin-1-yl)-phenyl]-amide



LC/MS 1.56 min. 555 (M+H, 100%); ¹H-NMR (300 MHz, DMSO-d₆) δ 9.89 (bs, 2H), 7.59 (d, J=9.3Hz, 2H), 7.52 (d, J=8.5Hz, 1H), 6.95 (d, J=9.3Hz, 2H), 6.62 (d, J=8.5Hz, 1H), 3.91 (s, 3H), 3.65 (m, 4H), 3.59 (m, 4H), 3.17 (m, 4H), 2.93 (s, 3H), 2.68 (m, 4H), 2.34 (s, 3H).

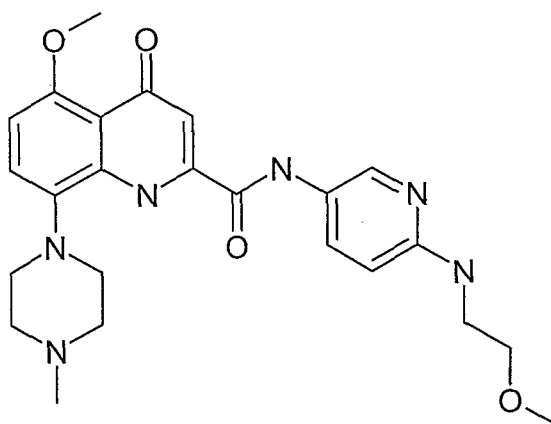
Example 7: 5-Methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-1,4-dihydro-quinoline-2-carboxylic acid [4-(4-ethanesulfonyl-piperazin-1-yl)-phenyl]-amide

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LC/MS 1.65 min. 569 (M+H, 100%); ¹H-NMR (300 MHz, DMSO-d₆) δ 9.89 (bs, 2H), 7.59 (d, J=9.3Hz, 2H), 7.52 (d, J=8.5Hz, 1H), 6.95 (d, J=9.3Hz, 2H), 6.62 (d, J=8.5Hz, 1H), 3.91 s, 3H), 3.65 (m, 4H), 3.59 (m, 4H), 3.17 (m, 4H), 3.13 (m, 2H), 2.93 (s, 3H), 2.68 (m, 4H),
 5 1.34 (t, J=7.6Hz, 3H).

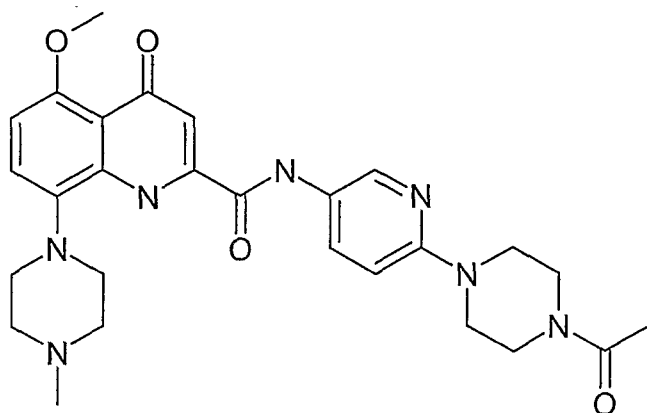
Example 8: 5-Methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-1,4-dihydro-quinoline-2-carboxylic acid [6-(2-methoxy-ethylamino)-pyridin-3-yl]-amide



10 LC/MS 1.20 min. 467 (M+H, 100%); ¹H-NMR (300 MHz, DMSO-d₆) δ 8.77 (bs, 3H), 8.71 (s, 1H), 8.20 (d, J=8.2Hz, 1H), 7.52 (d, J=8.5 Hz, 1H), 6.75 (s, 1H), 6.72 (d, J=8.2Hz, 1H), 6.62 (d, J=8.5Hz, 1H), 3.91 (s, 3H), 3.70 (s, 2H), 3.43 (s, 3H), 3.42 (s, 2H), 3.17 (m, 4H), 2.68 (m, 4H), 2.34 (s, 3H).

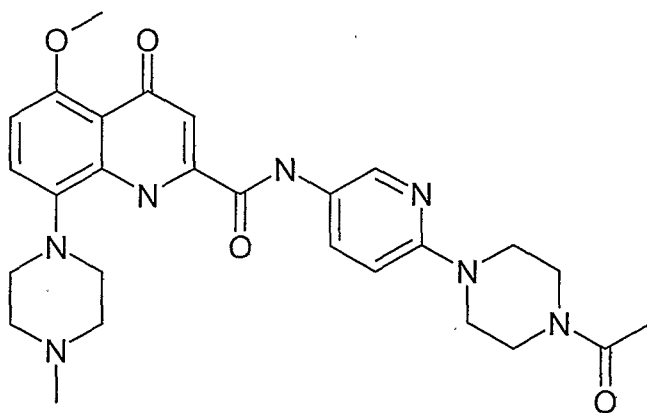
15 Example 9: 5-Methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-1,4-dihydro-quinoline-2-carboxylic acid [6-(4-propionyl-piperazin-1-yl)-pyridin-3-yl]-amide

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LC/MS 1.47 min. 534 (M+H, 100%); ¹H-NMR (300 MHz, DMSO-d₆) δ 10.09 (bs, 2H), 8.70 (s, 1H), 8.16 (d, J=8.2Hz, 1H), 7.52 (d, J=8.5 Hz, 1H), 6.98 (s, 1H), 6.75 (d, J=8.5 Hz, 1H), 6.62 (d, J=8.2 Hz, 1H), 3.91 (s, 3H), 3.88 (m, 4H), 3.18 (m, 4H), 3.17 (m, 4H), 2.68 (m, 4H),
 5 2.35 (m, 2H), 2.34 (s, 3H), 0.97 (t, J=7.4Hz, 3H).

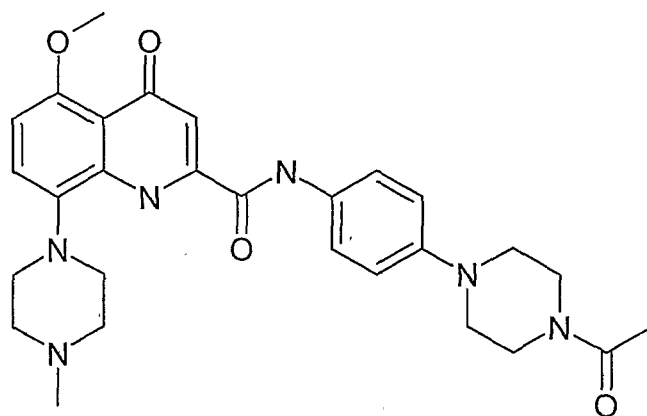
Example 10: 5-Methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-1,4-dihydro-quinoline-2-carboxylic acid [6-(4-acetyl-piperazin-1-yl)-pyridin-3-yl]-amide



10 LC/MS 1.32 min. 520 (M+H, 100%); ¹H-NMR (300 MHz, DMSO-d₆) δ 10.09 (bs, 2H), 8.70 (s, 1H), 8.16 (d, J=8.2Hz, 1H), 7.52 (d, J=8.5 Hz, 1H), 6.98 (s, 1H), 6.75 (d, J=8.5 Hz, 1H), 6.62 (d, J=8.2 Hz, 1H), 3.91 (s, 3H), 3.88 (m, 4H), 3.18 (m, 4H), 3.17 (m, 4H), 2.68 (m, 4H), 2.34 (s, 3H), 2.13 (s, 3H).

15 Example 11: 5-Methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-1,4-dihydro-quinoline-2-carboxylic acid [4-(4-acetyl-piperazin-1-yl)-phenyl]-amide

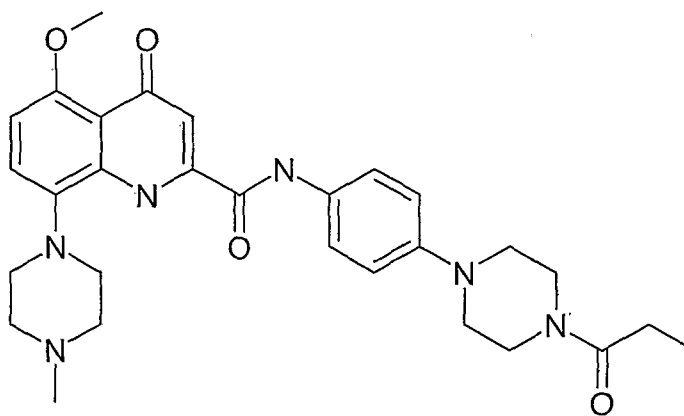
-33-



LC/MS 1.45 min. 519 (M+H, 100%); ¹H-NMR (300 MHz, DMSO-d₆) δ 9.89 (bs, 2H), 7.59 (d, J=9.3Hz, 2H), 7.52 (d, J=8.5 Hz, 1H), 6.89 (d, J=9.3 Hz, 2H), 6.62 (d, J=8.2 Hz, 1H), 3.91 (s, 3H), 3.82 (m, 4H), 3.17 (m, 4H), 3.08 (m, 4H), 2.68 (m, 4H), 2.34 (s, 3H), 2.07 (s, 3H).

5

Example 12: 5-Methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-1,4-dihydro-quinoline-2-carboxylic acid [4-(4-propionyl-piperazin-1-yl)-phenyl]-amide

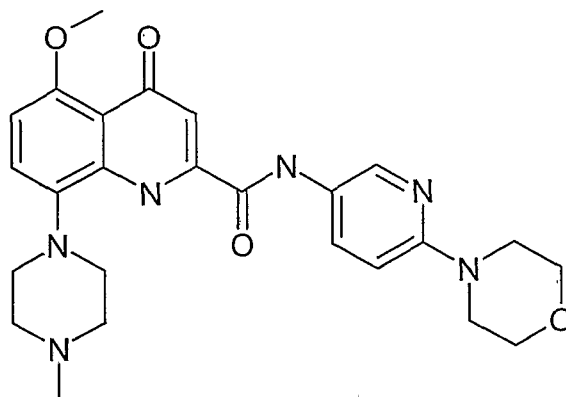


LC/MS 1.65 min. 533 (M+H, 100%); ¹H-NMR (300 MHz, DMSO-d₆) δ 9.89 (bs, 2H), 7.59 (d, J=9.3Hz, 2H), 7.52 (d, J=8.5 Hz, 1H), 6.89 (d, J=9.3 Hz, 2H), 6.62 (d, J=8.2 Hz, 1H), 3.91 (s, 3H), 3.82 (m, 4H), 3.17 (m, 4H), 3.08 (m, 4H), 2.68 (m, 4H), 2.34 (s, 3H), 2.32 (m, 2H), 0.97 (t, J=7.4Hz, 3H).

Example 13: 5-Methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-1,4-dihydro-quinoline-2-carboxylic acid (6-morpholin-4-yl-pyridin-3-yl)-amide

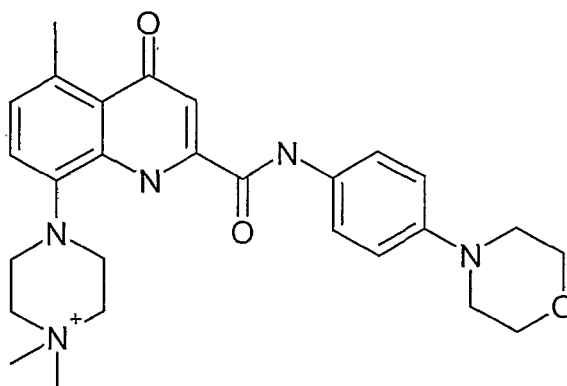
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LC/MS 1.40 min. 479 (M+H, 100%); ¹H-NMR (300 MHz, DMSO-d₆) δ 10.09 (bs, 2H), 8.70 (s, 1H), 8.16 (d, J=8.2Hz, 1H), 7.52 (d, J=8.5 Hz, 1H), 6.83 (s, 1H), 6.75 (d, J=8.5 Hz, 1H), 6.62 (d, J=8.2 Hz, 1H), 3.91 (s, 3H), 3.72 (m, 4H), 3.64 (m, 4H), 3.17 (m, 4H), 2.68 (m, 4H),
 5 2.34 (s, 3H).

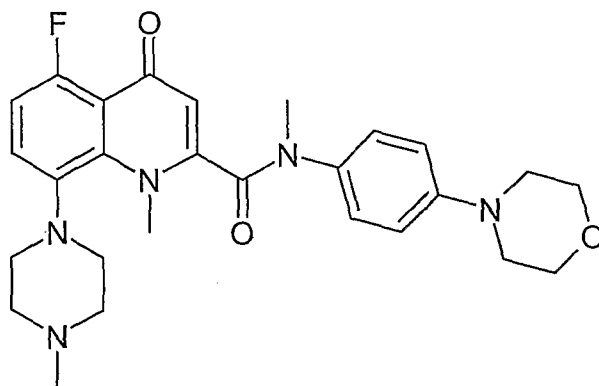
Example 14: 1,1-Dimethyl-4-[5-methyl-2-(4-morpholin-4-yl-phenylcarbamoyl)-4-oxo-1,4-dihydro-quinolin-8-yl]-piperazin-1-ium



10 LC/MS 1.53 min. 476 (M+H, 100%); ¹H-NMR (300 MHz, DMSO-d₆) δ 9.89 (bs, 2H), 7.59 (d, J=9.3Hz, 1H), 7.27 (d, J=8.0Hz, 1H), 6.94 (d, J=9.3Hz, 1H), 6.76 (d, J=8.0Hz, 1H), 6.61 (s, 1H), 3.74 (m, 4H), 3.69 (m, 4H), 3.30 (s, 6H), 3.27 (m, 4H), 3.13 (m, 4H), 2.58 (s, 3H).

Example 15: 5-Fluoro-1-methyl-8-(4-methyl-piperazin-1-yl)-4-oxo-1,4-dihydro-quinoline-2-carboxylic acid methyl-(4-morpholin-4-yl-phenyl)-amide
 15

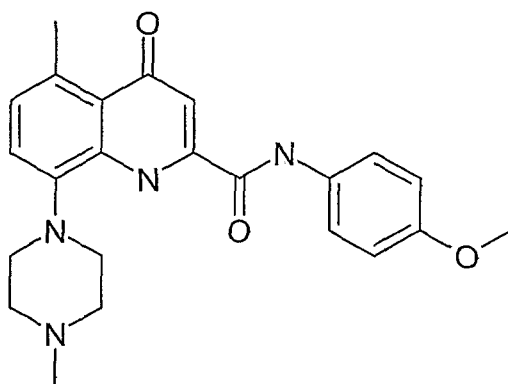
-35-



LC/MS 1.34 min. 494 (M+H, 100%); ¹H-NMR (300 MHz, DMSO-d₆) δ 7.52 (d, J=9.3Hz, 1H), 7.42 (d, J=8.0Hz, 1H), 7.23 (d, J=9.3Hz, 1H), 6.94 (d, J=8.0Hz, 1H), 6.56 (s, 1H), 3.69 (m, 4H), 3.50 (s, 3H), 3.36 (s, 3H), 3.31 (m, 4H), 3.26 (m, 4H), 2.69 (m, 4H), 2.34 (s, 3H).

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Example 16: 4-Hydroxy-5-methyl-8-(4-methyl-piperazin-1-yl)-quinoline-2-carboxylic acid (4-methoxy-phenyl)-amide

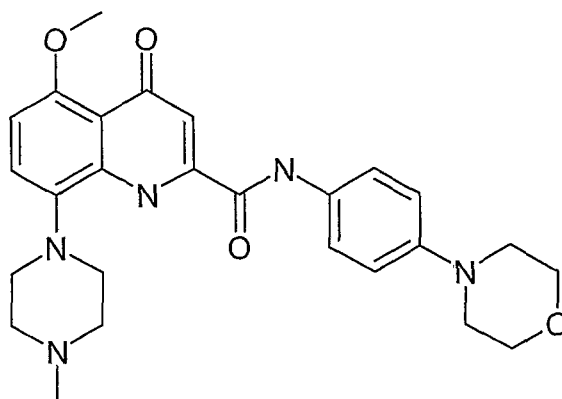


LC/MS 1.74 min. 407 (M+H, 100%); ¹H-NMR (300 MHz, DMSO-d₆) δ 9.89 (bs, 2H), 7.57 (d, J=9.3Hz, 1H), 7.49 (d, J=8.0Hz, 1H), 6.95 (d, J=9.3Hz, 1H), 6.83 (d, J=8.0Hz, 1H), 6.61 (s, 1H), 3.78 (s, 3H), 3.19 (m, 4H), 2.68 (m, 4H), 2.58 (s, 3H), 2.34 (s, 3H).

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Example 17: 4-Hydroxy-5-methoxy-8-(4-methyl-piperazin-1-yl)-quinoline-2-carboxylic acid (4-morpholin-4-yl-phenyl)-amide

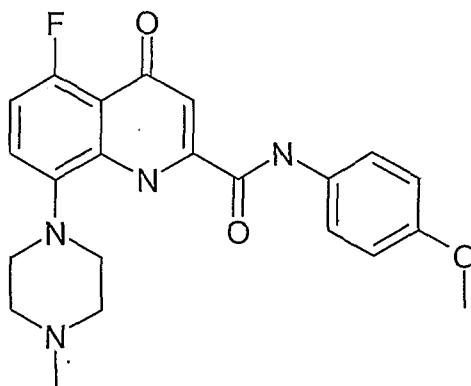
-36-



LC/MS 1.47 min. 478 (M+H, 100%); ¹H-NMR (300 MHz, DMSO-d₆) δ 11.87 (bs, 2H), 7.50 (d, J=9.3Hz, 1H), 7.22 (d, J=8.0Hz, 1H), 6.77 (d, J=9.3Hz, 1H), 6.57 (d, J=8.0Hz, 1H), 6.49 (s, 1H), 3.90 (s, 3H), 3.69 (m, 4H), 3.53 (m, 4H), 3.12 (m, 4H), 2.57 (m, 4H), 2.28 (s, 3H).

5

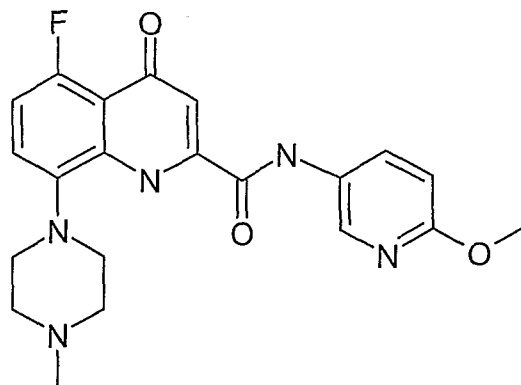
Example 18: 5-Fluoro-8-(4-methyl-piperazin-1-yl)-4-oxo-1,4-dihydro-quinoline-2-carboxylic acid (4-methoxy-phenyl)-amide



LC/MS 1.49 min. 411 (M+H, 100%); ¹H-NMR (300 MHz, DMSO-d₆) δ 9.89 (bs, 2H), 7.78 (d, J=9.3Hz, 1H), 7.57 (d, J=8.0Hz, 1H), 7.21 (d, J=9.3Hz, 1H), 6.83 (d, J=8.0Hz, 1H), 6.69 (s, 1H), 3.78 (m, 4H), 3.18 (m, 4H), 2.68 (m, 4H), 2.34 (s, 3H).

Example 19: 5-Fluoro-8-(4-methyl-piperazin-1-yl)-4-oxo-1,4-dihydro-quinoline-2-carboxylic acid (6-methoxy-pyridin-3-yl)-amide

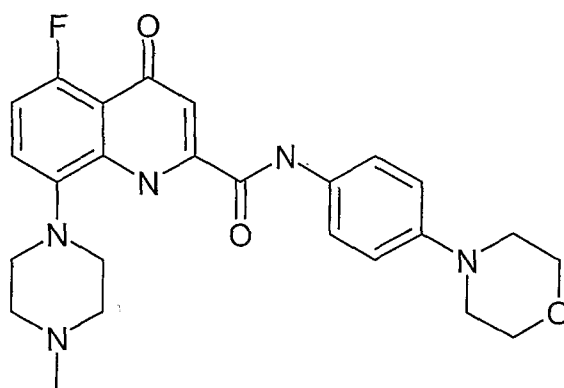
-37-



LC/MS 1.40 min. 412 (M+H, 100%); ¹H-NMR (300 MHz, DMSO-d₆) δ 10.09 (bs, 2H), 8.45 (d, J=8.0Hz, 1H), 8.36 (d, J=8.0Hz, 1H), 7.78 (d, J=8.0Hz, 1H), 7.21 (d, J=8.0Hz, 1H), 6.82 (s, 1H), 6.74 (d, J=8.0Hz, 1H), 3.82 (s, 3H), 3.18 (m, 4H), 2.68 (m, 4H), 2.34 (s, 3H).

5

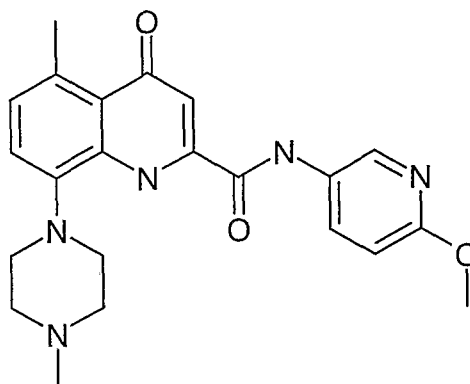
Example 20: 5-Fluoro-8-(4-methyl-piperazin-1-yl)-4-oxo-1,4-dihydro-quinoline-2-carboxylic acid (4-morpholin-4-yl-phenyl)-amide



LC/MS 1.53 min. 466 (M+H, 100%); ¹H-NMR (300 MHz, DMSO-d₆) δ 9.89 (bs, 2H), 7.78 (d, J=8.0Hz, 1H), 7.59 (d, J=9.3Hz, 1H), 7.21 (d, J=8.0Hz, 1H), 6.76 (d, J=9.3Hz, 1H), 6.69 (s, 1H), 3.69 (m, 4H), 3.27 (m, 4H), 3.18 (m, 4H), 2.68 (m, 4H), 2.34 (s, 3H).

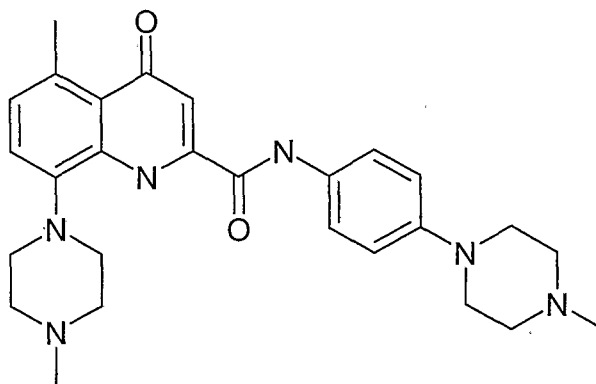
Example 21: 4-Hydroxy-5-methyl-8-(4-methyl-piperazin-1-yl)-quinoline-2-carboxylic acid (6-methoxy-pyridin-3-yl)-amide

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LC/MS 1.64 min. 408 (M+H, 100%); ¹H-NMR (300 MHz, DMSO-d₆) δ 10.09 (bs, 2H), 8.45 (s, 1H), 8.36 (d, J=8.0Hz, 1H), 7.49 (d, J=8.0Hz, 1H), 6.95 (d, J=8.0Hz, 1H), 6.74 (d, J=8.0Hz, 1H), 6.73 (s, 1H), 3.82 (s, 3H), 3.19 (m, 4H), 2.68 (m, 4H), 2.58 (s, 3H), 2.34 (s, 3H).

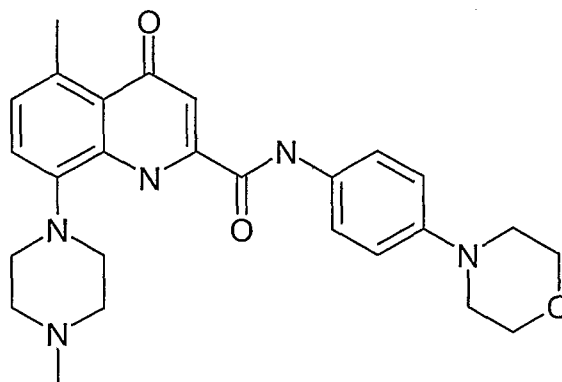
Example 22: 4-Hydroxy-5-methyl-8-(4-methyl-piperazin-1-yl)-quinoline-2-carboxylic acid [4-(4-methyl-piperazin-1-yl)-phenyl]-amide



LC/MS 1.38 min. 475 (M+H, 100%); ¹H-NMR (300 MHz, DMSO-d₆) δ 9.89 (bs, 2H), 7.59 (d, J=9.3Hz, 1H), 7.49 (d, J=8.0Hz, 1H), 6.95 (d, J=8.0Hz, 1H), 6.89 (d, J=9.3Hz, 1H), 6.61 (s, 1H), 3.19 (m, 4H), 3.07 (m, 4H), 2.68 (m, 4H), 2.58 (s, 3H), 2.54 (m, 4H), 2.34 (s, 3H), 2.31 (s, 3H).

Example 23: 4-Hydroxy-5-methyl-8-(4-methyl-piperazin-1-yl)-quinoline-2-carboxylic acid (4-morpholin-4-yl-phenyl)-amide

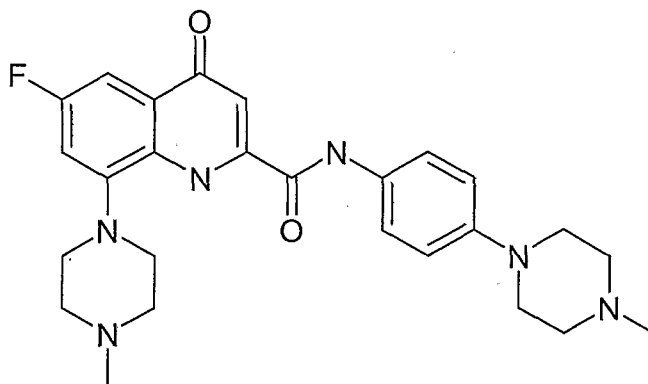
-39-



LC/MS 1.71 min. 462 (M+H, 100%); ¹H-NMR (300 MHz, DMSO-d₆) δ 9.89 (bs, 2H), 7.59 (d, J=9.3Hz, 1H), 7.49 (d, J=8.0Hz, 1H), 6.95 (d, J=8.0Hz, 1H), 6.76 (d, J=9.3Hz, 1H), 6.61 (s, 1H), 3.69 (m, 4H), 3.27 (m, 4H), 3.19 (m, 4H), 2.68 (m, 4H), 2.58 (s, 3H), 2.34 (s, 3H).

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Example 24: 6-Fluoro-8-(4-methyl-piperazin-1-yl)-4-oxo-1,4-dihydro-quinoline-2-carboxylic acid [4-(4-methyl-piperazin-1-yl)-phenyl]-amide



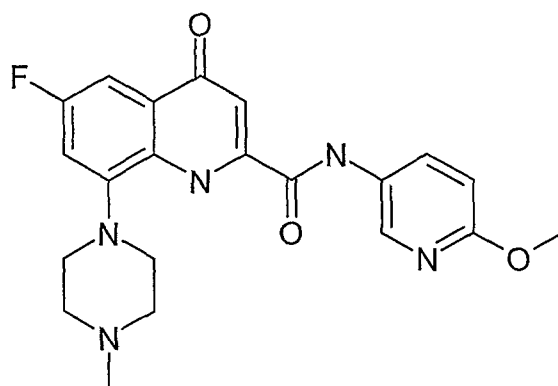
LC/MS 1.32 min. 479 (M+H, 100%); ¹H -NMR (300 MHz, DMSO-d₆, TFA shake) δ 7.78

10 (d, J = 8.8 Hz, 2H), 7.60 (s, 1H), 7.47 (d, J = 9.0 Hz, 1H); 7.26 (d, J = 10.9 Hz, 1H), 7.08 (d, J = 8.8 Hz, 2H), 4.15 (d, J = 12.8 Hz, 2H), 3.84 (d, J = 13.0 Hz, 2H), 3.67 (d, J = 11.3 Hz, 2H), 3.62 - 3.41 (m, 4H), 3.33 - 3.13 (m, 4H), 3.07 - 2.83 (m, 8H).

Example 25: 6-Fluoro-8-(4-methyl-piperazin-1-yl)-4-oxo-1,4-dihydro-quinoline-2-carboxylic acid (6-methoxy-pyridin-3-yl)-amide

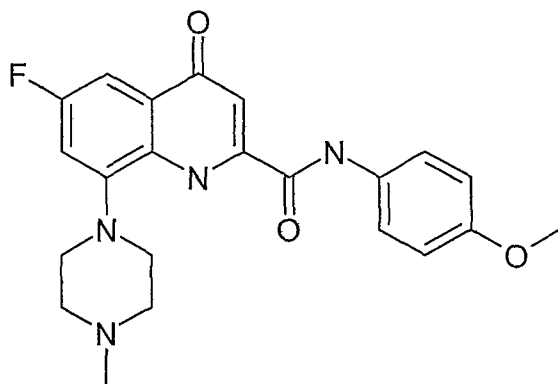
15

-40-



LC/MS 1.50 min. 412 (M+H, 100%); ¹H -NMR (300 MHz, DMSO-d₆, TFA shake) δ 8.61 (d, J = 2.6 Hz, 1H), 8.26 (dd, J = 8.9, 2.7 Hz, 1H), 7.61 (s, 1H), 7.47 (dd, J = 9.1, 2.6 Hz, 1H), 7.25 (dd, J = 11.0, 2.7 Hz, 1H), 6.93 (d, J = 8.9 Hz, 1H), 4.17 (d, J = 13.3 Hz, 2H), 3.89 (s, 3H), 3.68 (d, J = 12.1 Hz, 2H), 3.53 (t, J = 10.7 Hz, 2H), 3.24 (t, J = 11.7 Hz, 2H), 2.98 (s, 3H).

Example 26: 6-Fluoro-8-(4-methyl-piperazin-1-yl)-4-oxo-1,4-dihydro-quinoline-2-carboxylic acid (4-methoxy-phenyl)-amide



LC/MS 1.58 min. 411 (M+H, 100%); ¹H -NMR (300 MHz, DMSO-d₆, TFA shake) δ 7.80 (d, J = 9.0 Hz, 2H), 7.61 (s, 1H), 7.47 (dd, J = 9.2, 2.6 Hz, 1H), 7.25 (dd, J = 10.8, 2.6 Hz, 1H), 7.00 (d, J = 9.0 Hz, 2H), 4.15 (d, J = 13.0 Hz, 2H), 3.79 (s, 3H), 3.68 (d, J = 11.9 Hz, 2H), 3.53 (t, J = 10.7 Hz, 2H), 3.25 (t, J = 11.6 Hz, 2H), 2.98 (s, 3H).

Various modifications of the invention, in addition to those described herein, will be apparent to those skilled in the art from the foregoing description. Such modifications are also intended to fall within the scope of the appended claims.

WHAT IS CLAIMED IS:

1. A compound selected from the following:

5-Methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-1,4-dihydro-quinoline-2-carboxylic
 5 acid (6-methoxy-pyridin-3-yl)-amide;

5-Methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-1,4-dihydro-quinoline-2-carboxylic
 acid [4-(4-dimethylcarbamoyl-piperazin-1-yl)-phenyl]-amide;

4-(5-{[5-Methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-1,4-dihydro-quinoline-2-
 carbonyl]-amino}-pyridin-2-yl)-piperazine-1-carboxylic acid methyl ester;

10 4-(4-{[5-Methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-1,4-dihydro-quinoline-2-
 carbonyl]amino}-phenyl)-piperazine-1-carboxylic acid methyl ester;

5-Methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-1,4-dihydro-quinoline-2-carboxylic
 acid [6-(2-methoxy-ethoxy)-pyridin-3-yl]-amide;

5-Methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-1,4-dihydro-quinoline-2-carboxylic
 15 acid [4-(4-methanesulfonyl-piperazin-1-yl)-phenyl]-amide;

5-Methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-1,4-dihydro-quinoline-2-carboxylic
 acid [4-(4-ethanesulfonyl-piperazin-1-yl)-phenyl]-amide);

5-Methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-1,4-dihydro-quinoline-2-carboxylic
 acid [6-(2-methoxy-ethylamino)-pyridin-3-yl]-amide;

20 5-Methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-1,4-dihydro-quinoline-2-carboxylic
 acid [6-(4-propionyl-piperazin-1-yl)-pyridin-3-yl]-amide;

5-Methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-1,4-dihydro-quinoline-2-carboxylic
 acid [6-(4-acetyl-piperazin-1-yl)-pyridin-3-yl]-amide;

5-Methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-1,4-dihydro-quinoline-2-carboxylic
 25 acid [4-(4-acetyl-piperazin-1-yl)-phenyl]-amide;

5-Methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-1,4-dihydro-quinoline-2-carboxylic
 acid [4-(4-propionyl-piperazin-1-yl)-phenyl]-amide;

5-Methoxy-8-(4-methyl-piperazin-1-yl)-4-oxo-1,4-dihydro-quinoline-2-carboxylic
 acid (6-morpholin-4-yl-pyridin-3-yl)-amide;

30 1,1-Dimethyl-4-[5-methyl-2-(4-morpholin-4-yl-phenylcarbamoyl)-4-oxo-1,4-
 dihydro-quinolin-8-yl]-piperazin-1-ium;

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5-Fluoro-1-methyl-8-(4-methyl-piperazin-1-yl)-4-oxo-1,4-dihydro-quinoline-2-carboxylic acid methyl-(4-morpholin-4-yl-phenyl)-amide;

4-Hydroxy-5-methyl-8-(4-methyl-piperazin-1-yl)-quinoline-2-carboxylic acid (4-methoxy-phenyl)-amide;

5 4-Hydroxy-5-methoxy-8-(4-methyl-piperazin-1-yl)-quinoline-2-carboxylic acid (4-morpholin-4-yl-phenyl)-amide;

5-Fluoro-8-(4-methyl-piperazin-1-yl)-4-oxo-1,4-dihydro-quinoline-2-carboxylic acid (4-methoxy-phenyl)-amide;

10 5-Fluoro-8-(4-methyl-piperazin-1-yl)-4-oxo-1,4-dihydro-quinoline-2-carboxylic acid (6-methoxy-pyridin-3-yl)-amide;

5-Fluoro-8-(4-methyl-piperazin-1-yl)-4-oxo-1,4-dihydro-quinoline-2-carboxylic acid (4-morpholin-4-yl-phenyl)-amide;

4-Hydroxy-5-methyl-8-(4-methyl-piperazin-1-yl)-quinoline-2-carboxylic acid (6-methoxy-pyridin-3-yl)-amide;

15 4-Hydroxy-5-methyl-8-(4-methyl-piperazin-1-yl)-quinoline-2-carboxylic acid [4-(4-methyl-piperazin-1-yl)-phenyl]-amide;

4-Hydroxy-5-methyl-8-(4-methyl-piperazin-1-yl)-quinoline-2-carboxylic acid (4-morpholin-4-yl-phenyl)-amide;

20 6-Fluoro-8-(4-methyl-piperazin-1-yl)-4-oxo-1,4-dihydro-quinoline-2-carboxylic acid [4-(4-methyl-piperazin-1-yl)-phenyl]-amide;

6-Fluoro-8-(4-methyl-piperazin-1-yl)-4-oxo-1,4-dihydro-quinoline-2-carboxylic acid (6-methoxy-pyridin-3-yl)-amide;

6-Fluoro-8-(4-methyl-piperazin-1-yl)-4-oxo-1,4-dihydro-quinoline-2-carboxylic acid (4-methoxy-phenyl)-amide

25 or a pharmaceutically acceptable salt.

2. A composition comprising the compound of claim 1 and a pharmaceutically acceptable diluent or carrier.

30 3. The use of a compound according to claim 1 in the treatment of an anxiety disorder, cognitive disorder, and/or mood disorder.

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4. The use of a compound according to claim 1 in the treatment of an anxiety disorder.
5. The use of a compound according to claim 1 in the treatment of panic disorder, panic disorder without agoraphobia, panic disorder with agoraphobia, agoraphobia without
5 history of panic disorder, specific phobia, social phobia, social anxiety disorder, obsessive-compulsive disorder, posttraumatic stress disorder, acute stress disorder, generalized anxiety disorder, and/or generalized anxiety disorder due to a general medical condition.
6. The use of a compound according to claim 1 in the treatment of a cognitive disorder.
10
7. The use of a compound according to claim 1 in the treatment of Alzheimer's disease, dementia, dementia due to Alzheimer's disease, and/or dementia due to Parkinson's disease.
8. The use of a compound according to claim 1 in the treatment of a mood disorder.
15
9. The use of a compound according to claim 1 in the treatment of a depressive disorder.
10. The use of a compound according to claim 1 in the treatment of major depressive
20 disorder, dysthymic disorder, bipolar depression, bipolar mania, cyclothymic disorder, mood disorder due to a general medical condition, manic episode associated with bipolar disorder, and/or mixed episode associated with bipolar disorder.
11. A method of treating an animal suffering from an anxiety disorder, cognitive
25 disorder, and/or mood disorder comprising administering to such animal an effective amount of a compound according to claim 1 or a pharmaceutically acceptable salt of said compound.
12. The method according to claim 11 wherein the treatment is for an anxiety disorder.
- 30 13. The method according to claim 12 wherein the anxiety disorder is selected from panic disorder, panic disorder without agoraphobia, panic disorder with agoraphobia,

agoraphobia without history of panic disorder, specific phobia, social phobia, social anxiety disorder, obsessive-compulsive disorder, posttraumatic stress disorder, acute stress disorder, generalized anxiety disorder, and/or generalized anxiety disorder due to a general medical condition.

5 14. The method according to claim 11 wherein the treatment is for a cognitive disorder.

15. The method according to claim 14 wherein the cognitive disorder is selected from Alzheimer's disease, dementia, and dementia due to Alzheimer's disease, and/or dementia due to Parkinson's disease.

10

16. The method according to claim 11 wherein the treatment is for a mood disorder.

17. The method according to claim 16 wherein the mood disorder is a depressive disorder.

15

18. The method according to claim 17 wherein the depressive disorder is selected from major depressive disorder, dysthymic disorder, bipolar depression and/or bipolar mania, cyclothymic disorder, mood disorder due to a general medical condition, manic episode associated with bipolar disorder, and mixed episode associated with bipolar disorder.

20

19. The method according to claim 18 wherein the bipolar depression and/or bipolar mania is bipolar II, or bipolar I with or without manic, depressive or mixed episodes.

20. The use of any one of the compounds according to claim 1 in the preparation of a
25 medicament for the treatment of an anxiety disorder, a cognitive disorder, and/or a mood disorder.

30

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE2007/000164

A. CLASSIFICATION OF SUBJECT MATTER

IPC: see extra sheet

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)

IPC: C07D, A61K

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

SE,DK,FI,NO classes as above

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

EPO-INTERNAL, WPI DATA, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 03037871 A1 (ASTRAZENECA AB), 8 May 2003 (08.05.2003), example 32,45,47,66,67,88,89,91 --	1-20
X	WO 03037872 A1 (ASTRAZENECA AB), 8 May 2003 (08.05.2003), example 32,45,47,66,67,88,89,91 --	1-20
X	WO 02055012 A2 (ASTRAZENECA AB), 18 July 2002 (18.07.2002), example 32,45,47,66,67,88,89,91 --	1-20
X	WO 02055013 A2 (ASTRAZENECA AB), 18 July 2002 (18.07.2002), example 32,45,47,66,67,88,89,91 --	1-20

☒ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search

22 May 2007

Date of mailing of the international search report

24 -05- 2007

Name and mailing address of the ISA/

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE2007/000164

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 02055014 A2 (ASTRAZENECA AB), 18 July 2002 (18.07.2002), example 32,45,47,66,67,88,89,91 -- -----	1-20

International patent classification (IPC)

C07D 215/233 (2006.01)
A61K 31/47 (2006.01)
A61K 31/4709 (2006.01)
A61P 25/22 (2006.01)
A61P 25/24 (2006.01)
A61P 25/28 (2006.01)
C07D 401/12 (2006.01)

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Use the application number as username.

The password is **RHWRVHJQIX**.

Paper copies can be ordered at a cost of 50 SEK per copy from PRV InterPat (telephone number 08-782 28 85).

Cited literature, if any, will be enclosed in paper form.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE2007/000164

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. ☒ Claims Nos.: 3 - 19
because they relate to subject matter not required to be searched by this Authority, namely:

Claims 3-19 relate to a method of treatment of the human or animal body by surgery or by therapy, as well as diagnostic .../...
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 all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

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

International application No.
PCT/SE2007/000164

Box II.1

methods /Rule 39.1(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds.

INTERNATIONAL SEARCH REPORT

Information on patent family members

31/03/2007

International application No.

PCT/SE2007/000164

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INTERNATIONAL SEARCH REPORT

Information on patent family members

31/03/2007

International application No.

PCT/SE2007/000164

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