The invention relates to a compound having the formula of structure (I): or a pharmaceutically acceptable salt thereof, for use in treating a LH receptor-related condition.
before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))
COMPOUNDS AND USES

The invention relates to compounds which interact with the luteinising hormone (LH) receptor, and the application of such compounds.

BACKGROUND OF THE INVENTION

This listing or discussion of an apparently prior-published document in this specification should not necessarily be taken as an acknowledgement that the document is part of the state of the art or is common general knowledge.

The luteinizing hormone (LH) receptor is a member of the glycoprotein hormone receptor family within the class A subfamily of G protein-coupled receptors (GPCRs) (Vassart, G.; Pardo, L.; Costagliola, S., A molecular dissection of the glycoprotein hormone receptors. *Trends Biochem Sci* 2004, 29, 119-26).

While most class A GPCRs recognize low molecular weight (LMW) endogenous ligands that bind in the seven transmembrane (7-TM) domain, the LH receptor has two high molecular weight endogenous ligands, human chorionic gonadotropin (hCG) and LH. Both hormones bind with high affinity and selectivity to the N terminus of the LH receptor and thereby activate the receptor (Smits, G.; Campillo, M.; Govaerts, C.; Janssens, V.; Richter, C.; Vassart, G.; Pardo, L.; Costagliola, S., Glycoprotein hormone receptors: determinants in leucine-rich repeats responsible for ligand specificity. *EMBO J* 2003, 22, 2692-703).

These so-called gonadotropins which interact at the LH-receptor are currently used in infertility treatment. The hormones need to be administered by parenteral (subcutaneous or intramuscular) injection (Loumaye, E.; Martineau, I.; Piazzl, A.; O’Dea, L.; Ince, S.; Howies, C.; Decosterd, G.; Van Loon, K.; Galazka, A., Clinical assessment of human gonadotrophins produced by recombinant DNA technology. *Hum Reprod* 1996, 11 Suppl 1, 95-107; discussion 117-119). Administration by injection has inherent disadvantages with patient convenience and compliance. The advantage of LMW ligands is that they have the potential of oral bioavailability versus the need to be administered by parenteral injection when using hormonal therapeutics (Loumaye et al., 1996).

There is a continuing need to develop new drugs for treating conditions related to the LH receptors, such as fertility, polycystic ovarian syndrome, and cancer. To increase patient
convenience and compliance, there is a need to develop non-peptide (e.g. LMW or small molecule) drugs for the treatment of such conditions. Orally deliverable drugs would also be advantageous.

5 SUMMARY OF THE INVENTION

The subject invention addresses the foregoing and other needs and deficiencies by the provision of a compound having the formula of structure (I):

![Structure (I)]

or a pharmaceutically acceptable salt thereof, for use in treating a LH receptor-related condition, wherein:

- $R^1$ is aryl, cycloalkyl, alkenyl, alkynyl, heteroaryl or heterocycloalkyl, optionally substituted with one or two $R^3$ groups;
- each occurrence of $R^3$ is alkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocycloalkyl, cycloalkyl, alkylaryl, alkylheteroaryl, alkylheterocycloalkyl, alkoxy, CN, OH, oxo, halo, C(=O)OH, C(halo)$_3$, CH(halo)$_2$, CH$_2$(halo), NO$_2$, N(R$^4$)$_2$, C(=O)N(R$^4$)$_2$, OC(=O)N(R$^4$)$_2$, NR$_4$OH, C(=O)OR$_4$, OC(=O)OR$_4$, S-R$_4$, or S(=O)$_2$R$_4$;
- each occurrence of $R^4$ is independently H, alkyl, alkenyl, alkynyl, aryl, alkyl-O-alkyl, alkyl-NH-alkyl, heteroaryl, heterocycloalkyl, alkylaryl, alkylheteroaryl, or alkylheterocycloalkyl;
- L is -S-, -O- or NR$^5$, wherein R$^5$ is H, aryl, cycloalkyl or alkyl;
- $R^2$ is aryl, cycloalkyl, alkyl, OR$^6$ or NHR$^6$, wherein R$^6$ is aryl, heteroaryl, cycloalkyl, alkylaryl or alkyl, wherein $R^2$ and R$^6$ are optionally substituted with one or two $R^7$ groups, and provided that when $R^2$ is OR$^6$, L is NR$^5$; and
- each occurrence of $R^7$ is alkyl, halo, NO$_2$, CN, N(R$^4$)$_2$ or alkoxy.

The invention also provides a compound having the formula of structure (I):
or a pharmaceutically acceptable salt thereof, wherein:

R¹ is aryl, cycloalkyl, alkenyl, alkynyl, heteroaryl or heterocycloalkyl, optionally substituted with one or two R³ groups;

each occurrence of R³ is alkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocycloalkyl, cycloalkyl, alkyaryl, alkylheteroaryl, alkylheterocycloalkyl, alkoxy, CN, OH, oxo, halo, C(=O)OH, C(halo)₃, CH(halo)₂, CH₂(halo), NO₂, N(R⁴)₂, C(=O)N(R⁴)₂, OC(=O)N(R⁴)₂, NR₄OH, C(=O)R⁴, C(=O)OR₄, OC(=O)R⁴, S-R⁴, or S(=O)₂R⁴;

each occurrence of R⁴ is independently H, alkyl, alkenyl, alkynyl, aryl, alkyl-O-alkyl, alkyl-NH-alkyl, heteroaryl, heterocycloalkyl, alkyaryl, alkylheteroaryl, or alkylheterocycloalkyl;

L is -S-, -O- or NR⁵, wherein R⁵ is H, aryl, cycloalkyl or alkyl;

R² is aryl, cycloalkyl, alkyl, OR⁶ or NHR⁶, wherein R⁶ is aryl, heteroaryl, cycloalkyl, alkyaryl or alkyl, wherein R² and R⁶ are optionally substituted with one or two R⁷ groups, and provided that when R² is OR⁶, L is NR⁵; and

each occurrence of R⁷ is alkyl, halo, NO₂, CN, N(R⁴)₂ or alkoxy, provided that the compound is not:

Λ-[4-(2-Pyridyl)thiazol-2-yl]-benzamide,
Λ-[4-(2-Pyridyl)thiazol-2-yl]-4-chlorobenzamide,
Λ-[4-(2-Pyridyl)thiazol-2-yl]-4-iodobenzamide,
Λ-[4-(2-Pyridyl)thiazol-2-yl]-4-methylbenzamide,
Λ-[4-(2-Pyridyl)thiazol-2-yl]-4-methoxybenzamide,
Λ-[4-(2-Pyridyl)thiazol-2-yl]-3,4-dichlorobenzamide,
Λ-[4-(2-Pyridyl)thiazol-2-yl]-3-chlorobenzamide,
Λ-[4-(2-Pyridyl)thiazol-2-yl]-4-nitrobenzamide,
Λ-[4-(2-Pyridyl)thiazol-2-yl]-4-isopropoxybenzamide,
Λ-[4-(2-Pyridyl)thiazol-2-yl]-cyclopentamide,
Λ-Phenyl-Λ-[4-(2-pyridyl)thiazol-2-yl]urea,
Λ-(4-Methoxyphenyl)- Λ'-[4-(2-pyridyl)thiazol-2-yl]urea,
Λ-Phenyl-Λ-(4-phenylthiazol-2-yl)urea,
Λ-(4-phenylthiazol-2-yl)-4-methoxybenzamide,
Λ-(4-phenylthiazol-2-yl)-benzamide,
\(N\)-(4-phenylthiazol-2-yl)-3-chlorobenzamide,
\(N\)-(4-phenylthiazol-2-yl)-4-bromobenzamide,
\(N\)-(4-phenylthiazol-2-yl)-4-chlorobenzamide,
\(N\)-(4-phenylthiazol-2-yl)-4-nitrobenzamide,
\(N\)-(4-phenylthiazol-2-yl)-4-methylbenzamide,
\(N\)-(4-phenylthiazol-2-yl)-4-trifluoromethylbenzamide,
\(N\)-(4-phenylthiazol-2-yl)-3,4-dichlorobenzamide,
\(N\)-(4-phenylthiazol-2-yl)-2,4-dichlorobenzamide,

The compounds having the formula of structure (I) defined above are referred to herein as compounds of the invention.

The invention also provides a pharmaceutical composition comprising a compound of the invention and a pharmaceutical acceptable carrier. Such compositions are referred to herein as compositions of the invention. A process for preparing the compositions of the invention is also provided.

In another embodiment, the invention provides any allosteric enhancer of the LH receptor. Such enhancers are referred to herein as allosteric enhancers of the invention.

In other aspects the invention provides (i) a method of treating a LH-receptor-related condition comprising administering to a patient a compound or composition or allosteric enhancer of the invention; (ii) use of a compound or composition or allosteric enhancer of the invention in the manufacture of a medicament for treating a LH receptor-related condition; and (iii) a compound or composition or allosteric enhancer of the invention for use in treating a LH receptor-related condition.

In an embodiment, a compound (per se) of the invention or composition of the invention or allosteric enhancer of the invention for use in medicine is provided.

In another aspect, the invention provides a combination product comprising (a) a compound of the invention, and (b) another therapeutic agent that is useful in the treatment of a LH receptor-related condition, wherein each of the components (a) and (b) is formulated in admixture with a pharmaceutically acceptable carrier. A process for providing such a combination is also provided.
In another aspect, the invention provides a combination product which comprises a kit of parts comprising components:

(a) a pharmaceutical composition including a compound of formula (I) as defined herein, or a pharmaceutically-acceptable salt thereof, in admixture with a pharmaceutically-acceptable carrier; and

(b) a pharmaceutical composition including another therapeutic agent that is useful in the treatment of a LH receptor-related condition in admixture with a pharmaceutically-acceptable carrier,

which components (a) and (b) are each provided in a form that is suitable for administration in conjunction with the other.

The invention further provides a process for preparing a compound having the formula of structure (I) as defined in herein, the process comprising reaction of a compound of formula (II):

\[ \text{R}^1 \text{N} \]

\[ \text{LH} \]

with:

(i) in the case wherein \( \text{R}^2 \) is NHR\(^6 \), a compound of formula \( \text{R}^6 \cdot \text{N} = \text{C} = \text{O} \); or

(ii) in the case wherein \( \text{R}^2 \) is aryl, cycloalkyl, alkyl or OR\(^6 \), a compound of formula \( \text{R}^2 \cdot \text{C} (=\text{O})\text{Cl} \) or \( \text{R}^2 \cdot \text{C} (=\text{O})\text{OH} \),

wherein \( \text{R}^1 \), L and \( \text{R}^6 \) are as defined in herein.

DETAILED DESCRIPTION

Isomeric Purity and Isolation

The compounds of the invention can contain one or more chiral centers and/or double bonds and, therefore, exist as stereoisomers, such as double-bond isomers (i.e., geometric isomers), enantiomers, or diastereomers. According to the invention, the chemical structures depicted herein, and therefore the compounds of the invention, encompass the racemic form of compounds of the invention as well as all enantiomers and stereoisomers, that is, both the stereomerically pure form (e.g., geometrically pure, enantiomerically pure, or diastereomerically pure) and enantiomeric and stereoisomer^m mixtures.
A compound of the invention is considered optically active or enantiomerically pure (i.e., substantially the R-form or substantially the S-form) with respect to a chiral center when the compound is about 90% ee (enantiomeric excess) or greater, preferably, equal to or greater than 95% ee with respect to a particular chiral center. A compound of the invention is considered to be in enantiomerically enriched form when the compound has an enantiomeric excess of greater than about 80% ee, preferably greater than about 90% ee. As used herein, a racemic mixture means about 50% of one enantiomer and about 50% of its corresponding enantiomer relative to all chiral centers in the molecule. Thus, the invention encompasses all enantiomerically pure, enantiomerically enriched, and racemic mixtures of compounds of the invention.

Enantiomeric and stereoisomeric mixtures can be resolved into their component enantiomers or stereoisomers by well known methods, such as chiral-phase gas chromatography, chiral-phase high performance liquid chromatography, crystallizing the compound as a chiral salt complex, or crystallizing the compound in a chiral solvent. Enantiomers and stereoisomers can also be obtained from stereomerically- or enantiomerically-pure intermediates, reagents, and catalysts by well known asymmetric synthetic methods.

When administered to a patient, the compounds of the invention are administered in isolated form or as the isolated form in a pharmaceutical composition. As used herein, "isolated" means that the compounds of the invention are separated from other components of either (a) a natural source, such as a plant or cell, preferably bacterial culture, or (b) a synthetic organic chemical reaction mixture. Preferably, the compounds of the invention are purified by conventional techniques. As used herein, "purified" means that when isolated, the isolate contains at least 95%, preferably at least 98%, of a single compound of the invention (or an enantiomeric or diastereomeric mixture thereof) by weight of the isolate.

**Definitions**

The terms "treat," "treating" and "treatment," as used herein, contemplate an action that occurs while a patient is suffering from the specified disease, disorder or condition, which reduces the severity of the disease, disorder or condition.

The term "pharmaceutically acceptable salt(s)", as used herein includes but is not limited to salts of acidic or basic groups that may be present in the compounds of the invention.
Compounds that are basic in nature are capable of forming a wide variety of salts with various inorganic and organic acids. The acids that may be used to prepare pharmaceutically acceptable acid addition salts of such basic compounds are those that form non-toxic acid addition salts, i.e., salts containing pharmacologically acceptable anions. Compounds of the invention that include an amino moiety also can form pharmaceutically acceptable salts with various amino acids, in addition to the acids mentioned above. Compounds of the invention that are acidic in nature are capable of forming base salts with various pharmacologically acceptable cations. Examples of such salts include alkali metal or alkaline earth metal salts.

As used herein, the term "alkyl group" means a saturated, monovalent, unbranched or branched hydrocarbon chain. Examples of alkyl groups include, but are not limited to, (Ci-C6) alkyl groups.

As used herein, the term "alkenyl group" means a monovalent, unbranched or branched hydrocarbon chain having one or more double bonds therein. The double bond of an alkenyl group can be unconjugated or conjugated to another unsaturated group.

As used herein, the term "alkynyl group" means monovalent, unbranched or branched hydrocarbon chain having one or more triple bonds therein. The triple bond of an alkynyl group can be unconjugated or conjugated to another unsaturated group.

As used herein, the term "aryl group" means a monocyclic or polycyclic-aromatic radical comprising carbon and hydrogen atoms. Examples of suitable aryl groups include, but are not limited to, phenyl, tolyl, anthacenyl, fluorenyl, indenyl, azuleny1, naphthyl, and biphenyl as well as benzo-fused carbocyclic moieties such as 5,6,7,8-tetrahydronaphthyl. An aryl group optionally may be fused to a cycloalkyl group, fused to another aryl group, fused to a heteroaryl group, or fused to a heterocycloalkyl group. Preferably, an aryl group is a monocyclic ring, wherein the ring comprises 6 carbon atoms, referred to herein as "(C6) aryl".

As used herein, the term "heteroaryl group" means a monocyclic- or polycyclic aromatic ring comprising carbon atoms, hydrogen atoms, and one or more heteroatoms, preferably 1 to 3 heteroatoms, independently selected from nitrogen, oxygen, and sulfur. Illustrative examples of heteroaryl groups include, but are not limited to, pyridyl, pyridazinyl, pyrazyl, indolyl, triazinyl, pyrrolyl, pyrazolyl, imidazolyl, (1,2,3)-triazolyl, (1,2,4)-triazolyl, pyrazinyl, pyrimidinyl, tetrazolyl, furyl, thienyl, isoxazolyl, thiazolyl, furyl,
phenyl, isoxazolyl, oxazolyl, pyrazolyl, tetrazolyl, oxadiazole, thiadiazolyl, isoxazolyl, triazinyl, and pyrazinyl. A heteroaryl group optionally may be fused to another heteroaryl group, fused to an aryl group, fused to a cycloalkyl group, or fused to a heterocycloalkyl group. A preferred heteroaryl group is pyridyl.

As used herein, the term "cycloalkyl group" means a monocyclic or polycyclic saturated ring comprising carbon and hydrogen atoms and having no carbon—carbon multiple bonds. Examples of cycloalkyl groups include, but are not limited to, (C₃-C₇) cycloalkyl groups, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl, and saturated cyclic and bicyclic terpenes. A cycloalkyl group optionally may be fused to another cycloalkyl group, fused to an aryl group, fused to a heteroaryl group, or fused to a heterocycloalkyl group.

As used herein, the term "heterocycloalkyl group" means a monocyclic or polycyclic ring comprising carbon and hydrogen atoms and at least one heteroatom, preferably, 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur. A heterocycloalkyl group may be fused to an aryl or heteroaryl group. Examples of heterocycloalkyl groups include, but are not limited to, pyrrolidinyl, pyrrolidino, piperidinyl, piperidino, piperazinyl, piperazino, morpholinyl, morpholino, thiomorpholinyl, thiomorpholino, and pyranyl. A heterocycloalkyl group optionally may be fused to a cycloalkyl group, fused to an aryl group, fused to a heteroaryl group, or fused to another heterocycloalkyl group. For example, a heterocycloalkyl group can be fused to or substituted with an aryl group or heteroaryl group, for example, but not limited to, 1,2,3,4-tetrahydroisoquinolinyl and 1,2,3,4-tetrahydroquinolinyl, tetrahydronaphthyridinyl, phenylpiperidinyl, and piperidinylpyrindinyl. In a preferred embodiment, a heterocycloalkyl group is a monocyclic or bicyclic ring, more preferably, a monocyclic ring, wherein the ring comprises from 3 to 6 carbon atoms and form 1 to 3 heteroatoms, referred to herein as (C₃-C₆) heterocycloalkyl. In another preferred embodiment, a heterocycloalkyl group is fused to or substituted with an aryl group or a heteroaryl group.

As used herein, the term "alkoxy group" means an -O-alkyl group, wherein alkyl is as defined above. The alkoxy group may also be referred to herein as "(Ci-C₆) alkoxy".

As used herein, the term "aryloxy group" means an -O-aryl group, wherein aryl is as defined above. Preferably, the aryl ring of an aryloxy group is a monocyclic ring, wherein the ring comprises 6 carbon atoms, referred to herein as "(C₆) aryloxy."
As used herein, an "oxo" group is a group of the formula (=0). The skilled person will appreciate that this group is only applicable where the rules of valency are adhered to. For example, oxo is not a suitable substituent for groups such as aryl and heteroaryl.

As used herein, the term "halogen" means fluorine, chlorine, bromine, or iodine. Correspondingly, the meaning of the terms "halo" and "Hal" encompass fluoro, chloro, bromo, and iodo.

As used herein low molecular weight (LMW) includes the meaning of a molecule (e.g. a non-peptide and/or small molecule) having a molecular weight of less than 1500 Daltons, preferably less than 1000 Daltons, for example less than 500 Daltons.

Compounds of the Invention

The invention provides a compound having the formula of structure (I):

![Chemical Structure](image)

or a pharmaceutically acceptable salt thereof, for use in treating a LH receptor-related condition, wherein:

- $R^1$ is aryl, cycloalkyl, alkenyl, alkynyl, heteroaryl or heterocycloalkyl, optionally substituted with one or two $R^3$ groups;
- each occurrence of $R^3$ is alkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocycloalkyl, cycloalkyl, alkylaryl, alkylheteroaryl, alkylheterocycloalkyl, alkylcycloalkyl, alkoxy, CN, OH, oxo, halo, C(=O)OH, C(halo)$_3$, CH(halo)$_2$, CH$_2$(halo), NO$_2$, N(R$_4$)$_2$, C(=O)N(R$_4$)$_2$, OC(=O)N(R$_4$)$_2$, NR$_4$OH, C(=O)OR$_4$, C(=O)OR$_4$, OC(=O)R$_4$, S-R$_4$, or S(=O)$_2$R$_4$;
- each occurrence of $R^4$ is independently H, alkyl, alkenyl, alkynyl, aryl, alkyl-O-alkyl, alkyl-NH-alkyl, heteroaryl, heterocycloalkyl, alkylaryl, alkylheteroaryl, or alkylheterocycloalkyl;
- $L$ is -S-, -O- or NR$_5$, wherein $R^5$ is H, aryl, cycloalkyl or alkyl;
- $R^2$ is aryl, cycloalkyl, alkyl, OR$_6$ or NHR$_6$, wherein $R^6$ is aryl, heteroaryl, cycloalkyl, alkylaryl or alkyl, wherein $R^2$ and $R^6$ are optionally substituted with one or two $R^7$ groups, and provided that when $R^2$ is OR$_6$, $L$ is NR$_5$; and
each occurrence of $R_7$ is alkyl, halo, NO$_2$, CN, N(R$_4$)$_2$ or alkoxy.

In an embodiment, $R^1$ is aryl or heteroaryl, optionally substituted with one or two $R^3$ groups.

Preferably, $R^1$ is phenyl or pyridyl (e.g., 2-pyridyl), optionally substituted with one or two $R^3$ groups.

If $R^1$ is substituted with one or two $R^3$ groups, in one aspect $R^3$ is alkyl (e.g. methyl), alkoxy (e.g. methoxy) or halo, preferably halo.

In an embodiment, $L$ is NR$^5$. Preferably $R^5$ is H.

In one aspect, $R^2$ is aryl, cycloalkyl, alkyl, or NHR$^6$, wherein $R^6$ is aryl, heteroaryl, cycloalkyl, alkylaryl or alkyl, wherein $R^2$ and $R^6$ are optionally substituted with one or two $R^7$ groups.

In a preferred aspect, $R^2$ is aryl or NHR$^6$, optionally substituted with one or two $R^7$ groups. For the avoidance of doubt, by this we mean that aryl or $R^6$ may be substituted with one or two $R^7$ groups. Indeed, any $R^2$ moiety may be substituted with one or two $R^7$ groups.

Preferably, $R^6$ is aryl, optionally substituted with one or two $R^7$ groups.

Advantageously, $R^2$ or $R^6$ may be phenyl, optionally substituted with one or two $R^7$ groups.

In one embodiment, $R^7$ is halo, NO$_2$ or alkoxy. Preferably, $R^7$ is halo or alkoxy.

In one embodiment, the invention provides a compound having the formula of structure (I):
o or a pharmaceutically acceptable salt thereof, wherein:
R\(^1\) is aryl, cycloalkyl, alkenyl, alkynyl, heteroaryl or heterocycloalkyl, optionally substituted with one or two R\(^3\) groups;
each occurrence of R\(^3\) is alkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocycloalkyl,
cycloalkyl, alkylaryl, alkylheteroaryl, alkylheterocycloalkyl, alkoxy, CN, OH, oxo, halo, C(=O)OH, C(halo)\(_3\), CH(halo), \(\text{CH}_2\(\text{halo}\)\), NO\(_2\), N(R\(^4\))\(_2\), C(=O)N(R\(^4\))\(_2\),
OC(=O)N(R\(^4\))\(_2\), NR\(^4\)OH, C(=0)R\(^4\), C(=O)OR\(^4\),OC(=O)R\(^4\), S-R\(^4\), or S(=O)\(_2\)R\(^4\);
each occurrence of R\(^4\) is independently H, alkyl, alkenyl, alkynyl, aryl, alkyl-O-alkyl, alkyl-
NH-alkyl, heteroaryl, heterocycloalkyl, alkylaryl, alkylheteroaryl, or alkylheterocycloalkyl;
L is -S-, -O- or NR\(^5\), wherein R\(^5\) is H, aryl, cycloalkyl or alkyl;
R\(^2\) is aryl, cycloalkyl, alkyl, OR\(^6\) or NHR\(^6\), wherein R\(^6\) is aryl, heteroaryl, cycloalkyl,
alkylaryl or alkyl, wherein R\(^2\) and R\(^6\) are optionally substituted with one or two R\(^7\) groups,
and provided that when R\(^2\) is OR\(^6\), L is NR\(^5\); and
each occurrence of R\(^7\) is alkyl, halo, NO\(_2\), CN, N(R\(^4\))\(_2\) or alkoxy; provided that the
compound is not:
Λ/[4-(2-Pyridyl)thiazol-2-yl]-benzamide,
Λ/[4-(2-Pyridyl)thiazol-2-yl]-4-chlorobenzamide,
Λ/[4-(2-Pyridyl)thiazol-2-yl]-4-iodobenzamide,
20 Λ/[4-(2-Pyridyl)thiazol-2-yl]-4-methylbenzamide,
Λ/[4-(2-Pyridyl)thiazol-2-yl]-4-methoxybenzamide,
Λ/[4-(2-Pyridyl)thiazol-2-yl]-3,4-dichlorobenzamide,
Λ/[4-(2-Pyridyl)thiazol-2-yl]-3-chlorobenzamide,
Λ/[4-(2-Pyridyl)thiazol-2-yl]-4-nitrobenzamide,
25 Λ/[4-(2-Pyridyl)thiazol-2-yl]-4-isopropoxybenzamide,
Λ/[4-(2-Pyridyl)thiazol-2-yl]-cyclopentamidine,
Λ-Phenyl-Λ/[4-(2-pyridyl)thiazol-2-yl]urea,
Λ-(4-Methoxyphenyl)- Λ'[4-(2-pyridyl)thiazol-2-yl]urea,
Λ-Phenyl-Λ-(4-phenylthiazol-2-yl)urea,
30 Λ-(4-phenylthiazol-2-yl)-4-methoxybenzamide,
Λ-(4-phenylthiazol-2-yl)-benzamide,
\(\text{N}-(4\text{-phenylthiazol-2-yl})-3\text{-chlorobenzamide,}\)
\(\text{N}-(4\text{-phenylthiazol-2-yl})-4\text{-bromobenzamide,}\)
\(\text{N}-(4\text{-phenylthiazol-2-yl})-4\text{-chlorobenzamide,}\)
\(\text{N}-(4\text{-phenylthiazol-2-yl})-4\text{-nitrobenzamide,}\)
\(\text{N}-(4\text{-phenylthiazol-2-yl})-4\text{-methylbenzamide,}\)
\(\text{N}-(4\text{-phenylthiazol-2-yl})-4\text{-tert-butylbenzamide,}\)
\(\text{N}-(4\text{-phenylthiazol-2-yl})-4\text{-trifluoromethylbenzamide,}\)
\(\text{N}-(4\text{-phenylthiazol-2-yl})-3,4\text{-dichlorobenzamide,}\)
\(\text{N}-(4\text{-phenylthiazol-2-yl})-2,4\text{-dichlorobenzamide,}\)


In an alternative aspect, the invention provides a compound having the formula of structure (I):

\[
\text{R}^1 \quad \text{S} \quad \text{N} \quad \text{L} \quad \text{R}^2 \quad \text{O}
\]

or a pharmaceutically acceptable salt thereof, wherein:

- \(\text{R}^1\) is aryl, cycloalkyl, alkenyl, alkynyl, heteroaryl or heterocycloalkyl, optionally substituted with one or two \(\text{R}^3\) groups;
- each occurrence of \(\text{R}^3\) is alkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocycloalkyl, cycloalkyl, alkyaryl, alkylheteroaryl, alkylheterocycloalkyl, alkylcycloalkyl, alkoxy, CN, OH, oxo, halo, \(\text{C}(=\text{O})\text{OH}, \text{C}(\text{halo})_3, \text{CH}(\text{halo})_2, \text{CH}_2(\text{halo}), \text{NO}_2, \text{N}(\text{R}^4)_2, \text{C}(=\text{O})\text{N}(\text{R}^4)_2, \text{OC}(=\text{O})\text{N}(\text{R}^4)_2, \text{NR}^4\text{OH}, \text{C}(=\text{O})\text{R}^4, \text{C}(=\text{O})\text{OR}^4, \text{OC}(=\text{O})\text{R}^4, \text{S}-\text{R}^4, \text{or } \text{S}(=\text{O})_2\text{R}^4;\)
- each occurrence of \(\text{R}^4\) is independently \(\text{H}, \text{alkyl}, \text{alkenyl}, \text{alkynyl}, \text{aryl}, \text{alkyl-O-alkyl}, \text{alkyl-NH-alkyl}, \text{heteroaryl}, \text{heterocycloalkyl}, \text{alkylaryl}, \text{alkylheteroaryl}, \text{or alkylheterocycloalkyl;}\)

\(\text{L}\) is -S-, -O- or NR\(^5\), wherein \(\text{R}^5\) is \(\text{H}, \text{aryl}, \text{cycloalkyl}\) or alkyl;
R² is aryl, cycloalkyl, alkyl, OR⁶ or NHR⁶, wherein R⁶ is aryl, heteroaryl, cycloalkyl, alkylaryl or alkyl, wherein R² and R⁶ are optionally substituted with one or two R⁷ groups; and

each occurrence of R⁷ is alkyl, halo, NO₂, CN, N(R⁴)₂ or alkoxy; further wherein:

(i) when R¹ is aryl, it is substituted with one or two R³ groups, or
(ii) R¹ is aryl, cycloalkyl, alkenyl, alkynyl, heteroaryl or heterocycloalkyl, optionally substituted with one or two R³ groups, or
(iii) when R¹ is aryl, it is not phenyl, or
(iv) when R¹ is aryl, it is not 2-pyridyl, or
(v) R² is alkyl or NHR⁶, wherein R⁶ is aryl, heteroaryl, cycloalkyl, alkylaryl or alkyl, optionally substituted with one or two R⁷ groups.

For the avoidance of doubt, any of the (preferred or advantageous) aspects or embodiments of the compounds of the invention described herein may be combined in any way.

Some examples of compounds of the invention are set out below in Table 1.

Table 1

<table>
<thead>
<tr>
<th>Compound</th>
<th>Compound</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 (LUF5430)</td>
<td>7 (LUF5422)</td>
</tr>
<tr>
<td>3 (LUF5724)</td>
<td>8 (LUF5423)</td>
</tr>
<tr>
<td>4 (LUF5419)</td>
<td>9 (LUF5425)</td>
</tr>
</tbody>
</table>
Compound numbers 19, 20 and 21 are examples of compounds of the invention *per se*.

*Synthesis of the Compounds of the Invention*

The invention provides a process for preparing a compound having the formula of structure (I) as defined herein, the process comprising reaction of a compound of formula (II):
Starting materials useful for preparing the compounds of the invention and intermediates therefore, are commercially available or can be prepared from commercially available materials using known synthetic methods and reagents.

Protecting groups utilized herein denote groups which generally are not found in the final therapeutic compounds but which are intentionally introduced at some stage of the synthesis in order to protect groups which otherwise might be altered in the course of chemical manipulations. Such protecting groups are removed or converted to the desired group at a later stage of the synthesis and compounds bearing such protecting groups thus are of importance primarily as chemical intermediates (although some derivatives also exhibit biological activity). Accordingly, the precise structure of the protecting group is not critical.


Some convenient ways of carrying out the process of the invention are illustrated below in Scheme 1.
The compounds of the invention wherein L = NH, i.e. compounds having the formula of structure (IV), may be prepared starting from the corresponding amine (III). In reaction (i), the amine (III), or a salt thereof, is reacted with a compound of formula R^2-C(=O)Cl, for example by refluxing with NEt₃ in dioxane. Alternatively, in reaction (ii), the amine (III), or a salt thereof, is reacted with a compound of formula R^2-C(=O)OH, for example, in the presence of dicyclohexylcarboimide (DCC) and DMAP in DMF at room temperature. Detailed experimental procedure for such reactions may be found in Van Muijlwijk-Koezen et al, J. Med. Chem. 2001, 44, 749-762 and van Tiburg et al, Bioinorganic & Medicinal Chemistry Letters 11 (2001) 2017-2019, which both are herein incorporated by reference.

**Biological Studies**

Detailed experimental materials and methods for the following data are provided in the non-limiting examples.

**Allosteric Modulation of [³H]Org 43553 Binding**

The numbered compounds of the invention as set out above were screened for their effect on the dissociation rate of the radiolabeled LMW agonist for the LH receptor, [³H]43553, (Heitman, L. H.; Oosterom, J.; Bonger, K. M.; Timmers, C. M.; Wiegerinck, P. H. G.; Uzerman, A. P., [³H]Org 43553, the First Low-Molecular-Weight Agonistic and Allosteric Radioligand for the Human Luteinizing Hormone Receptor. Mol Pharmacol 2008, 73, 518-524, incorporated herein by reference), in a single point (t = 30 min) dissociation assay. The results are shown in Table 2.

**Table 2** Displacement and allosteric modulation of [³H]Org 43553 binding at the human LH receptor by 10 µM of certain compounds of the invention.
<table>
<thead>
<tr>
<th>Compound</th>
<th>% Displacement</th>
<th>% Allosteric Enhancement</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 (LUF5430)</td>
<td>-15</td>
<td>34</td>
</tr>
<tr>
<td>3 (LUF5724)</td>
<td>-19</td>
<td>25</td>
</tr>
<tr>
<td>4 (LUF5419)</td>
<td>-22</td>
<td>25</td>
</tr>
<tr>
<td>5 (LUF5420)</td>
<td>-1</td>
<td>19</td>
</tr>
<tr>
<td>6 (LUF5421)</td>
<td>-9</td>
<td>34</td>
</tr>
<tr>
<td>7 (LUF5422)</td>
<td>-17</td>
<td>40</td>
</tr>
</tbody>
</table>
% Displacement of specific [3H]Org 43553 binding from human luteinizing hormone receptors stably expressed on Chinese hamster ovary-K1 (CHO-K1) cell membranes at 10 μM concentrations (n = 2, duplicate)

% Allosteric enhancement of [3H]Org 43553 binding at human luteinizing hormone receptors stably expressed on CHO-K1 cell membranes in the absence (control; 0%) or presence of 10 μM of the compounds (n = 2, duplicate)

Table 2 shows that all of the numbered compounds of the invention are allosteric enhancers of the LH receptor, in contrast to the allosteric inhibitor LUF5771 (see UK patent application number 0902156.9).

**Radioligand Saturation Experiments**

Saturation binding assays with [3H]Og 43553 were performed in the absence (control) and presence of 10 μM LUF5419. The results of a representative saturation experiment are shown in Figure 1. In both conditions the saturation of [3H]Og 43553 to membranes of CHO cells expressing the human LH receptor was saturable and best characterized by a one-site receptor model. The K_D and B_max values obtained from the saturation experiments are given in Table 3.
Table 3  

<table>
<thead>
<tr>
<th>Condition</th>
<th>$K_D$ (nM)</th>
<th>$B_{\text{max}}$ (fmol/mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>2.2 ± 0.4</td>
<td>601 ± 61</td>
</tr>
<tr>
<td>+ 10 µM LUF5419</td>
<td>3.1 ± 0.2 **</td>
<td>798 ± 71 *</td>
</tr>
</tbody>
</table>

The values of the saturation binding constants were obtained by analysis of increasing concentrations of [³H]Org 43553 bound to human luteinizing hormone receptors. Values are means (± SEM) of three separate assays each performed in duplicate.

Under control conditions a $K_D$ and $B_{\text{max}}$ value of 2.2 ± 0.4 nM and 601 ± 61 fmol/mg was obtained for [³H]Org 43553. The presence of 10 µM LUF5419 resulted in a 33 % increase in the $B_{\text{max}}$ value (798 fmol/mg), while the $K_D$ value was somewhat increased to 3.1 ± 0.2 nM. The $K_D$ values obtained in the absence or presence of LUF5419 were used to derive $K_I$ rather than $IC_{50}$ values for Org 43553, as described in the next section.

Radioligand Displacement Experiments  

The affinity of Org 43553 in the absence and presence of 10 µM LUF5419 for the human luteinizing hormone receptor was determined (Figure 2). In the control condition Org 43553 had an affinity of 6.4 ± 1 nM. In the presence of 10 µM LUF5419, the affinity of Org 43553 was unchanged ($K_i = 6.8 ± 1$ nM), whereas the $B_{\text{max}}$ was enhanced, as already mentioned above for labelled Org 43553. In addition, the effect of LUF5419 on the equilibrium binding of the iodinated endogenous ligand, $^{125}$I-lI-IhCG, was examined. LUF5419 was not able to displace or enhance $^{125}$I-hCG binding (data not shown). Furthermore, the affinity of reclHLH was also unaffected by 10 µM LUF5419.

Kinetic Association and Dissociation Experiments  

The effect of LUF5419 on the kinetic association and dissociation parameters of [³H]Org 43553 at CHOOhLHrJuc membranes at 30°C were determined. As shown in Table 4 and Figure 3, [³H]Org 43553 associated to the receptor within 120 min with a $k_{on}$ value of 0.0082 ± 0.0004 nM⁻¹ min⁻¹.

Table 4  

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$k_{on}$</td>
<td>0.0082 ± 0.0004 nM⁻¹ min⁻¹</td>
</tr>
<tr>
<td>$k_{off}$</td>
<td></td>
</tr>
</tbody>
</table>

Association ($k_{on}$) rate constants, dissociation ($k_{off}$) rate constants and the apparent (kinetic) dissociation constant ($K_D$) of radiolabeled Org 43553.
<table>
<thead>
<tr>
<th></th>
<th>$k_{on}$ (nM$^{-1}$ min$^{-1}$)$^a$</th>
<th>$B_{max}$ (%)$^b$</th>
<th>$k_{off}$ (nM$^{-1})^a$</th>
<th>$K_D^c$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>0.0082 ± 0.0004</td>
<td>100 ± 1</td>
<td>0.020 ± 0.002</td>
<td>2.4</td>
</tr>
<tr>
<td>+ 10 µM LUF5419</td>
<td>0.0092 ± 0.0003</td>
<td>123 ± 3*</td>
<td>0.011 ± 0.001*</td>
<td>1.2</td>
</tr>
</tbody>
</table>

$^a$The values of the kinetic association and dissociation rate constants were obtained by analysis of the exponential association and dissociation of $^{[3]H}Og$ 43553 bound to human luteinizing hormone receptors.

$^b$Maximal amount of $^{[3]H}Og$ 43553 bound to human luteinizing hormone receptors after association in the absence (control = 100 %) or presence of 10 µM LUF5419.

$^c$The dissociation constant was defined as the ratio of $k_{off}$ and $k_{on}$-values. Values are means (± S.E.M.) of at least three separate assays performed in duplicate.

In the presence of 10 µM LUF5419, the association rate was not significantly altered ($k_{on}$ = 0.0092 ± 0.0003 nM$^{-1}$ min$^{-1}$). The $B_{max}$ was significantly increased by 23%, corresponding to the effect found in equilibrium saturation and displacement assays. The dissociation rate of $^{[3]H}Og$ 43553 was almost two-fold decreased in the presence of 10 µM LUF5419 (Table 4). Taken together, this resulted in a 'kinetic' $K_D$ ($k_{off}/k_{on}$) value of 2.4 nM for control conditions, which was in good agreement with the $K_D$ value (2.1 nM) obtained by saturation analysis. In the presence of 10 µM LUF5419, a 'kinetic' $K_D$ value of 1.2 nM was obtained, which was somewhat lower than the $K_D$ value obtained in the equilibrium saturation experiments. Similar to the results in equilibrium binding assays, the dissociation rate of $^{[25]}$-hCG was not changed by the presence of 10 µM LUF5419 (data not shown).

Moreover, the modulating potency of LUF5419 for $^{[3]H}Og$ 43553 was determined (Figure 5). Dissociation was induced by an excess unlabelled Org 43553 in the presence of different concentrations of LUF5419, which resulted in an EC$_{50}$ value of 23 ± 4 µM for this compound.

Allosteric Modulation of Receptor Activation

The effect of LUF5419 on receptor activation by the endogenous hormone, recLH, or the low molecular weight agonist, Org 43553, was measured using a CRE-induced luciferase assay (Figure 4 and Table 5).

**Table 5**  Receptor activation by recLH or Org 43553 in the presence or absence of 10 µM LUF5419, expressed as EC$_{50}$ and $E_{max}$ values.

<table>
<thead>
<tr>
<th>Activity in luciferase assay$^a$</th>
<th>EC$_{50}$ (nM)</th>
<th>$E_{max}$ (%)$^b$</th>
<th>$E_{max}$ (%)</th>
</tr>
</thead>
</table>

21
RecLH 0.14 ± 0.03 100 ± 2 100 ± 2
+ 10 µM LUF5419 0.13 ± 0.03 64 ± 9** 90 ± 12
Org 43553 0.78 ± 0.2 79 ± 2 79 ± 2
+ 10 µM LUF5419 1.0 ± 0.2 73 ± 3 103 ± 5**

a cAMP-mediated luciferase activity in CHO-K1 cells that stably express the human luteinizing hormone receptor and CRE-luciferase reporter gene.
b Maximal effect of either recLH or Org 43553 in the absence or presence of 10 µM LUF5419, where recLH in the absence of LUF5419 was set at 100 %.
c Maximal effect corrected for the effect of 10 µM LUF5419 on forskolin-induced luciferase activity.
Values are means (± S.E.M.) of at least three separate assays performed in duplicate.

RecLH fully activated the LH receptor with a potency of 140 ± 30 pM, while Org 43553 partially activated (E_{max} = 79 ± 2 %) the LH receptor with an EC_{50} value of 0.78 ± 0.2 nM. In the presence of 10 µM LUF5419, the potencies of recLH and Org 43553 were not shifted. The efficacy, however, was decreased for recLH, while it was unchanged for Org 43553. The decrease in luciferase activity with LUF5419 was also observed when the CRE-pathway was activated by 10 µM forskolin (Figure 4). After correction for the forskolin-effect, an enhancement of the efficacy of Org 43553 was observed. As a consequence, it appeared that Org 43553 was able to fully activate the receptor in the presence of 10 µM LUF5419 (E_{max} = 103 ± 5 %), similar to the effect by recLH alone.

The results described herein show that the compounds of the invention have surprisingly been found to be the first examples of (LMW) allosteric enhancers (of [3H]Org 43553 binding) at the human LH receptor. The compounds of the invention increased the maximum binding of [3H]Org 43553, reflected in an increase of the efficacy of Org 43553 in a functional assay to levels similar as obtained by stimulation with the endogenous hormone, recLH.

The compounds of the invention are thought to enhance the action of a synthetic or possibly endogenous agonist; this may offer therapeutic advantages. Occupancy of an allosteric site on a receptor may lead to conformational changes of the receptor, which, in turn, can render the (endogenous or synthetic) agonist more active. In the absence of the (endogenous or synthetic) agonist the allosteric enhancer might not be active, or induce a small agonistic effect by itself. Thus a dimmer effect rather than an on/off switch of the receptor is likely to occur which may be more physiologic.
Accordingly, the compounds of the invention may be used for the treatment of LH receptor-related disorders, for example in the form of pharmaceutical compositions (described hereinafter).

Thus, the invention provides (i) a method of treating a LH receptor-related condition comprising administering to a patient a compound or composition or allosteric enhancer of the invention; (ii) use of a compound or composition or allosteric enhancer of the invention in the manufacture for treating a LH receptor-related condition; and (iii) a compound or composition or allosteric enhancer of the invention for use in treating a LH receptor-related condition.

Examples of LH receptor-related conditions include cancer (e.g. prostate cancer, testicular cancer, uterine cancer, ovarian cancer, breast cancer), pituitary gonadotrophe adenomas, endometriosis, polycystic ovarian disease, uterine fibroids, primary hirsutism, LH surge, benign prostatic hypertrophy, vasomotor instability or precocious puberty.

The treatment of LH receptor-related conditions also comprises the treatment of fertility. This includes the use to prevent and/or retard pregnancy (i.e. as a contraceptive) and pro-fertility treatment, for example in-vitro fertilisation (IVF).

**Pharmaceutical Compositions and Administration**

The compounds of the invention may be formulated by any means known in the art, including but not limited to tablets, capsules, caplets, suspensions, powders, lyophilized forms and aerosols and may be mixed and formulated with buffers, binders, stabilizers, anti-oxidants and other agents known in the art. The compounds may be administered by any systemic or partially systemic means known in the art, including but not limited to intravenous injection, subcutaneous injection, administration through mucous membranes, oral administration, dermal administration, skin patches, aerosols and the like.

The invention provides a pharmaceutical composition (this may also be referred to herein as a formulation) comprising a compound of the invention and a pharmaceutically acceptable carrier. The invention also provides a process for the preparation of such a pharmaceutical composition, which process comprises bringing into association a compound of formula (I), as defined herein, or a pharmaceutically acceptable salt thereof, with a pharmaceutically acceptable carrier.
The compounds of the invention may thus be formulated or compounded into pharmaceutical compositions that include at least one compound of this invention together with one or more pharmaceutically acceptable carriers, including excipients, such as diluents, carriers and the like, and additives, such as stabilizing agents, preservatives, solubilizing agents, buffers and the like, as may be desired.

For injection or other liquid administration formulations, water containing at least one or more buffering constituents is suitable, and stabilizing agents, preservatives and solubilizing agents may also be employed. For solid administration formulations, any of a variety of thickening, filler, bulking and carrier additives may be employed, such as starches, sugars, fatty acids and the like. For topical administration formulations, any of a variety of creams, ointments, gels, lotions and the like may be employed. For most pharmaceutical formulations, non-active ingredients will constitute the greater part, by weight or volume, of the preparation. For pharmaceutical formulations, it is also contemplated that any of a variety of measured-release, slow-release or time-release formulations and additives may be employed, such that the dosage may be formulated so as to effect delivery of a compound of this invention over a period of time.

The compounds and pharmaceutical compositions of the invention may be administered by injection, which injection may be intravenous, subcutaneous, intramuscular, intraperitoneal or by any other means known in the art. Administration means preferably includes administration through mucous membranes, buccal administration, oral administration, dermal administration, inhalation administration, nasal administration and the like. The dosage for treatment is administration, by any of the foregoing means or any other means known in the art, of an amount sufficient to bring about the desired therapeutic effect.

Oral administration is a preferred route of administration for the compounds and compositions of the invention. Thus in one embodiment, the compounds and compositions of the invention are "orally deliverable". By the term "orally deliverable", we include the meaning suitable for oral, including peroral and intra-oral (e.g. sublingual or buccal) administration. Preferably, the compositions of the invention are designed for peroral administration to a patient, i.e. by swallowing (e.g. eating or drinking).

The orally deliverable compounds and compositions of the invention may be formulated in numerous different ways, including, but not limited to diffusion-controlled formulations
(such as wax matrices or pellets), dissolution-controlled formulations (such as press-coated formulations), dissolution/diffusion-controlled formulations, easily administrable formulations (such as chewable, fast dissolving, sprinkle or taste-masked formulations), enteric-coated formulations, osmotic pump technology formulations, tamper-resistant formulations, erosion-controlled formulations, ion exchange resins and combinations of the foregoing. Suitable oral dosage forms include, but are not limited to capsules, tablets, liquids, powders, granules, suspensions, matrices, microspheres, seeds, pellets and/or beads of the foregoing formulations. Combinations of these dosage forms may also be used.

Compounds of the invention may also be combined with other therapeutic agents that are useful in the treatment of a LH receptor-related condition. Thus, in a further aspect of the invention, there is provided a combination product comprising (a) a compound of the invention, or a pharmaceutically acceptable salt thereof, and (b) another therapeutic agent that is useful in the treatment of a LH receptor-related condition, wherein each of components (a) and (b) is formulated in admixture with a pharmaceutically acceptable carrier.

Such combination products provide for the administration of a compound of the invention in conjunction with the other therapeutic agent, and may thus be presented either as separate composition, wherein at least one of those compositions comprises a compound of the invention, and at least one comprises the other therapeutic agent, or may be presented (i.e. formulated) as a combined preparation (i.e. presented as a single formulation including a compound of the invention and the other therapeutic agent).

Thus, there is further provided:

(1) a pharmaceutical composition including a compound of formula (I) as defined herein, or a pharmaceutically acceptable salt thereof, another therapeutic agent that is useful in the treatment of a LH receptor-related condition, and a pharmaceutically acceptable carrier; and

(2) a kit of parts comprising components:

(a) a pharmaceutical composition including a compound of formula (I) as defined herein, or a pharmaceutically-acceptable salt thereof, in admixture with a pharmaceutically-acceptable carrier; and
(b) a pharmaceutical composition including another therapeutic agent that is useful in the treatment of a LH receptor-related condition in admixture with a pharmaceutically-acceptable carrier, which components (a) and (b) are each provided in a form that is suitable for administration in conjunction with the other.

EXAMPLES

The following information supplements the information set out above in relation to the *Synthesis of the Compounds of the Invention* and the *Biological Studies*.

*Compound Synthesis*


*Biological Studies*

**Materials**

Org 43553 and recLH were provided by Schering Plough (Oss, The Netherlands), where Org 43553 was synthesized as described in WO2003020726. Bovine serum albumin (BSA, fraction V) was purchased from Sigma (St. Louis, MO, U.S.A.), whereas BCA protein assay reagent was from Pierce Chemical Company (Rockford, IL, U.S.A.). $[3^{\text{H}}]$Og 43553 (16.6 Ci/mmol) was labelled as described previously by Heitman et al (Heitman LH, Oosterom J, Bonger KM, Timmers CM, Wiegerinck PHG and Uzerman AP 2008a) $[3^{\text{H}}]$Org 43553, the first low-molecular-weight agonistic and allosteric radioligand for the human luteinizing hormone receptor, *Mol Pharmacol* 73(2):518-524). $^{125}$I-hCG (4408 Ci/mmol) was purchased from Perkin Elmer Life Sciences Inc. (Boston, MA, U.S.A.). Chinese Hamster Ovary (CHO-K1) cells stably expressing the human luteinizing hormone (LH) receptor and cAMP-response-element luciferase reporter gene (CRE-luc) were kindly provided by Schering Plough (Oss, The Netherlands). All other chemicals and cell culture materials were obtained from standard commercial sources.

**Cell Culture and Membrane Preparation**
CHO cells with stable expression of the human LH receptor and CRE-luc (CHOhLHrJuc) were grown in culture medium consisting of Dulbecco's Modified Eagle's Medium (DMEM) and Ham's F12 medium (1:1) supplemented with 7.5% normal adult bovine serum, streptomycin (100 µg/ml), penicillin (100 U/I/ml) at 37 °C in 5% CO2. The cells were subcultured twice weekly at a ratio of 1:20. Cell membranes were prepared as described previously by Heitman et al (Mol Pharmacol 73(2):518-524).

Radioligand Saturation Assays
Membrane aliquots containing 50 µg protein were incubated in a total volume of 100 µl assay buffer (25 mM Tris-HCl, pH 7.4, supplemented with 2 mM MgCl2 and 0.1% BSA) at 30 °C for 90 min. For saturation experiments, total binding was determined at increasing concentrations (0.25-25 nM) of [3H]Org 43553, whereas non-specific binding was determined at three concentrations of radioligand in the presence of 10 µM Org 43553 and analyzed by linear regression. Incubations were terminated by dilution with 1 ml ice-cold Tris-HCl buffer. Bound from free radioligand was immediately separated by rapid filtration through Whatman GF/B filters using a Millipore manifold. Filters were subsequently washed three times with ice-cold wash buffer (25 mM Tris HCl, pH 7.4, supplemented with 2 mM MgCl2 and 0.05% BSA). Filter-bound radioactivity was determined by scintillation spectrometry (Tri-Carb 2900TR; PerkinElmer Life and Analytical Sciences) after addition of 3.5 ml of PerkinElmer Emulsifier Safe.

Radioligand Displacement Assays
Membrane aliquots containing 50 µg protein were incubated in a total volume of 100 µl assay buffer (25 mM Tris-HCl, pH 7.4, supplemented with 2 mM MgCl2 and 0.1% BSA) at 30 °C for 90 min. Displacement experiments were performed using 10 µM of competing ligand in the presence of 4.5 nM [3H]Org 43553. Non-specific binding was determined in the presence of 10 µM Org 43553 and represented approximately 30% of the total binding. [3H]Org 43553 did not bind specifically to membranes prepared from CHOJuc cells lacking the LH receptor. Total binding was determined in the presence of buffer and was set at 100% in all experiments, whereas non-specific binding was set at 0%. Incubations were terminated and samples were obtained and analyzed as described under Radioligand Saturation Assays. Displacement assays with 125I-hCG were performed as described previously by Heitman et al (Mol Pharmacol 73(2):518-524).

Kinetic Association and Dissociation Assays
Association experiments were performed by incubating membrane aliquots containing 50 µg protein in a total volume of 100 µl assay buffer (25 mM Tris HCl, pH 7.4, supplemented with 2 mM MgCl₂ and 0.1 % BSA) at 30 °C for 120 min with 4.5 nM [³H]Org 43553 in the absence (control) or presence of 10 µM LUF5419. The amount of radioligand bound to the receptor was measured at various time intervals during incubation. Dissociation experiments were performed by preincubating membrane aliquots containing 50 µg protein in a total volume of 100 µl assay buffer (25 mM Tris HCl, pH 7.4, supplemented with 2 mM MgCl₂ and 0.1 % BSA) with 4.5 nM [³H]Org 43553 at 30 °C for 90 min in the absence (control) or presence of 10 µM LUF5419. After preincubation, dissociation was initiated by addition of 10 µM Org 43553 in the absence (control) or presence of allosteric modulators in a total volume of 5 µl of which 25 % (v/v) DMSO. In a similar set-up, five different concentrations of LUF5419 were used (5 - 100 µM) to determine its potency for allosteric enhancement of Org 43553. The amount of radioligand still bound to the receptor was measured after 30 min of dissociation. The amount of specific radioligand binding obtained under control conditions was set at 0 % and the total binding (t = 0 min) was set at 100 %. In addition, the amount of [³H]Org 43553 still bound to the receptor was measured at various time intervals for a total of 120 min in the absence (control) and presence of 10 µM LUF5419. Incubations were terminated and samples were obtained and analyzed as described under Radioligand Saturation Assays. Dissociation assays with ¹²⁵I-hCG were performed as described previously by Heitman et al (Mol Pharmacol 73(2):518-524).

Luciferase Assays
CHOHLaHRJuc cells were grown as described above. On the day of the assay, cells were washed with phosphate-buffered saline (PBS) and then harvested using trypsol (0.25 % (w/v) in PBS containing 4.4 mM EDTA). Cells were resuspended in assay medium consisting of DMEM and F12 (1:1) supplemented with 1 µg/ml insulin, 5 µg/ml apotransferrin, 100 µg/ml streptomycin and 100 IU/ml penicillin. Typically, a well contained 30 µl of test compound, 30 µl of assay medium and 30 µl of cell suspension containing 7.5 x 10⁵ cells/ml. Luciferase assays were performed using ten concentrations of test compound. Basal activity was determined in the presence of assay medium and represented approximately 10 % of the maximal activity. Maximal receptor activity was determined in the presence of 1 nM recLH and was set at 100 % in all experiments, whereas basal activity was set at 0 % in all experiments. After 4 h stimulation, 45 µl of Britelite® (PerkinElmer, Groningen, The Netherlands) was added to each well for detection of luciferase protein. Finally, the luminescence signal was quantified on a
Microbeta Trilux 1450 Luminescence Counter (PerkinElmer, Groningen, The Netherlands).

Data Analysis

All binding data were analyzed using the non-linear regression curve-fitting program GraphPad Prism v. 5.00 (GraphPad Software Inc, San Diego, CA, U.S.A.). EC_{50} values were directly obtained from the dose-response curves and inhibitory binding constants (K_i values) were derived from the IC_{50} values according to $K_i = IC_{50}/(1 + [C]/K_o)$ where [C] is the concentration of the radioligand and K_0 its dissociation constant (Cheng and Prusoff, 1973). Dissociation rate constants, $k_{off}$, were obtained by computer analysis of the exponential decay of $[^3H]Org 43553$ bound to the receptor. Association rate constants were calculated according to the equation $k_{on} = (k_{obs} - lwV[L])$, where $k_{obs}$ was obtained by computer analysis of the exponential association of the percentage of $[^3H]Org 43553$ bound to the receptor and [L] is the amount of radioligand used for the association experiments. The EC_{50} from dissociation experiments was obtained from dose response-curves of decreased dissociation by different concentrations of LUF5419, where the non-specific binding was set at 0 % and the true control (buffer) after 30 min was set at 100 %. All values obtained are means of at least three independent experiments performed in duplicate.

The invention is defined by the following claims.
1. A compound having the formula of structure (I):

\[
\begin{array}{c}
\text{S} \\
\text{N} \\
\text{L} \\
\text{R}^2 \\
\text{O}
\end{array}
\]

or a pharmaceutically acceptable salt thereof, for use in treating a LH receptor-related condition, wherein:

- \( R^1 \) is aryl, cycloalkyl, alkenyl, alkynyl, heteroaryl or heterocycloalkyl, optionally substituted with one or two \( R^3 \) groups;
- each occurrence of \( R^3 \) is alkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocycloalkyl, cycloalkyl, alkylaryl, alkylheteroaryl, alkylheterocycloalkyl, alkoxy, CN, OH, oxo, halo, C(=O)OH, C(halo)\(_3\), CH(halo)\(_2\), CH\(_2\)(halo), NO\(_2\), N(R\(^4\))\(_2\), C(=O)N(R\(^4\))\(_2\), OC(=O)N(R\(^4\))\(_2\), NR\(^4\)OH, C(=0)R\(^4\), C(=O)OR\(^4\), OC(=O)R\(^4\), S-R\(^4\), or S(=O)\(_2\)R\(^4\);
- each occurrence of \( R^4 \) is independently H, alkyl, alkenyl, alkynyl, aryl, alkyl-O-aryl, alkyl-NH-alkyl, heteroaryl, heterocycloalkyl, alkylaryl, alkylheteroaryl, or alkylheterocycloalkyl;
- L is -S-, -O- or NR\(^5\), wherein \( R^5 \) is H, aryl, cycloalkyl or alkyl;
- \( R^2 \) is aryl, cycloalkyl, alkyl, OR\(^6\) or NHR\(^6\), wherein \( R^6 \) is aryl, heteroaryl, cycloalkyl, alkylaryl or alkyl, wherein \( R^2 \) and \( R^6 \) are optionally substituted with one or two \( R^7 \) groups, and provided that when \( R^2 \) is OR\(^6\), L is NR\(^5\); and
- each occurrence of \( R^7 \) is alkyl, halo, NO\(_2\), CN, N(R\(^4\))\(_2\) or alkoxy.

2. A compound of claim 1 wherein \( R^1 \) is aryl or heteroaryl, optionally substituted with one or two \( R^3 \) groups.

3. A compound of claim 2 wherein \( R^1 \) is phenyl or pyridyl (preferably 2-pyridyl), optionally substituted with one or two \( R^3 \) groups.

4. A compound of any of the preceding claims wherein \( R^3 \) is halo.

5. A compound of any of the preceding claims wherein L is NR\(^5\), preferably wherein \( R^5 \) is H.
6. A compound of any of the preceding claims wherein \( R^2 \) is aryl or \( \text{NHR}^6 \), optionally substituted with one or two \( R^7 \) groups.

7. A compound of any of the preceding claims wherein \( R^6 \) is aryl, optionally substituted with one or two \( R^7 \) groups.

8. A compound of claim 6 or 7 wherein \( R^2 \) or \( R^6 \) is phenyl, optionally substituted with one or two \( R^7 \) groups.

9. A compound of claim 8, wherein each occurrence of \( R^7 \) is halo, nitro or alkoxy, preferably, halo or alkoxy.

10. A compound according to claim 1 selected from the group consisting of:

11. A compound having the formula of structure (I):
or a pharmaceutically acceptable salt thereof, wherein:

$R^1$ is aryl, cycloalkyl, alkenyl, alkynyl, heteroaryl or heterocycloalkyl, optionally substituted with one or two $R^3$ groups;

each occurrence of $R^3$ is alkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocycloalkyl, cycloalkyl, alkyaryl, alkyheteroaryl, alkyheterocycloalkyl, alkylcycloalkyl, alkoxy, CN, OH, oxo, halo, C(=O)OH, C(halo)$_2$, CH(halo)$_2$, CH$_2$(halo), NO$_2$, N(R$_4$)$_2$, C(=O)N(R$_4$)$_2$, OC(=O)N(R$_4$)$_2$, NR$_4$OH, C(=O)R$_4$, C(=O)OR$_4$, OC(=O)R$_4$, S-R$_4$, or S(=O)$_2$R$_4$;

each occurrence of $R^4$ is independently H, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, alkylaryl, alkyheteroaryl, or alkyheterocycloalkyl;

$L$ is -S-, -O- or NR$_5$, wherein $R^5$ is H, aryl, cycloalkyl or alkyl;

$R^2$ is aryl, cycloalkyl, alkyl, OR$_6$ or NHR$_6$, wherein $R^6$ is aryl, heteroaryl, cycloalkyl, alkylaryl or alkyl, wherein $R^2$ and $R^6$ are optionally substituted with one or two $R^7$ groups, and provided that when $R^2$ is OR$_6$, $L$ is NR$_5$; and

each occurrence of $R^7$ is alkyl, halo, NO$_2$, CN, N(R$_4$)$_2$ or alkoxy; provided that the compound is not:

$N$-[4-(2-Pyridyl)thiazol-2-yl]-benzamide,
$N$-[4-(2-Pyridyl)thiazol-2-yl]-4-chlorobenzamide,
$N$-[4-(2-Pyridyl)thiazol-2-yl]-4-iodobenzamide,
$N$-[4-(2-Pyridyl)thiazol-2-yl]-4-methylbenzamide,
$N$-[4-(2-Pyridyl)thiazol-2-yl]-4-methoxybenzamide,
$N$-[4-(2-Pyridyl)thiazol-2-yl]-3,4-dichlorobenzamide,
$N$-[4-(2-Pyridyl)thiazol-2-yl]-3-chlorobenzamide,
$N$-[4-(2-Pyridyl)thiazol-2-yl]-4-nitrobenzamide,
$N$-[4-(2-Pyridyl)thiazol-2-yl]-4-isopropoxybenzamide,
$N$-[4-(2-Pyridyl)thiazol-2-yl]-cyclopentamide,
$N$-Phenyl-$N$-[4-(2-pyridyl)thiazol-2-yl]urea,
$N$-(4-Methoxyphenyl)-$N$-[4-(2-pyridyl)thiazol-2-yl]urea,
$N$-Phenyl-$N'$-[4-(4-phenylthiazol-2-yl])urea,
$N$-[4-(phenylthiazol-2-yl)]-4-methoxybenzamide,
$N$-[4-(phenylthiazol-2-yl)]-benzamide,
12. A pharmaceutical composition comprising a compound as defined in any of the preceding claims and a pharmaceutically acceptable carrier.

13. Any allosteric enhancer of the LH receptor, preferably wherein the allosteric enhancer is a low molecular weight (LMW) allosteric enhancer.

14. A compound or composition or allosteric enhancer as defined in any of claims 11 to 13 for use in medicine.

15. A composition of claim 12 or allosteric enhancer of claim 13 for use in treating a LH receptor-related condition.

16. Use of a compound or composition or allosteric enhancer as defined in any of claims 1 to 13 in the manufacture of a medicament for treating a LH receptor-related condition.

17. A method of treating a LH receptor-related condition, the method comprising administering to a patient a compound or composition or allosteric enhancer as defined in any of claims 1 to 13.

18. A method, use, compound or composition or allosteric enhancer of any of claims 15 to 17 wherein the LH receptor-related condition is prostate cancer, testicular cancer, uterine cancer, ovarian cancer, breast cancer, pituitary gonadotrope adenomas, endometriosis, polycystic ovarian disease, uterine fibroids, primary hirsutism, LH surge, benign prostatic hypertrophy, vasomotor instability or precocious puberty.

19. A method, use, compound or composition or allosteric enhancer of any of claims 15 to 17 wherein treating the LH receptor-related condition comprises fertility treatment.
20. A method, use, compound or composition or allosteric enhancer of claim 19 wherein fertility treatment comprises a pro-fertility treatment, for example *in-vitro* fertilisation (IVF).

21. A method, use, compound or composition or allosteric enhancer of claim 19 wherein fertility treatment comprises preventing pregnancy.

22. A combination product comprising (a) a compound as defined in any of claims 1 to 11, or a pharmaceutically acceptable salt thereof, and (b) another therapeutic agent that is useful in the treatment a LH receptor-related condition, wherein each of components (a) and (b) is formulated in admixture with a pharmaceutically acceptable carrier.

23. A combination product of claim 22 which comprises a pharmaceutical composition including a compound of formula (I) as defined in any of claims 1 to 11, or a pharmaceutically acceptable salt thereof, another therapeutic agent that is useful in the treatment of a LH receptor-related condition, and a pharmaceutically acceptable carrier.

24. A combination product of claim 22 which comprises a kit of parts comprising components:
(a) a pharmaceutical composition including a compound of formula (I) as defined in any of claims 1 to 11, or a pharmaceutically-acceptable salt thereof, in admixture with a pharmaceutically-acceptable carrier; and
(b) a pharmaceutical composition including another therapeutic agent that is useful in the treatment of a LH receptor-related condition in admixture with a pharmaceutically-acceptable carrier, which components (a) and (b) are each provided in a form that is suitable for administration in conjunction with the other.

25. A process for preparing a compound having the formula of structure (I) as defined in claim 1, the process comprising reaction of a compound of formula (II):

\[
\begin{align*}
\text{(II)} & \\
\end{align*}
\]

with:

(i) in the case wherein \( R^2 \) is \( \text{NHR}^6 \), a compound of formula \( R^6-N=C=O \); or
(ii) in the case wherein $R_2$ is aryl, cycloalkyl, alkyl or OR$_6$, a compound of formula $R_2$-C(=O)Cl or $R_2$-C(=O)OH,

wherein $R_1$, L and $R_5$ are as defined in claim 1.

26. A process for the preparation of a pharmaceutical composition as defined in claim 12, which process comprises bringing into association a compound of formula (I), as defined in any of claims 1 to 11, or a pharmaceutically acceptable salt thereof, with a pharmaceutically acceptable carrier.

27. A process for the preparation of a combination product as defined in any of claims 22 to 24, which process comprises bringing into association a compound of formula (I), as defined in any of claims 1 to 11, or a pharmaceutically acceptable salt thereof with the other therapeutic agent that is useful in the treatment of a LH receptor-related condition, and at least one pharmaceutically-acceptable carrier.

28. Any novel compound substantially as herein described.

29. Any novel composition substantially as herein described.

30. Any novel method of treatment, use, or compound or composition or allosteric enhancer for use substantially as herein described.

31. Any novel combination product substantially as herein described.

32. Any novel allosteric enhancer substantially as herein described.
Figure 1  Saturation of $[^3]$H]Org 43553 to luteinizing hormone receptors in the absence (control) or presence of 10 μM LUF5419. The control specific binding (■) was determined by subtracting the non-specific binding (▲) from the total binding (●) curve. A similar experiment was performed in the presence of 10 μM LUF5419, of which only the specific binding is shown (○). Representative graphs from one experiment performed in duplicate (see Table 3 for $K_D$ and $B_{max}$ values).
Figure 2    Displacement of $[^3]$HOrg 43553 binding from human luteinizing hormone receptors stably expressed on CHO-K1 cell membranes by unlabeled Org 43553 in the absence (●; control) or presence of 10 μM LUF5419 ( []). Representative graphs from one experiment performed in duplicate.
Figure 3  a) Association and b) dissociation kinetics of $[^3\text{H}]\text{Org} 43553$ binding to CHO-K1 membranes expressing the human luteinizing hormone receptor at 30°C. Dissociation was either initiated by the addition of 10 μM Org 43553 in the absence (■; control) or presence of 10 μM LUF5419 (○). Representative graphs from one experiment performed in duplicate (see Table 4 for kinetic parameters).
Figure 4  Concentration-effect curves of recLH and Org 43553 in the absence (■; recLH, △; Org 43553) or presence of 10 µM LUF5419 (○; recLH, Δ; Org 43553) for cAMP-mediated luciferase production through human luteinizing hormone receptors. a) curves of raw data, b) bargraph showing the effect of 10 µM LUF5419 on forskolin-induced (10 µM) luciferase activity, c) curves corrected for forskolin-effect. Representative graphs from one experiment performed in duplicate (see Table 5 for EC<sub>50</sub> and E<sub>max</sub> values).
Figure 5  Concentration-dependent effect of LUF5419 on dissociation of $[^3]$H]Org 43553 binding from human luteinizing hormone receptors stably expressed on CHO-K1 cell membranes measured at a single time point of 30 min. Data points corresponding to total binding (no dissociation) and control binding (dissociation after 30 min) are set at 100 and 0 %, respectively. Representative graph from one experiment performed in duplicate (see Table 6 for EC$_{50}$ values).
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D277/46 C07D277/48 C07D417/04 A61K31/426 A61K31/427

ADD. A61P5/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D A61K

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

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

EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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Further documents are listed in the continuation of Box C

See patent family annex

Date of the actual completion of the international search

29 July 2010

Date of mailing of the international search report

13/08/2010

Name and mailing address of the ISA/
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Authorized officer

Guspanova, Jana
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<td>HEITMAN L H ET AL: &quot;[3H]Org 43553, the First Low-Molecular-Weight Agonistic and allosteric Radioligand for the Human Luteinizing Hormone Receptor&quot; MOLECULAR PHARMACOLOGY, vol. 73, no. 2, 7 November 2007 (2007-11-07), pages 518-524, XP002594302 cited in the application Table 2 on page 522; page 518, column 1, paragraph 1 - page 519, column 1, paragraph 2</td>
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