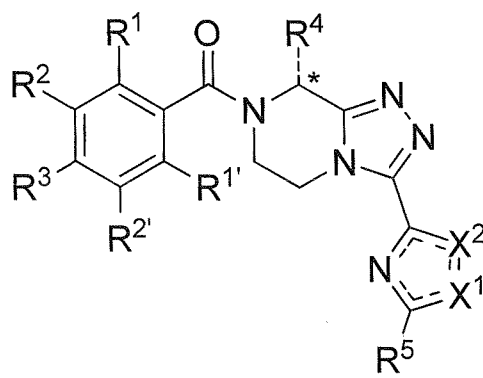


activities that can lead to safety concerns (for example, inhibition of hERG ion channel activity, a widely accepted marker of cardiovascular toxicity).

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:



and pharmaceutically acceptable solvates thereof, 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, nitrile or R³ is thiophen-2-yl under the condition that R⁵ is not methyl;

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

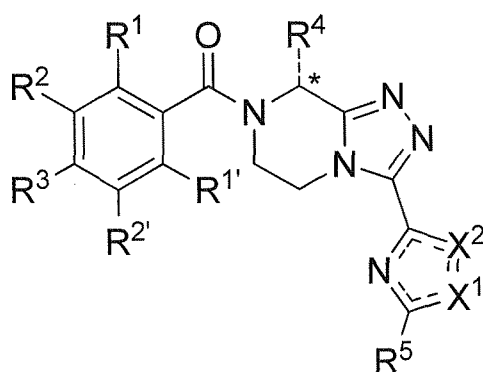
R^5 is methyl, ethyl, methoxymethyl, trifluoromethyl, difluoromethyl, fluoromethyl, 1-fluoroethyl, 1,1-difluoroethyl or 2,2,2-trifluoroethyl;

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.

In ~~one embodiment~~ ~~general aspect~~, ~~the invention~~ ~~disclosure~~ provides compounds of general Formula I:



and pharmaceutically acceptable solvates thereof, 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, nitrile or R^3 is thiophen-2-yl under the condition that R^5 is not methyl;

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~~ ~~another aspect~~, the present ~~invention~~ disclosure provides a pharmaceutical composition comprising at least one compound according to the ~~invention~~ disclosure or a pharmaceutically acceptable solvate thereof.

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

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

The ~~invention~~ 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

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 comprising the administration of a therapeutically effective amount of a compound or pharmaceutically acceptable solvate of Formula I, to a patient in need thereof. The ~~invention~~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, 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 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 human.

The ~~invention~~disclosure further provides methods of treatment for gynecological disorders and infertility. In particular, the ~~invention~~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 ~~invention~~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, or a pharmaceutically acceptable solvate thereof.

In another aspect, the present disclosure provides a compound as disclosed above or a pharmaceutically acceptable solvate thereof 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 or adrenal tumor), menorrhagia and adenomyosis.

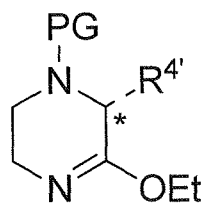
The ~~invention~~disclosure also provides the use of a compound of Formula I or a pharmaceutically acceptable solvate thereof as a medicament. Preferably, the medicament is used for the treatment and/or prevention of depression, anxiety, psychosis, schizophrenia, psychotic disorders, bipolar disorders, 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 or a pharmaceutically acceptable solvate thereof 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 or a pharmaceutically acceptable solvate thereof, characterized in that it comprises the following steps:

a) reacting a compound of Formula (i)



(i)

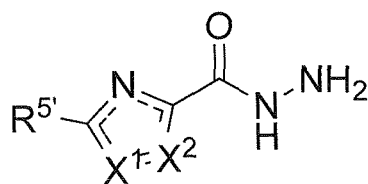
wherein:

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

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

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

with a compound of Formula (ii)



(ii)

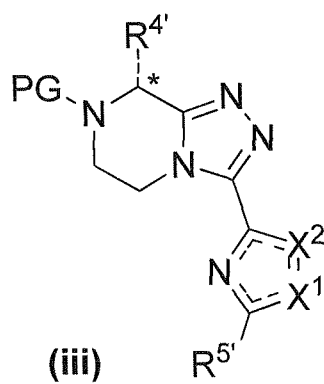
wherein:

R^{5'} is R⁵ as defined above, H or 1-((tert-butyldiphenylsilyl)oxy)ethyl;

X¹ and X² are as defined above;

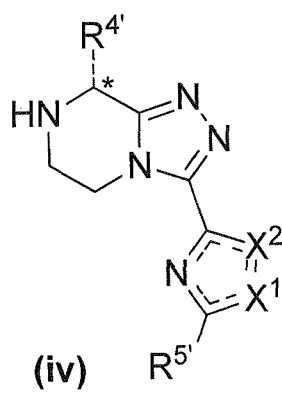
== represents a single or a double bond depending on X¹ and X²;

so as to obtain a compound of Formula (iii)



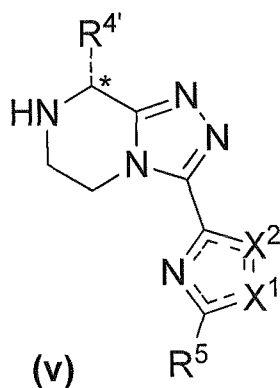
wherein **PG**, **R^{4'}**, **R^{5'}**, **X¹** and **X²** are as defined above, *--- stands for the (*R*)-enantiomer or for the racemate and --- represents a single or a double bond depending on **X¹** and **X²**;

b) deprotecting compound of Formula (iii) with a suitable deprotection agent to afford compound of Formula (iv)



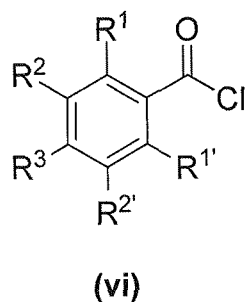
wherein **R^{4'}**, **R^{5'}**, **X¹** and **X²** are as defined above, *--- stands for the (*R*)-enantiomer or for the racemate and --- represents a single or a double bond depending on **X¹** and **X²**;

c) when **R^{5'}** is H, introducing a trifluoromethyl or difluoromethyl group by direct C-H trifluoro- or difluoromethylation, leading to compound of Formula (v)



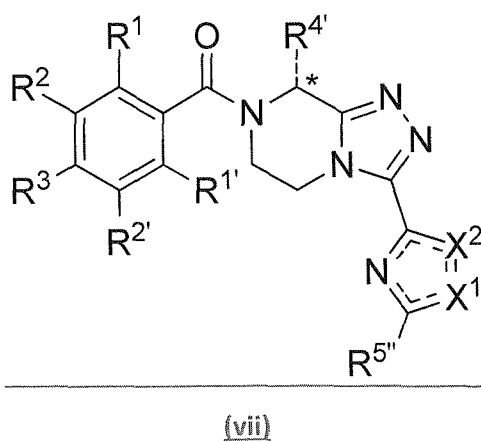
wherein $R^{4'}$, X^1 and X^2 are as defined above and R^5 is trifluoromethyl or difluoromethyl, *--- stands for the (*R*)-enantiomer or for the racemate and --- represents a single or a double bond depending on X^1 and X^2 ;

d) N-acylating compound of Formula (iv) wherein $R^{5'}$ is not H or compound of Formula (v), with a compound of Formula (vi)



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

leading to compound of Formula (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 above or 1-((tert-butyl)diphenylsilyl)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-butyl)diphenylsilyl)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.

DETAILED DESCRIPTION

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