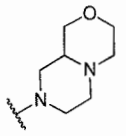
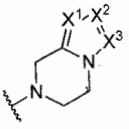
(a) $-C(CH_3)_2$-(4-R^4-piperazin-1-yl) where R^4 is hydrogen, alkyl, alkoxyalkyl, haloalkyl, alkylsulfonyl, alkoxycarbonyl, acyl, or oxetan-3-yl and the piperazinyl ring is additionally optionally substituted with one or two alkyl;

(b) $-C(CH_3)_2$-(3-oxo-4-R^a-piperazin-1-yl) where R^a is hydrogen, alkyl, cycloalkyl, alkoxyalkyl, haloalkyl, or oxetan-3-yl and the piperazinyl ring is additionally optionally substituted with one or two alkyl;

(c) $-C(CH_3)_2$-NR^boxetan-3-yl where R^b is hydrogen, alkyl, alkoxyalkyl, or cycloalkyl;

(d) $-C(CH_3)_2$-R^c where R^c is  or  where one or two of X^1, X^2 and X^3 are nitrogen and the rest are carbon and the ring is optionally substituted with one or two substituents independently selected from alkyl, haloalkyl, or halo; or

(e) $-C(CH_3)_2$-2-oxa-6-azaspiro[3.3]heptan-6-yl, or $-C(CH_3)_2-CH_2$morpholine-4-yl;

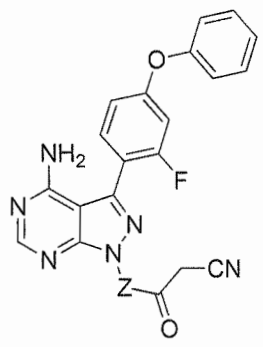
and/or a pharmaceutically acceptable salt thereof.

Another aspect relates to a pharmaceutical composition comprising a compound ~~as disclosed herein~~ and/or a pharmaceutically acceptable salt as disclosed herein and a pharmaceutically acceptable excipient.

Yet another aspect relates to the use of a compound as disclosed herein or a pharmaceutically acceptable salt there in the manufacture of a medicament for the treatment of a disease treatable by inhibition of Bruton tyrosine kinase, wherein the disease is chosen from autoimmune diseases, inflammatory diseases, and cancers.

A further aspect relates to a process of preparing a compound as disclosed herein, the method comprising:

(a) reacting a compound of formula (1):



(1)

wherein:

(S)-2-(3-(4-amino-3-(2-fluoro-4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-carbonyl)-4-methyl-4-(4-(methylsulfonyl)piperazin-1-yl)pent-2-enenitrile;

(R)-2-(3-(4-amino-3-(2-fluoro-4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-carbonyl)-4-methyl-4-(4-methyl-3-oxopiperazin-1-yl)pent-2-enenitrile;

(S)-2-(3-(4-amino-3-(2-fluoro-4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-carbonyl)-4-methyl-4-(4-methyl-3-oxopiperazin-1-yl)pent-2-enenitrile;

(R)-4-(4-acetylpiperazin-1-yl)-2-(3-(4-amino-3-(2-fluoro-4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-carbonyl)-4-methylpent-2-enenitrile;

(S)-4-(4-acetylpiperazin-1-yl)-2-(3-(4-amino-3-(2-fluoro-4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-carbonyl)-4-methylpent-2-enenitrile;

(R)-methyl 4-(5-(3-(4-amino-3-(2-fluoro-4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)-4-cyano-2-methyl-5-oxopent-3-en-2-yl)piperazine-1-carboxylate;

(S)-methyl 4-(5-(3-(4-amino-3-(2-fluoro-4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)-4-cyano-2-methyl-5-oxopent-3-en-2-yl)piperazine-1-carboxylate;

(R)-2-(3-(4-amino-3-(2-fluoro-4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-carbonyl)-4,4-dimethyl-5-morpholinopent-2-enenitrile;

(S)-2-(3-(4-amino-3-(2-fluoro-4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-carbonyl)-4,4-dimethyl-5-morpholinopent-2-enenitrile;

or a mixture of R and S isomers thereof; ~~or~~

an (E) or (Z) isomer of any one of the above compounds or a mixture thereof.

8. The compound of Claim 7 and/or a pharmaceutically acceptable salt thereof wherein the compound is:

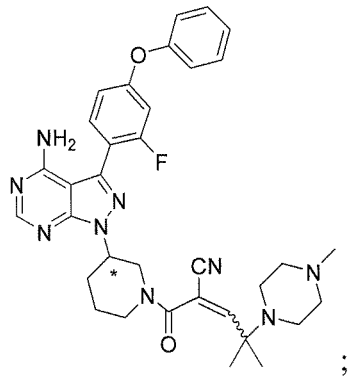
2-[[(3R)-3-[4-amino-3-(2-fluoro-4-phenoxyphenyl)-1H-pyrazolo[3,4-d]-pyrimidin-1-yl]-piperidin-1-yl]carbonyl]-4-methyl-4-(4-methylpiperazin-1-yl)pent-2-enenitrile;

2-[[(3S)-3-[4-amino-3-(2-fluoro-4-phenoxyphenyl)-1H-pyrazolo[3,4-d]-pyrimidin-1-yl]-piperidin-1-yl]carbonyl]-4-methyl-4-(4-methylpiperazin-1-yl)pent-2-enenitrile; or

a mixture of 2-[[(3R)-3-[4-amino-3-(2-fluoro-4-phenoxyphenyl)-1H-pyrazolo[3,4-d]-pyrimidin-1-yl]-piperidin-1-yl]carbonyl]-4-methyl-4-(4-methylpiperazin-1-yl)pent-2-enenitrile

and 2-[[(3S)-3-[4-amino-3-(2-fluoro-4-phenoxyphenyl)-1H-pyrazolo[3,4-d]-pyrimidin-1-yl]-piperidin-1-yl]carbonyl]-4-methyl-4-(4-methylpiperazin-1-yl)pent-2-enenitrile;

having the structure:

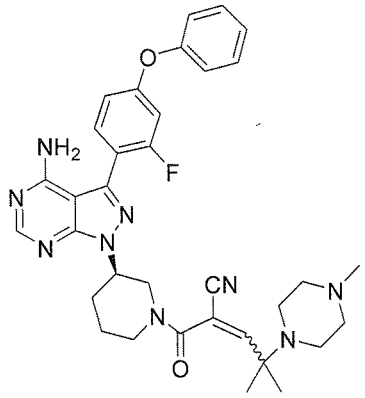


;

where *C is (R), (S), or a mixture of (R) and (S);

or an individual E or Z isomer of any one of the above compound or a mixture thereof.

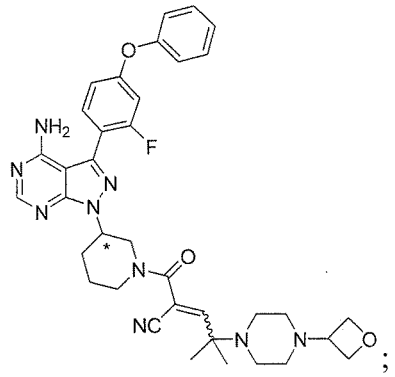
9. The compound of Claim 7 and/or a pharmaceutically acceptable salt thereof wherein the compound is (E) isomer or (Z) isomer of 2-[[(3R)-3-[4-amino-3-(2-fluoro-4-phenoxyphenyl)-1H-pyrazolo[3,4-d]-pyrimidin-1-yl]-piperidin-1-yl]carbonyl]-4-methyl-4-(4-methylpiperazin-1-yl)pent-2-enenitrile having the structure:



.

10. The compound of Claim 7 and/or a pharmaceutically acceptable salt thereof wherein the compound is a mixture of (E) isomer and (Z) isomer of 2-[[(3R)-3-[4-amino-3-(2-fluoro-4-phenoxyphenyl)-1H-pyrazolo[3,4-d]-pyrimidin-1-yl]-piperidin-1-yl]carbonyl]-4-methyl-4-(4-methylpiperazin-1-yl)-pent-2-enenitrile having the structure:

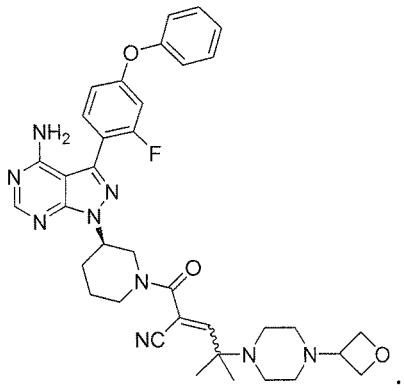
having the structure:



where *C is (R), (S), or a mixture of (R) and (S);

or an individual E or Z isomer of any one of the above compounds or a mixture thereof.

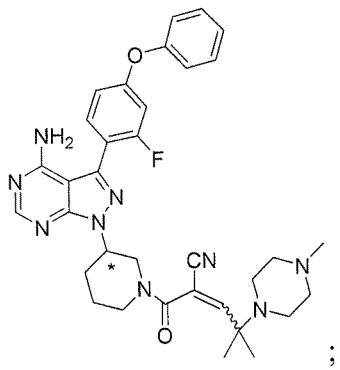
13. The compound of Claim 7 and/or a pharmaceutically acceptable salt thereof wherein the compound is (E) isomer or (Z) isomer of (R)-2-(3-(4-amino-3-(2-fluoro-4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-carbonyl)-4-methyl-4-(4-(oxetan-3-yl)piperazin-1-yl)pent-2-enenitrile having the structure:



14. The compound of Claim 7 and/or a pharmaceutically acceptable salt thereof wherein the compound is a mixture of (E) isomer and (Z) isomer of (R)-2-(3-(4-amino-3-(2-fluoro-4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-carbonyl)-4-methyl-4-(4-(oxetan-3-yl)piperazin-1-yl)pent-2-enenitrile having the structure:

and 2-[[(3S)-3-[4-amino-3-(2-fluoro-4-phenoxyphenyl)-1H-pyrazolo[3,4-d]-pyrimidin-1-yl]-piperidin-1-yl]carbonyl]-4-methyl-4-(4-methylpiperazin-1-yl)pent-2-enenitrile;

having the structure:



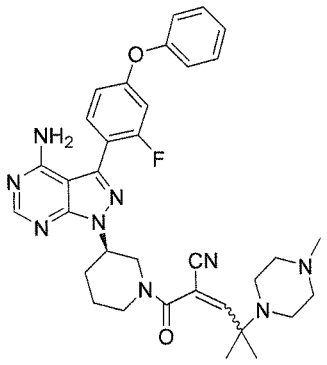
;

where *C is (R), (S), or a mixture of (R) and (S);

or an individual E or Z isomer of any of the above compounds or a mixture thereof; and/or

a pharmaceutically acceptable salt of any of the above compounds.

18. The pharmaceutical composition of Claim 16 comprising is a mixture of (E) isomer and (Z) isomer of 2-[[(3R)-3-[4-amino-3-(2-fluoro-4-phenoxyphenyl)-1H-pyrazolo[3,4-d]-pyrimidin-1-yl]-piperidin-1-yl]carbonyl]-4-methyl-4-(4-methylpiperazin-1-yl)-pent-2-enenitrile having the structure:



and/or a pharmaceutically acceptable salt thereof.

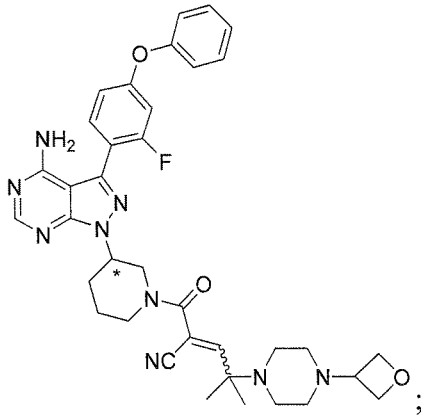
19. The pharmaceutical composition of Claim 16 comprising:

(R)-2-(3-(4-amino-3-(2-fluoro-4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-carbonyl)-4-methyl-4-(4-(oxetan-3-yl)piperazin-1-yl)pent-2-enenitrile;

(S)-2-(3-(4-amino-3-(2-fluoro-4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-carbonyl)-4-methyl-4-(4-(oxetan-3-yl)piperazin-1-yl)pent-2-enenitrile; or

a mixture of (R)-2-(3-(4-amino-3-(2-fluoro-4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-carbonyl)-4-methyl-4-(4-(oxetan-3-yl)piperazin-1-yl)pent-2-enenitrile and (S)-2-(3-(4-amino-3-(2-fluoro-4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-carbonyl)-4-methyl-4-(4-(oxetan-3-yl)piperazin-1-yl)pent-2-enenitrile;

having the structure:

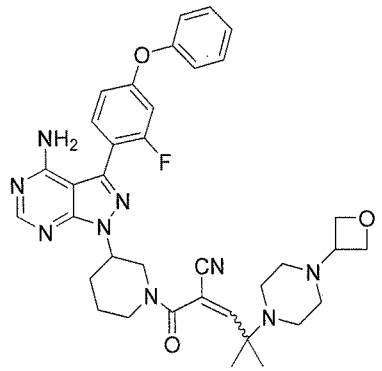


where *C is (R), (S), or a mixture of (R) and (S);

or an individual E or Z isomer of any of the above compounds or a mixture thereof; and/or

a pharmaceutically acceptable salt of any of the above compounds.

20. The pharmaceutical composition of Claim 19 comprising (E) isomer or (Z) isomer of (R)-2-(3-(4-amino-3-(2-fluoro-4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-carbonyl)-4-methyl-4-(4-(oxetan-3-yl)piperazin-1-yl)pent-2-enenitrile having the structure:



and/or a pharmaceutically acceptable salt thereof.

23. The pharmaceutical composition of any of the claims 16-22 wherein the pharmaceutical composition is an enteric coated or delayed release formulation.

24. Use of a compound of any one of Claims 1 to 15 and/or pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of a disease treatable by inhibition of Bruton tyrosine kinase.

~~25. The use of Claim 24~~ wherein the disease is chosen from autoimmune diseases, inflammatory diseases, and cancers.

~~26~~25. The use of Claim ~~25~~24 wherein the disease is chosen from autoimmune diseases and inflammatory diseases wherein the autoimmune disease is chosen from inflammatory bowel disease, arthritis, lupus, myasthenia gravis, Graves' disease, Sjogren's syndrome, Sjogren's dry eye, non-Sjogren's dry eye disease, multiple sclerosis, Guillain-Barre syndrome, ankylosing spondylitisis, idiopathic thrombocytopenic purpura scleroderma, warm autoimmune hemolytic anemia, Wegener's granulomatosis, and psoriasis; and the inflammatory disease is chosen from asthma, colitis, conjunctivitis, Behcet's disease, atopic dermatitis, uveitis, and eczema.

~~27~~26. The use of Claim ~~25~~24 wherein the disease is cancer chosen from diffuse large B cell lymphoma, follicular lymphoma, chronic lymphocytic lymphoma, chronic lymphocytic leukemia, B-ALL, B-cell prolymphocytic leukemia, small lymphocytic lymphoma (SLL), multiple myeloma, B-cell non-Hodgkin lymphoma, lymphoplamascytic lymphoma/

Waldenstrom macroglobulinemia, splenic marginal zone lymphoma, plasma cell myeloma, plasmacytoma, extranodal marginal zone B cell lymphoma, nodal marginal zone B cell lymphoma, mantle cell lymphoma, mediastinal (thymic) large B cell lymphoma, intravascular large B cell lymphoma, primary effusion lymphoma, burkitt's lymphoma/leukemia, and lymphomatoid granulomatosis.

~~28~~27. The use of Claim ~~26~~25 wherein the disease is chosen from rheumatoid arthritis, psoriatic arthritis, lupus, uveitis, myasthenia gravis, warm autoimmune hemolytic anemia, Wegener's granulomatosis, Sjogren's disease, Sjogren's dry eye, non-Sjogren's dry eye disease, psoriasis, and asthma.

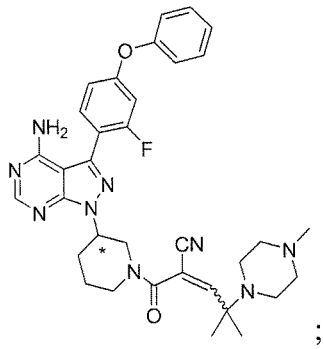
~~29~~28. The use of any one of Claims 24-~~28~~27 wherein the compound is:

2-[[(3R)-3-[4-amino-3-(2-fluoro-4-phenoxyphenyl)-1H-pyrazolo[3,4-d]-pyrimidin-1-yl]-piperidin-1-yl]carbonyl]-4-methyl-4-(4-methylpiperazin-1-yl)pent-2-enenitrile;

2-[[(3S)-3-[4-amino-3-(2-fluoro-4-phenoxyphenyl)-1H-pyrazolo[3,4-d]-pyrimidin-1-yl]-piperidin-1-yl]carbonyl]-4-methyl-4-(4-methylpiperazin-1-yl)pent-2-enenitrile; or

a mixture of 2-[[(3R)-3-[4-amino-3-(2-fluoro-4-phenoxyphenyl)-1H-pyrazolo[3,4-d]-pyrimidin-1-yl]-piperidin-1-yl]carbonyl]-4-methyl-4-(4-methylpiperazin-1-yl)pent-2-enenitrile and 2-[[(3S)-3-[4-amino-3-(2-fluoro-4-phenoxyphenyl)-1H-pyrazolo[3,4-d]-pyrimidin-1-yl]-piperidin-1-yl]carbonyl]-4-methyl-4-(4-methylpiperazin-1-yl)pent-2-enenitrile;

having the structure:



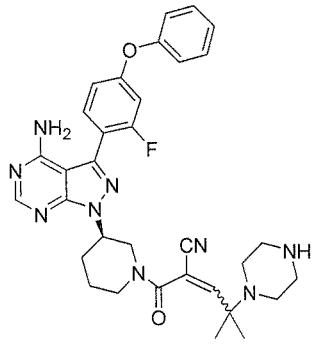
;

where *C is (R), (S), or a mixture of (R) and (S);

or an individual E or Z isomer of any of the above compounds; and/or

a pharmaceutically acceptable salt of any of the above compounds.

~~30~~29. The use of any one of Claims 24-~~28~~27 wherein the compound is a mixture of (E) isomer and (Z) isomer of 2-((R)-3-(4-amino-3-(2-fluoro-4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-carbonyl)-4-methyl-4-(piperazin-1-yl)pent-2-enenitrile having the structure:



and/or a pharmaceutically acceptable salt thereof.

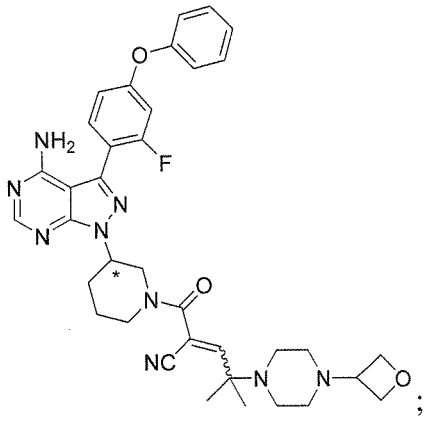
~~31~~30. The use of any one of Claims 24-~~28~~27 wherein the compound is:

(R)-2-(3-(4-amino-3-(2-fluoro-4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-carbonyl)-4-methyl-4-(4-(oxetan-3-yl)piperazin-1-yl)pent-2-enenitrile;

(S)-2-(3-(4-amino-3-(2-fluoro-4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-carbonyl)-4-methyl-4-(4-(oxetan-3-yl)piperazin-1-yl)pent-2-enenitrile; or

a mixture of (R)-2-(3-(4-amino-3-(2-fluoro-4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-carbonyl)-4-methyl-4-(4-(oxetan-3-yl)piperazin-1-yl)pent-2-enenitrile and (S)-2-(3-(4-amino-3-(2-fluoro-4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-carbonyl)-4-methyl-4-(4-(oxetan-3-yl)piperazin-1-yl)pent-2-enenitrile;

having the structure:

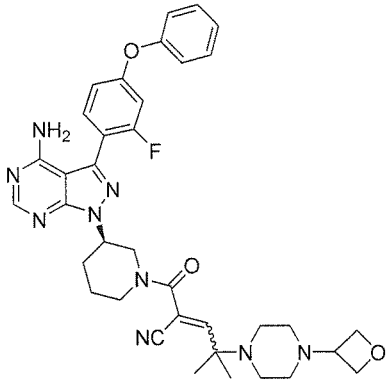


where *C is (R), (S), or a mixture of (R) and (S);

or an individual E or Z isomer of any of the above compounds; and/or

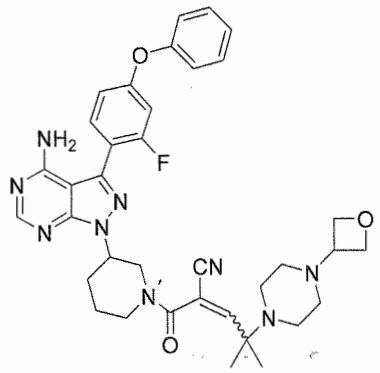
a pharmaceutically acceptable salt of any of the above compounds.

~~32~~31. The use of any one of Claims 24-~~28~~27 wherein the compound is a mixture of (E) isomer and (Z) isomer of (R)-2-(3-(4-amino-3-(2-fluoro-4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-carbonyl)-4-methyl-4-(4-(oxetan-3-yl)piperazin-1-yl)pent-2-enenitrile having the structure:



and/or a pharmaceutically acceptable salt thereof.

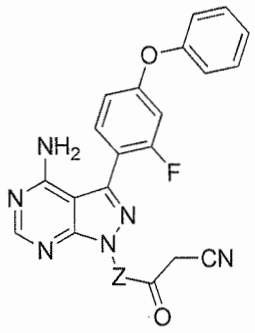
~~33~~32. The use of any one of Claims 24-~~28~~27 wherein the compound is wherein the compound is a mixture (S) and (R) isomers of 2-(3-(4-amino-3-(2-fluoro-4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-carbonyl)-4-methyl-4-(4-(oxetan-3-yl)piperazin-1-yl)pent-2-enenitrile having the structure:



~~34~~33. The use of any one of Claim ~~27~~26 and ~~29-33~~28-32 wherein the compound and/or pharmaceutically acceptable salt is administered in combination with one or more anti-cancer or anti-inflammatory agents.

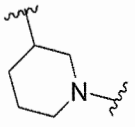
~~35~~34. A process of preparing a compound of any one of Claims 8, 11, and 12 comprising:

(a) reacting a compound of formula (1):



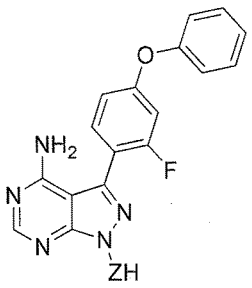
(1)

wherein:

-Z- is  ;

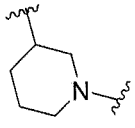
with an aldehyde of formula R^cCHO where R^c is $-C(CH_3)_2$-(piperazin-1-yl), $-C(CH_3)_2$-(4-methylpiperazin-1-yl), or $-C(CH_3)_2$-4-(oxetan-3-yl)piperazin-1-yl; or

(b) reacting a compound of formula (2):



(2)

wherein:

-Z- is  ;

with a compound of formula $R^cCH=C(CN)CO_2H$ or $R^cCH=C(CN)COX$ (where R^c is $-C(CH_3)_2$-(piperazin-1-yl), $-C(CH_3)_2$-(4-methylpiperazin-1-yl), or $-C(CH_3)_2$-4-(oxetan-3-yl)piperazin-1-yl) and X is a leaving group capable of being displaced by the nitrogen atom of the Z group under amide coupling reaction conditions;

(c) optionally making an acid addition salt of a compound obtained from Steps (a) or (b) above;

(d) optionally making a free base of a compound obtained from Steps (a), (b), or (c) above;

(e) optionally separating individual stereoisomers of the compounds obtained from Steps (a), (b), (c), or (d) above; and

(f) optionally separating individual (E) and (Z) isomers of the compounds obtained from steps (a), (b), (c), (d), or (e) above.

~~36~~35. The process of Claim 34 wherein R^c is $-C(CH_3)_2$-4-(oxetan-3-yl)piperazin-1-yl.