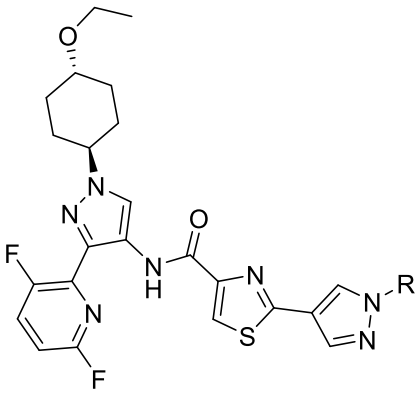
We claim:

1. A compound, having a formula 1



Formula 1

wherein:

R is aliphatic, acyl, heterocyclyl, carboxyl ester, amide, alkyl phosphoramidate, or alkyl phosphate; or

R is H and the compound is a salt.

2. The compound of claim 1, wherein R is alkyl, acyl, carboxyl ester, amide, nonaromatic heterocyclyl, alkyl phosphoramidate, or alkyl phosphate.

3. The compound of claim 1 or claim 2, wherein:

R is C_{1-4}alkyl phosphate, C_{1-4}alkyl phosphoramidate, C_{1-6}alkyl, C_{1-6}acyl, -C(O)O-C_{1-6}aliphatic, -C(O)N(R^b)$_2$, or 5- or 6-membered nonaromatic heterocyclyl; and

each R^b independently is H, unsubstituted C_{1-6}alkyl, C_{1-6}alkyl substituted with -N(R^g)$_2$, carboxyl ester, or 5- or 6-membered nonaromatic heterocyclyl, or two R^b together with the nitrogen to which they are attached form a C_{3-6}nonaromatic heterocyclyl moiety optionally interrupted with one or two –O– or –N(R^g), where R^g is H or C_{1-4}alkyl.

4. The compound of claim 3, wherein:

R is C_{1-6}alkyl optionally substituted with a 5- or 6-membered nonaromatic heterocyclyl, OH, -OC(O)-R^a, -N(R^b)$_2$, -OC(O)-R^c, carboxyl, or a combination thereof;

R^a is 5-membered nonaromatic heterocyclyl, aryl substituted with -CH_2N(R^b)$_2$, C_{3-6}cycloalkyl substituted with carboxyl, C_{1-6}alkoxy, unsubstituted C_{1-6}alkyl, or C_{1-6}alkyl substituted with one or more of N(R^b)$_2$, carboxyl, carboxyl ester, -OC_{1-6}acyl, -NHC(O)(NH_2)C_{1-6}alkyl, or -(OCH_2CH_2)$_{1-8}$N(R^b)$_2$; and

-OC(O)-R^c is derived from an amino acid where the -OC(O)- moiety of -OC(O)-R^c corresponds to an acid moiety on the amino acid and R^c comprises -$N(R^b)_2$ or a nitrogen-containing nonaromatic heterocyclyl.

5. The compound of claim 4, wherein the amino acid is a naturally occurring amino acid.

6. The compound of claim 4 wherein the amino acid is selected from glycine, valine, alanine, leucine, isoleucine, methionine, phenylalanine, tryptophan, tyrosine, serine, threonine, asparagine, glutamine, arginine, histidine, lysine, aspartic acid, glutamic acid, cysteine, or proline.

7. The compound of claim 3, wherein:

R is C_{1-6}acyl moiety optionally substituted with -C(O)O-C_{1-4}alkyl, -C(O)O-C_{1-4}alkyl-$N(R^b)_2$, $N(R^b)_2$, -NHC(O)C_{1-4}alkyl, or a combination thereof;

R is 5- or 6-membered nonaromatic heterocyclyl moiety optionally substituted with hydroxyl, hydroxymethyl, or a combination thereof;

R is -C(O)O-C_{1-6}alkyl optionally substituted with -OC(O)C_{1-4}alkyl or $N(R^b)_2$; or

R is -C(O)O-C_{3-6}cycloalkyl optionally substituted with C_{1-4}alkyl.

8. The compound of claim 1, wherein R is H and the salt is a hydrochloride, citrate, hemicitrate, hemitartrate, tartrate, benzene sulfonate, mesylate, sodium, hemisuccinate, or succinate salt.

9. The compound of claim 1 wherein R is alkyl phosphate or a salt thereof.

10. The compound of claim 9, wherein the compound is an alkali metal salt, an alkaline earth metal salt, an ammonium salt, an amino acid salt, an amino sugar salt, or a tris salt.

11. The compound of claim 9 or claim 10, wherein the compound is a mono-salt, or a di-salt.

12. The compound of any one of claims 9-11, wherein the alkyl phosphate is a mono-or di-sodium salt, mono-or di-potassium salt, calcium salt, magnesium salt, arginine salt, lysine salt, mono- or di-tris salt, ammonium salt, choline salt, or meglumine salt.

13. The compound of claim 1, selected from:

I-2: (4-(4-((3-(3,6-difluoropyridin-2-yl)-1-((1r,4r)-4-ethoxycyclohexyl)-1H-pyrazol-4-yl)carbamoyl)thiazol-2-yl)-1H-pyrazol-1-yl)methyl dihydrogen phosphate;

I-3: di-tert-butyl ((4-(4-((3-(3,6-difluoropyridin-2-yl)-1-((1r,4r)-4-ethoxycyclohexyl)-1H-pyrazol-4-yl)carbamoyl)thiazol-2-yl)-1H-pyrazol-1-yl)methyl) phosphate;

I-4: (4-(4-((3-(3,6-difluoropyridin-2-yl)-1-((1r,4r)-4-ethoxycyclohexyl)-1H-pyrazol-4-yl)carbamoyl)thiazol-2-yl)-1H-pyrazol-1-yl)methyl phosphate disodium salt;

I-5: N-(3-(3,6-difluoropyridin-2-yl)-1-((1r,4r)-4-ethoxycyclohexyl)-1H-pyrazol-4-yl)-2-(1-methyl-1H-pyrazol-4-yl)thiazole-4-carboxamide;

I-6: 2-(1-(acetyl-L-leucyl)-1H-pyrazol-4-yl)-N-(3-(3,6-difluoropyridin-2-yl)-1-((1r,4r)-4-ethoxycyclohexyl)-1H-pyrazol-4-yl)thiazole-4-carboxamide;

I-7: 1-methylcyclopropyl 4-(4-((3-(3,6-difluoropyridin-2-yl)-1-((1r,4r)-4-ethoxycyclohexyl)-1H-pyrazol-4-yl)carbamoyl)thiazol-2-yl)-1H-pyrazole-1-carboxylate;

I-8: 1-(isobutyryloxy)ethyl 4-(4-((3-(3,6-difluoropyridin-2-yl)-1-((1r,4r)-4-ethoxycyclohexyl)-1H-pyrazol-4-yl)carbamoyl)thiazol-2-yl)-1H-pyrazole-1-carboxylate;

I-9: N-(3-(3,6-difluoropyridin-2-yl)-1-((1r,4r)-4-ethoxycyclohexyl)-1H-pyrazol-4-yl)-2-(1-((5-methyl-2-oxo-1,3-dioxol-4-yl)methyl)-1H-pyrazol-4-yl)thiazole-4-carboxamide;

I-10: 2-morpholinoethyl 4-(4-((3-(3,6-difluoropyridin-2-yl)-1-((1r,4r)-4-ethoxycyclohexyl)-1H-pyrazol-4-yl)carbamoyl)thiazol-2-yl)-1H-pyrazole-1-carboxylate;

I-11: N-(3-(3,6-difluoropyridin-2-yl)-1-((1r,4r)-4-ethoxycyclohexyl)-1H-pyrazol-4-yl)-2-(1H-pyrazol-4-yl)thiazole-4-carboxamide hemi-tartrate salt;

I-12: N-(3-(3,6-difluoropyridin-2-yl)-1-((1r,4r)-4-ethoxycyclohexyl)-1H-pyrazol-4-yl)-2-(1-(morpholine-4-carbonyl)-1H-pyrazol-4-yl)thiazole-4-carboxamide;

I-13: N-(3-(3,6-difluoropyridin-2-yl)-1-((1r,4r)-4-ethoxycyclohexyl)-1H-pyrazol-4-yl)-2-(1-((3-morpholinopropyl)carbamoyl)-1H-pyrazol-4-yl)thiazole-4-carboxamide;

I-14: N-(3-(3,6-difluoropyridin-2-yl)-1-((1r,4r)-4-ethoxycyclohexyl)-1H-pyrazol-4-yl)-2-(1-((3-(dimethylamino)propyl)carbamoyl)-1H-pyrazol-4-yl)thiazole-4-carboxamide;

I-15: 3-morpholinopropyl 4-(4-((3-(3,6-difluoropyridin-2-yl)-1-((1r,4r)-4-ethoxycyclohexyl)-1H-pyrazol-4-yl)carbamoyl)thiazol-2-yl)-1H-pyrazole-1-carboxylate;

I-16: (4-(4-((3-(3,6-difluoropyridin-2-yl)-1-((1r,4r)-4-ethoxycyclohexyl)-1H-pyrazol-4-yl)carbamoyl)thiazol-2-yl)-1H-pyrazol-1-yl)methyl L-valinate hydrochloride;

I-17: (4-(4-((3-(3,6-difluoropyridin-2-yl)-1-((1r,4r)-4-ethoxycyclohexyl)-1H-pyrazol-4-yl)carbamoyl)thiazol-2-yl)-1H-pyrazol-1-yl)methyl L-prolinate hydrochloride;

I-18: 1-(4-(4-((3-(3,6-difluoropyridin-2-yl)-1-((1r,4r)-4-ethoxycyclohexyl)-1H-pyrazol-4-yl)carbamoyl)thiazol-2-yl)-1H-pyrazol-1-yl)ethyl dihydrogen phosphate;

I-19: (4-(4-((3-(3,6-difluoropyridin-2-yl)-1-((1r,4r)-4-ethoxycyclohexyl)-1H-pyrazol-4-yl)carbamoyl)thiazol-2-yl)-1H-pyrazol-1-yl)methyl glycinate hydrochloride;

I-20: 1-(4-(4-((3-(3,6-difluoropyridin-2-yl)-1-((1r,4r)-4-ethoxycyclohexyl)-1H-pyrazol-4-yl)carbamoyl)thiazol-2-yl)-1H-pyrazol-1-yl)ethyl phosphate disodium salt;

I-21: (4-(4-((3-(3,6-difluoropyridin-2-yl)-1-((1r,4r)-4-ethoxycyclohexyl)-1H-pyrazol-4-yl)carbamoyl)thiazol-2-yl)-1H-pyrazol-1-yl)methyl (S)-2-amino-3,3-dimethylbutanoate hydrochloride;

I-22: 2-(1-acetyl-1H-pyrazol-4-yl)-N-(3-(3,6-difluoropyridin-2-yl)-1-((1r,4r)-4-ethoxycyclohexyl)-1H-pyrazol-4-yl)thiazole-4-carboxamide;

I-23: (4-(4-((3-(3,6-difluoropyridin-2-yl)-1-((1r,4r)-4-ethoxycyclohexyl)-1H-pyrazol-4-yl)carbamoyl)thiazol-2-yl)-1H-pyrazol-1-yl)methyl 2-amino-2-methylpropanoate hydrochloride;

I-24: 4-((4-(4-((3-(3,6-difluoropyridin-2-yl)-1-((1r,4r)-4-ethoxycyclohexyl)-1H-pyrazol-4-yl)carbamoyl)thiazol-2-yl)-1H-pyrazol-1-yl)methoxy)-4-oxobutanoic acid;

I-25: methyl 4-(4-(4-((3-(3,6-difluoropyridin-2-yl)-1-((1r,4r)-4-ethoxycyclohexyl)-1H-pyrazol-4-yl)carbamoyl)thiazol-2-yl)-1H-pyrazol-1-yl)-4-oxobutanoate;

I-26: N-(3-(3,6-difluoropyridin-2-yl)-1-((1r,4r)-4-ethoxycyclohexyl)-1H-pyrazol-4-yl)-2-(1-(2-morpholinoacetyl)-1H-pyrazol-4-yl)thiazole-4-carboxamide;

I-27: N-(3-(3,6-difluoropyridin-2-yl)-1-((1r,4r)-4-ethoxycyclohexyl)-1H-pyrazol-4-yl)-2-(1-(2-hydroxy-3-morpholinopropyl)-1H-pyrazol-4-yl)thiazole-4-carboxamide;

I-28: (4-(4-((3-(3,6-difluoropyridin-2-yl)-1-((1r,4r)-4-ethoxycyclohexyl)-1H-pyrazol-4-yl)carbamoyl)thiazol-2-yl)-1H-pyrazol-1-yl)methyl 2-morpholinoacetate;

I-29: (4-(4-((3-(3,6-difluoropyridin-2-yl)-1-((1r,4r)-4-ethoxycyclohexyl)-1H-pyrazol-4-yl)carbamoyl)thiazol-2-yl)-1H-pyrazol-1-yl)methyl L-valinate;

I-30: (4-(4-((3-(3,6-difluoropyridin-2-yl)-1-((1r,4r)-4-ethoxycyclohexyl)-1H-pyrazol-4-yl)carbamoyl)thiazol-2-yl)-1H-pyrazol-1-yl)methyl L-valinate benzene sulfonate;

I-31: (4-(4-((3-(3,6-difluoropyridin-2-yl)-1-((1r,4r)-4-ethoxycyclohexyl)-1H-pyrazol-4-yl)carbamoyl)thiazol-2-yl)-1H-pyrazol-1-yl)methyl L-valinate mesylate;

I-32: 2-(4-methylpiperazin-1-yl)ethyl 4-(4-(4-((3-(3,6-difluoropyridin-2-yl)-1-((1r,4r)-4-ethoxycyclohexyl)-1H-pyrazol-4-yl)carbamoyl)thiazol-2-yl)-1H-pyrazol-1-yl)-4-oxobutanoate;

I-33: 1-((4-(4-((3-(3,6-difluoropyridin-2-yl)-1-((1r,4r)-4-ethoxycyclohexyl)-1H-pyrazol-4-yl)carbamoyl)thiazol-2-yl)-1H-pyrazol-1-yl)methyl) 4-methyl L-aspartate hydrochloride;

I-34: methyl N-(2-(4-(4-((3-(3,6-difluoropyridin-2-yl)-1-((1r,4r)-4-ethoxycyclohexyl)-1H-pyrazol-4-yl)carbamoyl)thiazol-2-yl)-1H-pyrazol-1-yl)-2-oxoethyl)-N-methylglycinate;

I-35: (4-(4-((3-(3,6-difluoropyridin-2-yl)-1-((1r,4r)-4-ethoxycyclohexyl)-1H-pyrazol-4-yl)carbamoyl)thiazol-2-yl)-1H-pyrazol-1-yl)methyl (S)-2-amino-3,3-dimethylbutanoate;

I-36: (4-(4-((3-(3,6-difluoropyridin-2-yl)-1-((1r,4r)-4-ethoxycyclohexyl)-1H-pyrazol-4-yl)carbamoyl)thiazol-2-yl)-1H-pyrazol-1-yl)methyl (S)-2-amino-3,3-dimethylbutanoate benzene sulfonate;

I-37: (4-(4-((3-(3,6-difluoropyridin-2-yl)-1-((1r,4r)-4-ethoxycyclohexyl)-1H-pyrazol-4-yl)carbamoyl)thiazol-2-yl)-1H-pyrazol-1-yl)methyl 4-(morpholinomethyl)benzoate;

I-38: 4-((4-(4-((3-(3,6-difluoropyridin-2-yl)-1-((1r,4r)-4-ethoxycyclohexyl)-1H-pyrazol-4-yl)carbamoyl)thiazol-2-yl)-1H-pyrazol-1-yl)methyl) 1-methyl L-aspartate hydrochloride;

I-39: (1R,2R)-2-(((4-(4-((3-(3,6-difluoropyridin-2-yl)-1-((1r,4r)-4-ethoxycyclohexyl)-1H-pyrazol-4-yl)carbamoyl)thiazol-2-yl)-1H-pyrazol-1-yl)methoxy)carbonyl)cyclohexane-1-carboxylic acid;

I-40: (4-(4-((3-(3,6-difluoropyridin-2-yl)-1-((1r,4r)-4-ethoxycyclohexyl)-1H-pyrazol-4-yl)carbamoyl)thiazol-2-yl)-1H-pyrazol-1-yl)methyl (S)-2-amino-3,3-dimethylbutanoate mesylate;

I-41: (S)-2-amino-4-((4-(4-((3-(3,6-difluoropyridin-2-yl)-1-((1r,4r)-4-ethoxycyclohexyl)-1H-pyrazol-4-yl)carbamoyl)thiazol-2-yl)-1H-pyrazol-1-yl)methoxy)-4-oxobutanoic acid hydrochloride;

I-42: N-(3-(3,6-difluoropyridin-2-yl)-1-((1r,4S)-4-ethoxycyclohexyl)-1H-pyrazol-4-yl)-2-(1-((2S,3S,4R,5R,6S)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)-1H-pyrazol-4-yl)thiazole-4-carboxamide;

I-43: N-(3-(3,6-difluoropyridin-2-yl)-1-((1r,4R)-4-ethoxycyclohexyl)-1H-pyrazol-4-yl)-2-(1-((2R,3R,4R,5R,6S)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)-1H-pyrazol-4-yl)thiazole-4-carboxamide;

I-44: tert-butyl (1-(4-(4-((3-(3,6-difluoropyridin-2-yl)-1-((1r,4r)-4-ethoxycyclohexyl)-1H-pyrazol-4-yl)carbamoyl)thiazol-2-yl)-1H-pyrazol-1-yl)ethyl) hydrogen phosphate sodium acetate salt;

I-45: (4-(4-((3-(3,6-difluoropyridin-2-yl)-1-((1r,4r)-4-ethoxycyclohexyl)-1H-pyrazol-4-yl)carbamoyl)thiazol-2-yl)-1H-pyrazol-1-yl)methyl isopropyl carbonate;

I-46: (4-(4-((3-(3,6-difluoropyridin-2-yl)-1-((1r,4r)-4-ethoxycyclohexyl)-1H-pyrazol-4-yl)carbamoyl)thiazol-2-yl)-1H-pyrazol-1-yl)methyl di(((isopropoxycarbonyl)oxy)methyl) phosphate;

I-47: 1-((4-(4-((3-(3,6-difluoropyridin-2-yl)-1-((1r,4r)-4-ethoxycyclohexyl)-1H-pyrazol-4-yl)carbamoyl)thiazol-2-yl)-1H-pyrazol-1-yl)methyl) 4-methyl L-aspartate;

I-48: 1-((4-(4-((3-(3,6-difluoropyridin-2-yl)-1-((1r,4r)-4-ethoxycyclohexyl)-1H-pyrazol-4-yl)carbamoyl)thiazol-2-yl)-1H-pyrazol-1-yl)methyl) 4-methyl L-aspartate benzene sulfonate;

I-49: 1-(4-(4-((3-(3,6-difluoropyridin-2-yl)-1-((1r,4r)-4-ethoxycyclohexyl)-1H-pyrazol-4-yl)carbamoyl)thiazol-2-yl)-1H-pyrazol-1-yl)ethyl dihydrogen phosphate tris salt;

I-50: (4-(4-((3-(3,6-difluoropyridin-2-yl)-1-((1r,4r)-4-ethoxycyclohexyl)-1H-pyrazol-4-yl)carbamoyl)thiazol-2-yl)-1H-pyrazol-1-yl)methyl glycinate benzene sulfonate;

I-51: 2-(4-methylpiperazin-1-yl)ethyl 4-(4-(4-((3-(3,6-difluoropyridin-2-yl)-1-((1r,4r)-4-ethoxycyclohexyl)-1H-pyrazol-4-yl)carbamoyl)thiazol-2-yl)-1H-pyrazol-1-yl)-4-oxobutanoate benzene sulfonate;

I-52: 2-(4-methylpiperazin-1-yl)ethyl 4-(4-(4-((3-(3,6-difluoropyridin-2-yl)-1-((1r,4r)-4-ethoxycyclohexyl)-1H-pyrazol-4-yl)carbamoyl)thiazol-2-yl)-1H-pyrazol-1-yl)-4-oxobutanoate succinate salt;

I-53: (2R,3R)-2,3-diacetoxy-4-((4-(4-((3-(3,6-difluoropyridin-2-yl)-1-((1r,4r)-4-ethoxycyclohexyl)-1H-pyrazol-4-yl)carbamoyl)thiazol-2-yl)-1H-pyrazol-1-yl)methoxy)-4-oxobutanoic acid;

I-54: (4-(4-((3-(3,6-difluoropyridin-2-yl)-1-((1r,4r)-4-ethoxycyclohexyl)-1H-pyrazol-4-yl)carbamoyl)thiazol-2-yl)-1H-pyrazol-1-yl)methyl acetate;

I-55: 4-((4-(4-((3-(3,6-difluoropyridin-2-yl)-1-((1r,4r)-4-ethoxycyclohexyl)-1H-pyrazol-4-yl)carbamoyl)thiazol-2-yl)-1H-pyrazol-1-yl)methyl) 1-methyl L-aspartate benzene sulfonate;

I-56: 4-((4-(4-((3-(3,6-difluoropyridin-2-yl)-1-((1r,4r)-4-ethoxycyclohexyl)-1H-pyrazol-4-yl)carbamoyl)thiazol-2-yl)-1H-pyrazol-1-yl)methoxy)-4-oxobutanoic acid tris salt;

I-57: (4-(4-((3-(3,6-difluoropyridin-2-yl)-1-((1r,4r)-4-ethoxycyclohexyl)-1H-pyrazol-4-yl)carbamoyl)thiazol-2-yl)-1H-pyrazol-1-yl)methyl 4-((S)-2-amino-3-methylbutanamido)butanoate hydrochloride;

I-58: N-(3-(3,6-difluoropyridin-2-yl)-1-((1r,4r)-4-ethoxycyclohexyl)-1H-pyrazol-4-yl)-2-(1-(2-hydroxyethyl)-1H-pyrazol-4-yl)thiazole-4-carboxamide;

I-59: 2-(4-(4-((3-(3,6-difluoropyridin-2-yl)-1-((1r,4r)-4-ethoxycyclohexyl)-1H-pyrazol-4-yl)carbamoyl)thiazol-2-yl)-1H-pyrazol-1-yl)acetic acid;

I-60: ((((4-(4-((3-(3,6-difluoropyridin-2-yl)-1-((1r,4r)-4-ethoxycyclohexyl)-1H-pyrazol-4-yl)carbamoyl)thiazol-2-yl)-1H-pyrazol-1-yl)methoxy)(hydroxy)phosphoryl)oxy)methyl isopropyl carbonate;

I-61: (4-(4-((3-(3,6-difluoropyridin-2-yl)-1-((1r,4r)-4-ethoxycyclohexyl)-1H-pyrazol-4-yl)carbamoyl)thiazol-2-yl)-1H-pyrazol-1-yl)methyl 1-amino-3,6,9,12,15,18-hexaoxahenicosan-21-oate hydrochloride;

I-62: isopropyl (((4-(4-((3-(3,6-difluoropyridin-2-yl)-1-((1r,4r)-4-ethoxycyclohexyl)-1H-pyrazol-4-yl)carbamoyl)thiazol-2-yl)-1H-pyrazol-1-yl)methoxy)(phenoxy)phosphoryl)-L-alaninate;

I-63: (4-(4-((3-(3,6-difluoropyridin-2-yl)-1-((1r,4r)-4-ethoxycyclohexyl)-1H-pyrazol-4-yl)carbamoyl)thiazol-2-yl)-1H-pyrazol-1-yl)methyl dihydrogen phosphate tris salt;

I-64: N-(3-(3,6-difluoropyridin-2-yl)-1-((1r,4r)-4-ethoxycyclohexyl)-1H-pyrazol-4-yl)-2-(1H-pyrazol-4-yl)thiazole-4-carboxamide hydrochloride;

I-65: N-(3-(3,6-difluoropyridin-2-yl)-1-((1r,4r)-4-ethoxycyclohexyl)-1H-pyrazol-4-yl)-2-(1H-pyrazol-4-yl)thiazole-4-carboxamide benzene sulfonate;

I-66: N-(3-(3,6-difluoropyridin-2-yl)-1-((1r,4r)-4-ethoxycyclohexyl)-1H-pyrazol-4-yl)-2-(1H-pyrazol-4-yl)thiazole-4-carboxamide tartrate;

I-67: N-(3-(3,6-difluoropyridin-2-yl)-1-((1r,4r)-4-ethoxycyclohexyl)-1H-pyrazol-4-yl)-2-(1H-pyrazol-4-yl)thiazole-4-carboxamide sodium salt;

I-68: N-(3-(3,6-difluoropyridin-2-yl)-1-((1r,4r)-4-ethoxycyclohexyl)-1H-pyrazol-4-yl)-2-(1H-pyrazol-4-yl)thiazole-4-carboxamide hemicitrate;

I-69: (4-(4-((3-(3,6-difluoropyridin-2-yl)-1-((1r,4r)-4-ethoxycyclohexyl)-1H-pyrazol-4-yl)carbamoyl)thiazol-2-yl)-1H-pyrazol-1-yl)methyl dihydrogen phosphate ditris salt;

I-70: benzyl ((S)-1-(4-(4-((3-(3,6-difluoropyridin-2-yl)-1-((1r,4r)-4-ethoxycyclohexyl)-1H-pyrazol-4-yl)carbamoyl)thiazol-2-yl)-1H-pyrazol-1-yl)-4-methyl-1-oxopentan-2-yl)carbamate;

I-71: (4-(4-((3-(3,6-difluoropyridin-2-yl)-1-((1r,4r)-4-ethoxycyclohexyl)-1H-pyrazol-4-yl)carbamoyl)thiazol-2-yl)-1H-pyrazol-1-yl)methyl L-prolinate;

I-72: (4-(4-((3-(3,6-difluoropyridin-2-yl)-1-((1r,4r)-4-ethoxycyclohexyl)-1H-pyrazol-4-yl)carbamoyl)thiazol-2-yl)-1H-pyrazol-1-yl)methyl glycinate;

I-73: (4-(4-((3-(3,6-difluoropyridin-2-yl)-1-((1r,4r)-4-ethoxycyclohexyl)-1H-pyrazol-4-yl)carbamoyl)thiazol-2-yl)-1H-pyrazol-1-yl)methyl (R)-2-amino-3,3-dimethylbutanoate;

I-74: (4-(4-((3-(3,6-difluoropyridin-2-yl)-1-((1r,4r)-4-ethoxycyclohexyl)-1H-pyrazol-4-yl)carbamoyl)thiazol-2-yl)-1H-pyrazol-1-yl)methyl 2-amino-2-methylpropanoate;

I-75: 4-((4-(4-((3-(3,6-difluoropyridin-2-yl)-1-((1r,4r)-4-ethoxycyclohexyl)-1H-pyrazol-4-yl)carbamoyl)thiazol-2-yl)-1H-pyrazol-1-yl)methyl) 1-methyl L-aspartate;

I-76: (S)-2-amino-4-((4-(4-((3-(3,6-difluoropyridin-2-yl)-1-((1r,4r)-4-ethoxycyclohexyl)-1H-pyrazol-4-yl)carbamoyl)thiazol-2-yl)-1H-pyrazol-1-yl)methoxy)-4-oxobutanoic acid;

I-77: (4-(4-((3-(3,6-difluoropyridin-2-yl)-1-((1r,4r)-4-ethoxycyclohexyl)-1H-pyrazol-4-yl)carbamoyl)thiazol-2-yl)-1H-pyrazol-1-yl)methyl 4-((S)-2-amino-3-methylbutanamido)butanoate;

I-78: (4-(4-((3-(3,6-difluoropyridin-2-yl)-1-((1r,4r)-4-ethoxycyclohexyl)-1H-pyrazol-4-yl)carbamoyl)thiazol-2-yl)-1H-pyrazol-1-yl)methyl 1-amino-3,6,9,12,15,18-hexaoxahenicosan-21-oate;

I-79: 2-(1-(acetyl-D-leucyl)-1H-pyrazol-4-yl)-N-(3-(3,6-difluoropyridin-2-yl)-1-((1r,4r)-4-ethoxycyclohexyl)-1H-pyrazol-4-yl)thiazole-4-carboxamide;

I-80: 2-(1-(acetylleucyl)-1H-pyrazol-4-yl)-N-(3-(3,6-difluoropyridin-2-yl)-1-((1r,4r)-4-ethoxycyclohexyl)-1H-pyrazol-4-yl)thiazole-4-carboxamide;

I-81: (4-(4-((3-(3,6-difluoropyridin-2-yl)-1-((1r,4r)-4-ethoxycyclohexyl)-1H-pyrazol-4-yl)carbamoyl)thiazol-2-yl)-1H-pyrazol-1-yl)methyl D-valinate;

I-82: (4-(4-((3-(3,6-difluoropyridin-2-yl)-1-((1r,4r)-4-ethoxycyclohexyl)-1H-pyrazol-4-yl)carbamoyl)thiazol-2-yl)-1H-pyrazol-1-yl)methyl valinate;

I-83: (4-(4-((3-(3,6-difluoropyridin-2-yl)-1-((1r,4r)-4-ethoxycyclohexyl)-1H-pyrazol-4-yl)carbamoyl)thiazol-2-yl)-1H-pyrazol-1-yl)methyl D-prolinate;

I-84: (4-(4-((3-(3,6-difluoropyridin-2-yl)-1-((1r,4r)-4-ethoxycyclohexyl)-1H-pyrazol-4-yl)carbamoyl)thiazol-2-yl)-1H-pyrazol-1-yl)methyl prolinate;

I-85: (4-(4-((3-(3,6-difluoropyridin-2-yl)-1-((1r,4r)-4-ethoxycyclohexyl)-1H-pyrazol-4-yl)carbamoyl)thiazol-2-yl)-1H-pyrazol-1-yl)methyl 2-amino-3,3-dimethylbutanoate;

I-86: (1S,2S)-2-(((4-(4-((3-(3,6-difluoropyridin-2-yl)-1-((1r,4r)-4-ethoxycyclohexyl)-1H-pyrazol-4-yl)carbamoyl)thiazol-2-yl)-1H-pyrazol-1-yl)methoxy)carbonyl)cyclohexane-1-carboxylic acid;

I-87: (1R,2S)-2-(((4-(4-((3-(3,6-difluoropyridin-2-yl)-1-((1r,4r)-4-ethoxycyclohexyl)-1H-pyrazol-4-yl)carbamoyl)thiazol-2-yl)-1H-pyrazol-1-yl)methoxy)carbonyl)cyclohexane-1-carboxylic acid;

I-88: (1S,2R)-2-(((4-(4-((3-(3,6-difluoropyridin-2-yl)-1-((1r,4r)-4-ethoxycyclohexyl)-1H-pyrazol-4-yl)carbamoyl)thiazol-2-yl)-1H-pyrazol-1-yl)methoxy)carbonyl)cyclohexane-1-carboxylic acid;

I-89: 2-(((4-(4-((3-(3,6-difluoropyridin-2-yl)-1-((1r,4r)-4-ethoxycyclohexyl)-1H-pyrazol-4-yl)carbamoyl)thiazol-2-yl)-1H-pyrazol-1-yl)methoxy)carbonyl)cyclohexane-1-carboxylic acid;

I-90: (R)-2-amino-4-((4-(4-((3-(3,6-difluoropyridin-2-yl)-1-((1r,4r)-4-ethoxycyclohexyl)-1H-pyrazol-4-yl)carbamoyl)thiazol-2-yl)-1H-pyrazol-1-yl)methoxy)-4-oxobutanoic acid;

I-91: 2-amino-4-((4-(4-((3-(3,6-difluoropyridin-2-yl)-1-((1r,4r)-4-ethoxycyclohexyl)-1H-pyrazol-4-yl)carbamoyl)thiazol-2-yl)-1H-pyrazol-1-yl)methoxy)-4-oxobutanoic acid;

I-92: 4-((4-(4-((3-(3,6-difluoropyridin-2-yl)-1-((1r,4r)-4-ethoxycyclohexyl)-1H-pyrazol-4-yl)carbamoyl)thiazol-2-yl)-1H-pyrazol-1-yl)methyl) 1-methyl D-aspartate;

I-93: 4-((4-(4-((3-(3,6-difluoropyridin-2-yl)-1-((1r,4r)-4-ethoxycyclohexyl)-1H-pyrazol-4-yl)carbamoyl)thiazol-2-yl)-1H-pyrazol-1-yl)methyl) 1-methyl aspartate;

I-94: 1-((4-(4-((3-(3,6-difluoropyridin-2-yl)-1-((1r,4r)-4-ethoxycyclohexyl)-1H-pyrazol-4-yl)carbamoyl)thiazol-2-yl)-1H-pyrazol-1-yl)methyl) 4-methyl D-aspartate;

I-95: 1-((4-(4-((3-(3,6-difluoropyridin-2-yl)-1-((1r,4r)-4-ethoxycyclohexyl)-1H-pyrazol-4-yl)carbamoyl)thiazol-2-yl)-1H-pyrazol-1-yl)methyl) 4-methyl aspartate;

I-96: (4-(4-((3-(3,6-difluoropyridin-2-yl)-1-((1r,4r)-4-ethoxycyclohexyl)-1H-pyrazol-4-yl)carbamoyl)thiazol-2-yl)-1H-pyrazol-1-yl)methyl 4-((R)-2-amino-3-methylbutanamido)butanoate;

I-97: (4-(4-((3-(3,6-difluoropyridin-2-yl)-1-((1r,4r)-4-ethoxycyclohexyl)-1H-pyrazol-4-yl)carbamoyl)thiazol-2-yl)-1H-pyrazol-1-yl)methyl 4-(2-amino-3-methylbutanamido)butanoate;

I-98: isopropyl (((4-(4-((3-(3,6-difluoropyridin-2-yl)-1-((1r,4r)-4-ethoxycyclohexyl)-1H-pyrazol-4-yl)carbamoyl)thiazol-2-yl)-1H-pyrazol-1-yl)methoxy)(phenoxy)phosphoryl)-D-alaninate;

I-99: isopropyl (((4-(4-((3-(3,6-difluoropyridin-2-yl)-1-((1r,4r)-4-ethoxycyclohexyl)-1H-pyrazol-4-yl)carbamoyl)thiazol-2-yl)-1H-pyrazol-1-yl)methoxy)(phenoxy)phosphoryl)alaninate;

I-100: (2R,3S)-2,3-diacetoxy-4-((4-(4-((3-(3,6-difluoropyridin-2-yl)-1-((1r,4r)-4-ethoxycyclohexyl)-1H-pyrazol-4-yl)carbamoyl)thiazol-2-yl)-1H-pyrazol-1-yl)methoxy)-4-oxobutanoic acid;

I-101: (2S,3R)-2,3-diacetoxy-4-((4-(4-((3-(3,6-difluoropyridin-2-yl)-1-((1r,4r)-4-ethoxycyclohexyl)-1H-pyrazol-4-yl)carbamoyl)thiazol-2-yl)-1H-pyrazol-1-yl)methoxy)-4-oxobutanoic acid;

I-102: (2S,3S)-2,3-diacetoxy-4-((4-(4-((3-(3,6-difluoropyridin-2-yl)-1-((1r,4r)-4-ethoxycyclohexyl)-1H-pyrazol-4-yl)carbamoyl)thiazol-2-yl)-1H-pyrazol-1-yl)methoxy)-4-oxobutanoic acid;

I-103: 2,3-diacetoxy-4-((4-(4-((3-(3,6-difluoropyridin-2-yl)-1-((1r,4r)-4-ethoxycyclohexyl)-1H-pyrazol-4-yl)carbamoyl)thiazol-2-yl)-1H-pyrazol-1-yl)methoxy)-4-oxobutanoic acid;

I-104: N-(3-(3,6-difluoropyridin-2-yl)-1-((1r,4r)-4-ethoxycyclohexyl)-1H-pyrazol-4-yl)-2-(1H-pyrazol-4-yl)thiazole-4-carboxamide phosphate;

I-105: N-(3-(3,6-difluoropyridin-2-yl)-1-((1r,4r)-4-ethoxycyclohexyl)-1H-pyrazol-4-yl)-2-(1H-pyrazol-4-yl)thiazole-4-carboxamide gentisate;

I-106: N-(3-(3,6-difluoropyridin-2-yl)-1-((1r,4r)-4-ethoxycyclohexyl)-1H-pyrazol-4-yl)-2-(1H-pyrazol-4-yl)thiazole-4-carboxamide succinate;

I-107: sodium 1-(4-(4-((3-(3,6-difluoropyridin-2-yl)-1-((1r,4r)-4-ethoxycyclohexyl)-1H-pyrazol-4-yl)carbamoyl)thiazol-2-yl)-1H-pyrazol-1-yl)ethyl hydrogen phosphate;

I-108: potassium 1-(4-(4-((3-(3,6-difluoropyridin-2-yl)-1-((1r,4r)-4-ethoxycyclohexyl)-1H-pyrazol-4-yl)carbamoyl)thiazol-2-yl)-1H-pyrazol-1-yl)ethyl hydrogen phosphate;

I-109: potassium 1-(4-(4-((3-(3,6-difluoropyridin-2-yl)-1-((1r,4r)-4-ethoxycyclohexyl)-1H-pyrazol-4-yl)carbamoyl)thiazol-2-yl)-1H-pyrazol-1-yl)ethyl phosphate;

I-110: 1-(4-(4-((3-(3,6-difluoropyridin-2-yl)-1-((1r,4r)-4-ethoxycyclohexyl)-1H-pyrazol-4-yl)carbamoyl)thiazol-2-yl)-1H-pyrazol-1-yl)ethyl dihydrogen phosphate arginine salt;

I-111: 1-(4-(4-((3-(3,6-difluoropyridin-2-yl)-1-((1r,4r)-4-ethoxycyclohexyl)-1H-pyrazol-4-yl)carbamoyl)thiazol-2-yl)-1H-pyrazol-1-yl)ethyl dihydrogen phosphate choline salt;

I-112: ammonium 1-(4-(4-((3-(3,6-difluoropyridin-2-yl)-1-((1r,4r)-4-ethoxycyclohexyl)-1H-pyrazol-4-yl)carbamoyl)thiazol-2-yl)-1H-pyrazol-1-yl)ethyl hydrogen phosphate;

I-113: 1-(4-(4-((3-(3,6-difluoropyridin-2-yl)-1-((1r,4r)-4-ethoxycyclohexyl)-1H-pyrazol-4-yl)carbamoyl)thiazol-2-yl)-1H-pyrazol-1-yl)ethyl dihydrogen phosphate lysine salt;

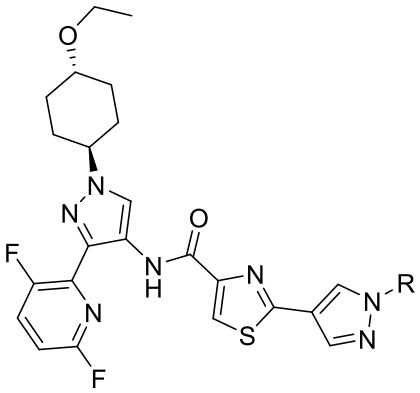
I-114: 1-(4-(4-((3-(3,6-difluoropyridin-2-yl)-1-((1r,4r)-4-ethoxycyclohexyl)-1H-pyrazol-4-yl)carbamoyl)thiazol-2-yl)-1H-pyrazol-1-yl)ethyl dihydrogen phosphate meglumine salt;

I-115: magnesium 1-(4-(4-((3-(3,6-difluoropyridin-2-yl)-1-((1r,4r)-4-ethoxycyclohexyl)-1H-pyrazol-4-yl)carbamoyl)thiazol-2-yl)-1H-pyrazol-1-yl)ethyl phosphate; or

I-116: Calcium 1-(4-(4-((3-(3,6-difluoropyridin-2-yl)-1-((1r,4r)-4-ethoxycyclohexyl)-1H-pyrazol-4-yl)carbamoyl)thiazol-2-yl)-1H-pyrazol-1-yl)ethyl phosphate.

14. A composition, comprising a compound according to any one of claims 1-13, and a pharmaceutically acceptable excipient.

15. A spray-dried composition, comprising a polymer carrier and a compound according to Formula I:



Formula I

where R is aliphatic, acyl, heterocyclyl, carboxyl ester, amide, alkyl phosphoramidate, or alkyl phosphate.

16. The spray-dried composition of claim 15, wherein the spray-dried composition comprises from 1% to 50% w/w of the compound with respect to the carrier.

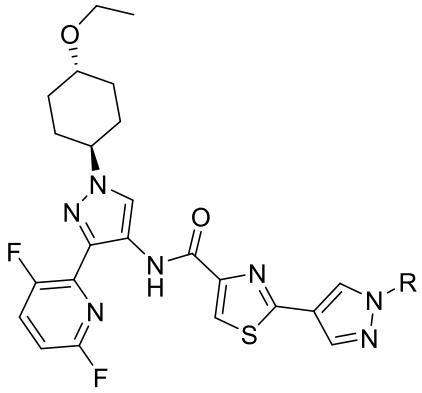
17. The spray-dried composition of claim 15 or claim 16, wherein the polymer is a cellulose derivative, vinyl polymer, lactide polymer, sugar, or a combination thereof.

18. The spray-dried composition of any one of claims 15-17, wherein the composition is amorphous.

19. The spray-dried composition of any one of claims 15-18, wherein the composition has a glass transition temperature of from 100 °C to 120 °C.

20. A method of making a spray-dried composition, comprising:

forming a mixture comprising a carrier, a solvent and a compound according to Formula I



Formula I

where R is aliphatic, acyl, heterocyclyl, carboxyl ester, amide, alkyl phosphoramidate, or alkyl phosphate; and

spray drying the mixture to form a spray-dried formulation comprising the compound and the carrier.

21. A compound according to any one of claims 1-13 or a composition according to any one of claims 14-19 for use in therapy.

22. Use of a compound according to any one of claims 1-13 or a composition according to any one of claims 14-19 in the manufacture of a medicament for treating a disease or condition for which an IRAK inhibitor is indicated.

23. The use of claim 22, wherein the disease is an auto-immune disease, inflammatory disorder, cardiovascular disease, neurodegenerative disorder, allergic disorder, multi-organ failure, kidney disease, platelet aggregation, cancer, transplantation, sperm motility, erythrocyte deficiency, graft

rejection, lung injury, respiratory disease, ischemic condition, bacterial infection, viral infection, immune regulatory disorder or a combination thereof.

24. The use of claim 21, further comprising a second therapeutic agent.

5

25. The use of claim 24, wherein the second therapeutic agent is an analgesic, an antibiotic, an anticoagulant, an antibody, an anti-inflammatory agent, an immunosuppressant, a guanylate cyclase-C agonist, an intestinal secretagogue, an antiviral, anticancer, antifungal, or a combination thereof.