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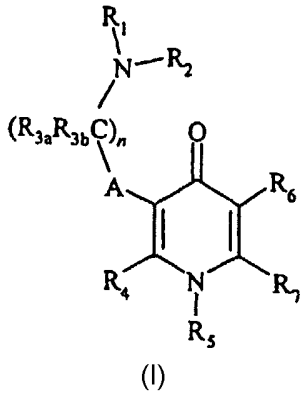
(54) Title: SUBSTITUTED PYRIDIN-4-ONES AND THEIR USE AS GONADOTROPIN-RELEASING HORMONE RECEPTOR ANTAGONISTS.



(I)

(57) Abstract: GnRH receptor antagonists of formula (I) are disclosed which have utility in the treatment of a variety of sex-hormone related conditions in both men and women. 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, including stereosomers, prodrugs and pharmaceutically acceptable salts thereof, wherein: A is O or a bond; n is 1, 2, 3 or 4; R_1 and R_2 are the same or different and independently hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heterocycle, substituted heterocycle, heterocyclealkyl, susbstituted heterocyclealkyl, $-C(R_8)(=NR_9)$ or $-C(NR_{10}R_{11})(=NR_9)$; or R_1 and R_2 taken together with the nitrogen atom to which they are attached form a heterocycle or a substituted heterocycle; R_{3a} and R_{3b} are the same or different and, at each occurrence, independently hydrogen, alkyl, substituted alkyl, alkoxy, alkylthio, alkylamino, aryl, substituted aryl, arylakyl, substituted arylalkyl, heterocycle, substituted heterocycle, heterocyclealkyl, substituted heterocyclealkyl, $-COOR_{12}$ or $-CONR_{10}R_{11}$; or R_{3ab} and R_{3b} taken together with the carbon atom to which they are attached form a homocycle, substituted homocycle, heterocycle or substituted heterocycle; or R_{3a} and the carbon to which it is attached taken together with R_1 and the nitrogen to which it is attached form a heterocycle or substituted heterocycle; R_4 is hydrogen, alkyl or substituted alkyl; R_5 is arylalkyl, substituted arylalkyl, heteroarylalkyl or substituted heteroalalkyl; R_6 is aryl, substituted aryl, heteroaryl or substituted heteroaryl; R_7 is hydrogen, alkyl or substituted alkyl; R_8, R_9, R_{10} and R_{11} are the same or different and, at each occurrence, independently hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heterocycle, substituted heterocycle, heterocyclealkyl or substituted heterocyclealkyl, and R_{12} is hydrogen, alkyl or substituted alkyl.

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GONADOTROPIN-RELEASING HORMONE RECEPTOR ANTAGONISTS AND METHODS RELATING THERETO

STATEMENT OF GOVERNMENT INTEREST

Partial funding of the work described herein was provided by the U.S. Government under Grant No. R43-HD38625 provided by the National Institute 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-NH_2) 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, and precocious puberty. 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 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).

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 reported, although they still must be delivered via sustained delivery routes (such as subcutaneous injection or intranasal spray) due to limited bioavailability.

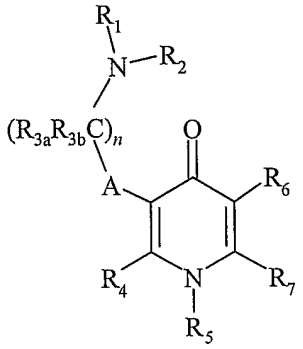
In view of the limitations associated with peptidic GnRH antagonists, a number of nonpeptidic compounds have been proposed. For example, Cho et al. (*J. Med. Chem. 41*:4190-4195, 1998) discloses thieno[2,3-*b*]pyridin-4-ones for use as GnRH receptor antagonists; U.S. Patent Nos. 5,780,437 and 5,849,764 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 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.

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.

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 A, R_1, R_2, R_{3a}, R_{3b}, R_4, R_5, R_6, R_7 and n 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 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 erythematosis. The compounds are also useful in combination with androgens, estrogens, progesterones, and antiestrogens and 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

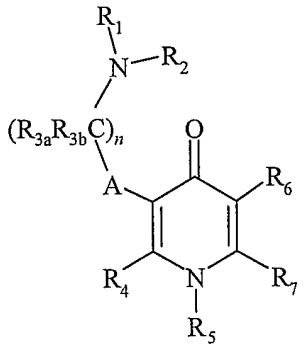
bone metabolism, and in combination with estrogens, progesterones and/or androgens for the prevention or treatment of bone loss or hypogonadal symptoms such as hot flashes during therapy with a GnRH antagonist.

The 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.

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):



(I)

including stereoisomers, prodrugs and pharmaceutically acceptable salts thereof,

wherein:

A is O or a bond;

n is 1, 2, 3 or 4;

R_1 and R_2 are the same or different and independently hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heterocycle,

substituted heterocycle, heterocyclealkyl, substituted heterocyclealkyl, $-C(R_8)(=NR_9)$ or $-C(NR_{10}R_{11})(=NR_9)$;

or R_1 and R_2 taken together with the nitrogen atom to which they are attached form a heterocycle or a substituted heterocycle;

R_{3a} and R_{3b} are the same or different and, at each occurrence, independently hydrogen, alkyl, substituted alkyl, alkoxy, alkylthio, alkylamino, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heterocycle, substituted heterocycle, heterocyclealkyl, substituted heterocyclealkyl, $-COOR_{12}$ or $-CONR_{10}R_{11}$;

or R_{3a} and R_{3b} taken together with the carbon atom to which they are attached form a homocycle, substituted homocycle, heterocycle or substituted heterocycle;

or R_{3a} and the carbon to which it is attached taken together with R_1 and the nitrogen to which it is attached form a heterocycle or substituted heterocycle;

R_4 is hydrogen, alkyl or substituted alkyl;

R_5 is arylalkyl, substituted arylalkyl, heteroarylalkyl or substituted heteroarylalkyl;

R_6 is aryl, substituted aryl, heteroaryl or substituted heteroaryl;

R_7 is hydrogen, alkyl or substituted alkyl;

R_8, R_9, R_{10} and R_{11} are the same or different and, at each occurrence, independently hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heterocycle, substituted heterocycle, heterocyclealkyl or substituted heterocyclealkyl; and

R_{12} is hydrogen, alkyl or substituted alkyl.

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

"Alkyl" means a straight chain or branched, noncyclic or cyclic, unsaturated or saturated aliphatic hydrocarbon containing from 1 to 10 carbon atoms, while the term "lower alkyl" has the same meaning as alkyl but contains from 1 to 6 carbon atoms. The term "higher alkyl" has the same meaning as alkyl but contains from 2 to 10 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 alkyls include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and the like; while unsaturated cyclic alkyls include cyclopentenyl and cyclohexenyl, and the like. Cyclic alkyls are also referred to herein as a "homocycles" or "homocyclic rings." 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, 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.

"Aryl" means an aromatic carbocyclic moiety such as phenyl or naphthyl.

"Arylalkyl" means an alkyl having at least one alkyl hydrogen atoms replaced with an aryl moiety, such as benzyl, $-(CH_2)_2$phenyl, $-(CH_2)_3$phenyl, $-CH(phenyl)_2$, and the like.

"Heteroaryl" means an aromatic heterocycle ring of 5- to 10 members and having at least one heteroatom selected from nitrogen, oxygen and sulfur, and containing at least 1 carbon atom, including both mono- and bicyclic ring systems. Representative heteroaryls are furyl, benzofuranyl, thiophenyl, benzothiophenyl, pyrrolyl, indolyl, isoindolyl, azaindolyl, pyridyl, quinolinyl, isoquinolinyl, oxazolyl, isooxazolyl, benzoxazolyl, pyrazolyl, imidazolyl, benzimidazolyl, thiazolyl, benzothiazolyl, isothiazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, cinnolinyl, phthalazinyl, and quinazolinyl.

"Heteroarylalkyl" means an alkyl having at least one alkyl hydrogen atom replaced with a heteroaryl moiety, such as $-CH_2$pyridinyl, $-CH_2$pyrimidinyl, and the like.

"Heterocycle" (also referred to herein as a "heterocyclic ring") means a 4- to 7-membered monocyclic, or 7- to 10-membered bicyclic, heterocyclic ring which is either saturated, unsaturated, or aromatic, and which contains from 1 to 4 heteroatoms independently selected from nitrogen, oxygen and sulfur, and wherein the nitrogen and

sulfur heteroatoms may be optionally oxidized, and the nitrogen heteroatom may be optionally quaternized, including bicyclic rings in which any of the above heterocycles are fused to a benzene ring. The heterocycle may be attached via any heteroatom or carbon atom. Heterocycles include heteroaryls as defined above. Thus, in addition to the heteroaryls listed above, heterocycles also include morpholinyl, pyrrolidinonyl, pyrrolidinyl, piperidinyl, hydantoinyl, valerolactamyl, oxiranyl, oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, tetrahydropyridinyl, tetrahydroprimidinyl, tetrahydrothiophenyl, tetrahydrothiopyranyl, tetrahydropyrimidinyl, tetrahydrothiophenyl, tetrahydrothiopyranyl, and the like.

"Heterocyclealkyl" means an alkyl having at least one alkyl hydrogen atom replaced with a heterocycle, such as -CH_2morpholinyl, and the like.

"Homocycle" (also referred to herein as "homocyclic ring") means a saturated or unsaturated (but not aromatic) carbocyclic ring containing from 3-7 carbon atoms, such as cyclopropane, cyclobutane, cyclopentane, cyclohexane, cycloheptane, cyclohexene, and the like.

The term "substituted" as used herein means any of the above groups (*i.e.*, alkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, homocycle, heterocycle and/or heterocyclealkyl) wherein at least one hydrogen atom is replaced with a substituent. In the case of an oxo substituent ("=O") two hydrogen atoms are replaced. When substituted one or more of the above groups are substituted, "substituents" within the context of this invention include halogen, hydroxy, oxo, cyano, nitro, amino, alkylamino, dialkylamino, alkyl, alkoxy, alkylthio, haloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocycle and heterocyclealkyl, as well as -NR_aR_b, -$NR_aC(=O)R_b$, -$NR_aC(=O)NR_aNR_b$, -$NR_aC(=O)OR_b$ -$NR_aSO_2R_b$, -$C(=O)R_a$, -$C(=O)OR_a$, -$C(=O)NR_aR_b$, -$OC(=O)NR_aR_b$, -OR_a, -SR_a, -SOR_a, -$S(=O)_2R_a$, -$OS(=O)_2R_a$ and -$S(=O)_2OR_a$. In addition, the above substituents may be further substituted with one or more of the above substituents, such that the substituent substituted alky, substituted aryl, substituted arylalkyl, substituted heterocycle or substituted heterocyclealkyl. R_a and R_b in this context may be the same or different and independently hydrogen, alkyl, haloalkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heterocycle, substituted heterocycle, heterocyclealkyl or substituted heterocyclealkyl.

"Halogen" means fluoro, chloro, bromo and iodo.

"Haloalkyl" means an alkyl having at least one hydrogen atom replaced with halogen, such as trifluoromethyl and the like.

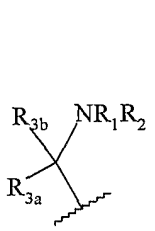
"Alkoxy" means an alkyl moiety attached through an oxygen bridge (*i.e.*, -O-alkyl) such as methoxy, ethoxy, and the like.

"Alkylthio" means an alkyl moiety attached through a sulfur bridge (*i.e.*, -S-alkyl) such as methylthio, ethylthio, and the like.

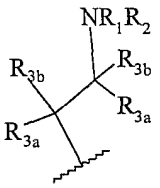
"Alkylsulfonyl" means an alkyl moiety attached through a sulfonyl bridge (*i.e.*, -SO_2-alkyl) such as methylsulfonyl, ethylsulfonyl, and the like.

"Alkylamino" and "dialkylamino" mean one or two alkyl moiety attached through a nitrogen bridge (*i.e.*, -N-alkyl) such as methylamino, ethylamino, dimethylamino, diethylamino, and the like.

With regard to the "$R_1R_2N(CR_{3a}R_{3b})_n$-" moiety of structure (I), *n* may be 1, 2, 3 or 4. Accordingly, this moiety may be represented by the following structure (i) when *n* is 1, (ii) when *n* is 2, structure (iii) when *n* is 3, and structure (iv) when *n* is 4:



(i)



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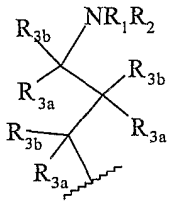
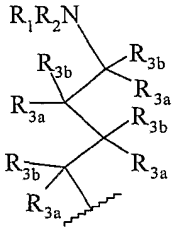


(iii)

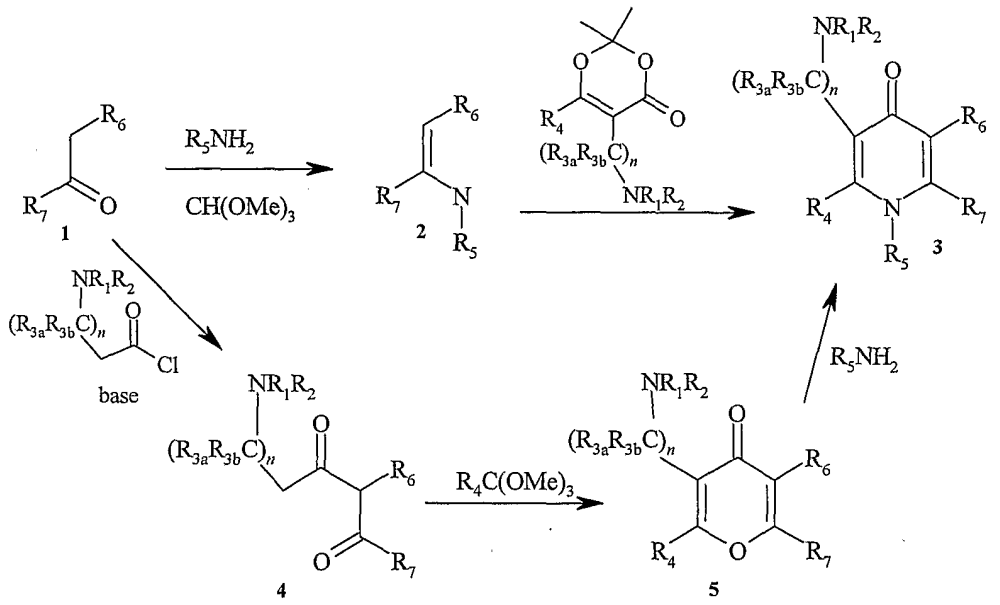


(iv)

wherein each occurrence of R_{3a} and R_{3b} above may be the same or different, and are as defined above. For example, when each occurrence of R_{3a} and R_{3b} in structures (i), (ii) (iii) and (iv) is hydrogen, the "$R_1R_2N(CR_{3a}R_{3b})_n$-" moiety has the structure $R_1R_2N(CH_2)$-, $R_1R_2N(CH_2)_2$-, $R_1R_2N(CH_2)_3$- and $R_1R_2N(CH_2)_4$-, respectively.

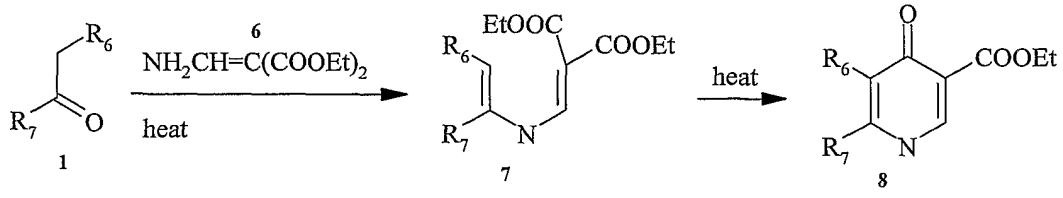
The compounds of the present invention may be prepared by known organic synthesis techniques, including the methods described in more detail in the Examples. However in general, the compounds of structure (I) above may be made by the following Reaction Schemes. All substituents in the following Reaction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

Reaction Scheme A



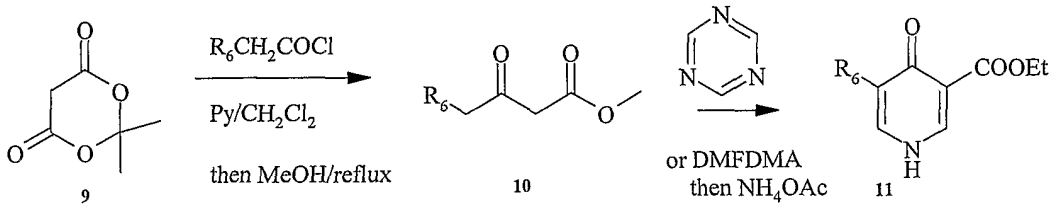
Ketone or aldehyde 1 and an amine are dissolved neat or with a cosolvent in an alkylorthoformate at a temperature of 0 – 50 °C for 12 to 36 hours to give enamine 2. Compound 2 in the presence of a substituted dioxinone in a protic solvent at elevated or reflux temperature for 1 – 12 hours gives product 3. Alternatively, compound 1 may be alkylated with a substituted acyl halide in the presence of a base such as sodium hydride or potassium t-butoxide in a solvent such as THF or dioxane for 1 – 24 hours at 0 to 50 °C to give 4. 4 in the presence of a substituted alkyl orthoester in a protic solvent at reflux for 1 – 24 hours gives 5. 5 and a primary amine, neat or in an inert solvent such as DMF or DMSO, are heated at an elevated temperature or at reflux temperature for 1-24 hours to give compound 3. (T. T. Tidwell, J. Org. Chem., 1998, 63, 8636)

Reaction Scheme B



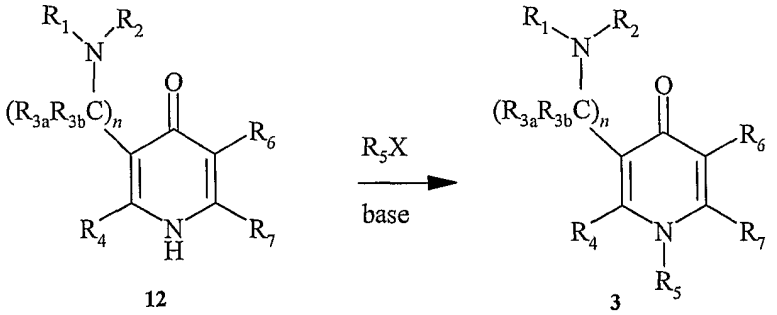
Compound 1 in the presence of a substituted aminocrotonate 6 is heated to 75-150 °C in a solvent such as toluene to give aminocrotonate 7 which cyclizes upon heating to give 8. (T. Kametani, J. Heterocycl. Chem., 1977, 477)

Reaction Scheme C



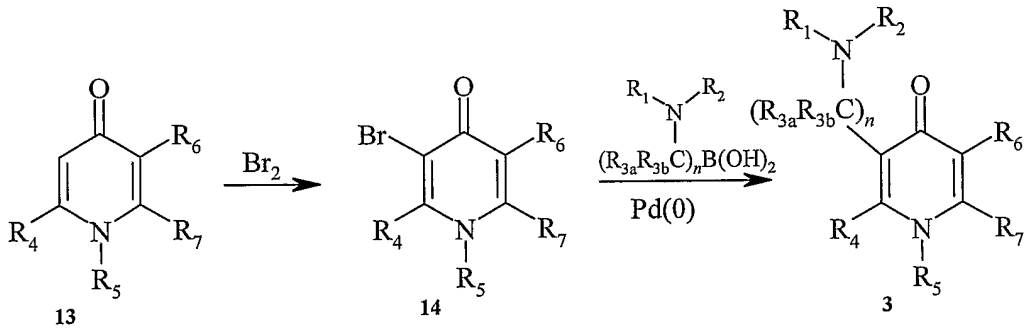
Meldrum's acid 9 and a substituted acetyl halide in the presence of a base such as TEA or pyridine in a solvent such as THF or dichloromethane is stirred for 1 – 24 hours at a temperature of 20 – 75 °C. The reaction mix is evaporated and following a quick workup, the residue is refluxed in an alcohol to give β-keto ester 10. Compound 10 in the presence of triazine or DMFDMA followed by ammonium acetate gives compound 11. Use of a primary amine in place of ammonium acetate gives 11 with a substitution on the nitrogen. (M. Balogh, J. Heterocycl. Chem., 1980, 359; R. Kiyama, Chem. Pharm. Bull., 1995, 43, 450)

Scheme D



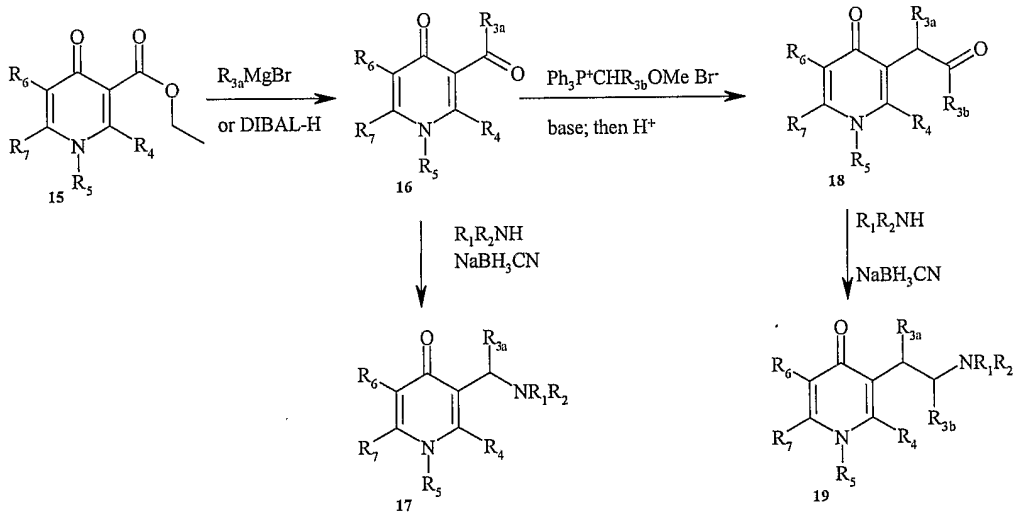
Pyridone 12 is alkylated with an alkyl halide in the presence of a base such as sodium hydride or potassium carbonate in a solvent such as DMF or acetonitrile at 0 to 50 °C for 1 – 24 hours to give alkylated compound 3.

Scheme E



Pyridone 13 may be halogenated using bromine/acetic acid, ICl in chloroform, or NIS or NBS in a solvent such as chloroform at 0 – 50 °C for 1-24 hours to give 14. Compound 14 and an appropriate boronic acid undergoes a Suzuki coupling to give compound 3.

Scheme F



Pyridone ester 15 and a Grignard reagent at –78 °C in ether or THF for ¼ to 4 hours, or using DIBAL-H at –78 °C for approximately 2 hours in THF or ether gives 16. Reductive amination of 16 with a primary or secondary amine using a reagent such as sodium cyanoborohydride or sodium triacetoxyborohydride at 0 – 50 °C in an aprotic solvent such as methylene chloride for 1-24 hours gives 17. Treatment of 16

with an appropriate phosphonum salt and a base such as LDA or HMDS gives an enol that is hydrolized by treatment with an aqueous acid such as HCl to give 18. Reductive amination with an appropriate amine gives compound 19.

Compounds of structure (I) may generally be referred to as substituted 1*H*-pyridin-4-one compounds, representative compounds of which include the following:

3-(2-Amino-2-phenyl-ethyl)-1-(2,6-difluoro-benzyl)-2,6-dimethyl-5-(2-fluoro-3-methoxy-phenyl)-1H-pyridin-4-one;

3-(2-Amino-2-phenyl-ethyl)-1-(2,6-dichloro-benzyl)-2,6-dimethyl-5-(2-fluoro-3-methoxy-phenyl)-1H-pyridin-4-one;

3-(2-Amino-2-phenyl-ethyl)-1-(2-fluoro-6-chloro-benzyl)-2,6-dimethyl-5-(2-fluoro-3-methoxy-phenyl)-1H-pyridin-4-one;

3-(2-Amino-2-phenyl-ethyl)-1-(2-fluoro-6-trifluoromethyl-benzyl)-2,6-dimethyl-5-(2-fluoro-3-methoxy-phenyl)-1H-pyridin-4-one;

3-(2-Amino-2-phenyl-ethyl)-1-(2-fluoro-6-methylsulfonyl-benzyl)-2,6-dimethyl-5-(2-fluoro-3-methoxy-phenyl)-1H-pyridin-4-one;

3-(2-Amino-2-phenyl-ethyl)-1-(2-fluoro-benzyl)-2,6-dimethyl-5-(2-fluoro-3-methoxy-phenyl)-1H-pyridin-4-one;

3-(2-Amino-2-phenyl-ethyl)-1-(2-chloro-benzyl)-2,6-dimethyl-5-(2-fluoro-3-methoxy-phenyl)-1H-pyridin-4-one;

3-(2-Amino-2-phenyl-ethyl)-1-(2-trifluoromethyl-benzyl)-2,6-dimethyl-5-(2-fluoro-3-methoxy-phenyl)-1H-pyridin-4-one;

3-(2-Amino-2-phenyl-ethyl)-1-(2-methylsulfonyl-benzyl)-2,6-dimethyl-5-(2-fluoro-3-methoxy-phenyl)-1H-pyridin-4-one;

3-(2-Amino-2-phenyl-ethyl)-1-(2,6-difluoro-benzyl)-2,6-dimethyl-5-(2-fluoro-phenyl)-1H-pyridin-4-one;

3-(2-Amino-2-phenyl-ethyl)-1-(2,6-dichloro-benzyl)-2,6-dimethyl-5-(2-fluoro-phenyl)-1H-pyridin-4-one;

3-(2-Amino-2-phenyl-ethyl)-1-(2-fluoro-6-chloro-benzyl)-2,6-dimethyl-5-(2-fluoro-phenyl)-1H-pyridin-4-one;

3-(2-Amino-2-phenyl-ethyl)-1-(2-fluoro-6-trifluoromethyl-benzyl)-2,6-dimethyl-5-(2-fluoro-phenyl)-1H-pyridin-4-one;

3-(2-Amino-2-phenyl-ethyl)-1-(2-fluoro-6-methylsulfonyl-benzyl)-2,6-dimethyl-5-(2-fluoro-phenyl)-1H-pyridin-4-one;

3-(2-Amino-2-phenyl-ethyl)-1-(2-fluoro-benzyl)-2,6-dimethyl-5-(2-fluoro-phenyl)-1H-pyridin-4-one;

3-(2-Amino-2-phenyl-ethyl)-1-(2-chloro-benzyl)-2,6-dimethyl-5-(2-fluoro-phenyl)-1H-pyridin-4-one;

3-(2-Amino-2-phenyl-ethyl)-1-(2-trifluoromethyl-benzyl)-2,6-dimethyl-5-(2-fluoro-phenyl)-1H-pyridin-4-one;

3-(2-Amino-2-phenyl-ethyl)-1-(2-methylsulfonyl-benzyl)-2,6-dimethyl-5-(2-fluoro-phenyl)-1H-pyridin-4-one;

3-(2-Amino-2-phenyl-ethyl)-1-(2,6-difluoro-benzyl)-2,6-dimethyl-5-(2-chloro-phenyl)-1H-pyridin-4-one;

3-(2-Amino-2-phenyl-ethyl)-1-(2,6-dichloro-benzyl)-2,6-dimethyl-5-(2-chloro-phenyl)-1H-pyridin-4-one;

3-(2-Amino-2-phenyl-ethyl)-1-(2-fluoro-6-chloro-benzyl)-2,6-dimethyl-5-(2-chloro-phenyl)-1H-pyridin-4-one;

3-(2-Amino-2-phenyl-ethyl)-1-(2-fluoro-6-trifluoromethyl-benzyl)-2,6-dimethyl-5-(2-chloro-phenyl)-1H-pyridin-4-one;

3-(2-Amino-2-phenyl-ethyl)-1-(2-fluoro-6-methylsulfonyl-benzyl)-2,6-dimethyl-5-(2-chloro-phenyl)-1H-pyridin-4-one;

3-(2-Amino-2-phenyl-ethyl)-1-(2-fluoro-benzyl)-2,6-dimethyl-5-(2-chloro-phenyl)-1H-pyridin-4-one;

3-(2-Amino-2-phenyl-ethyl)-1-(2-chloro-benzyl)-2,6-dimethyl-5-(2-chloro-phenyl)-1H-pyridin-4-one;

3-(2-Amino-2-phenyl-ethyl)-1-(2-trifluoromethyl-benzyl)-2,6-dimethyl-5-(2-chloro-phenyl)-1H-pyridin-4-one;

3-(2-Amino-2-phenyl-ethyl)-1-(2-methylsulfonyl-benzyl)-2,6-dimethyl-5-(2-chloro-phenyl)-1H-pyridin-4-one;

3-(2-Amino-2-phenyl-ethyl)-1-(2,6-difluoro-benzyl)-2,6-dimethyl-5-(3-methoxy-phenyl)-1H-pyridin-4-one;

3-(2-Amino-2-phenyl-ethyl)-1-(2,6-dichloro-benzyl)-2,6-dimethyl-5-(3-methoxy-phenyl)-1H-pyridin-4-one;

3-(2-Amino-2-phenyl-ethyl)-1-(2-fluoro-6-chloro-benzyl)-2,6-dimethyl-5-(3-methoxy-phenyl)-1H-pyridin-4-one;

3-(2-Amino-2-phenyl-ethyl)-1-(2-fluoro-6-trifluoromethyl-benzyl)-2,6-dimethyl-5-(3-methoxy-phenyl)-1H-pyridin-4-one;

3-(2-Amino-2-phenyl-ethyl)-1-(2-fluoro-6-methylsulfonyl-benzyl)-2,6-dimethyl-5-(3-methoxy-phenyl)-1H-pyridin-4-one;

3-(2-Amino-2-phenyl-ethyl)-1-(2-fluoro-benzyl)-2,6-dimethyl-5-(3-methoxy-phenyl)-1H-pyridin-4-one;

3-(2-Amino-2-phenyl-ethyl)-1-(2-chloro-benzyl)-2,6-dimethyl-5-(3-methoxy-phenyl)-1H-pyridin-4-one;

3-(2-Amino-2-phenyl-ethyl)-1-(2-trifluoromethyl-benzyl)-2,6-dimethyl-5-(3-methoxy-phenyl)-1H-pyridin-4-one;

3-(2-Amino-2-phenyl-ethyl)-1-(2-methylsulfonyl-benzyl)-2,6-dimethyl-5-(3-methoxy-phenyl)-1H-pyridin-4-one;

3-(2-Amino-2-phenyl-ethyl)-1-(2,6-difluoro-benzyl)-2,6-dimethyl-5-(2-chloro-3-methoxy-phenyl)-1H-pyridin-4-one;

3-(2-Amino-2-phenyl-ethyl)-1-(2,6-dichloro-benzyl)-2,6-dimethyl-5-(2-chloro-3-methoxy-phenyl)-1H-pyridin-4-one;

3-(2-Amino-2-phenyl-ethyl)-1-(2-fluoro-6-chloro-benzyl)-2,6-dimethyl-5-(2-chloro-3-methoxy-phenyl)-1H-pyridin-4-one;

3-(2-Amino-2-phenyl-ethyl)-1-(2-fluoro-6-trifluoromethyl-benzyl)-2,6-dimethyl-5-(2-chloro-3-methoxy-phenyl)-1H-pyridin-4-one;

3-(2-Amino-2-phenyl-ethyl)-1-(2-fluoro-6-methylsulfonyl-benzyl)-2,6-dimethyl-5-(2-chloro-3-methoxy-phenyl)-1H-pyridin-4-one;

3-(2-Amino-2-phenyl-ethyl)-1-(2-fluoro-benzyl)-2,6-dimethyl-5-(2-chloro-3-methoxy-phenyl)-1H-pyridin-4-one;

3-(2-Amino-2-phenyl-ethyl)-1-(2-chloro-benzyl)-2,6-dimethyl-5-(2-chloro-3-methoxy-phenyl)-1H-pyridin-4-one;

3-(2-Amino-2-phenyl-ethyl)-1-(2-trifluoromethyl-benzyl)-2,6-dimethyl-5-(2-chloro-3-methoxy-phenyl)-1H-pyridin-4-one; and

3-(2-Amino-2-phenyl-ethyl)-1-(2-methylsulfonyl-benzyl)-2,6-dimethyl-5-(2-chloro-3-methoxy-phenyl)-1H-pyridin-4-one.

In addition, representative compounds of the present invention also include those compounds where the primary amine of the above named compounds is substituted with a substituted alkyl group or a cycloalkyl group. As described in the examples, one method of alkylating amines and amides is by reductive alkylation. There are many alternative methods well known in the chemical arts for accomplishing the reductive alkylation procedure, and there are many alternative alkylation methods. When an aldehyde, ketone, carboxylic acid, or acid chloride is treated with a primary or secondary amine in the presence of a reducing agent reductive alkylation may take place. Suitable reducing agents include (but are not limited to) sodium borohydride, sodium triacetoxyborohydride, sodium cyanoborohydride, hydrogen gas and a hydrogenation catalyst, zinc and hydrochloric acid, iron pentacarbonyl and alcoholic potassium hydroxide, formic acid, pyridine borohydride. Amines and amides may also be alkylated by the reaction of formaldehyde and a Mannich base or by the nucleophilic displacement of an alkyl halide or other leaving groups. As an example, the Mitsunobu reaction allows the alkylation of amines with primary or secondary alcohols and carboxylic acids by activation of the hydroxyl group with triphenylphosphine to form the leaving group triphenylphoshine oxide. Other commonly used alkylation methods are described in March, Advanced Organic Chemistry, 4th Ed., pp 1276-1277 (1992).

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, 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 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 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.

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. Compounds of structure (I) may also possess axial chirality, which may result in atropisomers. 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 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 methods. Suitable GnRH antagonists of this invention 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). Briefly, twenty-five day old male Spraque-Dawley rats are administered an GnRH antagonist in saline or other suitable formulation by oral gavage, sub-cutaneous injection, or intravenous injection. This is followed by sub-cutaneous injection of 200 ng GnRH in 0.2 ml saline. Thirty minutes after the last injection, the animals are decapitated and trunk blood collected. After centrifugation, the separated plasma is stored at –20 °C until determination of the LH and FSH by radioimmunoassay. Other techniques for determining the activity of GnRH receptor antagonists are well known in the field, such as the use of cultured pituitary cells for measuring GnRH activity (Vale et al., *Endocrinology 91*:562-572, 1972), and a technique for measuring radioligand binding to rat pituitary membranes (Perrin et al., *Mol. Pharmacol. 23*:44-51, 1983).

For example, effectiveness of a compound as a GnRH receptor antagonist may be determined by one or more of the following assays.

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 digested with collagenase in a dispersion flask 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 suspended in 3% FBS/0.1 BSA/McCoy's 5A medium and plated into 96-well tissue culture plates at a cell density of 40,000 cells per well in 200 µl medium. The cells are then incubated at 37 °C for 3 days. One pituitary gland normally yields one 96-well plate of cells, which can be used for assaying three compounds. 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 µl 0.1% BSA/McCoy's 5A medium in triplicate

wells. Each sample is assayed at 5-dose levels to generate a dose-response curve for determination of its 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 determined by RIA.

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 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 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 antibody diluted 1:30,000 and the labeled rLH by the labeled rFSH.

Radio-iodination of GnRH peptide

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 Na125I, followed by 22.5 μg chloramine-T and the mixture vortexed for 20 sec. The reaction is stopped by the addition of 60 μg sodium metabisulfite and the free iodine is removed by passing the iodinated 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 for up to 4 weeks.

GnRH receptor membrane binding assay

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 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 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 ug protein in 130 ul binding buffer) to 50ul of [^{125}I]-labeled GnRH peptide (~100,000 cpm), and 20ul of competitor at varying concentrations. The 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).

Activity of GnRH receptor antagonists are typically calculated from the IC_{50} 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 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 μM or less. In a preferred embodiment of this invention, the GnRH receptor antagonists have a K_i of less than 10 μM, and more preferably less than 1μM, and even more preferably less than 0.1 μM (*i.e.*, 100 nM).

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 treatment of growth hormone deficiency and short stature, and for the treatment of systemic lupus erythematosis.

In addition, the compounds are useful in combination with androgens, estrogens, progesterones, and antiestrogens and 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. 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, 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.

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 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 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.

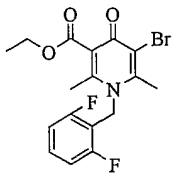
In another embodiment, the present invention provides a method for treating sex-hormone related conditions as discussed above. Such methods include administering of a compound of the present invention to a warm-blooded animal in an amount sufficient to treat the condition. In this context, "treat" includes 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.

EXAMPLE 1

SYNTHESIS OF 1-(2,6-DIFLUOROBENZYL)-2,6-DIMETHYL-3-BROMO-5-ETHOXYCARBONYL-4-PYRIDONE



Step 1A Ethyl-3-(2,6-difluorobenzylamino)crotonate:

2,6-Difluorobenzylamine (5.00 g, 35.0 mmol) was added to trimethyl orthoformate (88.0 mL) under N_2. The resulting solution was stirred at room temperature for 20 minutes. Ethyl acetoacetate (4.5 mL, 35.0 mmol) was then added dropwise and the resulting mixture stirred for 24 hours (reaction progress monitored by LC/MS). The volatiles were removed under vacuum and the product solidified upon standing. Yield 7.88 g (30.9 mmol, 88 %). ^{1}H NMR ($CDCl_3$, 300MHz): 8.86 (br, 1H), 7.30 – 7.21 (m, 1H), 6.94-6.81 (m, 2H), 4.48 (s, 2H), 4.07 (q, J = 6.9 Hz, 2H), 2.03 (s, 3H), 1.23 (t, J = 6.9 Hz, 3H); LRMS *m/z* 256.1 ($M^+ + 1$).

Step 1B 1-(2,6-Difluorobenzyl)-2,6-dimethyl-3-ethoxycarbonyl-4-pyridone:

A mixture of ethyl-3-(2,6-difluorobenzylamino)crotonate (2.55 g, 10.0 mmol) and 2,2,6-trimethyl-1,3-dioxin-4-one (1.85 g, 13.0 mmol) in toluene (100 mL) was heated at reflux for 3 hours. The reaction progress was monitored by LC/MS. An additional aliquot of 2,2,6-trimethyl-1,3-dioxin-4-one (2.0 mL) was added and the reaction mixture was refluxed for another 2 hours. LC/MS indicated complete conversion to product. The mixture was cooled down and the solvent was removed *in vacuo*. The solid residue was triturated with diethyl ether to yield the product as a tan solid (1.37 g, 4.3 mmol, 43 %). ^{1}H NMR ($CDCl_3$, 300MHz): 7.40 – 7.30 (m, 1H), 7.00

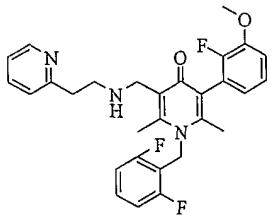
– 6.91 (m, 2H), 6.30 (s, 1H), 5.20 (s, 2H), 4.37 (q, J = 6.9 Hz, 2H), 2.37 (s, 3H), 2.31 (s, 3H), 1.35 (t, J = 6.9 Hz, 3H); LRMS *m/z* 322.1 ($M^+ + 1$).

Step 1C 1-(2,6-Difluorobenzyl)-2,6-dimethyl-3-bromo-5-ethoxycarbonyl-4-pyridone:

1-(2,6-Difluorobenzyl)-2,6-dimethyl-3-ethoxycarbonyl-4-pyridone (2.43 g, 7.6 mmol) was dissolved in glacial acetic acid (25 mL) and treated with bromine (490 μL, 9.5 mmol). The resulting mixture was stirred at room temperature for 8 hours and poured into ice/water. The product was extracted with dichloromethane, and the extracts were washed with 10 % aqueous $NaHCO_3$, 5 % aqueous $Na_2S_2O_3$ and brine. The organics were dried over anhydrous $MgSO_4$, filtered and evaporated *in vacuo*. The residue was triturated with diethyl ether to give the product as a white solid (1.32 g, 3.3 mmol, 43 %). ^1H NMR ($CDCl_3$, 300MHz): 7.41 – 7.31 (m, 1H), 7.00 – 6.92 (m, 2H), 5.31 (s, 2H), 4.37 (q, J = 6.9 Hz, 2H), 2.66 (s, 3H), 2.37 (s, 3H), 1.37 (t, J = 6.9 Hz, 3H); LRMS *m/z* 400.1 (M^+ - 1), 402.1 ($M^+ + 1$).

EXAMPLE 2

SYNTHESIS OF 1-(2,6-DIFLUOROBENZYL)-2,6-DIMETHYL-3-(2-FLUORO-3-METHOXYPHENYL)-5-[2-(2-PYRIDYL)ETHYLAMINOMETHYL]-4-PYRIDONE



Step 2A 1-(2,6-Difluorobenzyl)-2,6-dimethyl-3-(2-fluoro-3-methoxyphenyl)-5-ethoxycarbonyl-4-pyridone:

1-(2,6-Difluorobenzyl)-2,6-dimethyl-3-bromo-5-ethoxycarbonyl-4-pyridone (1.5g, 3.7mmol) was evacuated in a pressure vessel with 2-fluoro-3-methoxyphenyl boronic acid (764mg, 4.5mmol) and tetrakis(triphenylphosphine)

palladium (0) (428mg, 370μmol). A mixture of benzene/ethanol/1,2-dimethoxyethane (74ml in a 10/1/11 ratio) and barium hydroxide (saturated aqueous, about 0.5M) was then added under vacuum, the vessel sealed under N_2, and the reaction stirred at 90 °C for twelve hours, protected from light. The organic layer was concentrated and purified using flash silica chromatography (EtOAc/hexanes-1/4 to MeOH/CH_2Cl_2-2/98), with the product eluting as the third spot. The product was dried as an amber oil (1.12g, 2.5mmol, 68%). ^{1}H NMR ($CDCl_3$, 300MHz) δ 6.80-7.80 (m, 6H), 5.29 (s, 2H), 4.37-4.33 (m, 2H), 3.87 (s, 3H), 3.38 (s, 3H), 2.26 (s, 3H), 1.35 (t, 3H); LCMS = 446 (MH^+).

Step 2B 1-(2,6-Difluorobenzyl)-2,6-dimethyl-3-(2-fluoro-3-methoxyphenyl)-5-formyl-4-pyridone:

Diisobutylaluminum hydride (3.75 mmol, 3.75ml of a 1.0M solution in hexanes) was added dropwise to a stirring solution of 1-(2,6-difluorobenzyl)-2,6-dimethyl-3-(2-fluoro-3-methoxyphenyl)-3-bromo-5-ethoxycarbonyl-4-pyridone (1.12 g, 2.5 mmol) in THF/DCM (30 mL/ 12 mL), at –78 °C under N_2. A suspension was formed at the end of the addition. After 1 hour, an additional aliquot of DIBAL-H (2.5 mmol, 2.5 mL of a 1.0 M solution in hexanes) was added. The reaction was stirred for 1 hour at –78 °C. MeOH (50 mL) was carefully added to quench any unreacted DIBAL-H. The solution was concentrated, then partitioned between EtOAc and 1 M HCl. The organic layer was concentrated and purified using flash silica gel chromatography (100% hexanes to EtOAc/hexanes 3/2). The fourth spot which eluted was evaporated to give product as a cream colored solid. ^{1}H NMR ($CDCl_3$, 300MHz) δ 10.55 (s, 1H), 6.80-7.75 (m, 6H), 5.36 (s, 2H), 3.90 (s, 3H), 2.79 (s, 3H), 2.27 (s, 3H); LCMS = 402 (MH^+).

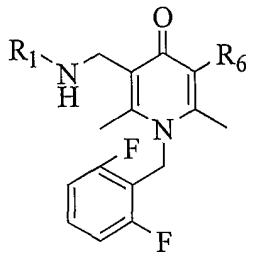
Step 2C 1-(2,6-Difluorobenzyl)-2,6-dimethyl-3-(2-fluoro-3-methoxyphenyl)-5-[2-(2-pyridyl)ethylamino-4-pyridone:

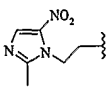
Sodium borohydride (30mg, 794μmol) was added to a pre-mixed solution of 1-(2,6-difluorobenzyl)-2,6-dimethyl-3-(2-fluoro-3-methoxybenzyl)-5-formyl-4-pyridone (20mg, 50 μmol) and the amine (excess) in MeOH (1 mL). Upon addition of the reducing agent, the solution quickly turned dark with the evolution of

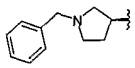
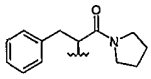
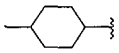
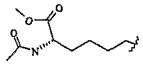
gas. Product formation was instantaneous. The crude solution was concentrated, taken up in acetonitrile, filtered and purified using a Gilson Prep-HPLC system, with the product obtained as a TFA salt in 32% yield. ^{1}H NMR ($CDCl_3$, 300MHz) δ 8.52 (d, 1H), 8.19 (t, 1H), 7.83 (d, 1H), 7.62 (t, 1H), 7.36 (m, 1H), 7.10 (t, 1H), 6.95 (m, 3H), 6.72 (t, 1H), 5.44 (s, 2H), 4.28 (s, 2H), 3.86 (s, 3H), 3.59 (m, 2H), 3.50 (m, 2H), 2.54 (s, 3H), 2.31 (s, 3H); MS = 508 (MH^+).

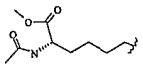
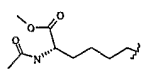
The following compounds were synthesized according to above procedure.

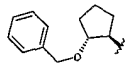
Table 1

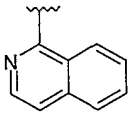
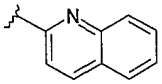
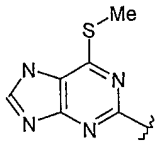
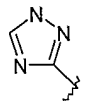
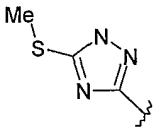
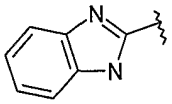
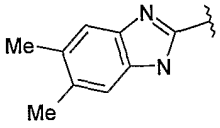
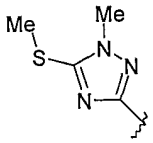
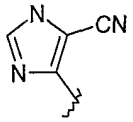


No.	R_6	R_1	MS (MH^+)
2-1	2-F-3-MeOPh	2-PyridylCH_2CH_2	508
2-2	2-F-3-MeOPh	$PhCH_2$	493
2-3	2-F-3-MeOPh	2-MeOPhCH_2	523
2-4	2-F-3-MeOPh	2-MePhCH_2	507
2-5	2-F-3-MeOPh	2-PyridylCH_2	494
2-6	3-MeOPh	2-PyridylCH_2CH_2	490
2-7	3-MeOPh	$PhCH_2$	475
2-8	3-MeOPh	2-MeOPhCH_2	505
2-9	3-MeOPh	2-MePhCH_2	489
2-10	3-MeOPh		494
2-11	3-MeOPh		538
2-12	3-MeOPh	$Me_2NCH_2CH_2$	456

No.	R_6	R_1	MS (MH^+)
2-13	3-MeOPh	$(iPr)_2NCH_2CH_2$	512
2-14	3-MeOPh	$(HOCH_2CH_2)_2NCH_2CH_2$	516
2-15	3-MeOPh		544
2-16	3-MeOPh		586
2-17	3-MeOPh		481.2
2-18	3-MeOPh		465.1
2-19	3-MeOPh		570.3
2-20	3-MeOPh		501.2
2-21	3-MeOPh	$PhCH(CH_3)$	489.2
2-22	3-MeOPh	$(CH_3)_3CCH(CH_3)$	469.2
2-23	3-MeOPh	F_3CCH_2	467.1
2-24	3-MeOPh	2-MeO-$PhCH_2CH_2$	519.2
2-25	3-MeOPh	3,4-di-(OMe)$PhCH_2CH_2$	549.2
2-26	3-MeOPh	n-Heptyl	483.6
2-27	3-MeOPh	3-NO_2PhCH_2	520.5
2-28	3-MeOPh	CyclopropylCH_2	439.2
2-29	3-MeOPh	4-$ClPhCH(CH_3)$	523.1
2-30	3-MeOPh	Et	413.5
2-31	3-MeOPh	Allyl	425.5
2-32	3-MeOPh	Isopropyl	441.5
2-33	3-MeOPh	2-CF_3-4-Cl-$PhCH_2$	561.2
2-34	3-MeOPh	3,4-di-Cl-$PhCH_2$	543.1
2-35	3-MeOPh	4-MeO-$PhCH_2CH_2$	519.2
2-36	3-MeOPh	n-Propyl	427.1
2-37	3-MeOPh	n-Butyl	441.5

No.	R_6	R_1	MS (MH^+)
2-38	3-MeOPh	3,4,5-tri-OMe-PhCH_2	565.2
2-39	3-MeOPh	$CH_3CH_2OCH_2CH_2$	457.5
2-40	3-MeOPh	$CH_3OCH_2(CH_3CH_2)CH$	471.5
2-41	2-F-3-MeOPh	4-CH_3-Cyclohexyl-CH_2	499.2
2-42	2-F-3-MeOPh	F_3CCH_2	485.1
2-43	2-F-3-MeOPh	$((CH_3)_2CH)_2NCH_2CH_2$	530.2
2-44	2-F-3-MeOPh	Cyclopropyl-CH_2	457.1
2-45	2-F-3-MeOPh	4-Cl-PhCH_2	527.1
2-46	Ph	4-CH_3-Cyclohexyl-CH_2	451.2
2-47	Ph	2-FurylCH_2	435.1
2-48	Ph		540.2
2-49	Ph		471.2
2-50	Ph	Ph$CH(CH_3)$	459.2
2-51	Ph	$(CH_3)_3CCH(CH_3)$	439.2
2-52	Ph	CF_3CH_2	437.1
2-53	Ph	3,4-di-OMe-PhCH_2CH_2	519.2
2-54	Ph	$(iPr)_2NCH_2CH_2$	482.2
2-55	Ph	2-CF_3-4-F-PhCH_2	531.2
2-56	Ph	2-F-PhCH_2CH_2	477.2
2-57	Ph	(S)-2-NaphthylCH(CH_3)	509.2
2-58	Ph	4-OMe-PhCH_2CH_2	489.6
2-59	2-CH_3-Thienyl	2-FurylCH_2	455.5
2-60	2-CH_3-Thienyl		560.6
2-61	2-CH_3-Thienyl		491.1
2-62	2-CH_3-Thienyl	Ph$CH(CH_3)$	479.1
2-63	2-CH_3-Thienyl	$(CH_3)_3CCH(CH_3)$	459.2

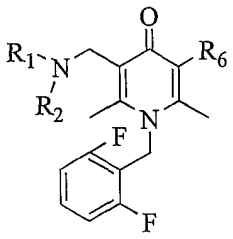
No.	R_6	R_1	MS (MH^+)
2-64	2-CH_3-Thienyl	CF_3CH_2	457.5
2-65	2-CH_3-Thienyl	3,4-di-OMe-$PhCH_2CH_2$	539.7
2-66	2-CH_3-Thienyl	4-F-$PhCH_2CH_2$	497.6
2-67	2-CH_3-Thienyl	$(CH_3)_2CHCH_2CH_2CH(CH_3)$	473.6
2-68	2-CH_3-Thienyl	$(iPr)_2NCH_2CH_2$	502.7
2-69	2-CH_3-Thienyl	4-Cl-$PhCH(CH_3)$	514.1
2-70	2-CH_3-Thienyl	2-CF_3-4-F-$PhCH_2$	551.6
2-71	2-CH_3-Thienyl	2-F-$PhCH_2CH_2$	497.1
2-72	2-CH_3-Thienyl		549.2
2-73	2-CH_3-Thienyl	$PhCH_2$	465.1
2-74	2-CH_3-Thienyl	3,4-di-Cl-$PhCH_2$	535
2-75	2-CH_3-Thienyl	4-MeO-$PhCH_2CH_2$	509.2
2-76	2-CH_3-Thienyl	n-Propyl	417.1
2-77	2-CH_3-Thienyl	n-Butyl	431.1
2-78	2-CH_3-Thienyl	$CH_3CH_2OCH_2CH_2$	447.6
2-79	2-CH_3-Thienyl	$CH_3OCH_2CH(CH_2CH_3)$	461.6
2-80	2-CH_3-Thienyl	2-PyridylCH_2CH_2	480.6
2-81	Ph	Propyl	397.5
2-82	Ph	$CH_3CH_2OCH_2CH_2$	427.5
2-83	Ph	$CH_3OCH_2CH(CH_2CH_3)$	441.5
2-84	Ph	2-PyridylCH_2CH_2	460.5
2-85	2-F-3-MeOPh	2-Pyridyl	480
2-86	2-F-3-MeOPh	3-Pyridyl	480
2-87	2-F-3-MeOPh	2-Pyridyl-6-Me	494
2-88	2-F-3-MeOPh	2-Pyridyl-5-Me	494
2-89	2-F-3-MeOPh	2-Pyridyl-3,5-diMe	508
2-90	2-F-3-MeOPh	2-Pyridyl-4-Cl	514

No.	R_6	R_1	MS (MH^+)
2-91	2-F-3-MeOPh	2-Pyridyl-4-Me	494
2-92	2-F-3-MeOPh	2-Pyridyl-3-Me	494
2-93	2-F-3-MeOPh		530
2-94	2-F-3-MeOPh		530
2-95	2-F-3-MeOPh	2-Pyridyl-5-F	498
2-96	2-F-3-MeOPh	2-Pyrimidyl-4-Me	495
2-97	2-F-3-MeOPh	2-Pyrimidyl-4,6-diMe	509
2-98	2-F-3-MeOPh		567
2-99	2-F-3-MeOPh		470
2-100	2-F-3-MeOPh		516
2-101	2-F-3-MeOPh		519
2-102	2-F-3-MeOPh		547
2-103	2-F-3-MeOPh		530
2-104	2-F-3-MeOPh		494
2-105	2-F-3-MeOPh	2-ClPh	513

No.	R_6	R_1	MS (MH^+)
2-106	2-F-3-MeOPh	2-MePh	493
2-107	2-F-3-MeOPh	3-ClPh	513
2-108	2-F-3-MeOPh	3-MeOPh	509
2-109	2-F-3-MeOPh	4-MeOPh	509
2-110	2-F-3-MeOPh	4-MePh	493

The following compounds were also synthesized according to the above procedure.

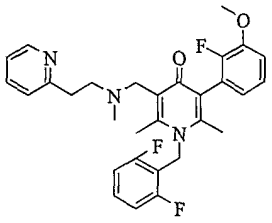
Table 2



No.	R_6	R_1R_2N	MS (MH^+)
2-111	2-F-3-MeOPh	1-Pyrrolidinyl	457.1
2-112	2-F-3-MeOPh	2,6-Dimethylmorpholinyl	501.2
2-113	2-CH_3-Thienyl	1-Pyrrolidinyl	429.5
2-114	2-CH_3-Thienyl	2,6-Dimethylmorpholinyl	473.2
2-115	Ph	1-Pyrrolidinyl	409.5

EXAMPLE 3

SYNTHESIS OF 1-(2,6-DIFLUOROBENZYL)-2,6-DIMETHYL-3-(2-FLUORO-3-METHOXYPHENYL)-5-[2-(2-PYRIDYL)ETHYLAMINOMETHYL]-4-PYRIDONE

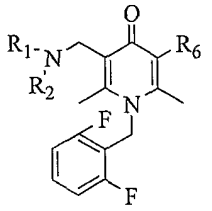


Step 3A 1-(2,6-Difluorobenzyl)-2,6-dimethyl-3-(2-fluoro-3-methoxyphenyl)-5-[N-{2-(2-pyridyl)ethyl}-N-methylaminomethyl]-4-pyridone:

Sodium triacetoxyborohydride (30 mg, 142 μmol) was added to a stirring solution of 1-(2,6-difluorobenzyl)-2,6-dimethyl-3-(2-fluoro-3-methoxybenzyl)-5-formyl-4-pyridone (20 mg, 50 μmol) and 2-(2-methylaminoethyl)pyridine (0.14 mL, 985 μmol) in dichloromethane (1 mL). The solution stirred overnight at r.t., MeOH (0.5 mL) was added and the solution concentrated, taken up in acetonitrile, filtered and purified using a Gilson Prep-HPLC system to give the product as a TFA salt in 34% yield.

The following compounds are synthesized according to above procedure.

Table 3

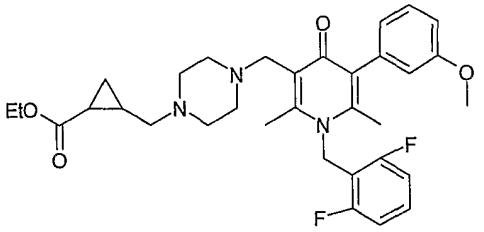


No.	R_6	R_1R_2N-	MS (MH^+)
3-1	2-F-3-MeOPh	2-$PyCH_2CH_2NMe$	522
3-2	2-F-3-MeOPh	$PhCH_2NMe$	507
3-3	2-F-3-MeOPh	2-$PyCH_2NMe$	508
3-4	2-F-3-MeOPh	2-$PyCH_2NEt$	522
3-5	2-F-3-MeOPh	$(2\text{-}PyCH_2)_2N$	585
3-6	3-MeOPh	2-$PyCH_2CH_2NMe$	504
3-7	3-MeOPh	$PhCH_2NMe$	489
3-8	2-F-3-MeOPh	Et_2N	516.2
3-9	2-CH_3-Thienyl	$PhCH_2NCH_3$	479.6
3-10	2-CH_3-Thienyl	2-$PyCH_2CH_2NCH_3$	494.6
3-11	2-CH_3-Thienyl	$Et_2NCH_2CH_2NCH_3$	488.7
3-12	Ph	$PhCH_2NCH_3$	459.6

No.	R_6	R_1R_2N-	MS (MH^+)
3-13	Ph	ButylNCH_3	425.5
3-14	Ph	2-Py$CH_2CH_2NCH_3$	474.2
3-15	Ph	$Et_2NCH_2CH_2NCH_3$	468.6

EXAMPLE 4

SYNTHESIS OF 1-(2,6-DIFLUOROBENZYL)-2,6-DIMETHYL-3-(2-FLUORO-3-METHOXYPHENYL)-5-[4-PROPYLPIPERAZINYLMETHYL]-4-PYRIDONE



Step 4A 1-(2,6-Difluorobenzyl)-2,6-dimethyl-3-(3-methoxyphenyl)-5-formyl-4-pyridone:

1-(2,6-Difluorobenzyl)-2,6-dimethyl-3-bromo-5-formyl-pyrid-4-one (1.36 g, 3.8 mmol) stirred with 3-methoxyphenyl boronic acid (696 mg, 4.6 mmol) and tetrakis(triphenylphosphine)palladium(0) (439 mg, 380 μmol) in benzene/ethanol/DME (76 mL, 10/1/11) and barium hydroxide (30 mL, sat., aq.) under N_2 at 90 °C, protected from light over 8 hours. The organic layer was then concentrated and purified using flash silica chromatography (ethyl acetate/hexane – 1/9), giving the product as a cream-colored solid (622 mg, 1.6 mmol, 42% yield). ^1H NMR ($CDCl_3$, 300MHz) δ 10.55 (s, 1H), 7.41-7.31 (m, 2H), 7.00-6.74 (m, 5H), 5.35 (s, 2H), 3.81 (s, 3H), 2.79 (s, 3H), 2.25 (s, 3H); MS: 384 (MH^+).

Step 4B 1-(2,6-Difluorobenzyl)-2,6-dimethyl-3-(3-methoxyphenyl)-5-[piperazinylmethyl]-4-pyridone:

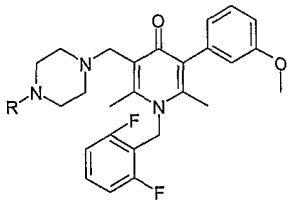
Sodium triacetoxyborohydride (2.75 g, 13 mmol) was added to a stirring solution of 1-(2,6-difluorobenzyl)-2,6-dimethyl-3-(3-methoxyphenyl)-5-formyl-4-pyridone (2.5 g, 6.5 mmol) and 1-boc-piperazine (1.33 g, 7.2 mmol) in CH_2Cl_2 (45 mL) at r.t. The

solution was quenched with 1M KOH (5 mL) and the organic layer purified using flash silica chromatography (1%MeOH in CH_2Cl_2) to give the boc protected product as a dark brown oil. The resulting oil was treated with trifluoroacetic acid (5 mL, 6.5 mmol) in CH_2Cl_2 (20 mL) for one hour at r.t. The crude solution was concentrated and purified using flash silica chromatography (2% MeOH in CH_2Cl_2 and dried to give the product as a white foam (1.9 g, 3.4 mmol, 52% yield). ^1H NMR ($CDCl_3$, 300MHz) δ 7.38-7.28 (m, 2H), 6.97-6.74 (m, 5H), 5.30 (s, 2, H), 3.80 (s, 3H), 3.49 (s, 2H), 3.20-2.80 (m, 8H), 2.52 (m, 3H) 2.19 (s, 3H). MS: 568 (MH^+).

Step 4C 1-(2,6-Difluorobenzyl)-2,6-dimethyl-3-(3-methoxyphenyl)-5-[4-(2-ethoxycarbonylcyclopropanemethyl)piperazinylmethyl]-4-pyridone:

Sodium triacetoxyborohydride (30 mg, 141 μmol) was added to a stirring solution of 1-(2,6-difluorobenzyl)-2,6-dimethyl-3-(3-methoxyphenyl)-5-[piperazinylmethyl]-4-pyridone (50 mg, 88 μmol) with ethyl-2-formyl-1-cyclopropane carboxylate (0.05 mL, 669 μmol) in CH_2Cl_2 (1 mL). The mixture stirred at r.t. for five hours before being filtered and purified using the Gilson Prep-HPLC system, giving the product as a TFA salt (13.4 mg, 19 μmol, 22% yield). ^1H NMR ($CDCl_3$, 300MHz) δ 7.40-7.32 (m, 2H), 7.00-6.69 (m, 5H), 5.42 (s, 2H), 4.37 (s, 2H), 4.19-4.07 (m, 2H), 3.80 (s, 3H), 3.68-3.48 (m, 8H), 3.00-2.88 (m, 1H), 2.58 (s, 3H), 2.28 (m, 3H), 1.67-1.54 (m, 3H), 1.36-1.22 (m, 5H). MS: 580 (MH^+).

Table 4

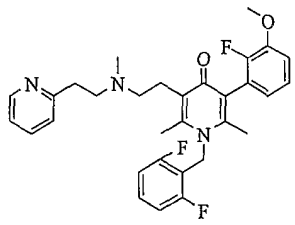


No.	R	MS (MH^+)
4-1	H	454
4-2	EtOCO(cPr)CH_2	580
4-3	5-MeFuranCH_2	548
4-4	3,4-MeOPhCH_2	604

4-5	1-NaphCH_2	594
4-6	iBu	510
4-7	Pr	496
4-8	c-PrCH_2	508

EXAMPLE 5

SYNTHESIS OF 1-(2,6-DIFLUOROBENZYL)-2,6-DIMETHYL-3-(2-FLUORO-3-METHOXYPHENYL)-5-[N-{2-(2-PYRIDYL)ETHYL}-N-METHYLAMINOMETHYL]4-PYRIDONE



Step 5A 1-(2,6-Difluorobenzyl)-2,6-dimethyl-3-bromo-5-formyl-4-pyridone:

DIBAL (5.3 mmol, 5.3 mL of a 1.0 M solution in hexanes) was added dropwise via syringe to a stirred solution of 1-(2,6-difluorobenzyl)-2,6-dimethyl-3-bromo-5-ethoxycarbonyl-4-pyridone (1.40 g, 3.5 mmol) in THF/DCM (60 mL/20 mL), at –78 °C under N_2. A suspension was formed at the end of the addition. After 1 hour, an additional aliquot of DIBAL (3.0 mmol, 3.0 mL of a 1.0 M solution in hexanes) was added. The reaction was deemed complete after 1 hour at –78 °C. MeOH (5 mL) was carefully added to quench any unreacted DIBAL and the mixture was partitioned between EtOAc and 1 M HCl. The organic layer was separated and washed with brine, dried over anhydrous $MgSO_4$ and filtered. Upon removal of the solvents in vacuum, the crude solid residue was triturated with Et_2O. The product was obtained as a beige solid (0.80 g, 2.25 mmol, 64 %). ^1H NMR ($CDCl_3$, 300MHz): 10.55 (s, 1H), 7.40 – 7.33 (m, 1H), 7.00 – 6.93 (m, 2H), 5.38 (s, 2H), 2.78 (s, 3H), 2.69 (s, 3H); LRMS *m/z* 356.0 (M^+ - 1), 358.0 (M^+ + 1).

Step 5B 1-(2,6-Difluorobenzyl)-2,6-dimethyl-3-bromo-5-(2-methoxyethenyl)4-pyridone:

KHMDS (2.4 mmol, 4.8 mL of a 0.5 M solution in toluene) was added dropwise to a vigorously stirred suspension of (methoxymethyl)triphenylphosphonium chloride (771 mg, 2.25 mmol) in anhydrous THF (8 mL), at –78 °C under N_2. The resulting orange suspension was stirred at –78 °C for 45 min. Then, a solution of 1-(2,6-difluorobenzyl)-2,6-dimethyl-3-bromo-5-formyl-4-pyridone (534 mg, 1.50 mmol) in THF (8 mL) was added dropwise and the reaction was allowed to warm slowly to room temperature. After 1 h at room temperature, the reaction was quenched with an aqueous saturated solution of $NaHCO_3$. The organics were extracted with EtOAc (50 mL), the organic layer was separated, washed with H_2O and brine, dried over $MgSO_4$, filtered and evaporated under vacuum. The crude residue was utilized in the next step. LRMS m/z 384.0 (M^+ - 1), 386.0 (M^+ + 1).

Step 5C 1-(2,6-Difluorobenzyl)-2,6-dimethyl-3-bromo-5-(carbonylmethyl)4-pyridone:

The crude product above was dissolved in THF/H_2O (20 mL, 1:1 v/v) and to that solution TFA (5 mL) was added. The mixture was heated at reflux for 19 h. After cooling down, the reaction was extracted with CH_2Cl_2 (50 mL), washed with sat. $NaHCO_3$ and brine. After drying over $MgSO_4$, the solvent was removed under vacuum and the residue was chromatographed on silica-gel, eluting with EtOAc. The product was obtained as a pale yellow oil (431 mg, 1.16 mmol, 78% over 2 steps). ^1H NMR ($CDCl_3$, 300MHz) δ 9.56 (t, J = 1.8 Hz, 1H), 7.38 – 7.33 (m, 1H), 6.98 – 6.93 (m, 2H), 5.37 (s, 2H), 3.83 (d, J = 1.8 Hz, 2H), 2.68 (s, 3H), 2.33 (s, 3H); LRMS *m/z* 247.1 [M^+ - (Br, CH_2CHO)], 370.0 (M^+ - 1), 372.0 (M^+ + 1).

Step 5D 1-(2,6-Difluorobenzyl)-2,6-dimethyl-3-bromo-5-[N-{2-(2-pyridyl)ethyl}-N-methylaminomethyl]-4-pyridone:

(2-Methylaminoethyl)pyridine (680 mg, 5.00 mmol) was added to a stirred solution of 1-(2,6-difluorobenzyl)-2,6-dimethyl-3-bromo-5-(carbonylmethyl)4-pyridone (430 mg, 1.16 mmol) in CH_2Cl_2 (15 mL). After 30 min., $NaBH(OAc)_3$ (1.23

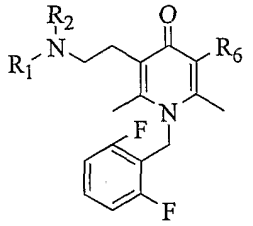
g, 5.80 mmol) was added in small portions, and the resulting mixture was stirred at room temperature for 1 h. The reaction mixture was diluted with H_2O (15 mL) and the organic layer was separated and washed with sat. $NaHCO_3$ and brine. The organics were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude was used in the next step without any further purification. Crude yield 426 mg (75%). LRMS *m/z* 490.0 (M^+ - 1), 492.0 (M^+ + 1).

Step 5E 1-(2,6-Difluorobenzyl)-2,6-dimethyl-3-(2-fluoro-3-methoxyphenyl)-5-[N-{2-(2-pyridyl)ethyl}-N-methylaminomethyl]4-pyridone:

The above crude bromide (98 mg, 0.20 mmol) and 3-methoxyphenyl boronic acid (36 mg, 0.24 mmol) were dissolved in DME/benzene/EtOH (11:10:1, 5 mL). To that, saturated aqueous $Ba(OH)_2$ (1.4 mL) was added and the mixture was degassed under N_2 for 30 minutes. $Pd[Ph_3P]_4$ (23 mg, 0.02 mmol) was then added and the sealed reaction vessel was stirred at 80 °C for 18 h. The reaction mixture was cooled down, extracted with EtOAc, washed with H_2O and brine, dried over $MgSO_4$, filtered and evaporated. The residue was purified by preparative TLC plate (0.5 mm, 20 x 20 cm), eluting with a $CHCl_3$/MeOH/NH_4OH (88.5 : 11.0 : 0.5) mixture to give product (15 mg, 0.03 mmol, 15 % yield). ^1H NMR ($CDCl_3$, 300MHz) δ 8.50 (d, J = 4.2 Hz, 1H), 7.57 (dt, J_1 = 1.8 Hz, J_2 = 7.5 Hz, 1H), 7.36 – 7.27 (m, 2H), 7.20 (d, J = 7.5 Hz, 1H), 7.11 –7.07 (m, 1H), 6.97 – 6.92 (m, 2H), 6.86 – 6.73 (m, 3H), 5.30 (s, 2H), 3.80 (s, 3H), 3.03 – 2.97 (m, 2H), 2.92 – 2.83 (m, 4H), 2.62 – 2.56 (m, 2H), 2.44 (s, 3H), 2.40 (s, 3H), 2.21 (s, 3H); LRMS *m/z* 518.3 (M^+ + 1).

The following compounds are synthesized according to above procedure.

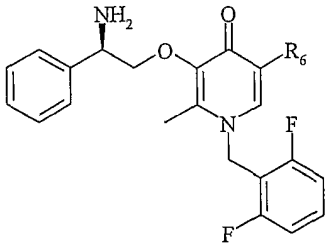
Table 5



No.	R_6	R_1R_2N	MS (MH^+)
5-1	2-F-3-MeOPh	2-PyCH_2CH_2NMe	536
5-2	3,4-CH_2O_2Ph	2-PyCH_2CH_2NMe	532
5-3	4-iPrPh	2-PyCH_2CH_2NMe	530
5-4	3-MeOPh	2-PyCH_2CH_2NMe	518

EXAMPLE 6

SYNTHESIS OF 1-(2,6-DIFLUOROBENZYL)-2-METHYL-3-[(2R)-AMINO-2-PHENYLETHOXYL]-5-ARYLPYRIDIN-4-ONE



Step 6A 2-Methyl-3-[(2R)-Boc-amino-2-phenylethoxy]-4H-pyran-4-one:

Diethyl azodicarboxylate (2.36 mL, 15.0 mmol) was added dropwise to a stirred solution of Maltol (1.26 g, 10.0 mmol), triphenylphosphine (3.93 g, 15.0 mmol) and (R)-N-boc-phenylglycinol (2.37 g, 10.0 mmol) in THF (100 mL). The initial yellow color faded quickly, and the resulting colorless solution was stirred under N_2 for 15h at room temperature. The solvent was removed in vacuo and the residue was purified on silica gel, eluting with a 2:1 v/v mixture of hexanes/EtOAc. The title product was obtained as a yellow oil, which was contaminated with some triphenylphosphine oxide. This mixture was carried onto the next step without any further purification. Yield = 2.35 g. LRMS *m/z* 246 (M^+ - boc + 1), 229 (246 – NH_3).

Step 6B 1-(2,6-Difluorobenzyl)-2-methyl-3-[(2R)-Boc-amino-2-phenylethoxy]-pyridin-4-one:

Crude 2-methyl-3-[(2R)-Boc-amino-2-phenylethoxy]-4H-pyran-4-one (1.00 g, ~2.90 mmol), 2,6-difluorobenzyl amine (700 μL, 5.8 mmol) and ethanol (3 mL) were combined and heated to 120 °C in a pressure vessel. After 16 h, the volatiles were

removed *in vacuo* and the residue purified by column chromatography, eluting with EtOAc. The product was isolated as a white foam (204 mg, 0.43 mmol, 15 %, assuming pure starting material). ^{1}H NMR ($CDCl_3$ – 300 MHz) δ 7.42 – 7.19 (m, 7H); 6.98 (t, J = 8.1 Hz, 2 H); 6.43 (d, J = 7.8 Hz, 1 H); 5.06 (s, 2 H); 4.87 – 4.83 (m, 1 H); 4.06 (dd, J_1 = 9.9 Hz, J_2 = 4.2 Hz, 1 H); 3.93 (dd, J_1 = 9.9 Hz, J_2 = 6.8 Hz, 1 H); 2.34 (s, 3 H); 1.42 (s, 9 H); LRMS *m/z* 471.1 (M^+ + 1), 371.0 (M^+ - boc + 1).

Step 6C 1-(2,6-Difluorobenzyl)-2-methyl-3-[(2R)-Boc-amino-2-phenylethoxy]-5-bromopyridin-4-one:

N-Bromosuccinimide (79 mg, 0.44 mmol) was added to a stirred solution of 1-(2,6-difluorobenzyl)-2-methyl-3-[(2R)-Boc-amino-2-phenylethoxy]-5-bromopyridin-4-one (173 mg, 0.37 mmol) in THF (2 mL), under an atmosphere of N_2. The resulting mixture was refluxed for 2 h and the mixture was cooled to room temperature and partitioned between EtOAc and H_2O. The organic layer was separated, washed with aqueous $NaHCO_3$ and brine, dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. The product was obtained as a yellow foam (185 mg, 0.34 mmol, 92 %). ^{1}H NMR ($CDCl_3$ – 300 MHz) δ 7.76 (s, 1 H); 7.47 – 7.19 (m, 6H); 7.00 (t, J = 8.1 Hz, 2 H); 5.09 (s, 2 H); 4.90 – 4.87 (m, 1 H); 4.09 – 4.00 (m, 2 H); 2.34 (s, 3 H); 1.41 (s, 9 H); LRMS *m/z* 551.1 (M^+ + 3), 549.1 (M^+ + 1), 451.0 (M^+ - boc + 3), 449.0 (M^+ - boc + 1).

Step 6D 1-(2,6-Difluorobenzyl)-2-methyl-3-[(2*R*)-Boc-amino-2-phenylethoxy]-5-arylpyridin-4-one (General procedure for Suzuki couplings):

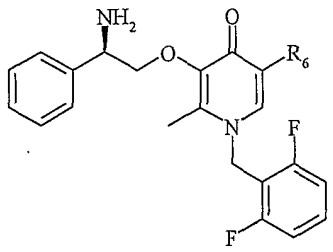
The aryl boronic acid (1.3 mmol) and aqueous saturated $Ba(OH)_2$ solution (7.1 mL) were added to a solution of 1-(2,6-difluorobenzyl)-2-methyl-3-[(2*R*)-Boc-amino-2-phenylethoxy]-5-bromopyridin-4-one (1.0 mmol) in a solvent mixture consisting of dimethoxyethane, benzene and ethanol, in a 50: 45.5 : 4.5 ratio (20 mL), respectively. The resulting mixture was degassed by bubbling N_2 for about 20 minutes. $Pd[PPh_3]_4$ (0.1 mmol) was then added, the vessel was sealed and immersed in an oil bath at 90 °C, with stirring. The reaction was monitored by TLC and LC/MS. When the starting material was consumed (typically 5-10 hours), the reaction was cooled and

partitioned between EtOAc and water. The organic layer was washed with brine, dried over $MgSO_4$ and filtered. The filtrates were concentrated in vacuum and the residue was purified by column chromatography on silica gel. Yields typically range from 65-95 %.

Step 6E 1-(2,6-Difluorobenzyl)-2-methyl-3-[(2*R*)-amino-2-phenylethoxy]-5-arylpyridin-4-one (General Procedure for N-boc deprotections)

Trifluoroacetic acid (2 mL) was added to a solution of 1-(2,6-difluorobenzyl)-2-methyl-3-[(2*R*)-Boc-amino-2-phenylethoxy]-5-arylpyridin-4-one (0.09 mmol) in CH_2Cl_2 (2 mL) and the resulting mixture was stirred at room temperature for 2 h. TLC and LC/MS analysis showed that all starting material had been consumed. The volatiles were removed *in vacuo* and the residues were either purified directly by preparative HPLC or neutralized with NH_3 in MeOH and then purified by preparative TLC, eluting with a 88:11:1 v/v mixture of $CHCl_3$/MeOH/NH_4OH.

Table 6

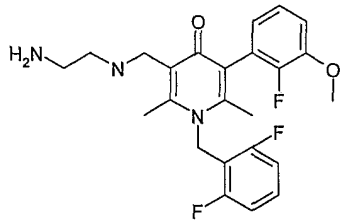


No.	R_6	^{1}H NMR($CDCl_3$, 300MHz)	MS (MH^+)
6-1	3-MeOPh	7.55 (s, 1 H); 7.44 – 7.22 (m, 8H); 7.11 (dd, J_1 = 1.0 Hz, J_2 = 7.7 Hz, 1 H); 6.99 (t, J = 8.1 Hz, 2 H); 6.86 (dd, J_1 = 1.7 Hz, J_2 = 8.3 Hz, 1 H); 5.12 (s, 2 H); 4.47 – 4.43 (m, 1 H); 4.19 (dd, J_1 = 4.1 Hz, J_2 = 9.5 Hz, 1 H); 4.00 (dd, J_1 = 9.0 Hz, J_2 = 9.5 Hz, 1 H); 3.83 (s, 3 H); 2.37 (s, 3 H)	477
6-2	3,4-CH_2O_2Ph	7.49 (s, 1 H); 7.44 - 7.22 (m, 6 H), 7.16 (d, J = 1.8 Hz, 1 H), 7.01 - 6.96 (m, 3 H); 6.83 (d, J = 8.1 Hz, 1 H);	491

		5.95 (s, 2 H); 5.11 (s, 2 H); 4.46 – 4.42 (m, 1 H); 4.17 (dd, J_1 = 4.0 Hz, J_2 = 9.3 Hz, 1 H); 3.99 (dd, J_1 = 8.7 Hz, J_2 = 9.3 Hz, 1 H); 2.36 (s, 3 H)	
6-3	2-F-3-MeOPh		495

EXAMPLE 7

Synthesis of 1-(2,6-difluorobenzyl)-2,6-dimethyl-3-[N-(2-aminoethyl)aminomethyl]-5-(2-fluoro-3-methoxy)pyridin-4-one



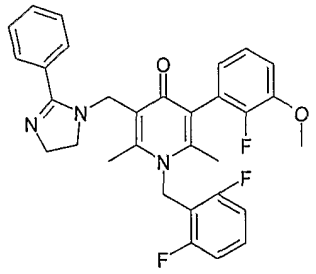
Step 7A 1-(2,6-Difluorobenzyl)-2,6-dimethyl-3-(2-fluoro-3-methoxyphenyl)-5-(2-aminoethyl)methylamino-4-pyridone

Butyl(*tert*)-N-(2-aminoethyl)carbamate (530mg, 3.3mmol) was added to a stirring solution of 1-(2,6-Difluorobenzyl)-2,6-dimethyl-3-(2-fluoro-3-methoxyphenyl)-5-formyl-4-pyridone (870mg, 2.2mmol) and magnesium sulfate (145mg, 1.2mmol) in methanol (29mL) at room temperature. The resulting mixture stirred 1 hour before addition of sodium borohydride (145mg, 3.8mmol). The crude reaction was concentrated *in vacuo* and purified by Flash silica chromatography, and dried as an amber oil. Yield 460mg (843μmol, 38%). LCMS *m/z* 546 (M^++1).

Trifluoroacetic acid (10mL, 130mmol) was added to the boc-protected diaminoethylpyridone (460mg, 843μmol) in dichloromethane (20mL) and stirred for 8h at r.t. The material was dried *in vacuo* as an oil, as TFA salt. Yield 470mg (840μmol, 99%). ^{1}H NMR (CDCl3, 300MHz) δ 7.37-7.29 (m, 1H), 7.13-7.09 (m, 1H), 6.97-6.92 (m, 3H), 6.83-6.79 (m, 1H), 5.34 (s, 2H), 3.89 (s, 3H), 3.84 (s, 2H), 3.39 (m, 2H), 3.08 (m, 2H), 2.50 (s, 3H), 2.25 (s, 3H); LCMS *m/z* 446 (M^++1).

EXAMPLE 9

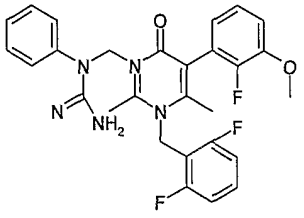
Synthesis of 1-(2,6-difluorobenzyl)-2,6-dimethyl-3-[N-(2-phenyl-2-imidiazoline)methyl]-5-(2-fluror-3-methoxyphenyl)-4-pyridinone



Ethyl alcohol (1mL, 17.7mmol) was added to 1-(2,6-difluorobenzyl)-2,6-dimethyl-3-[N-(2-aminoethyl)aminomethyl]-5-(2-fluoro-3-methoxy)-4-pyridone TFA salt (95mg, 170μmol) with methyl benzimidate hydrochloride (35mg, 204μmol), sealed in a glass pressure vessel and stirred for 2h at 75°C. The crude material was purified using Prep-HPLC-MS, and dried *in vacuo* as an oil (TFA salt). Yield 30.7mg (48μmol, 28%). ^{1}H NMR (CDCl3, 300MHz) δ 7.66-7.60 (m, 3H), 7.54-7.49 (m, 2H), 7.42-7.32 (m, 1H), 7.14-7.08 (m, 1H), 7.03-6.93 (m, 3H), 6.70-6.65 (m, 1H), 5.44 (s, 2H), 4.74 (s, 2H), 3.91(m, 3H), 3.88 (m, 4H), 2.37 (s, 3H), 2.30 (s, 3H); LCMS *m/z* 532 (M^++1).

EXAMPLE 10

Synthesis of 1-(2,6-difluorobenzyl)-2-methyl-3-[N-(quanyl)-N'-phenylaminomethyl]-5-(2-fluoro-3-methoxyphenyl)pyridin-4-one



N,N'-bis-boc-1-guanylpyrazole (195mg, 627μmol) was added to 1-(2,6-difluorobenzyl)-2-methyl-3-(N-phenylaminomethyl)-5-(2-fluoro-3-methoxyphenyl)pyridin-4-one (150mg, 313μmol) in 1,4-dioxane (6mL), sealed in a glass pressure vessel and stirred for 8h at 100°C. The crude material was purified using Flash silica chromatography, and dried *in vacuo* as a clear oil. Yield 50mg (69umol, 22%).

Trifluoroacetic acid (2mL, 26mmol) was added to the boc-protected guanylpyridone (50mg, 69μmol) in dichloromethane (5mL) and stirred for 2h at r.t. The crude material was purified using Flash silica chromatography, and dried *in vacuo* as a clear yellow oil. Yield 2mg (3.8μmol, 5.5%). ^{1}H NMR (CDCl3, 300MHz) δ 7.30-7.20 (m, 4H), 7.05-6.82 (m, 6H), 6.60-6.50 (m, 1H), 5.45 (s, 2H), 5.40-5.15 (m, 2H), 3.85 (s, 3H), 2.40 (s, 3H), 2.15 (s, 3H); LCMS *m/z* 521 (M^++1).

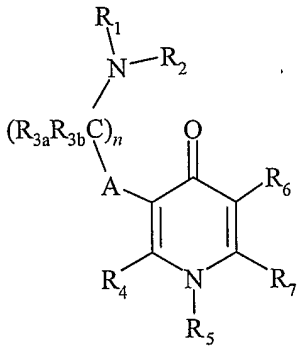
It will be appreciated that, although specific embodiments of the invention have been described herein for purposes of illustration, various modifications may be made without departing from the spirit and scope of the invention. Accordingly, the invention is not limited except as by the appended claims.

All of the above U.S. patents, U.S. patent application publications, U.S. patent applications, foreign patents, foreign patent applications and non-patent publications referred to int his specification and/or listed in the Application Data Sheet are incorporated herein by reference, in their entirety.

CLAIMS

We claim:

1. A compound having the following structure:



or a stereoisomer, prodrug or pharmaceutically acceptable salt thereof,

wherein:

A is O or a bond;

n is 1, 2, 3 or 4;

R_1 and R_2 are the same or different and independently hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heterocycle, substituted heterocycle, heterocyclealkyl, substituted heterocyclealkyl, $-C(R_8)(=NR_9)$ or $-C(NR_{10}R_{11})(=NR_9)$;

or R_1 and R_2 taken together with the nitrogen atom to which they are attached form a heterocycle or a substituted heterocycle;

R_{3a} and R_{3b} are the same or different and, at each occurrence, independently hydrogen, alkyl, substituted alkyl, alkoxy, alkylthio, alkylamino, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heterocycle, substituted heterocycle, heterocyclealkyl, substituted heterocyclealkyl, $-COOR_{12}$ or $-CONR_{10}R_{11}$;

or R_{3a} and R_{3b} taken together with the carbon atom to which they are attached form a homocycle, substituted homocycle, heterocycle or substituted heterocycle;

or R_{3a} and the carbon to which it is attached taken together with R_1 and the nitrogen to which it is attached form a heterocycle or substituted heterocycle;

R_4 is hydrogen, alkyl or substituted alkyl;

R_5 is arylalkyl, substituted arylalkyl, heteroarylalkyl or substituted heteroarylalkyl;

R_6 is aryl, substituted aryl, heteroaryl or substituted heteroaryl;

R_7 is hydrogen, alkyl or substituted alkyl;

R_8, R_9, R_{10} and R_{11} are the same or different and, at each occurrence, independently hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heterocycle, substituted heterocycle, heterocyclealkyl or substituted heterocyclealkyl; and

R_{12} is hydrogen, alkyl or substituted alkyl.

2. The compound of claim 1 wherein R_1 is hydrogen, alkyl, substituted alkyl, arylalkyl, substituted arylalkyl, heterocyclealkyl or substituted heterocyclealkyl.

3. The compound of claim 1 wherein R_5 is arylalkyl, substituted arylalkyl or heteroarylalkyl.

4. The compound of claim 1 wherein R_6 is substituted aryl, heteroaryl or substituted heteroaryl.

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

6. 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.

7. 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 5.

8. The method of claim 7 wherein the sex-hormone related condition is cancer, benign prostatic hypertrophy or myoma of the uterus.

9. The method of claim 8 wherein the cancer is prostatic cancer, uterine cancer, breast cancer or pituitary gonadotroph adenomas.

10. The method of claim 7 wherein the sex-hormone related condition is endometriosis, polycystic ovarian disease, uterine fibroids or precocious puberty.

11. A method for preventing pregnancy of a subject in need thereof, comprising administering an effective amount of the pharmaceutical composition of claim 5.

12. A method for treating lupus erythematosis, 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 5.

INTERNATIONAL SEARCH REPORT

ational Application No
PCT/US 02/24643

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/45 A61K31/443 A61K31/444 A61K31/4439 A61K31/4436
C07D213/68 C07D401/12 C07D405/12 C07D453/02 C07D487/04
C07D409/12 C07D213/69 C07D409/04 A61P5/04

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 A61K

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
WPI Data, PAJ, CHEM ABS Data, EPO-Internal, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,Y	WO 01 55119 A (STRUTHERS R SCOTT ;CHEN CHEN (US); TUCCI FABIO C (US); ZHU YUN FEI) 2 August 2001 (2001-08-02) the whole document	1-12
Y	WO 01 29044 A (CHEN CHEN ;ZHU YUN FEI (US); GAO YINGHONG (US); GROSS TIMOTHY D (U) 26 April 2001 (2001-04-26) the whole document	1-12
A	WO 98 55470 A (CHU LIN ;GOULET MARK (US); MERCK & CO INC (US); WALSH THOMAS F (US) 10 December 1998 (1998-12-10) cited in the application the whole document	1-12

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[X] Further documents are listed in the continuation of box C.

[X] 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	Date of mailing of the international search report
11 October 2002	22/10/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Scruton-Evans, I

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

itional Application No
PCT/US 02/24643

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 //(C07D487/04,249:00,235:00)

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

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)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	CHO N ET AL: "Discovery of a Novel, Potent and Orally Active Nonpeptide Antagonist of the Human Luteinizing Hormone Releasing Hormone (LHRH) Receptor" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 41, no. 22, 22 October 1998 (1998-10-22), pages 4190-4195, XP002156492 ISSN: 0022-2623 cited in the application the whole document	1-12

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

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

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"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	Date of mailing of the international search report
11 October 2002	

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Scruton-Evans, I

INTERNATIONAL SEARCH REPORT

ternational application No.
PCT/US 02/24643

Box I Observations where certain claims were found unsearchable (Continuation of item 1 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. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 6-12 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. [X] Claims Nos.: 1-12 (partly)
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:

see FURTHER INFORMATION sheet PCT/ISA/210

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 II Observations where unity of invention is lacking (Continuation of item 2 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.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-12 (partly)

Present claims 1-12 partly) relate to a compound defined by reference to a desirable characteristic or property, namely a prodrug of the compounds of claim 1.

The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compound by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the compounds of claim 1 and those specific derivatisations given on page 16, lines 17-21 of the description.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

ational Application No
PCT/US 02/24643

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO 0155119 A	02-08-2001	AU	3797501 A	07-08-2001
		WO	0155119 A2	02-08-2001
		US	2002132820 A1	19-09-2002
WO 0129044 A	26-04-2001	AU	1208901 A	30-04-2001
		EP	1220857 A1	10-07-2002
		WO	0129044 A1	26-04-2001
WO 9855470 A	10-12-1998	AU	729752 B2	08-02-2001
		AU	7806898 A	21-12-1998
		EP	0986550 A1	22-03-2000
		JP	2002502426 T	22-01-2002
		WO	9855470 A1	10-12-1998
		US	5981550 A	09-11-1999
		US	6077858 A	20-06-2000