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(54) Title: SUBSTITUTED 3-PYRIDYL PYRROLES AND 3-PYRIDYL PYRAZOLES AS C17,20 LYASE INHIBITORS

(57) Abstract: The invention provides novel substituted 3-pyridyl pyrroles and 3-pyridyl pyrazoles and pharmaceutical compositions thereof. The invention also provides methods of use of substituted 3-pyridyl pyrroles and 3-pyridyl pyrazoles and pharmaceutical compositions thereof as inhibitors of lyases, e.g., the 17 α -hydroxylase-C17,20 enzyme. The invention further provides methods for the treatment of cancer in a subject, comprising administering a substituted 3-pyridyl pyrroles and 3-pyridyl pyrazoles or a pharmaceutical composition comprising a substituted 3-pyridyl pyrroles and 3-pyridyl pyrazoles to a subject. The cancer can be, e.g., prostate cancer or breast cancer.

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APPLICATION FOR PATENT

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Substituted 3-Pyridyl Pyrroles and 3-Pyridyl Pyrazoles as C17,20 Lyase Inhibitors

Background of the Invention

10 Steroid biosynthesis begins in cells of the adrenal gland where the initial product in sterol biosynthesis, cholesterol, is converted into the adrenal steroid hormones aldosterone, hydrocortisone, and corticosterone by a series of P₄₅₀ -mediated hydroxylation steps. The cholesterol side-chain cleavage activity that represents the first step in steroid hormone biosynthesis is a P₄₅₀ -mediated oxidation and cleavage of a pair of adjacent methylene
15 groups to two carbonyl fragments, pregnenolone and isocaprylaldehyde (see Walsh (1979) Enzymatic Reaction Mechanisms; W.H. Freeman and Company, pp. 474-77). Another critical set of enzymatic conversions in steroid metabolism is facilitated by 17-alpha-hydroxylase-17,20-lyase (CYP17, P₄₅₀ 17). CYP17 is a bifunctional enzyme which possesses both a C17,20-lyase activity and a C17-hydroxylase activity. Significantly, these
20 two alternative enzymatic activities of CYP17 result in the formation of critically different intermediates in steroid biosynthesis and each activity appear to be differentially and developmentally regulated (see e.g. l'Allemand et al. (2000) Eur. J. Clin. Invest. 30: 28-33).

The C17,20-lyase activity of CYP17 catalyzes the conversion of 17 α -hydroxy-pregnenolone and 17 α -hydroxy-progesterone to dehydroepiandrosterone (DHEA) and
25 delta4-androstenedione (androstenedione) respectively. Both DHEA and androstenedione lyase products are key intermediates in the synthesis of not only the androgens testosterone and dihydrotestosterone (DHT), but also the estrogens 17-beta-estradiol and estrone. Indeed, adrenal and ovarian estrogens are the main sources of estrogens in postmenopausal women (see e.g. Harris et al. (1988) Br. J. Cancer 58: 493-6). In contrast, the C17-hydroxylase
30 activity of CYP17 catalyzes the conversion of the common intermediate progesterone to 17-hydroxyprogesterone, a precursor of cortisol. Therefore the first activity of CYP17, the C17-hydroxylase activity, promotes the formation of glucocorticoids while the second

activity of CYP17, the C17,20-lyase activity, promotes the formation of sex hormones - particularly androgens including testosterone as well as estrogens.

Prostate cancer is currently one of the most frequently diagnosed forms of cancer in men in the U.S. and Europe. Prostate cancer is typically androgen-dependent and, accordingly, the reduction in androgen production via surgical or pharmacological castration remains the major treatment option for this indication. However, complete rather than partial withdrawal of androgens may be more effective in treating prostate cancer (Labrie, F. *et al.*, *Prostate*, 1983, 4, 579 and Crawford, E.D. *et al.*, *N. Engl. J. Med.*, 1989, 321, 419). Pharmacological inhibition of CYP17 may be a promising alternative treatment to antiandrogens and LHRH agonists in that testicular, adrenal, and peripheral androgen biosynthesis would be reduced rather than only testicular androgen production (Njar V, *et al.*, *J. Med. Chem.*, 1998, 41, 902). One such CYP17 inhibitor, the fungicide ketoconazole, has been used previously for prostate cancer treatment (Trachtenberg, J., *J. Urol.*, 1984, 132, 61 and Williams, G. *et al.*, *Br. J. Urol.*, 1986, 58, 45). However, this drug is a relatively non-selective inhibitor of cytochrome P450 (CYP) enzymes, has weak CYP17 activity, and has a number of notable side effects associated with it including liver damage (De Coster, R. *et al.*, *J. Steroid Biochem. Mol. Biol.*, 1996, 56, 133 and Lake-Bakaar, G. *et al.*, *Br. Med. J.*, 1987, 294, 419).

The importance of potent and selective inhibitors of CYP17 as potential prostate cancer treatments has been the subject of numerous studies and reviews (Njar, V. *et al.*, *Curr. Pharm. Design*, 1999, 5, 163; Barrie, S.E. *et al.*, *Endocr. Relat. Cancer*, 1996, 3, 25 and Jarman, M. *et al.*, *Nat. Prod. Rep.*, 1998, 495). Finasteride, a 5 α -reductase inhibitor, is an approved treatment for benign prostatic hyperplasia (BPH), although it is only effective with patients exhibiting minimal disease. While finasteride reduces serum DHT levels, it increases testosterone levels, and may therefore be insufficient for prostate cancer treatment (Peters, D. H. *et al.*, *Drugs*, 1993, 46, 177). Certain anti-androgenic steroids, for example, cyproterone acetate (17 α -acetoxy-6-chloro-1 α , 2 α -methylene-4,6-pregnadiene-3,20-dione), have been tested as adjuvant treatments for prostate cancer. Many other steroids have been tested as hydroxylase/lyase inhibitors. See, for example, PCT Specification WO 92/00992 (Schering AG) which describes anti-androgenic steroids having a pyrazole or triazole ring fused to the A ring at the 2,3-position, or European specifications EP-A288053 and EP-

A413270 (Merrell Dow) which propose 17β -cyclopropylamino-androst-5-en- 3β -ol or -4-en-3-one and their derivatives.

In addition to the use of CYP17 inhibitors in the treatment of prostate cancer, a second potential indication would be for estrogen-dependent breast cancer. In
5 postmenopausal patients with advanced breast cancer, treatment with high doses of ketoconazole resulted in suppression of both testosterone and estradiol levels, implicating CYP17 as a potential target for hormone therapy (Harris, A. L. *et al.*, *Br. J. Cancer*, 1988, 58, 493).

Chemotherapy is usually not highly effective, and is not a practical option for most
10 patients with prostate cancer because of the adverse side effects which are particularly detrimental in older patients. However, the majority of patients initially respond to hormone ablative therapy although they eventually relapse, as is typical with all cancer treatments (McGuire, in: *Hormones and Cancer*,. Iacobelli *et al.* Eds.; Raven Press, New York, 1980, Vol. 15, 337-344). Current treatment by orchidectomy or administration of gonadotropin-releasing hormone (GnRH) agonists results in reduced androgen production by the testis, but
15 does not interfere with androgen synthesis by the adrenals. Following three months of treatment with a GnRH agonist, testosterone and DHT concentrations in the prostate remained at 25% and 10%, respectively, of pretreatment levels (Forti *et al.*, *J. Clin. Endocrinol. Metab.*, 1989, 68, 461). Similarly, about 20% of castrated patients in relapse
20 had significant levels of DHT in their prostatic tissue (Geller *et al.*, *J. Urol.*, 1984, 132, 693). These findings suggest that the adrenals contribute precursor androgens to the prostate. This is supported by clinical studies of patients receiving combined treatment with either GnRH or orchidectomy and an anti-androgen, such as flutamide, to block the actions of androgens, including adrenal androgens. Such patients have increased progression-free survival time
25 compared to patients treated with GnRH agonist or orchidectomy alone (Crawford *et al.*, *N. Engl. J. Med.*, 1989, 321, 419 and Labrie *et al.*, *Cancer Suppl.*, 1993, 71, 1059).

Although patients initially respond to endocrine therapy, they frequently relapse. It was reported recently that in 30% of recurring tumors of patients treated with endocrine therapy, high-level androgen receptor (AR) amplification was found (Visakorpi, *et al.*,
30 *Nature Genetics*, 1995, 9, 401). Also, flutamide tends to interact with mutant ARs, and stimulate prostatic cell growth. This suggests that AR amplification may facilitate tumor cell growth in low androgen concentrations. Thus, total androgen blockade as first line

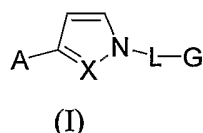
therapy may be more effective than conventional androgen deprivation by achieving maximum suppression of androgen concentrations which may also prevent AR amplification. It is presently unclear whether sequential treatment with different agents can prolong the benefits of the initial therapy. This strategy has been found effective in breast cancer treatment. New agents which act by different mechanisms could produce second responses in a portion of relapsed patients. Although the percentage of patients who respond to second-line hormonal therapy may be relatively low, a substantial number of patients may benefit because of the high incidence of prostate cancer. Furthermore, there is the potential for developing more potent agents than current therapies, none of which are completely effective in blocking androgen effects.

The need exists for C17,20 lyase inhibitors that overcome the above-mentioned deficiencies.

Summary of the Invention

The invention provides substituted 3-pyridyl heterocyclic compounds which inhibit the lyase activity of enzymes, e.g., 17 α -hydroxylase-C17,20 lyase.

Compounds of the invention have the formula I

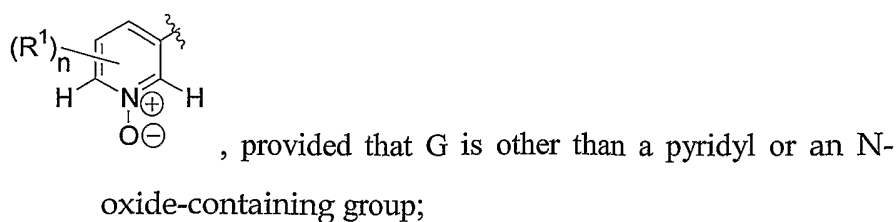
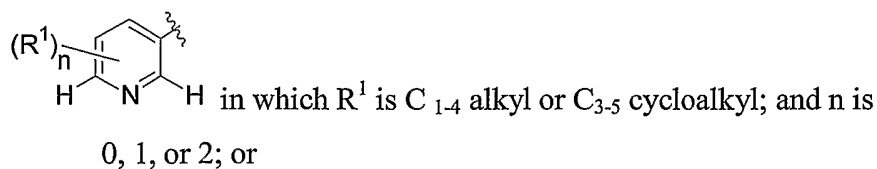


in which X represents CH or N.

When X is CH,

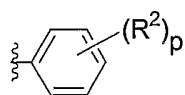
L represents a bond or a linker of formula $-(CH_2)_m-$ in which m is 1 or 2 ; and

A represents

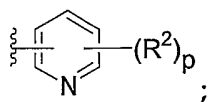


and

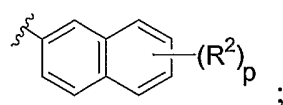
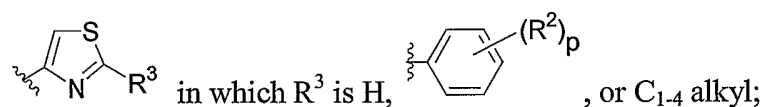
G represents



in which R^2 is C_{1-4} alkyl, C_{1-4} alkoxy, halogen, NO_2 , or CN; and p is 0, 1, or 2;



5

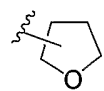


C_{1-6} alkyl;

C_{3-6} cycloalkyl;

10

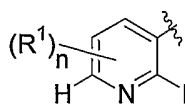
C_{2-4} alkenyl; or



When X is N,

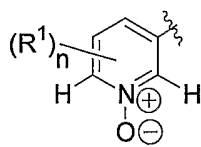
L represents a bond;

A represents



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in which R^1 is C_{1-4} alkyl or C_{3-5} cycloalkyl; and n is 0, 1, or 2; or

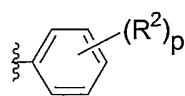


, provided that G is other than a pyridyl or an N-oxide-containing group;

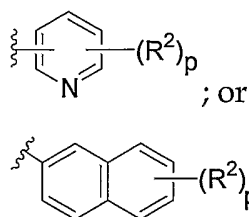
and

20

G represents



in which R^2 is C_{1-4} alkyl, C_{1-4} alkoxy, halogen, NO_2 , or CN; and p is 0, 1, or 2;



Pharmaceutically acceptable salts of these materials are also within the scope of the invention.

5

The invention also provides pharmaceutical compositions for inhibiting lyase activity, comprising a compound of the invention and a pharmaceutically acceptable carrier.

The invention also provides methods for inhibiting lyases, comprising contacting the lyase with a compound of the invention. More particularly, the invention provides a method of inhibiting a 17α -hydroxylase-C17,20 lyase, comprising contacting a 17α -hydroxylase-C17,20 lyase with a compound of the invention.

The invention further provides methods for treating diseases which can benefit from an inhibition of a lyase enzyme. Exemplary diseases are lyase-associated diseases, e.g., diseases resulting from an excess of androgens or estrogens. For example, the invention provides a method for treating cancer in a subject, comprising administering to the subject a pharmaceutically effective amount of a compound of the invention, such that the cancer is treated.

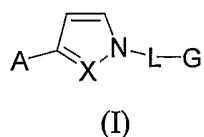
The method of treatment may be applied where the subject is equine, canine, feline, or a primate, in particular, a human.

The cancer may, for example, be prostate or breast cancer. Accordingly, a method for treating prostate cancer in a subject, comprises administering to the subject a therapeutically effective amount of a compound of the invention, such that the prostate cancer in the subject is treated. Similarly, a method for treating breast cancer in a subject comprises administering to the subject a therapeutically effective amount of a compound of the invention, such that the breast cancer in the subject is treated.

Detailed Description of the Invention

The invention is based at least in part on the discovery that substituted 3-pyridyl heterocyclic compounds inhibit the enzyme 17α -hydroxylase-C17,20 lyase.

In a preferred embodiment, compounds of the invention have the formula I

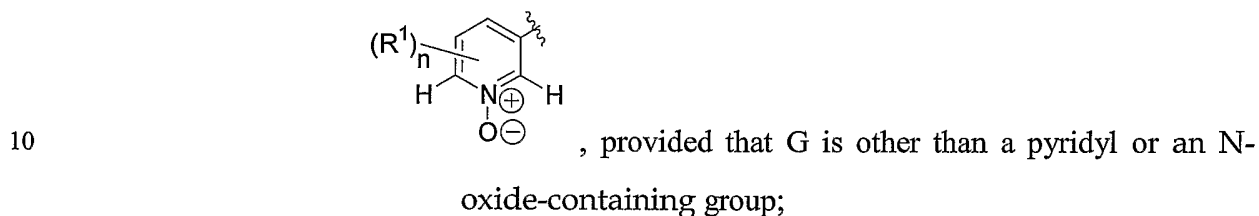
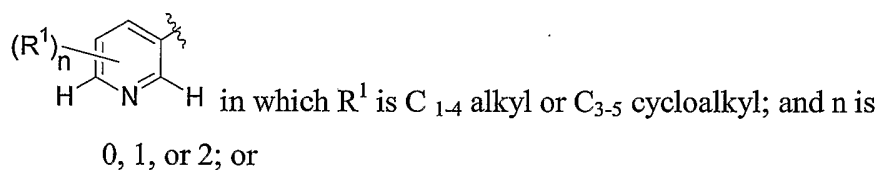


in which X represents CH or N.

5 When X is CH,

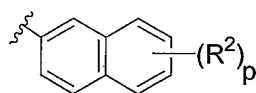
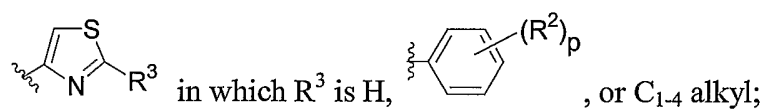
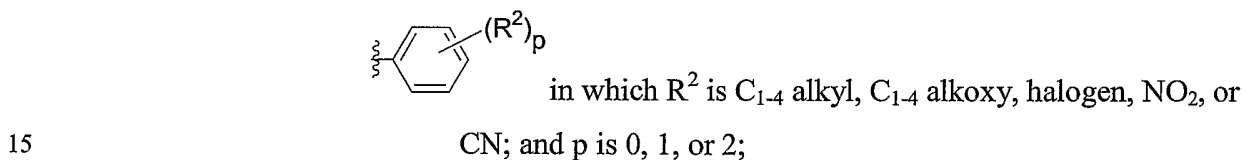
L represents a bond or a linker of formula $-(CH_2)_m-$ in which m is 1 or 2; and

A represents



and

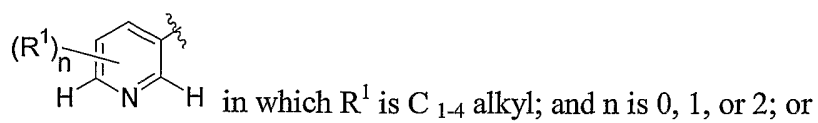
G represents

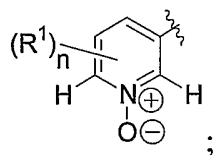


When X is N,

20 L represents a bond;

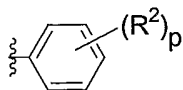
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and

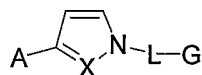
G represents



in which R^2 is halogen, and p is 0, 1, or 2.

5 Pharmaceutically acceptable salts of these materials are also within the scope of the invention.

In a more preferred embodiment, compounds of the invention have the formula I



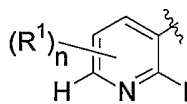
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(I)

in which X represents CH, and

L represents a bond or a linker of formula $-(CH_2)_m-$ in which m is 1 or 2; and

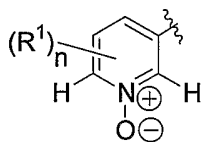
A represents



in which R^1 is C_{1-4} alkyl or C_{3-5} cycloalkyl; and n is

15

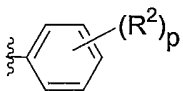
1; or



, provided that G is other than an N-oxide-containing group;

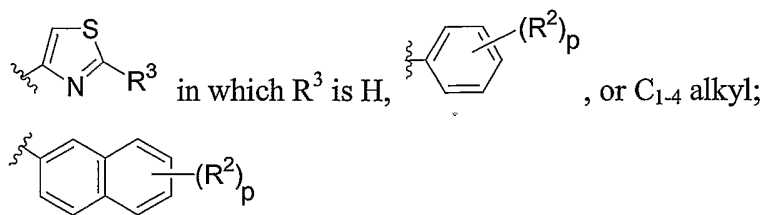
and

G represents



20

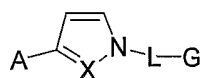
in which R^2 is C_{1-4} alkyl, C_{1-4} alkoxy, halogen, NO_2 , or CN; and p is 0, 1, or 2;



Pharmaceutically acceptable salts of these materials are also within the scope of the invention.

5

In a most preferred embodiment, compounds of the invention have the formula

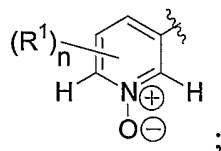
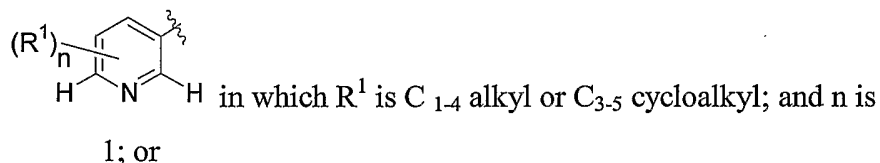


in which X represents CH and

L represents a bond or a linker of formula $-(CH_2)_m-$ in which m is 1 or 2 ; and

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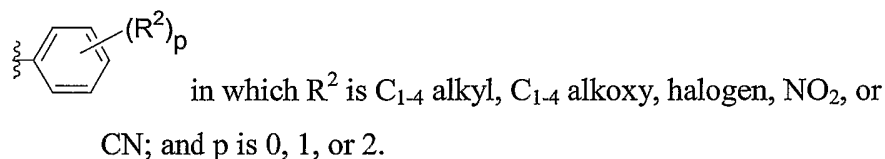
A represents



and

15

G represents



Pharmaceutically acceptable salts of these materials are also within the scope of the invention.

20

Definitions

The invention is based at least in part on the discovery that substituted 3-pyridyl pyrroles and pyrrazoles compounds inhibit the enzyme 17 α -hydroxylase-C17,20 lyase.

For convenience, certain terms employed in the specification, examples, and appended claims are collected here.

The term “agonist” of an enzyme refers to a compound that binds to the enzyme and stimulates the action of the naturally occurring enzyme, or a compound which mimics the activity of the naturally occurring enzyme.

The term “antagonist” of an enzyme refers to a compound that binds to the enzyme and inhibits the action of the naturally occurring enzyme.

The term “analog” of a compound refers to a compound having a some structural similarity to a particular compound and having essentially the same type of biological activity as the compound.

The term “CYP17 substrate” includes any of the various steroid hormones acted upon by a CYP17 or a CYP17-like P₄₅₀ enzyme. Examples include pregnenolone, progesterone and their 17 α -hydroxylated forms. Pregnenolone is converted to DHEA via a CYP17 C17,20-lyase reaction, but is also subject to C17 α -hydroxylation via the C17,20-lyase activity. Progesterone is converted to delta 4- androstenedione via a CYP17 C17,20-lyase reaction, but is also subject to C17 alpha-hydroxylation via the C17-hydroxylase activity to form 17-hydroxyl-progesterone, a precursor to hydrocortisone (i.e. cortisol).

The term “CYP17 metabolite” refers to any of the steroid hormones that are synthesized from a cholesterol precursor via a CYP17-mediated reaction, such as a C17-hydroxylase reaction or a C17,20-lyase reaction. Examples of CYP17 metabolites include the androgens, such as testosterone, which are synthesized via a CYP17 C17,20-lyase reaction from CYP17 substrate precursors such as pregnenolone (converted to DHEA by the CYP17 C17,20-lyase activity), and progesterone (converted to delta 4- androstenedione by the CYP17 C17,20-lyase activity). Progestagens such as progesterone are primarily synthesized in the corpus luteum. The androgens are responsible for, among other things, development of male secondary sex characteristics and are primarily synthesized in the testis. Other examples include the estrogens, which are also synthesized from a cholesterol precursor via a CYP17-mediated reaction. The estrogens are responsible for, among other things, the development of female secondary sex characteristics and they also participate in the ovarian cycle and are primarily synthesized in the ovary. Another group of CYP17 metabolites are the glucocorticoids, such as hydrocortisone (i.e. cortisol), which is

synthesized from progesterone via a CYP17-mediated reaction. The glucocorticoids, among other functions, promote gluconeogenesis and the formation of glycogen and also enhance the degradation of fat. The glucocorticoids are primarily synthesized in the adrenal cortex.

The term “CYP17 metabolite” is further meant to include other steroid hormones which, although not necessarily synthesized by a CYP17-mediated reaction, may nonetheless be understood by the skilled artisan to be readily affected by an alteration in a CYP17-mediated activity. For example, the mineralocorticoids, such as aldosterone, are derived from cholesterol via a progesterone intermediate. Since progesterone is also converted to the glucocorticoids and sex steroids via CYP17-mediated reactions, an alteration of a CYP17 activity can alter the amount of progesterone available for conversion to aldosterone. For example, inhibition of CYP17 activity can increase the amount of progesterone available for conversion into aldosterone. Therefore, inhibition of CYP17 can lead to an increase in the level of aldosterone. The mineralocorticoids function, among other things, to increase reabsorption of sodium ions, chloride ions, and bicarbonate ions by the kidney, which leads to an increase in blood volume and blood pressure. The mineralocorticoids are primarily synthesized in the adrenal cortex.

The term “CYP17 metabolite-associated disease or disorder” refers to a disease or disorder which may be treated by alteration of the level of one or more CYP17 metabolites. Examples include a hormone dependent cancer, such as an androgen-dependent prostate cancer, which may be treated by inhibiting CYP17-mediated androgen synthesis, and an estrogen-dependent breast cancer or ovarian cancer, which may be treated by inhibiting CYP17-mediated estrogen synthesis. Other examples of “CYP17 metabolite-associated diseases or disorders” are Cushing’s disease, hypertension, prostatic hyperplasia, and glucocorticoid deficiency. Patients with Cushing's syndrome are relatively insensitive to glucocorticoid feedback and exhibit an oversecretion of cortisol devoid of a circadian cycle (see e.g. Newell-Price & Grossman (2001) *Ann. Endocrinol.* 62: 173-9). Another CYP17 metabolite-associated disease or disorder is hypertension. Mineralocorticoid excess causes hypertension by facilitating the sodium retention at renal tubules.

The term “derivative” of a compound refers to another compound which can be derived, e.g., by chemical synthesis, from the original compound. Thus a derivative of a compound has certain structural similarities with the original compound.

“Disease associated with an abnormal activity or level of a lyase” refers to diseases in which an abnormal activity or protein level of a lyase is present in certain cells, and in which the abnormal activity or protein level of the lyase is at least partly responsible for the disease.

5 A “disease associated with a lyase” refers to a disease that can be treated with a lyase inhibitor, such as the compounds disclosed herein.

A “lyase” refers to an enzyme having a lyase activity.

“Lyase activity” refers to the activity of an enzyme to catalyze the cleavage of the bond C17-C20 in 17 α -hydroxy-pregnenolone and 17 α -hydroxy-progesterone to form
10 dehydroepiandrosterone (DHEA) and delta4-androstenedione, respectively. Lyase activity also refers to the cleavage of a similar bond in related compounds.

A “lyase inhibitor” is a compound which inhibits at least part of the activity of a lyase in a cell. The inhibition can be at least about 20%, preferably at least about 40%, even more preferably at least about 50%, 70%, 80%, 90%, 95%, and most preferably at least
15 about 98% of the activity of the lyase.

A "patient" or "subject" to be treated by the subject method can mean either a human or non-human animal.

“Treating” a disease refers to preventing, curing or improving at least one symptom of a disease.

20 The following definitions pertain to the chemical structure of compounds:

The term "heteroatom" as used herein means an atom of nitrogen, oxygen, or sulfur.

The term "alkyl" refers to the radicals of saturated aliphatic groups, including straight-chain alkyl groups and branched-chain alkyl groups.

The term “cycloalkyl” (alicyclic) refers to radicals of cycloalkyl compounds,
25 examples being cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, etc.

The term "aralkyl", as used herein, refers to an alkyl group substituted with an aryl group (e.g., an aromatic or heteroaromatic group).

The terms "alkenyl" and "alkynyl" refer to unsaturated aliphatic groups that contain at least one double or triple bond respectively.

Unless the number of carbons is otherwise specified, "lower alkyl" as used herein means an alkyl group but having from one to six carbons, preferably from one to four carbon atoms in its backbone structure. Likewise, "lower alkenyl" and "lower alkynyl" have similar chain lengths. Preferred alkyl groups are lower alkyls.

5 The term "aryl" as used herein means an aromatic group of 6 to 14 carbon atoms in the ring(s), for example, phenyl and naphthyl. As indicated, the term "aryl" includes polycyclic ring systems having two or more rings in which two or more carbons are common to two adjoining rings (the rings are "fused rings") wherein at least one of the rings is aromatic.

10 The term "heteroaryl" as used herein means an aromatic group which contains at least one heteroatom in at least one ring. Typical examples include 5-, 6- and 7-membered single-ring aromatic groups that may include from one to four heteroatoms. Examples include pyrrole, furan, thiophene, imidazole, oxazole, thiazole, triazole, tetrazole, pyrazole, pyridine, pyrazine, pyridazine and pyrimidine, and the like. These aryl groups may also be
15 referred to as "aryl heterocycles" or "heteroaromatics."

The terms *ortho*, *meta* and *para* apply to 1,2-, 1,3- and 1,4-disubstituted benzenes, respectively. For example, the names 1,2-dimethylbenzene and *ortho*-dimethylbenzene are synonymous.

20 The terms "alkoxyl" or "alkoxy" as used herein refer to moiety in which an alkyl group is bonded to an oxygen atom, which is in turn bonded to the rest of the molecule. Examples are methoxy, ethoxy, propyloxy, *tert*-butoxy, etc.

As used herein, the term "nitro" means -NO₂; the term "halogen" designates -F, -Cl, -Br or -I; the term "sulfhydryl" means -SH; the term "hydroxyl" means -OH; and the term "sulfonyl" means -SO₂-.

25 The terms triflyl, tosyl, mesyl, and nonaflyl are art-recognized and refer to trifluoromethanesulfonyl, *p*-toluenesulfonyl, methanesulfonyl, and nonafluorobutanesulfonyl groups, respectively. The terms triflate, tosylate, mesylate, and nonaflate are art-recognized and refer to trifluoromethanesulfonate ester, *p*-toluenesulfonate ester, methanesulfonate ester, and nonafluorobutanesulfonate ester functional groups and molecules that contain said
30 groups, respectively.

The abbreviations Me, Et, Ph, Tf, Nf, Ts, Ms represent methyl, ethyl, phenyl, trifluoromethanesulfonyl, nonafluorobutanesulfonyl, *p*-toluenesulfonyl and methanesulfonyl, respectively. A more comprehensive list of the abbreviations utilized by organic chemists of ordinary skill in the art appears in the first issue of each volume of the *Journal of Organic Chemistry*; (i.e., *J. Org. Chem.* **2002**, 67(1), 24A. The abbreviations contained in said list, and all abbreviations utilized by organic chemists of ordinary skill in the art are hereby incorporated by reference.

As used herein, the definition of each expression, e.g. alkyl, m, n, etc., when it occurs more than once in any structure, is intended to be independent of its definition elsewhere in the same structure.

It will be understood that "substitution" or "substituted with" includes the implicit proviso that such substitution is in accordance with permitted valence of the substituted atom and the substituent, and that the substitution results in a stable compound, e.g., which does not spontaneously undergo transformation such as by rearrangement, cyclization, elimination, etc.

As used herein, the term "substituted" is contemplated to include all permissible substituents of organic compounds. In a broad aspect, the permissible substituents include acyclic and cyclic, branched and unbranched, carbocyclic and heterocyclic, aromatic and nonaromatic substituents of organic compounds. Illustrative substituents include, for example, those described herein above. The permissible substituents can be one or more and the same or different for appropriate organic compounds. For purposes of this invention, the heteroatoms such as nitrogen may have hydrogen substituents and/or any permissible substituents of organic compounds described herein which satisfy the valences of the heteroatoms.

The phrase "protecting group" as used herein means temporary substituents which protect a potentially reactive functional group from undesired chemical transformations. Examples of such protecting groups include esters of carboxylic acids, silyl ethers of alcohols, and acetals and ketals of aldehydes and ketones, respectively. The field of protecting group chemistry has been reviewed (Greene, T.W.; Wuts, P.G.M. *Protective Groups in Organic Synthesis*, 3rd ed.; Wiley: New York, 1999).

Abbreviations and Acronyms

When the following abbreviations are used throughout the disclosure, they have the following meaning:

5	Å	angstrom
	amu	atomic mass units
	Ar	argon
	CD ₂ Cl ₂	methylene chloride-d ₂
	CDCl ₃	chloroform- <i>d</i>
10	CH ₂ Cl ₂	methylene chloride
	CI	chemical ionization (for mass spectrometry)
	CPM	counts per minute
	DMSO	dimethylsulfoxide
	DMSO- <i>d</i> ₆	dimethylsulfoxide- <i>d</i> ₆
15	EI	electron impact (for mass spectrometry)
	EPA	Environmental Protection Agency (as in EPA vial)
	eq	equivalent(s)
	ES	electrospray (for mass spectrometry)
	EtOAc	ethyl acetate
20	g	gram
	GCMS	gas chromatography/mass spectrometry
	h	hours
	HCl	hydrochloric acid
	¹ H NMR	proton nuclear magnetic resonance
25	HEPES	4-(2-Hydroxyethyl piperazine-1-ethane sulfonic acid)
	HPLC	high performance liquid chromatography
	LC/MS	liquid chromatography / mass spectroscopy
	M	molar
	MeOH	methanol
30	mg	milligram
	min	minute(s)
	mL	milliliter
	mm	millimeter

	mmol	millimol
	MS	mass spectrometry
	MTBE	methyl tert-butyl ether
	<i>m/z</i>	mass to charge ratio (for mass spectrometry)
5	NaHCO ₃	sodium bicarbonate
	NaOH	sodium hydroxide
	Na ₂ SO ₄	sodium sulfate
	NH ₄ Cl	ammonium chloride
	NMR	Nuclear magnetic
10	OTf	trifluoroacetate (triflate)
	OTs	<i>p</i> -toluenesulfonate (tosylate)
	psi	pounds per square inch
	R _f	TLC retention factor
	rt	room temperature
15	SPA	Scintillation Proximity Assay
	TFA	trifluoroacetic acid
	THF	tetrahydrofuran
	TMS	tetramethylsilane
	TLC	thin layer chromatography
20	t _R	retention time
	μL	microliter

Compounds of the Invention

Exemplary compounds of the invention are set forth in Table 1 below. The
 25 exemplary compounds of Tables 1 are producible from known compounds (or from starting
 materials which, in turn, are producible from known compounds), through the general
 preparative methods described in the General Methods or Examples.

Table 1. Exemplary Compounds of the Invention

Compound No.	Compound Name
1	3-[1-benzylpyrrol-3-yl]pyridine
2	3-{1-[(4-chlorophenyl)methyl]pyrrol-3-yl}pyridine
3	3-{1-[(3-chlorophenyl)methyl]pyrrol-3-yl}pyridine

Compound No.	Compound Name
4	3-{1-[(2-chlorophenyl)methyl]pyrrol-3-yl}pyridine
5	3-{1-[(4-chlorophenyl)methyl]pyrrol-3-yl}-4-methylpyridine
6	3-{1-[(4-bromophenyl)methyl]pyrrol-3-yl}-4-methylpyridine
7	4-methyl-3-{1-[(3-nitrophenyl)methyl]pyrrol-3-yl}pyridine
8	4-methyl-3-{1-[(2-nitrophenyl)methyl]pyrrol-3-yl}pyridine
9	3-{1-[(3-chlorophenyl)methyl]pyrrol-3-yl}-4-methylpyridine
10	3-{1-[(3,4-dichlorophenyl)methyl]pyrrol-3-yl}-4-methylpyridine
11	3-{1-[(2,4-dichlorophenyl)methyl]pyrrol-3-yl}-4-methylpyridine
12	2-{[3-(4-methyl-3-pyridyl)pyrrolyl]methyl}benzenecarbonitrile
13	4-{[3-(4-methyl-3-pyridyl)pyrrolyl]methyl}benzenecarbonitrile
14	3-{1-[(4-fluorophenyl)methyl]pyrrol-3-yl}-4-methylpyridine
15	4-methyl-3-(1-{[4-(2-propyl)phenyl]methyl}pyrrol-3-yl)pyridine
16	4-methoxy-1-{[3-(4-methyl(3-pyridyl))pyrrolyl]methyl}benzene
17	2-methyl-4-{[3-(4-methyl(3-pyridyl))pyrrolyl]methyl}-1,3-thiazole
18	2-(4-chlorophenyl)-4-{[3-(4-methyl(3-pyridyl))pyrrolyl]methyl}-1,3-thiazole
19	4-methyl-3-[1-(2-naphthylmethyl)pyrrol-3-yl]pyridine
20	3-[1-(cyclohexylmethyl)pyrrol-3-yl]-4-methylpyridine

Compound No.	Compound Name
21	3-[1-(cyclobutylmethyl)pyrrol-3-yl]-4-methylpyridine
22	2-{{3-(4-methyl-3-pyridyl)pyrrolyl}methyl}oxolane
23	3-[1-(2-ethylbutyl)pyrrol-3-yl]-4-methylpyridine
24	3-[1-((2E)-3-methylbut-2-enyl)pyrrol-3-yl]-4-methylpyridine
25	4-methyl-3-(1-phenylpyrrol-3-yl)pyridine
26	1-(2,4-dichlorophenyl)-3-(3-pyridyl)pyrazole
27	4-methoxy-1-(3-(3-pyridyl)pyrazolyl)benzene
28	1-(3-fluorophenyl)-3-(4-methyl(3-pyridyl))pyrazole
29	3-(4-methyl(3-pyridyl))-1-(4-methylphenyl)pyrazole
30	1-(3-chlorophenyl)-3-(4-methyl(3-pyridyl))pyrazole
31	1-(3,4-dichlorophenyl)-3-(4-methyl(3-pyridyl))pyrazole
32	3-(4-methyl(3-pyridyl))-1-(4-nitrophenyl)pyrazole
33	3-(4-methyl(3-pyridyl))-1-(2-naphthyl)pyrazole
34	1-(4-chlorophenyl)-3-(4-methyl(3-pyridyl))pyrazole
35	1-(4-fluorophenyl)-3-(4-methyl(3-pyridyl))pyrazole
36	3-(4-methyl(3-pyridyl))-1-(3-nitrophenyl)pyrazole

Certain compounds of the present invention may exist in particular geometric or stereoisomeric forms. The present invention contemplates all such compounds, including *cis*- and *trans*-isomers, *R*- and *S*-enantiomers, diastereomers, (D)-isomers, (L)-isomers, the racemic mixtures thereof, and other mixtures thereof, as falling within the scope of the invention. Additional asymmetric carbon atoms may be present in a substituent such as an alkyl group. All such isomers, as well as mixtures thereof, are intended to be included in this invention.

If, for instance, a particular enantiomer of a compound of the present invention is desired, it may be prepared by asymmetric synthesis, or by derivation with a chiral auxiliary, where the resulting diastereomeric mixture is separated and the auxiliary group cleaved to provide the pure desired enantiomers. Alternatively, where the molecule contains a basic functional group, such as amino, or an acidic functional group, such as carboxyl, diastereomeric salts are formed with an appropriate optically-active acid or base, followed by resolution of the diastereomers thus formed by fractional crystallization or

chromatographic means well known in the art, and subsequent recovery of the pure enantiomers.

Compounds may contain a basic functional group, such as amino or alkylamino, and are, thus, capable of forming pharmaceutically-acceptable salts with pharmaceutically-acceptable acids. The term "pharmaceutically-acceptable salts" in this respect, refers to the relatively non-toxic, inorganic and organic acid addition salts of compounds of the present invention. These salts can be prepared *in situ* during the final isolation and purification of the compounds of the invention, or by separately reacting a purified compound of the invention in its free base form with a suitable organic or inorganic acid, and isolating the salt thus formed. Representative salts include the hydrobromide, hydrochloride, sulfate, bisulfate, phosphate, nitrate, acetate, valerate, oleate, palmitate, stearate, laurate, benzoate, lactate, phosphate, tosylate, citrate, maleate, fumarate, succinate, tartrate, naphthylate, mesylate, glucoheptonate, lactobionate, and laurylsulphonate salts and the like. (See, for example, Berge et al. (1977) "Pharmaceutical Salts", *J. Pharm. Sci.* 66:1-19).

Pharmaceutically acceptable salts of the subject compounds include the conventional nontoxic salts or quaternary ammonium salts of the compounds, e.g., from non-toxic organic or inorganic acids. For example, such conventional nontoxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric, and the like; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, palmitic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isothionic, and the like.

In other cases, the compounds of the present invention may contain one or more acidic functional groups and, thus, are capable of forming pharmaceutically-acceptable salts with pharmaceutically-acceptable bases. These salts can be prepared *in situ* during the final isolation and purification of the compounds, or by separately reacting the purified compound in its free acid form with a suitable base, such as the hydroxide, carbonate or bicarbonate of a pharmaceutically-acceptable metal cation, with ammonia, or with a pharmaceutically-acceptable organic primary, secondary or tertiary amine. Representative alkali or alkaline earth salts include the lithium, sodium, potassium, calcium, magnesium, and aluminum salts and the like. Representative organic amines useful for the formation of base addition salts include ethylamine, diethylamine, ethylenediamine, ethanolamine, diethanolamine, piperazine and the like. (See, for example, Berge et al., *supra*).

Contemplated equivalents of the compounds described above include compounds which otherwise correspond thereto, and which have the same general properties thereof (e.g., functioning as 17 α -hydroxylase-C17,20-lyase inhibitors), wherein one or more simple

variations of substituents are made which do not adversely affect the efficacy of the compound in binding to 17 α -hydroxylase-C17,20-lyase receptors. In general, the compounds of the present invention may be prepared by the methods illustrated in the general reaction schemes as, for example, described below, or by modifications thereof, using readily available starting materials, reagents and conventional synthesis procedures. In these reactions, it is also possible to make use of variants which are in themselves known, but are not mentioned here.

Diseases that can be treated with the compounds of the invention

The present invention also provides a method of inhibiting a lyase, e.g., 17 α -hydroxylase-C17,20 lyase, comprising contacting a lyase with a compound of the invention. The activity can be inhibited by at least 20%, preferably at least about 50%, more preferably at least about 60%, 70%, 80%, 90%, 95%, and most preferably at least about 98%. In one embodiment, the invention provides a method for inhibiting a lyase *in vitro*. In a preferred embodiment, the lyase is *in vivo* or *ex vivo*. For example, the invention provides methods for inhibiting a lyase in a cell, comprising contacting the cell with a compound of the invention, such that the activity of the lyase is inhibited. The cell may further be contacted with a composition stimulating the uptake of the compound into the cell. In one embodiment, the invention provides a method for inhibiting a lyase in a cell of a subject, comprising administering to the subject a therapeutically effective amount of a compound of the present invention, or a formulation comprising a compound of the present invention, such that the lyase is inhibited in a cell of the subject. The subject can be a subject having a disease associated with a lyase, e.g., cancer. Preferred types of cancer that can be treated according to the invention include prostate cancer and breast cancer. Other diseases that can be treated include diseases in which it is desired to prevent or inhibit the formation of a hormone selected from the group consisting of the androgens testosterone and dihydrotestosterone (DHT) and the estrogens 17 β -estradiol and estrone. Generally, any disease that be treated by inhibiting the activity of a lyase, e.g., 17 α -Hydroxylase-C17,20-lyase, can be treated with the compounds of the invention.

In general, the invention provides methods and compositions for the treatment of CYP17 metabolite-associated diseases and disorders. Examples include particularly sex steroid hormone dependent cancers, such as androgen-dependent prostate cancer, which may be treated by inhibiting CYP17-mediated androgen synthesis, and estrogen-dependent breast

cancer or ovarian cancer, which may be treated by inhibiting CYP17-mediated estrogen synthesis.

For example, adenocarcinoma of the prostate is a common disease that causes significant morbidity and mortality in the adult male population (see Han and Nelson (2000) Expert Opin Pharmacother. 1: 443-9). Hormonal therapy for prostate cancer is considered when a patient fails with initial curative therapy, such as radical prostatectomy or definitive radiation therapy, or if he is found with an advanced disease. Hormonal agents have been developed to exploit the fact that prostate cancer growth is dependent on androgen. Non-steroidal anti-androgens (NSAAs) block androgen at the cellular level. Castration is another, albeit drastic means of decreasing androgens levels in order to treat or prevent prostate cancer. The methods and compositions of the invention are useful in inhibiting the C17,20 lyase activity of CYP17 and thereby decreasing levels of androgen production and the associated growth of androgen-dependent cancers such as prostate cancer.

In another example, breast cancer, particularly breast cancer in postmenopausal women, can be treated by administration of a C17,20-lyase inhibitor of the invention because adrenal and ovarian androgens are the main precursors of the estrogens which stimulate the growth of hormone dependent breast cancer. In addition, breast cancer can be treated with inhibitors of aromatase that prevent interconversion of estrogens and adrenal and ovarian androgens (see Harris et al. (1983) Eur. J. Cancer Clin. Oncol. 19: 11). Patients failing to respond to aromatase inhibitors show elevated levels of androgens in response to aromatase inhibitor treatment (see Harris et al. (1988) Br. J. Cancer 58: 493-6). Accordingly sequential blockade to inhibit androgen production as well as inhibit aromatase may produce greater estrogen suppression and enhanced therapeutic effects in treating breast and other estrogen hormone-dependent forms of cancer. Therefore the inhibitors of the invention may be used alone or in combination with other drugs to treat or prevent hormone-dependent cancers such as breast and prostate cancer.

Furthermore, susceptibility to prostate cancer and breast cancer has been associated with particular polymorphic alleles of the CYP17 gene (see e.g. McKean-Cowdin (2001) Cancer Res 61: 848-9; Haiman et al. (2001) Cancer Epidemiol Biomarkers 10: 743-8; Huang et al. (2001) Cancer Res 59: 4870-5). Accordingly, the compositions of the invention are particularly suited to treating or preventing hormone-dependent cancers in individuals

genetically predisposed to such cancers, particularly those predisposed due to an alteration in the CYP17 gene.

Another group of CYP17 metabolite-associated diseases or disorders amenable to treatment with the compositions and methods of the invention include those associated with mineralocorticoid excess such as hypertension caused by sodium retention at renal tubules. Such a mechanism operates in hypertension such as primary hyperaldosteronism and some forms of congenital adrenal hyperplasia. Recently, deficient cortisol metabolism in the aldosterone target organ has been recognized as a novel form of hypertension known as apparent mineralocorticoid excess. Disorders associated with mineralocorticoid synthesis include abnormalities of mineralocorticoid synthesis and/or metabolism which profoundly affect the regulation of electrolyte and water balance and of blood pressure (see e.g. Connell et al. (2001) *Baillieres Best Pract Res Clin Endocrinol Metab* 15:43-60). Characteristic changes in extracellular potassium, sodium and hydrogen ion concentrations are usually diagnostic of such disorders. Serious deficiency may be acquired, for example in Addison's disease, or inherited. In most of the inherited syndromes, the precise molecular changes in specific steroidogenic enzymes have been identified. Mineralocorticoid excess may be caused by aldosterone or 11-deoxycorticosterone by inadequate conversion of cortisol to cortisone by 11beta-hydroxysteroid dehydrogenase type 2 in target tissues, by glucocorticoid receptor deficiency or by constitutive activation of renal sodium channels. Changes in electrolyte balance and renin as well as the abnormal pattern of corticosteroid metabolism are usually diagnostic. Where these abnormalities are inherited (e.g. 11beta- or 17alpha-hydroxylase deficiencies, glucocorticoid remediable hyperaldosteronism (GRA), receptor defects, Liddle's syndrome), the molecular basis is again usually known and, in some cases, may provide the simplest diagnostic tests. Primary aldosteronism, although readily identifiable, presents problems of differential diagnosis, important because optimal treatment is different for each variant. Finally, a significant proportion of patients with essential hypertension show characteristics of mild mineralocorticoid excess, for example low renin levels. As described above, a decrease in CYP17 activity can result in an alteration in mineralocorticoid (e.g. aldosterone) biosynthesis. Accordingly, the "CYP17 metabolite-associated diseases or disorders" of the invention would include those associated with altered levels of aldosterone production (e.g. hypertension, primary adrenal hyperplasia).

Still other examples of CYP17 metabolite-associated diseases or disorders' are Cushing's disease, prostatic hyperplasia, glucocorticoid deficiency, and endometrial cancer.

The subject that can be treated according to the invention can be a mammal, e.g., a primate, equine, canine, bovine, ovine, porcine, or feline. In preferred embodiments of this method, the mammal is a human. In other embodiments, the invention provides methods for inhibiting the lyase activity of enzymes that are present in organisms other than mammals, e.g., yeast and fungus, e.g., mildew. Certain compounds of the invention may function as antifungal compounds.

10 Methods of administering the compounds of the invention

The therapeutic methods of the invention generally comprise administering to a subject in need thereof, a pharmaceutically effective amount of a compound. The compounds of the invention can be administered in an amount effective to inhibit the activity of a 17α -Hydroxylase-C17,20-lyase. The compounds of this invention may be administered to mammals, preferably humans, either alone or, preferably, in combination with pharmaceutically acceptable carriers, excipients or diluents, in a pharmaceutical composition, according to standard pharmaceutical practice. The compounds can be administered orally or parenterally, including the intravenous, intramuscular, intraperitoneal, subcutaneous, rectal and topical routes of administration.

20 Toxicity and therapeutic efficacy of the compounds can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, e.g., for determining the LD_{50} (the dose lethal to 50% of the population) and the ED_{50} (the dose therapeutically effective in 50% of the population). The dose ratio between toxic and therapeutic effects is the therapeutic index and it can be expressed as the ratio LD_{50}/ED_{50} . Compounds which exhibit large therapeutic indices are preferred. While compounds that exhibit toxic side effects may be used, care should be taken to design a delivery system that targets such reagents to the site of affected tissue in order to minimize potential damage to normal cells and, thereby, reduce side effects.

Data obtained from cell culture assays and animal studies can be used in formulating a range of dosage for use in humans. The dosage of such reagents lies preferably within a range of circulating concentrations that include the ED_{50} with little or no toxicity. The

dosage may vary within this range depending upon the dosage form employed and the route of administration utilized. For any reagent used in the method of the invention, the therapeutically effective dose can be estimated initially from cell culture assays. A dose may be formulated in animal models to achieve a circulating plasma concentration range that includes the IC_{50} (i.e., the concentration of the test compound which achieves a half-maximal inhibition of symptoms) as determined in cell culture. Such information can be used to more accurately determine useful doses in humans. The compounds of the invention have an IC_{50} less than $10\mu M$ as determined by the biochemical or cellular assay described herein. Some compounds of the invention are effective at concentrations of $10nM$, $100nM$, or $1\mu M$. Based on these numbers, it is possible to derive an appropriate dosage for administration to subjects.

Pharmaceutical compositions containing a compound of the invention may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, microcrystalline cellulose, sodium crosscarmellose, corn starch, or alginic acid; binding agents, for example starch, gelatin, polyvinyl-pyrrolidone or acacia, and lubricating agents, for example, magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to mask the unpleasant taste of the drug or delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a water soluble taste masking material such as hydroxypropylmethyl-cellulose or hydroxypropylcellulose, or a time delay material such as ethyl cellulose, cellulose acetate butyrate may be employed.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate,

calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water soluble carrier such as polyethyleneglycol or an oil medium, for example peanut oil, liquid paraffin, or olive oil.

Aqueous suspensions contain the active material in admixture with excipients
5 suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene
10 stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethylene-oxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous
15 suspensions may also contain one or more preservatives, for example ethyl, or n-propyl p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose, saccharin or aspartame.

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in mineral oil
20 such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as butylated hydroxyanisol or alpha-tocopherol.

25 Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the compound of the invention in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring
30 agents, may also be present. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Pharmaceutical compositions of the invention may also be in the form of an oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring phosphatides, for example soy bean lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening, flavouring agents, preservatives and antioxidants.

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative, flavoring and coloring agents and antioxidant.

Pharmaceutical compositions may be in the form of a sterile injectable aqueous solutions. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution.

Sterile injectable preparation may also be a sterile injectable oil-in-water microemulsion where the compound of the invention is dissolved in the oily phase. For example, the active ingredient may be first dissolved in a mixture of soybean oil and lecithin. The oil solution then introduced into a water and glycerol mixture and processed to form a microemulsion.

The injectable solutions or microemulsions may be introduced into a patient's bloodstream by local bolus injection. Alternatively, it may be advantageous to administer the solution or microemulsion in such a way as to maintain a constant circulating concentration of the instant compound. In order to maintain such a constant concentration, a continuous intravenous delivery device may be utilized. An example of such a device is the Deltec CADD-PLUS™ model 5400 intravenous pump.

The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleagenous suspension for intramuscular and subcutaneous administration. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1,3-butane diol. In

addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

5 Compounds of the invention may also be administered in the form of a suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials include cocoa butter, glycerinated gelatin, hydrogenated vegetable oils, mixtures of
10 polyethylene glycols of various molecular weights and fatty acid esters of polyethylene glycol.

For topical use, creams, ointments, jellies, solutions or suspensions, etc., containing the compound of the invention can be employed. For purposes of this application, topical application shall include mouth washes and gargles.

15 The compounds for the present invention can be administered in intranasal form via topical use of suitable intranasal vehicles and delivery devices, or via transdermal routes, using those forms of transdermal skin patches well known to those of ordinary skill in the art. To be administered in the form of a transdermal delivery system, the dosage administration will preferably be continuous rather than intermittent throughout the dosage
20 regimen.

The compounds of the invention may also be co-administered with other well known therapeutic agents that are selected for their particular usefulness against the condition that is being treated. The compounds may be administered simultaneously or sequentially. For example, the instant compounds may be useful in combination with known anti-cancer and
25 cytotoxic agents. Similarly, the instant compounds may be useful in combination with agents that are effective in the treatment and prevention of osteoporosis, inflammation, neurofibromatosis, restinosis, and viral infections. The instant compounds may also be useful in combination with inhibitors of other components of signaling pathways of cell surface growth factor receptors.

30 Drugs can be co-administered to a subject being treated with a compound of the invention include antineoplastic agents selected from vinca alkaloids, epipodophyllotoxins,

anthracycline antibiotics, actinomycin D, plicamycin, puromycin, gramicidin D, taxol, colchicine, cytochalasin B, emetine, maytansine, or amsacrine. Methods for the safe and effective administration of most of these chemotherapeutic agents are known to those skilled in the art. In addition, their administration is described in the standard literature. For
5 example, the administration of many of the chemotherapeutic agents is described in the "Physicians' Desk Reference" (PDR), e.g., 1996 edition (Medical Economics Company, Montvale, N.J. 07645-1742, USA).

Radiation therapy, including x-rays or gamma rays which are delivered from either an externally applied beam or by implantation of tiny radioactive sources, may also be used
10 in combination with a compound of the invention to treat a disease, e.g., cancer.

When a composition according to this invention is administered into a human subject, the daily dosage will normally be determined by the prescribing physician with the dosage generally varying according to the age, weight, and response of the individual patient, as well as the severity of the patient's symptoms.

15

Kits of the invention

In one embodiment, materials and reagents required for administering the compounds of the invention may be assembled together in a kit. When the components of the kit are provided in one or more liquid solutions, the liquid solution preferably is an aqueous
20 solution, with a sterile aqueous solution being particularly preferred.

The kit may further comprise one or more other drugs, e.g., a chemo- or radiotherapeutic agent. These normally will be a separate formulation, but may be formulated into a single pharmaceutically acceptable composition. The container means may itself be geared for administration, such as an inhalant, syringe, pipette, eye dropper, or other
25 such like apparatus, from which the formulation may be applied to an infected area of the body, such as the lungs, or injected into an animal, or even applied to and mixed with the other components of the kit.

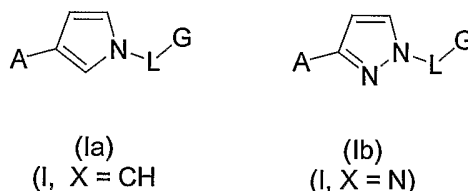
The compositions of these kits also may be provided in dried or lyophilized forms. When reagents or components are provided as a dried form, reconstitution generally is by the
30 addition of a suitable solvent. It is envisioned that the solvent also may be provided in

another container means. The kits of the invention may also include an instruction sheet defining administration of the agent.

The kits of the present invention also will typically include a means for containing the vials in close confinement for commercial sale such as, e.g., injection or blow-molded plastic containers into which the desired vials are retained. Irrespective of the number or type of containers, the kits of the invention also may comprise, or be packaged with a separate instrument for assisting with the injection/administration or placement of the ultimate complex composition within the body of an animal. Such an instrument may be an inhalant, syringe, pipette, forceps, measured spoon, eye dropper or any such medically approved delivery vehicle. Other instrumentation includes devices that permit the reading or monitoring of reactions or amounts of compounds or polypeptides.

General Method for the Preparation of Compounds of Formula I

3-(3-Pyridyl)pyrroles Ia (Formula I, where X represents CH) and the 3-(3-pyridyl)pyrazoles Ib (Formula I, where X represents N), wherein A, L, and G are as defined in hereinabove are prepared by the general method described below, according to methods described below, or according to methods commonly employed in the art.

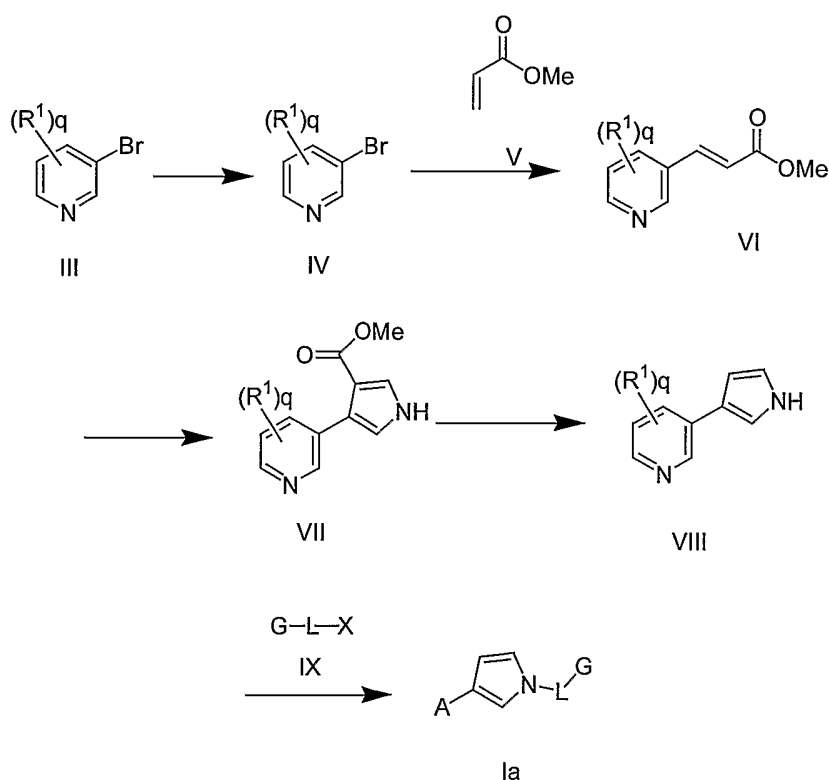


The 3-bromopyridines IV used to prepare compounds of Formula Ia are prepared according to method described by Comins (Comins, D. L., Smith, R., Stroud, E., Heterocycles, Vol. 22, No. 2, 1984, 339) or by other methods commonly employed in the art to prepare 4-alkyl-3-bromopyridines. The requisite 3-bromopyridines III, where q = 0 or 1, are commercially available, can be prepared by Suzuki coupling with alkyl or cycloalkylboronic acids with 3,5-dibromopyridine or with 3-(trifluoromethanesulfonyloxy)-5-bromopyridine, or by other methods commonly employed in the art. Treatment of 3-bromopyridines IV with an alkyl acrylate V, preferably methyl acrylate, in the presence of a palladium (II) or a palladium (0) catalyst, preferably a palladium (II) catalyst, and in the presence of a phosphine, preferably (o-tolyl)₃P, provides vinyl pyridines VI. Alternatively, vinyl pyridines VI can be prepared

according to the methods used in the preparation of Intermediates A, B, and I-N below, or by other methods commonly employed in the art. Treatment of vinyl pyridines VI with an aryl methyl isocyanide and an alkali bis(trimethylsilyl)amide, preferably tosyl methyl isocyanide and sodium bis(trimethylsilyl)amide respectively, affords intermediates VII. Hydrolysis and decarboxylation affords pyridyl pyrroles VIII. Alternatively, the methods used in the preparation of Intermediates A, B, and I-N below, or other methods commonly employed in the art, may be used to prepare intermediates VIII. Alkylation with a G-L-X alkylating agent IX (where L = CH₂ or (CH₂)₂, and X = chloride, bromide, iodide, tosylate, triflate, or other leaving group commonly employed in the art) then provides compounds of Formula Ia.

10 General methods A and B detail experimental procedures that may be employed to prepare compounds of Formula Ia, where L = CH₂ or (CH₂)₂. The requisite alkylating agents IX are commercially available or can be prepared from commercially available compounds employing methods commonly found in the art.

Scheme 1. General Preparation of Compounds of Formula Ia (L is CH₂ or (CH₂)₂)



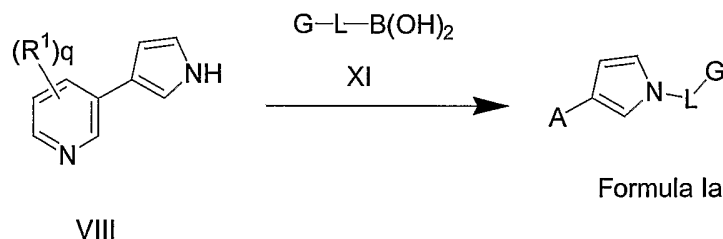
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Compounds of Formula Ia, where L is a bond, are prepared from intermediate VIII according to Method C described below, by the following literature methods (*Tetrahedron* **1999**, 55, 12757-12770, *Tetrahedron Lett.* **1998**, 39, 2941-2944, and *Tetrahedron Lett.* **1990**, 31,

12,1665-1668. or by other Suzuki conditions commonly employed in the art (Scheme 2).

The texts of the above references are hereby incorporated by reference.

Scheme 2. General Preparation of Compounds of Formula Ia (L is a Bond)



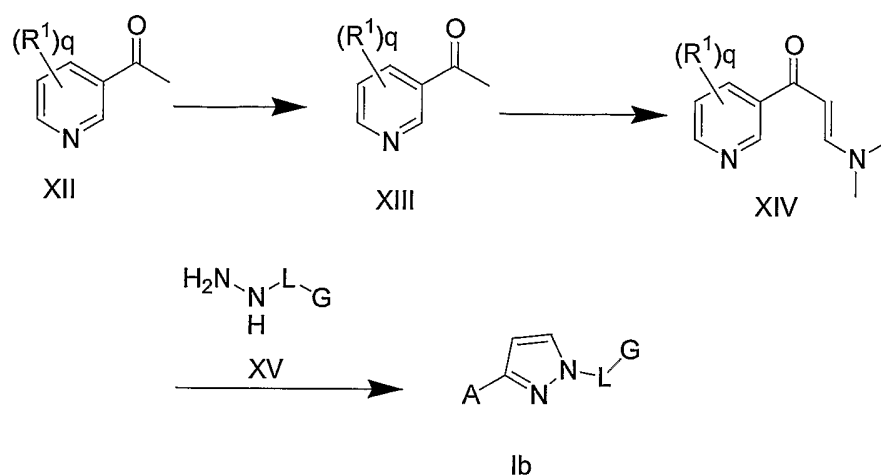
5 3-(3-Pyridyl)pyrazoles of Formula Ib are prepared by the route shown in Scheme 3 or according to methods commonly employed in the art. The 3-acetylpyridines XIII used to prepare compounds of Formula Ib are prepared according to method described by Comins (Comins, D. L., Smith, R., Stroud, E., *Heterocycles*, Vol. 22, No. 2, 1984, 339) or by other methods commonly employed in the art to prepare 4-alkyl-3-acetylpyridines. The requisite

10 3-acetylpyridines XII, where q = 0 or 1, are commercially available, can be prepared by Suzuki coupling with alkyl or cycloalkylboronic acids with 3-acetyl-5-bromopyridine or by other methods commonly employed in the art. The requisite 3-acetyl-5-bromopyridine can be prepared from 5-bromonicotinic acid, methyl 5-bromonicotinate, or from methyl 5-bromonicotinylacetate using methods commonly employed in the art. Alternatively, the

15 synthesis of XIII can begin with either 5-bromonicotinic acid, methyl 5-bromonicotinate, or from methyl 5-bromonicotinylacetate, rearranging the steps and employing methods commonly employed in the art to convert the acid, ester or acetate functionalities to the acetyl moiety of XIII. Treatment of XIII with an alkoxybis(dialkylamino)methane, preferably methoxybis(dimethylamino)methane at a temperature between 80 – 180 °C the

20 intermediate enamine XIV. Preferably the reaction is run neat and the temperature is between 100-120 °C. Other methods commonly employed in the art to prepare aryl enamines from aryl acetyl may be employed. Enamines XIV are then treated with arylhydrazines XV to provide compounds of Formula Ib. Hydrazines XV are commercially available or are prepared using literature methods employed in the art. Most preferably, the

25 Method D described below is used to convert acetyl pyridines XIII to compounds of Formula Ib.

Scheme 3. General Preparation of Compounds of Formula Ib

The present invention is further illustrated by the following examples which should not be construed as limiting in any way. The contents of all cited references (including literature references, issued patents, published patent applications as cited throughout this application) are hereby expressly incorporated by reference.

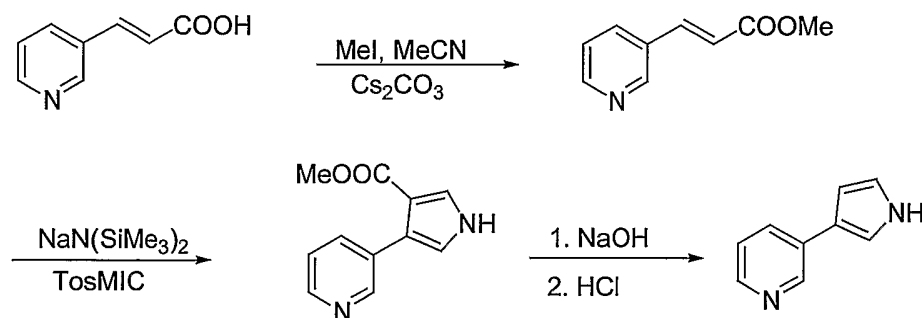
Examples**10 Preparation of the compounds of the invention**

General. All reagents are commercially available unless otherwise specified. Reagents were used as received unless otherwise specified. Proton NMR data is reported downfield from TMS; coupling constants are in hertz. LC/MS mass spectral data were obtained using a Hewlett-Packard 1100 HPLC equipped with a quaternary pump, a variable wavelength detector set at 254 nm, a YMC pro C-18 column (2 x 23 mm, 120A), and a Finnigan LCQ ion trap mass spectrometer with electrospray ionization. Spectra were scanned from 120-1200 amu using a variable ion time according to the number of ions in the source. The eluents were A: 2% acetonitrile in water with 0.02% TFA and B: 2% water in acetonitrile with 0.018% TFA. Gradient elution from 10% B to 95% B over 3.5 minutes at a flowrate of 1.0 mL/min was used with an initial hold of 0.5 minutes and a final hold at 95% B of 0.5 minutes. Total run time was 6.5 minutes. Purification by HPLC was performed using a Gilson HPLC system (UV/VIS-155 detector, 215 liquid handler, 306 pumps, 819 injection valve and an 811C mixer, the column was a YMC Pro C18 (75 x 30, 5 μ m, 120A); the eluents were A: water with 0.1% TFA, and B: acetonitrile with 0.1% TFA; gradient

elution from 10% B to 90% B over 12 minutes with a final hold at 90% B for 2 minutes; flowrate was 25 mL per minute. NMR data are in agreement with the structure of all prepared compounds. Elemental analyses were obtained at Robertson Microlit Laboratories, Madison NJ. Melting points are uncorrected.

5

Preparation of Intermediate A: 3-(1H-Pyrrol-3-yl)pyridine



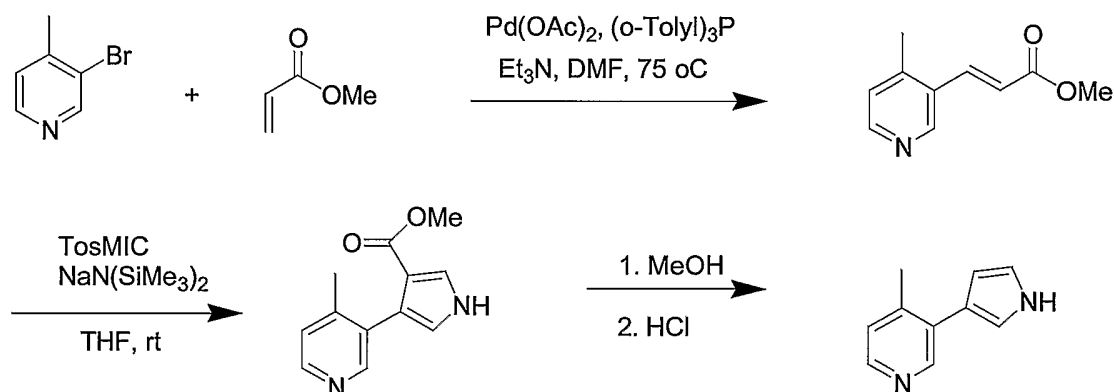
10 **Step 1.** Trans-3-(3-pyridyl)acrylic acid (7.0 g, 47 mmol), Cs₂CO₃ (18.35 g, 56 mmol), and methyl iodide (3.50 mL, 56 mmol) were refluxed together in acetonitrile (100 mL) for 2 h. The dark brown reaction was cooled, filtered, and the solid washed with acetonitrile (50 mL). The solvent of the combined filtrates was evaporated *in vacuo*, and the residue partitioned between EtOAc (150 mL) and H₂O (100 mL). The separated organic layer was washed with H₂O (3 x 100 mL), then with brine (50 mL) and dried over Na₂SO₄. After
15 filtration, the solvent was evaporated *in vacuo*, and the residue purified via flash chromatography (15-30% EtOAc/hexane), affording 4.92 g (64%) of the ester as a yellow solid.

Step 2. A solution of the ester (2.5 g, 15 mmol) and tosylmethyl isocyanide (TosMIC, 3.15 g, 16 mmol) in THF (100 mL) at rt was treated dropwise with 1.0 M sodium
20 bis(trimethylsilyl)amide in THF (16 mL, 16 mmol). The reaction became cloudy with a precipitate. The reaction was stirred overnight and then the solvent evaporated *in vacuo*. The residue was partitioned between EtOAc (200 mL) and H₂O (200 mL). The separated organic layer was washed with H₂O (2 x 125 mL), then brine (200 mL) and dried over Na₂SO₄. After
25 filtration, the solvent was evaporated *in vacuo*, and the residue purified via flash chromatography (40-70% EtOAc/hexane), giving 2.05 g (66%) of the pyrrole ester as a yellow-orange solid.

Step 3. A mixture of the pyrrole ester (3.0 g, 15 mmol) and sodium hydroxide (5.93 g, 150 mmol) in MeOH (40 mL) was heated at reflux for 3 h. The MeOH was evaporated *in vacuo*, the residue dissolved in H₂O (100 mL), and acidified to ~ pH 1 with concentrated aqueous HCl. The reaction mixture was heated to reflux overnight. After cooling, the reaction mixture was neutralized with solid NaHCO₃, giving a pinkish precipitate. The mixture was extracted with EtOAc (4 x 75 mL). The combined extracts were washed with H₂O (50 mL), brine (50 mL), and then dried over Na₂SO₄. After filtration, the solvent was evaporated *in vacuo* and the residue purified via flash chromatography (30-40% EtOAc/hexane), giving 2.03 g (95%) of the pyridyl pyrrole as a light-yellow solid.

10

Preparation of Intermediate B: 4-Methyl-3-(1H-pyrrol-3-yl) pyridine



Step 1. A suspension of 3-bromo-4-picoline (30.86 g, 0.174 mol), palladium acetate (1.95 g, 0.0087 mol), tri-*o*-tolyl phosphine (4.08 g, 0.013 mol), methyl acrylate (23.80 mL, 0.264 mol) and triethylamine (87.8 mL, 0.63 mol) in DMF (297 mL) was degassed with argon, then heated to 70-75 °C for 16 h. The reaction mixture was poured into water (1500 mL), then extracted with EtOAc (2 x 1.2 L, 1 x 0.6 L). Combined organic layer washed with water (2x 0.6L), dried over anhydrous sodium sulfate and concentrated to dryness to give 34.12g of crude methyl-3-(4-methyl-3-pyridinyl)-2-propenoate: GCMS (EI) $t_R = 7.2$ min, 177 (M^+); ¹H NMR (CDCl₃) δ 8.70 (1H, s), 8.45 (1H, d), 7.90 (1H, d), 7.12 (1H, d), 6.44 (1H, d), 3.82 (3H, s), 2.43 (3H, s).

Step 2. To a solution of the crude methyl-3-(4-methyl-3-pyridinyl)-2-propenoate (34.0 g, 0.192 mol), tosyl methyl isocyanide (40.0 g, 0.205 mol) in THF (1.7 L) was added at room temperature sodium bis(trimethylsilyl)amide (288 mL, 0.288 mol, 1.0M solution in THF) over a period of 30-40 min. The resulting brown suspension was stirred at rt for 12-14 h. As

the reaction was incomplete, an additional amount of sodium bis(trimethylsilyl)amide (100 mL, 0.10 mol, 1.0M solution in THF) was added to the reaction mixture at rt. After stirring for and additional 7 h, the reaction mixture was concentrated to dryness and the residue partitioned between EtOAc (3 x 200 mL) and water (225 mL). The combined organic layers was washed with water (2 x 150 mL) and dried over anhydrous sodium sulfate.

Concentration to dryness gave a 34.20 g of methyl-4-(4-methyl-3-pyridinyl)-1H-pyrrole-3-carboxylate as a brown oil: LCMS t_R 0.84 min, 217 ($M+H^+$); 1H NMR ($CDCl_3$) δ 8.30 (1H, d), 8.28 (1H, s), 7.45 (1H, t), 7.10 (1H, d), 6.60 (1H, t), 3.59 (3H, s), 2.15 (3H, s).

Step 3. A suspension of methyl-4-(4-methyl-3-pyridinyl)-1H-pyrrole-3-carboxylate (34.0 g, 0.16 mol), sodium hydroxide (64.0 g, 1.6 mol) in methanol (451 mL) was heated to reflux for 16-18 h. The reaction mixture was concentrated to dryness. Water (1.1 L) was added and the pH adjusted to ~1.0 using concentrated hydrochloric acid (250 mL). This suspension was then heated to reflux for 16-18 h. The reaction mixture was cooled to room temperature and neutralized with solid sodium bicarbonate. The aqueous mixture was extracted with EtOAc (4 x 500 mL). The combined organic layer was washed with water (500 mL), washed with brine (400 mL), and then dried over anhydrous sodium sulfate. The filtrate was concentrated to dryness giving a brown liquid which on silica gel chromatography, using 20-45% ethyl acetate-hexanes as eluent, gave 12.05 g of 4-methyl-3-(1H-pyrrol-3-yl) pyridine as a brownish white product: LC/MS t_R 0.63 min, 159 ($M+H^+$); 1H NMR ($CDCl_3$) δ 8.58 (1H, s), 8.32 (1H, d), 7.14 (1H, d), 6.95 (1H, m), 6.90 (1H, m), 6.43 (1H, m), 2.44 (3H, s).

Preparation of Intermediates C – H

Using the procedure described by Comins (Comins, D. L.; Smith, R. K.; Stroud, E. D. Heterocycles (1984) 22, 339-44) the following bromopyridines are prepared:

4-Ethyl-3-bromopyridine (Intermediate C)

4-Butyl-3-bromopyridine (Intermediate D)

4-(2-Propyl)-3-bromopyridine (Intermediate E)

4-(*tert*-Butyl)-3-bromopyridine (Intermediate F)

4-(Cyclohexyl)-3-bromopyridine (Intermediate G)

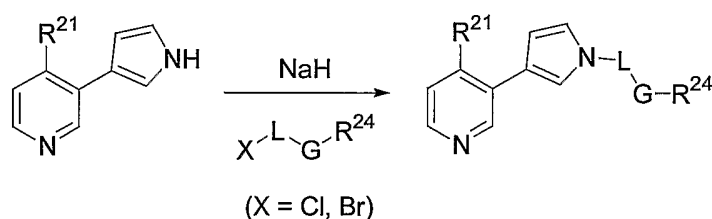
4-Phenyl-3-bromopyridine (Intermediate H)

Preparation of Intermediates I – N:

Using the procedure described above for 4-methyl-3-(1H-pyrrol-3-yl) pyridine, the following pyrrole intermediates are prepared:

- 5 4-Ethyl-3-(1H-pyrrol-3-yl) pyridine (Intermediate I)
 4-Butyl-3-(1H-pyrrol-3-yl) pyridine (Intermediate J)
 4-(2-Propyl)-3-(1H-pyrrol-3-yl) pyridine (Intermediate K)
 4-(*tert*-Butyl)-3-(1H-pyrrol-3-yl) pyridine (Intermediate L)
 4-Cyclohexyl-3-(1H-pyrrol-3-yl) pyridine (Intermediate M)
 10 4-Phenyl-3-(1H-pyrrol-3-yl) pyridine (Intermediate N)

General Method A.



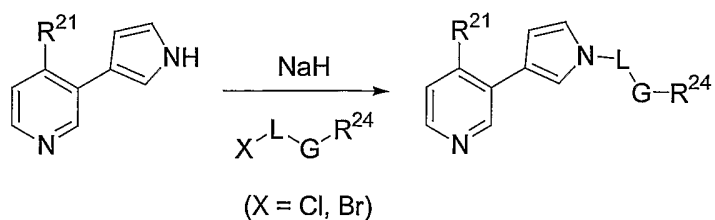
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To a suspension of 95% sodium hydride (0.76 mmol) in DMF (5 mL) is added a solution of the 4-(R²¹)-3-(1H-pyrrol-3-yl) pyridine (0.7 mmol) dissolved in anhydrous DMF (5 mL) dropwise at rt. The reaction is stirred 20 min. The alkyl or aryl halide (0.7 mmol) is added dropwise and the reaction mixture stirred overnight. The reaction mixture is diluted with

20 H₂O (60 mL), then extracted with EtOAc (4 x 15 mL). The combined organic extract is washed with H₂O (2 x 25 mL), then with brine (25 mL) and dried over Na₂SO₄. After filtration, the solvent is evaporated *in vacuo*, and the residue purified via column chromatography (15-20% EtOAc/hexane), affording the target pyrrole derivatives in 80-100% yields. The target pyrrole derivatives are characterized by NMR and MS.

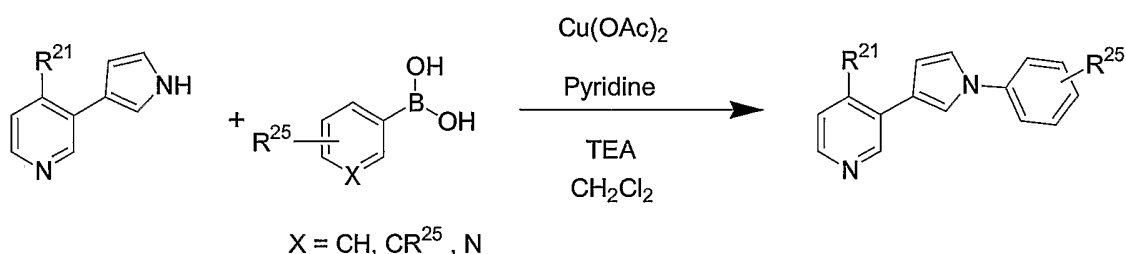
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General Method B.



The 4-(R¹)-3-(1H-pyrrol-3-yl) pyridine (100 mg, 1 eq) and anhydrous DMF (10 mL) are placed into a 40 mL EPA vial with NaH (1 eq) and the mixture is shaken at room temperature for 45 min. The halide is added into the vial and the resulting suspension is stirred at room temperature for 3 days. After the reaction is completed, the mixture is concentrated. The resulting residue is taken up into dichloromethane, washed with water, dried and concentrated. The crude product is purified using a Gilson HPLC and the products characterized by NMR and MS.

10

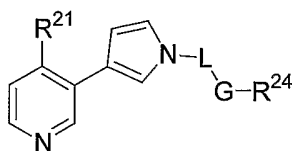
General Method C.

15 The 4-(R²¹)-3-(1H-pyrrol-3-yl)pyridine (0.63 mmol) and an aryl boronic acid (1.26 mmol) are dissolved in dichloromethane (7 mL, reagent grade). To this is added cupric acetate (1.26 mmol), pyridine (1.26 mmol) and triethylamine (1.26 mmol). Also, to this reaction is added 4Å activated molecular sieves (0.25 g). The reaction is stirred at rt for 48 h with a septum and needle exposing the reaction to air. The reaction is filtered and washed with

20 methanol. The filtrate is concentrated under reduced pressure to give a green residue. The compound is purified by a Gilson HPLC using a YMC-Pack Pro C18 Prep Column (150 mm x 20 mm I.D. S-5 μm, 12 nm). The mobile phase starts with 10 % CH₃CN/water (0.1 % TFA) for 3 min and then goes from 10 % to 90 % CH₃CN/water (0.1 % TFA) over 7 min. It is optionally further purified by preparative TLC, mobile phase 20 - 50 % EtOAc/Hexane.

25 Product yields are generally in the range of 10 – 50%.

Table 2. Examples 1 – 25: Pyridyl Pyrrole Derivatives Prepared from Intermediates A and B using General Methods A and B.



Ex. No.	R ²¹	L	G	R ²⁴	t _R min ^{a,b}	MS ^{a,b} (M+H) ⁺	TLC R _f (solvent)	General Method
1	H	CH ₂	Phenyl	--	--	235	0.39 (40% EtOAc/hexane)	A
2	H	CH ₂	Phenyl	4-Cl	--	269	0.33 (40% EtOAc/hexane)	A
3	H	CH ₂	Phenyl	3-Cl	--	269	0.35 (40% EtOAc/hexane)	A
4	H	CH ₂	Phenyl	2-Cl	--	269	0.39 (40% EtOAc/hexane)	A
5	Me	CH ₂	Phenyl	4-Cl	2.14	283.4	0.31 (50% EtOAc/hexane)	B
6	Me	CH ₂	Phenyl	4-Br	2.22	327.7	0.33 (50% EtOAc/hexane)	B
7	Me	CH ₂	Phenyl	3-NO ₂	1.90	294.28	0.46 (75% EtOAc/hexane)	B
8	Me	CH ₂	Phenyl	2-NO ₂	1.91	294.24	0.46 (75% EtOAc/hexane)	B
9	Me	CH ₂	Phenyl	3-Cl	2.12	283.3	0.54 (75% EtOAc/hexane)	B
10	Me	CH ₂	Phenyl	2,3-diCl	2.3	317.31	0.60 (75% EtOAc/hexane)	B

Ex. No.	R ²¹	L	G	R ²⁴	t _R min ^{a,b}	MS ^{a,b} (M+H) +	TLC R _f (solvent)	General Method
							hexane)	
11	Me	CH ₂	Phenyl	2,4-diCl	2.33	371.29	0.65 (75% EtOAc/ hexane)	B
12	Me	CH ₂	Phenyl	2-CN	1.79	274.33	0.48 (75% EtOAc/ hexane)	B
13	Me	CH ₂	Phenyl	4-CN	1.78	274.28	0.46 (75% EtOAc/ hexane)	B
14	Me	CH ₂	Phenyl	4-F	1.95	267.28	0.54 (75% EtOAc/ hexane)	B
15	Me	CH ₂	Phenyl	4- <i>i</i> -Pr	2.37	291.36	0.54 (75% EtOAc/ hexane)	B
16	Me	CH ₂	Phenyl	4-OMe	1.98	279.27	0.54 (75% EtOAc/ hexane)	B
17	Me	CH ₂	4-Thiazolyl	2-Me	0.73	270.24	0.08 (75% EtOAc/ hexane)	B
18	Me	CH ₂	4-Thiazolyl	4-Cl-Phenyl	2.4	366.29	0.54 (75% EtOAc/ hexane)	B
19	Me	CH ₂	2-Napthyl	H	2.27	299.31	0.47 (75% EtOAc/ hexane)	B
20	Me	CH ₂	Cyclohexyl	H	2.25	255.37	0.53 (75% EtOAc/ hexane)	B

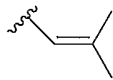
Ex. No.	R ²¹	L	G	R ²⁴	t _R min ^{a,b}	MS ^{a,b} (M+H) ⁺	TLC Rf (solvent)	General Method
21	Me	CH ₂	Cyclobutyl	H	1.91	227.27	0.58 (75% EtOAc/hexane)	B
22	Me	CH ₂	2-Furanyl	H	0.73	243.32	0.12 (75% EtOAc/hexane)	B
23	Me	CH ₂	3-Pentyl	H	2.21	243.36	0.57 (75% EtOAc/hexane)	B
24	Me	CH ₂		--	1.96	227.27	0.54 (75% EtOAc/hexane)	B
25	Me	--	Phenyl	H	1.93	235.2	0.11 (20% EtOAc/hexane)	C

Table 1 Note a: HPLC - electrospray mass spectra (HPLC ES-MS) were obtained using a Hewlett-Packard 1100 HPLC equipped with a quaternary pump, a variable wavelength detector set at 254 nm, a YMC pro C-18 column (2 x 23 mm, 120A), and a Finnigan LCQ ion trap mass spectrometer with electrospray ionization. Spectra were scanned from 120-1200 amu using a variable ion time according to the number of ions in the source. The eluents were A: 2% acetonitrile in water with 0.02% TFA and B: 2% water in acetonitrile with 0.018% TFA. Gradient elution from 10% B to 95% over 3.5 minutes at a flowrate of 1.0 mL/min was used with an initial hold of 0.5 minutes and a final hold at 95% B of 0.5 minutes. Total run time was 6.5 minutes.

Table Note b: Molecular ion data obtained via electrospray ionization.

The following Examples of 4-(substituted)-3-(3-pyrrolyl)pyridine derivatives are prepared from Intermediates I-N according to General Methods A and B:

Table 3. Examples 26 – 145 : Pyridyl Pyrrole Derivatives which may be Prepared from General Intermediates I-N by General Methods A and B.

Example No	Compound Name
Example 26	3-[1-(4-chlorobenzyl)-1H-pyrrol-3-yl]-4-ethylpyridine
Example 27	3-[1-(4-bromobenzyl)-1H-pyrrol-3-yl]-4-ethylpyridine
Example 28	2-{{3-(4-ethyl-3-pyridinyl)-1H-pyrrol-1-yl}methyl} benzonitrile
Example 29	4-{{3-(4-ethyl-3-pyridinyl)-1H-pyrrol-1-yl}methyl} benzonitrile
Example 30	3-[1-(4-fluorobenzyl)-1H-pyrrol-3-yl]-4-ethylpyridine
Example 31	4-ethyl-3-[1-(3-nitrobenzyl)-1H-pyrrol-3-yl]pyridine
Example 32	4-ethyl-3-[1-(2-nitrobenzyl)-1H-pyrrol-3-yl]pyridine
Example 33	3-[1-(3-chlorobenzyl)-1H-pyrrol-3-yl]-4-ethylpyridine
Example 34	3-[1-(3,4-dichlorobenzyl)-1H-pyrrol-3-yl]-4-ethylpyridine
Example 35	3-[1-(2,4-dichlorobenzyl)-1H-pyrrol-3-yl]-4-ethylpyridine
Example 36	3-[1-(4-isopropylbenzyl)-1H-pyrrol-3-yl]-4-ethylpyridine
Example 37	3-[1-(2-ethylbut-1-yl)-1H-pyrrol-3-yl]-4-ethylpyridine
Example 38	4-ethyl-3-[1-(3-methyl-2-butenyl)-1H-pyrrol-3-yl]pyridine
Example 39	3-[1-(4-methoxybenzyl)-1H-pyrrol-3-yl]-4-ethylpyridine
Example 40	4-ethyl-3-{1-[(2-methyl-1,3-thiazol-4-yl)methyl]-1H-pyrrol-3-yl} pyridine
Example 41	3-(1-{[2-(4-chlorophenyl)-1,3-thiazol-4-yl]methyl}-1H-pyrrol-3-yl)-4-ethylpyridine
Example 42	4-ethyl-3-[1-(2-naphthylmethyl)-1H-pyrrol-3-yl]pyridine
Example 43	3-[1-(cyclohexylmethyl)-1H-pyrrol-3-yl]-4-ethylpyridine
Example 44	3-[1-(cyclobutylmethyl)-1H-pyrrol-3-yl]-4-ethylpyridine
Example 45	4-ethyl-3-[1-(tetrahydro-2-furanylmethyl)-1H-pyrrol-3-yl]pyridine
Example 46	3-[1-(4-chlorobenzyl)-1H-pyrrol-3-yl]-4-(n-butyl)pyridine
Example 47	3-[1-(4-bromobenzyl)-1H-pyrrol-3-yl]-4-(n-butyl)pyridine
Example 48	2-{{3-(4-(n-butyl)-3-pyridinyl)-1H-pyrrol-1-yl}methyl} benzonitrile
Example 49	4-{{3-(4-(n-butyl)-3-pyridinyl)-1H-pyrrol-1-yl}methyl} benzonitrile

Example No	Compound Name
Example 50	3-[1-(4-fluorobenzyl)-1H-pyrrol-3-yl]-4-(n-butyl)pyridine
Example 51	4-(n-butyl)-3-[1-(3-nitrobenzyl)-1H-pyrrol-3-yl]pyridine
Example 52	4-(n-butyl)-3-[1-(2-nitrobenzyl)-1H-pyrrol-3-yl]pyridine
Example 53	3-[1-(3-chlorobenzyl)-1H-pyrrol-3-yl]-4-(n-butyl)pyridine.
Example 54	3-[1-(3,4-dichlorobenzyl)-1H-pyrrol-3-yl]-4-(n-butyl)pyridine
Example 55	3-[1-(2,4-dichlorobenzyl)-1H-pyrrol-3-yl]-4-(n-butyl)pyridine
Example 56	3-[1-(4-isopropylbenzyl)-1H-pyrrol-3-yl]-4-(n-butyl)pyridine
Example 57	3-[1-(2-ethylbut-1-yl)-1H-pyrrol-3-yl]-4-(n-butyl)pyridine
Example 58	4-(n-butyl)-3-[1-(3-methyl-2-butenyl)-1H-pyrrol-3-yl]pyridine
Example 59	3-[1-(4-methoxybenzyl)-1H-pyrrol-3-yl]-4-(n-butyl)pyridine
Example 60	4-(n-butyl)-3-{1-[(2-methyl-1,3-thiazol-4-yl)methyl]-1H-pyrrol-3-yl}pyridine
Example 61	3-(1-{[2-(4-chlorophenyl)-1,3-thiazol-4-yl]methyl}-1H-pyrrol-3-yl)-4-(n-butyl)pyridine
Example 62	4-(n-butyl)-3-[1-(2-naphthylmethyl)-1H-pyrrol-3-yl]pyridine
Example 63	3-[1-(cyclohexylmethyl)-1H-pyrrol-3-yl]-4-(n-butyl)pyridine
Example 64	3-[1-(cyclobutylmethyl)-1H-pyrrol-3-yl]-4-(n-butyl)pyridine
Example 65	4-(n-butyl)-3-[1-(tetrahydro-2-furanylmethyl)-1H-pyrrol-3-yl]pyridine
Example 66	3-[1-(4-chlorobenzyl)-1H-pyrrol-3-yl]-4-(2-propyl)pyridine
Example 67	3-[1-(4-bromobenzyl)-1H-pyrrol-3-yl]-4-(2-propyl)pyridine
Example 68	2-{[3-(4-(2-propyl)-3-pyridinyl)-1H-pyrrol-1-yl]methyl}benzotrile
Example 69	4-{[3-(4-(2-propyl)-3-pyridinyl)-1H-pyrrol-1-yl]methyl}benzotrile
Example 70	3-[1-(4-fluorobenzyl)-1H-pyrrol-3-yl]-4-(2-propyl)pyridine
Example 71	4-(2-propyl)-3-[1-(3-nitrobenzyl)-1H-pyrrol-3-yl]pyridine
Example 72	4-(2-propyl)-3-[1-(2-nitrobenzyl)-1H-pyrrol-3-yl]pyridine
Example 73	3-[1-(3-chlorobenzyl)-1H-pyrrol-3-yl]-4-(2-propyl)pyridine

Example No	Compound Name
Example 74	3-[1-(3,4-dichlorobenzyl)-1H-pyrrol-3-yl]-4-(2-propyl)pyridine
Example 75	3-[1-(2,4-dichlorobenzyl)-1H-pyrrol-3-yl]-4-(2-propyl)pyridine
Example 76	3-[1-(4-isopropylbenzyl)-1H-pyrrol-3-yl]-4-(2-propyl)pyridine
Example 77	3-[1-(2-ethylbut-1-yl)-1H-pyrrol-3-yl]-4-(2-propyl)pyridine
Example 78	4-(2-propyl)-3-[1-(3-methyl-2-butenyl)-1H-pyrrol-3-yl]pyridine
Example 79	3-[1-(4-methoxybenzyl)-1H-pyrrol-3-yl]-4-(2-propyl)pyridine
Example 80	4-(2-propyl)-3-{1-[(2-methyl-1,3-thiazol-4-yl)methyl]-1H-pyrrol-3-yl}pyridine
Example 81	3-(1-{[2-(4-chlorophenyl)-1,3-thiazol-4-yl]methyl}-1H-pyrrol-3-yl)-4-(2-propyl)pyridine
Example 82	4-(2-propyl)-3-[1-(2-naphthylmethyl)-1H-pyrrol-3-yl]pyridine
Example 83	3-[1-(cyclohexylmethyl)-1H-pyrrol-3-yl]-4-(2-propyl)pyridine
Example 84	3-[1-(cyclobutylmethyl)-1H-pyrrol-3-yl]-4-(2-propyl)pyridine
Example 85	4-(2-propyl)-3-[1-(tetrahydro-2-furanylmethyl)-1H-pyrrol-3-yl]pyridine
Example 86	3-[1-(4-chlorobenzyl)-1H-pyrrol-3-yl]-4-(tert-butyl)pyridine
Example 87	3-[1-(4-bromobenzyl)-1H-pyrrol-3-yl]-4-(tert-butyl)pyridine
Example 88	2-{[3-(4-(tert-butyl)-3-pyridinyl)-1H-pyrrol-1-yl]methyl}benzotrile
Example 89	4-{[3-(4-(tert-butyl)-3-pyridinyl)-1H-pyrrol-1-yl]methyl}benzotrile
Example 90	3-[1-(4-fluorobenzyl)-1H-pyrrol-3-yl]-4-(tert-butyl)pyridine
Example 91	4-(tert-butyl)-3-[1-(3-nitrobenzyl)-1H-pyrrol-3-yl]pyridine
Example 92	4-(tert-butyl)-3-[1-(2-nitrobenzyl)-1H-pyrrol-3-yl]pyridine
Example 93	3-[1-(3-chlorobenzyl)-1H-pyrrol-3-yl]-4-(tert-butyl)pyridine
Example 94	3-[1-(3,4-dichlorobenzyl)-1H-pyrrol-3-yl]-4-(tert-butyl)pyridine
Example 95	3-[1-(2,4-dichlorobenzyl)-1H-pyrrol-3-yl]-4-(tert-butyl)pyridine
Example 96	3-[1-(4-isopropylbenzyl)-1H-pyrrol-3-yl]-4-(tert-butyl)pyridine
Example 97	3-[1-(2-ethylbut-1-yl)-1H-pyrrol-3-yl]-4-(tert-butyl)pyridine

Example No	Compound Name
Example 98	4-(tert-butyl)-3-[1-(3-methyl-2-butenyl)-1H-pyrrol-3-yl]pyridine
Example 99	3-[1-(4-methoxybenzyl)-1H-pyrrol-3-yl]-4-(tert-butyl)pyridine
Example 100	4-(tert-butyl)-3-{1-[(2-methyl-1,3-thiazol-4-yl)methyl]-1H-pyrrol-3-yl}pyridine
Example 101	3-(1-{[2-(4-chlorophenyl)-1,3-thiazol-4-yl]methyl}-1H-pyrrol-3-yl)-4-(tert-butyl)pyridine
Example 102	4-(tert-butyl)-3-[1-(2-naphthylmethyl)-1H-pyrrol-3-yl]pyridine
Example 103	3-[1-(cyclohexylmethyl)-1H-pyrrol-3-yl]-4-(tert-butyl)pyridine
Example 104	3-[1-(cyclobutylmethyl)-1H-pyrrol-3-yl]-4-(tert-butyl)pyridine
Example 105	4-(tert-butyl)-3-[1-(tetrahydro-2-furanylmethyl)-1H-pyrrol-3-yl]pyridine
Example 106	3-[1-(4-chlorobenzyl)-1H-pyrrol-3-yl]-4-cyclohexylpyridine
Example 107	3-[1-(4-bromobenzyl)-1H-pyrrol-3-yl]-4-cyclohexylpyridine
Example 108	2-{[3-(4-cyclohexyl-3-pyridinyl)-1H-pyrrol-1-yl]methyl}benzotrile
Example 109	4-{[3-(4-cyclohexyl-3-pyridinyl)-1H-pyrrol-1-yl]methyl}benzotrile
Example 110	3-[1-(4-fluorobenzyl)-1H-pyrrol-3-yl]-4-cyclohexylpyridine
Example 111	4-cyclohexyl-3-[1-(3-nitrobenzyl)-1H-pyrrol-3-yl]pyridine
Example 112	4-cyclohexyl-3-[1-(2-nitrobenzyl)-1H-pyrrol-3-yl]pyridine
Example 113	3-[1-(3-chlorobenzyl)-1H-pyrrol-3-yl]-4-cyclohexylpyridine
Example 114	3-[1-(3,4-dichlorobenzyl)-1H-pyrrol-3-yl]-4-cyclohexylpyridine
Example 115	3-[1-(2,4-dichlorobenzyl)-1H-pyrrol-3-yl]-4-cyclohexylpyridine
Example 116	3-[1-(4-isopropylbenzyl)-1H-pyrrol-3-yl]-4-cyclohexylpyridine
Example 117	3-[1-(2-ethylbut-1-yl)-1H-pyrrol-3-yl]-4-cyclohexylpyridine
Example 118	4-cyclohexyl-3-[1-(3-methyl-2-butenyl)-1H-pyrrol-3-yl]pyridine
Example 119	3-[1-(4-methoxybenzyl)-1H-pyrrol-3-yl]-4-cyclohexylpyridine
Example 120	4-cyclohexyl-3-{1-[(2-methyl-1,3-thiazol-4-yl)methyl]-1H-pyrrol-3-yl}pyridine
Example 121	3-(1-{[2-(4-chlorophenyl)-1,3-thiazol-4-yl]methyl}-1H-pyrrol-3-yl)-4-cyclohexylpyridine

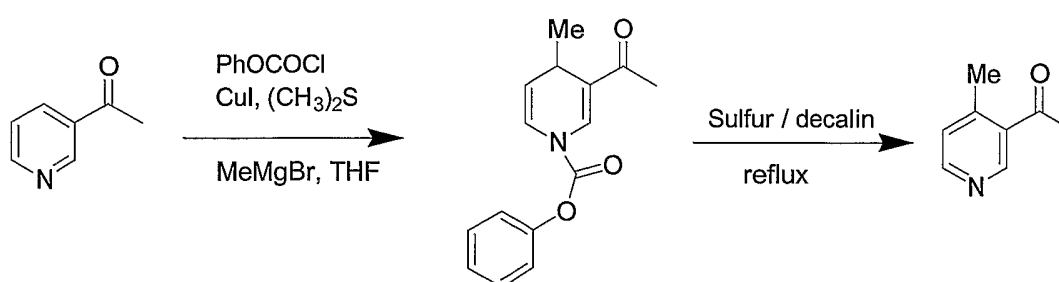
Example No	Compound Name
Example 122	4-cyclohexyl-3-[1-(2-naphthylmethyl)-1H-pyrrol-3-yl]pyridine
Example 123	3-[1-(cyclohexylmethyl)-1H-pyrrol-3-yl]-4-cyclohexylpyridine
Example 124	3-[1-(cyclobutylmethyl)-1H-pyrrol-3-yl]-4-cyclohexylpyridine
Example 125	4-cyclohexyl-3-[1-(tetrahydro-2-furanylmethyl)-1H-pyrrol-3-yl]pyridine
Example 126	3-[1-(4-chlorobenzyl)-1H-pyrrol-3-yl]-4-phenylpyridine
Example 127	3-[1-(4-bromobenzyl)-1H-pyrrol-3-yl]-4-phenylpyridine
Example 128	2-{{3-(4-phenyl-3-pyridinyl)-1H-pyrrol-1-yl}methyl}benzotrile
Example 129	4-{{3-(4-phenyl-3-pyridinyl)-1H-pyrrol-1-yl}methyl}benzotrile
Example 130	3-[1-(4-fluorobenzyl)-1H-pyrrol-3-yl]-4-phenylpyridine
Example 131	4-phenyl-3-[1-(3-nitrobenzyl)-1H-pyrrol-3-yl]pyridine
Example 132	4-phenyl-3-[1-(2-nitrobenzyl)-1H-pyrrol-3-yl]pyridine
Example 133	3-[1-(3-chlorobenzyl)-1H-pyrrol-3-yl]-4-phenylpyridine
Example 134	3-[1-(3,4-dichlorobenzyl)-1H-pyrrol-3-yl]-4-phenylpyridine
Example 135	3-[1-(2,4-dichlorobenzyl)-1H-pyrrol-3-yl]-4-phenylpyridine
Example 136	3-[1-(4-isopropylbenzyl)-1H-pyrrol-3-yl]-4-phenylpyridine
Example 137	3-[1-(2-ethylbut-1-yl)-1H-pyrrol-3-yl]-4-phenylpyridine
Example 138	4-phenyl-3-[1-(3-methyl-2-butenyl)-1H-pyrrol-3-yl]pyridine
Example 139	3-[1-(4-methoxybenzyl)-1H-pyrrol-3-yl]-4-phenylpyridine
Example 140	4-phenyl-3-{{1-[(2-methyl-1,3-thiazol-4-yl)methyl]-1H-pyrrol-3-yl}}pyridine
Example 141	3-(1-{{2-(4-chlorophenyl)-1,3-thiazol-4-yl}methyl}-1H-pyrrol-3-yl)-4-phenylpyridine
Example 142	4-phenyl-3-[1-(2-naphthylmethyl)-1H-pyrrol-3-yl]pyridine
Example 143	3-[1-(cyclohexylmethyl)-1H-pyrrol-3-yl]-4-phenylpyridine
Example 144	3-[1-(cyclobutylmethyl)-1H-pyrrol-3-yl]-4-phenylpyridine
Example 145	4-phenyl-3-[1-(tetrahydro-2-furanylmethyl)-1H-pyrrol-3-yl]pyridine

The following Examples of 4-(substituted)-3-(3-pyrrolyl)pyridine derivatives are prepared from Intermediates I-N according to General Methods A and B:

5 **Table 4. Examples 146 – 155: Pyridyl Pyrrole Derivatives which may be Prepared from Intermediate B by General Method C.**

Example No.	Compound Name
Example 146	4-methyl-3-(1-(4-methylphenyl)-1H-pyrrol-3-yl)pyridine
Example 147	4-methyl-3-(1-(3-methylphenyl)-1H-pyrrol-3-yl)pyridine
Example 148	4-methyl-3-(1-(2-methylphenyl)-1H-pyrrol-3-yl)pyridine
Example 149	4-methyl-3-(1-(4-methoxyphenyl)-1H-pyrrol-3-yl)pyridine
Example 150	4-methyl-3-(1-(4-fluorophenyl)-1H-pyrrol-3-yl)pyridine
Example 151	4-methyl-3-(1-(4-cyanophenyl)-1H-pyrrol-3-yl)pyridine
Example 152	4-methyl-3-(1-(3-(trifluoromethyl)phenyl)-1H-pyrrol-3-yl)pyridine
Example 153	4-methyl-3-(1-(3-pyridyl)-1H-pyrrol-3-yl)pyridine
Example 154	4-methyl-3-(1-(4-chlorophenyl)-1H-pyrrol-3-yl)pyridine
Example 155	4-methyl-3-(1-(2-thiophenyl)-1H-pyrrol-3-yl)pyridine

Preparation of Intermediate O: 4-Methyl-3-acetylpyridine



10

Step 1. A solution of 3-acetylpyridine (100 g, 0.82 mol), dimethyl sulfide (400 mL, 5.4 mol) and copper (I) iodide (7.94 g, 0.041 mol) in anhydrous THF (2 L) was stirred at rt under an Ar. Phenyl chloroformate (0.4 mL, 0.82 mol) was then added, producing a dark brown precipitate. After 30 minutes, the mixture was cooled below -21 °C and methyl

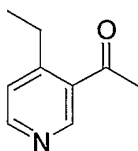
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magnesium bromide (1.4 M in 3:1 toluene-THF, 586 mL, 0.82 mol) was added over 50 min, keeping the reaction temperature below $-15\text{ }^{\circ}\text{C}$. The color lightened as the mixture became a solution; a lime green precipitate formed near the end of the addition, but redissolved upon completion. The mixture was stirred and allowed to warm slowly; after 2 h it had warmed to 8.8 $^{\circ}\text{C}$. Saturated aqueous ammonium chloride solution (500 mL) was added; after stirring 10 min, the mixture was poured into a separatory funnel with water (500 mL). The organic phase was separated, washed with brine (500 mL), dried (Na_2SO_4), filtered and then concentrated *in vacuo*. The residue was purified by silica gel chromatography using a hexane-EtOAc gradient to afford 134.3 g (63.7%) of the intermediate dihydropyridine.

Step 2. A solution of the intermediate dihydropyridine (134.3 g, 0.52 mol) in dichloromethane (100 mL) was added to a stirred suspension of sulfur (16.67 g, 0.52 mol) in decalin and slowly heated to reflux under an Ar sweep. After refluxing 1 h, the mixture was allowed to cool to rt, then filtered through a pad of silica gel. After eluting the decalin with hexane, elution with a hexane-diethyl ether gradient afforded 49.4 g (70.3%) of 4-methyl-3-acetylpyridine as a reddish-brown oil: TLC R_f 0.19 (diethyl ether); TLC R_f 0.14 (1:1 hexane-EtOAc); ^1H NMR (CD_2Cl_2) δ 8.9 (s, 1H), 8.5 (d, 1H), 7.2 (dd, 1H), 2.6 (s, 3H); GCMS 135 (M^+).

Preparation of Intermediate P: 4-Ethyl-3-acetylpyridine

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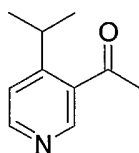
Step 1. 3-Acetylpyridine (5.0 g, 0.0413 mol), copper iodide (7.86 g, 0.0413 mol) and dimethyl sulfide (20.0 mL, 0.272 mol) were dissolved in THF (100 mL, anhydrous). This was stirred at rt for 15 min. To the reaction was added dropwise phenyl chloroformate (5.5 mL, 0.0441 mol) over 10 min. This reaction was then stirred under Ar for 1 h. The reaction was cooled to $-25\text{ }^{\circ}\text{C}$ and ethylmagnesium bromide (1M in THF, 44.1 mL, 0.0441 mol) was added dropwise over 40 min. The reaction was stirred at $-25\text{ }^{\circ}\text{C}$ for 30 min, then was warmed to rt and quenched with 20% NH_4Cl (35 mL). The mixture was extracted with EtOAc, washed with 20% NH_4Cl , brine, and then dried over sodium sulfate. Regioisomers were produced in a 2:1 ratio (desired: undesired). The organic was concentrated to dryness

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and the crude oil was purified by column chromatography (mobile phase 5% EtOAc/Hexane). Phenyl 3-acetyl-4-ethyl-1(4H)-pyridine carboxylate was obtained as an orange oil in 40.6 % yield, (4.55 g).

Step 2. Phenyl 3-acetyl-4-ethyl-1(4H)-pyridinecarboxylate (3.26 g, 0.0120 mol) and sulfur (0.385 g, 0.0120 mol) were dissolved into decalin (15 mL). The reaction was heated to reflux for 17 h under Ar. The reaction mixture was then poured onto a silica gel column and washed with copious amounts of hexane. The product was then eluted from the column with a gradient mobile phase (5% EtOAc/hexane to 30% EtOAc/hexane). The product-containing fractions were concentrated to dryness to give an orange oil, 1.16 g (64.8%): R_f 0.12 (20% EtOAc/hexane).

Preparation of Intermediate Q: 4-(2-Propyl)-3-acetylpyridine

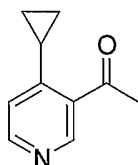


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Step 1. To a mixture of CuI (78.5g, 0.412 mol), dimethyl sulphide (203 mL, 2.76 mol) and 3-acetyl pyridine (50.0g, 0.412 mol) in anhydrous THF (1100 mL) at rt was added phenyl chloroformate (55.2 mL, 0.44 mol) and the mixture was stirred for 40-50 min. To this suspension at -25 to -20°C was added isopropyl magnesium chloride (220 mL, 0.44 mol, 2.0 M solution in THF) over 30-40 min. The mixture was stirred at this temperature for 30 min, then warmed slowly to rt over 1.0-1.5 h. The reaction mixture was quenched with 20% NH₄Cl (350 mL), followed by extraction of the aqueous layer with EtOAc (700 mL). The organic layer was washed with 20% NH₄Cl (350 mL), then brine (250 mL) and dried over anhydrous Na₂SO₄. Silica gel chromatography using a 3-10% EtOAc-hexane gradient yielded 43.5 g of crude 3-acetyl-4-isopropyl-1-phenoxycarbonyl-1,4-dihydropyridine.

Step 2. A mixture of the crude dihydropyridine (43.5 g, 0.153 mol) and sulphur (4.9 g, 0.153 mol) were heated at reflux in decalin (175 mL) for 3 h, then cooled to rt. Purification by silica gel chromatography, eluting first with hexanes, then with a 5-30% EtOAc-hexane gradient, gave 19.3 g (78%) of the title compound: TLC R_f 0.19 (25% EtOAc-hexane); GCMS (EI) t_R = 6.2 min, 163 (M^+); ¹H NMR (CDCl₃) δ 8.76 (s, 1H), 8.57 (d, 1H), 7.30 (d, 1H), 3.55 (m, 1H), 2.60 (s, 3H), 1.22 (d, 6H).

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Preparation of Intermediate R: 4-Cyclopropyl-3-acetylpyridine

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Step 1. Cyclopropyl bromide (50.0 g, 413 mmol) was dissolved in 500 mL of anhydrous THF. Dry magnesium (10.0 g, 411 mmol) was charged to a round-bottomed flask containing a catalytic amount of iodine. 20% of the solution of the cyclopropyl bromide solution was then charged into the flask. After observing bubble formation, the remaining
10 cyclopropyl bromide solution was added over 15 min, thereby causing the reaction mixture to reflux. After 30 min, a 5.0 mL aliquot of the reaction mixture was removed to determine the concentration of the Grignard reagent. This analysis was performed according to the following procedure: 2 mg of 1,10 phenanthroline was added to a 50 mL flask with 10 mL of benzene; the 5.0 mL aliquot was then added; and the resulting mixture was titrated to the
15 reddish-purple endpoint with 2.4 mL of 1.0 M butan-2-ol in p-xylene. Concentration was thus 0.48 M, which implied a 58% conversion to the desired Grignard reagent.

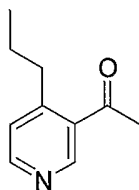
Step 2. 780 mg of CuI (4.10 mmol) was added to a round-bottomed flask under inert (Ar) conditions. A suspension was then formed by the addition of 100 mL of THF. 40 mL of dimethyl sulfide was added, yielding a clear yellow solution. 3-Acetylpyridine (10.0 g, 82.7
20 mmol) was then dissolved in 70 mL of THF and added to the yellow solution. Finally, 13.6 g (86.8 mmol) of phenyl chloroformate was dissolved in 50 mL of THF and the resulting solution was added slowly, resulting in the formation of a precipitate. The mixture was then cooled to -20 °C by packing the flask in dry ice. 172 mL (82.6 mmol) of the Grignard solution from above was then added dropwise over 20 minutes while maintaining the
25 temperature below -5 °C. The reaction mixture was allowed to warm to rt and then quenched with 400 mL of 20% aqueous ammonium chloride. Ethyl acetate (200 mL) was added. The organic layer was collected and the aqueous layer was washed with ethyl acetate (400 mL). The organic layers were combined, washed with brine, and then concentrated *in vacuo*. The residue was dissolved in dichloromethane and chromatographed on silica gel
30 using a Biotage Flash 75 L column, first eluting with 2 L of 10% EtOAc-hexane, and then eluting with 4 L of 15% EtOAc-hexane. The fractions containing the desired compound

were combined and concentrated *in vacuo*, providing 12.2 g of an oil: $^1\text{H NMR}$ (CDCl_3) δ 7.98 (s, 1H, broad) 7.44 (t, 2H), 7.31 (t, 1H), 7.21 (d, 2H), 6.99 (s, 1H, broad), 5.20 (s, 1H, broad), 3.23 (t, 1H, broad), 2.40 (s, 3H), 0.91 (m, 1H), 0.53-0.33 (m, 3H), 0.20 (sx, 1H); LCMS (ES) m/z 284.0 ($\text{M}+\text{H}^+$).

- 5 **Step 3.** 12.2 g (43.0 mmol) of the dihydropyridine was transferred into a round-bottomed flask containing 143 mL of decahydronaphthalene. Sulfur (1.38 g, 43.0 mmol) was added and the flask was heated in an oil bath at 180 °C. Over 4 h an additional 1.38 g of sulfur was added. The heat was then turned off and the reaction was diluted with 500 mL of MTBE. The organic layer was extracted twice with 250 mL portions of 1.0 N HCl. 500 mL of
- 10 dichloromethane was added to the aqueous layer, which was then made basic with 1.0 N NaOH. The organic layer was then washed with 250 mL of brine, dried with sodium sulfate, filtered, and concentrated to obtain 2.13 g of an oil. The acidic aqueous layers were extracted again with 500 mL of dichloromethane. The organic layer was dried with sodium sulfate, filtered into the oil obtained from above, and concentrated *in vacuo* to obtain a total
- 15 of 3.63 g (27% from 3-acetylpyridine): $^1\text{H NMR}$ (CDCl_3) δ 8.83 (s, 1H), 8.54 (d, 1H), 6.93 (d, 1H), 2.71 (m, 1H), 2.71 (s, 3H), 1.28 (d, 2H), 0.92 (d, 2H); LCMS (ES) m/z 162.1 (MH^+); GCMS (CI) m/z 162 ($\text{M}+\text{H}^+$).

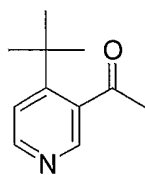
Preparation of Intermediate S: 4-(1-Propyl)-3-acetylpyridine

20



- 4-(1-Propyl)-3-acetylpyridine was prepared according to the method used to prepare 4-ethyl-3-acetylpyridine: LCMS t_R = 0.82 min; 164 ($\text{M}+\text{H}^+$); $^1\text{H NMR}$ (CDCl_3) δ 8.86 (s, 1H), 8.56
- 25 (d, J = 5 Hz, 1H), 7.20 (d, J = 5 Hz, 1H), 2.85 (t, J = 8 Hz, 2H), 2.63 (s, 3H), 1.61 (m, 2H), 0.97 t, J = 7 Hz, 3H).

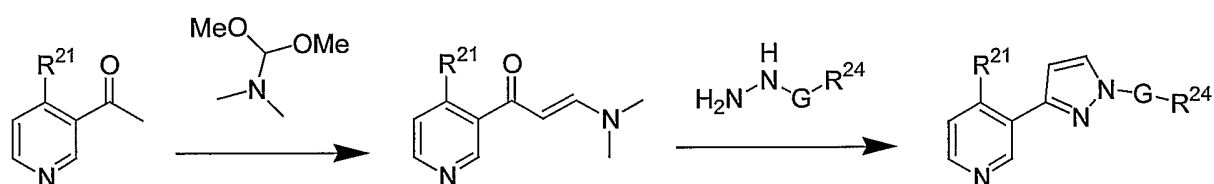
Preparation of Intermediate T: 4-(*tert*-Butyl)-3-acetylpyridine



4-(*tert*-Butyl)-3-acetylpyridine was prepared according to the method used to prepare 4-ethyl-3-acetylpyridine to first give the intermediate phenyl 3-acetyl-4-*tert*-butyl-1(4H)-pyridinecarboxylate [HPLC t_R = 3.32 min; TLC R_f = 0.51 (5% EtOAc/hexane); ^1H NMR (CD_2Cl_2) δ 0.82 (s, 9H), 2.38 (s, 3H), 3.44 (d, 1H), 5.36-5.32 (m, 1H), 6.82 (d, 1H) 7.48-7.19 (m, 5H), 8.02 (s, 1H); LCMS (ES) m/z 300.3 ($\text{M}+\text{H}^+$)], which was then aromatized with sulfur to give the desired product 4-(*tert*-butyl)-3-acetylpyridine: HPLC: t_R = 0.28; TLC R_f 0.31 (EtOAc); LCMS (ES) m/z 177.9 ($\text{M}+\text{H}^+$).

10

General Method D.



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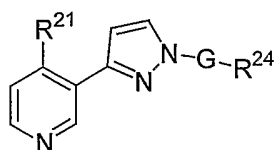
Step 1. A solution of the acetylpyridine (1 eq) and N, N-dimethylformamide dimethyl acetal (3 eq) is heated at 105 °C for 6.5 h. The volatile materials are evaporated and the crude enamine is used for the next reaction without further purification.

Step 2. A solution of the crude enamine (100 mg, 1 eq), and the hydrazine (1.5 eq) in EtOH is refluxed for 2 h. The reaction mixture is concentrated and the residue is purified by HPLC or column chromatography to give the desired pyridyl pyrrole.

20

Table 5. Examples 156-166: Pyridyl Pyrrole Derivatives Prepared from 3-Acetyl Pyridine and from Intermediate O by General Method D.

25



Example #	R ²¹	G	R ²⁴	t _R min ^{a,b}	MS ^{a,b} (M+H) ⁺	TLC R _f (solvent)	General Method
156	H	Phenyl	2,4-diCl	0.30	290.1	0.35 50% EtOAc/hexanes	D
157	H	Phenyl	4-OMe	1.75	252.2	0.26 50% EtOAc/hexanes	D
158	Me	Phenyl	3-F	0.48	254.2	0.44 50% EtOAc/hexanes	D
159	Me	Phenyl	4-Me	0.83	250.2	0.50 50% EtOAc/hexanes	D
160	Me	Phenyl	3-Cl	0.92	270.2	0.50 50% EtOAc/hexanes	D
161	Me	Phenyl	3,4-diCl	2.09	304.2	0.50 50% EtOAc/hexanes	D
162	Me	Phenyl	4-NO ₂	0.91	281.2	0.36 50% EtOAc/hexanes	D
163	Me	2-Napthyl	H	2.08	286.2	0.47 50% EtOAc/hexanes	D
164	Me	Phenyl	4-Cl	0.70	270.2	0.47 50% EtOAc/hexanes	D
165	Me	Phenyl	4-F	0.28	254.2	0.46 50% EtOAc/hexanes	D
166	Me	Phenyl	3-NO ₂	0.39	281.2	0.29 50% EtOAc/hexanes	D

Table 5 Note a: HPLC - electrospray mass spectra (HPLC ES-MS) were obtained using a Hewlett-Packard 1100 HPLC equipped with a quaternary pump, a variable wavelength detector set at 254 nm, a YMC pro C-18 column (2 x 23 mm, 120A), and a Finnigan LCQ ion trap mass spectrometer with electrospray ionization. Spectra were scanned from 120-1200 amu using a variable ion time according to the number of ions in the source. The eluents were A: 2% acetonitrile in water with 0.02% TFA and B: 2% water in acetonitrile with 0.018% TFA. Gradient elution from 10% B to 95% over 3.5 minutes at a flowrate of

1.0 mL/min was used with an initial hold of 0.5 minutes and a final hold at 95% B of 0.5 minutes. Total run time was 6.5 minutes.

Table Note b: Molecular ion data obtained via electrospray ionization.

5

The following Examples of 4-(substituted)-3-(3-pyrazolyl)pyridine derivatives are prepared from Intermediates P-R according to General Method D:

10

Table 6. Examples 167-221: Pyridyl Pyrazole Derivatives which may be Prepared from Intermediates P-T by General Method D.

Example No.	Compound Name
Example 167	4-Ethyl-[1-(2,4-dichlorophenyl)-1 <i>H</i> -pyrazol-3-yl]pyridine
Example 168	4-Ethyl-3-[1-(4-methoxyphenyl)-1 <i>H</i> -pyrazol-3-yl]pyridine
Example 169	4-Ethyl-3-[1-(3-fluorophenyl)-1 <i>H</i> -pyrazol-3-yl]pyridine
Example 170	4-Ethyl-3-[1-(4-methylphenyl)-1 <i>H</i> -pyrazol-3-yl]pyridine
Example 171	4-Ethyl-3-[1-(3-chlorophenyl)-1 <i>H</i> -pyrazol-3-yl]pyridine
Example 172	4-Ethyl-3-[1-(3,4-dichlorophenyl)-1 <i>H</i> -pyrazol-3-yl]pyridine
Example 173	4-Ethyl-3-[1-(4-nitrophenyl)-1 <i>H</i> -pyrazol-3-yl]pyridine
Example 174	4-Ethyl-3-[1-(2-naphthyl)-1 <i>H</i> -pyrazol-3-yl]pyridine
Example 175	4-Ethyl-3-[1-(4-chlorophenyl)-1 <i>H</i> -pyrazol-3-yl]pyridine
Example 176	4-Ethyl-3-[1-(4-fluorophenyl)-1 <i>H</i> -pyrazol-3-yl]pyridine
Example 177	4-Ethyl-3-[1-(3-nitrophenyl)-1 <i>H</i> -pyrazol-3-yl]pyridine
Example 178	4-(2-Propyl)-[1-(2,4-dichlorophenyl)-1 <i>H</i> -pyrazol-3-yl]pyridine
Example 179	4-(2-Propyl)-3-[1-(4-methoxyphenyl)-1 <i>H</i> -pyrazol-3-yl]pyridine
Example 180	4-(2-Propyl)-3-[1-(3-fluorophenyl)-1 <i>H</i> -pyrazol-3-yl]pyridine
Example 181	4-(2-Propyl)-3-[1-(4-methylphenyl)-1 <i>H</i> -pyrazol-3-yl]pyridine
Example 182	4-(2-Propyl)-3-[1-(3-chlorophenyl)-1 <i>H</i> -pyrazol-3-yl]pyridine
Example 183	4-(2-Propyl)-3-[1-(3,4-dichlorophenyl)-1 <i>H</i> -pyrazol-3-yl]pyridine
Example 184	4-(2-Propyl)-3-[1-(4-nitrophenyl)-1 <i>H</i> -pyrazol-3-yl]pyridine
Example 185	4-(2-Propyl)-3-[1-(2-naphthyl)-1 <i>H</i> -pyrazol-3-yl]pyridine

Example 186	4-(2-Propyl)-3-[1-(4-chlorophenyl)-1 <i>H</i> -pyrazol-3-yl]pyridine
Example 187	4-(2-Propyl)-3-[1-(4-fluorophenyl)-1 <i>H</i> -pyrazol-3-yl]pyridine
Example 188	4-(2-Propyl)-3-[1-(3-nitrophenyl)-1 <i>H</i> -pyrazol-3-yl]pyridine
Example 189	4-Cyclopropyl-[1-(2,4-dichlorophenyl)-1 <i>H</i> -pyrazol-3-yl]pyridine
Example 190	4-Cyclopropyl-3-[1-(4-methoxyphenyl)-1 <i>H</i> -pyrazol-3-yl]pyridine
Example 191	4-Cyclopropyl-3-[1-(3-fluorophenyl)-1 <i>H</i> -pyrazol-3-yl]pyridine
Example 192	4-Cyclopropyl-3-[1-(4-methylphenyl)-1 <i>H</i> -pyrazol-3-yl]pyridine
Example 193	4-Cyclopropyl-3-[1-(3-chlorophenyl)-1 <i>H</i> -pyrazol-3-yl]pyridine
Example 194	4-Cyclopropyl-3-[1-(3,4-dichlorophenyl)-1 <i>H</i> -pyrazol-3-yl]pyridine
Example 195	4-Cyclopropyl-3-[1-(4-nitrophenyl)-1 <i>H</i> -pyrazol-3-yl]pyridine
Example 196	4-Cyclopropyl-3-[1-(2-naphthyl)-1 <i>H</i> -pyrazol-3-yl]pyridine
Example 197	4-Cyclopropyl-3-[1-(4-chlorophenyl)-1 <i>H</i> -pyrazol-3-yl]pyridine
Example 198	4-Cyclopropyl-3-[1-(4-fluorophenyl)-1 <i>H</i> -pyrazol-3-yl]pyridine
Example 199	4-Cyclopropyl-3-[1-(3-nitrophenyl)-1 <i>H</i> -pyrazol-3-yl]pyridine
Example 200	4-(1-Propyl)-[1-(2,4-dichlorophenyl)-1 <i>H</i> -pyrazol-3-yl]pyridine
Example 201	4-(1-Propyl)-3-[1-(4-methoxyphenyl)-1 <i>H</i> -pyrazol-3-yl]pyridine
Example 202	4-(1-Propyl)-3-[1-(3-fluorophenyl)-1 <i>H</i> -pyrazol-3-yl]pyridine
Example 203	4-(1-Propyl)-3-[1-(4-methylphenyl)-1 <i>H</i> -pyrazol-3-yl]pyridine
Example 204	4-(1-Propyl)-3-[1-(3-chlorophenyl)-1 <i>H</i> -pyrazol-3-yl]pyridine
Example 205	4-(1-Propyl)-3-[1-(3,4-dichlorophenyl)-1 <i>H</i> -pyrazol-3-yl]pyridine
Example 206	4-(1-Propyl)-3-[1-(4-nitrophenyl)-1 <i>H</i> -pyrazol-3-yl]pyridine
Example 207	4-(1-Propyl)-3-[1-(2-naphthyl)-1 <i>H</i> -pyrazol-3-yl]pyridine
Example 208	4-(1-Propyl)-3-[1-(4-chlorophenyl)-1 <i>H</i> -pyrazol-3-yl]pyridine
Example 209	4-(1-Propyl)-3-[1-(4-fluorophenyl)-1 <i>H</i> -pyrazol-3-yl]pyridine
Example 210	4-(1-Propyl)-3-[1-(3-nitrophenyl)-1 <i>H</i> -pyrazol-3-yl]pyridine
Example 211	4-(<i>tert</i> -Butyl)-[1-(2,4-dichlorophenyl)-1 <i>H</i> -pyrazol-3-yl]pyridine
Example 212	4-(<i>tert</i> -Butyl)-3-[1-(4-methoxyphenyl)-1 <i>H</i> -pyrazol-3-yl]pyridine
Example 213	4-(<i>tert</i> -Butyl)-3-[1-(3-fluorophenyl)-1 <i>H</i> -pyrazol-3-yl]pyridine
Example 214	4-(<i>tert</i> -Butyl)-3-[1-(4-methylphenyl)-1 <i>H</i> -pyrazol-3-yl]pyridine
Example 215	4-(<i>tert</i> -Butyl)-3-[1-(3-chlorophenyl)-1 <i>H</i> -pyrazol-3-yl]pyridine
Example 216	4-(<i>tert</i> -Butyl)-3-[1-(3,4-dichlorophenyl)-1 <i>H</i> -pyrazol-3-yl]pyridine
Example 217	4-(<i>tert</i> -Butyl)-3-[1-(4-nitrophenyl)-1 <i>H</i> -pyrazol-3-yl]pyridine

Example 218	4-(<i>tert</i> -Butyl)-3-[1-(2-naphthyl)-1 <i>H</i> -pyrazol-3-yl]pyridine
Example 219	4-(<i>tert</i> -Butyl)-3-[1-(4-chlorophenyl)-1 <i>H</i> -pyrazol-3-yl]pyridine
Example 220	4-(<i>tert</i> -Butyl)-3-[1-(4-fluorophenyl)-1 <i>H</i> -pyrazol-3-yl]pyridine
Example 221	4-(<i>tert</i> -Butyl)-3-[1-(3-nitrophenyl)-1 <i>H</i> -pyrazol-3-yl]pyridine

Determination of the activity of the compounds of the invention

C17,20 Lyase inhibitory activity of compounds can be determined using, e.g.,
 5 the biochemical or the cellular assays set forth in the Examples. A person of skill in the art will recognize that variants of these assays can also be used.

The compounds of the invention can also be tested in animal models, e.g., animal models of prostate or breast cancer.

Each of the compounds of the invention was subjected to a biochemical assay and a
 10 cellular assay for determining its C17,20 lyase inhibitory activity.

Human and murine C17,20 lyase biochemical assays:

Recombinant human C17,20 lyase (hLyase) was expressed in (Sf9) cells, and hLyase enriched microsomes were prepared from cultures as described in the following reference:
 15 Baculovirus Expression of Bovine P₄₅₀ in Sf9 Cells and Comparison with Expression in Yeast, Mammalian Cells, and *E. Coli*. Barnes H. J.; Jenkins, C. M.; Waterman, M. R., *Archives of Biochemistry and Biophysics* (1994) 315(2) 489-494. Recombinant murine C17,20 lyase (mLyase) was prepared in a similar manner. hLyase and mLyase preparations were titrated using assay conditions to determine protein concentrations to be used for assays. Both mLyase and hLyase assays were run in an identical manner except that
 20 cytochrome b5 was omitted in the murine assays.

Test compounds were diluted 1:4, serially in six steps, with 100% DMSO starting from 800 μ M going to 51.2 nM reserving the first 2 columns for the generation of a standard curve. Each of these compound solutions in 100% DMSO was further diluted twenty fold in H₂O to obtain compound concentrations ranging from 40 μ M to 2.56 nM in 5% DMSO.
 25 Dehydroepiandrosterone (DHEA) standards were serially diluted in 100% DMSO from 400 μ M down to 120 nM in half-log dilutions. Each dilution was further diluted twenty fold in H₂O to obtain 20 μ M to 6 nM solutions in 5% DMSO using the first 2 columns. Five μ l of these 5% DMSO dilutions were used in the assay.

Clear-bottomed opaque 96 well assay plates were loaded with 50 μ L of assay buffer (50 mM Na_3PO_4 , pH 7.5) and 5 μ L of the diluted compounds were added to the wells. Thirty μ L of substrate solution (7 mM NADPH (Sigma N1630), 3.35 μ M 17-OH-pregnenolone (Steraloids Q4710), 3.35 μ g/mL human cytochrome b₅ (Panvera P2252) in 50 mM sodium phosphate pH 7.5 buffer) was added to all wells. Reactions were initiated with the addition of 10 μ L hLyase or mLyase in assay buffer.

Enzymatic reactions were allowed to run for 2 hours at room temperature with gentle agitation. Reactions were terminated with the addition of 50 μ M (final concentration) YM116, a potent C17,20 lyase inhibitor. The concentration of DHEA generated by hLyase was determined by radioimmunoassay (RIA) as described below.

0.08 μ Ci ³H-DHEA (1.6 μ Ci/mL) (NEN (NET814)) in scintillation proximity assay (SPA) buffer (100 mM Tris-HCl, pH 7.5, 50 mM NaCl, 0.5% BSA (Sigma A9647), 0.2% Tween 20) was added to each well. Fifty μ L DHEA rabbit antiserum with anti-rabbit SPA beads in SPA buffer was added to all wells. Anti DHEA rabbit antiserum was obtained from Endocrine Sciences (D7-421) (1 mL H₂O to the vial) and anti-Rabbit SPA Beads were obtained from Amersham (RPNQ 0016) (6mL SPA buffer to the bottle). Mixtures were allowed to equilibrate with gentle agitation for 1 hour followed by an overnight equilibration with no agitation. ³H-DHEA bound to the SPA beads was determined by scintillation counting.

The concentration of DHEA generated in each reaction was calculated from raw data (CPM) and the standard curve. The lyase inhibitory activity of each compound was determined as the concentration of DHEA generated in the presence of test compounds, expressed as a percent inhibition compared to the DHEA concentration generated in the absence of test compounds (1-(nM DHEA formed in the presence of test compound/nM DHEA formed in the absence of test compounds) x 100).

Human C17,20 cellular assay:

Human 293 lyase cells were prepared as described above for the Sf9 cells [Baculovirus Expression of Bovine Cytochrome P₄₅₀ in Sf9 Cells and Comparison with Expression in Yeast, Mammalian Cells, and *E.Coli*. Barnes, H. J.; Jenkins, C. M.; Waterman, M. R. *Archives of Biochemistry and Biophysics* (1994) 315 (2) 489-494]. The

cells were cultured in Dulbecco's Modified Eagle's Medium (DMEM) /10% FBS/
1%S/P/1%L-Glu/0.8mg/mL G418/HEPES.

On day one, human 293 lyase cells were plated at 10,000 cells/well/100 μ L in
columns 2-12 of a 96-well tissue culture plate (Falcon 3075), and allowed to attach overnight
5 (each mother plate needs two cell plates).

On day two, 100 μ L H₂O was added to all the wells of a daughter plate (one mother
plate one daughter plate Costar 3365). DHEA standard was diluted with RPMI (4.5 μ L of
500 μ M into 3 mL RPMI, then 1:3 serial dilutions). The media from columns 2-12 of the
cell plate was removed and replaced with 100 μ L RPMI without phenol red. Diluted DHEA
10 standards (100 μ L) at a concentration of 750, 250, 83.3, 27.7, 9.2, 3, 1 and 0.3 nM were
added to column 1 of the cell plate. 50 μ L of 100% DMSO was added to columns 1 and 2 of
the mother plate. 5 μ L of compound was transferred from mother plate to daughter plate,
then from the daughter plate to a cell plate using a robot. The cell plate was incubated for 10
minutes at room temperature. 15 μ L of 10 mM 17-OH-pregnenolone (Steraloids (Q4710)
15 (10 mM stock in 100% DMSO)) was diluted in 30 mL RPMI to obtain a solution of 5 μ M
17-OH-pregnenolone. 10 μ L of this solution was added to all the wells of the cell plate,
except that column received only DMSO. The plate was then incubated for one hour at
37°C.

The amount of DHEA produced was determined as follows. 90 μ L media was
20 removed from each well of the cell plate and placed into an SPA assay plate (Wallac Isoplate
#1450). 50 μ L of ³H-DHEA (1.6 μ Ci/mL, New England Nuclear (Catalog # NET814)) was
added to each well of the SPA assay plate. 50 μ L of anti-DHEA/anti-rabbit SPA beads (20
 μ L/mL AB with 10 mg/mL SPA beads) were then added to each well of the plate. The plate
was incubated overnight, and the radioactivity counted as described above. The first two
25 columns of the plate were reserved for a standard curve of DHEA and the no compound
controls.

The raw data (CPM) was converted to a concentration of DHEA formed (nM) by use
of the standard curve. The lyase inhibitory activity of the compounds was determined as the
amount of DHEA formed in the presence of compound compared to the amount formed in
30 the absence of compound in the form of a percent inhibition (1- (nM DHEA formed with
compound/nM DHEA formed without compound) x 100).

A test compound was considered to be active if the IC₅₀ in the human C17,20
biochemical assay or in the human C17,20 cellular assay was less than 10 μ M. All the

compounds tested have IC₅₀ in the human C17,20 biochemical assay or the human C17,20 cellular assay of less than 10 μM.

5

Equivalents

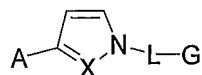
Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed by the following claims.

10

CLAIMS

We claim

1. A compound of the formula



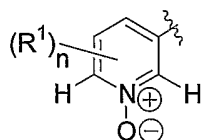
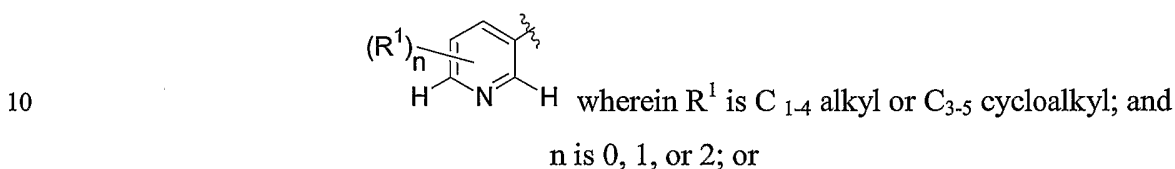
5 wherein

X represents CH or N;

when X is CH,

L represents a bond or a linker of formula $-(CH_2)_m-$ wherein m is 1 or 2 ; and

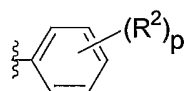
A represents



, provided that G is other than a pyridyl or an N-oxide-containing group;

and

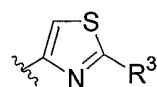
15 G represents



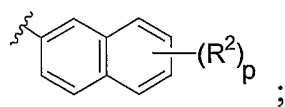
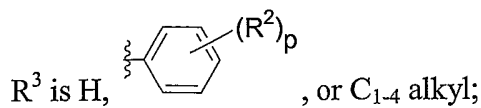
wherein

R² is C₁₋₄ alkyl, C₁₋₄ alkoxy, halogen, NO₂, or CN; and

p is 0, 1, or 2;



wherein

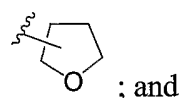


C₁₋₆ alkyl;

C₃₋₆ cycloalkyl;

5

C₂₋₄ alkenyl; or

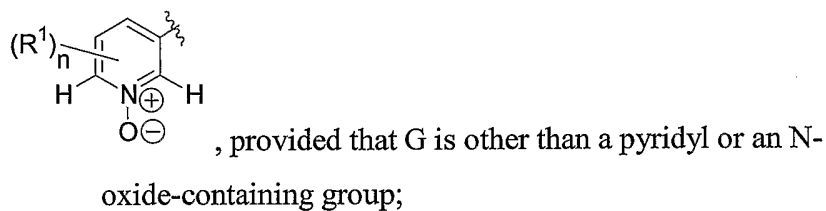
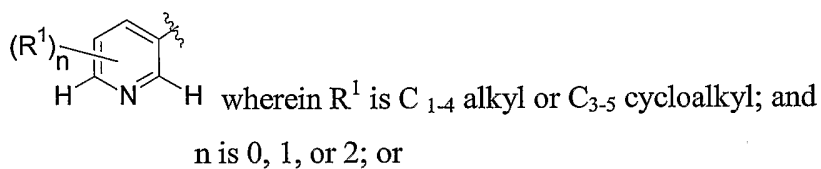


when X is N,

L represents a bond;

A represents

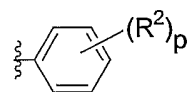
10



and

15

G represents

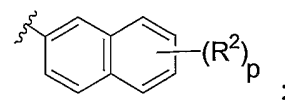
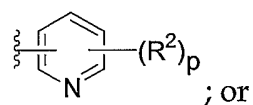


wherein

R² is C₁₋₄ alkyl, C₁₋₄ alkoxy, halogen, NO₂, or CN; and

p is 0, 1, or 2;

20



or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1

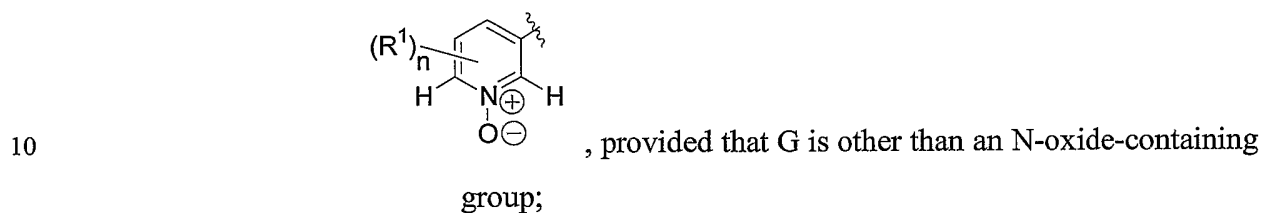
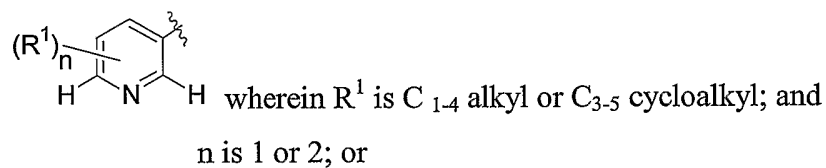
wherein

X represents CH or N;

5 when X is CH,

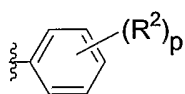
L represents a bond or a linker of formula $-(CH_2)_m-$ wherein m is 1 or 2 ; and

A represents



and

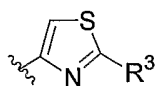
G represents



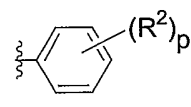
15 wherein

R^2 is C_{1-4} alkyl, C_{1-4} alkoxy, halogen, NO_2 , or CN, and

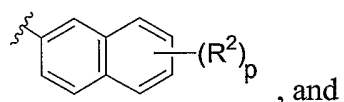
p is 0, 1, or 2;



wherein


 , or C_{1-4} alkyl, or

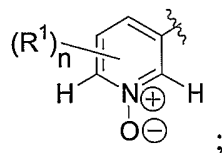
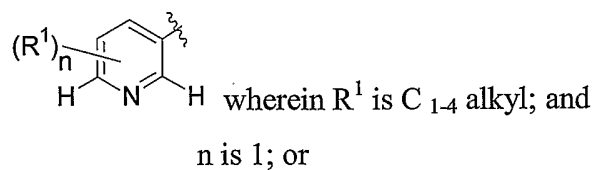
20



when X is N,

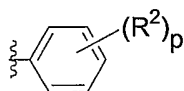
L represents a bond,

A represents



and

5 G represents



wherein

R^2 is halogen; and

p is 0, 1, or 2.

10

3. A compound according to claim 1

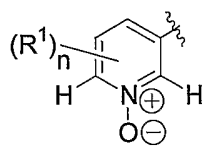
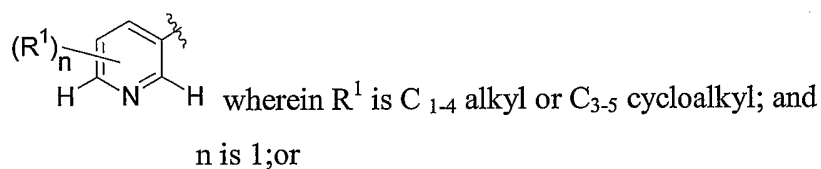
wherein

X represents CH; and

L represents a bond or a linker of formula $-(CH_2)_m-$ wherein m is 1 or 2 ; and

15

A represents

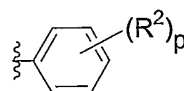


, provided that G is other than an N-oxide-containing group;

20

and

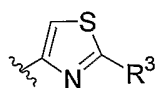
G represents



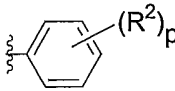
wherein

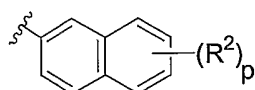
R^2 is C_{1-4} alkyl, C_{1-4} alkoxy, halogen, NO_2 , or CN; and

p is 0, 1, or 2;



wherein

R³ is H, , or C₁₋₄ alkyl; or



5

4. A compound according to claim 1

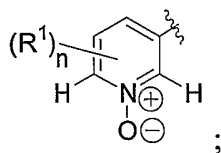
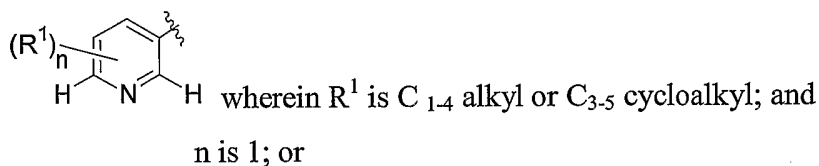
wherein

X represents CH; and

10

L represents a bond or a linker of formula $-(CH_2)_m-$ wherein m is 1 or 2; and

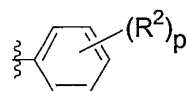
A represents



15

and

G represents



wherein

R² is C₁₋₄ alkyl, C₁₋₄ alkoxy, halogen, NO₂, or CN; and

20

p is 0, 1, or 2.

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

6. A method of inhibiting a lyase enzyme, comprising contacting said lyase enzyme with a compound of claim 1.
7. A method of inhibiting a 17α -hydroxylase-C17,20 lyase, comprising contacting a
5 17α -hydroxylase-C17,20 lyase with a compound of claim 1.
8. A method for treating a subject having a cancer associated with a 17α -hydroxylase-C17,20 lyase, comprising administering to the subject a therapeutically effective amount of a compound of claim 1.
10
9. A method for treating prostate cancer in a subject, comprising administering to said subject a therapeutically effective amount of a compound of claim 1, such that the prostate cancer in the subject is treated.
10. A method for treating breast cancer in a subject, comprising administering to said
15 subject a therapeutically effective amount of a compound of claim 1, such that the breast cancer in the subject is treated.
11. The method of any one of claims 8-10, wherein said subject is a primate, equine,
20 canine or feline.
12. The method of any one of claims 8-10, wherein said subject is a human.

25

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 02/30979

A. CLASSIFICATION OF SUBJECT MATTER IPC 7 C07D401/14 C07D401/04 A61K31/422 A61P35/00 A61K31/4439 //(C07D401/04,213:00,207:00),(C07D401/14,277:00,213:00,207:00), (C07D401/14,307:00,213:00,207:00) 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) 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) EPO-Internal		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 00 06556 A (ABBOTT LAB) 10 February 2000 (2000-02-10) claims 1,4 page 12 -page 16	1
A	NORTON P PEET ET AL: "Synthesis of a 2,5-diaryloxazoline as a potential platelet-activating factor antagonist" JOURNAL OF HETEROCYCLIC CHEMISTRY, HETERO CORP., TAMPA, FL, US, vol. 31, March 1994 (1994-03), pages 419-423, XP002121432 ISSN: 0022-152X Compound 5	1
<input checked="" type="checkbox"/> Further documents are listed in the continuation of box C. <input checked="" type="checkbox"/> 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
23 December 2002		10/01/2003
Name and mailing address of the ISA 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		Authorized officer Goss, I

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 02/30979

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	DN GRIGORYEV, BJ LONG, IP NANE, VCO NJAR, Y LIU AND AMH BRODIE: "Effects of new 17alpha-hydroxylase/C17,20-lyase inhibitors on LNCaP prostate cancer cell growth in vitro and in vivo" BRITISH JOURNAL OF CANCER, vol. 81, no. 4, 1999, pages 622-630, XP009001303 the whole document ---	1-12
A	YAN ZHUANG AND ROLF W. HARTMANN: "Synthesis and Evaluation of Azole-substituted 2-Aryl-6-methoxy-3,4-dihydronaphthalenes and -naphthalenes as Inhibitors of 17 alpha-Hydroxylase-C17,20-Lyase (P450 17)" ARCH. PHARM. PHARM. MED. CHEM., vol. 332, 1999, pages 25-30, XP002222972 Summary, Introduction, Results and discussion -----	1-12

INTERNATIONAL SEARCH REPORT

information on patent family members

International Application No

PCT/US 02/30979

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			WO	0006556 A1	10-02-2000
