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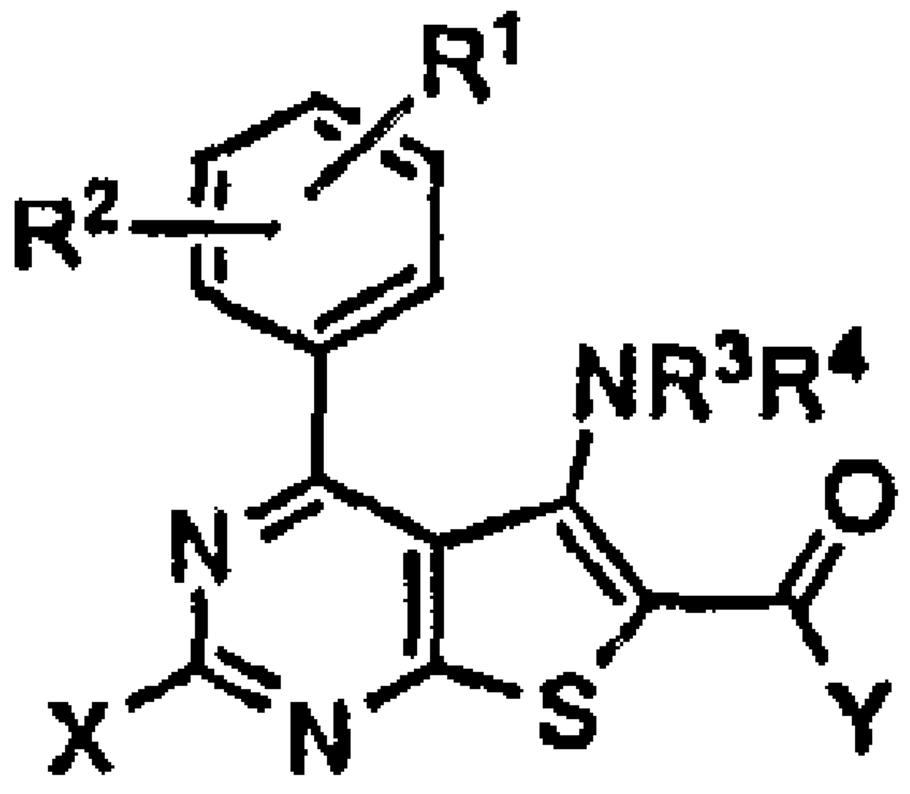
(54) Titre : LIGANDS DE PYRIMIDINE DE FAIBLE POIDS MOLECULAIRE DESTINES A MODULER DES RECEPTEURS HORMONAUX

(54) Title: PYRIMIDINE LOW MOLECULAR WEIGHT LIGANDS FOR MODULATING HORMONE RECEPTORS

(I)



(57) Abrégé/Abstract:
Disclosed herein are small molecule modulators hormone receptors, including agonists and antagonists of luteinizing hormone/choriogonadotropin, follicle stimulating hormone and thyroid stimulating hormone receptors. Exemplary disclosed compounds include those of the formula wherein X is $-S(O)_nR^5$; n is 0, 1 or 2; Y is $-OR^6$ or $-NR^7R^8$ R^1 and R^2 independently are selected from optionally substituted lower aliphatic, alkoxy, aralkyl, halogen, H and -OR5, wherein R5 is selected from lower alkyl, H, aralkyl, acyl, alkoxycarbonyl and aminocarbonyl; R^3 and R^4 independently are selected from acyl, alkoxycarbonyl, aminocarbonyl, aralkyl, H, lower alkyl and cycloalkyl; R^5 is selected from lower alkyl, aralkyl, cycloalkyl and haloalkyl; R^6 is selected from H, lower alkyl and aralkyl; R^7 and R8 independently are selected from H, lower alkyl, aralkyl and cycloalkyl.

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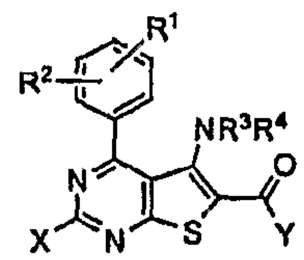
(54) Title: PYRIMIDINE LOW MOLECULAR WEIGHT LIGANDS FOR MODULATING HORMONE RECEPTORS



(I)

(57) Abstract: Disclosed herein are small molecule modulators hormone receptors, including agonists and antagonists of luteinizing hormone/choriogonadotropin, follicle stimulating hormone and thyroid stimulating hormone receptors. Exemplary disclosed compounds include those of the formula wherein X is $-S(O)_nR^5$; n is 0, 1 or 2; Y is $-OR^6$ or $-NR^7R^8$ R^1 and R^2 independently are selected from optionally substituted lower aliphatic, alkoxy, aralkyl, halogen, H and -OR5, wherein R5 is selected from lower alkyl, H, aralkyl, acyl, alkoxycarbonyl and aminocarbonyl; R^3 and R^4 independently are selected from acyl, alkoxycarbonyl, aminocarbonyl, aralkyl, H, lower alkyl and cycloalkyl; R^5 is selected from lower alkyl, aralkyl, cycloalkyl and haloalkyl; R^6 is selected from H, lower alkyl and aralkyl; R^7 and R8 independently are selected from H, lower alkyl, aralkyl and cycloalkyl.

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PYRIMIDINE LOW MOLECULAR WEIGHT LIGANDS FOR MODULATING HORMONE RECEPTORS

CROSS REFERENCE TO RELATED APPLICATION

This application claims the benefit of the earlier filing date of U.S. Provisional Patent Application No. 60/801,370 filed May 17, 2006.

FIELD

This disclosure concerns hormone receptor modulating compounds and methods for their use.

BACKGROUND

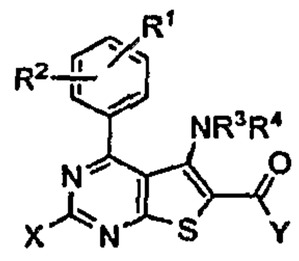
Luteinizing hormone/choriogonadotropin (LH/CG), follicle-stimulating hormone (FSH) and thyroid-stimulating hormone (TSH) are heterodimeric glycoprotein hormones that regulate reproduction and thyroid homeostasis. LH is responsible for ovulation induction in women and controls testosterone production in men. FSH causes ovarian follicle maturation in women and is involved in spermatogenesis in men. TSH is involved in the growth and function of thyroid follicular cells. Cellular responses to all three glycoprotein hormones are mediated via distinct seven transmembrane-spanning receptors, for example, the LHCG, FSH and TSH receptors. Each receptor is characterized by an elongated extracellular domain distinguished by several leucine-rich motifs that are involved in recognition and binding of the large glycoprotein hormones. The seven-transmembrane helices of each receptor are noteworthy because of their high degree of homology.

Disruption of physiological regulation of LHCG receptor, FSH receptor and TSH receptor by diverse pathogenic mutations has been implicated in a number of human diseases. The specific and potent control of these multifunctioning receptors could provide important therapeutic advancements. LH and FSH are currently used clinically for the treatment of infertility. Recombinant TSH is used in the diagnostic screen for thyroid cancer. TSH receptor agonists and antagonists may well have utility in the diagnosis and treatment of thyroid cancer, respectively. The

development of small molecule modulators of LHCG receptor and FSH receptor has also been pursued with varying degrees of success.

SUMMARY

Disclosed herein are modulators of hormone receptors, including agonists and antagonists of the luteinizing hormone receptor, follicle stimulating hormone receptor and thyroid-stimulating hormone receptor. Examples of such hormone receptor modulators include those of the formula



wherein X is $-S(O)_nR^5$;

n is 0, 1 or 2;

Y is $-OR^6$ or $-NR^7R^8$

R^1 and R^2 independently are selected from optionally substituted lower aliphatic, alkoxy, aralkyl, halogen, H and $-OR^5$, wherein R^5 is selected from lower alkyl, H, aralkyl, acyl, alkoxycarbonyl and aminocarbonyl;

R^3 and R^4 independently are selected from acyl, alkoxycarbonyl, aminocarbonyl, aralkyl, H, lower alkyl and cycloalkyl;

R^5 is selected from lower alkyl, aralkyl, cycloalkyl and haloalkyl;

R^6 is selected from H, lower alkyl and aralkyl; and

R^7 and R^8 independently are selected from H, lower alkyl, aralkyl and cycloalkyl.

The foregoing and other objects, features, and advantages of the invention will become more apparent from the following detailed description, which proceeds with reference to the accompanying figures.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 illustrates the analysis of compounds **3** and **20** at both the TSH receptor and the LHCG receptor, comparing activation of receptor and the LHCG receptor by compounds **3** and **20** relative to basal activities of both receptors.

FIG. 2 illustrates full concentration analyses of compounds **3**, **5**, and **7** at TSH receptor and LHCG receptor, with the data presented as mean ± SEM of two independent experiments, each performed in duplicate.

DETAILED DESCRIPTION

I. Introduction

Disclosed herein are small molecule compounds that can be used to modulate hormone receptors, such as seven transmembrane-spanning receptors. Because the seven-transmembrane helices of such receptors exhibit a high degree of homology it currently is believed, without limitation to any particular theory, that the disclosed compounds are useful for modulating many such receptors. Of particular interest is the modulation of the seven transmembrane-spanning receptors for luteinizing hormone/choriogonadotropin (LH/CG), follicle-stimulating hormone (FSH) and thyroid-stimulating hormone (TSH) which are heterodimeric glycoprotein hormones that regulate reproduction and thyroid homeostasis.

The TSH receptor regulates function of the thyroid gland and is important in several diseases. At present, recombinant human TSH (rhTSH, Thyrogen™) is an activator (agonist) of the TSH receptor that is used in the treatment of patients with thyroid cancer. In patients with hyperthyroidism (an "overactive thyroid"), the thyroid is overstimulated by antibodies (autoimmune hyperthyroidism or Graves's disease) or within a tumor ("toxic adenoma") via the TSH receptor. An antagonist (inverse agonist) would inhibit the overstimulated thyroid and could be used to treat these forms of hyperthyroidism. Disclosed herein are low molecular weight compounds that bind to the TSH receptor and either activate it, like rhTSH, or down regulate it. Exemplary compounds may be used in methods of activating or down regulating the TSH receptor, according to the disclosed activity of the compound. Hence compounds that activate the TSH receptor can be used as receptor agonists, and compounds that inhibit the action of the TSH receptor can be used as antagonists.

The following explanations of terms and methods are provided to better describe the present compounds, compositions and methods, and to guide those of ordinary skill in the art in the practice of the present disclosure. It is also to be

understood that the terminology used in the disclosure is for the purpose of describing particular embodiments and examples only and is not intended to be limiting.

As used herein, the singular terms "a," "an," and "the" include plural referents unless context clearly indicates otherwise. Similarly, the word "or" is intended to include "and" unless the context clearly indicates otherwise. Also, as used herein, the term "comprises" means "includes." Hence "comprising A or B" means including A, B, or A and B.

Variables such as R^1, R^2,R^3, R^4, R^5, R^6, R^7, R^8, R^9, n, X and Y, used throughout the disclosure are the same variables as previously defined unless stated to the contrary.

"Optional" or "optionally" means that the subsequently described event or circumstance can but need not occur, and that the description includes instances where said event or circumstance occurs and instances where it does not.

"Derivative" refers to a compound or portion of a compound that is derived from or is theoretically derivable from a parent compound.

The term "subject" includes both human and veterinary subjects.

"Treatment" refers to a therapeutic intervention that ameliorates a sign or symptom of a disease or pathological condition after it has begun to develop. As used herein, the term "ameliorating," with reference to a disease or pathological condition, refers to any observable beneficial effect of the treatment. The beneficial effect can be evidenced, for example, by a delayed onset of clinical symptoms of the disease in a susceptible subject, a reduction in severity of some or all clinical symptoms of the disease, a slower progression of the disease, an improvement in the overall health or well-being of the subject, or by other parameters well known in the art that are specific to the particular disease. The phrase "treating a disease" refers to inhibiting the full development of a disease or condition, for example, in a subject who is at risk for a disease such as a hormone receptor mediated disorder, particularly a thyroid disorder, such as a hyperthyroid or hypothyroid disorder. A "prophylactic" treatment is a treatment administered to a subject who does not exhibit signs of a disease or exhibits only early signs for the purpose of decreasing the risk of developing pathology. By the term "coadminister" is meant that each of

at least two compounds be administered during a time frame wherein the respective periods of biological activity overlap. Thus, the term includes sequential as well as coextensive administration of two or more drug compounds.

The terms "pharmaceutically acceptable salt" or "pharmacologically acceptable salt" refers to salts prepared by conventional means that include basic salts of inorganic and organic acids, including but not limited to hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, methanesulfonic acid, ethanesulfonic acid, malic acid, acetic acid, oxalic acid, tartaric acid, citric acid, lactic acid, fumaric acid, succinic acid, maleic acid, salicylic acid, benzoic acid, phenylacetic acid, mandelic acid and the like. When compounds disclosed herein include an acidic function such as a carboxy group, then suitable pharmaceutically acceptable cation pairs for the carboxy group are well known to those skilled in the art and include alkaline, alkaline earth, ammonium, quaternary ammonium cations and the like. Such salts are known to those of skill in the art. For additional examples of "pharmacologically acceptable salts," see Berge et al., *J. Pharm. Sci.* 66:1 (1977).

"Saturated or unsaturated" includes substituents saturated with hydrogens, substituents completely unsaturated with hydrogens and substituents partially saturated with hydrogens.

The term "acyl" refers group of the formula RC(O)– wherein R is an organic group.

The term "alkyl" refers to a branched or unbranched saturated hydrocarbon group of 1 to 24 carbon atoms, such as methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *t*-butyl, pentyl, hexyl, heptyl, octyl, decyl, tetradecyl, hexadecyl, eicosyl, tetracosyl and the like. A "lower alkyl" group is a saturated branched or unbranched hydrocarbon having from 1 to 10 carbon atoms.

The term "alkenyl" refers to a hydrocarbon group of 2 to 24 carbon atoms and structural formula containing at least one carbon-carbon double bond.

The term "alkynyl" refers to a hydrocarbon group of 2 to 24 carbon atoms and a structural formula containing at least one carbon-carbon triple bond.

The terms "halogenated alkyl" or "haloalkyl group" refer to an alkyl group as defined above with one or more hydrogen atoms present on these groups substituted

with a halogen (F, Cl, Br, I).

The term "cycloalkyl" refers to a non-aromatic carbon-based ring composed of at least three carbon atoms. Examples of cycloalkyl groups include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and the like. The term "heterocycloalkyl group" is a cycloalkyl group as defined above where at least one of the carbon atoms of the ring is substituted with a heteroatom such as, but not limited to, nitrogen, oxygen, sulfur, or phosphorous.

The term "aliphatic" is defined as including alkyl, alkenyl, alkynyl, halogenated alkyl and cycloalkyl groups as described above. A "lower aliphatic" group is a branched or unbranched aliphatic group having from 1 to 10 carbon atoms.

"Alkoxycarbonyl" refers to an alkoxy substituted carbonyl radical, –C(O)OR, wherein R represents an optionally substituted alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl or similar moiety.

"Aminocarbonyl" alone or in combination, means an amino substituted carbonyl (carbamoyl) radical, wherein the amino radical may optionally be mono- or di-substituted, such as with alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, alkanoyl, alkoxycarbonyl, aralkoxycarbonyl and the like.

The term "aryl" refers to any carbon-based aromatic group including, but not limited to, benzene, naphthalene, etc. The term "aromatic" also includes "heteroaryl group," which is defined as an aromatic group that has at least one heteroatom incorporated within the ring of the aromatic group. Examples of heteroatoms include, but are not limited to, nitrogen, oxygen, sulfur, and phosphorous. The aryl group can be substituted with one or more groups including, but not limited to, alkyl, alkynyl, alkenyl, aryl, halide, nitro, amino, ester, ketone, aldehyde, hydroxy, carboxylic acid, or alkoxy, or the aryl group can be unsubstituted. The term "alkyl amino" refers to alkyl groups as defined above where at least one hydrogen atom is replaced with an amino group.

"Carbonyl" refers to a radical of the formula –C(O)–. Carbonyl-containing groups include any substituent containing a carbon-oxygen double bond (C=O), including acyl groups, amides, carboxy groups, esters, ureas, carbamates, carbonates and ketones and aldehydes, such as substituents based on –COR or –RCHO where R

is an aliphatic, heteroaliphatic, alkyl, heteroalkyl, hydroxyl, or a secondary, tertiary, or quaternary amine.

"Carboxyl" refers to a -COOH radical. Substituted carboxyl refers to -COOR where R is aliphatic, heteroaliphatic, alkyl, heteroalkyl, or a carboxylic acid or ester.

The term "hydroxyl" is represented by the formula –OH. The term "alkoxy group" is represented by the formula –OR, where R can be an alkyl group, optionally substituted with an alkenyl, alkynyl, aryl, aralkyl, cycloalkyl, halogenated alkyl, or heterocycloalkyl group as described above.

The term "hydroxyaliphatic" refers to "hydroxyalkyl" refers to an alkyl group that has at least one hydrogen atom substituted with a hydroxyl group. The term "alkoxyalkyl group" is defined as an alkyl group that has at least one hydrogen atom substituted with an alkoxy group described above.

The term "amine" or "amino" refers to a group of the formula –NRR', where R and R' can be, independently, hydrogen or an alkyl, alkenyl, alkynyl, aryl, aralkyl, cycloalkyl, halogenated alkyl, or heterocycloalkyl group described above.

The term "amide group" is represented by the formula –C(O)NRR', where R and R' independently can be a hydrogen, alkyl, alkenyl, alkynyl, aryl, aralkyl, cycloalkyl, halogenated alkyl, or heterocycloalkyl group described above.

The term "aralkyl" refers to an aryl group having an alkyl group, as defined above, attached to the aryl group. An example of an aralkyl group is a benzyl group.

Optionally substituted groups, such as "optionally substituted alkyl," refers to groups, such as an alkyl group, that when substituted, have from 1–5 substituents, typically 1, 2 or 3 substituents, selected from alkoxy, optionally substituted alkoxy, acyl, acylamino, acyloxy, amino, aminoacyl, aminoacyloxy, aryl, carboxyalkyl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, halogen, optionally substituted heteroaryl, optionally substituted heterocyclyl, hydroxy, sulfonyl, thiol and thioalkoxy. In particular, optionally substituted alkyl groups include, by way of example, haloalkyl groups, such as fluoroalkyl groups, including, without limitation, trifluoromethyl groups.

Prodrugs of the disclosed hormone modulating compounds also are contemplated herein. A prodrug is an active or inactive compound that is modified

chemically through *in vivo* physiological action, such as hydrolysis, metabolism and the like, into an active compound following administration of the prodrug to a subject. The suitability and techniques involved in making and using prodrugs are well known by those skilled in the art. For a general discussion of prodrugs involving esters see Svensson and Tunek Drug Metabolism Reviews 165 (1988) and Bundgaard Design of Prodrugs, Elsevier (1985).

Pharmaceutically acceptable prodrugs refer to compounds that are metabolized, for example, hydrolyzed or oxidized, in the subject to form an antiviral compound of the present disclosure. Typical examples of prodrugs include compounds that have one or more biologically labile protecting groups on or otherwise blocking a functional moiety of the active compound. Prodrugs include compounds that can be oxidized, reduced, aminated, deaminated, hydroxylated, dehydroxylated, hydrolyzed, dehydrolyzed, alkylated, dealkylated, acylated, deacylated, phosphorylated, dephosphorylated to produce the active compound. In general the prodrug compounds disclosed herein possess hormone receptor modulating activity and/or are metabolized or otherwise processed *in vivo* to form a compound that exhibits such activity.

The term "prodrug" also is intended to include any covalently bonded carriers that release an active parent drug of the present invention *in vivo* when the prodrug is administered to a subject. Since prodrugs often have enhanced properties relative to the active agent pharmaceutical, such as, solubility and bioavailability, the compounds disclosed herein can be delivered in prodrug form. Thus, also contemplated are prodrugs of the presently claimed compounds, methods of delivering prodrugs and compositions containing such prodrugs. Prodrugs of the disclosed compounds typically are prepared by modifying one or more functional groups present in the compound in such a way that the modifications are cleaved, either in routine manipulation or *in vivo*, to yield the parent compound. Prodrugs include compounds having a phosphonate and/or amino group functionalized with any group that is cleaved *in vivo* to yield the corresponding amino and/or phosphonate group, respectively. Examples of prodrugs include, without limitation, compounds having an acylated amino group and/or a phosphonate ester or

phosphonate amide group. In particular examples, a prodrug is a lower alkyl phosphonate ester, such as an isopropyl phosphonate ester.

Protected derivatives of the disclosed compound also are contemplated. A variety of suitable protecting groups for use with the disclosed compounds are disclosed in Greene and Wuts Protective Groups in Organic Synthesis; 3rd Ed.; John Wiley & Sons, New York, 1999.

In general, protecting groups are removed under conditions which will not affect the remaining portion of the molecule. These methods are well known in the art and include acid hydrolysis, hydrogenolysis and the like. One preferred method involves the removal of an ester, such as cleavage of a phosphonate ester using Lewis acidic conditions, such as in TMS-Br mediated ester cleavage to yield the free phosphonate. A second preferred method involves removal of a protecting group, such as removal of a benzyl group by hydrogenolysis utilizing palladium on carbon in a suitable solvent system such as an alcohol, acetic acid, and the like or mixtures thereof. A t-butoxy-based group, including t-butoxy carbonyl protecting groups can be removed utilizing an inorganic or organic acid, such as HCl or trifluoroacetic acid, in a suitable solvent system, such as water, dioxane and/or methylene chloride. Another exemplary protecting group, suitable for protecting amino and hydroxy functions amino is trityl. Other conventional protecting groups are known and suitable protecting groups can be selected by those of skill in the art in consultation with Greene and Wuts Protective Groups in Organic Synthesis; 3rd Ed.; John Wiley & Sons, New York, 1999.

When an amine is deprotected, the resulting salt can readily be neutralized to yield the free amine. Similarly, when an acid moiety, such as a phosphonic acid moiety is unveiled, the compound may be isolated as the acid compound or as a salt thereof.

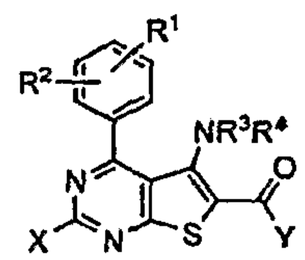
Particular examples of the presently disclosed hormone receptor modulating compounds include one or more asymmetric centers; thus these compounds can exist in different stereoisomeric forms. Accordingly, compounds and compositions may be provided as individual pure enantiomers or as stereoisomeric mixtures, including racemic mixtures. In certain embodiments the compounds disclosed herein are synthesized in or are purified to be in substantially enantiopure form, such as in a

90% enantiomeric excess, a 95% enantiomeric excess, a 97% enantiomeric excess or even in greater than a 99% enantiomeric excess, such as in enantiopure form.

It is understood that substituents and substitution patterns of the compounds described herein can be selected by one of ordinary skill in the art to provide compounds that are chemically stable and that can be readily synthesized by techniques known in the art and further by the methods set forth in this disclosure. Reference will now be made in detail to the presently preferred compounds.

II. Hormone Receptor Modulating Compounds

Certain embodiments of the disclosed hormone receptor modulating compounds are represented by the formula



wherein X is $-S(O)_nR^5$;

n is 0, 1 or 2;

Y is $-OR^6$ or $-NR^7R^8$

R^1 and R^2 independently are selected from optionally substituted lower aliphatic, alkoxy, aralkyl, halogen, hydrogen and $-OR^5$, wherein R^5 is selected from lower alkyl, hydrogen, aralkyl, acyl, alkoxycarbonyl and aminocarbonyl;

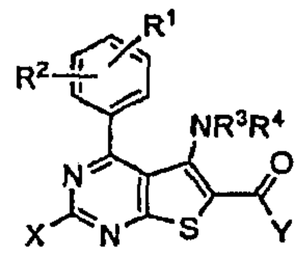
R^3 and R^4 independently are selected from acyl, alkoxycarbonyl, aminocarbonyl, aralkyl, hydrogen, lower alkyl and cycloalkyl;

R^5 is selected from lower alkyl, aralkyl, cycloalkyl and haloalkyl;

R^6 is selected from hydrogen, lower alkyl and aralkyl; and

R^7 and R^8 independently are selected from hydrogen, lower alkyl, aralkyl and cycloalkyl.

In one aspect such compounds have the formula



wherein X is $-S(O)_nR^5$;

n is 0, 1 or 2;

Y is $-OR^6$ or $-NR^7R^8$

R^1 and R^2 independently are selected from optionally substituted lower aliphatic, alkoxy, aralkyl, halogen, H and $-OR^5$, wherein R^5 is selected from lower alkyl, H, aralkyl, acyl, alkoxycarbonyl and aminocarbonyl;

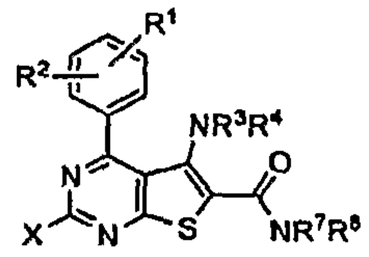
R^3 and R^4 independently are selected from acyl, alkoxycarbonyl, aminocarbonyl, aralkyl, H, lower alkyl and cycloalkyl;

R^5 is selected from lower alkyl, aralkyl, cycloalkyl and haloalkyl;

R^6 is selected from H, lower alkyl and aralkyl;

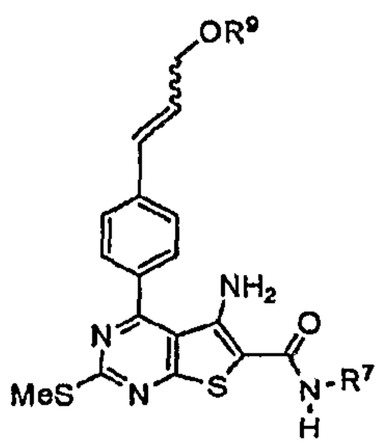
R^7 and R^8 independently are selected from H, lower alkyl, aralkyl and cycloalkyl; with the proviso that when R^1 is methoxy, R^2 is not H.

In certain embodiments of the disclosed hormone receptor modulating compounds, Y forms, together with the carbonyl moiety to which it is bound, an amide group. Such compounds can be represented by the formula

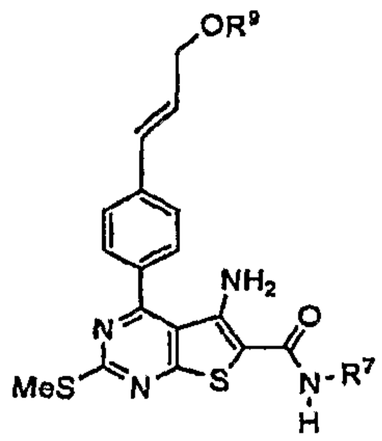


In certain disclosed compounds R^7 and R^8 independently are selected from hydrogen, lower alkyl, aralkyl and cycloalkyl. In certain examples of such compounds at least one of R^7 and R^8 is hydrogen. In particular embodiments, at least one of R^7 and R^8 is a sterically bulky substituent. Such sterically bulky substituents are known to those of ordinary skill in the art of organic chemistry and include alkyl groups, such as, without limitation, *tert*-butyl, *iso*-butyl, neopentyl, adamantyl and the like.

In certain embodiments, the disclosed compounds are represented by the formula

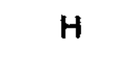
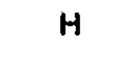
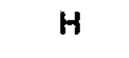
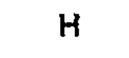


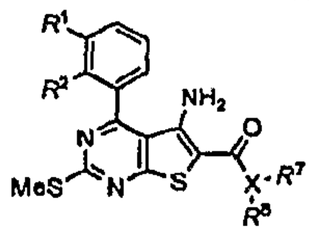
wherein R^9 is selected from acyl, alkoxycarbonyl, aminocarbonyl, aralkyl, H, lower alkyl and cycloalkyl. With reference to the formula presented above, such compounds can be provided as single isomer or alternatively as mixtures of *E* and *Z* isomers. The *E* compounds, which are believed to be particularly effective antagonists of the TSH receptor can be represented by the formula



With reference to Table 1, exemplary disclosed compounds were evaluated against human TSH receptor and human LHCG receptor that were stably expressed in HEK 293 EM cells as previously described by Libert et al. (*Biochem. Biophys. Res. Commun.* **1989**, *165*, 1250–1255); and by Schulz et al. (*Mol. Endocrinol.* **1999**, *13*, 181–190). Cell surface expression of TSH receptor and LHCG receptor were determined via FACS analysis (Kleinau, G.; Jäschke, H.; Neumann, S.; Lättig, S.; Paschke, R.; Krause, G. *J. Biol. Chem.* **2004**, *279*, 51590–51600). Agonism of compounds **3–20** were determined via measurement of intracellular cyclic AMP accumulation. Certain embodiments of the disclosed hormone receptor modulating compounds exhibit advantageous receptor selectivity. For example, certain compound preferentially interact with the certain compounds disclosed herein exerted no discernible effect on the FSH receptor.

Table 1. Pharmacological characterization of selected hormone receptor modulating compounds at TSHR and LHCGR stably expressed in HEK EM 293 cells

Analogue #	X	R^1	R^2	R^7	R^8	*EC_{50} (LHCGR) in µM [95% C. I.]*	*% Max. Resp. @ LHCGR in µM*	*EC_{50} (TSHR) in µM [95% C. I.]*	*% Max. Resp. @ TSHR in µM*
3	N	OMe	H	*t*Bu	H	0.3 [0.2 - 0.5]	45.8 ± 5.9	6.5 [4.9 - 8.5]	23.4 ± 3.6
4	O	OMe	H	Et	H	n.d.	4.2 ± 2.2	n.d.	1.5 ± 0.2
5	O	OMe	H	*t*Bu	H	1.1 [0.8 - 1.5]	23.8 ± 3.3	11.9**	> 30.3*
6	N	OMe	H	Et	H	n.d.	26.9 ± 4.8	n.d.	2.3 ± 0.4
7	N	OMe	H	*t*Bu	Me	0.8 [0.6 - 1.2]	47.8 ± 2.8	n.d.	3.6 ± 1.9
8	N	OMe	H	NH_2	H	n.d.	8.5 ± 3.6	n.d.	6.1 ± 0.8
9	N	OMe	H	$N(Me)_2$	H	n.d.	11.0 ± 1.5	n.d.	4.0 ± 0.1
10	N	OMe	H	NH(*t*Bu)	H	n.d.	6.0 ± 3.1	n.d.	6.4 ± 0.6
11	N	OMe	H	NH(Boc)	H	n.d.	2.4 ± 0.5	n.d.	1.9 ± 0.4
12	N	OMe	H		H	n.d.	20.5 ± 2.7	n.d.	2.9 ± 0.5
13	N	OMe	H		H	n.d.	20.3 ± 2.1	n.d.	3.6 ± 0.6
14	N	OMe	H		H	n.d.	7.8 ± 2.7	n.d.	3.0 ± 1.2
15	N	OMe	H		H	n.d.	25.6 ± 5.4	n.d.	4.3 ± 0.4
16	N	OMe	OMe	*t*Bu	H	0.8 [0.7 - 1.0]	50.1 ± 3.6	n.d.	3.0 ± 0.9
17	N	OMe	F	*t*Bu	H	1.5 [1.0 - 2.1]	46.3 ± 6.6	11.5**	> 24.0*
18	N	F	H	*t*Bu	H	1.2 [0.8 - 1.6]	51.1 ± 5.2	n.d.	8.1 ± 1.7
19	N	OH	H	*t*Bu	H	1.9 [1.1 - 3.4]	63.9 ± 14.2	n.d.	11.2 ± 1.0



Agonistic activity of compounds was determined via measurement of intracellular cyclic AMP. The efficacy (maximum response) is expressed as % of maximum response of LHCGR or TSHR to LH (1000 ng/ml) or TSH (100 mU/ml), respectively. EC_{50} values and 95% confidence intervals (C.I.) were obtained from dose response curves (0 - 100 µM compound) using the GraphPad Prism 4.0 software.
Confidence intervals were not calculated in dose response curves that did not reach an obvious plateau.
n.d. = not determined
* Estimated maximum response at 100 µM compound
** Estimated EC_{50} (dose response curve revealed no plateau)

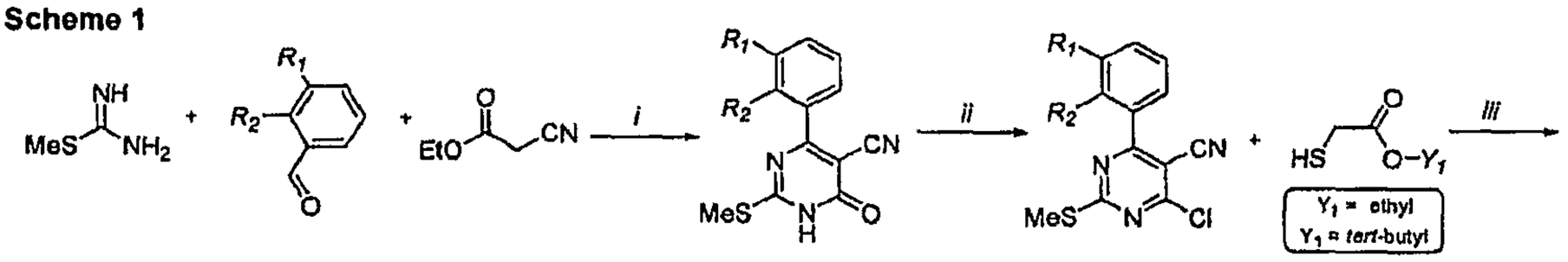
The specification and claims contain listing of species using the language "selected from the group consisting of...and . . . " and "selected from the group consisting of...or..." (sometimes referred to as Markush groups). When this language is used in this application, unless otherwise stated it is meant to include the group as a whole, any single members thereof, or any subgroups thereof. The use of this language is merely for shorthand purposes and is not meant in any way to limit the removal of individual elements or subgroups as needed.

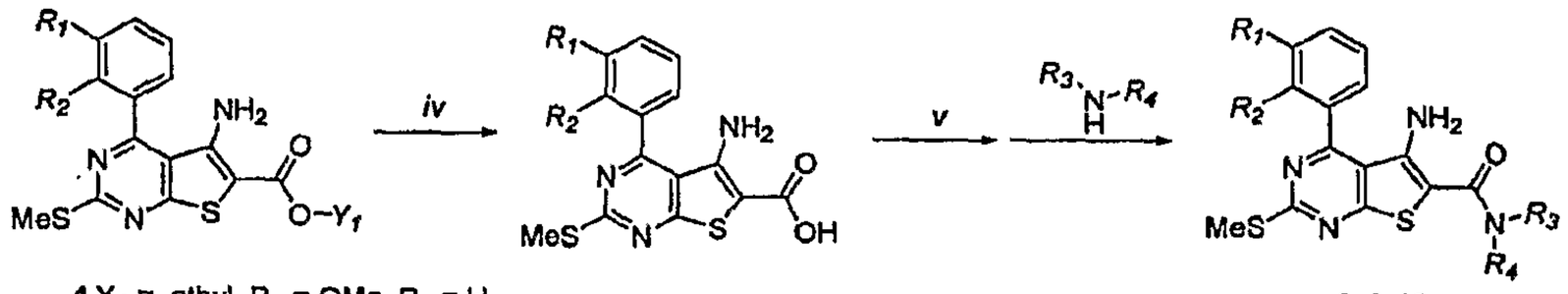
Pharmaceutical compositions that comprise *N*-tert-butyl-5-amino-4-(4-((*E*)-but-1-enyl)phenyl)-2-(methylthio)thieno[2,3-d]pyrimidine-6-carboxamide are particularly useful, for example, to inhibit TSH receptor activation. For example, this compound has been demonstrated to inhibit the activation of TSH receptor by antibodies (IgG) from Graves' disease sera.

III. Synthesis

With reference to Scheme 1, the synthesis disclosed hormone receptor modulating compounds was accomplished in a similar manner to that described by van Boeckel and coworkers (van Straten, N. C. R. Schoonus-Gerritsma, G. G.; van Someren, R. G.; Draaijer, J.; Adang, A. E. P.; Timmers, C. M.; Hanseen, R. G. J. M.; van Boeckel, C. A. A. *Chem. Bio. Chem.* **2002**, *10*, 1023). With continued reference to Scheme 1, a modified Biginelli condensation (step i) afforded the substituted pyrimidone scaffold.

Scheme 1





4 Y_1 = ethyl, R_1 = OMe, R_2 = H
5 Y_1 = *tert*-butyl, R_1 = OMe, R_2 = H

3, 6-19

[a] Reagents and conditions: (i) K_2CO_3, EtOH, 60 °C, 5 h; (ii) $POCl_3$, dioxane, reflux, 2 h; (iii) NaOEt, EtOH, 50 °C 3 h; (iv) LiOH, dioxane/H_2O; (v) PyBop, DIPEA, DMF followed by addition of amine (a subsequent benzyl deprotection was needed for the synthesis of analogue **19**).

Numerous aldehydes were tolerated within this system, including highly electron withdrawn (i.e. polyfluoro and nitro) and electron rich (polymethoxy and hydroxyl) aromatic ring systems. Treatment with $POCl_3$ afforded the 4-chloro-substituted pyrimidines in quantitative yields and substitution with either ethyl-2-mercaptoacetate or *tert*-butyl-2-mercaptoacetate afforded several thienopyrimidines, including biochemically relevant compounds **4** and **5**. Saponification of the ethyl esters with lithium hydroxide in a dioxane/water mixture provided the thienopyrimidine acids and PyBOP catalyzed amide couplings with several amines provided Org 41841 (**3**) and compounds **6–19**.

Initial docking experiments suggested a potential hydrogen bond between the amine functionality of **3** and E3.37 in transmembrane helix 3 of both TSH receptor and LHCG receptor. To fully examine this we chose to eliminate this potential

interaction via two distinct experimental means. Using the small molecule as a point of manipulation, the removal of the aromatic amine or the protection of the aromatic amine via dimethylation would accomplish the exclusion of H-bond donation capability. Unfortunately, all attempts to deaminate the Org 41841 structure were unsuccessful. However, direct treatment with methyl iodide in basic acetonitrile afforded the dimethylamine compound (**20**) along with the monomethylated analogue and the concomitant dimethyl amine - methyl amide addition. Purification via HPLC was performed prior to biological evaluation of **20**.

IV. Compositions, Administration and Use of the Disclosed Compounds

Another aspect of the disclosure includes pharmaceutical compositions prepared for administration to a subject and which include a therapeutically or diagnostically effective amount of one or more of the currently disclosed compounds. The therapeutically effective amount of a disclosed compound will depend on the route of administration, the species of subject and the physical characteristics of the subject being treated or evaluated. Specific factors that can be taken into account include disease severity and stage, weight, diet and concurrent medications. The relationship of these factors to determining a therapeutically or spectroscopically effective amount of the disclosed compounds is understood by those of skill in the art. In general, however, a suitable dose for consideration will be in the range of analogous hormone receptor agonists and antagonists, taking into account differences in potency observed *in vitro* testing, generally from about 0.1 to 400 mg per kilogram body weight of the subject per dose, such as in a range between about 0.1 mg and about 250 mg/kg/dose in increments of 0.5 mg/kg/dose such as 2.5 mg/kg/dose, 3.0 mg/kg/dose, 3.5 mg/kg/dose, etc), typically in the range 0.5 to 50 mg per kilogram body weight per dose and most usually in the range 1 to 300 mg per kilogram body weight per dose. The exact dosage and regimen for administration of the presently disclosed compounds will be dependent on the therapeutic effect sought (for example, thyroid modulation, infertility treatment, contraception) and may vary with the particular compound and individual subject to whom the compound is administered. The desired dose may be presented as one dose or as multiple subdoses administered at appropriate intervals throughout the

day, or, in case of female recipients, as doses to be administered at appropriate daily intervals throughout the menstrual cycle. The dosage as well as the regimen of administration may differ between a female and a male recipient. In case of *in vitro* or *ex vivo* applications, such as *in vitro* fertilization applications, the compounds of the inventions are to be used in the incubation media in a concentration of approximately 0.01–5 μg/mL.

Pharmaceutical compositions for administration to a subject can include carriers, thickeners, diluents, buffers, preservatives, surface active agents and the like in addition to the molecule of choice. Pharmaceutical compositions can also include one or more active ingredients such as antimicrobial agents, anti-inflammatory agents, anesthetics, and the like. Pharmaceutical formulations can include additional components, such as carriers. The pharmaceutically acceptable carriers useful for these formulations are conventional. *Remington's Pharmaceutical Sciences*, by E. W. Martin, Mack Publishing Co., Easton, PA, 19th Edition (1995), describes compositions and formulations suitable for pharmaceutical delivery of the disclosed compounds.

In general, the nature of the carrier will depend on the particular mode of administration being employed. For instance, parenteral formulations usually contain injectable fluids that include pharmaceutically and physiologically acceptable fluids such as water, physiological saline, balanced salt solutions, aqueous dextrose, glycerol or the like as a vehicle. For solid compositions (for example, powder, pill, tablet, or capsule forms), conventional non-toxic solid carriers can include, for example, pharmaceutical grades of mannitol, lactose, starch, or magnesium stearate. In addition to biologically-neutral carriers, pharmaceutical compositions to be administered can contain minor amounts of non-toxic auxiliary substances, such as wetting or emulsifying agents, preservatives, and pH buffering agents and the like, for example sodium acetate or sorbitan monolaurate. Pharmaceutical compositions suitable for oral administration may be presented as discrete dosage units such as pills, tablets or capsules, or as a powder or granules, or as a solution or suspension. The active ingredient may also be presented as a bolus or paste. The compositions can further be processed into a suppository or enema for rectal administration.

For parenteral administration, suitable compositions include aqueous and non-aqueous sterile injection. The compositions may be presented in unit-dose or multi-dose containers, for example sealed vials and ampoules, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of sterile liquid carrier, for example, water prior to use.

Compositions, or formulations, suitable for administration by nasal inhalation include fine dusts or mists which may be generated by means of metered dose pressurized aerosols or nebulizers.

The disclosed compounds also can be administered in the form of implantable pharmaceutical devices, consisting of a core of active material, encased by a release rate-regulating membrane. Such implants are to be applied subcutaneously or locally, and will release the active ingredient at an approximately constant rate over relatively large periods of time, for instance from weeks to years. Methods for the preparation of implantable pharmaceutical devices as such are known in the art, for example as described in European Patent 0,303,306 (AKZO N.V.).

The disclosed hormone receptor modulators can be administered to any subject in need thereof. Suitable compounds for treating subjects can be selected in part based on the condition to be treated. For example, certain compounds are TSH receptor antagonists. Such antagonist compounds may be used to treat disorders of hyperthyroidism, such as Graves' disease.

Follicle stimulating hormone currently is in clinical use for treating infertility. The disclosed FSH receptor agonists can be used to replace follicle stimulating hormone as infertility therapeutics. Similarly, compounds disclosed herein that have luteinizing hormone (LH) receptor activating activity can be used in fertility regulating therapies. For example, certain LH receptor activating compounds disclosed herein can be used for the same clinical purposes as native luteinizing hormone, with the advantage that the disclosed compounds display superior stability properties and thus can be administered differently. Thus, examples of the disclosed low molecular weight ligands of LHCG receptor and FSH receptor can be used as therapeutics for infertility treatment or oral contraception. It is noteworthy that *in vivo* efficacy of Organon lead compound Org41841 (*N-tert-*

butyl-5-amino-4-(3-methoxyphenyl)-2-(methylthio)thieno[2,3-*d*]pyrimidine-6-carboxamide) for LHCG receptor was demonstrated in an ovulation induction model supporting the pharmacological utility of the synthetic ligands disclosed herein (van Straten, N. C., Schoonus-Gerritsma, G. G., van Someren, R. G., Draaijer, J., Adang, A. E., Timmers, C. M., Hanssen, R. G., and van Boeckel, C. A. (2002) *Chembiochem.* **3,** 1023–1026). Similarly, the low molecular weight antagonists of TSH receptor have therapeutic application in treating TSH receptor-mediated hyperthyroidism and agonists might replace injected recombinant human TSH (rhTSH, Thyrogen™) in diagnostic screening for thyroid cancer.

EXAMPLES

The following examples are intended to be illustrative rather than limiting.

General Methods

^{1}H NMR data was recorded on a Varian Gemini 300 MHz. Spectra were recorded in d_6-DMSO, d_4-CD_3OD, and D_2O and were referenced to the residual solvent peak at 2.50, 3.31 and 4.79 ppm, respectively. Reverse-phase (C18) HPLC was carried out using an Agilent HPLC with a Zorbax™ SP-C18 semi-prep column. High-resolution mass spectroscopy measurements were performed on a Micromass/Waters LCT Premier Electrospray TOF mass spectrometer.

General Synthetic Procedures

The following general procedures were used to synthesize compounds having different but analogous structures. One of skill in the art will recognize how to modify these general procedures if necessary to accomplish the desired transformations.

5-carbonitrile-1,6-dihydro-2-(methylthio)-6-oxo-4-(substituted phenyl)pyrimidines. To a solution of *S*-methylisothiourea (1 equiv), the appropriately substituted benzaldehyde (2 equiv) and ethyl cyanoacetate (2 equiv) in ethanol was added K_2CO_3 (2 equiv). The reaction mixture was heated to 60 °C for 5h and filtered upon cooling to obtain products. Purification by flash

chromatography (using EtOAc:hexane 1:1) provided the final products as off white solids in 30–50% yields.

5-carbonitrile-4-chloro-2-(methylthio)-6-(3-substituted phenyl)pyrimidines. To a mixture of the oxopyrimidines in dioxane was added $POCl_3$ (excess) in dioxane. The reaction was heated to reflux for 3h and the solvent was removed by reduced pressure. Saturated $NaHCO_3$ was added to the resulting brown solids and the reaction mixtures were extracted with CH_2Cl_2 (3 X 100 mL). The organic layers were combined, dried over Na_2SO_4, and the solvent was removed under reduced pressure. Purification by silica plug filtration (using EtOAc:hexane 1:1) provided the final products as white crystalline solids in 80-90% yields.

ethyl-5-amino-2-(methylthio)-4-(substituted phenyl)thieno[2,3-*d*]pyrimidine-6-carboxylates. To a solution of the appropriate pyrimidine (1 equiv) and ethyl-2-mercaptoacetate - *or* – *tert*-butyl-2-mercaptoacetate (1.1 equiv) in ethanol was added sodium (0.910 equiv) in ethanol. The yellow reaction mixture was heated to 50 °C for 3h, cooled and the ethanol removed under reduced pressure. The yellow solids were dissolved in CH_2Cl_2 (50 mL), washed with DI water (3 X 25 mL), the organic layer was dried over Na_2SO_4, and the solvent removed under reduced pressure. Purification by flash chromatography (using EtOAc:hexane 1:1) provided the final products as yellow solids in 70-90% yields.

***N*-tert-butyl-5-amino-2-(methylthio)-4-(substituted phenyl)thieno[2,3-*d*]pyrimidine-6-carboxamides**. To a solution of the appropriate ethyl ester (1 equiv) in a dioxane and water mixture was added lithium hydroxide (2 equiv). The reaction mixture was heated to 50 °C for 3h, cooled and the solvent removed under reduced pressure. The crude acid was used without further purification. The yellow solids were dissolved in a minimal amount of DMF, followed by the addition of PyBOP (3 equiv), DIPEA (5.5 equiv) and *tert*-butylamine (3 equiv), respectively. Purification by flash chromatography (using EtOAc:hexane 2:1) provided the final products as yellow solids in 50–90% yields.

The following examples describe the purification and characterization of disclosed hormone receptor modulating compounds and intermediates and analogs thereof.

***N-tert*-butyl-5-amino-4-(3-methoxyphenyl)-2-(methylthio)thieno[2,3-*d*]pyrimidine-6-carboxamide (3).** Analysis by C_8 reversed phase LCMS using a linear gradient of H_2O with increasing amounts of CH_3CN (0 → 17 min, 30% → 70% CH_3CN at a flow rate of 1 mL/min, t_R 13.5 min) found greater than 99% purity by peak integration. ^1H NMR ($CDCl_3$) δ 1.45 (s, 9H), 2.64 (s, 3H), 3.86 (s, 3H), 5.99 (br. s, 2H), 7.07-7.26 (m, 3H), 7.41-7.47 (m, 1H); mass spectrometry (TOF); m/z = 403.1262 ($M + H^+$) (theoretical 403.1257).

ethyl-5-amino-4-(3-methoxyphenyl)-2-(methylthio)thieno[2,3-*d*]pyrimidine-6-carboxylate (4). Analysis by C_8 reversed phase LCMS using a linear gradient of H_2O with increasing amounts of CH_3CN (0 → 15 min, 30% → 90% CH_3CN at a flow rate of 1 mL/min, t_R 12.5 min) found greater than 92% purity by peak integration. ^1H NMR (d_6-DMSO) δ 1.37 (t, J = 7.2 Hz, 3H), 2.69 (s, 3H), 3.92 (s, 3H), 4.35 (q, J = 7.2 Hz, 2H), 6.15 (br. s, 2H), 7.27-7.31 (m, 3H), 7.59-7.64 (m, 1H); mass spectrometry (TOF); m/z = 376.0790 ($M + H^+$) (theoretical 376.0784).

***tert*-butyl-5-amino-4-(3-methoxyphenyl)-2-(methylthio)thieno[2,3-*d*]pyrimidine-6-carboxylate (5).** Analysis by C_8 reversed phase LCMS using a linear gradient of H_2O with increasing amounts of CH_3CN (0 → 15 min, 30% → 90% CH_3CN at a flow rate of 1 mL/min, t_R 13.2 min) found greater than 98% purity by peak integration. ^1H NMR ($CDCl_3$) δ 1.57 (s, 9H), 2.64 (s, 3H), 3.86 (s, 3H), 5.78 (br. s, 2H), 7.08-7.16 (m, 3H), 7.42-7.47 (m, 1H); mass spectrometry (TOF); m/z = 404.1097 ($M + H^+$) (theoretical 404.1103).

5-amino-*N*-(ethyl)-4-(3-methoxyphenyl)-2-(methylthio)thieno[2,3-*d*]pyrimidine-6-carboxamide (6). Analysis by C_8 reversed phase LCMS using a linear gradient of H_2O with increasing amounts of CH_3CN (0 → 18 min, 40% → 80% CH_3CN at a flow rate of 1 mL/min, t_R 9.8 min) found greater than 99% purity by peak integration. ^1H NMR (d_6-DMSO) δ 1.08 (t, J = 7.2 Hz, 3H), 2.59 (s, 3H), 3.22 (p, J = 7.2 Hz, 2H), 3.82 (s, 3H), 5.75 (s, 1H), 6.10 (br. s, 2H), 7.15-7.19 (m, 2H), 7.50 (t, J = 8.0 Hz, 1H), 7.87 (t, J = 8.0 Hz, 1H); mass spectrometry (TOF); m/z = 375.0944 ($M + H^+$) (theoretical 375.0949).

***N-tert*-butyl-5-amino-4-(3-methoxyphenyl)-*N*-methyl-2-(methylthio)thieno[2,3-*d*]pyrimidine-6-carboxamide (7).** Analysis by C_8 reversed phase LCMS using a

linear gradient of H_2O with increasing amounts of CH_3CN (0 → 18 min, 40% → 80% CH_3CN at a flow rate of 1 mL/min, t_R 14.6 min) found greater than 95% purity by peak integration. ^1H NMR (d_6-DMSO) δ 1.36 (s, 9H), 2.58 (s, 3H), 3.00 (s, 3H), 3.82 (s, 3H), 5.22 (br. s, 2H), 7.17-7.20 (m, 3H), 7.51 (t, J = 8 Hz, 1H); mass spectrometry (TOF); m/z = 417.1413 ($M + H^+$) (theoretical 417.1419).

5-amino-4-(3-methoxyphenyl)-2-(methylthio)thieno[2,3-*d*]pyrimidine-6-carbohydrazide (8). Analysis by C_8 reversed phase LCMS using a linear gradient of H_2O with increasing amounts of CH_3CN (0 → 18 min, 40% → 80% CH_3CN at a flow rate of 1 mL/min, t_R 13.7 min) found greater than 92% purity by peak integration. ^1H NMR (d_6-DMSO) δ 2.59 (s, 3H), 3.82 (s, 3H), 6.18 (br. s, 2H), 7.17-7.20 (m, 3H), 7.50 (t, J = 8.7 Hz, 1H), 9.20 (br. s, 1H); mass spectrometry (TOF); m/z = 362.074 ($M + H^+$) (theoretical 362.0745).

5-amino-4-(3-methoxyphenyl)-*N'*,*N'*-dimethyl-2-(methylthio)thieno[2,3-*d*]pyrimidine-6-carbohydrazide (9). Analysis by C_8 reversed phase LCMS using a linear gradient of 0.1 % TFA in H_2O with increasing amounts of CH_3CN (0 → 18 min, 30% → 80% CH_3CN at a flow rate of 1 mL/min, t_R 8.7 min) found greater than 93% purity by peak integration. ^1H NMR (d_6-DMSO) δ 2.55 (s, 6H), 2.58 (s, 3H), 3.82 (s, 3H), 6.45 (br. s, 2H), 7.16-7.18 (m, 3H), 7.50 (t, J = 8.7 Hz, 1H), 8.72 (s, 1H); mass spectrometry (TOF); m/z = 390.1053 ($M + H^+$) (theoretical 390.1058).

***N'*-*tert*-butyl-5-amino-4-(3-methoxyphenyl)-2-(methylthio)thieno[2,3-*d*]pyrimidine-6-carbohydrazide (10).** Analysis by C_8 reversed phase LCMS using a linear gradient of H_2O with increasing amounts of CH_3CN (0 → 10 min, 25% → 90% CH_3CN, 10 → 15 min, 90% → 25% CH_3CN at a flow rate of 1 mL/min, t_R 12.0 min) found greater than 95% purity by peak integration. ^1H NMR (d_6-DMSO) δ 1.08 (s, 9H), 2.59 (s, 3H), 3.82 (s, 3H), 4.93 (s, 1H), 6.45 (br. s, 2H), 7.16-7.18 (m, 3H), 7.50 (t, J = 8 Hz, 1H), 8.53 (s, 1H); mass spectrometry (TOF); m/z = 418.1366 ($M + H^+$) (theoretical 418.1371).

***N'*-Boc-5-amino-4-(3-methoxyphenyl)-2-(methylthio)thieno[2,3-*d*]pyrimidine-6-carbohydrazide (11).** Analysis by C_8 reversed phase LCMS using a linear gradient of H_2O with increasing amounts of CH_3CN (0 → 10 min, 25% → 90% CH_3CN, 10 → 15 min, 90% → 25% CH_3CN at a flow rate of 1 mL/min, t_R 11.0 min) found

greater than 97% purity by peak integration. ^{1}H NMR (d_6-DMSO) δ 1.08 (s, 9H), 2.59 (s, 3H), 3.82 (s, 3H), 4.93 (s, 1H), 6.45 (br. s, 2H), 7.16-7.18 (m, 3H), 7.50 (t, J = 8 Hz, 1H), 8.53 (s, 1H); mass spectrometry (TOF); m/z = 462.1264 (M + H^+) (theoretical 462.127).

5-amino-4-(3-methoxyphenyl)-*N*-(2-hydroxyethyl)-2-(methylthio)thieno[2,3-*d*]pyrimidine-6-carboxamide (12) Analysis by C_8 reversed phase LCMS using a linear gradient of H_2O with increasing amounts of CH_3CN (0 → 18 min, 30% →60% CH_3CN at a flow rate of 1 mL/min, t_R 7.4 min) found greater than 92% purity by peak integration.. ^{1}H NMR (d_6-DMSO) δ 2.59 (s, 3H), 3.20 – 3.40 (m, 2H), 3.41 – 3.55 (m, 2H), 3.82 (s, 3H), 4.71 (m, 1H), 6.10 (br. s, 2H), 7.19 (br. s, 2H), 7.50 (m, 1H), 7.80 (m, 1H); mass spectrometry (TOF); m/z = 391.0893 (M + H^+) (theoretical 391.0899).

5-amino-*N*-(cyanomethyl)-4-(3-methoxyphenyl)-2-(methylthio)thieno[2,3-*d*]pyrimidine-6-carboxamide (13). Analysis by C_8 reversed phase LCMS using a linear gradient of H_2O with increasing amounts of CH_3CN (0 → 10 min, 25% → 90% CH_3CN, 10 → 15 min, 90% → 25% CH_3CN at a flow rate of 1 mL/min, t_R 10.5 min) found greater than 91% purity by peak integration. ^{1}H NMR (d_6-DMSO) δ 2.60 (s, 3H), 3.82 (s, 3H), 4.22 (d, J = 5.4 Hz, 2H), 6.23 (br. s, 2H), 7.18 – 7.20 (m, 3H), 7.51 (t, J = 8.1 Hz, 1H), 8.53 (t, J = 5.4 Hz, 1H); mass spectrometry (TOF); m/z = 386.074 (M + H^+) (theoretical 386.0745).

5-amino-*N*-benzyl-4-(3-methoxyphenyl)-2-(methylthio)thieno[2,3-*d*]pyrimidine-6-carboxamide (14). Analysis by C_8 reversed phase LCMS using a linear gradient of H_2O with increasing amounts of CH_3CN (0 → 18 min, 40% → 80% CH_3CN at a flow rate of 1 mL/min, t_R 12.6 min) found greater than 99% purity by peak integration. ^{1}H NMR (d_6-acetone) δ 2.61 (s, 3H), 3.89 (s, 3H), 4.55 (d, J = 6 Hz, 2H), 6.29 (br. s, 2H), 7.18 – 7.37 (m, 8H), 7.49 (t, J = 8.4 Hz, 1H), 7.64 (t, J = 3 Hz, 1H); mass spectrometry (TOF); m/z = 437.1100 (M + H^+) (theoretical 437.1106).

5-amino-4-(3-methoxyphenyl)-2-(methylthio)-*N*-phenethylthieno[2,3-*d*]pyrimidine-6-carboxamide (15). Analysis by C_8 reversed phase LCMS using a linear gradient of H_2O with increasing amounts of CH_3CN (0 → 18 min, 40% → 80% CH_3CN at a flow rate of 1 mL/min, t_R 14.7 min) found greater than 98% purity

by peak integration. ^{1}H NMR (d_6-DMSO) δ 2.59 (s, 3H), 2.81 (t, J = 7.2 Hz, 2H), 3.43 (q, J = 8.4 Hz, 2H), 3.82 (s, 3H), 6.11 (br. s, 2H), 7.16 – 7.32 (m, 8H), 7.50 (t, J = 7.8 Hz, 1H), 7.96 (t, J = 3 Hz, 1H); mass spectrometry (TOF); m/z = 451.1257 (M + H^+) (theoretical 451.1262).

***N-tert*-butyl-5-amino-4-(2,3-dimethoxyphenyl)-2-(methylthio)thieno[2,3-*d*]pyrimidine-6-carboxamide (16).** Analysis by C_8 reversed phase LCMS using a linear gradient of H_2O with increasing amounts of CH_3CN (0 → 16 min, 35% → 95% CH_3CN at a flow rate of 1 mL/min, t_R 14.3 min) found greater than 93% purity by peak integration. ^{1}H NMR ($CDCl_3$) δ 1.45 (s, 9H), 2.66 (s, 3H), 3.76 (s, 3H), 3.95 (s, 3H), 5.77 (br. s, 2H), 6.91 (dd, J = 1.3, 7.5 Hz, 1H), 7.21 (t, J = 8.2 Hz, 1H); mass spectrometry (TOF); m/z = 433.1363 (M + H^+) (theoretical 433.1368).

***N-tert*-butyl-5-amino-4-(2-fluoro-3-methoxyphenyl)-2-(methylthio)thieno[2,3-*d*]pyrimidine-6-carboxamide (17).** Analysis by C_8 reversed phase LCMS using a linear gradient of H_2O with increasing amounts of CH_3CN (0 → 15 min, 35% → 90% CH_3CN at a flow rate of 1 mL/min, t_R 11.0 min) found greater than 92% purity by peak integration. ^{1}H NMR ($CDCl_3$) δ 1.44 (s, 9H), 2.63 (s, 3H), 3.95 (s, 3H), 5.79 (br. s, 2H), 6.98 (dt, J = 7.5, 1.8 Hz, 1H), 7.15 (dt, J = 8.1,1.8 Hz, 1H), 7.24 (t, J = 7.5 Hz, 1H); mass spectrometry (TOF); m/z = 421.1163 (M + H^+) (theoretical 421.1168).

***N-tert*-butyl-5-amino-4-(3-fluorophenyl)-2-(methylthio)thieno[2,3-*d*]pyrimidine-6-carboxamide (18).** Analysis by C_8 reversed phase LCMS using a linear gradient of H_2O with increasing amounts of CH_3CN (0 → 15 min, 45% → 90% CH_3CN at a flow rate of 1 mL/min, t_R 11.4 min) found greater than 92% purity by peak integration. ^{1}H NMR ($CDCl_3$) δ 1.54 (s, 9H), 2.68 (s, 3H), 7.19 - 7.50 (m, 4H); mass spectrometry (TOF); m/z = 391.1072 (M + H^+) (theoretical 391.1057).

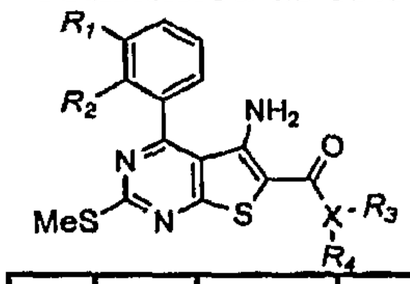
***N-tert*-butyl-5-amino-4-(3-hydroxyphenyl)-2-(methylthio)thieno[2,3-*d*]pyrimidine-6-carboxamide (19).** Analysis by C_8 reversed phase LCMS using a linear gradient of H_2O with increasing amounts of CH_3CN (0 → 10 min, 25% → 90% CH_3CN at a flow rate of 1 mL/min, t_R 10.1 min) found greater than 92% purity by peak integration. ^{1}H NMR ($CDCl_3$) δ 1.45 (s, 9H), 2.64 (s, 3H), 5.98 (br. s, 2H),

7.02 (d, J = 7.2 Hz, 2H), 7.12 (d, J = 7.5 Hz, 1H) 7.39 (t, J = 7.8 Hz, 1H); mass spectrometry (TOF); m/z = 389.110 ($M + H^+$) (theoretical 389.1106).

***N-tert*-butyl-5-(-dimethylamino)-4-(3-methoxyphenyl)-2-(methylthio)thieno[2,3-d]pyrimidine-6-carboxamide (20).** Analysis by C_8 reversed phase LCMS using a linear gradient of H_2O with increasing amounts of CH_3CN (0 → 5 min, 50% → 90% CH_3CN, 5 → 15 min, 90% CH_3CN at a flow rate of 1 mL/min, t_R 7.4 min) found greater than 93% purity by peak integration. ^1H NMR ($CDCl_3$) δ 1.43 (s, 9H), 2.37 (s, 6H), 2.63 (s, 3H), 3.84 (s, 3H), 7.03 (d, J= 8.4 Hz, 1H), 7.09 – 7.11 (m, 2H), 7.38 (t, J= 8.1 Hz, 1H), 7.48 (br s, 1H); mass spectrometry (TOF); m/z = 431.1553 ($M + H^+$) (theoretical 431.1575).

Confirmation of Structure and Purity

The structural characterization and purity of the above listed compounds were confirmed as follows for:



#	X	R1	R2	R3	R4	R5	HPLC Rt (min) a	HPLC purity	HPLC Rt (min)b	HPLC purity	HRMS theo. (m/z)	HRMS found (m/z)
3	N	OMe	H	*t*Bu	H	H	7.336	98%	11.927	98%	403.1257	403.1262
4	O	OMe	H	Et	H	H	7.494	96%	12.201	85%	376.0784	376.0790
5	O	OMe	H	*t*Bu	H	H	8.991	99%	14.695	98%	404.1097	404.1103
6	N	OMe	H	Et	H	H	5.735	99%	9.698	99%	379.0944	375.0949
7	N	OMe	H	*t*Bu	Me	H	7.851	98%	12.647	97%	417.1413	417.1419
8	N	OMe	H	NH_2	H	H	4.452	84%	7.272	80%	362.0740	362.0745
9	N	OMe	H	$N(Me)_2$	H	H	5.734	95%	9.639	90%	390.1053	390.1058
10	N	OMe	H	NH(*t*Bu)	H	H	6.272	99%	10.484	98%	418.1366	418.1371
11	N	OMe	H	NH(Boc)	H	H	5.385	99%	9.375	99%	462.1264	462.1270
12	N	OMe	H	EtOH	H	H	4.257	98%	7.084	97%	391.0893	391.0899
13	N	OMe	H	CH2CN	H	H	5.107	85%	8.762	81%	386.0740	386.0745
14	N	OMe	H	Bn	H	H	6.483	98%	10.876	99%	437.1100	437.1106
15	N	OMe	H	CH_2CH_2Ph	H	H	6.821	99%	11.301	99%	451.1257	451.1262
16	N	OMe	OMe	*t*Bu	H	H	6.899	97%	11.354	96%	433.1363	433.1368
17	N	OMe	F	*t*Bu	H	H	6.798	93%	11.247	95%	421.1163	421.1168
18	N	F	H	*t*Bu	H	H	7.315	98%	11.919	98%	391.1057	391.1072
19	N	OH	H	*t*Bu	H	H	5.848	91%	9.926	90%	389.1100	389.1106
20	N	OMe	H	*t*Bu	H	Me	7.39	95%	12.76	91%	431.1575	431.1553

a) linear gradient of H_2O containing increasing amounts of CH3CN (0-5 min, linear gradient from 50% - 95% CH3CN; 5-14.9 min, gradient maintained at 95% CH_3CN).

b) linear gradient of H_2O containing increasing amounts of CH3CN (0-7 min, linear gradient from 30% - 80% CH_3CN; 7-8 min, 80% - 90% CH3CN; 8-13 min, gradient maintained at 90%; 13-14 min, linear gradient 90% - 30% CH3CN; 14-15 min, gradient maintained at 30% CH3CN).

Tissue culture and cAMP assay

Cells were cultured for 48 h in 24-well plates before incubation for 1 h in serum-free DMEM containing 1 mM 3-isobutyl-1-methylxanthine (IBMX) (SIGMA) and bovine TSH (1.8 μM) (SIGMA) or human LH (1000 ng/ml) (Dr. A. Parlow, NIDDK National Hormone and Pituitary Program) or compounds **3-19** (0 – 100 μM) in a humidified 5% CO_2 incubator. Following aspiration of the medium after incubation with compounds, cells were lysed using lysis buffer 1 of the cAMP Biotrak Enzymeimmunoassay (EIA) System (Amersham Biosciences). The cAMP content of the cell lysate was determined using the manufacturer's protocol. The efficacy of receptor activation by small molecule modulators is expressed as % of maximum response of LHCG receptor or TSH receptor to LH or TSH, respectively. The potency (EC_{50}) was obtained from dose response curves (0 - 100 μM compound) by data analysis with GraphPad Prism 4 for Windows. With reference to FIG. 1, intracellular cAMP production was determined in response to 100 μM of each compound and is expressed as % of maximum response of TSHR/LHCGR to TSH (100 mU/ml)/LH (1000 ng/ml). The data are presented as mean ± SEM of two independent experiments, each performed in duplicate.

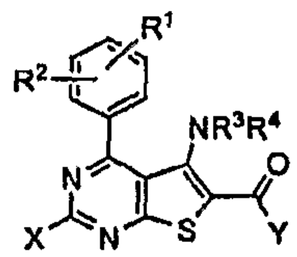
To determine cell surface expression, cells were cultured after transfection for 48 h, harvested using 1 mM EDTA/1 mM EGTA in PBS and transferred to Falcon 2058 tubes. Cells were washed once with PBS containing 0.1% BSA and 0.1% NaN_3 (binding buffer), incubated for 1 h with a 1:200 dilution of mouse anti-human TSH receptor antibody (Serotec) in binding buffer, washed twice and incubated for 1 h in the dark with a 1:200 dilution of an Alexa Fluor 488-labeled $F(ab')_2$ fragment of goat anti-mouse IgG (Molecular Probes) in binding buffer. Before FACS analysis (FACS Calibur, BD Biosciences), cells were washed twice and fixed with 1% paraformaldehyde. Receptor expression was estimated by fluorescence intensity and transfection efficiency was estimated from the percentage of fluorescent cells.

In view of the many possible embodiments to which the principles of the disclosed invention may be applied, it should be recognized that the illustrated embodiments are only preferred examples of the invention and should not be taken

as limiting the scope of the invention. Rather, the scope of the invention is defined by the following claims. We therefore claim as our invention all that comes within the scope and spirit of these claims.

We claim:

1. A compound according to the formula



wherein X is $-S(O)_nR^5$;

n is 0, 1 or 2;

Y is $-OR^6$ or $-NR^7R^8$

R^1 and R^2 independently are selected from optionally substituted lower aliphatic, alkoxy, aralkyl, halogen, H and $-OR^5$, wherein R^5 is selected from lower alkyl, H, aralkyl, acyl, alkoxycarbonyl and aminocarbonyl;

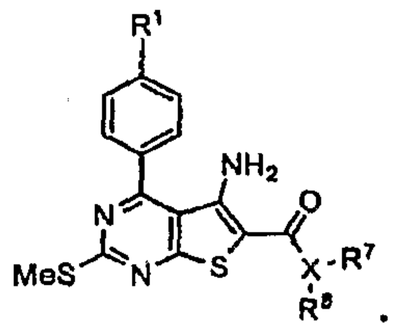
R^3 and R^4 independently are selected from acyl, alkoxycarbonyl, aminocarbonyl, aralkyl, H, lower alkyl and cycloalkyl;

R^5 is selected from lower alkyl, aralkyl, cycloalkyl and haloalkyl;

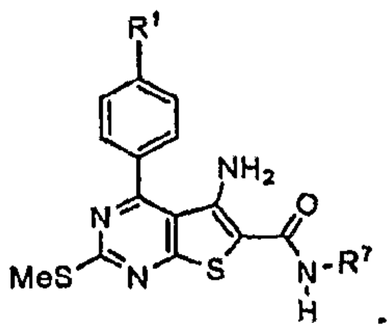
R^6 is selected from H, lower alkyl and aralkyl;

R^7 and R^8 independently are selected from H, lower alkyl, aralkyl and cycloalkyl; with the proviso that when R^1 is methoxy, R^2 is not H.

2. The compound of claim 1, according to the formula

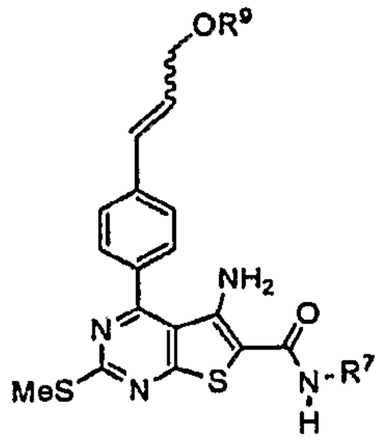


3. The compound of claim 1, according to the formula



4. The compound of claim 3, wherein R^7 is a sterically bulky alkyl group.

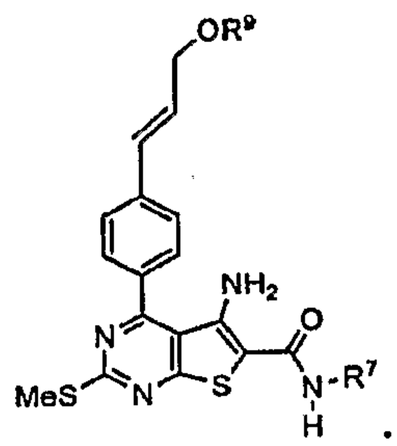
5. The compound of claim 1, according to the formula



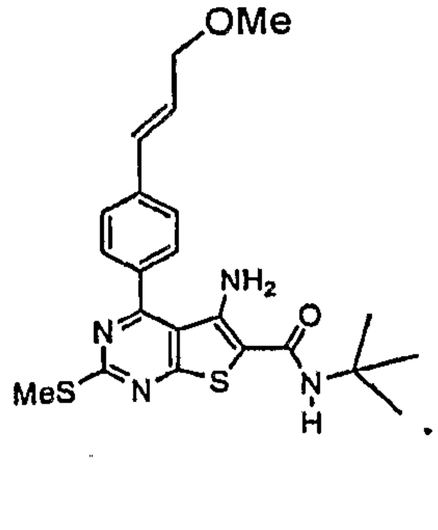
wherein R^9 is selected from acyl, alkoxycarbonyl, aminocarbonyl, aralkyl, H, lower alkyl and cycloalkyl.

6. The compound of claim 5, wherein R^9 is lower alkyl.

7. The compound of claim 5, according to the formula



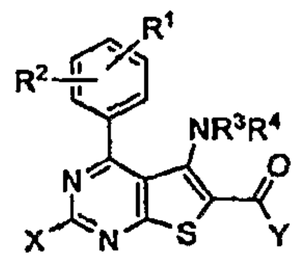
8. The compound of claim 5, according to the formula



9. A pharmaceutical composition, comprising:

a pharmaceutically acceptable, carrier, adjuvant or vehicle; and

a compound other than Org 41841 having the formula



or any pharmaceutically acceptable salt thereof;

wherein X is $-S(O)_nR^5$;

n is 0, 1 or 2;

Y is $-OR^6$ or $-NR^7R^8$

R^1 and R^2 independently are selected from optionally substituted lower aliphatic, alkoxy, aralkyl, halogen, H and $-OR^5$, wherein R^5 is selected from lower alkyl, H, aralkyl, acyl, alkoxycarbonyl and aminocarbonyl;

R^3 and R^4 independently are selected from acyl, alkoxycarbonyl, aminocarbonyl, aralkyl, H, lower alkyl and cycloalkyl;

R^5 is selected from lower alkyl, aralkyl, cycloalkyl and haloalkyl;

R^6 is selected from H, lower alkyl and aralkyl; and

R^7 and R^8 independently are selected from H, lower alkyl, aralkyl and cycloalkyl.

10. The pharmaceutical composition of claim 9, wherein the compound is a selective antagonist of the thyroid hormone receptor.

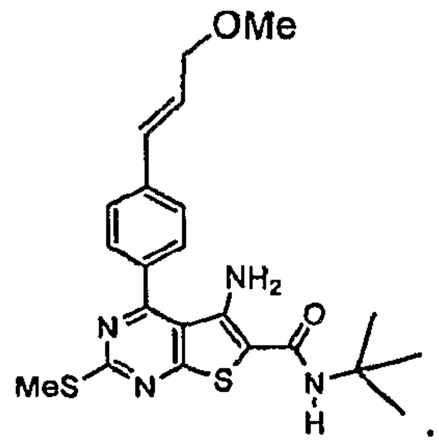
11. A method for treating a thyroid disorder, comprising providing a subject having a thyroid disorder and administering to the subject an effective amount of a compound of claim 1.

12. The method of claim 11, wherein the thyroid disorder is a hyperthyroid disorder.

13. The method of claim 12, wherein the hyperthyroid disorder is Graves' disease.

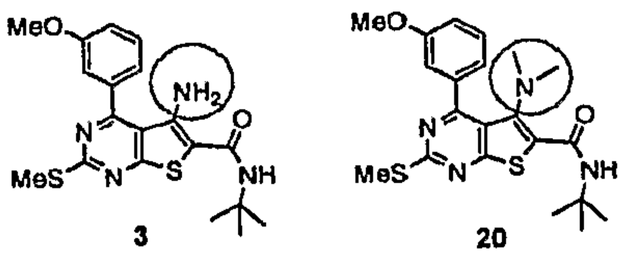
14. The method of claim 12, wherein the compound is a thyroid-stimulating hormone receptor antagonist.

15. The method of claim 14, wherein the compound has the formula



16. The method of claim 11, wherein the thyroid disorder is a hypothyroid disorder.

17. The method of claim 11, wherein the compound preferentially binds the thyroid-stimulating hormone receptor over the follicle-stimulating hormone receptor.


MeO
NH2
N
MeS
N
S
O
NH
3
MeO
N
MeS
N
S
O
NH
20

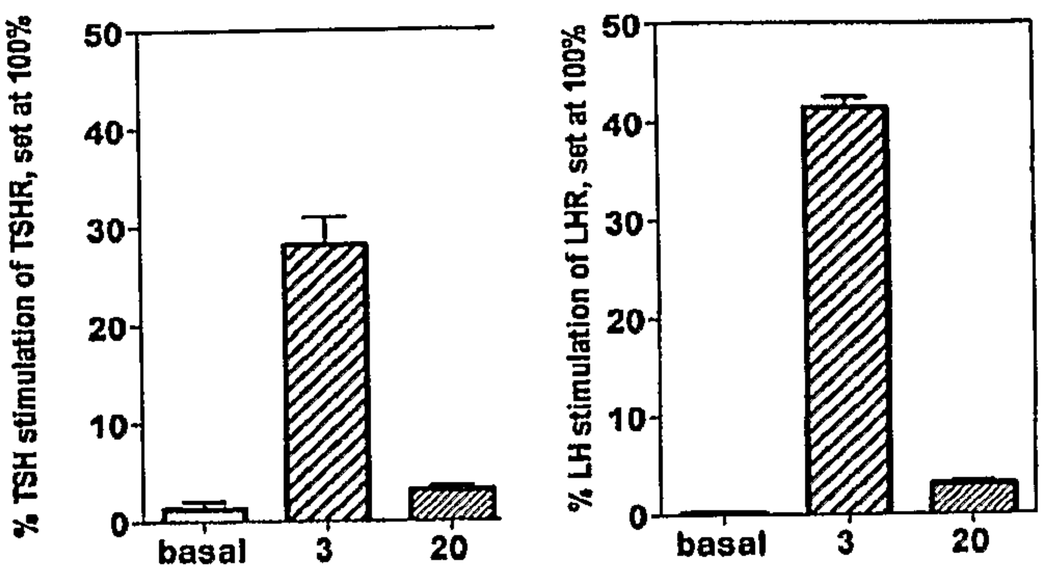

% TSH stimulation of TSHR, set at 100%
50
40
30
20
10
0
basal
3
20
% LH stimulation of LHR, set at 100%
50
40
30
20
10
0
basal
3
20

FIG. 1

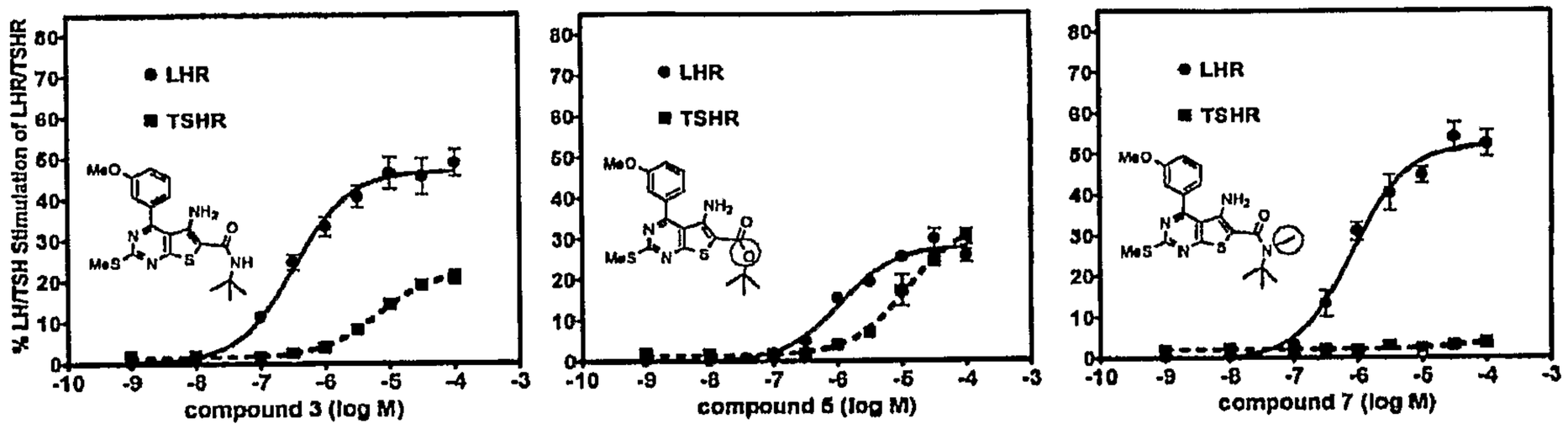

% LH/TSH Stimulation of LHR/TSHR
LHR
TSHR
MeO
NH2
MeS
NH
compound 3 (log M)
compound 5 (log M)
compound 7 (log M)

FIG 2

(I)