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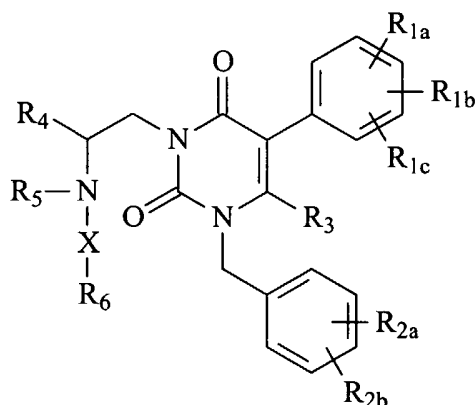
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(54) Title: PYRIMIDINE-2, 4-DIONE DERIVATIVES AS GONADOTROPIN-RELEASING HORMONE RECEPTOR ANTAGONISTS



(57) Abstract: GnRH receptor antagonists are disclosed that have utility in the treatment of a variety of sex-hormone related conditions in both men and women. The compounds of this invention have the structure: wherein R_{1a}, R_{1b}, R_{1c}, R_{2a}, R_{2b}, R₃, R₄, R₅, R₆ and X are as defined herein, including stereoisomers, prodrugs and pharmaceutically acceptable salts thereof. Also disclosed are compositions containing a compound of this invention in combination with a pharmaceutically acceptable carrier, as well as methods relating to the use thereof for antagonizing gonadotropin-releasing hormone in a subject in need thereof.

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PYRIMIDINE-2,4-DIONE DERIVATIVES AS GONADOTROPIN-RELEASING HORMONE RECEPTOR ANTAGONISTS

STATEMENT OF GOVERNMENT INTEREST

Partial funding of the work described herein was provided by the U.S. Government under Grant No. 1-R43-HD38625 and 2R44-HD38625-02 provided by the National Institutes of Health. The U.S. Government may have certain rights in this invention.

BACKGROUND OF THE INVENTION

Field of the Invention

This invention relates generally to gonadotropin-releasing hormone (GnRH) receptor antagonists, and to methods of treating disorders by administration of such antagonists to a warm-blooded animal in need thereof.

Description of the Related Art

Gonadotropin-releasing hormone (GnRH), also known as luteinizing hormone-releasing hormone (LHRH), is a decapeptide (pGlu-His-Trp-Ser-Tyr-Gly-Leu-Arg-Pro-Gly-NH₂) that plays an important role in human reproduction. GnRH is released from the hypothalamus and acts on the pituitary gland to stimulate the biosynthesis and release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH). LH released from the pituitary gland is responsible for the regulation of gonadal steroid production in both males and females, while FSH regulates spermatogenesis in males and follicular development in females.

Due to its biological importance, synthetic antagonists and agonists to GnRH have been the focus of considerable attention, particularly in the context of prostate cancer, breast cancer, endometriosis, uterine leiomyoma (fibroids), ovarian

cancer, prostatic hyperplasia, assisted reproductive therapy, and precocious puberty (*The Lancet* 358:1793-1803, 2001; *Mol. Cell. Endo.* 166:9-14, 2000). For example, peptidic GnRH agonists, such as leuprorelin (pGlu-His-Trp-Ser-Tyr-d-Leu-Leu-Arg-Pro-NHEt), have been used to treat such conditions. Such agonists appear to function
5 by binding to the GnRH receptor in the pituitary gonadotropins, thereby inducing the synthesis and release of gonadotropins. Chronic administration of GnRH agonists depletes gonadotropins and subsequently down-regulates the receptor, resulting in suppression of steroidal hormones after some period of time (*e.g.*, on the order of 2-3 weeks following initiation of chronic administration).

10 In contrast, GnRH antagonists are believed to suppress gonadotropins from the onset, and thus have received the most attention over the past two decades. To date, some of the primary obstacles to the clinical use of such antagonists have been their relatively low bioavailability and adverse side effects caused by histamine release. However, several peptidic antagonists with low histamine release properties have been
15 reported, although they still must be delivered via sustained delivery routes (such as subcutaneous injection or intranasal spray) due to limited bioavailability.

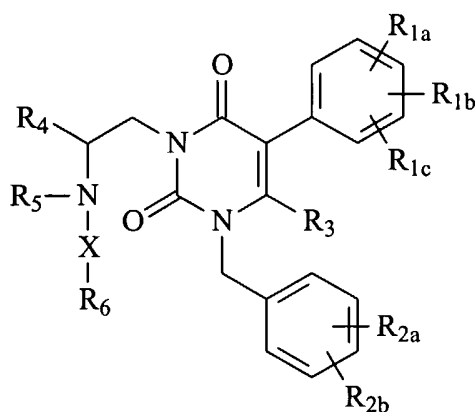
In view of the limitations associated with peptidic GnRH antagonists, a number of nonpeptidic compounds have been proposed. For example, Cho et al. (*J. Med. Chem.* 41:4190-4195, 1998) discloses thieno[2,3-b]pyridin-4-ones for use as
20 GnRH receptor antagonists; U.S. Patent Nos. 5,780,437 and 5,849,764 teach substituted indoles as GnRH receptor antagonists (as do published PCTs WO 97/21704, 98/55479, 98/55470, 98/55116, 98/55119, 97/21707, 97/21703 and 97/21435); published PCT WO 96/38438 discloses tricyclic diazepines as GnRH receptor antagonists; published PCTs WO97/14682, 97/14697 and 99/09033 disclose quinoline and thienopyridine
25 derivatives as GnRH antagonists; published PCTs WO 97/44037, 97/44041, 97/44321 and 97/44339 teach substituted quinolin-2-ones as GnRH receptor antagonists; and published PCT WO 99/33831 discloses certain phenyl-substituted fused nitrogen-containing bicyclic compounds as GnRH receptor antagonists. Recently published PCTs WO 02/066459 and WO 02/11732 disclose the use of indole derivatives and
30 novel bicyclic and tricyclic pyrrolidine derivatives as GnRH antagonists, respectively.

Other recently published PCTs which disclose compounds and their use as GnRH antagonists include WO 00/69859, WO 01/29044, WO 01/55119, WO 03/013528, WO 03/011870, WO 03/011841, WO 03/011839 and WO 03/011293.

While significant strides have been made in this field, there remains a need in the art for effective small molecule GnRH receptor antagonists. There is also a need for pharmaceutical compositions containing such GnRH receptor antagonists, as well as methods relating to the use thereof to treat, for example, sex-hormone related conditions. The present invention fulfills these needs, and provides other related advantages.

10 BRIEF SUMMARY OF THE INVENTION

In brief, this invention is generally directed to gonadotropin-releasing hormone (GnRH) receptor antagonists, as well as to methods for their preparation and use, and to pharmaceutical compositions containing the same. More specifically, the GnRH receptor antagonists of this invention are compounds having the following general structure (I):



(I)

including stereoisomers, prodrugs and pharmaceutically acceptable salts thereof, wherein R_{1a} , R_{1b} , R_{1c} , R_{2a} , R_{2b} , R_3 , R_4 , R_5 , R_6 and X are as defined below.

The GnRH receptor antagonists of this invention have utility over a wide range of therapeutic applications, and may be used to treat a variety of sex-hormone related conditions in both men and women, as well as a mammal in general (also

referred to herein as a "subject"). For example, such conditions include endometriosis, uterine fibroids, polycystic ovarian disease, hirsutism, precocious puberty, gonadal steroid-dependent neoplasia such as cancers of the prostate, breast and ovary, gonadotrophe pituitary adenomas, sleep apnea, irritable bowel syndrome, premenstrual
5 syndrome, benign prostatic hypertrophy, contraception and infertility (*e.g.*, assisted reproductive therapy such as in vitro fertilization). The compounds of this invention are also useful as an adjunct to treatment of growth hormone deficiency and short stature, and for the treatment of systemic lupus erythematosus. The compounds are also useful in combination with androgens, estrogens, progesterones, and antiestrogens and
10 antiprogestogens for the treatment of endometriosis, fibroids, and in contraception, as well as in combination with an angiotensin-converting enzyme inhibitor, an angiotensin II-receptor antagonist, or a renin inhibitor for the treatment of uterine fibroids. In addition, the compounds may be used in combination with bisphosphonates and other agents for the treatment and/or prevention of disturbances of calcium, phosphate and
15 bone metabolism, and in combination with estrogens, progesterones and/or androgens for the prevention or treatment of bone loss or hypogonadal symptoms such as hot flashes during therapy with a GnRH antagonist.

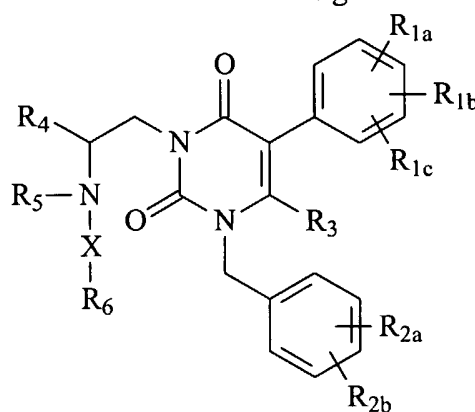
The compounds of the present invention, in addition to their GnRH receptor antagonist activity, possess a reduced interaction with the major metabolic
20 enzymes in the liver, namely the Cytochrome P450 enzymes. This family of enzymes, which includes the subtypes CYP2D6 and CYP3A4, is responsible for the metabolism of drugs and toxins leading to their disposition from the body. Inhibition of these enzymes can lead to life-threatening conditions where the enzyme is not able to perform this function.

25 The methods of this invention include administering an effective amount of a GnRH receptor antagonist, preferably in the form of a pharmaceutical composition, to a mammal in need thereof. Thus, in still a further embodiment, pharmaceutical compositions are disclosed containing one or more GnRH receptor antagonists of this invention in combination with a pharmaceutically acceptable carrier and/or diluent.

These and other aspects of the invention will be apparent upon reference to the following detailed description. To this end, various references are set forth herein which describe in more detail certain background information, procedures, compounds and/or compositions, and are each hereby incorporated by reference in their entirety.

5 DETAILED DESCRIPTION OF THE INVENTION

As mentioned above, the present invention is directed generally to compounds useful as gonadotropin-releasing hormone (GnRH) receptor antagonists. The compounds of this invention have the following structure (I):



10

(I)

or a stereoisomer, prodrug or pharmaceutically acceptable salt thereof,

wherein:

15 R_{1a} , R_{1b} and R_{1c} are the same or different and independently hydrogen, halogen, C_{1-4} alkyl, hydroxy or alkoxy, or R_{1a} and R_{1b} taken together form $-OCH_2O-$ or $-OCH_2CH_2-$;

R_{2a} and R_{2b} are the same or different and independently hydrogen, halogen, trifluoromethyl, cyano or $-SO_2CH_3$;

R_3 is hydrogen or methyl;

R_4 is phenyl or C_{3-7} alkyl;

20

R_5 is hydrogen or C_{1-4} alkyl;

R_6 is $-COOH$ or an acid isostere; and

X is C₁₋₆alkanediyl optionally substituted with from 1 to 3 C₁₋₆alkyl groups.

As used herein, the above terms have the following meaning:

5 “C₁₋₆alkyl” means a straight chain or branched, noncyclic or cyclic, unsaturated or saturated aliphatic hydrocarbon containing from 1 to 6 carbon atoms. Representative saturated straight chain alkyls include methyl, ethyl, n-propyl, n-butyl, n-pentyl, n-hexyl, and the like; while saturated branched alkyls include isopropyl, *sec*-butyl, isobutyl, *tert*-butyl, isopentyl, and the like. Representative saturated cyclic
10 alkyls include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and the like; while unsaturated cyclic alkyls include cyclopentenyl and cyclohexenyl, and the like. Unsaturated alkyls contain at least one double or triple bond between adjacent carbon atoms (referred to as an “alkenyl” or “alkynyl”, respectively). Representative straight chain and branched alkenyls include ethylenyl, propylenyl, 1-butenyl, 2-butenyl,
15 isobutylenyl, 1-pentenyl, 2-pentenyl, 3-methyl-1-butenyl, 2-methyl-2-butenyl, 2,3-dimethyl-2-butenyl, and the like; while representative straight chain and branched alkynyls include acetylenyl, propynyl, 1-butynyl, 2-butynyl, 1-pentynyl, 2-pentynyl, 3-methyl-1-butynyl, and the like.

“C₁₋₄alkyl” means a straight chain or branched, noncyclic or cyclic
20 hydrocarbon containing from 1 to 4 carbon atoms. Representative straight chain alkyls include methyl, ethyl, n-propyl, n-butyl, and the like; branched alkyls include isopropyl, *sec*-butyl, isobutyl, *tert*-butyl, and the like; while cyclic alkyls include cyclopropyl and the like.

“C₃₋₇alkyl” means a straight chain or branched, noncyclic or cyclic
25 hydrocarbon containing from 3 to 7 carbon atoms. Representative straight chain alkyls include n-propyl, n-butyl, n-hexyl, and the like; while branched alkyls include isopropyl, *sec*-butyl, isobutyl, *tert*-butyl, isopentyl, and the like. Representative cyclic alkyls include cyclopropyl, cyclopentyl, cyclohexyl, and the like.

“C₁₋₆alkanediyyl” means a divalent C₁₋₆alkyl from which two hydrogen atoms are taken from the same carbon atom or from difference carbon atoms, such as –CH₂–, –CH₂CH₂–, –CH₂CH₂CH₂–, –CH(CH₃)CH₂CH₂–, –CH₂C(CH₃)₂CH₂–, and the like.

“Halogen” means fluoro, chloro, bromo or iodo, typically fluoro and
5 chloro.

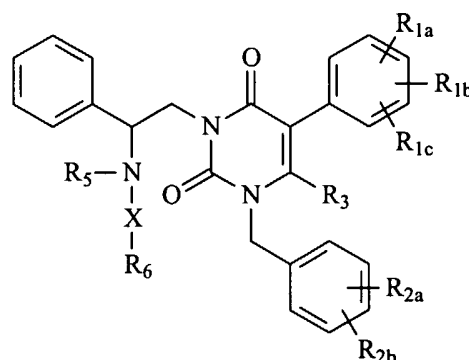
“Hydroxy” means –OH.

“Alkoxy” means –O-(C₁₋₆alkyl).

“Cyano” means –CN.

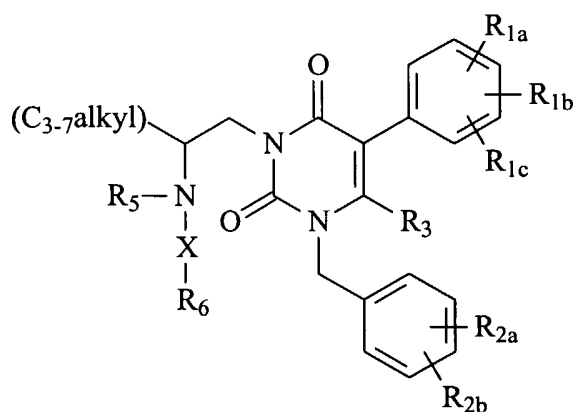
“Acid isostere” means an moiety that exhibits properties similar to
10 carboxylic acid, and which has a pKa of less than 8 and preferably less than 7. Representative acid isosteres include tetrazole, 3H-[1,3,4]oxadiazol-2-one, [1,2,4]oxadiazol-3-one, 1,2-dihydro-[1,2,4]triazol-3-one, 2H-[1,2,4]oxadiazol-5-one, triazole substituted with a sulfonyl or sulfoxide group, imidazole substituted with a sulfonyl or sulfoxide group, [1,2,4]-oxadiazolidine-3,5-dione, [1,2,4]-thiadiazolidine-
15 3,5-dione, imidazolidine-2,4-dione, imidazolidine-2,4,5-trione, pyrrolidine-2,5-dione and pyrrolidine-2,3,5-trione. Acid isosteres also include –C(=O)NHSO₂NR_aR_b, –C(=O)NHSO₂R_b, –C(=O)NHC(=O)NR_aR_b and –C(=O)NHC(=O)R_b, where R_a is hydrogen or C₁₋₄alkyl and R_b is C₁₋₄alkyl.

In one embodiment, R₄ is phenyl and representative GnRH antagonists
20 of the present invention include compounds having the following structure (II).



(II)

In another embodiment, R_4 is C_{3-7} alkyl and representative GnRH antagonists of the present invention include compounds having the following structure (III).

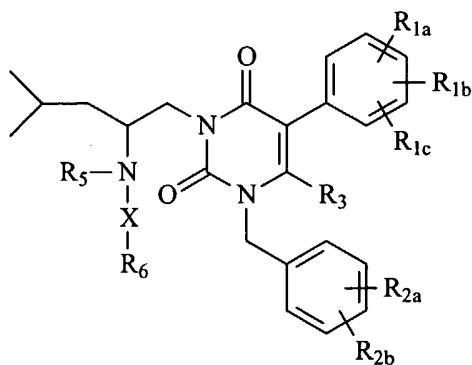


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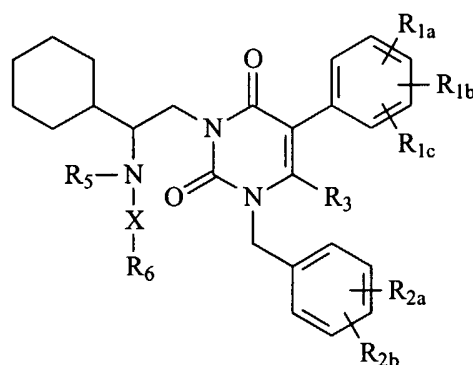
(III)

In more specific embodiments of structure (III), C_{3-7} alkyl is a straight chain or branched C_{3-7} alkyl such as isobutyl as represented by structure (IV), or is a cyclic C_{3-7} alkyl such as cyclohexyl as represented by structure (V):

10



(IV)



(V)

In another embodiment, R_{1a} , R_{1b} and R_{1c} are hydrogen, alkoxy and halogen, respectively. A representative substitution pattern includes 2-halo-3-alkoxy-phenyl. Representative alkoxy groups include methoxy and ethoxy, while representative halogen moieties include fluoro and chloro.

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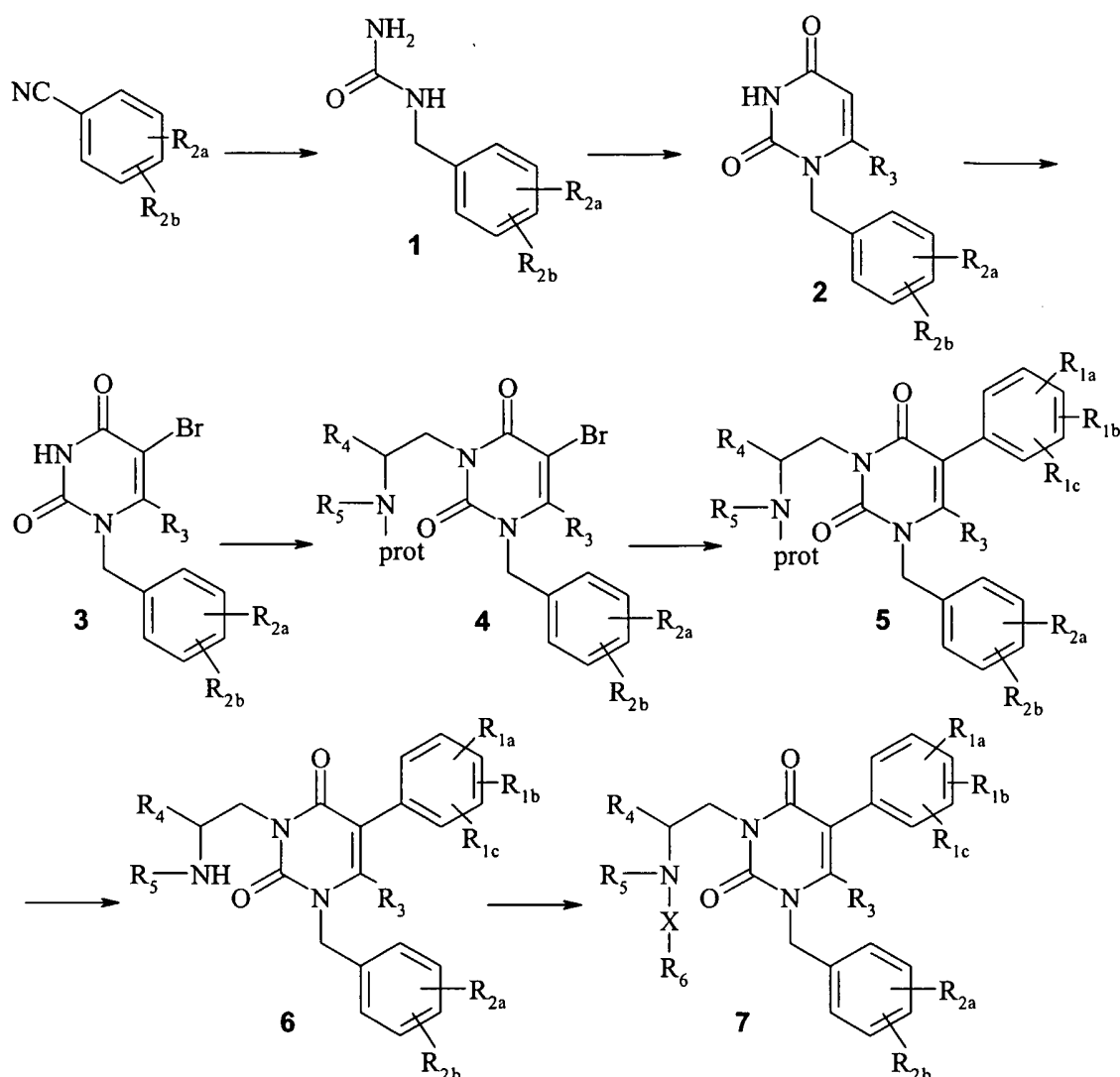
In an alternative embodiment, R_{1a} and R_{1b} taken together form -OCH₂O-, such as 3,4-methylene-dioxy.

In a further embodiment, R_{2a} and R_{2b} are hydrogen, trifluoromethyl, halogen or -SO₂CH₃. A representative substitution pattern includes R_{2a} as halogen at the 2-position and R_{2b} as hydrogen, trifluoromethyl, halogen or -SO₂CH₃ at the 6-position.

Further embodiments include those wherein R₅ is H or methyl; R₆ is -COOH, and/or X is -CH₂CH₂-, -CH₂CH₂CH₂- or -CH₂CH₂CH₂CH₂-.

The compounds of the present invention may be prepared by known organic synthesis techniques, including the methods described in more detail in the Examples. In general, the compounds of structure (I) above may be made by the following reaction schemes, wherein all substituents are as defined above unless indicated otherwise.

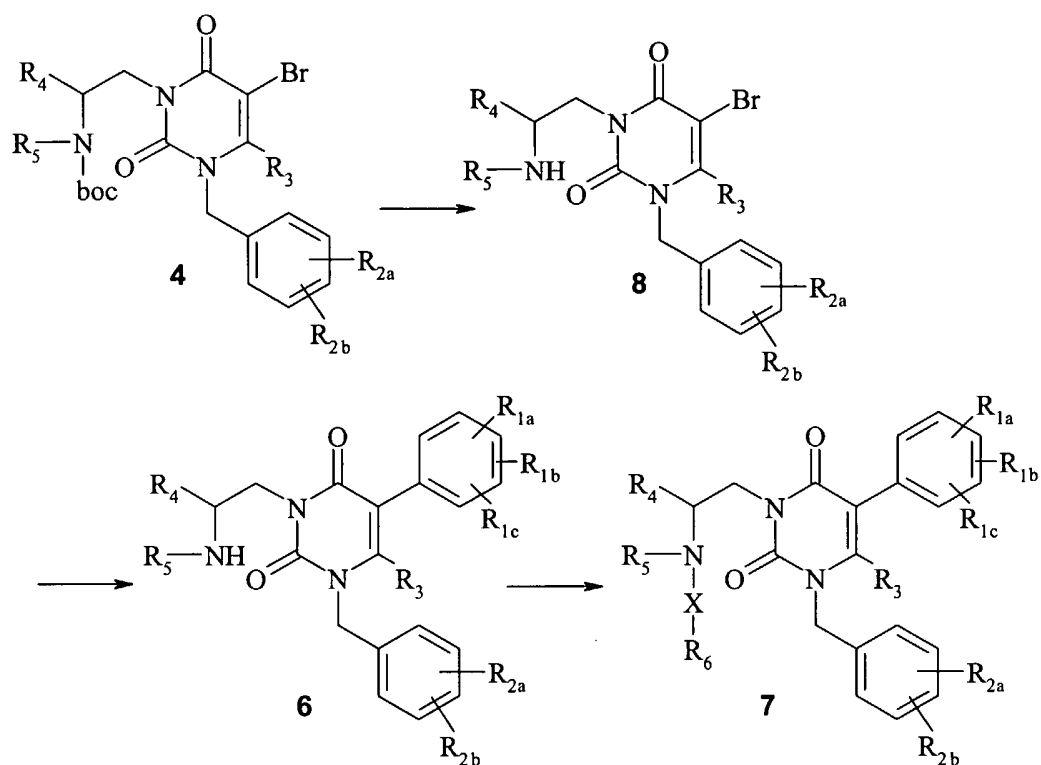
Reaction Scheme 1



An appropriately substituted benzonitrile may be reduced using an appropriate reagent such as borane in THF to the corresponding amine and then forms urea 1. Cyclization with a reagent such as diketene gives compound 2 which may be brominated with bromine in acetic acid, N-bromosuccinimide or other brominating agent to give compound 3. Alkylation gives compound 4 and Suzuki condensation with a boronic acid or boronic acid ester gives compound 5. Deprotection of the protected amine using a typical reagent (such as trifluoroacetic acid in methylene chloride in the case of a BOC group) gives compound 6 which may be alkylated or condensed with an

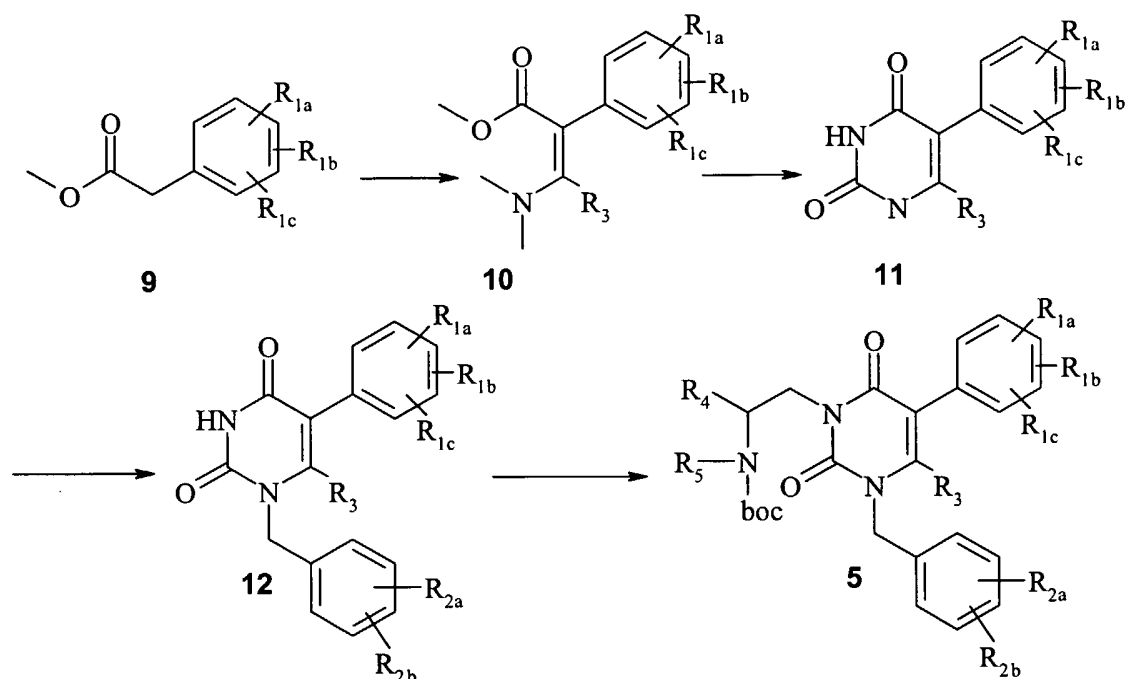
aldehyde via reductive amination conditions to give a compound of formula 7. It is possible to alter the order of the various reductive amination, alkylation, bromination and Suzuki condensation steps to give compounds of the present invention.

5

Reaction Scheme 2

In a variation of Scheme 1, compound 4 undergoes deprotection to give compound 8 which under Suzuki conditions gives compound 6. The -X-R₆ group may be added by alkylation, reductive amination or other reaction to give compound 7.

10

Reaction scheme 3

Substituted phenylacetic acid ester **9** (made from the corresponding acid or purchased) and reagent such as dimethylformamide dimethylacetal are condensed to give **10**. Cyclization with urea gives a compound of formula **11**. Alkylation using, for example, a substituted benzyl bromide gives **12** which may be alkylated with an appropriate alkyl halide, undergo a Mitsunobu coupling reaction with an appropriate alcohol, or react with a mesylate or sulfonate to give **5**.

The compounds of the present invention may generally be utilized as the free acid or free base. Alternatively, the compounds of this invention may be used in the form of acid or base addition salts. Acid addition salts of the free amino compounds of the present invention may be prepared by methods well known in the art, and may be formed from organic and inorganic acids. Suitable organic acids include maleic, fumaric, benzoic, ascorbic, succinic, methanesulfonic, acetic, trifluoroacetic, oxalic, propionic, tartaric, salicylic, citric, gluconic, lactic, mandelic, cinnamic, aspartic, stearic, palmitic, glycolic, glutamic, and benzenesulfonic acids. Suitable inorganic acids include hydrochloric, hydrobromic, sulfuric, phosphoric, and nitric acids. Base

addition salts included those salts that form with the carboxylate anion and include salts formed with organic and inorganic cations such as those chosen from the alkali and alkaline earth metals (for example, lithium, sodium, potassium, magnesium, barium and calcium), as well as the ammonium ion and substituted derivatives thereof (for example, 5 dibenzylammonium, benzylammonium, 2-hydroxyethylammonium, and the like). Thus, the term "pharmaceutically acceptable salt" of structure (I) is intended to encompass any and all acceptable salt forms.

In addition, prodrugs are also included within the context of this invention. Prodrugs are any covalently bonded carriers that release a compound of 10 structure (I) *in vivo* when such prodrug is administered to a patient. Prodrugs are generally prepared by modifying functional groups in a way such that the modification is cleaved, either by routine manipulation or *in vivo*, yielding the parent compound. Prodrugs include, for example, compounds of this invention wherein hydroxy, amine or sulfhydryl groups are bonded to any group that, when administered to a patient, cleaves 15 to form the hydroxy, amine or sulfhydryl groups. Thus, representative examples of prodrugs include (but are not limited to) acetate, formate and benzoate derivatives of alcohol and amine functional groups of the compounds of structure (I). Further, in the case of a carboxylic acid (-COOH), esters may be employed, such as methyl esters, ethyl esters, and the like.

20 With regard to stereoisomers, the compounds of structure (I) may have chiral centers and may occur as racemates, racemic mixtures and as individual enantiomers or diastereomers. All such isomeric forms are included within the present invention, including mixtures thereof. Furthermore, some of the crystalline forms of the compounds of structure (I) may exist as polymorphs, which are included in the 25 present invention. In addition, some of the compounds of structure (I) may also form solvates with water or other organic solvents. Such solvates are similarly included within the scope of this invention.

The effectiveness of a compound as a GnRH receptor antagonist may be determined by various assay techniques. Assay techniques well known in the field 30 include the use of cultured pituitary cells for measuring GnRH activity (Vale et al.,

Endocrinology 91:562-572, 1972) and the measurement of radioligand binding to rat pituitary membranes (Perrin et al., *Mol. Pharmacol.* 23:44-51, 1983) or to membranes from cells expressing cloned receptors as described below. Other assay techniques include (but are not limited to) measurement of the effects of GnRH receptor antagonists on the inhibition of GnRH-stimulated calcium flux, modulation of phosphoinositol hydrolysis, and the circulating concentrations of gonadotropins in the castrate animal. Descriptions of these techniques, the synthesis of radiolabeled ligand, the employment of radiolabeled ligand in radioimmunoassay, and the measurement of the effectiveness of a compound as a GnRH receptor antagonist follow.

10 Inhibition of GnRH stimulated LH release

Suitable GnRH antagonists are capable of inhibiting the specific binding of GnRH to its receptor and antagonizing activities associated with GnRH. For example, inhibition of GnRH stimulated LH release in immature rats may be measured according to the method of Vilchez-Martinez (*Endocrinology* 96:1130-1134, 1975).
15 Briefly, twenty-five day old male Sprague-Dawley rats are administered an GnRH antagonist in saline or other suitable formulation by oral gavage, subcutaneous injection, or intravenous injection. This is followed by subcutaneous injection of 200 ng GnRH in 0.2 ml saline. Thirty minutes after the last injection, the animals are decapitated and trunk blood is collected. After centrifugation, the separated plasma is
20 stored at -20 °C until determination of the concentrations of LH and/or FSH by radioimmunoassay (see below.)

Rat Anterior Pituitary Cell Culture Assay of GnRH Antagonists

Anterior pituitary glands are collected from 7-week-old female Sprague-Dawley rats and the harvested glands are digested with collagenase in a dispersion flask
25 for 1.5 hr at 37 °C. After collagenase digestion, the glands are further digested with neuraminidase for 9 min at 37 °C. The digested tissue is then washed with 0.1 % BSA/McCoy's 5A medium, and the washed cells are suspended in 3 % FBS/0.1 BSA/McCoy's 5A medium and plated onto 96-well tissue culture plates at a cell density

of 40,000 cells per well in 200 μ l medium. The cells are then incubated at 37 °C for 3 days. For assay of an GnRH antagonist, the incubated cells are first washed with 0.1 % BSA/McCoy's 5A medium once, followed by addition of the test sample plus 1nM GnRH in 200 μ l 0.1 % BSA/McCoy's 5A medium in triplicate wells. Each sample is
5 assayed at 5-dose levels to generate a dose-response curve for determination of the potency on the inhibition of GnRH stimulated LH and/or FSH release. After 4-hr incubation at 37 °C, the medium is harvested and the level of LH and/or FSH secreted into the medium is determined by RIA.

Membrane Binding Assays 1

10 Cells stably, or transiently, transfected with GnRH receptor expression vectors are harvested, resuspended in 5% sucrose and homogenized using a polytron homogenizer (2x15 sec). Nucleii are removed by centrifugation (3000 x g for 5 min.), and the supernatant is centrifuged (20,000 x g for 30 min, 4 °C) to collect the membrane fraction. The final membrane preparation is resuspended in binding buffer (10mM
15 Hepes (pH 7.5), 150 mM NaCl, and 0.1% BSA) and stored at -70 °C. Binding reactions are performed in a Millipore MultiScreen 96-well filtration plate assembly with polyethylenimine coated GF/C membranes. The reaction is initiated by adding membranes (40 μ g protein in 130 μ l binding buffer) to 50 μ l of [¹²⁵I]-labeled GnRH peptide (~100,000 cpm) and 20 μ l of competitor at varying concentrations. The
20 reaction is terminated after 90 minutes by application of vacuum and washing (2X) with phosphate buffered saline. Bound radioactivity is measured using 96-well scintillation counting (Packard Topcount) or by removing the filters from the plate and direct gamma counting. K_i values are calculated from competition binding data using non-linear least squares regression using the Prism software package (GraphPad Software).

25 Membrane Binding Assays 2

For additional membrane binding assays, stably transfected HEK293 cells are harvested by striking tissue culture flasks against a firm surface and collected by centrifugation at 1000xg for 5 minutes. Cell pellets are resuspended in 5% sucrose

and homogenized using a polytron homogenizer for two 15 second homogenization steps. Cell homogenates are then centrifuged for 5 minutes at 3000xg to remove nuclei, and the supernatant is subsequently centrifuged for 30 minutes at 44,000xg to collect the membrane fraction. The membrane pellet is resuspended in GnRH binding buffer
5 (10 mM HEPES, pH 7.5, 150 mM NaCl and 0.1%BSA,) and aliquots are immediately snap-frozen in liquid nitrogen and stored at -80°C . Protein content of the membrane suspension is determined using the Bio-Rad protein assay kit (Bio-Rad, Hercules, CA).

Competitive radioligand binding assays with membrane preparations are performed in Millipore 96-well filtration plates with GF/C membrane filters which are
10 pre-coated with 200 μl of 0.1% polyethylenimine (Sigma, St. Louis, MO). Prior to use, the plates are washed 3X with phosphate buffered saline solution. Membrane fraction in GnRH binding buffer (130 μl containing 25 μg protein for human and macaque receptors or 12 μg for rat receptors) are added to wells together with 20 μl of competing
15 ligand at varying concentrations. The binding reaction is initiated by addition of radioligand (0.1nM in 50 μl GnRH binding buffer.) The reaction is allowed to proceed for 90 min on a platform shaker at room temperature and then terminated by placing assay plate on a Millipore vacuum manifold (Millipore, Bedford, MA), aspirating the solvent, and washing wells twice with 200 μl ice cold phosphate buffered saline (PBS).
Filters in the wells are removed and counted in a gamma counter. K_i values are
20 calculated from each competition binding curves using non-linear least square regression and corrected for radioligand concentration using the Cheng-Prusoff equation (Prism, GraphPad Software, San Diego, CA) assuming a radioligand affinity of 0.5 nM. Mean K_i values are calculated from the antilog of the mean of the $\text{p}K_i$ values for each receptor ligand pair.

25 Membrane Binding Assays 3

Stably transfected human GNRH receptor RBL cells are grown to confluence. The medium is removed and the cell monolayer is washed once with DPBS. A solution of 0.5 mM EDTA/PBS (Ca^{++} Mg^{++} free) is added to the plate which is then incubated at 37°C for 10 min. Cells are dislodged by gentle rapping of the

flasks. The cells are collected and pelleted by centrifugation at 800g for 10 min at 4 °C. The cell pellet is then resuspended in buffer [DPBS (1.5 mM KH₂PO₄, 8.1mM Na₂HPO₄, 2.7 mM KCl, and 138 mM NaCl) supplemented with 10 mM MgCl₂, 2 mM EGTA, pH=7.4 with NaOH]. Cell lysis is then performed using a pressure cell and
5 applying N₂ at a pressure of 900psi for 30 min at 4 °C. Unbroken cells and larger debris are removed by centrifugation at 1200g for 10 min at 4 °C. The cell membrane supernatant is then centrifuged at 45,000g and the resulting membrane pellet is resuspended in assay buffer and homogenized on ice using a tissue homogenizer. Protein concentrations are determined using the Coomassie Plus Protein Reagent kit
10 (Pierce, Rockford, IL) using bovine serum albumin as a standard. The pellets are aliquoted and stored at -80 °C until use. Titration analysis using a range of protein concentrations determined the optimal protein concentration to be 15 µg per well final concentration.

UniFilter GF/C filter plates (Perkin Elmer, Boston MA) are pretreated
15 with a solution of 0.5% polyethyleneimine in distilled water for 30 minutes. Filters are pre-rinsed with 200 µl per well of PBS, 1% BSA (Fraction V) and 0.01% Tween-20, pH = 7.4) using a cell harvester (UniFilter-96 Filtermate; Packard). Membranes are harvested by rapid vacuum filtration and washed 3 times with 250 µl of ice-cold buffer (PBS, 0.01% Tween-20, pH = 7.4). Plates are air dried, 50 µl scintillation fluid
20 (Microscint 20; Packard) is added, and the plate is monitored for radioactivity using a TopCount NXT (Packard Instruments, IL).

Binding experiments are performed in buffer containing 10mM HEPES, 150mM NaCl, and 0.1% BSA, pH=7.5. Membranes are incubated with 50 µl [¹²⁵I] His⁵, D-Tyr⁶ GnRH (0.2nM final concentration) and 50 µl of small molecule
25 competitors at concentrations ranging from 30 pM to 10 µM for a total volume in each well of 200 µl. Incubations are carried out for 2hrs at room temperature. The reaction is terminated by rapid filtration over GF/C filters as previously described. Curve fitting is performed using Excel Fit Software (IDBS, Emeryville, CA). The K_i values are calculated using the method of Cheng and Prusoff (Cheng and Prusoff, 1973) using a

Kd value of 0.7nM for the radioligand which was previously determined in saturation binding experiments.

Ca⁺⁺ flux measurement

To determine the inhibition of GnRH-stimulated calcium flux in cells
5 expressing the human GnRH receptor, a 96-well plate is seeded with RBL cells stably
transfected with the human GnRH receptor at a density of 50,000 cells/well and allowed
to attach overnight. Cells are loaded for 1hr at 37 °C in the following medium: DMEM
with 20 mM HEPES, 10%FBS, 2 µM Fluo-4, 0.02% pluronic acid and 2.5 mM
probenecid. Cells are washed 4 times with wash buffer (Hanks balanced salt, 20 mM
10 HEPES, 2.5mM probenecid) after loading, leaving 150 µl in the well after the last
wash. GnRH is diluted in 0.1% BSA containing FLIPR buffer (Hanks balanced salt, 20
mM HEPES) to a concentration of 20nM and dispensed into a 96-well plate (Low
protein binding). Various concentrations of antagonists are prepared in 0.1%
BSA/FLIPR buffer in a third 96-well plate. Measurement of fluorescence due to GnRH
15 stimulated (50 µl of 20nM, or 4 nM final) Ca⁺⁺ flux is performed according to
manufacturer's instructions on a FLIPR system (Molecular Devices, FLIPR384 system,
Sunnyvale, CA) following a 1-minute incubation with 50 µl of antagonist at varying
concentrations.

Phosphoinositol hydrolysis assay

20 The procedure is modified from published protocols (W.Zhou et al;
J.Biol.Chem. 270(32), pp18853-18857, 1995). Briefly, RBL cells stably transfected
with human GnRH receptors are seeded in 24 well plates at a density of 200, 000
cell/well for 24 hrs. Cells are washed once with inositol-free medium containing 10%
dialyzed FBS and then labeled with 1µCi/mL of [*myo*-³H]-inositol. After 20-24 hrs,
25 cells are washed with buffer (140 nM NaCl, 4 mM KCl, 20 mM Hepes, 8.3 mM
glucose, 1 mM MgCl₂, 1 mM CaCl₂ and 0.1%BSA) and treated with native GnRH
peptide in the same buffer with or without various concentrations of antagonist and 10
mM LiCl for 1 hour at 37 °C. Cells are extracted with 10 mM formic acid at 4 °C for

30min and loaded on a Dowex AG1-X8 column, washed and eluted with 1 M ammonium formate and 0.1 M formic acid. The eluate is counted in a scintillation counter. Data from PI hydrolysis assay are plotted using non-linear least square regression by the Prism program (Graphpad, GraphPad Software, San Diego, CA), from
5 which dose ratio is also calculated. The Schild linear plot is generated from the dose-ratios obtained in four independent experiments by linear regression, and the X-intercept is used to determine the affinity of the antagonist.

Castrate animal studies

Studies of castrate animals provide a sensitive *in vivo* assay for the
10 effects of GnRH antagonist (*Andrology* 25: 141-147, 1993). GnRH receptors in the pituitary gland mediate GnRH-stimulated LH release into the circulation. Castration results in elevated levels of circulating LH due to reduction of the negative feedback of gonadal steroids resulting in enhancement of GnRH stimulated LH release. Consequently, measurement of suppression of circulating LH levels in castrated
15 macaques can be used as a sensitive *in vivo* measure of GnRH antagonism. Therefore, male macaques are surgically castrated and allowed to recover for four-weeks at which point elevated levels of LH are present. Animals are then administered the test compound as an oral or i.v. dose and serial blood samples taken for measurement of LH. LH concentrations in serum from these animals can be determined by
20 immunoassay or bioassay techniques (*Endocrinology* 107: 902-907, 1980).

Preparation of GnRH Radioligand

The GnRH analog is labeled by the chloramine-T method. To 10 μg of peptide in 20 μl of 0.5M sodium phosphate buffer, pH 7.6, is added 1 mCi of Na^{125}I , followed by 22.5 μg chloramine-T in 15 μl 0.05M sodium phosphate buffer and the
25 mixture is vortexed for 20 sec. The reaction is stopped by the addition of 60 μg sodium metabisulfite in 30 μl 0.05M sodium phosphate buffer and the free iodine is removed by passing the reaction mixture through a C-8 Sep-Pak cartridge (Millipore Corp., Milford, MA). The peptide is eluted with a small volume of 80% acetonitrile/water. The

recovered labeled peptide is further purified by reverse phase HPLC on a Vydac C-18 analytical column (The Separations Group, Hesperia, CA) on a Beckman 334 gradient HPLC system using a gradient of acetonitrile in 0.1% TFA. The purified radioactive peptide is stored in 0.1% BSA/20% acetonitrile/0.1% TFA at -80 °C and can be used
5 for up to 4 weeks.

RIA of LH and FSH

For determination of the LH levels, each sample medium is assayed in duplicates and all dilutions are done with RIA buffer (0.01M sodium phosphate buffer/0.15M NaCl/1% BSA/0.01% NaN₃, pH 7.5) and the assay kit is obtained from
10 the Nation Hormone and Pituitary Program supported by NIDDK. To a 12x75 mm polyethylene test tube is added 100 µl of sample medium diluted 1:5 or rLH standard in RIA buffer and 100 µl of [125I]-labeled rLH (~30,000 cpm) plus 100 µl of rabbit anti-rLH antibody diluted 1:187,500 and 100 µl RIA buffer. The mixture is incubated at room temperature over-night. In the next day, 100 µl of goat anti-rabbit IgG diluted
15 1:20 and 100 µl of normal rabbit serum diluted 1:1000 are added and the mixture incubated for another 3 hr at room temperature. The incubated tubes are then centrifuged at 3,000 rpm for 30 min and the supernatant removed by suction. The remaining pellet in the tubes is counted in a gamma-counter. RIA of FSH is done in a similar fashion as the assay for LH with substitution of the LH antibody by the FSH
20 antibody diluted 1:30,000 and the labeled rLH by the labeled rFSH.

Activity of GnRH receptor antagonists

Activity of GnRH receptor antagonists are typically calculated from the IC₅₀ as the concentration of a compound necessary to displace 50% of the radiolabeled ligand from the GnRH receptor, and is reported as a “K_i” value calculated by the
25 following equation:

$$K_i = \frac{IC_{50}}{1 + L / K_D}$$

where L = radioligand and K_D = affinity of radioligand for receptor (Cheng and Prusoff, *Biochem. Pharmacol.* 22:3099, 1973). GnRH receptor antagonists of this invention have a K_i of 100 μ M or less. In a preferred embodiment of this invention, the GnRH receptor antagonists have a K_i of less than 10 μ M, and more preferably less than 1 μ M, and even more preferably less than 0.1 μ M (*i.e.*, 100 nM). To this end, all compounds specifically disclosed in the Examples have K_i 's of less than 100 nM in one or more of Membrane Binding Assays 1 through 3 above.

The ability of the GnRH antagonists to inhibit the major drug metabolizing enzymes in the human liver, namely, CYP2D6 and CYP3A4, can be evaluated *in vitro* according to a microtiter plate-based fluorimetric method described by Crespi et al. (*Anal. Biochem.* 248: 188-190; 1997). AMMC (*i.e.*, 3-[2-(N,N-Diethyl-N-methylammonium)ethyl]-7-methoxy-4-methylcoumarin) and BFC (*i.e.*, 7-benzyloxy-4-(trifluoromethyl)coumarin) at a concentration equal to K_m (that is, the concentration of substrate that produces one half of the maximal velocity) are used as marker substrates for CYP2D6 and CYP3A4, respectively. Briefly, recombinant CYP2D6 or CYP3A4 is incubated with marker substrate and NADPH generating system (consisting of 1 mM NADP⁺, 46 mM glucose-6-phosphate and 3 units/mL glucose-6-phosphate dehydrogenase) at 37°C, in the absence or presence of 0.03, 0.09, 0.27, 0.82, 2.5, 7.4, 22, 67 and 200 μ M of a sample GnRH antagonist. Reactions are stopped by the addition of an equal volume of acetonitrile. The precipitated protein is removed by centrifugation and the clear supernatant fluid is analyzed using a microtiter plate fluorimeter. GnRH antagonists of the present invention preferably have K_i 's greater than 250 nM, more preferably greater than 1 μ M and most preferably greater than 5 μ M.

As mentioned above, the GnRH receptor antagonists of this invention have utility over a wide range of therapeutic applications, and may be used to treat a variety of sex-hormone related conditions in both men and women, as well as mammals in general. For example, such conditions include endometriosis, uterine fibroids, polycystic ovarian disease, hirsutism, precocious puberty, gonadal steroid-dependent neoplasia such as cancers of the prostate, breast and ovary, gonadotrophe pituitary

adenomas, sleep apnea, irritable bowel syndrome, premenstrual syndrome, benign prostatic hypertrophy, contraception and infertility (*e.g.*, assisted reproductive therapy such as *in vitro* fertilization).

The compounds of this invention are also useful as an adjunct to
5 treatment of growth hormone deficiency and short stature, and for the treatment of systemic lupus erythematosus.

In addition, the compounds are useful in combination with androgens, estrogens, progestones, and antiestrogens and antiprogestogens for the treatment of endometriosis, fibroids, and in contraception, as well as in combination with an
10 angiotensin-converting enzyme inhibitor, an angiotensin II-receptor antagonist, or a renin inhibitor for the treatment of uterine fibroids. The compounds may also be used in combination with bisphosphonates and other agents for the treatment and/or prevention of disturbances of calcium, phosphate and bone metabolism, and in combination with estrogens, progestones and/or androgens for the prevention or
15 treatment of bone loss or hypogonadal symptoms such as hot flashes during therapy with a GnRH antagonist.

In another embodiment of the invention, pharmaceutical compositions containing one or more GnRH receptor antagonists are disclosed. For the purposes of administration, the compounds of the present invention may be formulated as
20 pharmaceutical compositions. Pharmaceutical compositions of the present invention comprise a GnRH receptor antagonist of the present invention and a pharmaceutically acceptable carrier and/or diluent. The GnRH receptor antagonist is present in the composition in an amount which is effective to treat a particular disorder--that is, in an amount sufficient to achieve GnRH receptor antagonist activity, and preferably with
25 acceptable toxicity to the patient. Typically, the pharmaceutical compositions of the present invention may include a GnRH receptor antagonist in an amount from 0.1 mg to 250 mg per dosage depending upon the route of administration, and more typically from 1 mg to 60 mg. Appropriate concentrations and dosages can be readily determined by one skilled in the art.

Pharmaceutically acceptable carrier and/or diluents are familiar to those skilled in the art. For compositions formulated as liquid solutions, acceptable carriers and/or diluents include saline and sterile water, and may optionally include antioxidants, buffers, bacteriostats and other common additives. The compositions can also be formulated as pills, capsules, granules, or tablets which contain, in addition to a GnRH receptor antagonist, diluents, dispersing and surface active agents, binders, and lubricants. One skilled in this art may further formulate the GnRH receptor antagonist in an appropriate manner, and in accordance with accepted practices, such as those disclosed in *Remington's Pharmaceutical Sciences*, Gennaro, Ed., Mack Publishing Co., Easton, PA 1990.

In another embodiment, the present invention provides a method for treating sex-hormone related conditions as discussed above. Such methods include administering of a compound of the present invention to a warm-blooded animal in an amount sufficient to treat the condition. In this context, "treat" includes prophylactic administration. Such methods include systemic administration of a GnRH receptor antagonist of this invention, preferably in the form of a pharmaceutical composition as discussed above. As used herein, systemic administration includes oral and parenteral methods of administration. For oral administration, suitable pharmaceutical compositions of GnRH receptor antagonists include powders, granules, pills, tablets, and capsules as well as liquids, syrups, suspensions, and emulsions. These compositions may also include flavorants, preservatives, suspending, thickening and emulsifying agents, and other pharmaceutically acceptable additives. For parental administration, the compounds of the present invention can be prepared in aqueous injection solutions which may contain, in addition to the GnRH receptor antagonist, buffers, antioxidants, bacteriostats, and other additives commonly employed in such solutions.

The following example is provided for purposes of illustration, not limitation. In summary, the GnRH receptor antagonists of this invention may be assayed by the general methods disclosed above, while the following Examples disclose the synthesis of representative compounds of this invention.

EXAMPLES

A. HPLC Methods for analyzing the samples

Retention time, t_R , in minutesMethod 1 -- Supercritical Fluid Chromatography Mass Spectrum (SFC-MS)

- 5 Column: 4.6 x 150 mm Deltabond Cyano 5 μ M from Thermo-Hypersil-Keystone.
Mobile phase: SFC grade carbon dioxide and optima grade methanol with 1mM disodium diethylmalonate modifier.
Temperature: 50 °C
Pressure: 120 bar
- 10 Flow Rate: 4.8 mL/min
Gradient: 5% to 55% methanol over 1.7 min and hold at 55% for 0.8 min then return to 5% in 0.1 min for total run time of 2.6 min

Method 2 (HPLC-MS)

- Column: Waters ODS-AQ, 2.0 x 50 mm
- 15 Mobile phase: A = water with 0.05% trifluoroacetic acid; B= acetonitrile with 0.05% trifluoroacetic acid
Gradient: 95% A/ 5%B to 5%A/95%B over 13.25 min and hold 5%A/95%B over 2 min then return to 95%A/5%B over 0.25 min.
Flow Rate: 1 mL/min
- 20 UV wavelength: 220 and 254 nM

Method 3 (HPLC-MS)

- Column: BHK Lab ODS-O/B, 4.6 x 50 mm, 5 μ M
Mobile phase: A = water with 0.05% trifluoroacetic acid; B = acetonitrile with 0.05% trifluoroacetic acid

Gradient: 95%A/5%B for 0.5 min, then to 90% A/10%B for 0.05 min. from 90%A/10%B to 5%A/95%B over 18.94 min, then to 1%A/99%B over 0.05 min and hold 1%A/99%B over 2.16 min. then return to 95%/5%B over 0.50 min.

Flow rate: 2.5 mL/min.

- 5 UV wavelength: 220 and 254 nM

Method 4 (HPLC-MS)

Column: Waters ODS-AQ, 2.0 x 50 mm

Mobile phase: A = water with 0.05% trifluoroacetic acid; B = acetonitrile with 0.05% trifluoroacetic acid

- 10 Gradient: 95% A/5%B to 10%A/90%B over 2.25 min and hold 10%A/90%B over 1.0 min then return to 95%A/5%B over 0.1 min.

Flow Rate: 1 mL/min

UV wavelength: 220 and 254 nM

Method 5 (HPLC)

- 15 Column: Agilent, Zorbax SB-C18, 5 μ M, 4.6x250 mm.

Mobile phase: A = water with 0.05% trifluoroacetic acid; B = acetonitrile with 0.05% trifluoroacetic acid

Gradient: 95%A/5%B to 5%A/95%B over 50 min, then 5%A/95%B to 1%A/99%B over 0.1 min, then hold 1%A/99% for 0.8 min and back to 95%A/5% over 0.2

- 20 min, hold such gradient for 4 min.

Flow rate 2.0 mL/min.

UV wavelength: 220 and 254 nM

Method 6 (HPLC-MS)

Column: Phenomenex Synergi 4 μ Max-RP 80A, 50.0 x2.0 mm

- 25 Mobile Phase: A=water with 0.025 % of trifluoroacetic acid; B=acetonitrile with 0.025% of trifluoroacetic acid

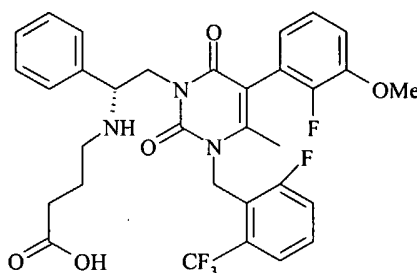
Gradient: 95% A/5% B 0.25min, then 95% A/5%B to 95% B/5%A over 13 min, maintaining 95% A/5%B to 95% B/5%A over 2 min, then back to 95% A/5% B in 0.25 min.

Flow rate: 1 mL/min

5 UV wavelength: 220 nM and 254 nM

EXAMPLE 1

3-[2(R)-{HYDROXYCARBONYLPROPYL-AMINO}-2-PHENYLETHYL]-5-(2-FLUORO-3-METHOXYPHENYL)-1-[2-FLUORO-6-(TRIFLUOROMETHYL)BENZYL]-6-METHYL-PYRIMIDINE-2,4(1H,3H)-DIONE



Step 1A: Preparation of 2-fluoro-6-(trifluoromethyl)benzylamine 1a

To 2-fluoro-6-(trifluoromethyl)benzylamine (45 g, 0.238 mmol) in 60 mL of THF was added 1 M BH₃:THF slowly at 60 °C and the resulting solution was refluxed overnight. The reaction mixture was cooled to ambient temperature. Methanol (420 mL) was added slowly and stirred well. The solvents were then evaporated and the residue was partitioned between EtOAc and water. The organic layer was dried over Na₂SO₄. Evaporation gave **1a** as a yellow oil (46 g, 0.238 mmol). MS (CI) *m/z* 194.0 (MH⁺).

15

Step 1B: Preparation of N-[2-fluoro-6-(trifluoromethyl)benzyl]urea 1b

To 2-fluoro-6-(trifluoromethyl)benzylamine **1a** (51.5 g, 0.267 mmol) in a flask, urea (64 g, 1.07 mmol), HCl (conc., 30.9 mmol, 0.374 mmol) and water (111

20

mL) were added. The mixture was refluxed for 6 hours. The mixture was cooled to ambient temperature, further cooled with ice and filtered to give a yellow solid. Recrystallization with 400 mL of EtOAc gave **1b** as a white solid (46.2 g, 0.196 mmol). MS (CI) m/z 237.0 (MH^+).

5 Step 1C: Preparation of 1-[2-fluoro-6-(trifluoromethyl)benzyl]-6-methylpyrimidine-2,4(1H,3H)-dione 1c

NaI (43.9 g, 293 mmol) was added to *N*-[2-fluoro-6-(trifluoromethyl)benzyl]urea **1b** (46.2 g, 19.6 mmol) in 365 mL of acetonitrile. The resulting mixture was cooled in an ice-water bath. Diketene (22.5 mL, 293 mmol) was added slowly *via* dropping funnel followed by addition of TMSCl (37.2 mL, 293 mmol) in the same manner. The resulting yellow suspension was allowed to warm to room temperature slowly and was stirred for 20 hours. LC-MS showed the disappearance of starting material. To the yellow mixture 525 mL of water was added and stirred overnight. After another 20 hours stirring, the precipitate was filtered *via* Buchner funnel and the yellow solid was washed with water and EtOAc to give **1c** as a white solid (48.5 g, 16 mmol). 1H NMR ($CDCl_3$) δ 2.15 (s, 3H), 5.37 (s, 2H), 5.60 (s, 1H), 7.23-7.56 (m, 3H), 9.02 (s, 1H); MS (CI) m/z 303.0 (MH^+).

Step 1D: Preparation of 5-bromo-1-[2-fluoro-6-(trifluoromethyl)benzyl]-6-methylpyrimidine-2,4(1H,3H)-dione 1d

20 Bromine (16.5 mL, 0.32 mmol) was added to 1-[2-fluoro-6-(trifluoromethyl)benzyl]-6-methylpyrimidine-2,4(1H,3H)-dione **1c** (48.5 g, 0.16 mol) in 145 mL of acetic acid. The resulting mixture became clear then formed precipitate within an hour. After 2 hours stirring, the yellow solid was filtered and washed with cold EtOAc to an almost white solid. The filtrate was washed with sat. $NaHCO_3$ and dried over Na_2SO_4 . Evaporation gave a yellow solid which was washed with EtOAc to give a light yellow solid. The two solids were combined to give 59.4 g of **1d** (0.156 mol) total. 1H NMR ($CDCl_3$) δ 2.4 (s, 3H), 5.48 (s, 2H), 7.25-7.58 (m, 3H), 8.61 (s, 1H); MS (CI) m/z 380.9 (MH^+).

5-Bromo-1-[2, 6-difluorobenzyl]-6-methylpyrimidine-2,4(1*H*,3*H*)-dione **1d.1** was made using the same procedure.

Step 1E: Preparation of 5-bromo-1-[2-fluoro-6-(trifluoromethyl)benzyl]-6-methyl-3-[2(R)-tert-butoxycarbonylamino-2-phenylethyl]-pyrimidine-2,4(1*H*,3*H*)-dione

5 **1e**

To 5-bromo-1-[2-fluoro-6-(trifluoromethyl)benzyl]-6-methylpyrimidine-2,4(1*H*,3*H*)-dione **1d** (15 g, 39.4 mmol) in 225 mL of THF were added N-*t*-Boc-D-phenylglycinol (11.7 g, 49.2 mmol) and triphenylphosphine (15.5 g, 59.1 mmol), followed by addition of di-*tert*-butyl azodicarboxylate (13.6 g, 59.1 mmol). The resulting yellow solution was stirred overnight. The volatiles were evaporated and the residue was purified by silica gel with 3:7 EtOAc/Hexane to give **1e** as a white solid (23.6 g, 39.4 mmol). MS (CI) *m/z* 500.0 (MH⁺-Boc).

Step 1F: Preparation of 3-[2(R)-amino-2-phenylethyl]-5-(2-fluoro-3-methoxyphenyl)-1-[2-fluoro-6-(trifluoromethyl)benzyl]-6-methyl-pyrimidine-

15 **2,4(1*H*,3*H*)-dione 1f**

To 5-bromo-1-[2-fluoro-6-(trifluoromethyl)benzyl]-6-methyl-3-[2(R)-tert-butoxycarbonylamino-2-phenylethyl]-pyrimidine-2,4(1*H*,3*H*)-dione **1e** (15 g, 25 mmol) in 30 mL/90 mL of H₂O/dioxane in a pressure tube were added 2-fluoro-3-methoxyphenylboronic acid (4.25 g, 25 mmol) and sodium carbonate (15.75 g, 150 mmol). N₂ gas was bubbled through for 10 min. Tetrakis(triphenylphosphine)palladium (2.9 g, 2.5 mmol) was added, the tube was sealed and the resulting mixture was heated with stirring at 90 °C overnight. After cooling to ambient temperature, the precipitate was removed by filtration. The volatiles were removed by evaporation and the residue was partitioned between EtOAc/sat. NaHCO₃. The organic solvent was evaporated and the residue was chromatographed with 2:3 EtOAc/Hexane to give 13.4 g (20.8 mmol, 83 %) yellow solid.

This yellow solid (6.9 g, 10.7 mmol) was dissolved in 20 mL/20 mL CH₂Cl₂/TFA. The resulting yellow solution was stirred at room temperature for 2

hours. The volatiles were evaporated and the residue was partitioned between EtOAc/sat. NaHCO₃. The organic phase was dried over Na₂SO₄. Evaporation gave **1f** as a yellow oil (4.3 g, 7.9 mmol, 74%). ¹H NMR (CDCl₃) δ 2.03 (s, 3H), 3.72-4.59 (m, 6H), 5.32-5.61 (m, 2H), 6.74-7.56 (m, 11H); MS (CI) *m/z* 546.0 (MH⁺).

5 3-[2(R)-amino-2-phenylethyl]-5-(2-fluoro-3-methoxyphenyl)-1-[2,6-difluorobenzyl]-6-methyl-pyrimidine-2,4(1*H*,3*H*)-dione **1f.1** was made using the same procedure described in this example.

Step 1G: Preparation of 3-[2(R)-{ethoxycarbonylpropyl-amino}-2-phenylethyl]-5-(2-fluoro-3-methoxyphenyl)-1-[2-fluoro-6-(trifluoromethyl)benzyl]-6-methyl-

10 pyrimidine-2,4(1*H*,3*H*)-dione **1g**

To compound 3-[2(R)-amino-2-phenylethyl]-5-(2-fluoro-3-methoxyphenyl)-1-[2-fluoro-6-(trifluoromethyl)benzyl]-6-methyl-pyrimidine-2,4(1*H*,3*H*)-dione **1f** (5 g, 9.4 mmol) in 100 mL of acetonitrile were added ethyl 4-bromobutyrate (4 mL, 28.2 mmol) and Hunig's base (1.6 mL, 9.4 mmol). After reflux
15 at 95 °C overnight, the reaction mixture was cooled to ambient temperature and the volatiles were removed. The residue was chromatographed with 10:10:1 EtOAc/Hexane/Et₃N to give **1g** as a yellow oil (3.0 g, 4.65 mmol). MS (CI) *m/z* 646.2 (MH⁺).

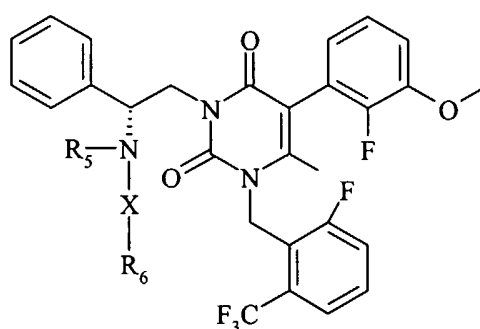
Step 1H: Preparation of 3-[2(R)-{hydroxycarbonylpropyl-amino}-2-phenylethyl]-

20 5-(2-fluoro-3-methoxyphenyl)-1-[2-fluoro-6-(trifluoromethyl)benzyl]-6-methyl-pyrimidine-2,4(1*H*,3*H*)-dione **1-1**

Compound 3-[2(R)-{ethoxycarbonylpropyl-amino}-2-phenylethyl]-5-(2-fluoro-3-methoxyphenyl)-1-[2-fluoro-6-(trifluoromethyl)benzyl]-6-methyl-pyrimidine-2,4(1*H*,3*H*)-dione **1g** (2.6 g, 4.0 mmol) was dissolved in 30 mL/30 mL of THF/water.
25 Solid NaOH (1.6 g, 40 mmol) was added and the resulting mixture was heated at 50 °C overnight. The mixture was cooled to ambient temperature and the volatiles were evaporated. Citric acid was added to the aqueous solution until pH = 3. Extraction with EtOAc followed by evaporation of solvent gave 1.96 g of a white gel. The gel was

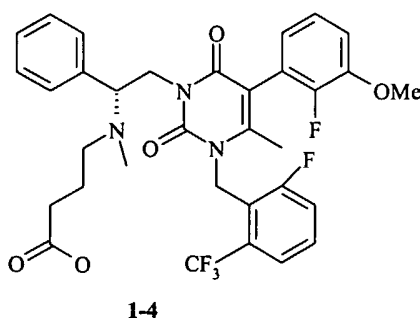
passed through a Dowex MSC-1 macroporous strong cation-exchange column to convert to sodium salt. Lyophilization gave white solid **1-1** as the sodium salt (1.58 g, 2.47 mmol). $^1\text{H NMR}$ (CD_3OD) δ 1.69-1.77 (m, 2H), 2.09 (s, 3H), 2.09-2.19 (t, $J = 7.35$ Hz, 2H), 2.49-2.53 (t, $J = 7.35$ Hz, 2H), 3.88 (s, 3H), 4.15-4.32 (m, 3H), 5.36-5.52 (m, 2H), 6.60-7.63 (m, 11H); HPLC-MS (CI) m/z 632.2 (MH^+), $t_R = 26.45$, (method 5)

The following compounds were synthesized according to the above procedure.



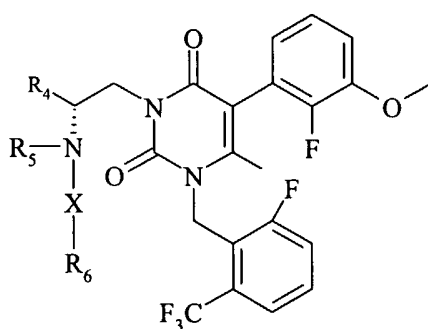
No.	-N(R ₅)-X-R ₆	M.W.	Mass	t_R (Method #)
1-1		631.60	632.2	26.45 (5)
1-2		617.57	618.0	2.777 (4)
1-3		645.62	646.0	2.789 (4)

Step II: Preparation of 3-[2(R)-{N-methyl-N-hydroxycarbonylpropyl-amino}-2-phenylethyl]-5-(2-fluoro-3-methoxyphenyl)-1-[2-fluoro-6-(trifluoromethyl)benzyl]-6-methyl-pyrimidine-2,4(1H,3H)-dione **1-4**



To compound 1-1 (0.045 mmol) in 1 mL MeOH, formaldehyde (0.0475 mmol) was added followed by addition of 8 M BH₃:Pyridine (0.0475 mmol). After overnight shaking, compound 1-4 was purified by prep. LC-MS. HPLC-MS (CI) *m/z* 646.5 (MH⁺), *t_R* = 2.231, (method 4)

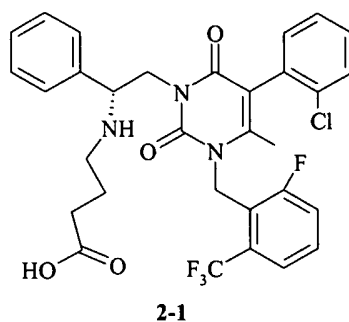
- 5 The following compounds were synthesized according to the above procedure.



No.	-N(R ₅)-X-R ₆	R ₄	M.W.	Mass	<i>t_R</i> (Method #)
1-4		Ph	645.62	646.2	2.231 (4)
1-5		Ph	659.65	660.2	2.235 (4)
1-6		cyclopentyl	637.64	638.3	2.259 (4)
1-7		cyclopentyl	651.67	652.3	2.294 (4)
1-8		isobutyl	625.63	626.0	2.594 (4)

EXAMPLE 2

3-[2(R)-{HYDROXYCARBONYLPROPYL-AMINO}-2-PHENYLETHYL]-5-(2-CHLOROPHENYL)-
1-[2-FLUORO-6-(TRIFLUOROMETHYL)BENZYL]-6-METHYL-PYRIMIDINE-2,4(1H,3H)-
DIONE



5

Step 2A: Preparation of 5-bromo-1-[2-fluoro-6-(trifluoromethyl)benzyl]-6-methyl-3-[2(R)-amino-2-phenylethyl]-pyrimidine-2,4(1H,3H)-dione 2a

5-Bromo-1-[2-fluoro-6-(trifluoromethyl)benzyl]-6-methyl-3-[2(R)-tert-butoxycarbonylamino-2-phenylethyl]-pyrimidine-2,4(1H,3H)-dione **1e** was dissolved in
10 20 mL/20 mL CH₂Cl₂/TFA. The resulting yellow solution was stirred at room temperature for 2 hours. The volatiles were evaporated and the residue was partitioned between EtOAc/ sat. NaHCO₃. The organic phase was dried over Na₂SO₄. Evaporation gave **2a** as a yellow oil.

Step 2B: Preparation of 5-(2-chlorophenyl)-1-[2-fluoro-6-(trifluoromethyl)benzyl]-6-methyl-3-[2(R)-amino-2-phenylethyl]-pyrimidine-2,4(1H,3H)-dione 2b

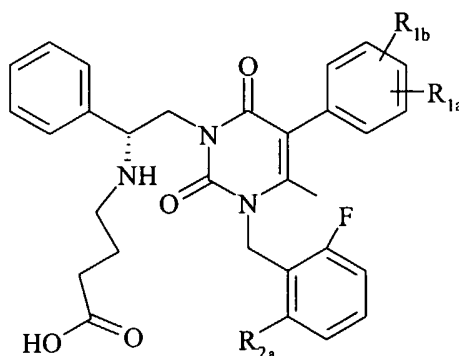
To compound **2a** (40 mg, 0.08 mmol) in 0.25 mL/0.75 mL of H₂O/dioxane in a 4 mL vial was added 2-chlorophenyl boronic acid (0.12 mmol) and sodium carbonate (51 mg, .48 mmol, 6 eq). Nitrogen gas was bubbled through the
20 solution for 1 minute and tetrakis(triphenylphosphine)palladium (9.24 mg, 0.008 mmol) was added. The resulting mixture was sealed and heated at 90 °C overnight. After

cooling to ambient temperature, the precipitate was removed by filtration and was purified by prep. LC-MS to give **2b**.

Step 2C: 3-[2(R)-{hydroxycarbonylpropyl-amino}-2-phenylethyl]-5-(2-chlorophenyl)-1-[2-fluoro-6-(trifluoromethyl)benzyl]-6-methyl-pyrimidine-2,4(1*H*,3*H*)-dione **2-1**

To compound **2b** (0.03 mmol) in 1 mL MeOH, succinic semialdehyde (0.03 mmol) was added followed by addition of 8 M BH₃:Pyridine (0.03 mmol). After overnight shaking, the compound **2-1** was purified by prep. LC-MS. MS (CI) *m/z* 618.2 (MH⁺) *t_R* = 1.005 (method 1)

The following compounds were synthesized according to the above procedure.

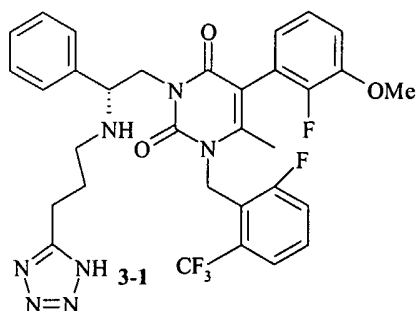


No.	R _{2a}	R _{1a}	R _{1b}	M.W.	Mass	<i>t_R</i> (Method #)
2-1	CF ₃	2-Cl	H	618.02	618.2	1.005 (1)
2-2	CF ₃	2-F	H	601.57	602.2	0.976 (1) 5.194 (6)
2-3	CF ₃	H	H	583.58	584.3	1.000 (1) 5.572 (6)
2-4	CF ₃	3-isopropyl	H	625.66	626.3	6.882 (1)
2-5	CF ₃	3-ethoxy	H	627.63	628.3	0.913 (1)
2-6	CF ₃	3,4-methyl-enedioxy		627.59	628.2	0.932 (1)

No.	R _{2a}	R _{1a}	R _{1b}	M.W.	Mass	t _R (Method #)
2-7	CF ₃	2-F	3-OH	617.57	618.2	0.979(1)
2-8	CF ₃	3-methyl	H	597.61	598.2	5.455 (6)
2-9	SO ₂ CH ₃	2-F	3-methoxy	641.69	642.1	4.820 (6)
2-10	F	2-F	3-methoxy	581.59	582.2	5.532 (6)
2-11	CF ₃	3-Cl	H	618.02	617.9	5.216 (6)
2-12	CF ₃	3,4-O-CH ₂ -CH ₂ -		625.62	626.0	4.774 (6)
2-13	CF ₃	2-F	3-methyl	615.60	616.2	6.381 (6)
2-14	CF ₃	3-isopropoxy	H	641.66	642.2	6.676 (6)

EXAMPLE 3

3-[2(R)-{2-[5-TETRAZOYLPROPYL]-AMINO}-2-PHENYLETHYL]-5-(2-FLUORO-3-METHOXYPHENYL)-1-[2-FLUORO-6-(TRIFLUOROMETHYL)BENZYL]-6-METHYLPYRIMIDINE-2,4(1H,3H)-DIONE



5

Step 3A: 3-[2(R)-{3-cyanopropyl-amino}-2-phenylethyl]-5-(2-fluoro-3-methoxyphenyl)-1-[2-fluoro-6-(trifluoromethyl)benzyl]-6-methyl-pyrimidine-2,4(1H,3H)-dione 3a

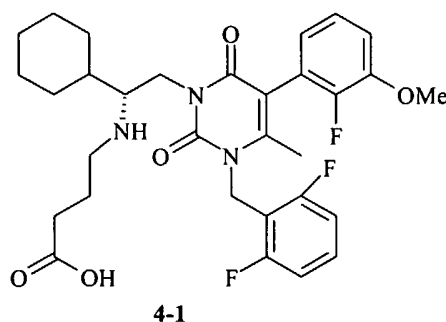
Compound **1f** (110 mg, 0.2 mmol) was dissolved in acetonitrile (5 mL) and diisopropylethyl amine (52 mg, 0.4 mmol) was added, followed by the addition of 4-bromobutyronitrile (90 mg, 0.6 mmol). The reaction mixture was refluxed for 16 hours. Volatiles were evaporated and the residue was purified by flash chromatography (silica, 5 % MeOH/CH₂Cl₂) to give compound **3a** (115 mg, 94 %). MS (CI) *m/z* 613.3 (MH⁺).

10 Step 3B: 3-[2(R)-{2-[5-tetrazoylpropyl]-amino}-2-phenylethyl]-5-(2-fluoro-3-methoxyphenyl)-1-[2-fluoro-6-(trifluoromethyl)benzyl]-6-methyl-pyrimidine-2,4(1H,3H)-dione 3-1

A solution of **3a** (38 g, 0.06 mmol) in toluene (5 mL) was added tributyltin azide (42 mg, 0.12 mmol), and the reaction mixture was heated at 100 °C for 14 hours. The mixture was cooled, partitioned between EtOAc and 1 N NaOH, and the organic layer was washed with 1 N HCl and brine. The organic layer was dried (sodium sulfate), evaporated, and the residue was purified by flash chromatography (silica, 7 % MeOH/CH₂Cl₂) to give compound **3-1** (10 mg, 25 %). HPLC-MS (CI) *m/z* 656.2 (MH⁺), *t_R* = 2.128 min, (method 4)

EXAMPLE 4

3-[2(R)-{HYDROXYCARBONYLPROPYL-AMINO}-2-CYCLOHEXYLETHYL]-5-(2-FLUORO-3-METHOXYPHENYL)-1-[2, 6-DIFLUOROBENZYL]-6-METHYL-PYRIMIDINE-2,4(1*H*,3*H*)-DIONE



5

Step 4A: Preparation of *tert*-butyl 1-cyclohexyl-2-hydroxyethylcarbamate 4a

A solution of *N*-(*t*-butoxycarbonyl)cyclohexylglycine (2.0 g, 7.77 mmol) in anhydrous THF (10 mL) was cooled to 0 °C. Borane solution (1 M in THF, 15.5 mL, 15.5 mmol) was added slowly and the reaction mixture was warmed to room temperature and stirred for 2 hours. The reaction was quenched with MeOH (5 mL), volatiles were evaporated and the residue was partitioned between water and EtOAc. The organic layer was washed with saturated NaHCO₃/water, brine, dried (sodium sulfate), and evaporated to give *tert*-butyl 1-cyclohexyl-2-hydroxyethylcarbamate **4a** (1.26 g, 66.7 %), MS (CI) *m/z* 144.2 (MH⁺-Boc).

Step 4B: Preparation of 5-bromo-3-[2(R)-*tert*-butoxycarbonylamino-2-cyclohexylethyl]-1-[2, 6-difluorobenzyl]-6-methylpyrimidine-2,4(1*H*,3*H*)-dione 4b

A solution of *tert*-butyl 1-cyclohexyl-2-hydroxyethylcarbamate **4a** (638 mg, 2.62 mmol) in THF (10 mL) was treated with 5-bromo-1-(2,6-difluorobenzyl)-6-methylpyrimidine-2,4(1*H*,3*H*)-dione **1d.1** (869 mg, 2.62 mmol) and triphenylphosphine (1.03g, 3.93 mmol) at ambient temperature, then di-*tert*-butylazodicarboxylate (906 mg, 3.93 mmol) was introduced. The reaction mixture was stirred at ambient temperature

for 16 hours and volatiles were evaporated. The residue was partitioned between saturated $\text{NaHCO}_3/\text{H}_2\text{O}$ and EtOAc. The organic layer was dried (sodium sulfate), evaporated, and purified by flash chromatography (silica, 25 % EtOAc/hexanes) to give compound **4b** (1.39 g, 95.4 %). MS (CI) m/z 456.1, 458.1 ($\text{MH}^+ - \text{Boc}$).

5 Step 4C: Preparation of 3-[2(R)-tert-butoxycarbonylamino-2-cyclohexylethyl]-5-(2-fluoro-3-methoxyphenyl)-1-[2, 6-difluorobenzyl]-6-methyl-pyrimidine-2,4(1H,3H)-dione **4c**

5-Bromo-3-[2(R)-tert-butoxycarbonylamino-2-cyclohexylethyl]-1-[2, 6-difluorobenzyl]-6-methyl-pyrimidine-2,4(1H,3H)-dione **4b** (1.0 g, 1.79 mmol) in
10 benzene/EtOH/ethylene glycol dimethyl ether (20/2/22 mL) was added 2-fluoro-3-methoxyphenylboronic acid (382 mg, 2.24 mmol) and saturated $\text{Ba}(\text{OH})_2/\text{water}$ (~ 0.5 M, 15 mL). The reaction mixture was deoxygenated with N_2 for 10 minutes, tetrakis(triphenylphosphine) palladium (0) (208 mg, 0.18 mmol) was added and the
15 reaction mixture was heated at 80 °C overnight under N_2 . The reaction mixture was partitioned between brine and EtOAc. The organic layer was dried (sodium sulfate), evaporated, and purified by flash chromatography (silica, 30 % EtOAc/hexanes) to give compound **4c** (348 mg, 32.3 %). MS (CI) m/z 502.2 ($\text{MH}^+ - \text{Boc}$).

Step 4D: Preparation of 3-[2(R)-amino-2-cyclohexylethyl]-5-(2-fluoro-3-methoxyphenyl)-1-[2, 6-difluorobenzyl]-6-methyl-pyrimidine-2,4(1H,3H)-dione **4d**

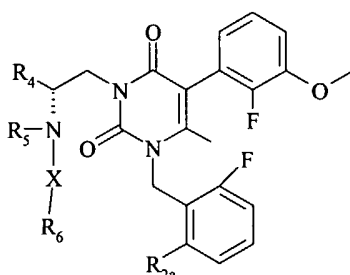
20 To compound **4c** (300 mg, 0.5 mmol) in dichloromethane (2 mL) was added TFA (2 mL) and the reaction mixture was stirred at ambient temperature for 1 hour. Volatiles were evaporated and the residue was partitioned between saturated $\text{NaHCO}_3/\text{water}$ and EtOAc. The organic layer was dried (sodium sulfate), evaporated, purified by reverse phase HPLC (C-18 column, 15-75 % ACN/water) to give compound
25 **4d**. MS (CI) m/z 502.2 (MH^+).

Step 4E: Preparation of 3-[2(R)-{hydroxycarbonylpropyl-amino}-2-cyclohexylethyl]-5-(2-fluoro-3-methoxyphenyl)-1-[2,6-difluorobenzyl]-6-methyl-pyrimidine-2,4(1H,3H)-dione 4-1

A solution of compound **4d** (10 mg, 0.02 mmol) in methanol (2 mL) was added succinic semialdehyde (15 mg, 15 % aqueous solution), followed by the addition of borane/pyridine (8 M, 3 μ L). The reaction mixture was stirred at ambient temperature for 1 hour. Volatiles were evaporated and the residue was purified directly on preparative TLC plate eluting with 7% MeOH/CH₂Cl₂ to give compound **4-1** (5 mg). MS (CI) *m/z* 588.3 (MH⁺).

3-[2(R)-{hydroxycarbonylpropyl-amino}-2-cyclohexylethyl]-5-(2-fluoro-3-methoxyphenyl)-1-[2-fluoro-6-(trifluoromethyl)benzyl]-6-methyl-pyrimidine-2,4(1H,3H)-dione **4-2** was synthesized using the same procedure and intermediate **1d**.

The following compounds were synthesized according to the above procedure.



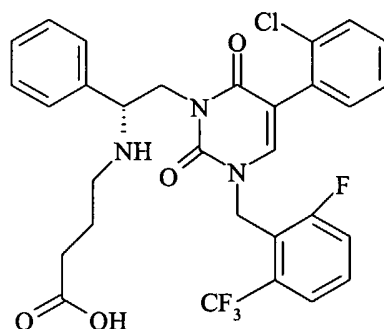
15

No.	-N(R ₅)-X-R ₆	R _{2a}	R ₄	MW	Mass	t _R (Method #)
4-1		F	cyclohexyl	587.63	588.4	5.350 (3)
4-2		CF ₃	cyclohexyl	637.64	638.3	27.56 (5)
4-3		CF ₃	cyclopentyl	623.60	624.2	2.290 (4)
4-4		CF ₃	isobutyl	611.61	612.3	6.480 (6)
4-5		CF ₃	cyclohexyl	651.67	652.1	2.340 (4)

No.	-N(R ₅)-X-R ₆	R _{2a}	R ₄	MW	Mass	t _R (Method #)
4-6		CF ₃	isobutyl	625.63	626.0	2.593 (4)
4-7		CF ₃	isobutyl	639.66	640.0	2.61 (4)
4-8		CF ₃	isobutyl	597.58	598.0	2.571 (4)

EXAMPLE 5

3-[2(R)-{HYDROXYCARBONYLPROPYL-AMINO}-2-PHENYLETHYL]-5-(2-CHLOROPHENYL)-
1-[2-FLUORO-6-(TRIFLUOROMETHYL)BENZYL]-PYRIMIDINE-2,4(1H,3H)-DIONE



5 Step 5A: Preparation of 5-bromo-1-[2-fluoro-6-(trifluoromethyl)benzyl]pyrimidine-2,4(1H,3H)-dione 5a

A suspension of 5-bromouracil (31.0 g) in 300 mL of dichloroethane is treated with *N,O*-bis(trimethylsilyl)acetamide (80 mL). The reaction mixture is heated under nitrogen. The solution is cooled to ambient temperature, 2-fluoro-6-(trifluoromethyl)benzyl bromide (50 g) is added and the reaction mixture is heated overnight under the nitrogen. The reaction is cooled, quenched with MeOH, and partitioned between dichloromethane and water. The organic layer is washed with brine, dried (sodium sulfate), and evaporated to give a solid. The crude product is triturated with ether, filtered, and washed with ether three times providing 40.7 g of 5-

bromo-1-[2-fluoro-6-(trifluoromethyl)benzyl]pyrimidine-2,4(1*H*,3*H*)-dione **5a**. MS (CI) *m/z* 366.0, 368.0 (MH⁺).

Step 5B: Preparation of 3-[2(R)-amino-2-phenylethyl]-5-bromo-1-[2-fluoro-6-(trifluoromethyl)benzyl]-pyrimidine-2,4(1*H*,3*H*)-dione **5b**

5 A solution of 5-bromo-1-[2-fluoro-6-(trifluoromethyl)benzyl]pyrimidine-2,4(1*H*,3*H*)-dione **5a** (19.2 g, 52.3 mmol) in THF (180 mL) was treated with *N*-(*t*-butyloxycarbonyl)-*D*- α -phenylglycinol (13.6 g, 57.5 mmol) and triphenylphosphine (20.6 g, 78.5 mmol) at room temperature, then di-*tert*-butylazodicarboxylate (18.0 g, 78.5 mmol) was introduced in several portions over 5
10 minutes. The mixture was stirred at room temperature for 16 hour, additional THF (90 mL) was added, and the mixture was heated to 50 °C. Concentrated HCl (34.6 mL, 418 mmol) was added, and the reaction mixture was stirred at 50 °C for 40 hours. After dilution with ethyl acetate (100 mL), the solid was filtered, washed with additional ethyl acetate (100 mL), and dried to give compound **5b** (26.9 g, 98 %) as a white
15 powder. MS (CI) *m/z* 485.0, 487.0 (MH⁺).

Step 5C: Preparation of 3-[2(R)-amino}-2-phenylethyl]-5-(2-chlorophenyl)-1-[2-fluoro-6-(trifluoromethyl)benzyl]-pyrimidine-2,4(1*H*,3*H*)-dione **5c**

To compound **5b** (10.45 g, 20 mmol) in dioxane/water (180/20 mL) was added 2-chlorophenylboronic acid (6.26 g, 40 mmol) and Na₂CO₃ (12.72 g, 120 mmol).
20 The mixture was deoxygenated with N₂ for 15 minutes, tetrakis(triphenylphosphine) palladium (0) (2.31 g, 2 mmol) was added and the reaction mixture was heated at 90 °C for 16 hours. The reaction was partitioned between EtOAc and H₂O. The organic layer was washed with brine, dried over Na₂SO₄, concentrated and purified by column chromatography on silica gel with ethyl acetate/hexanes/triethylamine 500/500/6 to
25 800/200/7 to afford compound **5c** (7.26 g, 70 %) as a white foam. MS (CI) *m/z* 518.0, 520.1 (MH⁺).

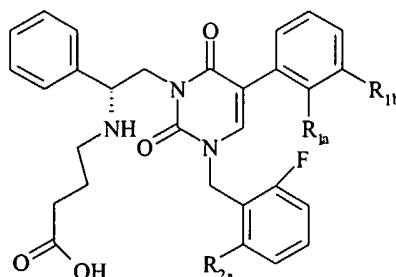
Step 5D: Preparation of 3-[2(R)-{ethoxycarbonylpropyl-amino}-2-phenylethyl]-5-(2-chlorophenyl)-1-[2-fluoro-6-(trifluoromethyl)benzyl]-pyrimidine-2,4(1H,3H)-dione **5d**

A mixture of compound **5c** (4.1 g, 7.93 mmol), ethyl 4-bromobutyrate (3.6 mL, 23.79 mmol) and K₂CO₃ (2.2 g, 15.86 mmol) in MeCN (80 mL) was refluxed for 16 hours. MeCN was removed, and the residue was partitioned between EtOAc and H₂O. The organic layer was washed with brine, dried over Na₂SO₄, concentrated and purified by column chromatography on silica gel with ethyl acetate/hexanes/triethylamine 400/600/7 to afford compound **5d** (2.5 g, 50%) as a yellowish syrup. MS (CI) *m/z* 632.2, 634.2 (MH⁺).

Step 5E: Preparation of 3-[2(R)-{hydroxycarbonylpropyl-amino}-2-phenylethyl]-5-(2-chlorophenyl)-1-[2-fluoro-6-(trifluoromethyl)benzyl]-pyrimidine-2,4(1H,3H)-dione **5-1**

To compound **5d** (2.4 g, 3.8 mmol) was added THF (30 mL) and H₂O (30 mL) followed by NaOH (1.588 g, 39.7 mmol). The mixture was stirred at 50 °C for 16 hours. THF was removed *in vacuo*, the aq. solution was washed with ether, and cooled at 0 °C. Neutralization with 10 % aq. citric acid (26.0 mL, 40.6 mmol) gave a precipitate, which was washed with H₂O and dried to give compound **5-1** (1.88 g, 82 %). HPLC-MS (CI) *m/z* 604.1, 606.1 (MH⁺), *t_R* = 2.511 (method 4), *t_R* = 26.98 (method 5)

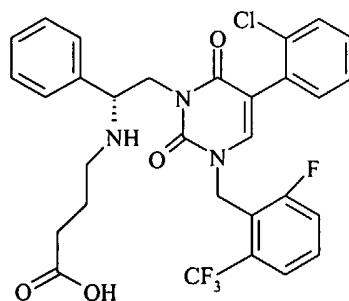
The following compounds were synthesized according to the above procedure.



No.	R _{1a}	R _{1b}	R _{2a}	MW	Mass	t _R (Method #)
5-1	Cl	H	CF ₃	604.00	604.1, 606.1	2.511 (4) 26.98 (5)
5-2	F	OCH ₃	CF ₃	617.57	618.2	2.482 (4) 25.45 (5)
5-3	cyano	H	CF ₃	594.56	594.9	5.548 (6)
5-4	F	CH ₃	CF ₃	601.57	602.2	6.144 (6)
5-5	Cl	CH ₃	CF ₃	618.02	617.9	5.104 (6)
5-6	F	H	CF ₃	587.54	588.2	5.172 (6)
5-7	F	OCH ₃	F	567.56	568.2	2.108 (4)
5-8	Cl	H	F	553.99	554.1	2.137 (4)
5-9	Cl	H	SO ₂ CH ₃	614.09	614.2	5.020 (6)
5-10	F	OCH ₃	SO ₂ CH ₃	627.66	628.2	1.178 (1)

EXAMPLE 6

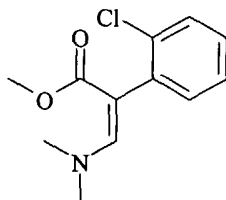
3-[2(R)-{HYDROXYCARBONYLPROPYL-AMINO}-2-PHENYLETHYL]-5-(2-CHLOROPHENYL)-
1-[2-FLUORO-6-(TRIFLUOROMETHYL)BENZYL]-PYRIMIDINE-2,4(1H,3H)-DIONE



Step 6A: Preparation of compound methyl (2-chlorophenyl)acetate 6a

To 2-chlorophenylacetic acid (1.04 g, 6mmol) in MeOH (25 mL) was added sulfuric acid (6 drops) and the solution was refluxed for 16 hours. After concentration, the residue was taken up in ethyl acetate and washed with sat'd aq. NaHCO₃, H₂O and brine. The organic layer was dried over Na₂SO₄ and concentrated to give methyl (2-chlorophenyl)acetate **6a** (1.08 g, 97.5 %) as a yellowish oil. GCMS (EI) *m/z* 184, 186 (M⁺).

Step 6B: Preparation of methyl 2-(2-chlorophenyl)-3-(dimethylamino)acrylate 6b



A solution of methyl (2-chlorophenyl)acetate **6a** (1.08 g, 5.85 mmol) in DMFDMA (10 mL, 70.8 mmol) was refluxed for 16 hours. After evaporation, the residue was purified by column chromatography on silica gel with ethyl acetate/hexanes 1/3 to 1/2 to afford unreacted methyl (2-chlorophenyl)acetate **6a** (0.67 g, 62 %) first, and then methyl 2-(2-chlorophenyl)-3-(dimethylamino)acrylate **6b** (0.38 g, 27 %; 71 % based on recovered starting material) as a colorless syrup. MS (CI) *m/z* 240.2, 242.2 (MH⁺).

Step 6C: Preparation of 5-(2-chlorophenyl)pyrimidine-2,4(1H,3H)-dione 6c

To a mixture of methyl 2-(2-chlorophenyl)-3-(dimethylamino)acrylate **6b** (0.26 g, 1.08 mmol), urea (0.2 g, 3.26 mmol) and NaI (0.49 g, 3.26 mmol) in acetonitrile (5 mL) was added TMSCl (0.41 mL, 3.26 mmol). The resulting mixture was refluxed for 16 hours, cooled to room temperature, and 1.0 M NaOH (8 mL) was added. The resultant solution was stirred for 20 hr, and acetonitrile was removed *in vacuo*. The aq. solution was washed with ether, cooled in ice bath, and neutralized with 1 N HCl (8 mL). The precipitate was filtered, washed with additional H₂O, and dried to

give 5-(2-chlorophenyl)pyrimidine-2,4(1*H*,3*H*)-dione **6c** (0.16 g, 66 %) as a white solid. MS (CI) *m/z* 222.9, 224.9 (MH⁺).

Step 6D: Preparation of 5-(2-chlorophenyl)-1-[2-fluoro-6-(trifluoromethyl)-benzyl]pyrimidine-2,4(1*H*,3*H*)-dione **6d**

5 To a suspension of 5-(2-chlorophenyl)pyrimidine-2,4(1*H*,3*H*)-dione **6c** (0.16 g, 0.72 mmol) in acetonitrile (5 mL) was added bis(trimethylsilyl)acetamide (0.36 mL, 1.44 mmol), and the resulting solution was refluxed for 1.5 hours. After cooling to room temperature, 2-fluoro-3-trifluoromethylbenzyl bromide (0.22 g, 0.86 mmol) was added, and reflux was resumed for 16 hours. The reaction was quenched by addition of
10 MeOH (5 mL) and stirring for 2 hours. After concentration, the residue was purified by column chromatography on silica gel with ethyl acetate/hexanes 1/1 to afford 5-(2-chlorophenyl)-1-[2-fluoro-6-(trifluoromethyl)benzyl]pyrimidine-2,4(1*H*,3*H*)-dione **6d** (0.25 g, 87 %) as a white solid. MS (CI) *m/z* 398.9, 400.9 (MH⁺).

Step 6E: Preparation of 3-[2(R)-{tert-butoxycarbonyl-amino}-2-phenylethyl]-5-(2-chlorophenyl)-1-[2-fluoro-6-(trifluoromethyl)benzyl]-pyrimidine-2,4(1*H*,3*H*)-dione **6e**

A mixture of 5-(2-chlorophenyl)-1-[2-fluoro-6-(trifluoromethyl)benzyl]pyrimidine-2,4(1*H*,3*H*)-dione **6d** (125 mg, 0.32 mmol), K₂CO₃ (130 mg, 0.96 mmol) and *N*-(*t*-butyloxycarbonyl)-*D*- α -phenylglycinol mesylate (0.2 g, 0.64 mmol) in DMF (3 mL) was heated at 75 °C for 16 hours. The reaction was diluted with ethyl acetate, washed with H₂O and brine, dried over Na₂SO₄ and concentrated. The residue was purified by column chromatography on silica gel with ethyl acetate/hexanes 2/3 to afford compound **6e** (144 mg, 74 %). MS (CI) *m/z* 518.0, 520.0 (MH⁺-Boc).

Step 6F: Preparation of 3-[2(R)-amino-2-phenylethyl]-5-(2-chlorophenyl)-1-[2-fluoro-6-(trifluoromethyl)benzyl]-pyrimidine-2,4(1H,3H)-dione 6f

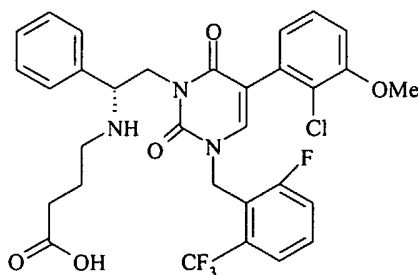
To a solution of compound **6e** (0.144 g, 0.23 mmol) in DCM (1 mL) was added TFA (0.5 mL, 6.5 mmol) and the mixture was stirred at room temperature for 1.5
 5 hours. After concentration, the residue was taken up in DCM and sat'd aq. NaHCO₃ was added. The aqueous layer was extracted with DCM. Combined organic extracts were dried over Na₂SO₄ and concentrated to give compound **6f** (0.12 g). MS (CI) *m/z* 518.0, 520.1 (MH⁺).

Step 6G: Preparation of 3-[2(R)-{hydroxycarbonylpropyl-amino}-2-phenylethyl]-5-(2-chlorophenyl)-1-[2-fluoro-6-(trifluoromethyl)benzyl]-pyrimidine-2,4(1H,3H)-dione 6-1

A solution of compound **6f** (0.1 g, 0.19 mmol) and succinic semialdehyde (15 wt % solution in water; 0.13 mL, 0.21 mmol) in MeCN was stirred at room temperature for 5 minutes. Borane pyridine complex (8 M; 72 μL) was added and
 15 stirred for 16 hours. After concentration, the residue was purified first on prep TLC plate, and then by prep LCMS to give compound **6-1**. HPLC-MS (CI) *m/z* 604.1, 606.1 (MH⁺), *t_R* = 26.98 (method 5), *t_R* = 2.511 (method 4)

EXAMPLE 7

3-[2(R)-{HYDROXYCARBONYLPROPYL-AMINO}-2-PHENYLETHYL]-5-(2-CHLORO-3-METHOXYPHENYL)-1-[2-FLUORO-6-(TRIFLUOROMETHYL)BENZYL]PYRIMIDINE-2,4(1H,3H)-DIONE



Step 7A: Preparation of 2-chloro-3-methoxybenzaldehyde 7a

To a suspension of 3-hydroxybenzaldehyde (20.12 g, 160 mmol) in HOAc (40 mL) was added carefully tBuOCl (20 mL, 176 mmol) with stirring. The reaction became a clear solution and strongly exothermic. It was allowed to cool and stirred for 16 hours, resulting in a white precipitate. The solid was filtered, washed with H₂O and dried to give 2-chloro-3-hydroxybenzaldehyde (13.77 g, 55 %), GCMS (EI) *m/z* 156, 158 (M⁺).

To a solution of 2-chloro-3-hydroxybenzaldehyde (4.55 g, 29 mmol) in DMF (30 mL) was added K₂CO₃ (4.8 g, 34.9 mmol) followed by MeI (2.7 mL, 43.6 mmol), and the mixture was stirred at room temperature for 16 hours. Following concentration *in vacuo*, the residual was taken up in ethyl acetate, washed with H₂O, brine, dried over Na₂SO₄, and concentrated. Purification by column chromatography on silica gel with ethyl acetate/hexanes 1/5 afforded 2-chloro-3-methoxybenzaldehyde 7a (4.68 g, 94 %) as a colorless oil, which solidified upon standing. GCMS (EI) *m/z* 170, 172 (M⁺).

Step 7B: Preparation of 2-chloro-1-methoxy-3-[2-(methylsulfinyl)-2-(methylsulfinyl)vinyl]benzene 7b

To a solution of 2-chloro-3-methoxybenzaldehyde 7a (4.65 g, 27.3 mmol) and methyl (methylthio)methyl sulfoxide (4.3 mL, 43.9 mmol) in THF (25 mL) was added a 40 % methanolic solution of Triton B (6.2 mL, 13.6 mmol) and the resulting solution was refluxed for 16 hours. After THF was removed, the residue was taken up in ethyl acetate, washed with 1 N HCl, H₂O, and brine, then was dried over Na₂SO₄, and concentrated. Purification by column chromatography on silica gel with dichloromethane afforded 2-chloro-1-methoxy-3-[2-(methylsulfinyl)-2-(methylsulfinyl)vinyl]benzene 7b (3.61 g, 48 %) as a yellow oil. GCMS (EI) *m/z* 225 (M⁺-Cl-16), 210 (M⁺-Cl-OMe).

Step 7C: Preparation of ethyl (2-chloro-3-methoxyphenyl)acetate 7c

To a solution of 2-chloro-1-methoxy-3-[2-(methylsulfanyl)-2-(methylsulfinyl)vinyl]benzene **7b** (3.58 g, 12.9 mmol) in ethanol (20 mL) was added a 5 M ethanolic solution of HCl (5.2 mL) and the resulting solution was refluxed for 3 hours. After evaporation, the residue was purified by column chromatography on silica gel with dichloromethane to afford ethyl (2-chloro-3-methoxyphenyl)acetate **7c** (2.78 g, 94 %) as a yellow oil. GCMS (EI) m/z 228, 230 (M^+).

Step 7D: Preparation of ethyl 2-(2-chloro-3-methoxyphenyl)-3-(dimethylamino)acrylate 7d

A solution of ethyl (2-chloro-3-methoxyphenyl)acetate **7c** (2.78 g, 12 mmol) in DMFDMA (16 mL, 120 mmol) was refluxed for 16 hours. After evaporation, the residue was purified by column chromatography on silica gel with ethyl acetate/hexanes 1/2 to 1/1 to afford unreacted ethyl (2-chloro-3-methoxyphenyl)acetate **7c** (1.8 g, 65 %) first, and then ethyl 2-(2-chloro-3-methoxyphenyl)-3-(dimethylamino)acrylate **7d** (1.1 g, 32 %; 90 % based on recovered starting material) as a yellow syrup. MS (CI) m/z 284.0, 286.0 (MH^+).

Step 7E: Preparation of 5-(2-chloro-3-methoxyphenyl)pyrimidine-2,4(1H,3H)-dione 7e

To a mixture of ethyl 2-(2-chloro-3-methoxyphenyl)-3-(dimethylamino)acrylate **7d** (1.7 g, 6 mmol), urea (1.08 g, 18 mmol) and NaI (2.7 g, 18 mmol) in acetonitrile (20 mL) was added TMSCl (2.3 mL, 18 mmol). The resulting mixture was refluxed for 16 hours, cooled to room temperature, and 1.0 M NaOH (30 mL) was added. The resultant solution was stirred for 20 hours, and acetonitrile was removed *in vacuo*. The aqueous solution was washed with ether, cooled in ice bath, and neutralized with 1 N HCl (30 mL). The precipitate was filtered, washed with additional H₂O, and dried to give 5-(2-chloro-3-methoxyphenyl)pyrimidine-2,4(1H,3H)-dione **7e** (1.24 g, 82 %) as a pale yellow solid. MS (CI) m/z 253.1, 255.1 (MH^+).

Step 7F: Preparation of 5-(2-chloro-3-methoxyphenyl)-1-[2-fluoro-6-(trifluoromethyl)benzyl]pyrimidine-2,4(1H,3H)-dione 7f

To a suspension of 5-(2-chloro-3-methoxyphenyl)pyrimidine-2,4(1H,3H)-dione **7e** (2.2 g, 8.7 mmol) in acetonitrile (25 mL) was added
5 bis(trimethylsilyl)acetamide (4.3 mL, 17.4 mmol), and the resulting solution was refluxed for 1.5 hours. The mixture was cooled to room temperature, 2-fluoro-3-trifluoromethylbenzyl bromide (2.7 g, 10.5 mmol) was added, and reflux was resumed for 16 hours. The reaction was quenched by addition of MeOH (25 mL) and stirring for 2 hours. After concentration, the residue was purified by column chromatography on
10 silica gel with ethyl acetate/hexanes 1/1 to afford 5-(2-chloro-3-methoxyphenyl)-1-[2-fluoro-6-(trifluoromethyl)benzyl]pyrimidine-2,4(1H,3H)-dione **7f** (3.3 g, 88 %) as a white solid. MS (CI) m/z 429.0, 431.0 (MH⁺).

Step 7G: Preparation of 3-[2(R)-(tert-butoxycarbonylamino)-2-phenylethyl]-5-(2-chloro-3-methoxyphenyl)-1-[2-fluoro-6-(trifluoromethyl)benzyl]pyrimidine-2,4(1H,3H)-dione 7g

A mixture of 5-(2-chloro-3-methoxyphenyl)-1-[2-fluoro-6-(trifluoromethyl)benzyl]pyrimidine-2,4(1H,3H)-dione **7f** (75 mg, 0.175 mmol), K₂CO₃ (72 mg, 0.525 mmol) and *N*-(*t*-butyloxycarbonyl)-*D*- α -phenylglycinol mesylate (0.11 g, 0.35 mmol) in DMF (2 mL) was heated at 75 °C for 16 hours. The reaction was diluted
20 with ethyl acetate, washed with H₂O and brine, dried over Na₂SO₄ and concentrated. The residue was purified by column chromatography on silica gel with ethyl acetate/hexanes 2/3 to afford compound **7g** (82 mg, 72 %) as a white solid. MS (CI) m/z 548.0, 550.0 (MH⁺-Boc).

Step 7H: Preparation of 3-[2(R)-amino-2-phenylethyl]-5-(2-chloro-3-methoxyphenyl)-1-[2-fluoro-6-(trifluoromethyl)benzyl]pyrimidine-2,4(1H,3H)-dione 7h

Compound **7g** (2.7 g, 4.2 mmol) was dissolved in dichloromethane (10 mL), TFA (14 mL, 175 mmol) was added, and the mixture was stirred at room

temperature for 4.5 hours. After concentration, the residue was taken up in DCM and saturated aqueous NaHCO₃ was added. The aq. layer was extracted with DCM. Combined organic extracts were dried over Na₂SO₄ and concentrated to give compound **7h** (2.2 g, 96 %). MS (CI) *m/z* 548.0, 550.0 (MH⁺).

- 5 3-[2(R)-amino-2-phenylethyl]-5-(2-chloro-3-methoxyphenyl)-1-[2, 6-difluorobenzyl]pyrimidine-2,4(1*H*,3*H*)-dione **7h.1** was prepared by substitution of the appropriate starting material using the procedures provided above.

Step 7I: Preparation of 3-[2(R)-{ethoxycarbonylpropyl-amino}-2-phenylethyl]-5-(2-chloro-3-methoxyphenyl)-1-[2-fluoro-6-(trifluoromethyl)benzyl]pyrimidine-

- 10 2,4(1*H*,3*H*)-dione **7i**

To a solution of compound **7h** (2.0 g, 3.65 mmol) in DMF (8 mL) was added Na₂CO₃ (0.47 g, 4.38 mmol) followed by ethyl 4-bromobutyrate (0.83 mL, 5.48 mmol). The mixture was heated at 95 °C for 1.5 hours, cooled to room temperature, and partitioned between ethyl acetate and H₂O. The organic layer was washed with
15 brine, dried over Na₂SO₄ and concentrated. The residue was purified by column chromatography on silica gel with ethyl acetate/hexanes/triethylamine 500/500/5 to afford compound **7i** (1.29 g) as a white solid. MS (CI) *m/z* 662.2, 664.2 (MH⁺)

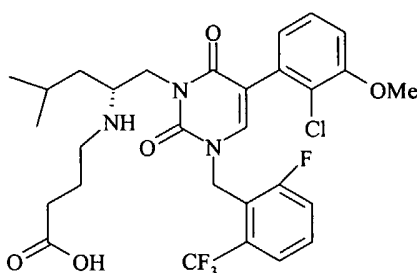
Step 7J: Preparation of 3-[2(R)-{hydroxycarbonylpropyl-amino}-2-phenylethyl]-5-(2-chloro-3-methoxyphenyl)-1-[2-fluoro-6-(trifluoromethyl)benzyl]pyrimidine-

- 20 2,4(1*H*,3*H*)-dione **7-1**

To compound **7i** (0.7 g, 1.06 mmol) was added THF (6 mL) and H₂O (6 mL) followed by NaOH (0.17 g, 4.24 mmol). The mixture was stirred at 50 °C for 16 hours. THF was removed *in vacuo*, the aq. solution was washed with ether, and cooled at 0 °C. Neutralization with 5 % aq. citric acid (6.0 mL, 4.7 mmol) gave a precipitate,
25 which was collected and further purified by column chromatography on silica gel with MeOH/DCM/triethylamine 8/100/2 to afford compound **7-1** (0.56 g, 84 %) as a white solid. HPLC-MS (CI) *m/z* 634.2, 636.2 (MH⁺), *t_R* = 24.925, (method 5)

EXAMPLE 8

3-[2(R)-{HYDROXYCARBONYLPROPYL-AMINO}-2-(ISOBUTYL)ETHYL]-5-(2-CHLORO-3-METHOXYPHENYL)-1-[2-FLUORO-6-(TRIFLUOROMETHYL)BENZYL]PYRIMIDINE-2,4(1H,3H)-DIONE



5

Step 8A: Preparation of 3-[2(R)-{tert-butoxycarbonyl-amino}-2-(isobutyl)ethyl]-5-(2-chloro-3-methoxyphenyl)-1-[2-fluoro-6-(trifluoromethyl)benzyl]pyrimidine-2,4(1H,3H)-dione 8a

To a solution of *N*-(*t*-butoxycarbonyl)-*D*- α -leucinol (1.21 g, 5.57 mmol) in pyridine (6 mL) was added tosyl chloride (1.6 g, 8.35 mmol). The reaction mixture was stirred at room temperature for 3 hours, diluted with EtOAc, and washed sequentially with 1 N HCl, H₂O, sat'd aq. NaHCO₃ and brine. The organic layer was dried over Na₂SO₄, concentrated and purified by column chromatography on silica gel with ethyl acetate/hexanes 1/3 to afford [3-methyl-1-[[[(4-methylphenyl)sulfonyl]oxy]methyl]butyl]-1,1-dimethylethyl carbamic ester (1.66 g, 80 %), MS (CI) *m/z* 272.2 (MH⁺-Boc).

A mixture of 5-(2-chloro-3-methoxyphenyl)-1-[2-fluoro-6-(trifluoromethyl)benzyl]pyrimidine-2,4(1H,3H)-dione **7f** (56 mg, 0.13 mmol), K₂CO₃ (754 mg, 0.39 mmol) and [3-methyl-1-[[[(4-methylphenyl)sulfonyl]oxy]methyl]butyl]-1,1-dimethylethyl carbamic ester (97 mg, 0.26 mmol) in DMF (2 mL) was heated at 95 °C for 16 hours. The reaction was diluted with ethyl acetate, washed with H₂O and brine, dried over Na₂SO₄ and concentrated. The residue was purified by column chromatography on silica gel with ethyl acetate/hexanes 1/1 to afford recovered [3-

methyl-1-[[[(4-methylphenyl)sulfonyl]oxy]methyl]butyl]-1,1-dimethylethyl carbamic ester (30 mg, 54 %) and compound **8a** (30 mg, 37 %), MS (CI) *m/z* 528.0, 530.0 (MH⁺-Boc).

Step 8B: Preparation of 3-[2(R)-amino-2-(isobutyl)ethyl]-5-(2-chloro-3-methoxyphenyl)-1-[2-fluoro-6-(trifluoromethyl)benzyl]pyrimidine-2,4(1H,3H)-dione **8b**

To a solution of compound **8a** (30 mg, 0.048 mmol) in DCM (1 mL) was added TFA (0.1 mL, 1.3 mmol) and stirred at room temperature for 1.5 hours. After concentration, the residue was taken up in DCM and sat'd aq. NaHCO₃ was added. The aq. layer was extracted with DCM. Combined organic extracts were dried over Na₂SO₄ and concentrated to give compound **8b**. MS (CI) *m/z* 528.0, 530.0 (MH⁺).

Step 8C: Preparation of 3-[2(R)-{ethoxycarbonylpropyl-amino}-2-(isobutyl)ethyl]-5-(2-chloro-3-methoxyphenyl)-1-[2-fluoro-6-(trifluoromethyl)benzyl]pyrimidine-2,4(1H,3H)-dione **8c**

To a solution of compound **8b** (25 mg, 0.048 mmol) in DMF (1 mL) was added K₂CO₃ (21 mg, 0.15 mmol) followed by ethyl 4-bromobutyrate (0.015 mL, 0.1mmol). The mixture was heated at 95 °C for 16 hours, cooled to room temperature, and partitioned between ethyl acetate and H₂O. The organic layer was washed with brine, dried over Na₂SO₄ and concentrated. The residue was purified by column chromatography on silica gel with ethyl acetate/hexanes/triethylamine 500/500/5 to afford compound **8c**. MS (CI) *m/z* 642.2, 644.2 (MH⁺).

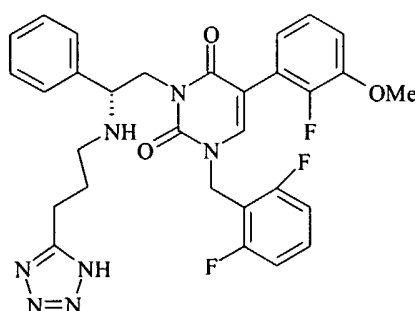
Step 8D: Preparation of 3-[2(R)-{hydroxycarbonylpropyl-amino}-2-(isobutyl)ethyl]-5-(2-chloro-3-methoxyphenyl)-1-[2-fluoro-6-(trifluoromethyl)benzyl]pyrimidine-2,4(1H,3H)-dione **8-1**

To compound **8c** (10 mg, 0.016 mmol) was added THF (0.3 mL) and H₂O (0.3 mL) followed by NaOH (6.4 mg, 0.16 mmol). The mixture was stirred at 50

°C for 16 hours, and purified by prep LCMS to give compound **8-1**. MS (CI) m/z 614.1, 616.1 (MH⁺), t_R = 6.550 min (method 6)

EXAMPLE 9

3-[2(R)-{2-[1-(5-TETRAZOYL)PROPYL]-AMINO}-2-PHENYLETHYL]-5-(2-FLUORO-3-METHOXYPHENYL)-1-[2, 6-DIFLUOROBENZYL]PYRIMIDINE-2,4(1*H*,3*H*)-DIONE



Step 9A: Preparation of 3-[2(R)-{2-[3-cyanopropyl]-amino}-2-phenylethyl]-5-(2-fluoro-3-methoxyphenyl)-1-[2, 6-difluorobenzyl]pyrimidine-2,4(1*H*,3*H*)-dione **9a**

A solution of **7h.1** (2.59 g, 5 mmol) in CH₃CN (25 mL) was added diisopropylethyl amine (2.61 mL, 15 mmol), followed by the addition of 4-bromobutyronitrile (2.22 g, 15 mmol). The reaction mixture was refluxed for 16 hours. Volatiles were evaporated and the residue was purified by flash chromatography (silica, 4 % MeOH/CH₂Cl₂) to give compound **9a** (2.62 g, 95.5 %). MS (CI) m/z 549.1 (MH⁺).

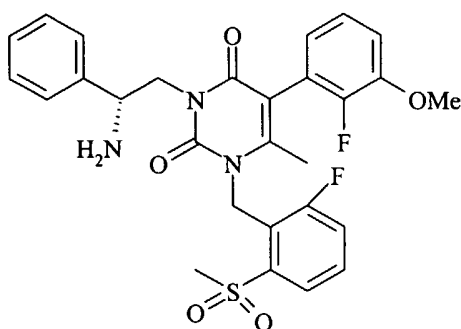
Step 9B: Preparation of 3-[2(R)-{2-[5-tetrazoylpropyl]-amino}-2-phenylethyl]-5-(2-fluoro-3-methoxyphenyl)-1-[2, 6-difluorobenzyl]pyrimidine-2,4(1*H*,3*H*)-dione **9-1**

A solution of **9a** (274 mg, 0.5 mmol) in DMF (5 mL) was added sodium azide (97 mg, 1.5 mmol) and ammonium chloride (120 mg, 2.25 mmol). The reaction mixture was heated at 110 °C for 12 hours. The mixture was cooled, partitioned between EtOAc and saturated NaHCO₃/water, washed with brine, dried (sodium sulfate), and evaporated. The residue was purified by flash chromatography (silica, 6 %

MeOH/CH₂Cl₂) to give compound **9-1** (52 mg, 17.6 %). HPLC-MS (CI) *m/z* 592.3 (MH⁺), *t_R* = 2.150, (method 4)

EXAMPLE 10

3-[2(R)-AMINO-2-PHENYLETHYL]-5-(2-FLUORO-3-METHOXYPHENYL)-1-[2-FLUORO-6-METHYLSULFONYLBENZYL]-6-METHYL-PYRIMIDINE-2,4(1*H*,3*H*)-DIONE



Step 10A: Preparation of 3-[2(R)-tert-butoxycarbonylamino-2-phenylethyl]-5-(2-fluoro-3-methoxyphenyl)-1-[2,6-difluorobenzyl]-6-methyl-pyrimidine-2,4(1*H*,3*H*)-dione **10a**

10 To a solution of compound **1f.1** (28 g, 56 mmol) in dichloromethane (200 mL) was added a solution of di-tert-butylidicarbonate (12 g, 56 mmol) in dichloromethane (100 mL) dropwise through an addition funnel. The reaction mixture was stirred at room temperature for 2 hours. The reaction mixture was concentrated by vacuum to yield the desired product **10a** as a light yellow solid (33 g, 56 mmol, 100%).

15 HPLC-MS (CI) *m/z* = 496.1 (M+H⁺ - Boc), *t_R* = 3.052 (method 4)

Step 10B: Preparation of 3-[2(R)-tert-butoxycarbonylamino-2-phenylethyl]-5-(2-fluoro-3-methoxyphenyl)-1-[2-fluoro-6-methylthiobenzyl]-6-methyl-pyrimidine-2,4(1*H*,3*H*)-dione **10b**

To a solution of compound **10a** (33 g, 56 mmol) in dry DMSO (100 mL)

20 was added sodium thiomethoxide (4.0 g, 56 mmol) under nitrogen. The reaction

mixture was heated to 100 °C under nitrogen for 1 hour. Another 0.28 eq. of sodium thiomethoxide (1.1 g, 16 mmol) was added, and the reaction mixture was heated to 100 °C under nitrogen for 1 hour. The reaction mixture was cooled and partitioned between ethyl ether and water. The organic layer was washed with saturated aqueous sodium bicarbonate solution and brine, dried with sodium sulfate, filtered and concentrated. The crude product was purified with a flash chromatography on silica gel eluted with 50 % ethyl acetate in hexane to yield compound **10b** as a pale yellow solid (27 g, 44 mmol, 78 %). HPLC-MS (CI) $m/z = 524.1$ ($M+H^+$ - Boc), $t_R = 3.134$ (method 4). 1H NMR ($CDCl_3$): 1.38 (s, 9H), 2.07 (s, 3H), 2.51 (s, 3H), 3.90 (s, 3H), 4.07 – 4.13 (m, 1H), 4.29 – 4.39 (m, 1H), 5.30 – 5.53 (m, 2H), 5.79 – 5.85 (m, 1H), 6.80 – 6.91 (m, 2H), 6.70 (dd, 1H), 7.06 – 7.15 (m, 2H), 7.22 – 7.41 (m, 6H).

Step 10C: Preparation of 3-[2(R)-tert-butoxycarbonylamino-2-phenylethyl]-5-(2-fluoro-3-methoxyphenyl)-1-[2-fluoro-6-methylsulfonylbenzyl]-6-methyl-pyrimidine-2,4(1H,3H)-dione **10c**

To a solution of compound **10b** (27 g, 44 mmol) in anhydrous dichloromethane (400 mL) was added 3-chloroperoxybenzoic acid (mCPBA, 30 g, 180 mmol). The reaction mixture was stirred at room temperature overnight. The reaction mixture was partitioned between dichloromethane and water. The organic layer was washed with saturated aqueous sodium bicarbonate solution and brine, dried with sodium sulfate, filtered and concentrated. The crude product was purified with a by chromatography on silica gel eluting with 50 % ethyl acetate in hexane to yield the desired product compound **10c** as a pale yellow solid (15 g, 24 mmol, 53 %). HPLC-MS (CI) $m/z = 556.0$ ($M+H^+$ - Boc), $t_R = 2.941$ (method 4). 1H NMR ($CDCl_3$): 1.38 (s, 9H), 2.27 (brs, 3H), 3.48 (s, 3H), 3.92 (s, 3H), 4.01 – 4.15 (m, 1H), 4.24 – 4.40 (m, 1H), 4.95 – 5.05 (m, 1H), 5.58 – 5.68 (m, 2H), 6.85 – 6.91 (dd, 1H), 7.02 (dd, 1H), 7.14 (d, $J = 7.6$ Hz, 1H), 7.19 – 7.55 (m, 7H), 7.97 (d, $J = 7.6$ Hz, 1H).

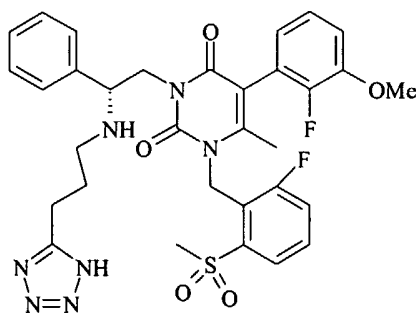
Step 10D: Preparation of 3-[2(R)-amino-2-phenylethyl]-5-(2-fluoro-3-methoxyphenyl)-1-[2-fluoro-6-methylsulfonylbenzyl]-6-methyl-pyrimidine-2,4(1H,3H)-dione **10-1**

To a solution of compound **10c** (10 g, 15 mmol) in anhydrous dichloromethane (60 mL) was added trifluoroacetic acid (TFA, 16 mL). The reaction mixture was stirred at room temperature for 4 hours. The reaction mixture was concentrated, and partitioned between ethyl acetate and diluted aqueous NaOH solution. The organic layer was washed with saturated aqueous sodium bicarbonate solution and brine, dried with sodium sulfate, filtered and concentrated to yield **10-1** as a tan solid (8.0 g, 14 mmol, 94 %). HPLC-MS (CI) $m/z = 556.2$ ($M+H^+$), $t_R = 2.354$ (method 4). 1H NMR ($CDCl_3$): 2.25 (s, 3H), 3.42 (s, 1.5H), 3.43 (s, 1.5H), 3.91 (s, 1.5H), 3.92 (s, 1.5H), 3.98 – 4.22 (m, 2H), 4.33 – 4.38 (m, 1H), 5.60 (brs, 2H), 6.80 – 6.89 (m, 1H), 6.97 – 7.03 (m, 1H), 7.11 – 7.17 (m, 1H), 7.22 – 7.37 (m, 6H), 7.46 – 7.54 (m, 1H), 7.95 (dd, 1H).

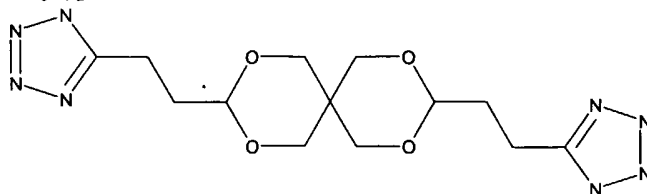
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EXAMPLE 11

3-[2(R)-{2-[1-(5-TETRAZOYL)PROPYL]-AMINO}-2-PHENYLETHYL]-5-(2-FLUORO-3-METHOXYPHENYL)-1-[2-FLUORO-6-METHYLSULFONYLBENZYL]-6-METHYLPYRIMIDINE-2,4(1H,3H)-DIONE



Step 11A: Preparation of 5,5'-[2,4,8,10-tetraoxaspiro[5.5]undecane-3,9-diylbis(ethane-2,1-diyl)]bis-1*H*-tetrazole



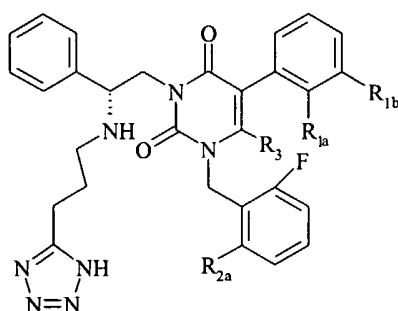
3,9-bis(2-Cyanoethyl)-2,4,8,10-tetraoxaspiro[5.5]undecane (5.38 g , 20
 5 mmol), azidotrimethylsilane (10.6 mL, 80 mmol), and dibutyl tin oxide (2.48 g, 4
 mmol) were suspended in 40 mL toluene and 40 mL dioxane and heated at reflux for 18
 hours. The reaction was cooled to room temperature and diluted with 100 mL hexane.
 The solid precipitate was collected, washed with hexane (2 x 30 mL) and dried in air.
 The solid was suspended in 100 mL 5 % sodium carbonate solution, enough ethyl
 10 acetate was added to dissolve most of the solid, and the mixture was stirred for 1 hour.
 The layers were separated, the aqueous layer was washed with ethyl acetate (2 x 100
 mL), and the organic layers were back extracted with 5 % sodium carbonate (1 x 50
 mL). The aqueous layers were combined, acidified to pH 7 with concentrated
 hydrochloric acid, filtered through Celite, and acidified to pH 3. The solid was
 15 collected, washed with water (2 x 50 mL) and acetone (2 x 50 mL) and dried under
 vacuum to give 5,5'-[2,4,8,10-tetraoxaspiro[5.5]undecane-3,9-diylbis(ethane-2,1-
 diyl)]bis-1*H*-tetrazole **11a** (4.71 g, 67%). ¹H NMR (300 MHz, DMSO-d₆) δ 4.56 (t,
 2H, *J* = 5 Hz), 4.28 (dd, 2H, *J* = 9, 2 Hz), 3.58 (d, 2H, *J* = 11 Hz), 3.57 (dd, 2H, *J* =
 11, 2 Hz), 3.36 (d, 2H, *J* = 11 Hz), 2.94 (t, 4H, *J* = 7.5 Hz), 1.97 (dt, 4H, *J* = 8, 4 Hz).

20 Step 11B: Preparation of 3-[2(R)-{2-[1-(5-tetrazoyl)propyl]-amino}-2-
 phenylethyl]-5-(2-fluoro-3-methoxyphenyl)-1-[2-fluoro-6-methylsulfonylbenzyl]-6-
 methylpyrimidine-2,4(1*H*,3*H*)-dione **11-1**

A 25 mg sample of 5,5'-[2,4,8,10-tetraoxaspiro[5.5]undecane-3,9-
 diylbis(ethane-2,1-diyl)]bis-1*H*-tetrazole **11a** (70 μmol) and p-toluenesulfonic acid (20
 25 mg, 100 μmol) were suspended in 1 mL of water and heated at 80 °C for 18 hours. The
 solution was cooled and added to compound **10-1** (29 mg, 50 μmol) dissolved in 1mL
 ethanol and 17 uL triethylamine (100 μmol)..) Borane-pyridine complex (24 μL, 240

μmol) was then added and the mixture stirred 0.25 hours until bubbling ceased. The volatiles were removed and the residue taken up in 2 mL ethyl acetate and washed with water (1 x 0.5 mL). The ethyl acetate layer was evaporated and purified by preparative LC/MS to give 11-1 (5 mg, 12 % yield).

- 5 The following compounds were synthesized according to the above procedure.



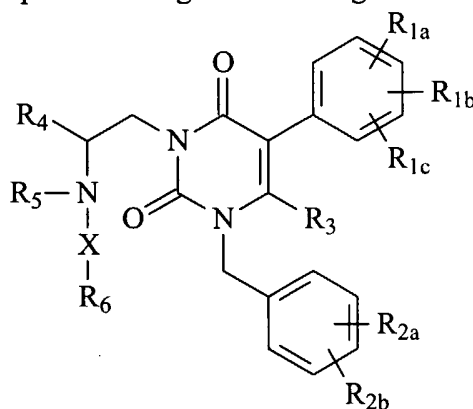
No.	R _{1a}	R _{1b}	R _{2a}	R ₃	MW	Mass	t _R (Method #)
11-1	F	OMe	SO ₂ Me	CH ₃	665.7	666.2	20.92 (5)
11-2	Cl	H	CF ₃	H	628.0	628.2	27.34 (5)
11-3	F	OMe	F	CH ₃	605.6	606.2	24.19 (5)
11-4	F	OMe	CF ₃	CH ₃	655.6	656.2	2.540 (4)

- 10 It will be appreciated that, although specific embodiments of the invention have been described herein for purposes of illustration, various modifications may be made without departing from the spirit and scope of the invention. Accordingly, the invention is not limited except as by the appended claims.

CLAIMS

We claim:

1. A compound having the following structure:



(I)

or a stereoisomer, prodrug or pharmaceutically acceptable salt thereof,

wherein:

R_{1a} , R_{1b} and R_{1c} are the same or different and independently hydrogen, halogen, C_{1-4} alkyl, hydroxy or alkoxy, or R_{1a} and R_{1b} taken together form $-OCH_2O-$ or $-OCH_2CH_2-$;

R_{2a} and R_{2b} are the same or different and independently hydrogen, halogen, trifluoromethyl, cyano or $-SO_2CH_3$;

R_3 is hydrogen or methyl;

R_4 is phenyl or C_{3-7} alkyl;

R_5 is hydrogen or C_{1-4} alkyl;

R_6 is $-COOH$ or an acid isostere; and

X is C_{1-6} alkanediyl optionally substituted with from 1 to 3 C_{1-6} alkyl groups.

2. The compound of claim 1 wherein R_{1a} is halogen.
3. The compound of claim 1 wherein R_{1b} is alkoxy.

4. The compound of claim 3 wherein R_{1b} is methoxy.
5. The compound of claim 1 wherein R_{1c} is halogen.
6. The compound of claim 5 wherein R_{1c} is fluoro or chloro.
7. The compound of claim 1 wherein R_{2a} is halogen.
8. The compound of claim 1 wherein R_{2b} is hydrogen, halogen or -SO₂CH₃.
9. The compound of claim 1 wherein R₃ is hydrogen.
10. The compound of claim 1 wherein R₃ is methyl.
11. The compound of claim 1 wherein R₄ is phenyl.
12. The compound of claim 1 wherein R₄ is C₃₋₇alkyl.
13. The compound of claim 12 wherein C₃₋₇alkyl is cyclopentyl or cyclohexyl.
14. The compound of claim 1 wherein R₅ is H or methyl.
15. The compound of claim 1 wherein R₆ is -COOH.
16. The compound of claim 1 wherein R₆ is an acid isostere.
17. The compound of claim 16 wherein the acid isostere is tetrazol-5-yl.

18. The compound of claim 1 wherein X is a straight chain C₁₋₆alkanediyl.
19. The compound of claim 18 wherein the straight chain C₁₋₆alkanediyl is -CH₂CH₂CH₂-.
20. The compound of claim 19 wherein R₄ is phenyl.
21. The compound of claim 20 wherein R_{1a} and R_{2a} are halogen.
22. The compound of claim 21 wherein R₃ is methyl.
23. The compound of claim 21 wherein R₃ is hydrogen.
24. The compound of claim 1 wherein X is a branched C₁₋₆alkanediyl.
25. The compound of claim 1 wherein the compound is 3-[2(R)-{hydroxycarbonylpropyl-amino}-2-phenylethyl]-5-(2-fluoro-3-methoxyphenyl)-1-[2-fluoro-6-(trifluoromethyl)benzyl]-6-methyl-pyrimidine-2,4(1H,3H)-dione, 3-[2(R)-{hydroxycarbonylpropyl-amino}-2-phenylethyl]-5-(3-isopropylphenyl)-1-[2-fluoro-6-(trifluoromethyl)benzyl]-6-methyl-pyrimidine-2,4(1H,3H)-dione, 3-[2(R)-{hydroxycarbonylpropyl-amino}-2-(cyclohexyl)ethyl]-5-(2-fluoro-3-methoxyphenyl)-1-[2-fluoro-6-(trifluoromethyl)benzyl]-6-methyl-pyrimidine-2,4(1H,3H)-dione, or 3-[2(R)-{2-[1-(5-tetrazoyl)propyl]-amino}-2-phenylethyl]-5-(2-fluoro-3-methoxyphenyl)-1-[2-fluoro-6-methylsulfonylbenzyl]-6-methylpyrimidine-2,4(1H,3H)-dione.
26. The compound of claim 1 wherein the compound is 3-[2(R)-{hydroxycarbonylpropyl-amino}-2-phenylethyl]-5-(2-chlorophenyl)-1-[2-fluoro-6-(trifluoromethyl)benzyl]-pyrimidine-2,4(1H,3H)-dione, 3-[2(R)-{hydroxycarbonylpropyl-amino}-2-phenylethyl]-5-(2-fluoro-3-methoxyphenyl)-1-[2-fluoro-6-(trifluoromethyl)benzyl]-pyrimidine-2,4(1H,3H)-dione, 3-[2(R)-{hydroxycarbonylpropyl-

amino}-2-phenylethyl]-5-(2-chloro-3-methylphenyl)-1-[2-fluoro-6-(trifluoromethyl)benzyl]-pyrimidine-2,4(1H,3H)-dione, 3-[2(R)-{hydroxycarbonylpropyl-amino}-2-phenylethyl]-5-(2-chlorophenyl)-1-[2-fluoro-6-(methylsulfonyl)benzyl]-pyrimidine-2,4(1H,3H)-dione, 3-[2(R)-{hydroxycarbonylpropyl-amino}-2-phenylethyl]-5-(2-chloro-3-methoxyphenyl)-1-[2-fluoro-6-(trifluoromethyl)benzyl]-pyrimidine-2,4(1H,3H)-dione, or 3-[2(R)-{hydroxycarbonylpropyl-amino}-2-(isobutyl)ethyl]-5-(2-chloro-3-methoxyphenyl)-1-[2-fluoro-6-(trifluoromethyl)benzyl]-pyrimidine-2,4(1H,3H)-dione.

27. A pharmaceutical composition comprising a compound of claim 1 and a pharmaceutically acceptable carrier or diluent.

28. A method for antagonizing gonadotropin-releasing hormone in a subject in need thereof, comprising administering to the subject an effective amount of a compound of claim 1.

29. A method for treating a sex-hormone related condition of a subject in need thereof, comprising administering to the subject an effective amount of the pharmaceutical composition of claim 27.

30. The method of claim 29 wherein the sex-hormone related condition is cancer, benign prostatic hypertrophy or myoma of the uterus.

31. The method of claim 30 wherein the cancer is prostatic cancer, uterine cancer, breast cancer or pituitary gonadotroph adenomas.

32. The method of claim 31 wherein the cancer is prostatic cancer.

33. The method of claim 29 wherein the sex-hormone related condition is endometriosis, polycystic ovarian disease, uterine fibroids or precocious puberty.

34. The method of claim 33 wherein the sex-hormone related condition is endometriosis.

35. The method of claim 29 wherein the sex-hormone related condition is uterine fibroids.

36. A method for treating infertility of a subject in need thereof, comprising administering to the subject an effective amount of the pharmaceutical composition of claim 27.

37. A method for treating lupus erythematosus, irritable bowel syndrome, premenstrual syndrome, hirsutism, short stature or sleep disorders of a subject in need thereof, comprising administering to the subject an effective amount of the pharmaceutical composition of claim 27.

INTERNATIONAL SEARCH REPORT

International Application No

.../US2004/021593

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/513 C07D239/54 C07D401/12 C07D405/04 A61P5/02

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D

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, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 01/55119 A (STRUTHERS R SCOTT ; CHEN CHEN (US); TUCCI FABIO C (US); ZHU YUN FEI (U) 2 August 2001 (2001-08-02) claims 1,39	1-37
A	ZHU ET AL.: "Identification of 1-arylmethyl-3-(2-aminoethyl)-5-aryluracil as novel gonadotropin-releasing hormone receptor antagonists" JOURNAL OF MEDICINAL CHEMISTRY, vol. 46, 2003, pages 2023-2026, XP002307123 the whole document	1-37

 Further documents are listed in the continuation of box C. Patent family members are listed in annex.

* Special categories of cited documents:

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

E earlier document but published on or after the international filing date

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

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

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

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

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

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

& document member of the same patent family

Date of the actual completion of the international search

23 November 2004

Date of mailing of the international search report

06/12/2004

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Authorized officer

Bérillon, L

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2004/021593

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: 28-37
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 28-37 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
- No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

US2004/021593

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0155119	A	02-08-2001	
		AU 767585 B2	20-11-2003
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