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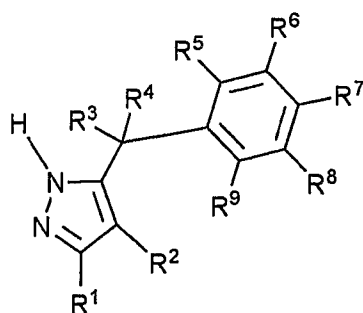
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(54) Title: THERAPEUTIC COMPOUNDS



(I)

(57) Abstract: The present invention provides compounds of formula (I), or pharmaceutically acceptable salts or solvates thereof, methods for their preparation, methods for their use, and pharmaceutical formulations comprising them.

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THERAPEUTIC COMPOUNDS

This application claims the benefit of United States Provisional Application No. 60/806,597, filed July 5, 2006, and United States Provisional Application No. 60/915,199, filed May 1, 2007, both of which are herein incorporated by reference in their entirety.

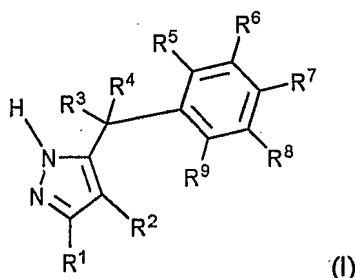
BACKGROUND

The cytochrome P450 (CYP450) enzyme system is responsible for the biotransformation of drugs from active to inactive metabolites that are readily excreted by the body. Furthermore, the rapid metabolism of certain drugs by the CYP450 enzyme system can markedly alter their pharmacokinetic (PK) profile and can result in sub-therapeutic plasma levels of those drugs over time. In the area of anti-infective therapy, such as treating viral infections such as human immunodeficiency virus (HIV) infections, such sub-therapeutic drug plasma levels can lead to an increase in resistance of the virus.

Ritonavir (RTV) is a marketed HIV protease inhibitor (PI) that, due to its ability to inhibit the cytochrome P450 3A4 enzyme, is also used to "boost" the pharmacokinetic exposure of many co-administered anti-retrovirals. However, RTV is associated with clinically significant gastrointestinal and metabolic side effects including nausea, emesis, diarrhea, and dyslipidemia. Administering low doses of a compound with potent antiviral activity may also contribute to the selection of drug-resistant strains of HIV. A novel CYP3A4 inhibitor capable of boosting antivirals as effectively as RTV but devoid of antiviral activity and significant side-effects would offer significant advantages and therapeutic value in the treatment of those suffering from infection with the HIV virus. The present invention discloses compounds that are useful in the inhibition of the CYP450 enzyme system and may be used to boost the pharmacokinetic exposure of co-administered drugs, including anti-retrovirals. It also discloses pharmaceutical formulations comprising such compounds, methods of making them, and methods of using them.

SUMMARY

In one embodiment, the present invention provides compounds of formula (I),



wherein:

R¹ is 5 to 6 membered heteroaryl, which is optionally substituted with one or more R¹⁴ groups;

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R^2 is selected from hydrogen, halo, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, $-(CR^{10}R^{11})_t(C_3$ - C_8 cycloalkyl), $-(CR^{10}R^{11})_tOR^{12}$, $-(CR^{10}R^{11})_tN(R^{12}R^{13})$, $-CN$, $-NO_2$, $-CF_3$, $-(CR^{10}R^{11})_tC(O)R^{12}$, $-(CR^{10}R^{11})_tC(O)N(R^{12}R^{13})$, and $-(CR^{10}R^{11})_tC(O)_2R^{12}$;

R^3 and R^4 are each independently selected from hydrogen and C_1 - C_8 alkyl; or

5 R^3 and R^4 , together with the atom to which they are attached, form a C_3 - C_8 cycloalkyl group;

R^5 , R^6 , R^7 , R^8 , and R^9 are each independently selected from hydrogen, halo, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, $-(CR^{10}R^{11})_t(C_3$ - C_8 cycloalkyl), $-(CR^{10}R^{11})_tOR^{12}$, $-(CR^{10}R^{11})_tN(R^{12}R^{13})$, $-CN$, $-NO_2$, $-CF_3$, $-(CR^{10}R^{11})_tC(O)R^{12}$, $-(CR^{10}R^{11})_tC(O)N(R^{12}R^{13})$, and $-(CR^{10}R^{11})_tC(O)_2R^{12}$; or

10 R^5 and R^6 , or R^6 and R^7 , or R^7 and R^8 , or R^8 and R^9 , together with the atoms to which they are attached form a 3 to 10 membered heterocyclyl group or a 5 to 10 membered heteroaryl group;

each R^{10} and R^{11} is independently selected from hydrogen and C_1 - C_8 alkyl;

15 each R^{12} and R^{13} is independently selected from hydrogen, C_1 - C_8 alkyl, $-(CR^{10}R^{11})_t(C_3$ - C_8 cycloalkyl), $-(CR^{10}R^{11})_t(3$ to 10 membered heterocyclyl), $-(CR^{10}R^{11})_t(5$ to 10 membered heteroaryl) and $-(CR^{10}R^{11})_t(C_6$ - C_{10} aryl), wherein each of said C_3 - C_8 cycloalkyl, 3 to 10 membered heterocyclyl, 5 to 10 membered heteroaryl, and C_6 - C_{10} aryl is optionally substituted with one or more R^{15} groups; or

20 R^{12} and R^{13} , together with the atom to which they are attached, form a 3 to 10 membered heterocyclyl group, which is optionally substituted with one or more R^{15} groups;

each R^{14} is independently selected from C_1 - C_8 alkyl, C_3 - C_8 cycloalkyl, C_6 - C_{10} aryl, 3 to 10 membered heterocyclyl, 5 to 10 membered heteroaryl, $-CN$, halo, $-(CR^{10}R^{11})_tOR^{15}$, $-(CR^{10}R^{11})_tC(O)N(R^{15}R^{16})$, and $-(CR^{10}R^{11})_tC(O)R^{15}$;

25 each R^{15} and R^{16} is independently selected from hydrogen, C_1 - C_8 alkyl, 3 to 10 membered heterocyclyl, and 5 to 10 membered heteroaryl; or

R^{15} and R^{16} , together with the atom to which they are attached, form a 3 to 10 membered heterocyclyl group; and

each t is independently 0, 1, 2, 3, or 4; or

30 a pharmaceutically acceptable salt or solvate thereof, provided the compound of formula (I) is not 4-(5-benzyl-1H-pyrazol-3-yl)pyridine, 3-(5-benzyl-1H-pyrazol-3-yl)pyridine, or 2-(5-(1-(4-fluorophenyl)cyclopropyl)-1H-pyrazol-3-yl)pyridine, or any salts thereof.

35 In another embodiment are provided compounds of formula (I), wherein R^1 is selected from pyridyl, imidazolyl, pyrimidinyl, pyrazinyl, pyridazinyl, imidazolyl, and triazolyl, each of which is optionally substituted with one or more R^{14} groups, and R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , and R^9 are as defined above.

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In yet another embodiment are provided compounds of formula (I), wherein R^1 is selected from pyridyl, pyrimidinyl, and imidazolyl, each of which is optionally substituted with one or more R^{14} groups, and R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , and R^9 are as defined above.

5 Still another embodiment provides compounds of formula (I), wherein R^1 is selected from 2-pyridyl, 3-pyridyl, or 4-pyridyl, each of which is optionally substituted with one or more R^{14} groups, and R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , and R^9 are as defined above.

Another embodiment provides compounds of formula (I), wherein R^1 is 4-pyridyl, which is optionally substituted with one or more R^{14} groups, and R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , and R^9 are as defined above.

10 A further embodiment provides compounds of formula (I), wherein R^1 is optionally substituted with one or more substituents independently selected from C_1 - C_8 alkyl, halo, -CN, $-(CR^{10}R^{11})_tOR^{15}$, and $-(CR^{10}R^{11})_tC(O)N(R^{15}R^{16})$, and R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , and R^9 are as defined above.

15 Also provided herein are compounds of formula (I), wherein R^1 is optionally substituted with one or more substituents independently selected from $-CH_3$, $-CH_2CH_3$, fluoro, chloro, bromo, -CN, -OH, $-OCH_3$, and $-C(O)N(C_1-C_8 \text{ alkyl})_2$, and R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , and R^9 are as defined above.

20 Yet another embodiment provides compounds of formula (I), wherein R^1 is optionally substituted with one or more substituents independently selected from $-CH_3$, $-CH_2CH_3$, fluoro, chloro, -CN, -OH, and $-OCH_3$, and R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , and R^9 are as defined above.

Further provided herein are compounds of formula (I), wherein R^1 is substituted with $-CH_3$, $-CH_2CH_3$, fluoro, chloro, -CN, -OH, or $-OCH_3$, and R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , and R^9 are as defined above.

25 In another embodiment are provided compounds of formula (I), wherein R^5 , R^6 , R^7 , R^8 , and R^9 are each independently selected from hydrogen, halo, C_1 - C_8 alkyl, $-CF_3$, $-(CR^{10}R^{11})_tOR^{12}$, $-(CR^{10}R^{11})_tN(R^{12}R^{13})$, and -CN, and R^1 , R^2 , R^3 , and R^4 are as defined above.

30 A still further embodiment provides compounds of formula (I), wherein R^5 , R^6 , R^7 , R^8 , and R^9 are each independently selected from hydrogen, fluoro, chloro, bromo, C_1 - C_8 alkyl, $-CF_3$, -OH, $-OCH_3$, and -CN, and R^1 , R^2 , R^3 , and R^4 are as defined above.

Further provided herein are compounds of formula (I), wherein R^5 , R^6 , R^7 , R^8 , and R^9 are each independently selected from hydrogen, fluoro, chloro, bromo, $-CH_3$, $-CF_3$, -OH, $-OCH_3$, and -CN, and R^1 , R^2 , R^3 , and R^4 are as defined above.

35 Another embodiment provides compounds of formula (I), wherein R^7 is fluoro, and R^5 , R^6 , R^8 , and R^9 are hydrogen, and R^1 , R^2 , R^3 , and R^4 are as defined above.

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Further provided herein are compounds of formula (I), wherein R^2 is hydrogen, and R^1 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , and R^9 are as defined above.

In yet another embodiment is provided compounds of formula (I), wherein R^3 and R^4 are hydrogen, and R^1 , R^2 , R^5 , R^6 , R^7 , R^8 , and R^9 are as defined above.

5 An additional embodiment provides compounds of formula (I), wherein:

R^1 is selected from pyridyl, imidazolyl, pyrimidinyl, pyrazinyl, pyridazinyl, imidazolyl, and triazolyl, each of which is optionally substituted with one or more R^{14} groups;

R^2 is hydrogen;

10 R^3 and R^4 are each independently selected from hydrogen and C_1 - C_8 alkyl; or

R^3 and R^4 , together with the atom to which they are attached, form a C_3 - C_8 cycloalkyl group;

R^5 , R^6 , R^7 , R^8 , and R^9 are each independently selected from hydrogen, halo, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, $-(CR^{10}R^{11})_t(C_3$ - C_8 cycloalkyl), $-(CR^{10}R^{11})_tOR^{12}$,
15 $-(CR^{10}R^{11})_tN(R^{12}R^{13})$, $-CN$, $-NO_2$, $-CF_3$, $-(CR^{10}R^{11})_tC(O)R^{12}$, $-(CR^{10}R^{11})_tC(O)N(R^{12}R^{13})$, and $-(CR^{10}R^{11})_tC(O)_2R^{12}$;

each R^{10} and R^{11} is independently selected from hydrogen and C_1 - C_8 alkyl;

each R^{12} and R^{13} is independently selected from hydrogen, C_1 - C_8 alkyl, $-(CR^{10}R^{11})_t(C_3$ - C_8 cycloalkyl), $-(CR^{10}R^{11})_t(3$ to 10 membered heterocyclyl), $-(CR^{10}R^{11})_t(5$ to
20 10 membered heteroaryl) and $-(CR^{10}R^{11})_t(C_6$ - C_{10} aryl), wherein each of said C_3 - C_8 cycloalkyl, 3 to 10 membered heterocyclyl, 5 to 10 membered heteroaryl, and C_6 - C_{10} aryl is optionally substituted with one or more R^{15} groups; or

R^{12} and R^{13} , together with the atom to which they are attached, form a 3 to 10 membered heterocyclyl group, which is optionally substituted with one or more R^{15} groups;

25 each R^{14} is independently selected from C_1 - C_8 alkyl, C_3 - C_8 cycloalkyl, C_6 - C_{10} aryl, 3 to 10 membered heterocyclyl, 5 to 10 membered heteroaryl, $-CN$, halo, $-(CR^{10}R^{11})_tOR^{15}$, $-(CR^{10}R^{11})_tC(O)N(R^{15}R^{16})$, and $-(CR^{10}R^{11})_tC(O)R^{15}$;

each R^{15} and R^{16} is independently selected from hydrogen, C_1 - C_8 alkyl, 3 to 10 membered heterocyclyl, and 5 to 10 membered heteroaryl; and

30 each t is independently 0, 1, 2, 3, or 4; or

a pharmaceutically acceptable salt or solvate thereof, provided the compound of formula (I) is not 4-(5-benzyl-1H-pyrazol-3-yl)pyridine, 3-(5-benzyl-1H-pyrazol-3-yl)pyridine, or 2-(5-(1-(4-fluorophenyl)cyclopropyl)-1H-pyrazol-3-yl)pyridine, or any salts thereof.

35 In another embodiment are provided compounds of formula (I), wherein:

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R¹ is selected from pyridyl, imidazolyl, pyrimidinyl, pyrazinyl, pyridazinyl, imidazolyl, and triazolyl, each of which is optionally substituted with one or more R¹⁴ groups;

R² is hydrogen;

5 R³ and R⁴ are hydrogen;

R⁵, R⁶, R⁷, R⁸, and R⁹ are each independently selected from hydrogen, halo, C₁-C₈ alkyl, -CN, and -CF₃; or

10 R⁵ and R⁶, or R⁶ and R⁷, or R⁷ and R⁸, or R⁸ and R⁹, together with the atoms to which they are attached form a 3 to 10 membered heterocyclyl group or a 5 to 10 membered heteroaryl group;

each R¹⁰ and R¹¹ is independently selected from hydrogen and C₁-C₈ alkyl;

each R¹⁴ is independently selected from C₁-C₈ alkyl, C₃-C₈ cycloalkyl, C₆-C₁₀ aryl, 3 to 10 membered heterocyclyl, 5 to 10 membered heteroaryl, -CN, halo, -(CR¹⁰R¹¹)_tOR¹⁵, -(CR¹⁰R¹¹)_tC(O)N(R¹⁵R¹⁶), and -(CR¹⁰R¹¹)_tC(O)R¹⁵;

15 each R¹⁵ and R¹⁶ is independently selected from hydrogen, C₁-C₈ alkyl, 3 to 10 membered heterocyclyl, and 5 to 10 membered heteroaryl; or

R¹⁵ and R¹⁶, together with the atom to which they are attached, form a 3 to 10 membered heterocyclyl group; and

each t is independently 0, 1, 2, 3, or 4; or

20 a pharmaceutically acceptable salt or solvate thereof, provided the compound of formula (I) is not 4-(5-benzyl-1H-pyrazol-3-yl)pyridine, 3-(5-benzyl-1H-pyrazol-3-yl)pyridine, or 2-(5-(1-(4-fluorophenyl)cyclopropyl)-1H-pyrazol-3-yl)pyridine, or any salts thereof.

In still another embodiment are provided compounds of formula (I), wherein:

25 R¹ is selected from pyridyl, imidazolyl, pyrimidinyl, pyrazinyl, pyridazinyl, imidazolyl, and triazolyl, each of which is optionally substituted with one or more R¹⁴ groups;

R² is hydrogen;

R³ and R⁴ are hydrogen;

30 R⁵, R⁶, R⁷, R⁸, and R⁹ are each independently selected from hydrogen, halo, C₁-C₈ alkyl, -CN, and -CF₃; and

each R¹⁴ is independently selected from -CH₃, -CH₂CH₃, fluoro, chloro, bromo, -CN, -OH, -OCH₃, and -C(O)N(C₁-C₈ alkyl)₂; or

35 a pharmaceutically acceptable salt or solvate thereof, provided the compound of formula (I) is not 4-(5-benzyl-1H-pyrazol-3-yl)pyridine, 3-(5-benzyl-1H-pyrazol-3-yl)pyridine, or 2-(5-(1-(4-fluorophenyl)cyclopropyl)-1H-pyrazol-3-yl)pyridine, or any salts thereof.

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In still another embodiment are provided compounds of formula (I), wherein:

R¹ is selected from 2-pyridyl, 3-pyridyl, and 4-pyridyl, each of which is optionally substituted with one or more R¹⁴ groups;

R² is hydrogen;

5 R³ and R⁴ are hydrogen;

R⁵, R⁶, R⁷, R⁸, and R⁹ are each independently selected from hydrogen, halo, C₁-C₈ alkyl, -CN, and -CF₃; and

each R¹⁴ is independently selected from -CH₃, -CH₂CH₃, fluoro, chloro, bromo, -CN, -OH, -OCH₃, and -C(O)N(C₁-C₈ alkyl)₂; or

10 a pharmaceutically acceptable salt or solvate thereof, provided the compound of formula (I) is not 4-(5-benzyl-1H-pyrazol-3-yl)pyridine, 3-(5-benzyl-1H-pyrazol-3-yl)pyridine, or 2-(5-(1-(4-fluorophenyl)cyclopropyl)-1H-pyrazol-3-yl)pyridine, or any salts thereof.

A further embodiment provides compounds of formula (I), wherein:

15 R¹ is 4-pyridyl, which is optionally substituted with one or more R¹⁴ groups;

R² is hydrogen;

R³ and R⁴ are hydrogen;

R⁵, R⁶, R⁷, R⁸, and R⁹ are each independently selected from hydrogen, halo, C₁-C₈ alkyl, -CN, and -CF₃; and

20 each R¹⁴ is independently selected from -CH₃, -CH₂CH₃, fluoro, chloro, bromo, -CN, -OH, -OCH₃, and -C(O)N(C₁-C₈ alkyl)₂; or

a pharmaceutically acceptable salt or solvate thereof, provided the compound of formula (I) is not 4-(5-benzyl-1H-pyrazol-3-yl)pyridine, 3-(5-benzyl-1H-pyrazol-3-yl)pyridine, or 2-(5-(1-(4-fluorophenyl)cyclopropyl)-1H-pyrazol-3-yl)pyridine, or any salts
25 thereof.

Another embodiment provides compounds of formula (I), wherein:

R¹ is 4-pyridyl, which is optionally substituted with one or more R¹⁴ groups;

R² is hydrogen;

R³ and R⁴ are hydrogen;

30 R⁵, R⁶, R⁷, R⁸, and R⁹ are each independently selected from hydrogen and halo;
and

each R¹⁴ is independently selected from -CH₃, -CH₂CH₃, fluoro, chloro, bromo, -CN, -OH, -OCH₃, and -C(O)N(C₁-C₈ alkyl)₂; or

a pharmaceutically acceptable salt or solvate thereof, provided the compound of
35 formula (I) is not 4-(5-benzyl-1H-pyrazol-3-yl)pyridine, 3-(5-benzyl-1H-pyrazol-3-yl)pyridine, or 2-(5-(1-(4-fluorophenyl)cyclopropyl)-1H-pyrazol-3-yl)pyridine, or any salts thereof.

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A further embodiment provides compounds of formula (I), wherein:

R¹ is 4-pyridyl, which is optionally substituted with one or more R¹⁴ groups;

R² is hydrogen;

R³ and R⁴ are hydrogen;

R⁵ and R⁶ are hydrogen;

R⁷ is halo;

R⁸ and R⁹ are hydrogen; and

each R¹⁴ is independently selected from -CH₃, -CH₂CH₃, fluoro, chloro, bromo, -CN, -OH, -OCH₃, and -C(O)N(C₁-C₈ alkyl)₂; or

a pharmaceutically acceptable salt or solvate thereof, provided the compound of formula (I) is not 4-(5-benzyl-1H-pyrazol-3-yl)pyridine, 3-(5-benzyl-1H-pyrazol-3-yl)pyridine, or 2-(5-(1-(4-fluorophenyl)cyclopropyl)-1H-pyrazol-3-yl)pyridine, or any salts thereof.

Yet another embodiment provides compounds of formula (I), wherein:

R¹ is 4-pyridyl;

R² is hydrogen;

R³ and R⁴ are hydrogen;

R⁵ and R⁶ are hydrogen;

R⁷ is halo; and

R⁸ and R⁹ are hydrogen; or

a pharmaceutically acceptable salt or solvate thereof, provided the compound of formula (I) is not 4-(5-benzyl-1H-pyrazol-3-yl)pyridine, 3-(5-benzyl-1H-pyrazol-3-yl)pyridine, or 2-(5-(1-(4-fluorophenyl)cyclopropyl)-1H-pyrazol-3-yl)pyridine, or any salts thereof.

In yet another embodiment are provided compounds of formula (I), selected from 4-[3-(4-methylbenzyl)-1H-pyrazol-5-yl]pyridine; 4-[3-(4-fluorobenzyl)-1H-pyrazol-5-yl]pyridine; 4-[5-(2,4-dimethylbenzyl)-1H-pyrazol-3-yl]pyridine; 4-[5-(3-fluorobenzyl)-1H-pyrazol-3-yl]pyridine; 4-[5-(2-chlorobenzyl)-1H-pyrazol-3-yl]pyridine; 4-[5-(2,4-dichlorobenzyl)-1H-pyrazol-3-yl]pyridine; 1-(5-benzyl-3-pyridin-4-yl-1H-pyrazol-4-yl)-N-(cyclopropylmethyl)methanamine; 4-[5-(4-bromobenzyl)-1H-pyrazol-3-yl]pyridine; 4-[5-(3,4-dichlorobenzyl)-1H-pyrazol-3-yl]pyridine; 4-[5-(2,6-difluorobenzyl)-1H-pyrazol-3-yl]pyridine; 4-[5-(2-chloro-6-fluorobenzyl)-1H-pyrazol-3-yl]pyridine; 4-[5-(3-chlorobenzyl)-1H-pyrazol-3-yl]pyridine; 2-(5-benzyl-1H-pyrazol-3-yl)pyridine; 3-chloro-4-[3-(4-methylbenzyl)-1H-pyrazol-5-yl]pyridine; 3-methoxy-4-[5-(4-methylbenzyl)-1H-pyrazol-3-yl]pyridine; 4-[5-(4-methylbenzyl)-1H-pyrazol-3-yl]pyridin-3-ol; 3-ethyl-4-[5-(4-methylbenzyl)-1H-pyrazol-3-yl]pyridine; 3-ethyl-4-[5-(4-fluorobenzyl)-1H-pyrazol-3-yl]pyridine; 3-chloro-4-[5-(4-fluorobenzyl)-1H-pyrazol-3-yl]pyridine; 4-[5-(4-fluorobenzyl)-

1H-pyrazol-3-yl]nicotinamide; 4-[5-(4-fluorobenzyl)-1H-pyrazol-3-yl]-3-methoxypyridine; 4-[5-(4-fluorobenzyl)-1H-pyrazol-3-yl]pyridin-3-ol; 3-chloro-4-[5-(4-methoxybenzyl)-1H-pyrazol-3-yl]pyridine; 4-[[3-(3-chloropyridin-4-yl)-1H-pyrazol-5-yl]methyl]phenol; 4-[(3-pyridin-4-yl-1H-pyrazol-5-yl)methyl]benzonitrile; 4-[5-(4-fluorobenzyl)-1H-pyrazol-3-yl]-N,N-dimethylnicotinamide; methyl 5-(4-fluorobenzyl)-3-pyridin-4-yl-1H-pyrazole-4-carboxylate; 4-[5-(2-methylbenzyl)-1H-pyrazol-3-yl]pyridine; 4-[(4-[5-(4-fluorobenzyl)-1H-pyrazol-3-yl]pyridin-3-yl)carbonyl]morpholine; 4-[5-(4-fluorobenzyl)-1H-pyrazol-3-yl]nicotinonitrile; 4-[5-(4-fluorobenzyl)-1H-pyrazol-3-yl]-3-(pyrrolidin-1-ylcarbonyl)pyridine; [5-(4-fluorobenzyl)-3-pyridin-4-yl-1H-pyrazol-4-yl]methanol; N-ethyl-5-(4-fluorobenzyl)-N-methyl-3-pyridin-4-yl-1H-pyrazole-4-carboxamide; N-cyclobutyl-5-(4-fluorobenzyl)-3-pyridin-4-yl-1H-pyrazole-4-carboxamide; 5-(4-fluorobenzyl)-3-pyridin-4-yl-N-(2-pyrrolidin-1-ylethyl)-1H-pyrazole-4-carboxamide; 1-[[5-(4-fluorobenzyl)-3-pyridin-4-yl-1H-pyrazol-4-yl]carbonyl]-4-pyridin-2-ylpiperazine; 5-(4-fluorobenzyl)-3-pyridin-4-yl-1H-pyrazole-4-carboxylic acid; 4-[5-(4-fluorobenzyl)-1H-pyrazol-3-yl]pyrimidine; 5-(4-fluorobenzyl)-3-(1H-imidazol-4-yl)-1H-pyrazole; 4-[5-(4-fluorobenzyl)-1H-pyrazol-3-yl]-1H-1,2,3-triazole; 4-[5-(4-fluorobenzyl)-1H-pyrazol-3-yl]pyridazine; 3-chloro-4-[5-(2-methoxybenzyl)-1H-pyrazol-3-yl]pyridine; 3-chloro-4-[5-(2-chloro-6-fluorobenzyl)-1H-pyrazol-3-yl]pyridine; 4-[5-(4-bromobenzyl)-1H-pyrazol-3-yl]-3-chloropyridine; 3-chloro-4-[5-(3-chlorobenzyl)-1H-pyrazol-3-yl]pyridine; 3-chloro-4-[5-(3,4-dichlorobenzyl)-1H-pyrazol-3-yl]pyridine; 3-chloro-4-[5-(2-fluorobenzyl)-1H-pyrazol-3-yl]pyridine; 3-chloro-4-[5-[3-(trifluoromethyl)benzyl]-1H-pyrazol-3-yl]pyridine; 3-chloro-4-[5-(2,5-dimethylbenzyl)-1H-pyrazol-3-yl]pyridine; 3-chloro-4-[5-(2-chlorobenzyl)-1H-pyrazol-3-yl]pyridine; 3-chloro-4-[5-(2-methylbenzyl)-1H-pyrazol-3-yl]pyridine; 4-[5-(2-bromo-4,5-dimethoxybenzyl)-1H-pyrazol-3-yl]-3-chloropyridine; 3-chloro-4-[5-(3-methylbenzyl)-1H-pyrazol-3-yl]pyridine; 3-chloro-4-[5-(3-fluorobenzyl)-1H-pyrazol-3-yl]pyridine; 3-chloro-4-[5-(2,3-dimethoxybenzyl)-1H-pyrazol-3-yl]pyridine; 4-[5-(5-bromo-2-methoxybenzyl)-1H-pyrazol-3-yl]-3-chloropyridine; 3-chloro-4-[5-(4-ethylbenzyl)-1H-pyrazol-3-yl]pyridine; 3-chloro-4-[5-(2,5-dimethoxybenzyl)-1H-pyrazol-3-yl]pyridine; 3-chloro-4-[5-(4-isopropylbenzyl)-1H-pyrazol-3-yl]pyridine; 4-[5-(2-methoxybenzyl)-1H-pyrazol-3-yl]pyridine; 3-chloro-4-[5-(2,4-dimethylbenzyl)-1H-pyrazol-3-yl]pyridine; 4-[5-(3-bromo-4-methoxybenzyl)-1H-pyrazol-3-yl]-3-chloropyridine; 3-chloro-4-[5-(2,6-difluorobenzyl)-1H-pyrazol-3-yl]pyridine; 4-[5-(3,4-dimethoxybenzyl)-1H-pyrazol-3-yl]pyridine; 4-[5-(4-methoxybenzyl)-1H-pyrazol-3-yl]pyridine; 3-chloro-4-[5-(2-ethoxybenzyl)-1H-pyrazol-3-yl]pyridine; 3-chloro-4-[5-(4-fluoro-3-methoxybenzyl)-1H-pyrazol-3-yl]pyridine; 4-[5-(2,4-dimethoxybenzyl)-1H-pyrazol-3-yl]pyridine; 4-[5-(4-methylbenzyl)-1H-pyrazol-3-yl]pyridine; 4-[5-(3-methoxybenzyl)-1H-pyrazol-3-yl]pyridine; 4-[5-(2-fluorobenzyl)-1H-pyrazol-3-yl]pyridine; 4-[5-(4-ethylbenzyl)-1H-pyrazol-3-yl]pyridine; 4-[5-(3-methylbenzyl)-1H-pyrazol-3-yl]pyridine; 4-[5-[3-(trifluoromethyl)benzyl]-1H-pyrazol-

3-yl]pyridine; 4-[5-(3,5-dichlorobenzyl)-1H-pyrazol-3-yl]pyridine; 4-[5-(2,5-dimethoxybenzyl)-1H-pyrazol-3-yl]pyridine; 4-[5-(5-bromo-2-methoxybenzyl)-1H-pyrazol-3-yl]pyridine; 4-[5-(2,5-dimethylbenzyl)-1H-pyrazol-3-yl]pyridine; 4-[5-(4-fluorobenzyl)-1H-pyrazol-3-yl]pyridine; 4-[5-(3-bromo-4-methoxybenzyl)-1H-pyrazol-3-yl]pyridine; 4-[5-(2-bromo-4,5-dimethoxybenzyl)-1H-pyrazol-3-yl]pyridine; 4-[5-(2,6-dimethoxybenzyl)-1H-pyrazol-3-yl]pyridine; 4-[5-(3-ethoxybenzyl)-1H-pyrazol-3-yl]pyridine; 4-[5-(3,5-dimethoxybenzyl)-1H-pyrazol-3-yl]pyridine; 4-[5-(4-isopropylbenzyl)-1H-pyrazol-3-yl]pyridine; 4-[5-(4-ethoxybenzyl)-1H-pyrazol-3-yl]pyridine; 4-[5-(2,5-dichlorobenzyl)-1H-pyrazol-3-yl]pyridine; 4-[5-(3-chloro-4-methoxybenzyl)-1H-pyrazol-3-yl]pyridine; 4-[5-(2-ethoxybenzyl)-1H-pyrazol-3-yl]pyridine; 4-[5-(2,3-dihydro-14-benzodioxin-6-ylmethyl)-1H-pyrazol-3-yl]pyridine; 4-[5-(4-methoxy-3-methylbenzyl)-1H-pyrazol-3-yl]pyridine; and 4-[5-(4-fluoro-3-methoxybenzyl)-1H-pyrazol-3-yl]pyridine; or a pharmaceutically acceptable salt thereof.

The present invention also provides pharmaceutical compositions, comprising an effective amount of at least one compound of formula (I), and a pharmaceutically acceptable carrier. Also provided herein are such pharmaceutical compositions, further comprising an effective amount of at least one additional compound that is metabolized by cytochrome P450. Also provided are such pharmaceutical compositions, wherein said at least one additional compound is 6-cyclopentyl-6-[2-(2,6-diethylpyridin-4-yl)ethyl]-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one, or a pharmaceutically acceptable salt thereof.

Further provided are such pharmaceutical compositions, wherein said at least one additional compound is an anti-HIV compound. Also provided are such pharmaceutical compositions, wherein said at least one additional compound is an HIV protease inhibitor. In yet another embodiment are provided such pharmaceutical compositions, wherein said at least one additional compound is selected from amprenavir, CGP-73547, CGP-61755, DMP-450, nelfinavir, ritonavir, saquinavir, invirase, lopinavir, TMC-126, atazanavir, palinavir, GS-3333, KN I-413, KNI-272, LG-71350, CGP-61755, PD 173606, PD 177298, PD 178390, PD 178392, U-140690, ABT-378, DMP-450, AG-1776, MK-944, VX-478, indinavir, tipranavir, duranavir, DPC-681, DPC-684, (4R)-N-allyl-3-[(2S,3S)-2-hydroxy-3-[(3-hydroxy-2-methylbenzoyl)amino]-4-phenylbutanoyl]-5,5-dimethyl-1,3-thiazolidine-4-carboxamide, and fosamprenavir calcium. Still another embodiment provides such pharmaceutical compositions, wherein said at least one additional compound is selected from amprenavir, nelfinavir, ritonavir, saquinavir, invirase, lopinavir, atazanavir, palinavir, indinavir, tipranavir, duranavir, (4R)-N-allyl-3-[(2S,3S)-2-hydroxy-3-[(3-hydroxy-2-methylbenzoyl)amino]-4-phenylbutanoyl]-5,5-dimethyl-1,3-thiazolidine-4-carboxamide, and fosamprenavir calcium. Another embodiment provides such pharmaceutical compositions,

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wherein said at least one additional compound is (4R)-N-allyl-3-[(2S,3S)-2-hydroxy-3-[(3-hydroxy-2-methylbenzoyl)amino]-4-phenylbutanoyl]-5,5-dimethyl-1,3-thiazolidine-4-carboxamide.

Yet another embodiment provides such pharmaceutical compositions, comprising
5 at least one compound of formula (I), and an anti-HIV compound as a combined preparation for simultaneous, separate, or sequential administration to an HIV-infected mammal for the treatment of HIV in said mammal.

Still another embodiment affords pharmaceutical compositions, comprising an effective amount of (N-[(1S)-3-[3-isopropyl-5-methyl-4H-1,2,4-triazole-4-yl]-exo-8-
10 azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl)-4,4-difluorocyclohexanecarboxamide), ethyl 1-endo-[8-[(3S)-3-(acetylamino)-3-(3-fluorophenyl)propyl]-8-azabicyclo[3.2.1]oct-3-yl]-2-methyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine-5-carboxylate, or N-[(1S)-3-[3-endo-(5-isobutyryl-2-methyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridin-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-(3-fluorophenyl)propyl]acetamide), at least one compound of
15 formula (I), and a pharmaceutically acceptable carrier. Still another embodiment provides such pharmaceutical compositions, comprising an effective amount of (N-[(1S)-3-[3-isopropyl-5-methyl-4H-1,2,4-triazole-4-yl]-exo-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl)-4,4-difluorocyclohexanecarboxamide), at least compound of formula (I), and a pharmaceutically acceptable carrier.

20 A further embodiment provides methods of inhibiting the metabolism in a mammal of a first compound that is metabolized by cytochrome P450, comprising administering to said mammal said first compound and an effective amount of a second compound, wherein said second compound is selected from those of formula (I). Further provided are such methods, wherein said first compound is an anti-HIV compound. Also provided are
25 such methods, wherein said anti-HIV compound is an HIV protease inhibitor. In yet another embodiment are provided such methods, wherein said HIV protease inhibitor is selected from amprenavir, CGP-73547, CGP-61755, DMP-450, nelfinavir, ritonavir, saquinavir, invirase, lopinavir, TMC-126, atazanavir, palinavir, GS-3333, KN I-413, KNI-272, LG-71350, CGP-61755, PD 173606, PD 177298, PD 178390, PD 178392, U-140690,
30 ABT-378, DMP-450, AG-1776, MK-944, VX-478, indinavir, tipranavir, duranavir, DPC-681, DPC-684, (4R)-N-allyl-3-[(2S,3S)-2-hydroxy-3-[(3-hydroxy-2-methylbenzoyl)amino]-4-phenylbutanoyl]-5,5-dimethyl-1,3-thiazolidine-4-carboxamide, and fosamprenavir calcium. In still a further embodiment are provided such methods, wherein said HIV protease inhibitor is selected from amprenavir, nelfinavir, ritonavir, saquinavir, invirase, lopinavir,
35 atazanavir, palinavir, indinavir, tipranavir, duranavir, (4R)-N-allyl-3-[(2S,3S)-2-hydroxy-3-[(3-hydroxy-2-methylbenzoyl)amino]-4-phenylbutanoyl]-5,5-dimethyl-1,3-thiazolidine-4-carboxamide, and fosamprenavir calcium. Also included are such methods, wherein said

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HIV protease inhibitor is (4R)-N-allyl-3-[(2S,3S)-2-hydroxy-3-[(3-hydroxy-2-methylbenzoyl)amino]-4-phenylbutanoyl]-5,5-dimethyl-1,3-thiazolidine-4-carboxamide.

Further provided are methods of inhibiting the metabolism in a mammal of a first compound that is metabolized by cytochrome P450, comprising administering to said mammal said first compound and an effective amount of a second compound, wherein said first compound is 6-cyclopentyl-6-[2-(2,6-diethylpyridin-4-yl)ethyl]-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one, or a pharmaceutically acceptable salt thereof, and the second compound is any one of formula (I).

Further included herein are methods of inhibiting the metabolism in a mammal of a first compound that is metabolized by cytochrome P450, comprising administering to said mammal said first compound and an effective amount of a second compound, wherein said first compound is (N-[(1S)-3-[3-isopropyl-5-methyl-4H-1,2,4-triazole-4-yl]-exo-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl)-4,4-difluorocyclohexanecarboxamide), ethyl 1-endo-{8-[(3S)-3-(acetylamino)-3-(3-fluorophenyl)propyl]-8-azabicyclo[3.2.1]oct-3-yl}-2-methyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine-5-carboxylate, or N-[(1S)-3-[3-endo-(5-isobutyryl-2-methyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridin-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-(3-fluorophenyl)propyl]acetamide), and said second compound is any one of formula (I). Further provided herein are such methods, wherein said first compound is (N-[(1S)-3-[3-isopropyl-5-methyl-4H-1,2,4-triazole-4-yl]-exo-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl)-4,4-difluorocyclohexanecarboxamide).

In another embodiment are provided methods of improving the pharmacokinetics in a mammal of a first compound, comprising administering to said mammal said first compound and an effective amount of a second compound, wherein said second compound is selected from those of formula (I). Further included herein are such methods, wherein said first compound is 6-cyclopentyl-6-[2-(2,6-diethylpyridin-4-yl)ethyl]-3-[(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)methyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one, or a pharmaceutically acceptable salt thereof. A further embodiment provides such methods, wherein said first compound is (N-[(1S)-3-[3-isopropyl-5-methyl-4H-1,2,4-triazole-4-yl]-exo-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl)-4,4-difluorocyclohexanecarboxamide), ethyl 1-endo-{8-[(3S)-3-(acetylamino)-3-(3-fluorophenyl)propyl]-8-azabicyclo[3.2.1]oct-3-yl}-2-methyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine-5-carboxylate, or N-[(1S)-3-[3-endo-(5-isobutyryl-2-methyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridin-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-(3-fluorophenyl)propyl]acetamide). Also included herein are such methods, wherein said first compound is (N-[(1S)-3-[3-isopropyl-5-methyl-4H-1,2,4-triazole-4-yl]-exo-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl)-4,4-difluorocyclohexanecarboxamide).

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Further included herein are methods of improving the pharmacokinetics in a mammal of a first compound, comprising administering to said mammal said first compound and an effective amount of a second compound, wherein said first compound is an anti-HIV compound and wherein said second compound is selected from those of formula (I). Also included herein are such methods, wherein said anti-HIV compound is an HIV protease inhibitor. In another embodiment are provided such methods, wherein said HIV protease inhibitor is selected from amprenavir, CGP-73547, CGP-61755, DMP-450, nelfinavir, ritonavir, saquinavir, invirase, lopinavir, TMC-126, atazanavir, palinavir, GS-3333, KN I-413, KNI-272, LG-71350, CGP-61755, PD 173606, PD 177298, PD 178390, PD 178392, U-140690, ABT-378, DMP-450, AG-1776, MK-944, VX-478, indinavir, tipranavir, duranavir, DPC-681, DPC-684, (4R)-N-allyl-3-[(2S,3S)-2-hydroxy-3-[(3-hydroxy-2-methylbenzoyl)amino]-4-phenylbutanoyl]-5,5-dimethyl-1,3-thiazolidine-4-carboxamide, and fosamprenavir calcium. Further included are such methods, wherein said HIV protease inhibitor is selected from amprenavir, nelfinavir, ritonavir, saquinavir, invirase, lopinavir, atazanavir, palinavir, indinavir, tipranavir, duranavir, (4R)-N-allyl-3-[(2S,3S)-2-hydroxy-3-[(3-hydroxy-2-methylbenzoyl)amino]-4-phenylbutanoyl]-5,5-dimethyl-1,3-thiazolidine-4-carboxamide, and fosamprenavir calcium. Another embodiment provides such methods, wherein said HIV protease inhibitor is (4R)-N-allyl-3-[(2S,3S)-2-hydroxy-3-[(3-hydroxy-2-methylbenzoyl)amino]-4-phenylbutanoyl]-5,5-dimethyl-1,3-thiazolidine-4-carboxamide. A further embodiment provides any of the above methods, wherein the administration of said first and second compounds occurs sequentially, or wherein the administration of said first and second compounds occurs at the same time.

Another embodiment provides methods of treating HIV in an HIV-infected mammal, comprising administering to said mammal an effective amount of a first compound and an effective amount of a second compound, wherein said first compound is an anti-HIV compound and said second compound is selected from those of formula (I). Another embodiment provides such methods, wherein said first compound is (N-[(1S)-3-[3-isopropyl-5-methyl-4H-1,2,4-triazole-4-yl]-exo-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl)-4,4-difluorocyclohexanecarboxamide), ethyl 1-endo-[8-[(3S)-3-(acetylamino)-3-(3-fluorophenyl)propyl]-8-azabicyclo[3.2.1]oct-3-yl]-2-methyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine-5-carboxylate, or N-[(1S)-3-[3-endo-(5-isobutyryl)-2-methyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridin-1-yl]-8-azabicyclo[3.2.1]oct-8-yl]-1-(3-fluorophenyl)propyl}acetamide). In yet another embodiment are provided such methods, wherein said first compound is (N-[(1S)-3-[3-isopropyl-5-methyl-4H-1,2,4-triazole-4-yl]-exo-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl)-4,4-difluorocyclohexanecarboxamide). A further embodiment provides such methods, where said first compound is an HIV protease inhibitor. A further embodiment provides such methods, wherein said first compound is

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selected from amprenavir, CGP-73547, CGP-61755, DMP-450, nelfinavir, ritonavir, saquinavir, invirase, lopinavir, TMC-126, atazanavir, palinavir, GS-3333, KN I-413, KNI-272, LG-71350, CGP-61755, PD 173606, PD 177298, PD 178390, PD 178392, U-140690, ABT-378, DMP-450, AG-1776, MK-944, VX-478, indinavir, tipranavir, duranavir, DPC-681, DPC-684, (4R)-N-allyl-3-[(2S,3S)-2-hydroxy-3-[(3-hydroxy-2-methylbenzoyl)amino]-4-phenylbutanoyl]-5,5-dimethyl-1,3-thiazolidine-4-carboxamide, and fosamprenavir calcium. Yet another embodiment provides such methods, wherein said first compound is selected from amprenavir, nelfinavir, ritonavir, saquinavir, invirase, lopinavir, atazanavir, palinavir, indinavir, tipranavir, duranavir, (4R)-N-allyl-3-[(2S,3S)-2-hydroxy-3-[(3-hydroxy-2-methylbenzoyl)amino]-4-phenylbutanoyl]-5,5-dimethyl-1,3-thiazolidine-4-carboxamide, and fosamprenavir calcium. Additionally provided herein are such methods, wherein said first compound is (4R)-N-allyl-3-[(2S,3S)-2-hydroxy-3-[(3-hydroxy-2-methylbenzoyl)amino]-4-phenylbutanoyl]-5,5-dimethyl-1,3-thiazolidine-4-carboxamide. A further embodiment provides any of the above methods, wherein the administration of said first and second compounds occurs sequentially, or wherein the administration of said first and second compounds occurs at the same time.

Also provided herein are methods of inhibiting HIV replication in an HIV-infected mammal, comprising administering to said mammal an effective amount of a first compound and an effective amount of a second compound, wherein said first compound is an HIV replication-inhibiting compound and said second compound is selected from those of formula (I). Also provided are such methods, wherein said first compound is (N-[(1S)-3-[3-isopropyl-5-methyl-4H-1,2,4-triazole-4-yl]-exo-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl)-4,4-difluorocyclohexanecarboxamide), ethyl 1-endo-[8-[(3S)-3-(acetylamino)-3-(3-fluorophenyl)propyl]-8-azabicyclo[3.2.1]oct-3-yl]-2-methyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine-5-carboxylate, or N-[(1S)-3-[3-endo-(5-isobutyryl)-2-methyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridin-1-yl]-8-azabicyclo[3.2.1]oct-8-yl]-1-(3-fluorophenyl)propyl)acetamide). Further included are such methods wherein said first compound is (N-[(1S)-3-[3-isopropyl-5-methyl-4H-1,2,4-triazole-4-yl]-exo-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl)-4,4-difluorocyclohexanecarboxamide). In still another embodiment are afforded such methods, where said first compound is an HIV protease inhibitor. Another embodiment affords such methods, wherein said first compound is selected from amprenavir, CGP-73547, CGP-61755, DMP-450, nelfinavir, ritonavir, saquinavir, invirase, lopinavir, TMC-126, atazanavir, palinavir, GS-3333, KN I-413, KNI-272, LG-71350, CGP-61755, PD 173606, PD 177298, PD 178390, PD 178392, U-140690, ABT-378, DMP-450, AG-1776, MK-944, VX-478, indinavir, tipranavir, duranavir, DPC-681, DPC-684, (4R)-N-allyl-3-[(2S,3S)-2-hydroxy-3-[(3-hydroxy-2-methylbenzoyl)amino]-4-phenylbutanoyl]-5,5-dimethyl-1,3-thiazolidine-4-carboxamide, and

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fosamprenavir calcium. Further included are such methods, wherein said first compound is selected from amprenavir, nelfinavir, ritonavir, saquinavir, invirase, lopinavir, atazanavir, palinavir, indinavir, tipranavir, duranavir, (4R)-N-allyl-3-[(2S,3S)-2-hydroxy-3-[(3-hydroxy-2-methylbenzoyl)amino]-4-phenylbutanoyl]-5,5-dimethyl-1,3-thiazolidine-4-carboxamide, and fosamprenavir calcium. Still another embodiment provides such methods, wherein said first compound is (4R)-N-allyl-3-[(2S,3S)-2-hydroxy-3-[(3-hydroxy-2-methylbenzoyl)amino]-4-phenylbutanoyl]-5,5-dimethyl-1,3-thiazolidine-4-carboxamide. Further included are any such methods, wherein the administration of said first and second compounds occurs sequentially, or wherein the administration of said first and second compounds occurs at the same time.

A further embodiment affords the use of a first compound and a second compound in the preparation of a medicament for the treatment of HIV infection in an HIV-infected mammal, wherein said first compound is selected from those of formula (I), and said second compound is an anti-HIV compound. Another embodiment includes such uses, wherein said second compound is (N-[(1S)-3-[3-isopropyl-5-methyl-4H-1,2,4-triazole-4-yl]-exo-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl)-4,4-difluorocyclohexanecarboxamide, ethyl 1-endo-[8-[(3S)-3-(acetlamino)-3-(3-fluorophenyl)propyl]-8-azabicyclo[3.2.1]oct-3-yl]-2-methyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine-5-carboxylate, or N-[(1S)-3-[3-endo-(5-isobutyryl-2-methyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridin-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-(3-fluorophenyl)propyl]acetamide). Further included herein are such uses, wherein said second compound is (N-[(1S)-3-[3-isopropyl-5-methyl-4H-1,2,4-triazole-4-yl]-exo-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl)-4,4-difluorocyclohexanecarboxamide). Additionally included are such uses, wherein said second compound is an HIV protease inhibitor. Also included are such uses, wherein said second compound is selected from amprenavir, CGP-73547, CGP-61755, DMP-450, nelfinavir, ritonavir, saquinavir, invirase, lopinavir, TMC-126, atazanavir, palinavir, GS-3333, KN I-413, KNI-272, LG-71350, CGP-61755, PD 173606, PD 177298, PD 178390, PD 178392, U-140690, ABT-378, DMP-450, AG-1776, MK-944, VX-478, indinavir, tipranavir, duranavir, DPC-681, DPC-684, (4R)-N-allyl-3-[(2S,3S)-2-hydroxy-3-[(3-hydroxy-2-methylbenzoyl)amino]-4-phenylbutanoyl]-5,5-dimethyl-1,3-thiazolidine-4-carboxamide, and fosamprenavir calcium. Further provided herein are such uses, wherein said second compound is selected from amprenavir, nelfinavir, ritonavir, saquinavir, invirase, lopinavir, atazanavir, palinavir, indinavir, tipranavir, duranavir, (4R)-N-allyl-3-[(2S,3S)-2-hydroxy-3-[(3-hydroxy-2-methylbenzoyl)amino]-4-phenylbutanoyl]-5,5-dimethyl-1,3-thiazolidine-4-carboxamide, and fosamprenavir calcium. In yet another embodiment are provided such uses, wherein said

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second compound is (4R)-N-allyl-3-[(2S,3S)-2-hydroxy-3-[(3-hydroxy-2-methylbenzoyl)amino]-4-phenylbutanoyl]-5,5-dimethyl-1,3-thiazolidine-4-carboxamide.

Another embodiment included herein provides the use of a first compound and a second compound in the preparation of a medicament for improving the pharmacokinetics of said second compound in a mammal, wherein said first compound is selected from those of formula (I), and said second compound is metabolized by cytochrome P450. Further provided herein are such uses, wherein said second compound is (N-[(1S)-3-[3-isopropyl-5-methyl-4H-1,2,4-triazole-4-yl]-exo-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl)-4,4-difluorocyclohexanecarboxamide), ethyl 1-endo-[8-[(3S)-3-(acetylamino)-3-(3-fluorophenyl)propyl]-8-azabicyclo[3.2.1]oct-3-yl]-2-methyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine-5-carboxylate, or N-[(1S)-3-[3-endo-(5-isobutyryl-2-methyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridin-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-(3-fluorophenyl)propyl]acetamide). A further embodiment provides such uses, wherein said second compound is (N-[(1S)-3-[3-isopropyl-5-methyl-4H-1,2,4-triazole-4-yl]-exo-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl)-4,4-difluorocyclohexanecarboxamide). Another embodiment affords such uses, wherein said second compound is an anti-HIV compound. Still further are included such uses wherein the second compound is an HIV protease inhibitor. Further provided are such uses, wherein said second compound is selected from amprenavir, CGP-73547, CGP-61755, DMP-450, nelfinavir, ritonavir, saquinavir, invirase, lopinavir, TMC-126, atazanavir, palinavir, GS-3333, KN I-413, KNI-272, LG-71350, CGP-61755, PD 173606, PD 177298, PD 178390, PD 178392, U-140690, ABT-378, DMP-450, AG-1776, MK-944, VX-478, indinavir, tipranavir, duranavir, DPC-681, DPC-684, (4R)-N-allyl-3-[(2S,3S)-2-hydroxy-3-[(3-hydroxy-2-methylbenzoyl)amino]-4-phenylbutanoyl]-5,5-dimethyl-1,3-thiazolidine-4-carboxamide, and fosamprenavir calcium. Still further are provided such uses, wherein said second compound is selected from amprenavir, nelfinavir, ritonavir, saquinavir, invirase, lopinavir, atazanavir, palinavir, indinavir, tipranavir, duranavir, (4R)-N-allyl-3-[(2S,3S)-2-hydroxy-3-[(3-hydroxy-2-methylbenzoyl)amino]-4-phenylbutanoyl]-5,5-dimethyl-1,3-thiazolidine-4-carboxamide, and fosamprenavir calcium. A further embodiment provides such uses, wherein said second compound is (4R)-N-allyl-3-[(2S,3S)-2-hydroxy-3-[(3-hydroxy-2-methylbenzoyl)amino]-4-phenylbutanoyl]-5,5-dimethyl-1,3-thiazolidine-4-carboxamide.

Further provided are any of the medicaments described herein, wherein said medicament is for simultaneous, separate, or sequential administration to an HIV-infected mammal for the treatment of HIV.

In another embodiment are provided any of the above-described methods or uses wherein the cytochrome P450 enzyme is the 3A4 isoform.

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As used herein, the terms "comprising" and "including" are used in their open, non-limiting sense.

As used herein, the term "HIV" means Human Immunodeficiency Virus. The term "HIV integrase," as used herein, means the Human Immunodeficiency Virus integrase enzyme.

The term "C₁-C₈ alkyl," as used herein, means saturated monovalent hydrocarbon radicals having straight or branched moieties and containing from 1 to 8 carbon atoms. Examples of such groups include, but are not limited to, methyl, ethyl, propyl, iso-propyl, n-butyl, iso-butyl, and tert-butyl.

The term "C₂-C₈ alkenyl", as used herein, unless otherwise indicated, includes alkyl moieties having at least one carbon-carbon double bond wherein alkyl is as defined above and including E and Z isomers of said alkenyl moiety, and having from 2 to 8 carbon atoms.

The term "C₂-C₈ alkynyl", as used herein, unless otherwise indicated, includes alkyl moieties having at least one carbon-carbon triple bond wherein alkyl is as defined above, and containing from 2-8 carbon atoms.

The term "C₃-C₈ cycloalkyl" means a saturated, monocyclic, fused, or spiro, polycyclic ring structure having a total of from 3 to 8 carbon ring atoms. Examples of such groups include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cycloheptyl, and adamantyl.

The term "C₆-C₁₀ aryl", as used herein, means a group derived from an aromatic hydrocarbon containing from 6 to 10 carbon atoms. Examples of such groups include, but are not limited to, phenyl or naphthyl. The terms "Ph" and "phenyl," as used herein, mean a -C₆H₅ group. The term "benzyl," as used herein, means a -CH₂C₆H₅ group.

The term "3 to 10 membered heterocyclyl" as used herein, means a non-aromatic, monocyclic, bicyclic, tricyclic, or tetracyclic group having a total of from 3 to 10 atoms in its ring system, and containing from 1 to 9 carbon atoms and from one to four heteroatoms each independently selected from O, S and N, and with the proviso that the ring of said group does not contain two adjacent O atoms or two adjacent S atoms. Furthermore, such 3 to 10 membered heterocyclyl groups may comprise polycyclic, spiro ring systems. Also, such groups may be optionally benzofused. Additionally, such 3 to 10 membered heterocyclyl groups may contain an oxo substituent at any available atom that will result in a stable compound. For example, such a group may contain an oxo atom at an available carbon or nitrogen atom. Such a group may contain more than one oxo substituent if chemically feasible. In addition, it is to be understood that when such a 3 to 10 membered heterocyclyl group contains a sulfur atom, said sulfur atom may be oxidized with one or two oxygen atoms to afford either a sulfoxide or sulfone. An example of a 4-membered heterocyclic group is azetidyl (derived from azetidine). An example of a 5-membered

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heterocyclic group is thiazolyl and an example of a 10 membered heterocyclic group is quinolinyl. Further examples of such 3 to 10 membered heterocyclyl groups include, but are not limited to, pyrrolidinyl, tetrahydrofuranyl, dihydrofuranyl, tetrahydrothienyl, tetrahydropyranyl, dihydropyranyl, tetrahydrothiopyranyl, piperidino, morpholino, thiomorpholino, thioxanyl, piperazinyl, azetidiny, oxetanyl, thietanyl, homopiperidinyl, oxepanyl, thiepanyl, oxazepinyl, diazepinyl, thiazepinyl, 1,2,3,6-tetrahydropyridinyl, 2-pyrrolinyl, 3-pyrrolinyl, indolinyl, 2H-pyranyl, 4H-pyranyl, dioxanyl, 1,3-dioxolanyl, pyrazolinyl, dithianyl, dithiolanyl, dihydropyranyl, dihydrothienyl, dihydrofuranyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, 3-azabicyclo[3.1.0]hexanyl, 3-azabicyclo[4.1.0]heptanyl, 3H-indolyl and quinoliziny.

The term "5 to 6 membered heteroaryl," as used herein means an aromatic heterocyclic group having a total of from 5 to 6 atoms in its ring, and containing from 1 to 5 carbon atoms and from one to four heteroatoms each independently selected from O, S and N, and with the proviso that the ring of said group does not contain two adjacent O atoms or two adjacent S atoms. Examples of 5 to 6 membered heteroaryl groups include, but are not limited to, pyridinyl, imidazolyl, 1,2,4-oxadiazolyl, pyrimidinyl, pyrazolyl, triazolyl, pyrazinyl, tetrazolyl, furyl, thienyl, isoxazolyl, thiazolyl, oxazolyl, isothiazolyl, pyrrolyl, pyridazinyl, triazinyl, oxadiazolyl, thiadiazolyl, and furazanyl. The 5 to 6 membered heteroaryl groups may be C-attached or N-attached where such is possible. For instance, a group derived from pyrrole may be pyrrol-1-yl (N-attached) or pyrrol-3-yl (C-attached). Further, a group derived from imidazole may be imidazol-1-yl (N-attached) or imidazol-3-yl (C-attached).

The term "5 to 10 membered heteroaryl," as used herein means an aromatic heterocyclic group having a total of from 5 to 10 atoms in its ring, and containing from 1 to 8 carbon atoms and from one to four heteroatoms each independently selected from O, S and N, and with the proviso that the ring of said group does not contain two adjacent O atoms or two adjacent S atoms. The 5 to 10 membered heteroaryl groups include benzo-fused ring systems. Examples of aromatic heterocyclic groups are pyridinyl, imidazolyl, 1,2,4-oxadiazolyl, pyrimidinyl, pyrazolyl, triazolyl, pyrazinyl, tetrazolyl, furyl, thienyl, isoxazolyl, thiazolyl, oxazolyl, isothiazolyl, pyrrolyl, quinolinyl, isoquinolinyl, indolyl, benzimidazolyl, benzofuranyl, cinnolinyl, indazolyl, indoliziny, phthalazinyl, pyridazinyl, triazinyl, isoindolyl, pteridinyl, purinyl, oxadiazolyl, thiadiazolyl, furazanyl, benzofurazanyl, benzothiophenyl, benzothiazolyl, benzoxazolyl, quinazolinyl, quinoxaliny, naphthyridinyl, and furopyridinyl. The 5 to 10 membered heteroaryl groups may be C-attached or N-attached where such is possible. For instance, a group derived from pyrrole may be pyrrol-1-yl (N-attached) or pyrrol-3-yl (C-attached). Further, a group derived from imidazole may be imidazol-1-yl (N-attached) or imidazol-3-yl (C-attached).

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The terms "halogen" and "halo," as used herein, mean fluorine, chlorine, bromine or iodine.

The term "substituted," means that the specified group or moiety bears one or more substituents. The term "unsubstituted," means that the specified group bears no substituents. The term "optionally substituted" means that the specified group is unsubstituted or substituted by one or more substituents. It is to be understood that in the compounds of the present invention when a group is said to be "unsubstituted," or is "substituted" with fewer groups than would fill the valencies of all the atoms in the compound, the remaining valencies on such a group are filled by hydrogen. For example, if a C₆ aryl group, also called "phenyl" herein, is substituted with one additional substituent, one of ordinary skill in the art would understand that such a group has 4 open positions left on carbon atoms of the C₆ aryl ring (6 initial positions, minus one to which the remainder of the compound of the present invention is bonded, minus an additional substituent, to leave 4). In such cases, the remaining 4 carbon atoms are each bound to one hydrogen atom to fill their valencies. Similarly, if a C₆ aryl group in the present compounds is said to be "disubstituted," one of ordinary skill in the art would understand it to mean that the C₆ aryl has 3 carbon atoms remaining that are unsubstituted. Those three unsubstituted carbon atoms are each bound to one hydrogen atom to fill their valencies.

The term "solvate," as used herein, means a pharmaceutically acceptable solvate form of a compound of the present invention that retains the biological effectiveness of such compound. Examples of solvates include, but are not limited to, compounds of the invention in combination with water, isopropanol, ethanol, methanol, dimethylsulfoxide (DMSO), ethyl acetate, acetic acid, ethanolamine, or mixtures thereof. It is specifically contemplated that in the present invention one solvent molecule can be associated with one molecule of the compounds of the present invention, such as a hydrate. Furthermore, it is specifically contemplated that in the present invention, more than one solvent molecule may be associated with one molecule of the compounds of the present invention, such as a dihydrate. Additionally, it is specifically contemplated that in the present invention less than one solvent molecule may be associated with one molecule of the compounds of the present invention, such as a hemihydrate. Furthermore, solvates of the present invention are contemplated as solvates of compounds of the present invention that retain the biological effectiveness of the non-hydrate form of the compounds.

The term "pharmaceutically acceptable salt," as used herein, means a salt of a compound of the present invention that retains the biological effectiveness of the free acids and bases of the specified derivative and that is not biologically or otherwise undesirable.

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The terms "cytochrome P450-inhibiting amount" and "cytochrome P450 enzyme activity-inhibiting amount," as used herein, refer to an amount of a compound required to decrease the activity of cytochrome P450 enzymes or a particular cytochrome P450 enzyme isoform in the presence of such compound. Whether a particular compound of
5 decreases cytochrome P450 enzyme activity, and the amount of such a compound required to do so, can be determined by methods known to those of ordinary skill in the art and the methods described herein.

The terms "inhibiting" or "inhibition," as used herein, refer to decreasing the activity of a cytochrome P450 enzyme or enzymes using an agent that is capable of decreasing
10 such activity either *in vitro* or *in vivo* after administration to a mammal, such as a human. Such inhibition may take place by the compound binding directly to the cytochrome P450 enzyme or enzymes. In addition, the activity of such cytochrome P450 enzymes may be decreased in the presence of such a compound when such direct binding between the enzyme and the compound does not take place. Furthermore, such inhibition may be
15 competitive, non-competitive, or uncompetitive, as described in T.F. Woolf, Handbook of Drug Metabolism, Marcel Dekker, Inc., New York, 1999. Such inhibition may be determined using *in vitro* or *in vivo* systems, or a combination of both, using methods known to those of ordinary skill in the art.

As used herein, the term "bioavailability" refers to the systemic availability of a
20 given amount of a chemical compound administered to a mammal. Bioavailability can be assessed by measuring the area under the curve (AUC) or the maximum serum or plasma concentration (C_{max}) of the unchanged form of a compound following administration of the compound to a mammal. AUC is a determination of the Area Under the Curve plotting the serum or plasma concentration of a compound along the ordinate (Y-axis) against time
25 along the abscissa (X-axis). Generally, the AUC for a particular compound can be calculated using methods known to those of ordinary skill in the art and as described in G.S. Banker, Modern Pharmaceutics, Drugs and the Pharmaceutical Sciences, v. 72, Marcel Dekker, New York, Inc., 1996. The C_{max} value is defined as the maximum concentration of the compound achieved in the serum or plasma of a mammal following
30 administration of the compound to the mammal. The C_{max} value of a particular compound can be measured using methods known to those of ordinary skill in the art. The phrase "increasing bioavailability," as used herein means that the systemic availability of a first compound, measured as AUC or C_{max} , in a mammal is greater when co-administered with a compound of the present invention than when such co-administration does not take
35 place.

The term "improving the pharmacokinetics in a mammal" of a compound, as used herein, means increasing the overall exposure of a mammal to a particular compound.

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The term "exposure," as used herein, refers to the concentration of a particular compound in the plasma of a mammal as measured over a period of time. An increase of the exposure of a mammal to a particular compound can be measured by first administering the compound to a mammal in an appropriate form and in the absence of the administration of a compound of the invention, including those of formula (I), withdrawing plasma samples at predetermined times, and measuring the amount of the compound in the plasma using an appropriate analytical technique, such as liquid chromatography or liquid chromatography/mass spectroscopy. The same study is then repeated, except that a compound of the present invention, including those of formula (I), is co-administered with the particular compound. The amount of the particular compound present in the plasma at a certain time is determined and the concentration and time data from all the samples are plotted to afford a curve. The area under this curve is calculated and affords the exposure of the mammal to the particular compound. The difference in the areas under the curve in the presence and absence of a compound of the present invention, including those of formula (I), affords a measure of the increase of the exposure to the particular compound in the plasma of the mammal. The terms "exposure," "area under the curve," and "area under the concentration/time curve" are intended to have the same meaning and may be used interchangeably throughout.

The terms "administration", "administering", "dosage," and "dosing," as used herein refer to the delivery of a compound, or a pharmaceutically acceptable salt or solvate thereof, or of a pharmaceutical composition containing the compound, or a pharmaceutically acceptable salt or solvate thereof, to a mammal such that the compound is absorbed into the serum or plasma of the mammal.

The terms "co-administration" or "co-administering," as used herein, refer to the administration of a combination of a first compound and a compound of the present invention, or a pharmaceutically acceptable salt or solvate thereof. Such co-administration can be performed such that the first compound and the compound of the present invention are part of the same composition or part of the same unitary dosage form. Co-administration also includes administering a first compound and a compound of the present invention separately, but as part of the same therapeutic regimen. The two components, if administered separately, need not necessarily be administered at essentially the same time, although they can be if so desired. Thus co-administration includes, for example, administering a first compound and a compound of the present invention as separate dosages or dosage forms, but at the same time. Co-administration also includes separate administration at different times and in any order.

The term "pharmaceutically acceptable formulation," as used herein, means a combination of a compound of the invention, or a pharmaceutically acceptable salt or

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solvate thereof, and a carrier, diluent, and/or excipients that are compatible with a compound of the present invention, and is not deleterious to the recipient thereof. Pharmaceutical formulations can be prepared by procedures known to those of ordinary skill in the art. For example, the compounds of the present invention can be formulated with common excipients, diluents, or carriers, and formed into tablets, capsules, and the like. Examples of excipients, diluents, and carriers that are suitable for such formulations include the following: fillers and extenders such as starch, sugars, mannitol, and silicic derivatives; binding agents such as carboxymethyl cellulose and other cellulose derivatives, alginates, gelatin, and polyvinyl pyrrolidone; moisturizing agents such as glycerol; disintegrating agents such as povidone, sodium starch glycolate, sodium carboxymethylcellulose, agar agar, calcium carbonate, and sodium bicarbonate; agents for retarding dissolution such as paraffin; resorption accelerators such as quaternary ammonium compounds; surfactive agents such as cetyl alcohol, glycerol monostearate; adsorptive carriers such as kaolin and bentonite; and lubricants such as talc, calcium and magnesium stearate and solid polyethylene glycols. Final pharmaceutical forms may be pills, tablets, powders, lozenges, sachets, cachets, or sterile packaged powders, and the like, depending on the type of excipient used. Additionally, it is specifically contemplated that pharmaceutically acceptable formulations of the present invention can contain more than one active ingredient. For example, such formulations may contain more than one compound according to the present invention. Alternatively, such formulations may contain one or more compounds of the present invention and one or more additional anti-HIV agents.

The term "inhibiting HIV replication" means inhibiting human immunodeficiency virus (HIV) replication in a cell. Such a cell may be present *in vitro*, or it may be present *in vivo*, such as in a mammal, such as a human. Such inhibition may be accomplished by administering a compound of the present invention, or a pharmaceutically acceptable salt or solvate thereof, to the cell, such as in a mammal, in an HIV-inhibiting amount. The quantification of inhibition of HIV replication in a cell, such as in a mammal, can be measured using methods known to those of ordinary skill in the art. For example, an amount of a compound of the invention may be administered to a mammal, either alone or as part of a pharmaceutically acceptable formulation. Blood samples may then be withdrawn from the mammal and the amount of HIV virus in the sample may be quantified using methods known to those of ordinary skill in the art. A reduction in the amount of HIV virus in the sample compared to the amount found in the blood before administration of a compound of the invention would represent inhibition of the replication of HIV virus in the mammal. The administration of a compound of the invention to the cell, such as in a mammal, may be in the form of single dose or a series of doses. In the case of more than

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one dose, the doses may be administered in one day or they may be administered over more than one day.

The terms "anti-HIV compound" and "HIV-inhibiting agent," as used herein, mean a compound or combination of compounds capable of inhibiting the replication of HIV in a cell, such as a cell in a mammal. Such compounds may inhibit the replication of HIV through any mechanism known to those of ordinary skill in the art.

The terms "human immunodeficiency virus-inhibiting amount," "HIV-inhibiting amount," and "HIV replication-inhibiting amount" as used herein, refer to the amount of an anti-HIV compound, or a pharmaceutically acceptable salt or solvate thereof, required to inhibit replication of the human immunodeficiency virus (HIV) *in vivo*, such as in a mammal, or *in vitro*. The amount of such compounds required to cause such inhibition can be determined without undue experimentation using methods described herein and those known to those of ordinary skill in the art.

The terms "therapeutically effective amount" or "effective amount," as used herein, means an amount of a compound of the present invention, or a pharmaceutically acceptable salt or solvate thereof, that, when administered to a mammal in need of such treatment, is sufficient to effect treatment, as defined herein. Thus, a therapeutically effective amount or effective amount of a compound of the present invention, or a pharmaceutically acceptable salt or solvate thereof, is a quantity sufficient to modulate or inhibit the activity of a particular enzyme target or biological process. In particular, the compounds of the present invention, including those of formula (I), are intended to modulate or inhibit the activity of a cytochrome P450 enzyme or enzyme, or a particular P450 enzyme isoform, such as the 3A4 isoform, such that the metabolism of an additional compound by such cytochrome P450 enzyme or enzymes is reduced. When the compounds of the present invention, including those of formula (I), are administered to a mammal in addition to a second compound that is useful for the treatment of a particular disease, it is contemplated that the compounds of the present invention will reduce the metabolism of the second compound such that the exposure of the mammal to the second compound is increased. Increasing the exposure of the mammal to such second compound results in improved treatment of a particular disease or condition that the second compound is intended to treat.

The terms "treat", "treating", and "treatment" refer to any treatment of any disease or condition in a mammal, particularly a human, and include: (i) preventing the disease or condition from occurring in a subject which may be predisposed to the condition, such that the treatment constitutes prophylactic treatment for the pathologic condition; (ii) modulating or inhibiting the disease or condition, i.e., arresting its development; (iii) relieving the disease or condition, i.e., causing regression of the disease or condition; or

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(iv) relieving and/or alleviating the disease or condition or the symptoms resulting from the disease or condition, e.g., relieving an inflammatory response without addressing the underlying disease or condition.

The terms "resistant," "resistance," and "resistant HIV," as used herein, refer to HIV virus demonstrating a reduction in sensitivity to a particular drug. A mammal infected with HIV that is resistant to a particular anti-HIV agent or combination of agents usually manifests an increase in HIV viral load despite continued administration of the agent or agents. Resistance may be either genotypic, meaning that a mutation in the HIV genetic make-up has occurred, or phenotypic, meaning that resistance is discovered by successfully growing laboratory cultures of HIV virus in the presence of an anti-HIV agent or a combination of such agents.

The terms "protease inhibitor" and "HIV protease inhibitor," as used herein, refer to compounds or combinations of compounds that interfere with the proper functioning of the HIV protease enzyme that is responsible for cleaving long strands of viral protein into the separate proteins making up the viral core.

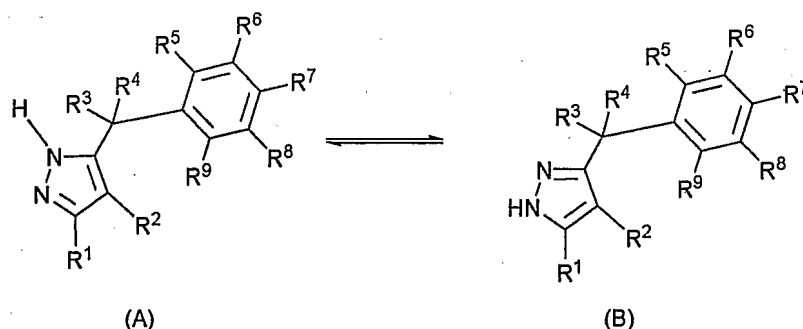
The terms "viral load" and "HIV viral load," as used herein, mean the amount of HIV in the circulating blood of a mammal, such as a human. The amount of HIV virus in the blood of mammal can be determined by measuring the quantity of HIV RNA in the blood using methods known to those of ordinary skill in the art.

The term, "compound of the present invention" refers to any of the above-mentioned compounds, as well as those in the Examples that follow, and include those generically described or those described as species. The term also refers to pharmaceutically acceptable salts or solvates of these compounds.

DETAILED DESCRIPTION

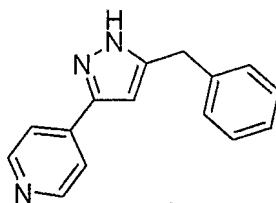
The compounds of the present invention may exist in several tautomeric forms. For example, a compound of the invention may exist in either form (A) or (B), as shown below. These forms may be in equilibrium and the compounds of the invention, including those of formula (I), may exist in more than one of these forms at the same time. For example, in a particular compound of the invention, a certain percentage of the molecules may be present in form (A) while the remainder is present in form (B). Which form predominates in a particular compound of the invention depends on several factors that include, but are not limited to, whether the compound is in solid, liquid, or crystalline form, whether the compound is dissolved in a solvent and the identity of the solvent, the environmental temperature, and the relative humidity. It is specifically contemplated that when the compounds of the present invention are drawn in a particular form, form (A) for example, all the tautomeric forms, form (B) for example, are meant to be included as well.

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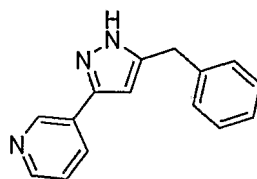
It is to be understood that the compounds of the present invention, including those of formula (I), do not include 4-(5-benzyl-1H-pyrazol-3-yl)pyridine, 3-(5-benzyl-1H-pyrazol-3-yl)pyridine, or 2-(5-(1-(4-fluorophenyl)cyclopropyl)-1H-pyrazol-3-yl)pyridine, or any salts thereof.

As used herein, the term "4-(5-benzyl-1H-pyrazol-3-yl)pyridine or any salts thereof" is meant to describe a chemical compound with the following structure:



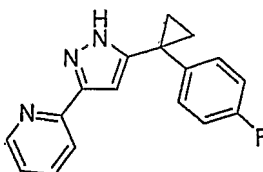
or any salts thereof.

As used herein, the term "3-(5-benzyl-1H-pyrazol-3-yl)pyridine or any salts thereof" is meant to describe a chemical compound with the following structure:



or any salts thereof.

As used herein, the term "2-(5-(1-(4-fluorophenyl)cyclopropyl)-1H-pyrazol-3-yl)pyridine or any salts thereof" is meant to describe a chemical compound with the following structure:

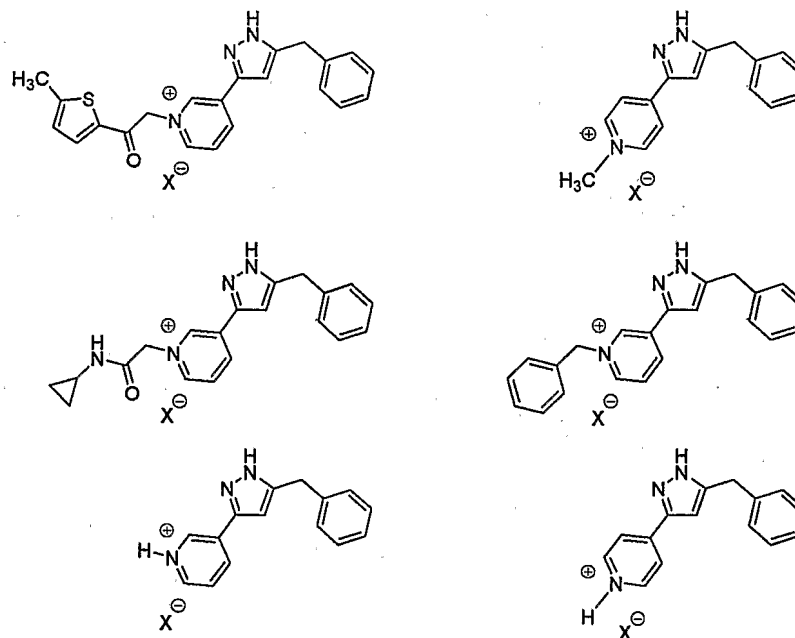


or any salts thereof.

The term "salts," as used herein, means any salt of a compound, including salts formed by reaction of a compound with a Bronstead acid or base, such as hydrochloric acid, or a salt formed by reaction of a compound with an alkylating agent, such as an alkyl

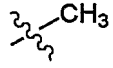
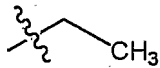
- 25 -

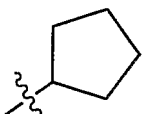
halide. Examples of such salts include, but are not limited to, those of the following structure:



In accordance with a convention used in the art, the symbol  is use

5 The term "stereoisomers" refers to compounds that have identical chemical d in structural formulas herein to depict the bond that is the point of attachment of the moiety or substituent to the core or backbone structure. In accordance with another convention, in some structural formulae herein the carbon atoms and their bound hydrogen atoms are

not explicitly depicted, e.g.,  represents a methyl group,  represents

10 an ethyl group,  represents a cyclopentyl group, etc. constitution, but differ with regard to the arrangement of their atoms or groups in space. In particular, the term "enantiomers" refers to two stereoisomers of a compound that are non-superimposable mirror images of one another. The terms "racemic" or "racemic mixture," as used herein, refer to a 1:1 mixture of enantiomers of a particular compound. The term "diastereomers",
15 on the other hand, refers to the relationship between a pair of stereoisomers that comprise two or more asymmetric centers and are not mirror images of one another.

The compounds of the present invention may have asymmetric carbon atoms. The bonds between atoms in the compounds of the present invention may be depicted herein using a solid line (—), a solid wedge (), or a dotted wedge ().

20 The use of a solid line to depict bonds from asymmetric carbon atoms is meant to indicate

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that all possible stereoisomers at that carbon atom are included. The use of either a solid or dotted wedge to depict bonds from asymmetric carbon atoms is meant to indicate that only the stereoisomer shown is meant to be included. It is possible that compounds of the invention may contain more than one asymmetric carbon atom. In those compounds, the use of a solid line to depict bonds from asymmetric carbon atoms is meant to indicate that all possible stereoisomers are meant to be included. The use of a solid line to depict bonds from one or more asymmetric carbon atoms in a compound of the invention and the use of a solid or dotted wedge to depict bonds from other asymmetric carbon atoms in the same compound is meant to indicate that a mixture of diastereomers is present.

The compounds of the present invention may be administered to a mammal, such as a human, in combination with an additional compound so that there is an increase of the exposure of the mammal to the additional compound. The term "exposure," as used herein, refers to the concentration of a particular compound in the plasma of a mammal as measured over a period of time. An increase of the exposure of a mammal to a particular compound can be measured by first administering the compound to a mammal in an appropriate form and in the absence of the administration of a compound of the invention, including those of formula (I), withdrawing plasma samples at predetermined times, and measuring the amount of the compound in the plasma using an appropriate analytical technique, such as liquid chromatography or liquid chromatography/mass spectroscopy. The same study is then repeated, except that a compound of the present invention, including those of formula (I), is co-administered with the particular compound. The amount of the particular compound present in the plasma at a certain time is determined and the concentration and time data from all the samples are plotted to afford a curve. The area under this curve is calculated and affords the exposure of the mammal to the particular compound. The difference in the areas under the curve in the presence and absence of a compound of the present invention, including those of formula (I), affords a measure of the increase of the exposure to the particular compound in the plasma of the mammal. The terms "exposure," "area under the curve," and "area under the concentration/time curve" are intended to have the same meaning and may be used interchangeably throughout.

Such co-administration to a mammal of a compound of the present invention and a second or additional compound, as described above, may occur such that a compound or compounds of the present invention are present in the same formulation as the additional agents described above. Alternatively, such a combination may be administered such that the compound or compounds of the present invention are present in a formulation that is separate from the formulation in which the additional agent is found. If the compound or compounds of the present invention are administered separately from

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the additional agent, such administration may take place at the same or sequentially with an appropriate period of time in between. The choice of whether to include the compound or compounds of the present invention in the same formulation as the additional agent or agents is within the knowledge of one of ordinary skill in the art.

5 If a derivative used in the method of the invention is a base, a desired salt may be prepared by any suitable method known to the art, including treatment of the free base with an inorganic acid, such as hydrochloric acid; hydrobromic acid; sulfuric acid; nitric acid; phosphoric acid; and the like, or with an organic acid, such as acetic acid; maleic acid; succinic acid; mandelic acid; fumaric acid; malonic acid; pyruvic acid; oxalic acid; 10 glycolic acid; salicylic acid; pyranosidyl acid, such as glucuronic acid or galacturonic acid; alpha-hydroxy acid, such as citric acid or tartaric acid; amino acid, such as aspartic acid or glutamic acid; aromatic acid, such as benzoic acid or cinnamic acid; sulfonic acid, such as p-toluenesulfonic acid or ethanesulfonic acid; and the like.

15 If a derivative used in the method of the invention is an acid, a desired salt may be prepared by any suitable method known to the art, including treatment of the free acid with an inorganic or organic base, such as an amine (primary, secondary, or tertiary); an alkali metal or alkaline earth metal hydroxide; or the like. Examples of suitable salts include organic salts derived from amino acids such as glycine and arginine; ammonia; primary, secondary, and tertiary amines; and cyclic amines, such as piperidine, morpholine, and 20 piperazine; as well as inorganic salts derived from sodium, calcium, potassium, magnesium, manganese, iron, copper, zinc, aluminum, and lithium.

 A "solvate" is intended to mean a pharmaceutically acceptable solvate form of a specified compound that retains the biological effectiveness of such compound. Examples of solvates include, but are not limited to, compounds of the invention in combination with 25 water, isopropanol, ethanol, methanol, dimethylsulfoxide (DMSO), ethyl acetate, acetic acid, ethanolamine, or mixtures thereof.

 A "pharmaceutically acceptable salt" is intended to mean a salt that retains the biological effectiveness of the free acids and bases of the specified derivative, containing pharmacologically acceptable anions, and is not biologically or otherwise undesirable. 30 Examples of pharmaceutically acceptable salts include, but are not limited to, acetate, acrylate, benzenesulfonate, benzoate (such as chlorobenzoate, methylbenzoate, dinitrobenzoate, hydroxybenzoate, and methoxybenzoate), bicarbonate, bisulfate, bisulfite, bitartrate, borate, bromide, butyne-1,4-dioate, calcium edetate, camsylate, carbonate, chloride, caproate, caprylate, clavulanate, citrate, decanoate, dihydrochloride, 35 dihydrogenphosphate, edetate, edislyate, estolate, esylate, ethylsuccinate, formate, fumarate, gluceptate, gluconate, glutamate, glycollate, glycollylarsanilate, heptanoate, hexyne-1,6-dioate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, γ -

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hydroxybutyrate, iodide, isobutyrate, isothionate, lactate, lactobionate, laurate, malate, maleate, malonate, mandelate, mesylate, metaphosphate, methane-sulfonate, methylsulfate, monohydrogenphosphate, mucate, napsylate, naphthalene-1-sulfonate, naphthalene-2-sulfonate, nitrate, oleate, oxalate, pamoate (embonate), palmitate, 5 pantothenate, phenylacetates, phenylbutyrate, phenylpropionate, phthalate, phosphate/diphosphate, polygalacturonate, propanesulfonate, propionate, propiolate, pyrophosphate, pyrosulfate, salicylate, stearate, subacetate, suberate, succinate, sulfate, sulfonate, sulfite, tannate, tartrate, teoclate, tosylate, triethiodode, and valerate salts.

The compounds of the present invention that are basic in nature are capable of 10 forming a wide variety of different salts with various inorganic and organic acids. Although such salts must be pharmaceutically acceptable for administration to animals, it is often desirable in practice to initially isolate the compound of the present invention from the reaction mixture as a pharmaceutically unacceptable salt and then simply convert the latter back to the free base compound by treatment with an alkaline reagent and subsequently 15 convert the latter free base to a pharmaceutically acceptable acid addition salt. The acid addition salts of the base compounds of this invention can be prepared by treating the base compound with a substantially equivalent amount of the selected mineral or organic acid in an aqueous solvent medium or in a suitable organic solvent, such as methanol or ethanol. Upon evaporation of the solvent, the desired solid salt is obtained. The desired acid salt can 20 also be precipitated from a solution of the free base in an organic solvent by adding an appropriate mineral or organic acid to the solution.

Those compounds of the present invention that are acidic in nature are capable of forming base salts with various pharmacologically acceptable cations. Examples of such salts include the alkali metal or alkaline-earth metal salts and particularly, the sodium and 25 potassium salts. These salts are all prepared by conventional techniques. The chemical bases which are used as reagents to prepare the pharmaceutically acceptable base salts of this invention are those which form non-toxic base salts with the acidic compounds of the present invention. Such non-toxic base salts include those derived from such pharmacologically acceptable cations as sodium, potassium calcium and magnesium, etc. 30 These salts can be prepared by treating the corresponding acidic compounds with an aqueous solution containing the desired pharmacologically acceptable cations, and then evaporating the resulting solution to dryness, preferably under reduced pressure. Alternatively, they may also be prepared by mixing lower alkanolic solutions of the acidic compounds and the desired alkali metal alkoxide together, and then evaporating the 35 resulting solution to dryness in the same manner as before. In either case, stoichiometric quantities of reagents are preferably employed in order to ensure completeness of reaction and maximum yields of the desired final product.

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In the case of agents that are solids, it is understood by those skilled in the art that the inventive compounds, agents and salts may exist in different crystal or polymorphic forms, all of which are intended to be within the scope of the present invention and specified formulas.

5 The compounds of the present invention may be formulated into pharmaceutical compositions as described below in any pharmaceutical form recognizable to the skilled artisan as being suitable. Pharmaceutical compositions of the invention comprise a therapeutically effective amount of at least one compound of the present invention and an inert, pharmaceutically acceptable carrier or diluent.

10 The pharmaceutical carriers employed may be either solid or liquid. Exemplary solid carriers are lactose, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, stearic acid and the like. Exemplary liquid carriers are syrup, peanut oil, olive oil, water and the like. Similarly, the inventive compositions may include time-delay or time-release material known in the art, such as glyceryl monostearate or glyceryl distearate alone or
15 with a wax, ethylcellulose, hydroxypropylmethylcellulose, methylmethacrylate or the like. Further additives or excipients may be added to achieve the desired formulation properties. For example, a bioavailability enhancer, such as Labrasol[®], Gelucire[®] or the like, or formulator, such as CMC (carboxy-methylcellulose), PG (propyleneglycol), or PEG (polyethyleneglycol), may be added. Gelucire[®], a semi-solid vehicle that protects active
20 ingredients from light, moisture and oxidation, may be added, e.g., when preparing a capsule formulation.

If a solid carrier is used, the preparation can be tableted, placed in a hard gelatin capsule in powder or pellet form, or formed into a troche or lozenge. The amount of solid carrier may vary, but generally will be from about 25 mg to about 1 g. If a liquid carrier is
25 used, the preparation may be in the form of syrup, emulsion, soft gelatin capsule, sterile injectable solution or suspension in an ampoule or vial or non-aqueous liquid suspension. If a semi-solid carrier is used, the preparation may be in the form of hard and soft gelatin capsule formulations. The inventive compositions are prepared in unit-dosage form appropriate for the mode of administration, e.g., parenteral or oral administration.

30 To obtain a stable water-soluble dose form, a pharmaceutically acceptable salt of a compound of the present invention may be dissolved in an aqueous solution of an organic or inorganic acid, such as 0.3 M solution of succinic acid or citric acid. If a soluble salt form is not available, the agent may be dissolved in a suitable cosolvent or combinations of cosolvents. Examples of suitable cosolvents include alcohol, propylene
35 glycol, polyethylene glycol 300, polysorbate 80, glycerin and the like in concentrations ranging from 0-60% of the total volume. In an exemplary embodiment, a compound of Formula I is dissolved in DMSO and diluted with water. The composition may also be in

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the form of a solution of a salt form of the active ingredient in an appropriate aqueous vehicle such as water or isotonic saline or dextrose solution.

Proper formulation is dependent upon the route of administration selected. For injection, the agents of the compounds of the present invention may be formulated into aqueous solutions, preferably in physiologically compatible buffers such as Hanks solution, Ringer's solution, or physiological saline buffer. For transmucosal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art.

For oral administration, the compounds can be formulated by combining the active compounds with pharmaceutically acceptable carriers known in the art. Such carriers enable the compounds of the invention to be formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspensions and the like, for oral ingestion by a subject to be treated. Pharmaceutical preparations for oral use can be obtained using a solid excipient in admixture with the active ingredient (agent), optionally grinding the resulting mixture, and processing the mixture of granules after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores. Suitable excipients include: fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol; and cellulose preparations, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum, methyl cellulose, hydroxypropylmethyl-cellulose, sodium carboxymethylcellulose, or polyvinylpyrrolidone (PVP). If desired, disintegrating agents may be added, such as crosslinked polyvinyl pyrrolidone, agar, or alginic acid or a salt thereof such as sodium alginate.

Dragee cores are provided with suitable coatings. For this purpose, concentrated sugar solutions may be used, which may optionally contain gum arabic, polyvinyl pyrrolidone, Carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to the tablets or dragee coatings for identification or to characterize different combinations of active agents.

Pharmaceutical preparations that can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. The push-fit capsules can contain the active ingredients in admixture with fillers such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate, and, optionally, stabilizers. In soft capsules, the active agents may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In addition, stabilizers may be added. All formulations for oral administration should be in dosages suitable for such administration. For buccal

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administration, the compositions may take the form of tablets or lozenges formulated in conventional manner.

For administration intranasally or by inhalation, the compounds for use according to the present invention may be conveniently delivered in the form of an aerosol spray presentation from pressurized packs or a nebuliser, with the use of a suitable propellant, e.g., dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol the dosage unit may be determined by providing a valve to deliver a metered amount. Capsules and cartridges of gelatin for use in an inhaler or insufflator and the like may be formulated containing a powder mix of the compound and a suitable powder base such as lactose or starch.

The compounds may be formulated for parenteral administration by injection, e.g., by bolus injection or continuous infusion. Formulations for injection may be presented in unit-dosage form, e.g., in ampoules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents.

Pharmaceutical formulations for parenteral administration include aqueous solutions of the active compounds in water-soluble form. Additionally, suspensions of the active agents may be prepared as appropriate oily injection suspensions. Suitable lipophilic solvents or vehicles include fatty oils such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate or triglycerides, or liposomes. Aqueous injection suspensions may contain substances that increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Optionally, the suspension may also contain suitable stabilizers or agents that increase the solubility of the compounds to allow for the preparation of highly concentrated solutions.

Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g., sterile pyrogen-free water, before use.

In addition to the formulations described above, the compounds of the present invention may also be formulated as a depot preparation. Such long-acting formulations may be administered by implantation (for example, subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds may be formulated with suitable polymeric or hydrophobic materials (for example, as an emulsion in an acceptable oil) or ion-exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt. A pharmaceutical carrier for hydrophobic compounds is a cosolvent system comprising benzyl alcohol, a nonpolar surfactant, a water-miscible organic polymer, and an aqueous phase. The cosolvent system may be a VPD co-solvent system. VPD is a solution of 3% w/v benzyl alcohol, 8% w/v of the nonpolar surfactant polysorbate

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80, and 65% w/v polyethylene glycol 300, made up to volume in absolute ethanol. The VPD co-solvent system (VPD: 5W) contains VPD diluted 1:1 with a 5% dextrose in water solution. This co-solvent system dissolves hydrophobic compounds well, and itself produces low toxicity upon systemic administration. The proportions of a co-solvent system may be suitably varied without destroying its solubility and toxicity characteristics. Furthermore, the identity of the co-solvent components may be varied: for example, other low-toxicity nonpolar surfactants may be used instead of polysorbate 80; the fraction size of polyethylene glycol may be varied; other biocompatible polymers may replace polyethylene glycol, e.g. polyvinyl pyrrolidone; and other sugars or polysaccharides may be substituted for dextrose.

Alternatively, other delivery systems for hydrophobic pharmaceutical compounds may be employed. Liposomes and emulsions are known examples of delivery vehicles or carriers for hydrophobic drugs. Certain organic solvents such as dimethylsulfoxide also may be employed, although usually at the cost of greater toxicity due to the toxic nature of DMSO. Additionally, the compounds may be delivered using a sustained-release system, such as semipermeable matrices of solid hydrophobic polymers containing the therapeutic agent. Various sustained-release materials have been established and are known by those skilled in the art. Sustained-release capsules may, depending on their chemical nature, release the compounds for a few weeks up to over 100 days. Depending on the chemical nature and the biological stability of the therapeutic reagent, additional strategies for protein stabilization may be employed.

The pharmaceutical compositions also may comprise suitable solid- or gel-phase carriers or excipients. These carriers and excipients may provide marked improvement in the bioavailability of poorly soluble drugs. Examples of such carriers or excipients include calcium carbonate, calcium phosphate, sugars, starches, cellulose derivatives, gelatin, and polymers such as polyethylene glycols. Furthermore, additives or excipients such as Gelucire®, Capryol®, Labrafil®, Labrasol®, Lauroglycol®, Plurol®, Peceol®, Transcutol® and the like may be used. Further, the pharmaceutical composition may be incorporated into a skin patch for delivery of the drug directly onto the skin.

It will be appreciated that the actual dosages of the agents of this invention will vary according to the particular agent being used, the particular composition formulated, the mode of administration, and the particular site, host, and disease being treated. Those skilled in the art using conventional dosage-determination tests in view of the experimental data for a given compound may ascertain optimal dosages for a given set of conditions. For oral administration, an exemplary daily dose generally employed will be from about 0.001 to about 1000 mg/kg of body weight, with courses of treatment repeated at appropriate intervals.

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Furthermore, the pharmaceutically acceptable formulations of the present invention may contain a compound of the present invention, or a pharmaceutically acceptable salt or solvate thereof, in an amount of about 10 mg to about 2000 mg, or from about 10 mg to about 1500 mg, or from about 10 mg to about 1000 mg, or from about 10 mg to about 750 mg, or from about 10 mg to about 500 mg, or from about 25 mg to about 500 mg, or from about 50 to about 500 mg, or from about 100 mg to about 500mg.

Additionally, the pharmaceutically acceptable formulations of the present invention may contain a compound of the present invention, or a pharmaceutically acceptable salt or solvate thereof, in an amount from about 0.5 w/w% to about 95 w/w%, or from about 1 w/w% to about 95 w/w%, or from about 1 w/w% to about 75 w/w%, or from about 5 w/w% to about 75 w/w%, or from about 10 w/w% to about 75 w/w%, or from about 10 w/w% to about 50 w/w%.

To treat or prevent diseases or conditions mediated by HIV, a pharmaceutical composition of the invention in a suitable formulation is administered in combination with at least one anti-HIV agent. A combined formulation of a compound of the present invention and an at least anti-HIV agent may be prepared by combining a therapeutically effective amount (i.e., an HIV replication-inhibiting amount effective to achieve therapeutic efficacy) of at least one compound of the present invention (as an active ingredient) with one or more anti-HIV agents and at least one pharmaceutically suitable carrier, which may be selected, for example, from diluents, excipients and auxiliaries that facilitate processing of the active compounds into the final pharmaceutical preparations.

Alternatively, to treat or prevent diseases or conditions mediated by HIV, a pharmaceutical composition of the invention in a suitable formulation is administered at the same time as at least one anti-HIV agent that is in a separate, pharmaceutically acceptable formulation. Such a dosing regimen may be designed such that a compound of the present invention is administered to an HIV-infected mammal prior to, at the same time as, or after the administration of the pharmaceutical formulation containing at least one anti-HIV agent. The pharmaceutically acceptable formulation of the compound of the present invention may be prepared by combining the compound and at least one pharmaceutically suitable carrier, which may be selected, for example, from diluents, excipients and auxiliaries that facilitate processing of the active compounds into the final pharmaceutical preparations.

The compounds of the present invention, or a pharmaceutically acceptable salt or solvate thereof, may be administered to a mammal suffering from infection with HIV, such as a human, either alone or as part of a pharmaceutically acceptable formulation, once a day, twice a day, or three times a day in combination with an anti-HIV agent.

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Those of ordinary skill in the art will understand that with respect to the compounds of the present invention, the particular pharmaceutical formulation, the dosage, and the number of doses given per day to a mammal requiring such treatment, and the choice of a particular anti-HIV agent or agents are all choices within the knowledge of one of ordinary skill in the art and can be determined without undue experimentation. For example, see "Guidelines for the Use of Antiretroviral Agents in HIV-1 Infected Adults and Adolescents," United States Department of Health and Human Services, available at <http://www.aidsinfo.nih.gov/guidelines/> as of May 31, 2006.

The compounds of the present invention may be administered in combination with an additional agent or agents for the treatment of a mammal, such as a human, that is suffering from an infection with the HIV virus; AIDS, AIDS-related complex (ARC), or any other disease or condition which is related to infection with the HIV virus. The agents that may be used in combination with the compounds of the present invention include, but are not limited to, those useful as HIV protease inhibitors, HIV reverse transcriptase inhibitors, non-nucleoside HIV reverse transcriptase inhibitors, inhibitors of HIV integrase, CCR5 inhibitors, HIV fusion inhibitors, compounds useful as immunomodulators, compounds that inhibit the HIV virus by an unknown mechanism, compounds useful for the treatment of herpes viruses, compounds useful as anti-infectives, and others as described below.

Compounds useful as HIV protease inhibitors that may be used in combination with the compounds of the present invention include, but are not limited to, 141 W94 (amprenavir), CGP-73547, CGP-61755, DMP-450, nelfinavir, ritonavir, saquinavir (invirase), lopinavir, TMC-126, atazanavir, palinavir, GS-3333, KN I-413, KNI-272, LG-71350, CGP-61755, PD 173606, PD 177298, PD 178390, PD 178392, U-140690, ABT-378, DMP-450, AG-1776, MK-944, VX-478, indinavir, tipranavir, duranavir, DPC-681, DPC-684, fosamprenavir calcium (Lexiva), benzenesulfonamide derivatives disclosed in WO 03053435, R-944, Ro-03-34649, VX-385, GS-224338, OPT-TL3, PL-100, SM-309515, AG-148, DG-35-VIII, DMP-850, GW-5950X, KNI-1039, L-756423, LB-71262, LP-130, RS-344, SE-063, UIC-94-003, Vb-19038, A-77003, BMS-182193, BMS-186318, SM-309515, JE-2147, GS-9005, and (4*R*)-*N*-allyl-3-[(2*S*,3*S*)-2-hydroxy-3-[(3-hydroxy-2-methylbenzoyl)amino]-4-phenylbutanoyl]-5,5-dimethyl-1,3-thiazolidine-4-carboxamide.

Compounds useful as inhibitors of the HIV reverse transcriptase enzyme that may be used in combination with the compounds of the present invention include, but are not limited to, abacavir, FTC, GS-840, lamivudine, adefovir dipivoxil, beta-fluoro-ddA, zalcitabine, didanosine, stavudine, zidovudine, tenofovir, amdoxovir, SPD-754, SPD-756, racivir, reverset (DPC-817), MIV-210 (FLG), beta-L-Fd4C (ACH-126443), MIV-310 (alovudine, FLT), dOTC, DAPD, entecavir, GS-7340, emtricitabine, and alovedine.

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Compounds useful as non-nucleoside inhibitors of the HIV reverse transcriptase enzyme that may be used in combination with the compounds of the present invention include, but are not limited to, efavirenz, HBV-097, nevirapine, TMC-120 (dapivirine), TMC-125, etravirine, delavirdine, DPC-083, DPC-961, TMC-120, capravirine, GW-678248, GW-695634, calanolide, and tricyclic pyrimidinone derivatives as disclosed in WO 03062238.

Compounds useful as CCR5 inhibitors that may be used in combination with the compounds of the present invention include, but are not limited to, TAK-779, SC-351125, SCH-D, (N-((1S)-3-[3-isopropyl-5-methyl-4H-1,2,4-triazole-4-yl]-exo-8-azabicyclo[3.2.1]oct-8-yl)-1-phenylpropyl)-4,4-difluorocyclohexanecarboxamide), ethyl 1-endo-[8-((3S)-3-(acetylamino)-3-(3-fluorophenyl)propyl)-8-azabicyclo[3.2.1]oct-3-yl]-2-methyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine-5-carboxylate, or N-((1S)-3-[3-endo-(5-isobutyl-2-methyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridin-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-(3-fluorophenyl)propyl)acetamide), PRO-140, and GW-873140 (Ono-4128, AK-602).

Compounds useful as inhibitors of HIV integrase enzyme that may be used in combination with the compounds of the present invention include, but are not limited to, GW-810781, 1,5-naphthyridine-3-carboxamide derivatives disclosed in WO 03062204, compounds disclosed in WO 03047564, compounds disclosed in WO 03049690, and 5-hydroxypyrimidine-4-carboxamide derivatives disclosed in WO 03035076.

Fusion inhibitors for the treatment of HIV that may be used in combination with the compounds of the present invention include, but are not limited to enfuvirtide (T-20), T-1249, AMD-3100, and fused tricyclic compounds disclosed in JP 2003171381.

Other compounds that are useful inhibitors of HIV that may be used in combination with the compounds of the present invention include, but are not limited to, Soluble CD4, TNX-355, PRO-542, BMS-806, tenofovir disoproxil fumarate, and compounds disclosed in JP 2003119137.

Compounds useful in the treatment or management of infection from viruses other than HIV that may be used in combination with the compounds of the present invention include, but are not limited to, acyclovir, fomivirsen, penciclovir, HPMP, oxetanocin G, AL-721, cidofovir, cytomegalovirus immune globin, cytovene, fomivganciclovir, famciclovir, foscarnet sodium, Isis 2922, KNI-272, valacyclovir, virazole ribavirin, valganciclovir, ME-609, PCL-016

Compounds that act as immunomodulators and may be used in combination with the compounds of the present invention include, but are not limited to, AD-439, AD-519, Alpha Interferon, AS-101, bropirimine, acemannan, CL246,738, EL10, FP-21399, gamma interferon, granulocyte macrophage colony stimulating factor, IL-2, immune globulin

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intravenous, IMREG-1, IMREG-2, imuthiol diethyl dithio carbamate, alpha-2 interferon, methionine-enkephalin, MTP-PE, granulocyte colony stimulating factor, remune, rCD4, recombinant soluble human CD4, interferon alfa-2, SK&F106528, soluble T4 yhmopentin, tumor necrosis factor (TNF), tucaresol, recombinant human interferon beta, and interferon alfa n-3.

Anti-infectives that may be used in combination with the compounds of the present invention include, but are not limited to, atovaquone, azithromycin, clarithromycin, trimethoprim, trovafloxacin, pyrimethamine, daunorubicin, clindamycin with primaquine, fluconazole, pastill, ornidyl, eflornithine pentamidine, rifabutin, spiramycin, intraconazole-R51211, trimetrexate, daunorubicin, recombinant human erythropoietin, recombinant human growth hormone, megestrol acetate, testosterone, and total enteral nutrition.

Antifungals that may be used in combination with the compounds of the present invention include, but are not limited to, anidulafungin, C31G, caspofungin, DB-289, fluconazole, itraconazole, ketoconazole, micafungin, posaconazole, and voriconazole.

Other compounds that may be used in combination with the compounds of the present invention include, but are not limited to, acmannan, ansamycin, LM 427, AR177, BMS-232623, BMS-234475, CI-1012, curdlan sulfate, dextran sulfate, STOCRINE EL10, hypericin, lobucavir, novapren, peptide T octabpeptide sequence, trisodium phosphonoformate, probucol, and RBC-CD4.

In addition, the compounds of the present invention may be used in combination with anti-proliferative agents for the treatment of conditions such as Kaposi's sarcoma. Such agents include, but are not limited to, inhibitors of metallo-matrix proteases, A-007, bevacizumab, BMS-275291, halofuginone, interleukin-12, rituximab, paclitaxel, porfimer sodium, rebimastat, and COL-3.

The particular choice of an additional agent or agents will depend on a number of factors that include, but are not limited to, the condition of the mammal being treated; the particular condition or conditions being treated, the identity of the compound or compounds of the present invention and the additional agent or agents, and the identity of any additional compounds that are being used to treat the mammal. The particular choice of the compound or compounds of the invention and the additional agent or agents is within the knowledge of one of ordinary skill in the art and can be made without undue experimentation.

The compounds of the present invention may be administered in combination with any of the above additional agents for the treatment of a mammal, such as a human, that is suffering from an infection with the HIV virus, AIDS, AIDS-related complex (ARC), or any other disease or condition which is related to infection with the HIV virus. Such a combination may be administered to a mammal such that a compound or compounds of

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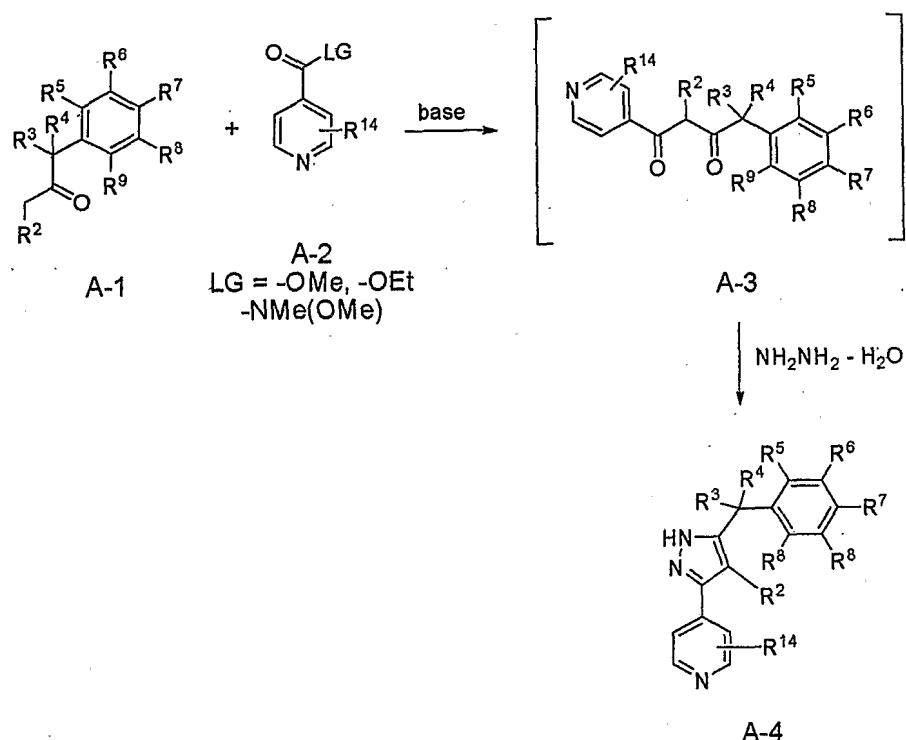
the present invention are present in the same formulation as the additional agents described above. Alternatively, such a combination may be administered to a mammal suffering from infection with the HIV virus such that the compound or compounds of the present invention are present in a formulation that is separate from the formulation in which the additional agent is found. If the compound or compounds of the present invention are administered separately from the additional agent, such administration may take place concomitantly or sequentially with an appropriate period of time in between. The choice of whether to include the compound or compounds of the present invention in the same formulation as the additional agent or agents is within the knowledge of one of ordinary skill in the art.

The inventive agents may be prepared using the reaction routes and synthesis schemes as described below, employing the techniques available in the art using starting materials that are readily available. The preparation of certain embodiments of the present invention are described in detail in the following examples, but those of ordinary skill in the art will recognize that the preparations described may be readily adapted to prepare other embodiments of the present invention. For example, the synthesis of non-exemplified compounds according to the invention may be performed by modifications apparent to those skilled in the art, e.g., by appropriately protecting interfering groups, by changing to other suitable reagents known in the art, or by making routine modifications of reaction conditions. Alternatively, other reactions disclosed herein or known in the art will be recognized as having adaptability for preparing other compounds of the invention.

The compounds of formula (I) can be prepared according to the methods shown in Scheme A. Phenylacetones such as A-1 are commercially available or can be prepared using methods described herein or methods known to those of ordinary skill in the art. Similarly, isonicotinic esters or Weinreb amides such as A-2 are either commercially available or can be prepared using methods described herein or methods known to those of ordinary skill in the art. The reaction of A-1 with A-2 can be effected using a suitable base, such as sodium methoxide, in a suitable, aprotic solvent, such as tetrahydrofuran (THF), and at a temperature from about 25 °C to about 100 °C, such as at about 66 °C to about 80 °C, to provide intermediate A-3. Intermediate A-3 may then be isolated in pure form, or may be used without further purification, and subsequently treated with hydrazine – hydrate in a suitable solvent, such as ethanol, and at a temperature of from about 25 °C to about 100 °C, to provide a compound of formula (I), A-4.

Scheme A

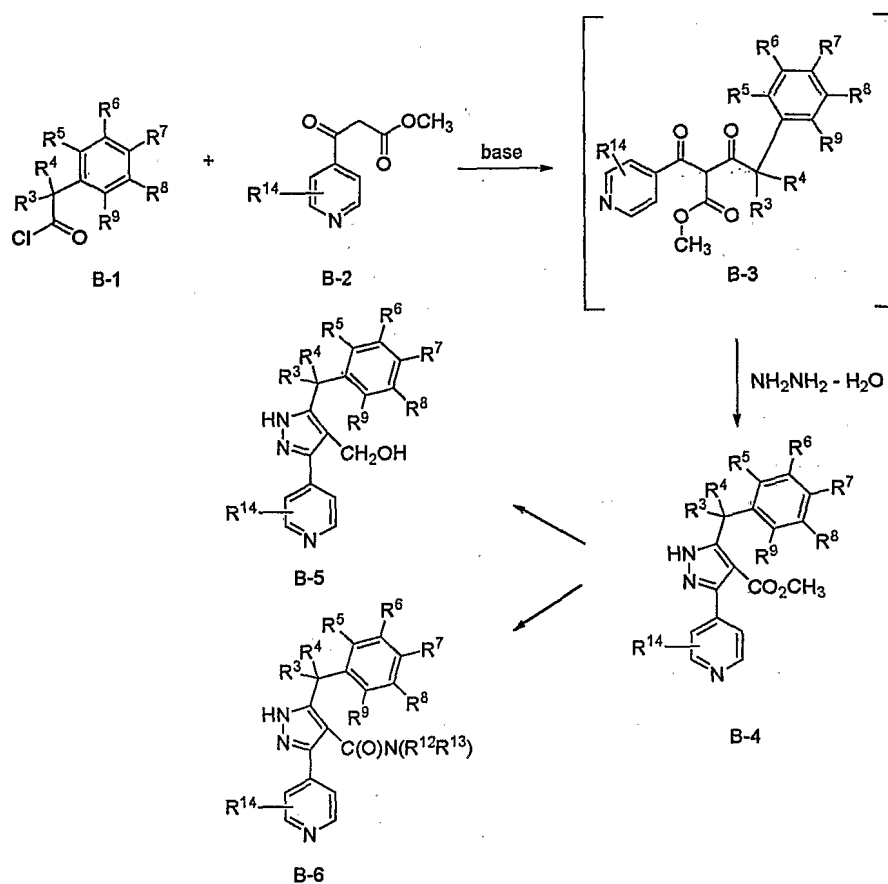
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Compounds of formula (I) may also be prepared according to the methods shown in Scheme B. The magnesium salt of β -ketoester B-2 may be formed by reaction of a compound of formula B-2 with magnesium chloride in an aprotic solvent, such as acetonitrile, and at a temperature from about 25 °C to about -78 °C, such as about -40 °C. Such a magnesium salt may then be allowed to react with an acid chloride of formula B-1. Such a reaction may be performed in the presence of a suitable base, such as pyridine or triethylamine, and in an aprotic solvent, such as acetonitrile, to afford an intermediate of formula B-3. These intermediates may then be treated with hydrazine under the conditions described above to afford 3,4,5-trisubstituted pyrazoles such as B-4. Intermediates of this type can be reduced using methods known to those of ordinary skill in the art to afford 4-hydroxymethyl compounds (B-5). Alternatively, the ester B-4 can be hydrolyzed with a suitable base, such as aqueous sodium hydroxide, in the presence of a suitable co-solvent if necessary, such as ethyl alcohol or methyl alcohol, to afford the corresponding carboxylic acid. The carboxylic acid may then be allowed to react with a primary or secondary amine to afford 4-amido pyrazoles, such as B-6. Such reactions may be performed in the presence of a suitable carboxylic acid activating agent, in a suitable aprotic solvent, to afford compounds of formula B-6. Suitable primary or secondary amines are either commercially available or can be prepared using methods known to those of ordinary skill in the art.

Method B

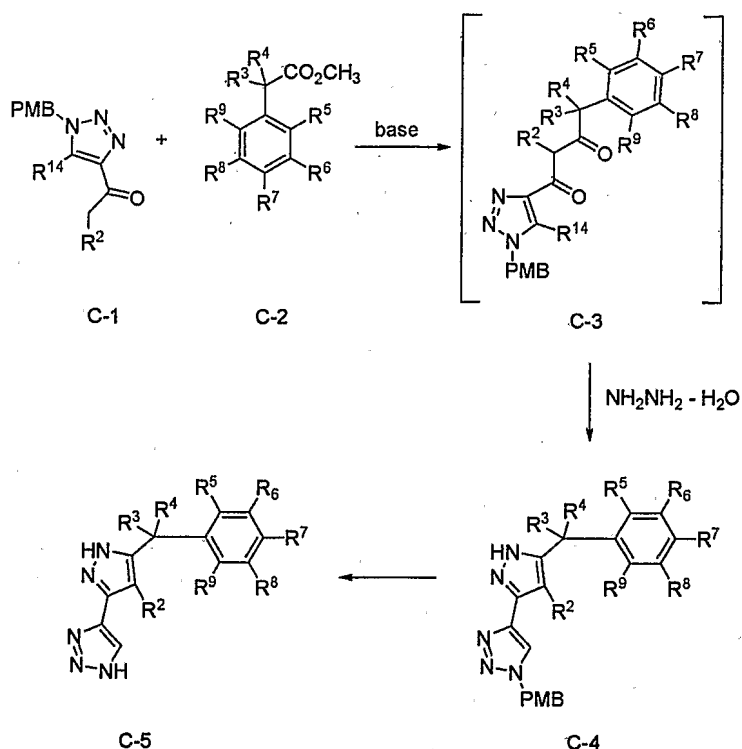
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Compounds of formula (I) can also be prepared using methods as shown in Scheme C. Compounds of formula C-5 can be prepared by reaction of a compound of formula C-1 with a compound of formula C-2. A suitable enolate of a compound of formula C-1, such as a sodium enolate, can be prepared using a suitable base, such as sodium hydride, lithium hexamethyldisilazide (LHMDS), lithium diisopropyl amide (LDA), or sodium hexamethyldisilazide (NaHMDS), in a suitable, aprotic solvent, such as THF, and at a temperature from about -78 °C to about 25 °C, such as at about 0 °C. Such an enolate can then be allowed to react with a compound of formula C-1 to afford a 1,3-dicarbonyl intermediate C-3. Intermediate C-3 may then be isolated in pure form, or may be used without further purification, and subsequently treated with hydrazine – hydrate in a suitable solvent, such as ethanol, and at a temperature of from about 25 °C to about 100 °C, to provide a compound of formula C-4. If the compounds of formula C-4 contain a protecting group, suitable methods for the cleavage of such a protecting group can be used to afford a compound of formula (I), C-5. Suitable protecting groups and methods for their removal are known to those of ordinary skill in the art and can be found in, for example, T. Greene and P. Wuts, "Protective Groups in Organic Synthesis", 3rd Edition 1999, John Wiley & Sons).

Scheme C

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Examples

The examples below are intended only to illustrate particular embodiments of the present invention and are not meant to limit the scope of the invention in any manner.

5 In the examples described below, unless otherwise indicated, all temperatures in the following description are in degrees Celsius (°C) and all parts and percentages are by weight, unless indicated otherwise.

Various starting materials and other reagents were purchased from commercial suppliers, such as Aldrich Chemical Company or Lancaster Synthesis Ltd., and used
10 without further purification, unless otherwise indicated.

The reactions set forth below were performed under a positive pressure of nitrogen, argon or with a drying tube, at ambient temperature (unless otherwise stated), in anhydrous solvents. Analytical thin-layer chromatography was performed on glass-backed silica gel 60°F 254 plates (Analtech (0.25 mm)) and eluted with the appropriate solvent
15 ratios (v/v). The reactions were assayed by high-pressure liquid chromatography (HPLC) or thin-layer chromatography (TLC) and terminated as judged by the consumption of starting material. The TLC plates were visualized by UV, phosphomolybdic acid stain, or iodine stain.

Unless otherwise indicated, ¹H-NMR spectra were recorded on a Bruker
20 instrument operating at 300 MHz and ¹³C-NMR spectra were recorded at 75 MHz. NMR spectra were obtained as DMSO-d₆ or CDCl₃ solutions (reported in ppm), using chloroform as the reference standard (7.25 ppm and 77.00 ppm) or DMSO-d₆ ((2.50 ppm

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and 39.52 ppm)). Other NMR solvents were used as needed. When peak multiplicities are reported, the following abbreviations are used: s = singlet, d = doublet, t = triplet, m = multiplet, br = broadened, dd = doublet of doublets, dt = doublet of triplets. Coupling constants, when given, are reported in Hertz.

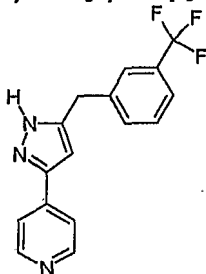
5 Infrared spectra were recorded on a Perkin-Elmer FT-IR Spectrometer as neat oils, as KBr pellets, or as CDCl_3 solutions, and when reported are in wave numbers (cm^{-1}). The mass spectra were obtained using LC/MS or APCI. All melting points are uncorrected.

All final products had greater than 95% purity (by HPLC at wavelengths of 220nm and 254nm).

10 All elemental analyses for compounds herein, unless otherwise specified, provided values for C, H, and N analysis that were within 0.4% of the theoretical value, and are reported as "C, H, N."

In the following examples and preparations, "LDA" means lithium diisopropyl amide, "Et" means ethyl, "Ac" means acetyl, "Me" means methyl, "Ph" means phenyl, 15 (PhO) $_2$ POCl means chlorodiphenylphosphate, "HCl" means hydrochloric acid, "EtOAc" means ethyl acetate, "Na $_2$ CO $_3$ " means sodium carbonate, "NaOH" means sodium hydroxide, "NaCl" means sodium chloride, "NEt $_3$ " means triethylamine, "THF" means tetrahydrofuran, "DIC" means diisopropylcarbodiimide, "HOBT" means hydroxy benzotriazole, "H $_2$ O" means water, "NaHCO $_3$ " means sodium hydrogen carbonate, 20 "K $_2$ CO $_3$ " means potassium carbonate, "MeOH" means methanol, "i-PrOAc" means isopropyl acetate, "MgSO $_4$ " means magnesium sulfate, "DMSO" means dimethylsulfoxide, "AcCl" means acetyl chloride, "CH $_2$ Cl $_2$ " means methylene chloride, "MTBE" means methyl t-butyl ether, "DMF" means dimethyl formamide, "SOCl $_2$ " means thionyl chloride, "H $_3$ PO $_4$ " means phosphoric acid, "CH $_3$ SO $_3$ H" means methanesulfonic acid, "Ac $_2$ O" means acetic 25 anhydride, "CH $_3$ CN" means aceto-CN, and "KOH" means potassium hydroxide.

Example 1: 4-(5-(3-(trifluoromethyl)benzyl)-1H-pyrazol-3-yl)pyridine

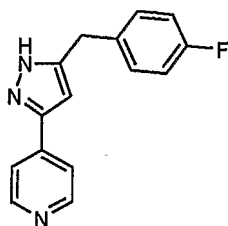


A 500 mL round bottom flask was charged with (3-(trifluoromethyl)phenyl)acetone (14.7 g, 72.9 mmol) and methyl isonicotinate (8.61 mL, 72.9 mmol). THF (150 mL) was added followed by solid NaOMe (10.0 g, 186 mmol), which was added in small portions. A fairly strong exotherm was noted and heating was continued at reflux for 2 h. The diketone intermediate with expected mass (307) was observed as a new peak as analyzed 30

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by LCMS. After cooling the reaction to ambient temperature, the mixture was poured into a 500 mL Erlenmeyer flask and chilled to 0 °C. Acetic acid (10.7 mL, 186 mmol) was added dropwise. Water (400 mL) and Et₂O (250 mL) were added and the aqueous layer was extracted with Et₂O (2 x 250 mL). The combined organic extracts washed with water (x1) and brine (x1). After removing both the Et₂O and THF by evaporation, the diketone was dissolved in EtOH (150 mL) and hydrazine-hydrate was added in one portion. A weak exotherm was noted and this mixture was allowed to stir for 18 h at ambient temperature. The EtOH was removed *in vacuo* and an aqueous work-up was carried out extracting the product into EtOAc, washing with water and brine, then drying over MgSO₄. After removal of the organic solvent, the product was purified via flash chromatography eluting with a gradient of 5% to 100% EtOAc to afford the title compound as a white solid (9.4 g, 43%). ¹H NMR (400 MHz, CHLOROFORM-d) δ ppm 12.4 (br s, 1 H), 8.52 (d, 2 H), 7.55 – 7.63 (m, 2 H), 7.46 – 7.52 (m, 2 H), 7.36 – 7.43 (m, 2 H), 6.47 (s, 1 H), 4.08 (s, 2 H); m/z (APCI+) for C₁₆H₁₂F₃N₃ 304.2 (M+H)⁺.

Example 2: 4-(5-(4-fluorobenzyl)-1H-pyrazol-3-yl)pyridine

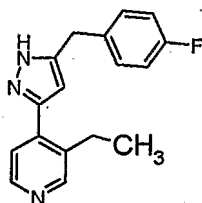


A 12 L three neck round bottom flask equipped with a mechanical stirrer, thermocouple, and reflux condenser with N₂ inlet adapter was charged with THF (3.0 L), methyl isonicotinate (128 g, 0.930 mol), and 4-fluorophenylacetone (142 g, 0.930 mol). Sodium methoxide (100 g, 1.86 mol) was added in several portions. The resulting mixture was heated to reflux for 2 hours. After 2 hours, the absence of methyl isonicotinate and the formation of the β-diketone was verified by LC-MS. After the addition of ethanol (3 L) and acetic acid (180 mL), the temperature of the reaction mixture decreased to 45 °C. The reflux condenser was replaced with an addition funnel and hydrazine (194 g, 6.00 mol) was added dropwise. During the addition, the temperature of the reaction rose to about 60 °C. The resulting mixture was stirred overnight slowly cooling to room temperature. The majority of the solvents were removed by rotary evaporation. The reaction mixture was partitioned between water (3 L) and ethyl acetate (3 L). The layers were separated and the aqueous layer extracted with ethyl acetate (1.5 L). The combined organic layers were then washed with dilute aqueous NaHCO₃, brine, dried (Na₂SO₄), filtered and concentrated. The title compound purified by silica gel chromatography, using 5% methanol : 95% methylene chloride as eluant. The fractions containing the product were pooled and concentrated and the resulting solid was dissolved in methylene chloride

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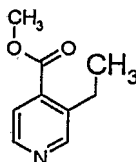
(500 mL) and hexanes (500 mL) was added. After removing about three quarters of this mixture by rotary evaporation, the resulting solid was filtered, washed with hexanes, and dried under reduced pressure to provide 100 g (43%) of the title compound as a white solid. ¹H NMR (400 MHz, DMSO-D₆) δ ppm 13.10 (s, 1 H) 8.44 - 8.60 (m, 2 H) 7.68 (d, 2 H) 7.30 (t, 2 H) 7.13 (t, 2 H) 6.62 (s, 1 H) 4.00 (s, 2 H); m/z (APCI+) for C₁₅H₁₂FN₃ 254. (M+H)⁺.

Example 3: 3-ethyl-4-[5-(4-fluorobenzyl)-1H-pyrazol-3-yl]pyridine



To a suspension of methyl 3-ethylisonicotinate (1.58 g, 9.56 mmol) in THF (50 mL) was added 1-(4-fluorophenyl)acetone (2.70 mL, 20.08 mmol) followed by sodium methoxide powder (1.63 g, 30.19 mmol) and the resulting mix heated to reflux for 4 hours. The reaction was then cooled to ambient temperature, quenched with acetic acid (3 mL) and the resulting thick slurry diluted with ethanol (60 mL). Hydrazine hydrate (3 mL) was added and the mix heated at 80 °C for 30 minutes. The reaction was cooled to ambient, and the volatiles removed *in vacuo*. The residue was partitioned between EtOAc (150 mL) and water (50 mL), and the layers separated. The organics were washed with brine (50 mL), dried over MgSO₄, filtered and stripped to a crude yellow/green gum that was purified by Biotage flash chromatography, eluting with a 0 - 10% MeOH/ DCM gradient to afford the title compound as a yellow gum, 774 mg, 29%. ¹H NMR (400 MHz, DMSO-D₆) δ ppm 13.05 (1 H, s) 8.44 (1 H, s) 8.36 (1 H, d, J=4.80 Hz) 7.47 (1 H, d, J=4.80 Hz) 7.31 (2 H, dd, J=8.34, 5.56 Hz) 7.14 (2 H, t, J=8.72 Hz) 6.45 (1 H, s) 4.01 (2 H, s) 2.92 (2 H, q, J=7.33 Hz) 1.13 (3 H, t, J=7.45 Hz); m/z (APCI+) for C₁₇H₁₆N₃F 282.2 (M+H)⁺.

Example 4a: methyl 3-ethylisonicotinate

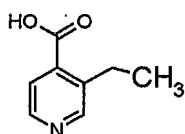


To a suspension of 3-ethylisonicotinic acid (12.5 g, 82.69 mmol) in methanol (100 mL) and toluene (200 mL) was added a solution of TMS-diazomethane (2 M in hexanes, 42 mL, 82.69 mmol) portion-wise *via* syringe. On addition, nitrogen was seen bubbling off and an exotherm was observed (temperature rising to 40 °C). After complete addition, the reaction was allowed to stir at 40 °C for 30 minutes then cooled to 10 °C using an ice bath. The reaction was quenched with AcOH (2 mL) and the solvents removed *in vacuo*. The

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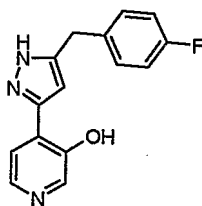
residue was partitioned between EtOAc (300 mL) and water (150 mL) and the bi-phasic mixture was basified with NaHCO₃ with stirring. The aqueous layer was then removed and the organics dried over MgSO₄, filtered and stripped to yield a dark oil. The desired product was further purified by Biotage flash chromatography, eluting with 5 – 25% EtOAc/Hexane to afford the title compound as an orange oil, 8.5 g, 62%. ¹H NMR (400 MHz, CDCl₃) δ ppm 8.57 (1 H, s) 8.53 (1 H, d, J=5.05 Hz) 7.62 (1 H, d, J=4.80 Hz) 3.92 (3 H, s) 2.95 (2 H, q, J=7.49 Hz) 1.18 - 1.30 (3 H, m); m/z (APCI+) for C₉H₁₁NO₂ 166.2 (M+H)⁺.

Example 4b: 3-ethylisonicotinic acid



To a solution of 3-ethyl-4-methylpyridine (20.0 g, 0.165 mol) in pyridine (120 mL) was added freshly crushed SeO₂ (28 g, 0.252 mol) and the mixture heated at 95 °C (oil bath temperature) for 90 minutes. The reaction was then cooled to ambient temperature and the inorganics filtered off and washed with EtOAc (100 mL). The combined liquors were concentrated *in vacuo* to provide a black tar that was diluted with DCM (200 mL) and stirred for 10 minutes. The resulting precipitate was filtered off, washed with DCM (250 mL) and dried to yield the title compound as a tan solid, 12.5 g, 50%. ¹H NMR (400 MHz, DMSO-D₆) δ ppm 8.58 (1 H, s) 8.52 (1 H, d, J=5.05 Hz) 7.59 (1 H, d, J=5.05 Hz) 2.88 (2 H, q, J=7.33 Hz) 1.16 (3 H, t, J=7.45 Hz); m/z (APCI+) for C₈H₉NO₂ 152.1 (M+H)⁺.

Example 5: 4-[5-(4-fluorobenzyl)-1H-pyrazol-3-yl]pyridin-3-ol

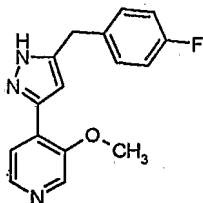


To a solution of 4-[5-(4-fluorobenzyl)-1H-pyrazol-3-yl]-3-methoxypyridine (447 mg, 1.58 mmol) in DMF (20 mL) was added sodium ethanethiolate (663 mg, 7.89 mmol) and the mixture was heated to 120 °C (oil bath temperature) for 18 hours. The reaction mixture was then cooled and the volatiles removed *in vacuo* and the residue suspended in water (50 mL) and extracted with EtOAc (3 x 50 mL). The combined extracts were dried over MgSO₄, filtered and stripped to yield a yellow gum that was purified by Biotage flash chromatography, eluting with 0 – 10% MeOH / DCM, to yield an off-white solid that was triturated with ether to yield the title compound as a white solid, 160 mg, 38%. ¹H NMR (400 MHz, DMSO-D₆) δ ppm 13.31 (1 H, s) 10.71 (1 H, s) 8.24 (1 H, s) 8.05 (1 H, d,

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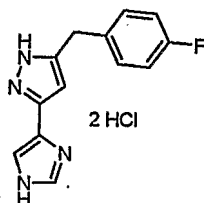
$J=5.05$ Hz) 7.64 (1 H, d, $J=5.05$ Hz) 7.31 (2 H, dd, $J=8.46$, 5.68 Hz) 7.14 (2 H, t, $J=8.84$ Hz) 6.75 (1 H, s) 4.02 (2 H, s); m/z (APCI+) for $C_{15}H_{12}N_3FO$ 270.1 (M+H)⁺.

Example 6: 4-[5-(4-fluorobenzyl)-1H-pyrazol-3-yl]-3-methoxypyridine



To a solution of methyl 3-fluoroisonicotinate (1.28 g, 8.25 mmol) in THF (50 mL) was added 1-(4-fluorophenyl)acetone (1.44 mL, 10.73 mmol) followed by sodium methoxide powder (1.02 g, 18.89 mmol) and the resulting mixture was heated at 75 °C (oil bath temperature) for 2 hours. The reaction was then cooled to 50 °C, quenched with acetic acid (3 mL) and the resulting thick slurry diluted with ethanol (50 mL). Hydrazine hydrate (3 mL) was added and the mix heated at 70 °C for 15 minutes. The reaction was allowed to cool to ambient temperature, and the volatiles removed *in vacuo*. The residue was partitioned between EtOAc (200 mL) and water (100 mL), and the layers separated. The organics were washed with water (2 x 50 mL), brine (50 mL), dried over $MgSO_4$, filtered and stripped to a crude yellow gum that was purified by Biotage flash chromatography eluting with a 0- 3.5 % MeOH/DCM gradient to afford crude material as a yellow solid. This was recrystallized from EtOAc to yield a white solid that was triturated with ether to afford the title compound, 561 mg, 24%. ¹H NMR (400 MHz, DMSO- D_6) δ ppm 13.02 (1 H, s) 8.42 (1 H, s) 8.19 (1 H, s) 7.59 - 7.91 (1 H, m) 7.29 (2 H, dd, $J=8.46$, 5.68 Hz) 7.12 (2 H, s) 6.64 (1 H, s) 3.95 (5 H, s); m/z (APCI+) for $C_{16}H_{14}N_3FO$ 284.1 (M+H)⁺.

Example 7: 5-(4-fluorobenzyl)-3-(1H-imidazol-4-yl)-1H-pyrazole, dihydrochloride salt



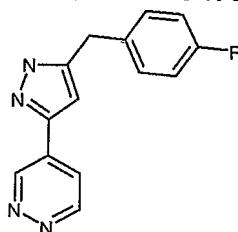
To a solution of methyl 1-trityl-1H-imidazole-4-carboxylate (see *Org. Proc. Res. Dev.*, 2000, 4, 613, 2.0 g, 5.43 mmol) in THF (40 mL) was added 1-(4-fluorophenyl)acetone (0.78 mL, 5.97 mmol) followed by sodium methoxide powder (586 mg, 10.85 mmol) and the resulting mixture was heated at 75 °C (oil bath temperature) for 150 minutes. The reaction was then allowed to cool to 50 °C and quenched with acetic acid (10 mL), and ethanol (40 mL) was added to the mixture. Hydrazine hydrate (2 mL) was added and the mixture was heated at 75 °C for 90 minutes and was then allowed to cool to ambient temperature overnight. The volatiles were removed *in vacuo* and the

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residue was basified with aqueous saturated NaHCO_3 solution and then diluted with EtOAc (200 mL) and water (100 mL). The solid was filtered, washed with water (50 mL) and EtOAc (200 mL), and suspended in EtOAc (100 mL) with stirring for 16 hours. The resulting solid was filtered, the organic solutions were combined and the solvents were evaporated to provide 5-(4-fluorobenzyl)-3-(1-trityl-1H-imidazol-4-yl)-1H-pyrazole. The product was suspended in 4 M HCl /1,4-dioxane (10 mL) for 16 hours and the resulting solid was filtered and dried *in vacuo* to afford the title compound as a tan solid, 206 mg, 12 %.

^1H NMR (400 MHz, DMSO- D_6) δ ppm 14.29 - 15.31 (2 H, m) 9.12 (1 H, d, $J=1.26$ Hz) 7.92 (1 H, d, $J=1.26$ Hz) 7.19 - 7.40 (2 H, m) 6.98 - 7.22 (2 H, m) 6.48 (1 H, s) 4.01 (2 H, s); m/z (APCI+) for $\text{C}_{13}\text{H}_{11}\text{N}_4\text{F}$ 243.1 ($\text{M}+\text{H}$) $^+$; CHN calc for $\text{C}_{13}\text{H}_{11}\text{N}_4\text{F} \cdot 2 \text{HCl}$ 49.54, 4.16, 17.78, found 49.30, 4.09, 17.62.

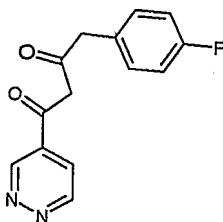
Example 8: 4-(5-(4-fluorobenzyl)-1H-pyrazol-3-yl)pyridazine



To a mixture of 4-(4-fluorophenyl)-1-(pyridazin-4-yl)butane-1,3-dione (7.0 g, 0.027 mol) and anhydrous EtOH/AcOH (50 mL/10 mL) was added dropwise $\text{NH}_2\text{NH}_2 \cdot \text{H}_2\text{O}$ (7.0 mL, 0.067 mol) at 0 °C. After the addition, the mixture was stirred at r.t overnight, after which time thin-layer chromatography (EtOAc/Petroleum ether 1:2) showed that the starting material was consumed. The solvents were removed by evaporation and the resulting residue was washed with anhydrous Et_2O (4x25 mL). The resulting solid was dried to yield 4-(5-(4-fluorobenzyl)-1H-pyrazol-3-yl)pyridazine (5.6 g, 81.6%) as a yellow solid.

^1H NMR (400 MHz, CDCl_3) δ ppm 9.83 (s, 1 H) 9.21 (d, $J=6.4$ Hz, 1 H) 7.85 (m, 2 H) 7.22 (m, 2 H) 7.05 (m, 1 H) 6.56 (s, 1 H) 4.09 (s, 2 H); m/z (APCI+) for $\text{C}_{14}\text{H}_{11}\text{FN}_4$ 255.3 ($\text{M}+\text{H}$) $^+$.

Example 9: 4-(4-fluorophenyl)-1-(pyridazin-4-yl)butane-1,3-dione

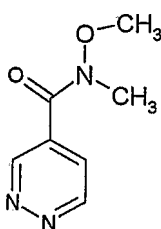


To a solution of 1-(4-fluorophenyl)-propan-2-one (6.0 g, 0.039 mol) in anhydrous THF (50 mL) was added NaOMe (4.3 g, 0.08 mol) at 0 °C. The mixture was stirred at r.t for 2 hours and N-methoxy-N-methylpyridazine-4-carboxamide (7.9 g, 0.047 mol) was added

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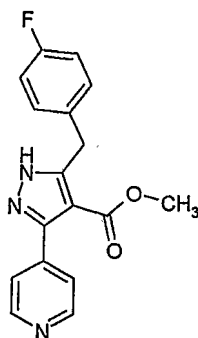
at 0 °C. The mixture was refluxed overnight, after which time thin-layer chromatography (EtOAc/Petroleum ether 1:2) showed that the starting material was consumed. The solvents were removed by evaporation and the resulting residue was purified via column chromatography (silica gel, EtOAc/Petroleum ether 1:5) to yield provide the title compound
5 as colorless oil (7.0 g, 69.5%). ¹H NMR (400 MHz, CDCl₃) δ ppm 9.44 (d, J=4Hz, 1 H) 9.33 (d, J=4Hz, 1 H) 7.77 (s, 1 H) 7.24 (m, 2 H) 7.08 (m, 2 H) 6.20 (s, 1 H) 3.78 (s, 2 H); m/z (APCI+) for C₁₄H₁₁FN₂O₂ 259.2 (M+H)⁺.

Example 10: N-methoxy-N-methylpyridazine-4-carboxamide



10 To a solution of pyridazine-4-carboxylic acid (16.0 g, 0.12 mol) in anhydrous CH₂Cl₂ (150 mL) was added CDI (24.0 g, 0.13 mol) in an ice bath. The mixture was stirred at r.t for 1.0 hour. O, N-dimethyl-hydroxylamine (14.0 g, 0.14 mol) was added. The resulting mixture was stirred overnight at r.t, after which time thin-layer chromatography (EtOAc/Petroleum ether 1:2) showed that the starting material was consumed. The
15 reaction mixture was diluted with water (100 mL), extracted with CH₂Cl₂ (3×50 mL). The combined organic phases were washed with water (3×25 mL) and brine (50 mL), dried over Na₂SO₄, and the solvents were evaporated to afford N-methoxy-N-methylpyridazine-4-carboxamide as a dark solid (21.0 g, 96.4 %) that was used without further purification.

Example 11: methyl 5-(4-fluorobenzyl)-3-pyridin-4-yl-1H-pyrazole-4-carboxylate

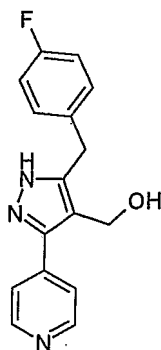


20 A 200-mL flask with spin bar was equipped with a pressure-equalizing addition funnel and flame-dried and cooled under vacuum. The flask was then charged with magnesium chloride (3.19 g, 33.5 mmol) and acetonitrile (35 mL) and cooled to – 40 °C with a dry ice/acetonitrile bath. To this white suspension was added methyl 3-oxo-3-
25 pyridin-4-ylpropanoate (6.00 g, 33.5 mmol), and the resulting orange suspension was next

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5 treated with pyridine (5.42 mL, 67.0 mmol). The mixture was stirred at -40°C for 15 minutes and then treated dropwise with a solution of (4-fluorophenyl)acetyl chloride (4.59 mL) in acetonitrile (4 mL) over 30 minutes. After complete addition, the red-orange mixture was stirred for 2 hours at -20°C , and then quenched with 5 N aqueous hydrochloric acid (27 mL). The reaction mixture was extracted first with diethyl ether, then with dichloromethane. The aqueous layer was adjusted to pH 4 using 5 N aqueous sodium hydroxide, then extracted further with dichloromethane. All organic layers were combined and concentrated *in vacuo* to give the diketo ester intermediate as an orange
10 amber syrup. Purification by chromatography on a short pad of silica gel eluting with 5% methanol-dichloromethane yielded the intermediate (6.5 g), which was immediately dissolved in acetic acid (70 mL) and treated with hydrazine (1.0 mL, 50.2 mmol). The resulting orange amber solution was stirred at room temperature for 17 hours and then concentrated *in vacuo* to provide a yellow solid. Residual acetic acid was quenched with saturated aqueous sodium bicarbonate and followed by solid sodium bicarbonate until the
15 pH was adjusted to about pH 7. The aqueous phase was extracted with ethyl acetate (3 x 200 mL). The combined organic layers were washed with 1 N aqueous sodium hydroxide (2 x 75 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo* to afford the title compound as a yellow foam (3.45 g, 33%). ^1H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 10.28 (br. s., 1 H), 8.65 (d, $J=5.8$ Hz, 2 H), 7.56 (dd, $J=4.5, 1.5$ Hz, 2 H), 7.24 - 7.28 (m, 2 H), 7.03 - 7.09 (m, 2 H), 4.35 (s, 2 H), 3.77 (s, 3 H); MS (ESI+) for $\text{C}_{17}\text{H}_{14}\text{FN}_3\text{O}_2$ m/z 312.20 ($\text{M}+\text{H}^+$); HRMS (ESI+) Calcd for $\text{C}_{17}\text{H}_{14}\text{FN}_3\text{O}_2+\text{H}^+$ 312.1143, found 312.1144; Anal. Calcd for $\text{C}_{17}\text{H}_{14}\text{FN}_3\text{O}_2 \cdot 0.02 \text{ DCM} \cdot 0.18 \text{ H}_2\text{O}$: C, 64.64; H, 4.59; N, 13.29. Found: C, 64.67; H, 4.46; N, 13.28.

Example 12: [5-(4-Fluorobenzyl)-3-pyridin-4-yl-1H-pyrazol-4-yl]methanol

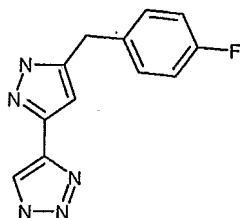


25 A solution of methyl 5-(4-fluorobenzyl)-3-pyridin-4-yl-1H-pyrazole-4-carboxylate (311 mg, 1.00 mmol) in anhydrous diethyl ether (7 mL) and tetrahydrofuran (4 mL) was added dropwise to a solution of lithium aluminum hydride (1.0 M in diethyl ether, 2.03 mL, 2.03 mmol) diluted with diethyl ether (9 mL). The mixture was stirred at room temperature
30 under N_2 (g) for 2.5 hours, then cooled to 0°C with an ice bath, and treated successively

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with water (0.13 mL), 15% aqueous sodium hydroxide (0.13 mL), and water (0.38 mL). The yellow mixture was stirred for 10 minutes, dried over sodium sulfate, filtered, and concentrated *in vacuo* to furnish a pale yellow solid. Purification by Biotage MPLC (25+S column, 1% to 10% methanol-dichloromethane gradient) afforded 203 mg (72%) of the title compound as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 13.01 (br. s., 1 H), 8.47 - 8.73 (m, 2 H), 7.68 - 7.88 (m, 2 H), 7.29 (dd, *J*=8.2, 5.7 Hz, 2 H), 7.11 (t, *J*=8.3 Hz, 2 H), 5.05 (t, *J*=4.3 Hz, 1 H), 4.40 - 4.48 (m, 2 H), 4.02 (s, 2 H); MS (ESI+) for C₁₆H₁₄FN₃O *m/z* 284.10 (M+H)⁺; HRMS (ESI+) Calcd for C₁₆H₁₄FN₃O+H⁺ 284.1194, found 284.1193; Anal. Calcd for C₁₆H₁₄FN₃O • 0.24 H₂O: C, 66.81; H, 5.07; N, 14.61. Found: C, 66.98; H, 5.13; N, 14.32.

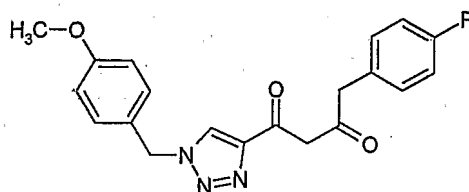
Example 13: 4-(5-(4-fluorobenzyl)-1H-pyrazol-3-yl)-1H-1,2,3-triazole



To a mixture of 4-(4-fluorophenyl)-1-(pyridazin-4-yl)butane-1,3-dione (0.6 g, 1.6 mmol) and anhydrous EtOH/AcOH (20 mL/5 mL) was added dropwise NH₂NH₂·H₂O (1.0 mL, 9.6 mmol) at 0 °C. After the addition, the mixture was stirred at r.t. overnight, after which time thin-layer chromatography (EtOAc/Petroleum ether 1:2) showed that the starting material was consumed. The solvents were evaporated and the resulting residue was washed with anhydrous Et₂O (4×5 mL), and the resulting precipitate was oven dried to yield 1-(1-(4-methoxybenzyl)-1H-1,2,3-triazol-4-yl)-4-(4-fluorophenyl)butane-1,3-dione (0.5 g, 84%) as a yellow solid. A solution of 1-(1-(4-methoxybenzyl)-1H-1,2,3-triazol-4-yl)-4-(4-fluorophenyl)butane-1,3-dione (0.3 g, 0.8 mmol) in TFA (5.0 mL) was heated to reflux temperature and was allowed to stir overnight, after which time thin-layer chromatography (CH₂Cl₂/MeOH 20:1) showed that the deprotection reaction was complete. The solvent was removed *in vacuo* and the residue was purified via HPLC to yield 4-(5-(4-fluorobenzyl)-1H-pyrazol-3-yl)-1H-1,2,3-triazole (0.10 g, 40%) as a white solid. ¹H NMR (400 MHz, MeOD) δ ppm 8.06 (s, 1 H), 7.27 (m, 2 H), 7.03 (m, 2 H), 6.50 (s, 1 H), 4.04 (s, 2 H); MS (APCI+) for C₁₂H₁₀FN₅ *m/z* 244.1 (M+H)⁺

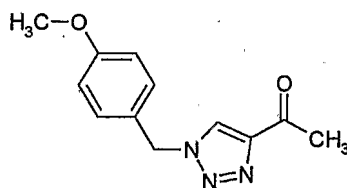
Example 14: 1-(1-(4-methoxybenzyl)-1H-1,2,3-triazol-4-yl)-4-(4-fluorophenyl)butane-1,3-dione

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To a solution of 1-(1-(4-methoxybenzyl)-1H-1,2,3-triazol-4-yl)ethanone (1.0 g, 4.30 mmol) in anhydrous THF (25 mL) was added NaH (0.38 g, 9.5 mmol) at 0 °C. The resulting mixture was stirred at r.t for 1 hours, and (4-fluorophenyl)-acetic acid methyl ester (1.67 g, 10.0 mmol) was added at 0 °C. The mixture was heated to reflux temperature overnight, after which time thin-layer chromatography (EtOAc/Petroleum ether 1:1) showed that the starting material was consumed. The solvents were removed by evaporation and the resulting residue was purified via column chromatography (silica gel, EtOAc/Petroleum ether 1:5) to afford the title compound (0.6 g, 38.0%) as colorless oil. ¹H NMR (400 MHz, CDCl₃) δ ppm 7.88 (s, 1H), 7.24 (m, 4H), 7.02 (m, 2 H), 6.91 (m, 2 H), 6.55 (s, 1 H), 5.48 (s, 2 H), 3.81 (s, 3 H), 3.67 (s, 2 H).

Example 15: 1-(1-(4-methoxybenzyl)-1H-1,2,3-triazol-4-yl)ethanone



To a solution of 1-(4-methoxybenzyl)-1H-1,2,3-triazole-4-carboxylic acid (33.0 g, 0.14 mol, (prepared according to the method described in WO 2004054974) in anhydrous CH₂Cl₂ (80 mL), cooled using an ice bath, was added CDI (27.5 g, 0.160 mol). The resulting mixture was stirred at r.t for 1 hour, and then O, N-dimethyl-hydroxylamine (14.5 g, 0.150 mol) was added. The mixture was stirred at r.t. overnight, after which time thin-layer chromatography (EtOAc/Petroleum ether 1:2) showed that the starting material was consumed. The mixture was diluted with water (120 mL) and extracted with CH₂Cl₂ (3×100 mL). The combined organic phases were washed with water (3×50 mL) and brine (100 mL), dried over Na₂SO₄, and the solvents were evaporated to afford 1-(4-methoxybenzyl)-N-methoxy-N-methyl-1H-1,2,3-triazole-4-carboxamide (35.0 g, 84%) as a white solid. To a solution of 1-(4-methoxybenzyl)-N-methoxy-N-methyl-1H-1,2,3-triazole-4-carboxamide (8.0 g, 0.03 mol) in anhydrous THF (75 mL) was added dropwise methyl magnesium bromide (3.0 M in hexane, 20 mL, 0.058 mol) at 0 °C. After addition was complete, the mixture was stirred at r.t. overnight, after which time thin-layer chromatography (EtOAc/Petroleum ether 1:2) showed that the reaction was complete. The mixture was quenched with saturated aqueous NH₄Cl (30 mL). The mixture was extracted with CH₂Cl₂ (3×50 mL), the organic layers were combined, washed with 1 N aq. NaOH (3×20 mL),

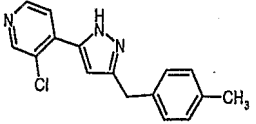
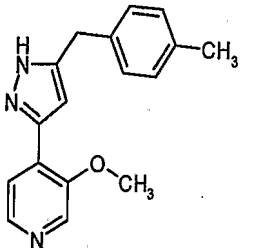
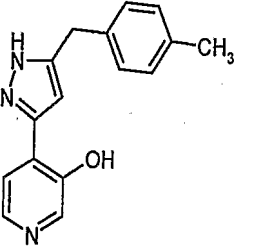
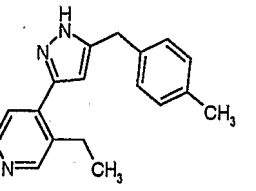
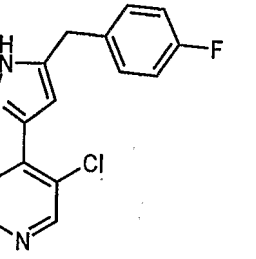
water (3×20 mL) and brine (50 mL), dried over MgSO₄, and the solvents were evaporated to yield 1-(1-(4-methoxybenzyl)-1H-1,2,3-triazol-4-yl)ethanone (8.0 g, 75%) as a white solid that was used without any further purification. ¹H NMR (400 MHz, DMSO-D₆) δ ppm 8.76 (s, 1 H), 7.30 (d, J = 8.0 Hz, 2 H), 6.90 (d, J = 8.0 Hz, 2 H), 5.54 (s, 2 H), 3.70 (s, 3 H).

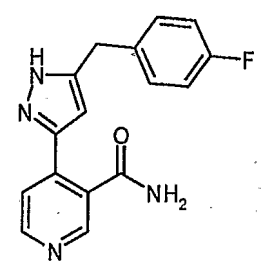
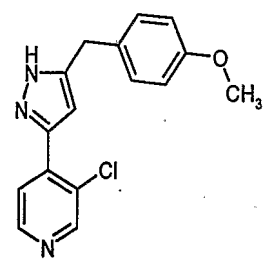
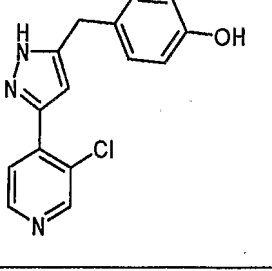
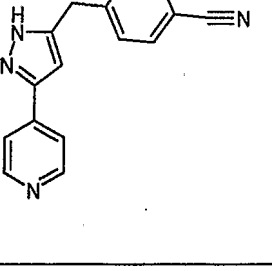
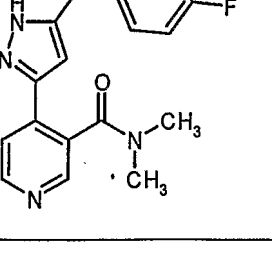
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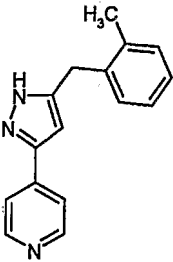
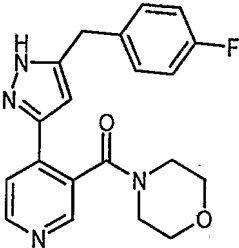
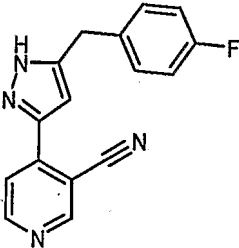
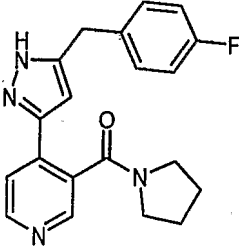
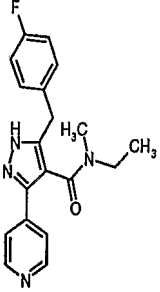
Examples 16 to 94:

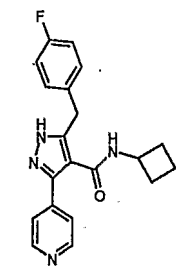
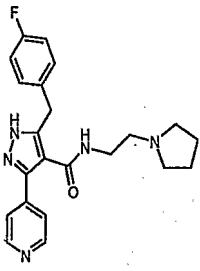
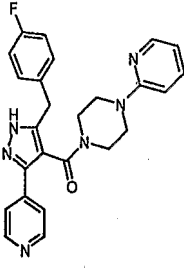
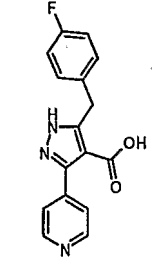
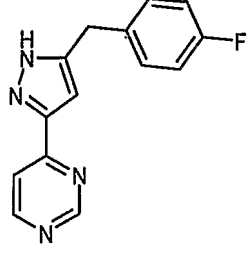
Example No.	Structure	Name	¹ H NMR
16		4-[5-(3,5-dichlorobenzyl)-1H-pyrazol-3-yl]pyridine	(500 MHz, DMSO-d ₆) δ ppm 8.73 (d, J = 6.0 Hz, 2 H) 8.11 (d, J = 6.0 Hz, 2 H) 7.49 (s, 1 H) 7.36 (s, 2 H) 6.92 (s, 1 H) 4.08 (s, 2 H)
17		4-[3-(4-methylbenzyl)-1H-pyrazol-5-yl]pyridine	(400 MHz, DMSO-D ₆) δ ppm 13.03 (1 H, s) 8.52 (2 H, d, J=4.55 Hz) 7.69 (2 H, d, J=4.80 Hz) 7.13 (4 H, q, J=7.92 Hz) 6.60 (1 H, s) 3.94 (2 H, s) 2.25 (3 H, s)
18		4-[5-(2,4-dimethylbenzyl)-1H-pyrazol-3-yl]pyridine	(500 MHz, DMSO-d ₆) δ ppm 8.72 (d, J=6.59 Hz, 2 H) 8.14 (s, 2 H) 7.06 (d, J=7.42 Hz, 1 H) 7.00 (s, 2 H) 6.74 (s, 1 H) 3.97 (s, 2 H) 2.24 (s, 6 H)
19		4-[5-(3-fluorobenzyl)-1H-pyrazol-3-yl]pyridine	(500 MHz, DMSO-d ₆) δ ppm 8.74 (d, J=6.32 Hz, 2 H) 8.14 (s, 2 H) 7.32 - 7.40 (m, 1 H) 7.11 - 7.15 (m, 2 H) 7.07 (s, 1 H) 6.91 (s, 1 H) 4.08 (s, 2 H)
20		4-[5-(2-chlorobenzyl)-1H-pyrazol-3-yl]pyridine	(500 MHz, DMSO-d ₆) δ ppm 8.73 (d, J=6.04 Hz, 2 H) 8.13 (s, 2 H) 7.47 (s, 1 H) 7.35 (d, J=16.21 Hz, 2 H) 7.31 (d, J=1.92 Hz, 1 H) 6.81 (s, 1 H) 4.16 (s, 2 H)

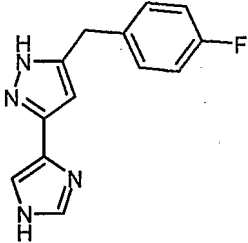
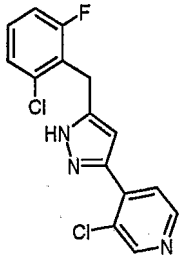
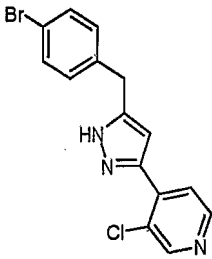
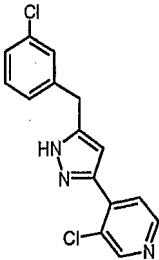
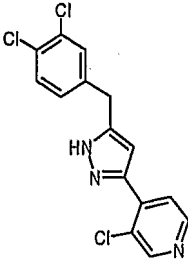
21		4-[5-(2,4-dichlorobenzyl)-1H-pyrazol-3-yl]pyridine	(500 MHz, DMSO-d ₆) δ ppm 8.73 (d, J=6.04 Hz, 2 H) 8.13 (s, 2 H) 7.63 (d, J=1.65 Hz, 1 H) 7.39 - 7.47 (m, 2 H) 6.81 (s, 1 H) 4.14 (s, 2 H)
22		4-[5-(4-bromobenzyl)-1H-pyrazol-3-yl]pyridine	(500 MHz, DMSO-d ₆) δ ppm 8.73 (d, J=6.32 Hz, 2 H) 8.13 (s, 2 H) 7.52 (d, J=8.24 Hz, 2 H) 7.25 (d, J=8.24 Hz, 2 H) 6.87 (s, 1 H) 4.03 (s, 2 H)
23		4-[5-(3,4-dichlorobenzyl)-1H-pyrazol-3-yl]pyridine	(500 MHz, DMSO-d ₆) δ ppm 8.72 (s, 2 H) 8.09 (s, 2 H) 7.58 (d, J=6.32 Hz, 2 H) 7.29 (s, 1 H) 6.88 (s, 1 H) 4.07 (s, 2 H)
24		4-[5-(2,6-difluorobenzyl)-1H-pyrazol-3-yl]pyridine	(500 MHz, DMSO-d ₆) δ ppm 8.73 (d, J=1.37 Hz, 2 H) 8.72 (s, 1 H) 8.12 (s, 2 H) 7.40 (s, 1 H) 7.13 (t, J=7.69 Hz, 1 H) 6.78 (s, 1 H) 4.07 (s, 2 H)
25		4-[5-(2-chloro-6-fluorobenzyl)-1H-pyrazol-3-yl]pyridine	(500 MHz, DMSO-d ₆) δ ppm 8.72 (d, J=6.04 Hz, 2 H) 8.12 (s, 2 H) 7.38 (m, 2 H) 7.29 (s, 1 H) 6.73 (s, 1 H) 4.18 (s, 2 H)
26		4-[5-(3-chlorobenzyl)-1H-pyrazol-3-yl]pyridine	(500 MHz, DMSO-d ₆) δ ppm 8.74 (d, J=1.37 Hz, 1 H) 8.73 (s, 1 H) 8.13 (s, 2 H) 7.31 - 7.39 (m, 2 H) 7.30 (d, J=8.2 Hz, 1 H) 7.26 (d, J=8.24 Hz, 1 H) 6.91 (s, 1 H) 4.07 (s, 2 H)

27		3-chloro-4-[3-(4-methylbenzyl)-1H-pyrazol-5-yl]pyridine	(400 MHz, DMSO-D6) δ ppm 13.26 (1 H, s) 8.64 (1 H, s) 8.48 (1 H, d, J=4.80 Hz) 7.84 (1 H, s) 7.02 - 7.30 (4 H, m) 6.72 (1 H, s) 3.97 (2 H, s) 2.25 (3 H, s)
28		3-methoxy-4-[5-(4-methylbenzyl)-1H-pyrazol-3-yl]pyridine	(400 MHz, DMSO-D6) δ ppm 12.91 - 13.07 (1 H, m) 8.37 - 8.48 (1 H, m) 8.13 - 8.27 (1 H, m) 7.59 - 7.89 (1 H, m) 7.05 - 7.18 (4 H, m) 6.57 - 6.69 (1 H, m) 3.86 - 4.03 (5 H, m) 2.25 (3 H, s)
29		4-[5-(4-methylbenzyl)-1H-pyrazol-3-yl]pyridin-3-ol	(400 MHz, DMSO-D6) δ ppm 13.29 (1 H, s) 10.78 (1 H, s) 8.24 (1 H, s) 8.04 (1 H, d, J=5.05 Hz) 7.64 (1 H, d, J=4.80 Hz) 7.01 - 7.28 (4 H, m) 6.73 (1 H, s) 3.98 (2 H, s) 2.25 (3 H, s)
30		3-ethyl-4-[5-(4-methylbenzyl)-1H-pyrazol-3-yl]pyridine	(400 MHz, DMSO-D6) δ ppm 13.02 (1 H, s) 8.44 (1 H, s) 8.35 (1 H, d, J=4.55 Hz) 7.47 (1 H, d, J=4.55 Hz) 7.05 - 7.24 (4 H, m) 6.42 (1 H, s) 3.95 (2 H, s) 2.83 - 3.08 (2 H, m) 2.25 (3 H, s) 1.12 (3 H, t, J=7.20 Hz)
31		3-chloro-4-[5-(4-fluorobenzyl)-1H-pyrazol-3-yl]pyridine	(400 MHz, DMSO-D6) δ ppm 13.28 (1 H, s) 8.64 (1 H, s) 8.48 (1 H, d, J=4.55 Hz) 7.85 (1 H, d, J=4.55 Hz) 7.31 (2 H, dd, J=8.46, 5.68 Hz) 7.14 (2 H, t, J=8.72 Hz) 6.75 (1 H, s) 3.86 - 4.23 (2 H, m)

32		4-[5-(4-fluorobenzyl)-1H-pyrazol-3-yl]nicotinamide	(400 MHz, DMSO-D6) δ ppm 13.07 (1 H, s) 8.53 (1 H, d, J=4.29 Hz) 8.44 (1 H, s) 7.96 (1 H, s) 7.74 (1 H, d, J=3.79 Hz) 7.57 (1 H, s) 7.28 (2 H, dd, J=8.46, 5.68 Hz) 7.13 (2 H, t, J=8.59 Hz) 6.45 (1 H, s) 3.98 (2 H, s)
33		3-chloro-4-[5-(4-methoxybenzyl)-1H-pyrazol-3-yl]pyridine	(400 MHz, DMSO-D6) δ ppm 13.25 (1 H, s) 8.64 (1 H, s) 8.48 (1 H, d, J=5.05 Hz) 7.83 (1 H, s) 7.13 - 7.29 (2 H, m) 6.82 - 6.93 (2 H, m) 6.71 (1 H, s) 3.95 (2 H, s) 3.70 (3 H, s)
34		4-[[3-(3-chloropyridin-4-yl)-1H-pyrazol-5-yl]methyl]phenol	(400 MHz, DMSO-D6) δ ppm 13.21 (1 H, s) 9.24 (1 H, s) 8.63 (1 H, s) 8.48 (1 H, d, J=4.55 Hz) 7.84 (1 H, s) 7.06 (2 H, d, J=8.59 Hz) 6.61 - 6.74 (3 H, m) 3.90 (2 H, s)
35		4-[(3-pyridin-4-yl-1H-pyrazol-5-yl)methyl]benzonitrile	(400 MHz, DMSO-D6) δ ppm 13.13 (1 H, s) 8.53 (2 H, d, J=5.81 Hz) 7.58 - 7.99 (4 H, m) 7.47 (2 H, d, J=8.08 Hz) 6.68 (1 H, s) 4.12 (2 H, s)
36		4-[5-(4-fluorobenzyl)-1H-pyrazol-3-yl]-N,N-dimethylnicotinamide	(400 MHz, DMSO-D6) δ ppm 13.15 (1 H, s) 8.56 (1 H, d, J=4.55 Hz) 8.37 (1 H, s) 7.74 (1 H, d, J=5.31 Hz) 7.28 (2 H, dd, J=8.46, 5.68 Hz) 7.14 (2 H, t, J=8.84 Hz) 6.24 (1 H, s) 3.98 (2 H, s) 2.88 (3 H, s) 2.55 (3 H, s)

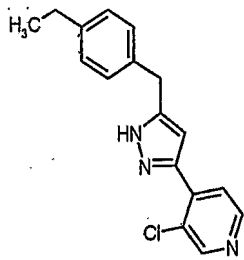
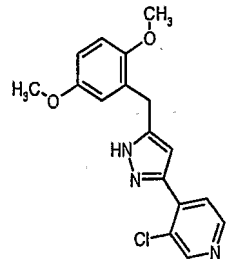
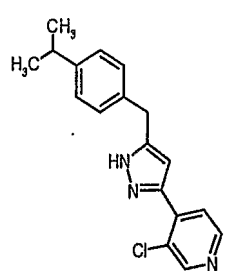
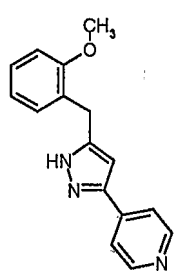
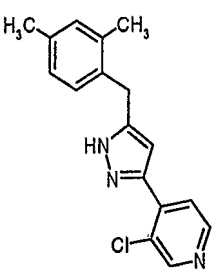
37		4-[5-(2-methylbenzyl)-1H-pyrazol-3-yl]pyridine	(500 MHz, DMSO-d ₆) δ ppm 8.73 (d, J=6.32 Hz, 2 H) 8.14 (s, 2 H) 7.14 - 7.21 (m, 3 H) 6.78 (s, 1 H) 4.02 (s, 2 H) 2.29 (s, 3 H)
38		4-({4-[5-(4-fluorobenzyl)-1H-pyrazol-3-yl]pyridin-3-yl}carbonyl)morpholine	(400 MHz, DICHLOROMETHANE-D ₂) δ ppm 8.60 (1 H, d, J=5.31 Hz) 8.49 (1 H, s) 7.54 (1 H, d, J=5.31 Hz) 7.15 - 7.29 (2 H, m) 6.91 - 7.01 (2 H, m) 6.37 (1 H, s) 4.04 (2 H, s) 3.68 - 3.83 (1 H, m) 3.56 - 3.67 (3 H, m) 3.33 - 3.49 (1 H, m) 3.06 - 3.27 (2 H, m) 2.89 - 3.01 (1 H, m)
39		4-[5-(4-fluorobenzyl)-1H-pyrazol-3-yl]nicotinonitrile	(400 MHz, DICHLOROMETHANE-D ₂) δ ppm 10.90 (1 H, s) 8.88 (1 H, s) 8.72 (1 H, d, J=5.56 Hz) 7.79 (1 H, d, J=5.31 Hz) 7.25 (2 H, dd, J=8.21, 5.43 Hz) 7.04 (2 H, t, J=8.72 Hz) 6.82 (1 H, s) 4.12 (2 H, s)
40		4-[5-(4-fluorobenzyl)-1H-pyrazol-3-yl]-3-(pyrrolidin-1-ylcarbonyl)pyridine	(400 MHz, DICHLOROMETHANE-D ₂) δ ppm 8.58 (1 H, d, J=5.05 Hz) 8.52 (1 H, s) 7.57 (1 H, d, J=5.05 Hz) 7.16 - 7.28 (2 H, m) 6.89 - 7.09 (2 H, m) 6.35 (1 H, s) 4.00 (2 H, s) 3.55 (2 H, t, J=6.95 Hz) 3.04 (2 H, s) 1.80 - 1.93 (2 H, m) 1.65 - 1.79 (2 H, m)
41		N-ethyl-5-(4-fluorobenzyl)-N-methyl-3-pyridin-4-yl-1H-pyrazole-4-carboxamide	(400 MHz, CHLOROFORM-d) δ ppm 12.85 (br. s., 1 H), 8.51 (d, J=4.5 Hz, 2 H), 7.48 - 7.53 (m, 2 H), 7.11 - 7.17 (m, 2 H), 6.86 - 6.94 (m, 2 H), 3.94 (s, 2 H), 3.48, 2.80 (2m, 2 H), 2.98, 2.38 (2s, 3 H), 1.11, 0.60 (2t, J=7.2 Hz, 3 H)

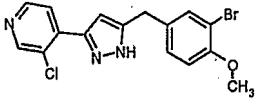
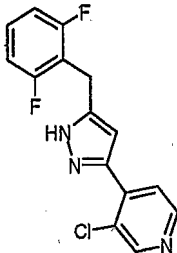
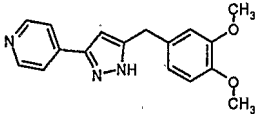
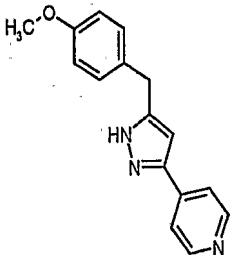
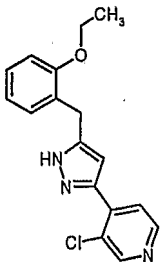
42		N-cyclobutyl-5-(4-fluorobenzyl)-3-pyridin-4-yl-1H-pyrazole-4-carboxamide	(400 MHz, DMSO-d ₆) δ ppm 12.93 (br. s., 1 H), 8.56 (d, J=5.8 Hz, 2 H), 8.35 (d, J=7.6 Hz, 1 H), 7.57 (d, J=5.8 Hz, 2 H), 7.23 (dd, J=8.5, 5.7 Hz, 2 H), 7.10 (t, J=8.8 Hz, 2 H), 4.27 - 4.38 (m, 1 H), 4.03 (s, 2 H), 2.11 - 2.21 (m, 2 H), 1.80 - 1.92 (m, 2 H), 1.56 - 1.65 (m, 2 H)
43		5-(4-fluorobenzyl)-3-pyridin-4-yl-N-(2-pyrrolidin-1-ylethyl)-1H-pyrazole-4-carboxamide	(400 MHz, DMSO-d ₆) δ ppm 13.28 (s, 1 H), 8.55 (d, J=6.1 Hz, 2 H), 8.00 (t, J=5.7 Hz, 1 H), 7.63 (d, J=6.1 Hz, 2 H), 7.26 (dd, J=8.6, 5.6 Hz, 2 H), 7.10 (t, J=8.8 Hz, 2 H), 4.07 (s, 2 H), 3.29 (q, J=6.6 Hz, 2 H), 2.44 - 2.48 (m, 2 H), 2.38 - 2.43 (m, 4 H), 1.58 - 1.63 (m, 4 H)
44		1-([5-(4-fluorobenzyl)-3-pyridin-4-yl-1H-pyrazol-4-yl]carbonyl)-4-pyridin-2-ylpiperazine	(400 MHz, DMSO-d ₆) δ ppm 13.51 (s, 1 H), 8.58 (d, J=5.1 Hz, 2 H), 8.06 (dd, J=4.9, 1.4 Hz, 1 H), 7.51 (d, J=6.1 Hz, 2 H), 7.46 - 7.50 (m, 1 H), 7.24 (dd, J=8.6, 5.6 Hz, 2 H), 7.09 (t, J=8.8 Hz, 2 H), 6.71 (d, J=8.6 Hz, 1 H), 6.63 (dd, J=7.1, 5.1 Hz, 1 H), 3.97 (s, 2 H), 3.56 - 3.75 (m, J=34.4 Hz, 2 H), 3.40 - 3.50 (m, 2 H), 2.75 - 3.03 (m, 4 H)
45		5-(4-fluorobenzyl)-3-pyridin-4-yl-1H-pyrazole-4-carboxylic acid	(400 MHz, DMSO-d ₆) δ ppm 13.46 (br. s., 1 H), 12.56 (br. s., 1 H), 8.58 (d, J=3.8 Hz, 2 H), 7.60 (d, J=6.1 Hz, 2 H), 7.29 (dd, J=8.6, 5.6 Hz, 2 H), 7.12 (t, J=8.8 Hz, 2 H), 4.25 (s, 2 H)
46		4-[5-(4-fluorobenzyl)-1H-pyrazol-3-yl]pyrimidine	(400 MHz, DMSO-D ₆) δ ppm 13.25 (1 H, s), 9.11 (1 H, s), 8.75 (1 H, s), 7.89 (1 H, s), 7.31 (2 H, dd, J=8.21, 5.68 Hz), 7.13 (2 H, t, J=8.59 Hz), 6.68 (1 H, s), 3.88 - 4.13 (2 H, m)

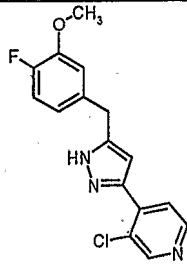
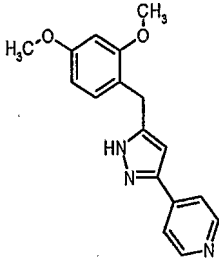
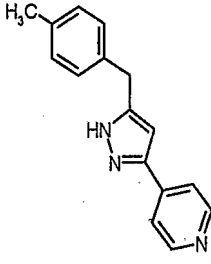
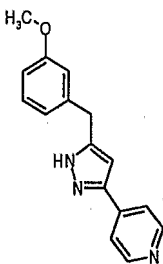
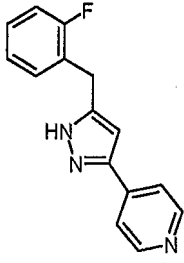
47		5-(4-fluorobenzyl)-3-(1H-imidazol-4-yl)-1H-pyrazole	(400 MHz, DMSO-D6) δ ppm 14.29 - 15.31 (2 H, m) 9.12 (1 H, d, $J=1.26$ Hz) 7.92 (1 H, d, $J=1.26$ Hz) 7.19 - 7.40 (2 H, m) 6.98 - 7.22 (2 H, m) 6.48 (1 H, s) 4.01 (2 H, s)
48		3-chloro-4-[5-(2-chloro-6-fluorobenzyl)-1H-pyrazol-3-yl]pyridine	(500 MHz, DMSO-d6) δ ppm 8.65 (s, 1 H), 8.50 (d, $J=4.67$ Hz, 1 H), 7.81 (s, 1 H), 7.37 (d, $J=3.57$ Hz, 2 H), 7.27 (s, 1 H), 6.61 (s, 1 H), 4.18 (s, 2 H)
49		4-[5-(4-bromobenzyl)-1H-pyrazol-3-yl]-3-chloropyridine	(500 MHz, DMSO-d6) δ ppm 8.66 (s, 1 H), 8.50 (d, $J=5.22$ Hz, 1 H), 7.84 (d, $J=5.22$ Hz, 1 H), 7.51 (d, $J=8.24$ Hz, 2 H), 7.25 (d, $J=8.24$ Hz, 2 H), 6.76 (s, 1 H), 4.02 (s, 2 H)
50		3-chloro-4-[5-(3-chlorobenzyl)-1H-pyrazol-3-yl]pyridine	(500 MHz, DMSO-d6) δ ppm 8.66 (s, 1 H), 8.51 (d, $J=5.22$ Hz, 1 H), 7.84 (d, $J=4.94$ Hz, 1 H), 7.33 - 7.40 (m, 2 H), 7.23 - 7.32 (m, 2 H), 6.80 (s, 1 H), 4.06 (s, 2 H)
51		3-chloro-4-[5-(3,4-dichlorobenzyl)-1H-pyrazol-3-yl]pyridine	(500 MHz, DMSO-d6) δ ppm 8.66 (s, 1 H), 8.51 (d, $J=4.94$ Hz, 1 H), 7.84 (s, 1 H), 7.54 - 7.60 (m, 2 H), 7.30 (s, 1 H), 6.81 (s, 1 H), 4.07 (s, 2 H)

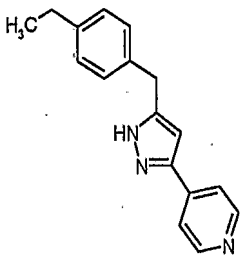
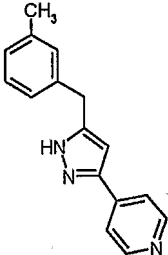
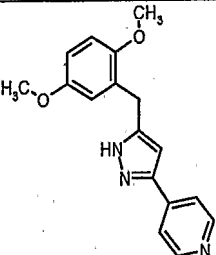
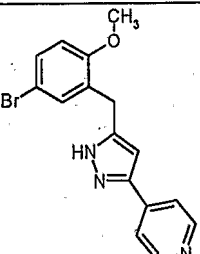
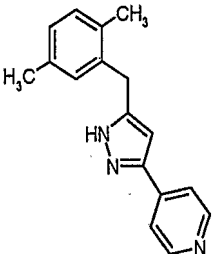
52		3-chloro-4-[5-(2-fluorobenzyl)-1H-pyrazol-3-yl]pyridine	(500 MHz, DMSO-d ₆) δ ppm 8.66 (s, 1 H), 8.51 (d, J=4.94 Hz, 1 H), 7.84 (d, J=5.22 Hz, 1 H), 7.28 - 7.36 (m, 2 H), 7.15 - 7.22 (m, 2 H), 6.72 (s, 1 H), 4.07 (s, 2 H).
53		3-chloro-4-[5-[3-(trifluoromethyl)benzyl]-1H-pyrazol-3-yl]pyridine	(500 MHz, DMSO-d ₆) δ ppm 8.66 (s, 1 H), 8.51 (d, J=5.22 Hz, 1 H), 7.84 (d, J=4.94 Hz, 1 H), 7.67 (s, 1 H), 7.59 (d, J=10.71 Hz, 3 H), 6.81 (s, 1 H), 4.16 (s, 2 H).
54		3-chloro-4-[5-(2,5-dimethylbenzyl)-1H-pyrazol-3-yl]pyridine	(500 MHz, DMSO-d ₆) δ ppm 8.65 (s, 1 H), 8.50 (d, J=4.94 Hz, 1 H), 7.85 (d, J=4.94 Hz, 1 H), 7.05 (d, J=7.42 Hz, 1 H), 7.00 (s, 1 H), 6.95 (d, J=8.52 Hz, 1 H), 6.64 (s, 1 H), 3.97 (s, 2 H), 2.23 (d, J=3.85 Hz, 6 H)
55		3-chloro-4-[5-(2-chlorobenzyl)-1H-pyrazol-3-yl]pyridine	(500 MHz, DMSO-d ₆) δ ppm 8.66 (s, 1 H), 8.51 (d, J=4.94 Hz, 1 H), 7.84 (d, J=5.22 Hz, 1 H), 7.47 (d, J=7.42 Hz, 1 H), 7.35 - 7.39 (m, 1 H), 7.27 - 7.35 (m, 2 H), 6.71 (s, 1 H), 4.15 (s, 2 H)
56		3-chloro-4-[5-(2-methylbenzyl)-1H-pyrazol-3-yl]pyridine	(500 MHz, DMSO-d ₆) δ ppm 8.65 (s, 1 H), 8.50 (d, J=4.94 Hz, 1 H), 7.85 (d, J=5.22 Hz, 1 H), 7.13 - 7.21 (m, 4 H), 6.65 (s, 1 H), 4.02 (s, 2 H), 2.29 (s, 3 H)

57		4-[5-(2-bromo-4,5-dimethoxybenzyl)-1H-pyrazol-3-yl]-3-chloropyridine	(500 MHz, DMSO-d6) δ ppm 8.65 (s, 1 H), 8.50 (d, J=5.22 Hz, 1 H), 7.83 (d, J=4.67 Hz, 1 H), 7.14 (s, 1 H), 7.06 (s, 1 H), 6.69 (s, 1 H), 4.06 (s, 2 H), 3.75 (d, J=7.14 Hz, 6 H).
58		3-chloro-4-[5-(3-methylbenzyl)-1H-pyrazol-3-yl]pyridine	(500 MHz, DMSO-d6) δ ppm 8.66 (s, 1 H), 8.50 (d, J=4.94 Hz, 1 H), 7.85 (d, J=4.67 Hz, 1 H), 7.15 - 7.23 (m, 1 H), 7.10 (s, 3 H), 6.75 (s, 1 H), 3.99 (s, 2 H), 2.27 (s, 3 H)
59		3-chloro-4-[5-(3-fluorobenzyl)-1H-pyrazol-3-yl]pyridine	(500 MHz, DMSO-d6) δ ppm 8.66 (s, 1 H), 8.51 (d, J=5.22 Hz, 1 H), 7.85 (d, J=5.22 Hz, 1 H), 7.36 (d, J=6.32 Hz, 1 H), 7.14 (s, 2 H), 7.05 (s, 1 H), 6.80 (s, 1 H), 4.07 (s, 2 H).
60		3-chloro-4-[5-(2,3-dimethoxybenzyl)-1H-pyrazol-3-yl]pyridine	(500 MHz, DMSO-d6) δ ppm 8.65 (s, 1 H), 8.50 (d, J=5.22 Hz, 1 H), 7.84 (d, J=5.22 Hz, 1 H), 7.01 (t, J=7.83 Hz, 1 H), 6.92 - 6.97 (m, 1 H), 6.81 (d, J=7.42 Hz, 1 H), 6.66 (s, 1 H), 3.99 (s, 2 H), 3.79 (s, 4 H), 3.69 (s, 2 H)
61		4-[5-(5-bromo-2-methoxybenzyl)-1H-pyrazol-3-yl]-3-chloropyridine	(500 MHz, DMSO-d6) δ ppm 8.65 (s, 1 H), 8.50 (d, J=5.22 Hz, 1 H), 7.84 (d, J=4.94 Hz, 1 H), 7.40 (dd, J=8.79, 2.47 Hz, 1 H), 7.31 (d, J=2.20 Hz, 1 H), 6.98 (d, J=8.79 Hz, 1 H), 6.71 (s, 1 H), 3.97 (s, 2 H), 3.81 (s, 4 H).

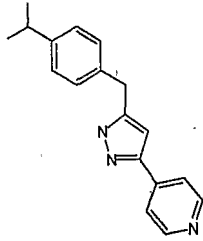
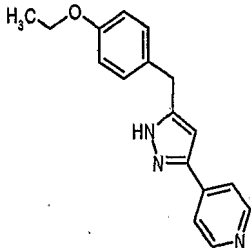
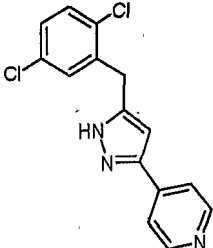
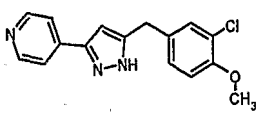
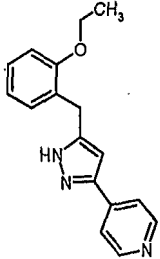
62		3-chloro-4-[5-(4-ethylbenzyl)-1H-pyrazol-3-yl]pyridine	(500 MHz, DMSO-d ₆) δ ppm 8.65 (s, 1 H), 8.50 (d, J=5.22 Hz, 1 H), 7.84 (d, J=4.94 Hz, 1 H), 7.11 - 7.21 (m, 4 H), 6.75 (s, 1 H), 3.99 (s, 2 H), 2.68 (s, 2 H), 1.10 - 1.18 (m, 3 H)
63		3-chloro-4-[5-(2,5-dimethoxybenzyl)-1H-pyrazol-3-yl]pyridine	(500 MHz, DMSO-d ₆) δ ppm 8.65 (s, 1 H), 8.50 (d, J=5.22 Hz, 1 H), 7.85 (d, J=5.22 Hz, 1 H), 6.92 (d, J=8.52 Hz, 1 H), 6.75 - 6.82 (m, 2 H), 6.69 (s, 1 H), 3.94 (s, 2 H), 3.75 (s, 3 H), 3.63 - 3.72 (m, 3 H).
64		3-chloro-4-[5-(4-isopropylbenzyl)-1H-pyrazol-3-yl]pyridine	(500 MHz, DMSO-d ₆) δ ppm 8.65 (s, 1 H), 8.50 (d, J=4.94 Hz, 1 H), 7.84 (d, J=4.94 Hz, 1 H), 7.21 (s, 1 H), 7.19 (d, J=3.30 Hz, 3 H), 7.14 (s, 1 H), 6.76 (s, 1 H), 3.99 (s, 2 H), 2.84 (d, J=6.32 Hz, 1 H), 1.17 (d, J=6.87 Hz, 6 H)
65		4-[5-(2-methoxybenzyl)-1H-pyrazol-3-yl]pyridine	(500 MHz, DMSO-d ₆) δ ppm 8.65 - 8.80 (m, 2 H), 8.14 (s, 2 H), 7.20 - 7.30 (m, 1 H), 7.15 (d, J=7.69 Hz, 1 H), 7.01 (d, J=7.97 Hz, 1 H), 6.90 (t, J=7.42 Hz, 1 H), 6.78 (s, 1 H), 3.98 (s, 2 H), 3.81 (s, 3 H)
66		3-chloro-4-[5-(2,4-dimethylbenzyl)-1H-pyrazol-3-yl]pyridine	(500 MHz, DMSO-d ₆) δ ppm 8.65 (s, 1 H), 8.50 (d, J=5.22 Hz, 1 H), 7.84 (d, J=4.67 Hz, 1 H), 7.06 (d, J=7.97 Hz, 1 H), 6.94 - 7.01 (m, 2 H), 6.62 (s, 1 H), 3.96 (s, 2 H), 2.24 (d, J=4.40 Hz, 6 H)

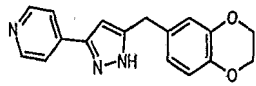
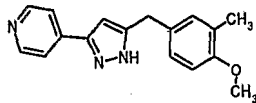
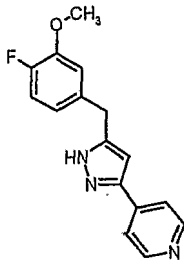
67		4-[5-(3-bromo-4-methoxybenzyl)-1H-pyrazol-3-yl]-3-chloropyridine	(500 MHz, DMSO-d ₆) δ ppm 8.66 (s, 1 H), 8.50 (d, J=4.94 Hz, 1 H), 7.84 (d, J=5.22 Hz, 1 H), 7.50 (d, J=1.65 Hz, 1 H), 7.27 (d, J=6.32 Hz, 1 H), 7.06 (d, J=8.52 Hz, 1 H), 6.77 (s, 1 H), 3.98 (s, 2 H), 3.81 (s, 4 H).
68		3-chloro-4-[5-(2,6-difluorobenzyl)-1H-pyrazol-3-yl]pyridine	(500 MHz, DMSO-d ₆) δ ppm 8.66 (s, 1 H), 8.50 (d, J=5.22 Hz, 1 H), 7.80 (d, J=5.22 Hz, 1 H), 7.39 (s, 1 H), 7.12 (t, J=7.97 Hz, 2 H), 6.64 (s, 1 H), 4.07 (s, 2 H).
69		4-[5-(3,4-dimethoxybenzyl)-1H-pyrazol-3-yl]pyridine	(500 MHz, DMSO-d ₆) δ ppm 8.75 (d, J=6.59 Hz, 2 H), 8.17 (s, 2 H), 6.90 (s, 1 H), 6.88 (d, J=4.12 Hz, 1 H), 6.79 (s, 2 H), 3.97 (s, 2 H), 3.73 (d, J=12.36 Hz, 6 H).
70		4-[5-(4-methoxybenzyl)-1H-pyrazol-3-yl]pyridine	(500 MHz, DMSO-d ₆) δ ppm 8.75 (d, J=6.59 Hz, 2 H), 8.18 (s, 2 H), 7.20 (d, J=8.24 Hz, 2 H), 6.89 (d, J=8.79 Hz, 2 H), 6.87 (s, 1 H), 3.97 (s, 2 H), 3.72 (s, 3 H).
71		3-chloro-4-[5-(2-ethoxybenzyl)-1H-pyrazol-3-yl]pyridine	(500 MHz, DMSO-d ₆) δ ppm 8.65 (s, 1 H), 8.49 (d, J=5.22 Hz, 1 H), 7.85 (d, J=4.94 Hz, 1 H), 7.15 - 7.23 (m, 2 H), 6.97 (d, J=8.24 Hz, 1 H), 6.88 (t, J=7.42 Hz, 1 H), 6.70 (s, 1 H), 4.05 (q, J=7.05 Hz, 2 H), 3.97 (s, 2 H), 1.34 (t, J=7.00 Hz, 3 H).

72		3-chloro-4-[5-(4-fluoro-3-methoxybenzyl)-1H-pyrazol-3-yl]pyridine	(500 MHz, DMSO-d ₆) δ ppm 8.66 (s, 1 H), 8.51 (d, J=4.94 Hz, 1 H), 7.84 (d, J=5.22 Hz, 1 H), 7.09 - 7.17 (m, 2 H), 6.80 - 6.85 (m, 1 H), 6.78 (s, 1 H), 4.01 (s, 2 H), 3.82 (s, 3 H)
73		4-[5-(2,4-dimethoxybenzyl)-1H-pyrazol-3-yl]pyridine	(500 MHz, DMSO-d ₆) δ ppm 8.72 (s, 1 H) 7.70 (d, J=8.79 Hz, 1 H) 6.63 - 6.59 (m, 2H) 6.56 - 6.58 (m, 3 H) 3.82 (s, 3 H) 3.81 (s, 3 H) 3.74 (s, 2 H)
74		4-[5-(4-methylbenzyl)-1H-pyrazol-3-yl]pyridine	(500 MHz, DMSO-d ₆) δ ppm 8.73 (d, J=6.32 Hz, 2 H), 8.14 (s, 2 H), 7.11 - 7.19 (m, 4 H), 6.85 (s, 1 H), 3.99 (s, 2 H), 2.27 (s, 3 H)
75		4-[5-(3-methoxybenzyl)-1H-pyrazol-3-yl]pyridine	(500 MHz, DMSO-d ₆) δ ppm 8.72 (s, 2 H), 8.12 (s, 2 H), 7.21 - 7.26 (m, 1 H), 6.88 (s, 3 H), 6.81 (s, 1 H), 4.01 (s, 2 H), 3.74 (s, 3 H).
76		4-[5-(2-fluorobenzyl)-1H-pyrazol-3-yl]pyridine	(500 MHz, DMSO-d ₆) δ ppm 8.76 (s, 2 H) 8.22 (s, 2 H) 7.35 (s, 2 H) 7.17 - 7.22 (m, 2 H) 6.88 (s, 1 H) 4.08 (s, 2 H)

77		4-[5-(4-ethylbenzyl)-1H-pyrazol-3-yl]pyridine	(500 MHz, DMSO-d6) δ ppm 8.73 (d, J=6.32 Hz, 2 H), 8.14 (s, 2 H), 7.14 - 7.23 (m, 4 H), 6.87 (s, 1 H), 4.00 (s, 2 H), 2.68 (s, 2 H), 1.15 (t, J=7.55 Hz, 3 H)
78		4-[5-(3-methylbenzyl)-1H-pyrazol-3-yl]pyridine	(500 MHz, DMSO-d6) δ ppm 8.74 (d, J=6.04 Hz, 2 H) 8.16 (d, J=4.94 Hz, 2 H) 7.21 (t, J=7.42 Hz, 1 H) 7.04 - 7.11 (m, 3 H) 6.88 (s, 1 H) 4.00 (s, 2 H)
79		4-[5-(2,5-dimethoxybenzyl)-1H-pyrazol-3-yl]pyridine	(500 MHz, DMSO-d6) δ ppm 8.72 (d, J=6.32 Hz, 2 H) 8.13 (s, 2 H) 6.92 (d, J=8.79 Hz, 1 H) 6.75 - 6.82 (m, 3 H) 3.95 (s, 3 H) 3.75 (s, 3 H) 3.68 (s, 2 H)
80		4-[5-(5-bromo-2-methoxybenzyl)-1H-pyrazol-3-yl]pyridine	(500 MHz, DMSO-d6) δ ppm 8.73 (d, J=6.32 Hz, 2 H) 8.14 (s, 2 H) 7.42 (m, 1 H) 7.32 (s, 1 H) 6.99 (d, J=8.79 Hz, 1 H) 6.81 (s, 1 H) 3.97 (s, 2 H) 3.81 (s, 3 H)
81		4-[5-(2,5-dimethylbenzyl)-1H-pyrazol-3-yl]pyridine	(500 MHz, DMSO-d6) δ ppm 8.73 (d, J=6.32 Hz, 2 H) 8.15 (s, 2 H) 7.07 (d, J=7.42 Hz, 1 H) 6.95 - 7.02 (m, 2 H) 6.77 (s, 1 H) 3.97 (s, 2 H) 2.23 (s, 6 H)

82		4-[5-(3-bromo-4-methoxybenzyl)-1H-pyrazol-3-yl]pyridine	(500 MHz, DMSO-d6) δ ppm 8.73 (d, J=6.04 Hz, 2 H) 8.13 (s, 2 H) 7.49 (s, 1 H) 7.25 (d, J=1.92 Hz, 1 H) 7.07 (d, J=8.52 Hz, 1 H) 6.87 (s, 1 H) 3.99 (s, 2 H) 3.81 (s, 3 H)
83		4-[5-(2-bromo-4,5-dimethoxybenzyl)-1H-pyrazol-3-yl]pyridine	(500 MHz, DMSO-d6) δ ppm 8.73 (s, 2 H) 8.13 (s, 2 H) 7.14 (s, 1 H) 7.08 (s, 1 H) 6.76 (s, 1 H) 4.07 (s, 2 H) 3.76 (s, 6 H)
84		4-[5-(2,6-dimethoxybenzyl)-1H-pyrazol-3-yl]pyridine	(500 MHz, DMSO-d6) δ ppm 8.70 (d, J=6.04 Hz, 2 H) 8.13 (s, 2 H) 7.23 (s, 1 H) 6.68 (d, J=8.52 Hz, 2 H) 6.58 (s, 1 H) 3.94 (s, 2 H) 3.79 (s, 6 H)
85		4-[5-(3-ethoxybenzyl)-1H-pyrazol-3-yl]pyridine	(500 MHz, DMSO-d6) δ ppm 8.74 (s, 2 H) 8.14 (s, 2 H) 7.22 (t, J=7.97 Hz, 1 H) 6.89 (s, 1 H) 6.80 - 6.86 (m, 2 H) 6.78 (s, 1 H) 3.95 - 4.04 (m, 4 H) 1.30 (t, J=7.00 Hz, 3 H)
86		4-[5-(3,5-dimethoxybenzyl)-1H-pyrazol-3-yl]pyridine	(500 MHz, DMSO-d6) δ ppm 8.73 (d, J=6.04 Hz, 2 H) 8.14 (s, 2 H) 6.89 (s, 1 H) 6.46 (d, J=1.92 Hz, 2 H) 6.37 (s, 1 H) 3.96 (s, 2 H) 3.72 (s, 6 H)

87		4-[5-(4-isopropylbenzyl)-1H-pyrazol-3-yl]pyridine	(500 MHz, DMSO-d ₆) δ ppm 8.73 (d, J=6.59 Hz, 2 H) 8.14 (s, 2 H) 7.19 (s, 4 H) 6.89 (s, 1 H) 4.00 (s, 2 H) 2.79 - 2.88 (m, 1 H) 1.11 - 1.19 (m, 6 H)
88		4-[5-(4-ethoxybenzyl)-1H-pyrazol-3-yl]pyridine	(500 MHz, DMSO-d ₆) δ ppm 8.71 (s, 2 H) 8.10 (s, 2 H) 7.18 (d, J=8.52 Hz, 2 H) 6.87 (d, J=8.24 Hz, 2 H) 6.82 (s, 1 H) 3.93 - 4.01 (m, 4 H) 1.30 (t, J=6.87 Hz, 3 H)
89		4-[5-(2,5-dichlorobenzyl)-1H-pyrazol-3-yl]pyridine	(500 MHz, DMSO-d ₆) δ ppm 8.74 (d, J=6.04 Hz, 2 H) 8.14 (s, 2 H) 7.47 - 7.55 (m, 2 H) 7.38 - 7.43 (m, 1 H) 6.85 (s, 1 H) 4.16 (s, 2 H)
90		4-[5-(3-chloro-4-methoxybenzyl)-1H-pyrazol-3-yl]pyridine	(500 MHz, DMSO-d ₆) δ ppm 8.73 (d, J=6.32 Hz, 2 H) 8.13 (s, 2 H) 7.34 (s, 1 H) 7.22 (dd, J=8.38, 2.06 Hz, 1 H) 7.10 (d, J=8.24 Hz, 1 H) 6.87 (s, 1 H) 3.99 (s, 2 H) 3.82 (s, 3 H)
91		4-[5-(2-ethoxybenzyl)-1H-pyrazol-3-yl]pyridine	(500 MHz, DMSO-d ₆) δ ppm 8.72 (d, J=6.32 Hz, 2 H) 8.13 (s, 2 H) 7.21 (s, 1 H) 7.15 (d, J=7.69 Hz, 1 H) 6.98 (d, J=8.52 Hz, 1 H) 6.87 - 6.92 (m, 1 H) 6.77 (s, 1 H) 4.05 (q, J=6.87 Hz, 2 H) 3.98 (s, 2 H) 1.33 (t, J=6.87 Hz, 3 H)

92		4-[5-(2,3-dihydro-14-benzodioxin-6-ylmethyl)-1H-pyrazol-3-yl]pyridine	(500 MHz, DMSO-d ₆) δ ppm 8.74 (d, J=1.37 Hz, 1 H) 8.73 (s, 1 H) 8.14 (s, 2 H) 6.86 (s, 1 H) 6.76 - 6.81 (m, 2 H) 6.71 - 6.74 (m, 1 H) 4.20 (s, 4 H) 3.91 (s, 2 H)
93		4-[5-(4-methoxy-3-methylbenzyl)-1H-pyrazol-3-yl]pyridine	(500 MHz, DMSO-d ₆) δ ppm 8.74 (s, 2 H) 8.14 (s, 2 H) 7.03 - 7.08 (m, 2 H) 6.87 (d, J=8.24 Hz, 1 H) 6.84 (s, 1 H) 3.93 (s, 2 H) 3.75 (s, 3 H) 2.12 (s, 3 H)
94		4-[5-(4-fluoro-3-methoxybenzyl)-1H-pyrazol-3-yl]pyridine	(500 MHz, DMSO-d ₆) δ ppm 8.73 (d, J=6.0 Hz, 2 H) 8.12 (s, 2 H) 7.11 - 7.18 (m, 2 H) 6.87 (s, 1 H) 6.82 (s, 1 H) 4.02 (s, 2 H) 3.83 (s, 3 H)

Example 95: In vitro activity data for Examples 1 to 94**1. Determination of compound K_{iapp}**

A determination of the K_{iapp} of the compounds of the invention against recombinant CYP3A4 enzyme was performed as follows. The assay was performed in a 100mM sodium phosphate buffer pH 7.0, 5 mM TCEP and containing 2 % dimethylformamide (final concentration) upon addition of substrate and inhibitor. A typical reaction for the determination of K_{iapp} values was carried at room temperature in a solid black Costar u-bottom 96-well polypropylene plate. In each well, recombinant CYP3A4 enzyme (5.5 nM or 8 nM, final concentration depending on the commercial source of the enzyme) was pre-incubated in the presence of the inhibitor for at least 30 minutes in the assay buffer. When pre-incubation was completed (~ 30 min), the reaction was initiated by adding NADPH (200 uM, final concentration), and 7-benzyloxy-4-(trifluoromethyl)-coumarin (BFC) (5 uM, final concentration). The oxidation of the coumarin substrate was recorded by a 96-well plate reader POLARstar (BMG LABTECH, Offenburg, Germany).

The initial reaction velocities were measured during the first 5 min of the reaction when the release of the fluorescent product is linear with time, in the absence and in the presence of various concentrations of inhibitors. For non-partial & partial inhibitors, the

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K_{iapp} values were determined by using the equation for tight-binding inhibitor developed by Morrison, JF (Morrison JF. *Biochim Biophys Acta*. 1969, 185: 269-86) and by Szedlaseck SE et al. (Szedlaseck, S.E., Ostafe, V., Serban, M., and Vlad, M.O. *Biochem. J.* 1988, 254:311-312), respectively.

5 The fluorescent substrate BFC was purchased from Sigma (St Louis, MO). Two commercial sources of recombinant enzymes were used in this study: recombinant CYP3A4 - b5 enzyme (Baculosomes[®]) was purchased from Invitrogen (Carlsbad, CA) and the recombinant CYP3A4 + b5 enzyme (Supersomes[®]) was purchased from BD Biosciences (Woburn, MA).

10 **2. Determination of IC_{50} against CYP3A4 by measurement of inhibition of testosterone metabolism**

This assay was performed using a standard 96 well plate design. IC_{50} values are calculated from the percent inhibition determined for each test compound at 6 concentrations (for example: 750, 250, 83.3, 27.8, 9.3 and 3.1 nM). The incubation
15 substrate mix contains 25 μ M testosterone, 0.1 mg/mL human liver microsomes, 1 mM NADPH, and potassium phosphate buffer (100 mM, pH 7.4). Quantitation of metabolite peak area ratio against an internal standard is determined by LC-MS/MS analysis. The production of 6- β -OH-testosterone from testosterone metabolism is determined after incubation for eight minutes by comparison to a standard curve generated for the
20 metabolite

Samples were analyzed in the MRM mode using a Sciex API 3000 mass spectrometer (Applied Biosystems, Foster City, CA) with a Paradigm MS4 binary pump (Michrom BioResources Inc., Auburn, CA) and a LEAP CTC PAL autosampler (LEAP Technologies, Carrboro, NC). A Phenomenex Synergi, 4 μ , Polar-RP, 10 X 2.0 mm
25 column (Phenomenex, Torrance, CA) was used for separation with a mobile phase composition of: 0.1% formic acid in water (A) and: 0.1% formic acid in methanol (B). The following gradient was used:

Time (minutes)	%B	Flow rate (mL/min)
0.0	0	0.8
0.1	95	0.8
0.55	95	0.8
0.6	0	0.8

The sample injection volume was 10 μ L and flow was split post-column with 0.4
30 mL/min going to the mass spectrometer. Analysis was performed using the following API 3000 mass spectrometer settings:
Instrument settings

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Ionization Method	ESI, positive
Interface	Turbo-ionspray
Desolvation Temperature (TEM)	450°C
Ionspray Voltage (IS)	5000
Curtain Gas (CUR)	15
Nebulizer (NEB)	10
Collision Gas (CAD)	6
Entrance Potential (EP)	10

Compound		Transition (m/z)	DP	FP	CE	CXP	Ret. Time (min)
6-OH-Testosterone	Analyte	305.4>269.2	56	170	21	18	0.44

3. Determination of IC₅₀ against CYP3A4 by measurement of inhibition of midazolam metabolism

5 This assay was performed using a standard 96 well plate design. IC₅₀s are calculated from the percent inhibition determined for each test compound at 6 concentrations (for example: 750, 250, 83.3, 27.8, 9.3 and 3.1 nM). The incubation substrate mix contains 2 µM midazolam, 0.1 mg/mL human liver microsomes, 1 mM NADPH, and potassium phosphate buffer (100 mM, pH 7.4). Quantitation of metabolite peak area ratio against internal standard is determined by LC-MS/MS analysis. The production of 1-hydroxymidazolam from midazolam metabolism is determined after incubation for eight minutes by comparison to a standard curve generated for the metabolite.

15 Samples were analyzed in the MRM mode using a Sciex API 3000 mass spectrometer (Applied Biosystems, Foster City, CA) with a Paradigm MS4 binary pump (Michrom BioResources Inc., Auburn, CA) and a LEAP CTC PAL autosampler (LEAP Technologies, Carrboro, NC). A Phenomenex Synergi, 4 µ, Polar-RP, 10 X 2.0 mm column (Phenomenex, Torrance, CA) was used for separation with a mobile phase composition of: 0.1% formic acid in water (A) and: 0.1% formic acid in methanol (B). The following gradient was used:

Time (minutes)	%B	Flow rate (mL/min)
0.0	0	0.8
0.1	95	0.8
0.55	95	0.8
0.6	0	0.8

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The sample injection volume was 10 μ L and flow was split post-column with 0.4 mL/min going to the mass spectrometer. Analysis was performed using the following API 3000 mass spectrometer settings:

Instrument settings

Ionization Method	ESI, positive
Interface	Turbo-ionspray
Desolvation Temperature (TEM)	450°C
Ionspray Voltage (IS)	5000
Curtain Gas (CUR)	15
Nebulizer (NEB)	10
Collision Gas (CAD)	6
Entrance Potential (EP)	10

5

Compound		Transition (m/z)	DP	FP	CE	CXP	Ret. time
1-hydroxymidazolam	Analyte	342.2>203.1	46	130	29	18	0.44

Example No.	IC ₅₀ , μ M (HLM, testosterone)	IC ₅₀ , μ M (HLM, midazolam)	Ki _{app} , μ M (Baculosomes®, BFC)	Ki _{app} , μ M (Supersomes®, BFC)
1	<0.00300	0.018	0.0105	0.002
2	<0.0220	0.077	0.0557	0.0064
3	0.03		0.0509	
5	0.016		0.0215	
6	0.028		0.286	
7	>2.03	>3.00	0.384	0.356
8	0.431	>0.750	0.389	0.181
11	0.73			
12	0.094			
13	>0.750		>1.00	
16	0.019	0.0335	0.00573	0.00101
17	0.029		0.124	
18			0.0196	0.0107
19			0.0456	0.0171
20			0.0496	0.0183
21	<0.00300	0.037	0.0043	0.002
22	0.008	0.051	0.0155	0.0034
23	0.008	0.027	0.0054	0.0024
24			0.205	0.112
25			0.0922	0.0234
26			0.0246	0.0108
27	0.084		0.0638	
28	0.074		0.272	
29	0.021		0.0338	
30	0.045		0.0629	
31	0.084		0.0387	0.0341
32	0.693			

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33	0.038	0.174	0.201	
34	0.735		0.822	
35	0.28		0.422	
36	0.574			
37	0.044		0.0799	
38	2.26			
39	0.169			
40	1.61			
41	1.13		>1.00	
42	1.25		>1.00	
43	>3.00		>1.00	
44	0.945		0.705	
45				
46	0.0783	0.481	>0.768	
47				
48			0.0526	0.122
49			0.0167	0.0155
50			0.0237	0.022
51			0.0087	0.0178
52			0.099	0.177
53			0.0151	0.0199
54			0.0557	0.0311
55			0.0472	0.114
56			0.0876	0.0412
57			0.0525	0.0226
58			0.0256	0.0332
59			0.0725	0.0605
60			0.205	0.137
61			0.0462	0.0211
62			0.059	0.0448
63			0.128	0.112
64			0.0759	0.0585
65			0.0773	0.0194
66			0.0552	0.0176
67			0.024	0.0174
68			0.196	0.164
69			0.17	0.0217
70			0.0602	0.0126
71			0.241	0.0799
72			0.0586	0.0119
73			0.069	0.014
74			0.061	0.0134
75			0.048	0.0159
76			0.215	0.0617
77			0.164	0.012
78			0.0287	0.0191
79			0.0676	0.0201
80	<0.00300	0.045	0.0118	0.0049
81	0.018	0.054	0.0196	0.0048
82	0.009	0.04	0.0127	0.0042
83			0.046	0.0102
84			0.0947	0.0163
85			0.158	0.0459
86			0.141	0.0281

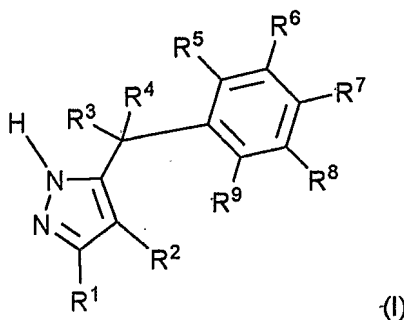
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87			0.0595	0.0178
88			0.155	0.0331
89			0.0334	0.0111
90			0.0273	0.01
91			0.0735	0.0185
92			0.183	0.0605
93	0.009	0.042	0.022	0.0051
94			0.0516	0.0199

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We claim:

1. A compound of formula (I),



wherein:

R^1 is 5 to 6 membered heteroaryl, which is optionally substituted with one or more R^{14} groups;

R^2 is selected from hydrogen, halo, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, $-(CR^{10}R^{11})_t(C_3$ - C_8 cycloalkyl), $-(CR^{10}R^{11})_tOR^{12}$, $-(CR^{10}R^{11})_tN(R^{12}R^{13})$, $-CN$, $-NO_2$, $-CF_3$, $-(CR^{10}R^{11})_tC(O)R^{12}$, $-(CR^{10}R^{11})_tC(O)N(R^{12}R^{13})$, and $-(CR^{10}R^{11})_tC(O)_2R^{12}$;

R^3 and R^4 are each independently selected from hydrogen and C_1 - C_8 alkyl; or

R^3 and R^4 , together with the atom to which they are attached, form a C_3 - C_8 cycloalkyl group;

R^5 , R^6 , R^7 , R^8 , and R^9 are each independently selected from hydrogen, halo, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, $-(CR^{10}R^{11})_t(C_3$ - C_8 cycloalkyl), $-(CR^{10}R^{11})_tOR^{12}$, $-(CR^{10}R^{11})_tN(R^{12}R^{13})$, $-CN$, $-NO_2$, $-CF_3$, $-(CR^{10}R^{11})_tC(O)R^{12}$, $-(CR^{10}R^{11})_tC(O)N(R^{12}R^{13})$, and $-(CR^{10}R^{11})_tC(O)_2R^{12}$; or

R^5 and R^6 , or R^6 and R^7 , or R^7 and R^8 , or R^8 and R^9 , together with the atoms to which they are attached form a 3 to 10 membered heterocyclyl group or a 5 to 10 membered heteroaryl group;

each R^{10} and R^{11} is independently selected from hydrogen and C_1 - C_8 alkyl;

each R^{12} and R^{13} is independently selected from hydrogen, C_1 - C_8 alkyl, $-(CR^{10}R^{11})_t(C_3$ - C_8 cycloalkyl), $-(CR^{10}R^{11})_t(3$ to 10 membered heterocyclyl), $-(CR^{10}R^{11})_t(5$ to 10 membered heteroaryl) and $-(CR^{10}R^{11})_t(C_6$ - C_{10} aryl), wherein each of said C_3 - C_8 cycloalkyl, 3 to 10 membered heterocyclyl, 5 to 10 membered heteroaryl, and C_6 - C_{10} aryl is optionally substituted with one or more R^{15} groups; or

R^{12} and R^{13} , together with the atom to which they are attached, form a 3 to 10 membered heterocyclyl group, which is optionally substituted with one or more R^{15} groups;

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each R^{14} is independently selected from C_1 - C_8 alkyl, C_3 - C_8 cycloalkyl, C_6 - C_{10} aryl, 3 to 10 membered heterocyclyl, 5 to 10 membered heteroaryl, -CN, halo, $-(CR^{10}R^{11})_tOR^{15}$, $-(CR^{10}R^{11})_tC(O)N(R^{15}R^{16})$, and $-(CR^{10}R^{11})_tC(O)R^{15}$;

each R^{15} and R^{16} is independently selected from hydrogen, C_1 - C_8 alkyl, 3 to 10 membered heterocyclyl, and 5 to 10 membered heteroaryl; or

R^{15} and R^{16} , together with the atom to which they are attached, form a 3 to 10 membered heterocyclyl group; and

each t is independently 0, 1, 2, 3, or 4; or

a pharmaceutically acceptable salt or solvate thereof, provided the compound of formula (I) is not 4-(5-benzyl-1H-pyrazol-3-yl)pyridine, 3-(5-benzyl-1H-pyrazol-3-yl)pyridine, or 2-(5-(1-(4-fluorophenyl)cyclopropyl)-1H-pyrazol-3-yl)pyridine, or any salts thereof.

2. A compound according to claim 1, wherein R^1 is selected from pyridyl, imidazolyl, pyrimidinyl, pyrazinyl, pyridazinyl, imidazolyl, and triazolyl, each of which is optionally substituted with one or more R^{14} groups.

3. A compound according to claim 2, wherein R^1 is selected from pyridyl, pyrimidinyl, and imidazolyl, each of which is optionally substituted with one or more R^{14} groups.

4. A compound according to claim 3, wherein R^1 is selected from 2-pyridyl, 3-pyridyl, or 4-pyridyl, each of which is optionally substituted with one or more R^{14} groups.

5. A compound according to claim 4, wherein R^1 is 4-pyridyl, which is optionally substituted with one or more R^{14} groups.

6. A compound according to any one of claims 1 to 5, wherein R^1 is optionally substituted with one or more substituents independently selected from C_1 - C_8 alkyl, halo, -CN, $-(CR^{10}R^{11})_tOR^{15}$, and $-(CR^{10}R^{11})_tC(O)N(R^{15}R^{16})$.

7. A compound according to any one of claims 1 to 5, wherein R^1 is optionally substituted with one or more substituents independently selected from $-CH_3$, $-CH_2CH_3$, fluoro, chloro, bromo, -CN, -OH, $-OCH_3$, and $-C(O)N(C_1-C_8 \text{ alkyl})_2$.

8. A compound according to any one of claims 1 to 5, wherein R^1 is optionally substituted with one or more substituents independently selected from $-CH_3$, $-CH_2CH_3$, fluoro, chloro, -CN, -OH, and $-OCH_3$.

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9. A compound according to any one of claims 1 to 5, wherein R¹ is substituted with -CH₃, -CH₂CH₃, fluoro, chloro, -CN, -OH, or -OCH₃.
- 5 10. A compound according to any one of claims 1 to 9, wherein R⁵, R⁶, R⁷, R⁸, and R⁹ are each independently selected from hydrogen, halo, C₁-C₈ alkyl, -CF₃, -(CR¹⁰R¹¹)_tOR¹², -(CR¹⁰R¹¹)_tN(R¹²R¹³), and -CN.
- 10 11. A compound according to any one of claims 1 to 9, wherein R⁵, R⁶, R⁷, R⁸, and R⁹ are each independently selected from hydrogen, fluoro, chloro, bromo, C₁-C₈ alkyl, -CF₃, -OH, -OCH₃, and -CN.
- 15 12. A compound according to any one of claims 1 to 9, wherein R⁵, R⁶, R⁷, R⁸, and R⁹ are each independently selected from hydrogen, fluoro, chloro, bromo, -CH₃, -CF₃, -OH, -OCH₃, and -CN.
13. A compound according to any of claims 1 to 9, wherein R⁷ is fluoro, and R⁵, R⁶, R⁸, and R⁹ are hydrogen.
- 20 14. A pharmaceutical composition, comprising an effective amount of at least one compound according to any one of claims 1 to 13, and a pharmaceutically acceptable carrier.
- 25 15. A method of inhibiting the metabolism in a mammal of a first compound that is metabolized by cytochrome P450, comprising administering to said mammal said first compound and an effective amount of a second compound, wherein said second compound is selected from those according to any one of claims 1 to 13.