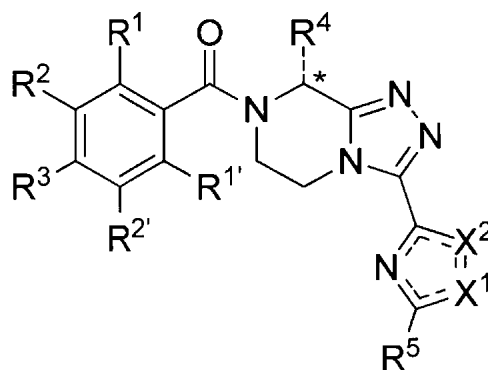


activities that can lead to safety concerns (for example, inhibition of hERG ion channel activity, a widely accepted marker of cardiovascular toxicity).

The invention thus encompasses compounds of general Formula I, their pharmaceutically acceptable solvates as well as methods of use of such compounds or compositions comprising such compounds as antagonists to the NK-3 receptor. Compounds of Formula I are *N*-acyl-(3-substituted)-(8-substituted)-5,6-dihydro-[1,2,4]triazolo[4,3-*a*]pyrazines. The compounds of the invention are generally disclosed in international patent application WO2011/121137 but none is specifically exemplified therein. On another hand, unsubstituted and thus non-chiral 5,6,7,8-tetrahydro[1,2,4]triazolo[4,3-*a*]pyrazines have been disclosed in WO2010/125102 as modulators of an unrelated target, namely P2X7.

SUMMARY

In one aspect, the present disclosure provides a compound of Formula I:



wherein:

R¹ is H, F or methyl;

R^{1'} is H;

R² is H, F, Cl or methoxy;

R^{2'} is H or F;

R³ is H, F, Cl, methyl, trifluoromethyl or nitrile;

R⁴ is methyl, ethyl, *n*-propyl, hydroxyethyl, methoxyethyl, trifluoromethyl, difluoromethyl or fluoromethyl;

R^4 is methyl, ethyl, *n*-propyl, hydroxyethyl, methoxyethyl, trifluoromethyl, difluoromethyl or fluoromethyl;

R^5 is methyl, ethyl, methoxymethyl, trifluoromethyl, difluoromethyl, fluoromethyl, 1-fluoroethyl, 1,1-difluoroethyl or 2,2,2-trifluoroethyl, preferably R^5 is methyl, ethyl, methoxymethyl, trifluoromethyl, difluoromethyl or fluoromethyl;

X^1 is N and X^2 is S or O; or X^1 is S and X^2 is N;

== represents a single or a double bond depending on X^1 and X^2 ;

*-- stands for the (*R*)-enantiomer or for the racemate of compound of Formula I.

In one embodiment, the present disclosure provides a pharmaceutical composition comprising at least one compound according to the disclosure or a pharmaceutically acceptable solvate thereof.

In another aspect, the present disclosure provides a pharmaceutical composition comprising a compound as disclosed above and at least one pharmaceutically acceptable carrier, diluent, excipient and/or adjuvant.

The disclosure also relates to the use of the above compounds or their pharmaceutically acceptable solvates as modulators of NK-3 receptors, preferably as antagonists of NK-3 receptors.

The disclosure also relates to the use of the above compounds or their pharmaceutically acceptable solvates as lowering agents of the circulating LH levels.

The disclosure further provides methods of treatment and/or prevention of depression, anxiety, psychosis, schizophrenia, psychotic disorders, bipolar disorders, cognitive disorders, Parkinson's disease, Alzheimer's disease, attention deficit hyperactivity disorder (ADHD), pain, convulsion, obesity, inflammatory diseases including irritable bowel syndrome (IBS) and inflammatory bowel disorders, emesis, pre-eclampsia, airway related diseases including chronic obstructive pulmonary disease, asthma, airway hyperresponsiveness, bronchoconstriction and cough, reproduction disorders, contraception and sex hormone-dependent diseases including but not limited to benign prostatic hyperplasia (BPH), prostatic hyperplasia, metastatic prostatic carcinoma, testicular cancer, breast cancer, ovarian cancer, androgen dependent acne, male pattern baldness, endometriosis, abnormal puberty, uterine fibrosis, uterine fibroid tumor, hormone-dependent cancers, hyperandrogenism, hirsutism, virilization, polycystic

The disclosure further provides methods of treatment for gynecological disorders and infertility. In particular, the disclosure provides methods to lower and/or suppress the LH-surge in assisted conception comprising the administration of a therapeutically effective amount of a compound or pharmaceutically acceptable solvate of Formula I, to a patient in need thereof. Preferably the patient is a warm-blooded animal, more preferably a woman.

The disclosure further provides methods to affect androgen production to cause male castration and to inhibit the sex drive in male sexual offenders comprising the administration of a therapeutically effective amount of a compound or pharmaceutically acceptable solvate of Formula I, to a patient in need thereof. Preferably the patient is a warm-blooded animal, more preferably a man.

In another aspect, the present disclosure provides a medicament comprising a compound as disclosed above.

In another aspect, the present disclosure provides a compound as disclosed above for use in treating and/or preventing depression, anxiety, psychosis, schizophrenia, psychotic disorders, bipolar disorders, cognitive disorders, Parkinson's disease, Alzheimer's disease, attention deficit hyperactivity disorder (ADHD), pain, convulsion, obesity, inflammatory diseases including irritable bowel syndrome (IBS) and inflammatory bowel disorders, emesis, pre-eclampsia, airway related diseases including chronic obstructive pulmonary disease, asthma, airway hyperresponsiveness, bronchoconstriction and cough, urinary incontinence, reproduction disorders, contraception and sex hormone-dependent diseases including but not limited to benign prostatic hyperplasia (BPH), prostatic hyperplasia, metastatic prostatic carcinoma, testicular cancer, breast cancer, ovarian cancer, androgen dependent acne, male pattern baldness, endometriosis, abnormal puberty, uterine fibrosis, uterine fibroid tumor, uterine leiomyoma, hormone-dependent cancers, hyperandrogenism, hirsutism, virilization, polycystic ovary syndrome (PCOS), premenstrual dysphoric disease (PMDD), HAIR-AN syndrome (hyperandrogenism, insulin resistance and acanthosis nigricans), ovarian hyperthecosis (HAIR-AN with hyperplasia of luteinized theca cells in ovarian stroma), other manifestations of high intraovarian androgen concentrations (e.g. follicular maturation arrest, atresia, anovulation, dysmenorrhea,

dysfunctional uterine bleeding, infertility), androgen-producing tumor (virilizing ovarian tumor or virilizing adrenal tumor), menorrhagia, or adenomyosis.

The disclosure also provides the use of a compound of Formula I or a pharmaceutically acceptable solvate thereof as a medicament. Preferably, the medicament is used for the treatment and/or prevention of depression, anxiety, psychosis, schizophrenia, psychotic disorders, bipolar disorders, cognitive disorders, Parkinson's disease, Alzheimer's disease, attention deficit hyperactivity disorder (ADHD), pain, convulsion, obesity, inflammatory diseases including irritable bowel syndrome (IBS) and inflammatory bowel disorders, emesis, pre-eclampsia, airway related diseases including chronic obstructive pulmonary disease, asthma, airway hyperresponsiveness, bronchoconstriction and cough, reproduction disorders, contraception and sex hormone-dependent diseases including but not limited to benign prostatic hyperplasia (BPH), prostatic hyperplasia, metastatic prostatic carcinoma, testicular cancer, breast cancer, ovarian cancer, androgen dependent acne, male pattern baldness, endometriosis, abnormal puberty, uterine fibrosis, uterine fibroid tumor, hormone-dependent cancers, hyperandrogenism, hirsutism, virilization, polycystic ovary syndrome (PCOS), premenstrual dysphoric disease (PMDD), HAIR-AN syndrome (hyperandrogenism, insulin resistance and acanthosis nigricans), ovarian hyperthecosis (HAIR-AN with hyperplasia of luteinized theca cells in ovarian stroma), other manifestations of high intraovarian androgen concentrations (e.g. follicular maturation arrest, atresia, anovulation, dysmenorrhea, dysfunctional uterine bleeding, infertility), androgen-

producing tumor (virilizing ovarian or adrenal tumor), menorrhagia and adenomyosis. Preferably, the medicament is used for the treatment and/or prevention of depression, anxiety, psychosis, schizophrenia, psychotic disorders, bipolar disorders, cognitive disorders, Parkinson's disease, Alzheimer's disease, attention deficit hyperactivity disorder (ADHD), pain, convulsion, obesity, inflammatory diseases including irritable bowel syndrome (IBS) and inflammatory bowel disorders, emesis, pre-eclampsia, airway related diseases including chronic obstructive pulmonary disease, asthma, airway hyperresponsiveness, bronchoconstriction and cough, urinary incontinence, reproduction disorders, contraception and sex hormone-dependent diseases including but not limited to benign prostatic hyperplasia (BPH), prostatic hyperplasia, metastatic prostatic carcinoma, testicular cancer, breast cancer, ovarian cancer, androgen dependent acne, male pattern baldness, endometriosis, abnormal puberty, uterine fibrosis, uterine fibroid tumor, uterine leiomyoma, hormone-dependent cancers, hyperandrogenism, hirsutism, virilization, polycystic ovary syndrome (PCOS), premenstrual dysphoric disease (PMDD), HAIR-AN syndrome (hyperandrogenism, insulin resistance and acanthosis nigricans), ovarian hyperthecosis (HAIR-AN with hyperplasia of luteinized theca cells in ovarian stroma), other manifestations of high intraovarian androgen concentrations (e.g. follicular maturation arrest, atresia, anovulation, dysmenorrhea, dysfunctional uterine bleeding, infertility), androgen-producing tumor (virilizing ovarian or adrenal tumor), menorrhagia and adenomyosis. The medicament may also be used for the treatment of gynecologic disorders, infertility and to affect androgen production to cause male castration.

In another aspect, the present disclosure provides a compound as disclosed above for use in treating and/or preventing hot flashes.

In another aspect, the present disclosure provides a process of manufacturing a compound as disclosed above, characterized in that it comprises the following steps:

- a) reacting a compound of Formula (i)

wherein R^1 , $R^{1'}$, R^2 , $R^{2'}$, R^3 , $R^{4'}$, X^1 and X^2 are as defined above,

*-- stands for the (*R*)-enantiomer or for the racemate,

== represents a single or a double bond depending on X^1 and X^2 ; and

$R^{5''}$ is R^5 as defined above or 1-((tert-butyldiphenylsilyl)oxy)ethyl;

e) optionally further conducting one or both of the two following steps e') and e''):

e') when $R^{4'}$ is a reducible precursor of hydroxyethyl and consequently a further precursor of methoxyethyl, a step of reduction optionally followed by methyl ether formation;

e'') when $R^{5''}$ is 1-((tert-butyldiphenylsilyl)oxy)ethyl, a step of alcohol deprotection and subsequent fluorination to form 1-fluoroethyl R^5 group; or a step of alcohol deprotection, followed by an oxidation step and a subsequent fluorination step to afford 1,1-difluoroethyl R^5 group;

to afford compound of Formula I as disclosed above.

In another aspect, the present disclosure provides a compound as disclosed above for use as a lowering agent of the circulating LH levels.

In another aspect, there is provided a use of a compound as disclosed above for the manufacture of a medicament to treat and/or prevent depression, anxiety, psychosis, schizophrenia, psychotic disorders, bipolar disorders, cognitive disorders, Parkinson's disease, Alzheimer's disease, attention deficit hyperactivity disorder (ADHD), pain, convulsion, obesity, inflammatory diseases including irritable bowel syndrome (IBS) and inflammatory bowel disorders, emesis, pre-eclampsia, airway related diseases including chronic obstructive pulmonary disease, asthma, airway hyperresponsiveness, bronchoconstriction and cough, urinary incontinence, reproduction disorders, contraception and sex hormone-dependent diseases including but not limited to benign prostatic hyperplasia (BPH), prostatic hyperplasia, metastatic prostatic carcinoma, testicular cancer, breast cancer, ovarian cancer, androgen dependent acne, male pattern baldness, endometriosis, abnormal puberty, uterine fibrosis, uterine fibroid tumor, uterine leiomyoma, hormone-dependent cancers, hyperandrogenism, hirsutism, virilization, polycystic ovary syndrome (PCOS), premenstrual dysphoric disease (PMDD), HAIR-AN syndrome (hyperandrogenism, insulin resistance and acanthosis nigricans), ovarian hyperthecosis (HAIR-AN with hyperplasia of luteinized theca cells in ovarian stroma), other manifestations of high intraovarian androgen

concentrations (e.g. follicular maturation arrest, atresia, anovulation, dysmenorrhea, dysfunctional uterine bleeding, infertility), androgen-producing tumor (virilizing ovarian tumor or virilizing adrenal tumor), menorrhagia, or adenomyosis.

In another aspect, there is provided a use of a compound as disclosed above for the manufacture of a medicament to treat and/or prevent hot flashes.

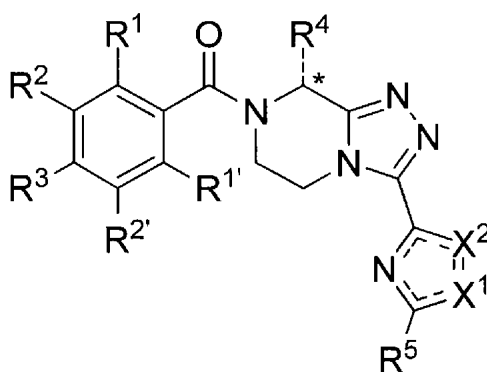
In another aspect, there is provided a use of a compound as disclosed above for the manufacture of a medicament to lower the circulating LH levels.

DETAILED DESCRIPTION

As noted above, the invention relates to compounds of Formula I:

CLAIMS

1. A compound of Formula I:



wherein:

R^1 is H, F or methyl;

$R^{1'}$ is H;

R^2 is H, F, Cl or methoxy;

$R^{2'}$ is H or F;

R^3 is H, F, Cl, methyl, trifluoromethyl or nitrile;

R^4 is methyl, ethyl, *n*-propyl, hydroxyethyl, methoxyethyl, trifluoromethyl, difluoromethyl or fluoromethyl;

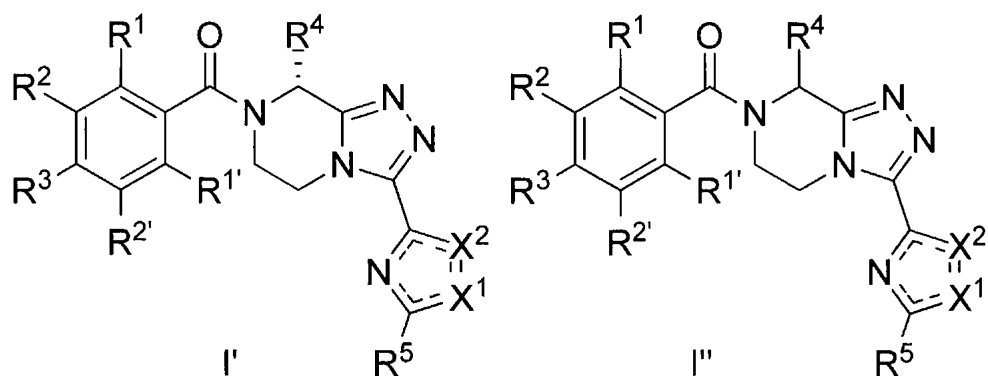
R^5 is methyl, ethyl, methoxymethyl, trifluoromethyl, difluoromethyl, fluoromethyl, 1-fluoroethyl, 1,1-difluoroethyl or 2,2,2-trifluoroethyl;

X^1 is N and X^2 is S or O; or X^1 is S and X^2 is N;

== represents a single or a double bond depending on X^1 and X^2 ;

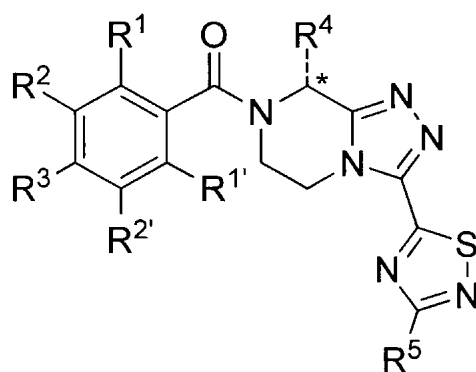
* -- stands for the (*R*)-enantiomer or for the racemate of compound of Formula I.

2. The compound according to claim 1, having Formula I' and I'':



wherein R^1 , $R^{1'}$, R^2 , $R^{2'}$, R^3 , R^4 , R^5 , X^1 and X^2 are as defined in claim 1; and
 --- represents a single or a double bond depending on X^1 and X^2 .

3. The compound according to claim 1 or claim 2, having Formula Ia:



wherein:

R^1 is H, F or methyl;

$R^{1'}$ is H;

R^2 is H, F, Cl or methoxy;

$R^{2'}$ is H or F;

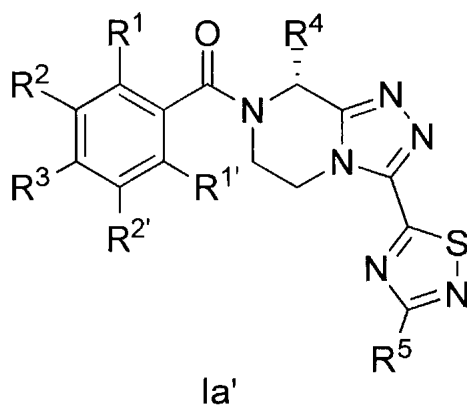
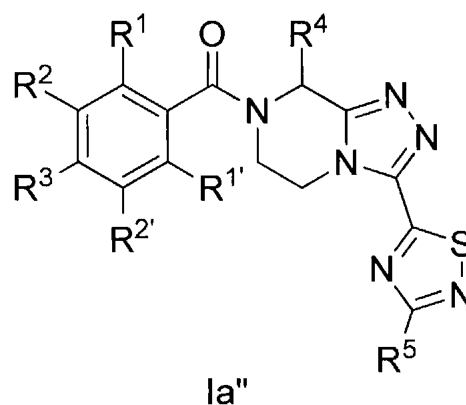
R^3 is H, F, Cl, methyl, trifluoromethyl or nitrile;

R^4 is methyl, ethyl, *n*-propyl, hydroxyethyl, methoxyethyl, trifluoromethyl, difluoromethyl or fluoromethyl;

R^5 is methyl, ethyl, methoxymethyl, trifluoromethyl, difluoromethyl or fluoromethyl;

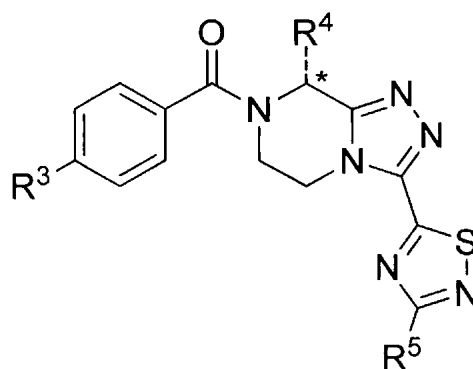
*--- stands for the (*R*)-enantiomer or for the racemate of compound of Formula Ia.

4. The compound according to any one of claims 1 to 3, selected from Formulae Ia' and Ia'':



wherein R¹, R^{1'}, R², R^{2'}, R³, R⁴ and R⁵ are as defined in claim 3.

5. The compound according to any one of claims 1 to 4, having Formula Ia-1:



wherein:

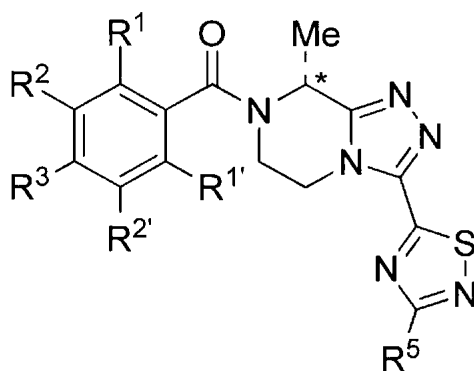
R³ is H, F, Cl, methyl, trifluoromethyl or nitrile;

R⁴ is methyl, ethyl, *n*-propyl, hydroxyethyl, methoxyethyl, trifluoromethyl, difluoromethyl or fluoromethyl;

R⁵ is methyl, ethyl, methoxymethyl, trifluoromethyl, difluoromethyl or fluoromethyl;

*-- stands for the (*R*)-enantiomer or for the racemate of compound of Formula Ia-1.

6. The compound according to any one of claims 1 to 5, having Formula Ia-2:



wherein:

R¹ is H, F or methyl;

R^{1'} is H;

R² is H, F, Cl or methoxy;

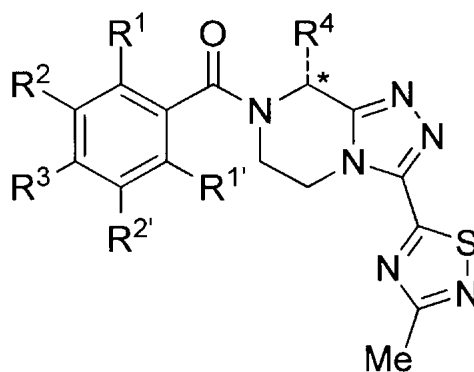
R^{2'} is H or F;

R³ is H, F, Cl, methyl, trifluoromethyl or nitrile;

R⁵ is methyl, ethyl, methoxymethyl, trifluoromethyl, difluoromethyl or fluoromethyl;

* -- stands for the (*R*)-enantiomer or for the racemate of compound of Formula Ia-2.

7. The compound according to any one of claims 1 to 6, having Formula Ia-3:



wherein:

R¹ is H, F or methyl;

$R^{1'}$ is H;

R^2 is H, F, Cl or methoxy;

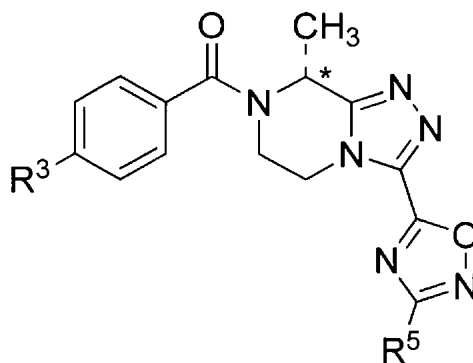
$R^{2'}$ is H or F;

R^3 is H, F, Cl, methyl, trifluoromethyl or nitrile;

R^4 is methyl, ethyl, *n*-propyl, hydroxyethyl, methoxyethyl, trifluoromethyl, difluoromethyl or fluoromethyl;

*-- stands for the (*R*)-enantiomer or for the racemate of compound of Formula Ia-3.

8. The compound according to claim 1 or claim 2, having Formula Ib:



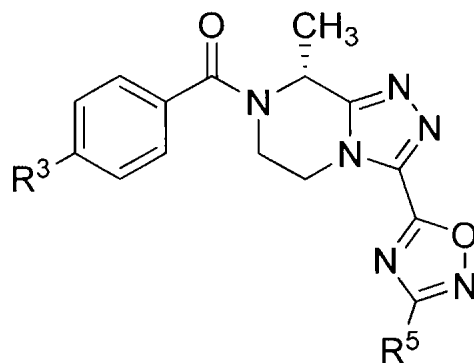
wherein:

R^3 is F;

R^5 is methyl, ethyl, trifluoromethyl, difluoromethyl, fluoromethyl, 1-fluoroethyl, 1,1-difluoroethyl or 2,2,2-trifluoroethyl;

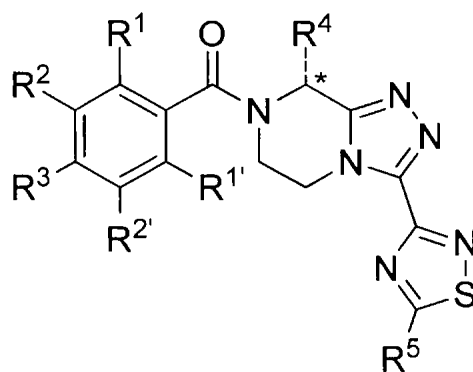
*-- stands for the (*R*)-enantiomer or for the racemate of compound of Formula Ib.

9. The compound according to any one of claims 1, 2 or 8, having Formula Ib':



wherein R^3 and R^5 are defined as in claim 8.

10. The compound according to claim 1 or claim 2, having Formula Ic:



wherein:

R^1 is H, F or methyl;

$R^{1'}$ is H;

R^2 is H, F, Cl or methoxy;

$R^{2'}$ is H or F;

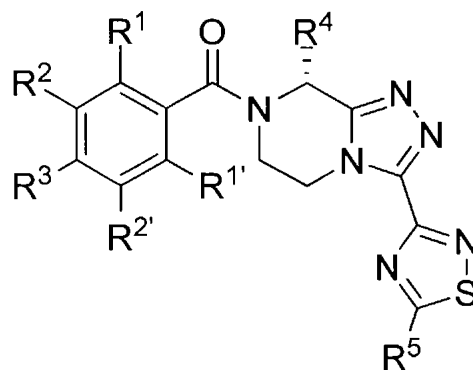
R^3 is H, F, Cl, methyl, trifluoromethyl or nitrile;

R^4 is methyl, ethyl, *n*-propyl or hydroxyethyl;

R^5 is methyl, ethyl or trifluoromethyl;

*-- stands for the (*R*)-enantiomer or for the racemate of compound of Formula Ic.

11. The compound according to any one of claims 1, 2 or 10, having Formula Ic':



wherein:

R^1 is H, F or methyl;

$R^{1'}$ is H;

R^2 is H, F, Cl or methoxy;

$R^{2'}$ is H or F;

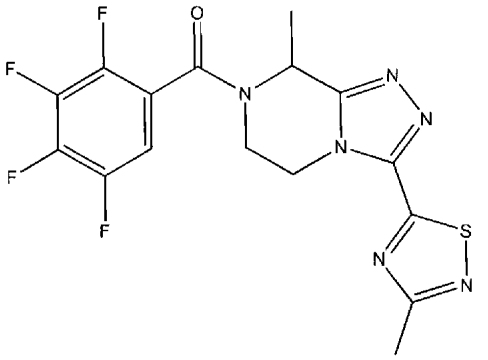
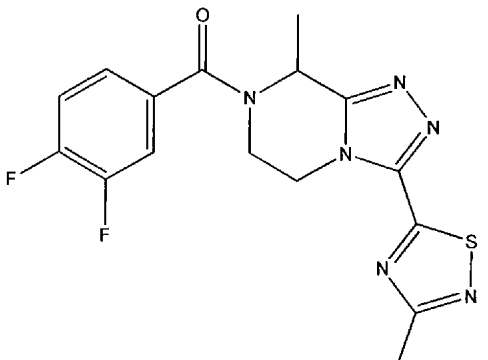
R^3 is H, F, Cl, methyl, trifluoromethyl or nitrile;

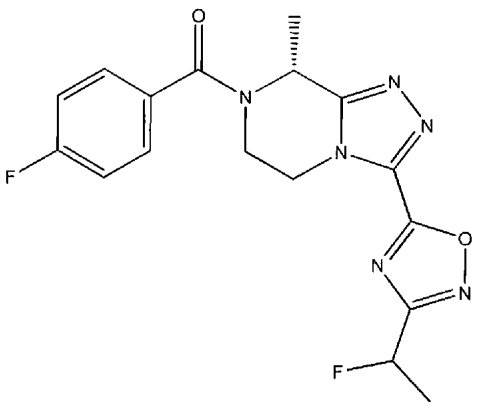
R^4 is methyl, ethyl, *n*-propyl or hydroxyethyl;

R^5 is methyl, ethyl or trifluoromethyl.

12. The compound according to any one of claims 1 to 11, selected from the group consisting of:

1		(R)-(3,4-dichlorophenyl)(8-methyl-3-(3-methyl-1,2,4-thiadiazol-5-yl)-5,6-dihydro-[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl)methanone
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31		(8-methyl-3-(3-methyl-1,2,4-thiadiazol-5-yl)-5,6-dihydro-[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl)(2,3,4,5-tetrafluorophenyl)methanone
32		(3,4-difluorophenyl)(8-methyl-3-(3-methyl-1,2,4-thiadiazol-5-yl)-5,6-dihydro-[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl)methanone

45		((8R)-3-(3-(1-fluoroethyl)-1,2,4-oxadiazol-5-yl)-8-methyl-5,6-dihydro-[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl)(4-fluorophenyl)methanone
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13. The compound according to any one of claims 1 to 12, selected from the group consisting of:
- (R)-(3-(3-ethyl-1,2,4-thiadiazol-5-yl)-8-methyl-5,6-dihydro-[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl)(4-fluorophenyl)methanone;
- (R)-(4-chlorophenyl)(8-methyl-3-(3-methyl-1,2,4-thiadiazol-5-yl)-5,6-dihydro-[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl)methanone;
- (R)-(4-fluorophenyl)(8-methyl-3-(3-methyl-1,2,4-thiadiazol-5-yl)-5,6-dihydro-[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl)methanone;
- (4-fluorophenyl)(8-methyl-3-(3-methyl-1,2,4-thiadiazol-5-yl)-5,6-dihydro-[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl)methanone;
- (R)-(4-fluorophenyl)(8-methyl-3-(3-methyl-1,2,4-oxadiazol-5-yl)-5,6-dihydro-[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl)methanone.
14. The compound according to any one of claims 1 to 13, which is (R)-(4-fluorophenyl)(8-methyl-3-(3-methyl-1,2,4-thiadiazol-5-yl)-5,6-dihydro-[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl)methanone.
15. A pharmaceutical composition comprising a compound according to any one of claims 1 to 14 and at least one pharmaceutically acceptable carrier, diluent, excipient and/or adjuvant.

16. Medicament comprising a compound according to any one of claims 1 to 14.
17. A compound according to any one of claims 1 to 14 for use in treating and/or preventing depression, anxiety, psychosis, schizophrenia, psychotic disorders, bipolar disorders, cognitive disorders, Parkinson's disease, Alzheimer's disease, attention deficit hyperactivity disorder (ADHD), pain, convulsion, obesity, inflammatory diseases including irritable bowel syndrome (IBS) and inflammatory bowel disorders, emesis, pre-eclampsia, airway related diseases including chronic obstructive pulmonary disease, asthma, airway hyperresponsiveness, bronchoconstriction and cough, urinary incontinence, reproduction disorders, contraception and sex hormone-dependent diseases including but not limited to benign prostatic hyperplasia (BPH), prostatic hyperplasia, metastatic prostatic carcinoma, testicular cancer, breast cancer, ovarian cancer, androgen dependent acne, male pattern baldness, endometriosis, abnormal puberty, uterine fibrosis, uterine fibroid tumor, uterine leiomyoma, hormone-dependent cancers, hyperandrogenism, hirsutism, virilization, polycystic ovary syndrome (PCOS), premenstrual

dysphoric disease (PMDD), HAIR-AN syndrome (hyperandrogenism, insulin resistance and acanthosis nigricans), ovarian hyperthecosis (HAIR-AN with hyperplasia of luteinized theca cells in ovarian stroma), other manifestations of high intraovarian androgen concentrations (e.g. follicular maturation arrest, atresia, anovulation, dysmenorrhea, dysfunctional uterine bleeding, infertility), androgen-producing tumor (virilizing ovarian tumor or virilizing adrenal tumor), menorrhagia, or adenomyosis.

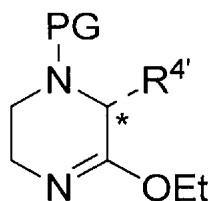
18. The compound for use according to claim 17, wherein the compound is (*R*)-(4-fluorophenyl)(8-methyl-3-(3-methyl-1,2,4-thiadiazol-5-yl)-5,6-dihydro-[1,2,4]triazolo[4,3-*a*]pyrazin-7(8H)-yl)methanone.
19. A compound according to any one of claims 1 to 14 for use in treating and/or preventing hot flashes.
20. The compound for use according to claim 19, wherein the compound is (*R*)-(4-fluorophenyl)(8-methyl-3-(3-methyl-1,2,4-thiadiazol-5-yl)-5,6-dihydro-[1,2,4]triazolo[4,3-*a*]pyrazin-7(8H)-yl)methanone.
21. A compound according to any one of claims 1 to 14 for use as a lowering agent of the circulating LH levels.
22. The compound for use according to claim 21, wherein the compound is (*R*)-(4-fluorophenyl)(8-methyl-3-(3-methyl-1,2,4-thiadiazol-5-yl)-5,6-dihydro-[1,2,4]triazolo[4,3-*a*]pyrazin-7(8H)-yl)methanone.
23. Use of a compound according to any one of claims 1 to 14 for the manufacture of a medicament to treat and/or prevent depression, anxiety, psychosis, schizophrenia, psychotic disorders, bipolar disorders, cognitive disorders, Parkinson's disease, Alzheimer's disease, attention deficit hyperactivity disorder (ADHD), pain, convulsion, obesity, inflammatory diseases including irritable bowel syndrome (IBS) and inflammatory bowel disorders, emesis, pre-eclampsia, airway related diseases including chronic obstructive pulmonary disease, asthma,

airway hyperresponsiveness, bronchoconstriction and cough, urinary incontinence, reproduction disorders, contraception and sex hormone-dependent diseases including but not limited to benign prostatic hyperplasia (BPH), prostatic hyperplasia, metastatic prostatic carcinoma, testicular cancer, breast cancer, ovarian cancer, androgen dependent acne, male pattern baldness, endometriosis, abnormal puberty, uterine fibrosis, uterine fibroid tumor, uterine leiomyoma, hormone-dependent cancers, hyperandrogenism, hirsutism, virilization, polycystic ovary syndrome (PCOS), premenstrual dysphoric disease (PMDD), HAIR-AN syndrome (hyperandrogenism, insulin resistance and acanthosis nigricans), ovarian hyperthecosis (HAIR-AN with hyperplasia of luteinized theca cells in ovarian stroma), other manifestations of high intraovarian androgen concentrations (e.g. follicular maturation arrest, atresia, anovulation, dysmenorrhea, dysfunctional uterine bleeding, infertility), androgen-producing tumor (virilizing ovarian tumor or virilizing adrenal tumor), menorrhagia, or adenomyosis.

24. The use according to claim 23, wherein the compound is (*R*)-(4-fluorophenyl)(8-methyl-3-(3-methyl-1,2,4-thiadiazol-5-yl)-5,6-dihydro-[1,2,4]triazolo[4,3-*a*]pyrazin-7(8H)-yl)methanone.
25. Use of a compound according to any one of claims 1 to 14 for the manufacture of a medicament to treat and/or prevent hot flashes.
26. The use according to claim 25, wherein the compound is (*R*)-(4-fluorophenyl)(8-methyl-3-(3-methyl-1,2,4-thiadiazol-5-yl)-5,6-dihydro-[1,2,4]triazolo[4,3-*a*]pyrazin-7(8H)-yl)methanone.
27. Use of a compound according to any one of claims 1 to 14 for the manufacture of a medicament to lower the circulating LH levels.
28. The use according to claim 27, wherein the compound is (*R*)-(4-fluorophenyl)(8-methyl-3-(3-methyl-1,2,4-thiadiazol-5-yl)-5,6-dihydro-[1,2,4]triazolo[4,3-*a*]pyrazin-7(8H)-yl)methanone.

29. Process of manufacturing a compound according to any one of claims **1** to **14**, characterized in that it comprises the following steps:

a) reacting a compound of Formula (i)



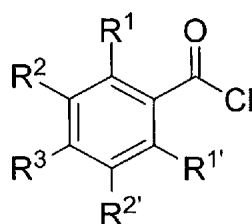
(i)

wherein:

PG represents a suitable protecting group such as for example DMB, PMB, Boc, allyl, diphenyl-phosphinamide or 2-trimethylsilylethanesulfonyl;

R^{4'} is **R⁴** as defined in claim **1** or a reducible precursor of hydroxyethyl and consequently a further precursor of methoxyethyl;

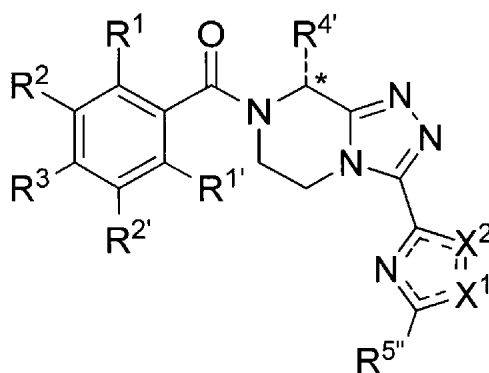
* --- stands for the (*R*)-enantiomer or for the racemate;



(vi)

wherein R^1 , $R^{1'}$, R^2 , $R^{2'}$ and R^3 are as defined in claim 1;

leading to compound of Formula (vii)



(vii)

wherein R^1 , $R^{1'}$, R^2 , $R^{2'}$, R^3 , $R^{4'}$, X^1 and X^2 are as defined above,

*--- stands for the (*R*)-enantiomer or for the racemate,

== represents a single or a double bond depending on X^1 and X^2 ; and

$R^{5''}$ is R^5 as defined in claim 1 or 1-((tert-butyldiphenylsilyl)oxy)ethyl;

e) optionally further conducting one or both of the two following steps e') and e''):

e') when $R^{4'}$ is a reducible precursor of hydroxyethyl and consequently a further precursor of methoxyethyl, a step of reduction optionally followed by methyl ether formation;

e'') when $R^{5''}$ is 1-((tert-butyldiphenylsilyl)oxy)ethyl, a step of alcohol deprotection and subsequent fluorination to form 1-fluoroethyl R^5 group; or a step of alcohol deprotection, followed by an oxidation step and a subsequent fluorination step to afford 1,1-difluoroethyl R^5 group;

to afford compound of Formula I according to any one of claims 1 to 14.