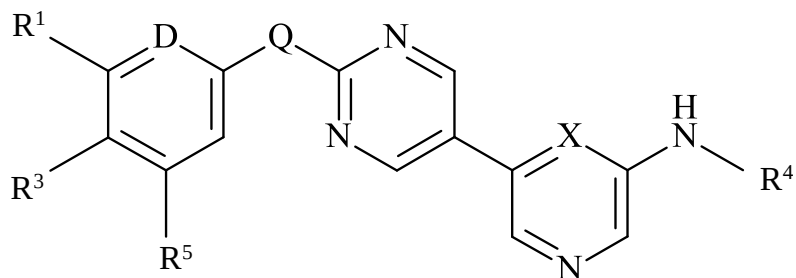


inhibitors have shown efficacy in collagen-induced arthritis and lupus models (See e.g. *Bruton's tyrosine kinase inhibitors for the treatment of rheumatoid arthritis*, Whang J. A. and Chang B.Y., Drug Discovery Today (2014), Volume 19, Number 8, 1200-1224). Targeting BTK with small molecule inhibitors may provide advantages over biological therapies for RA such as modulating B cell responses, and/or activation, while better maintaining desirable immunocompetence (See e.g. *Targeting B cells in treatment of autoimmunity*, Franks, S. E., et al., Current Opinion in Immunology (2016), 43:39-45).

Accordingly, there remains an unmet need for improved agents that may provide a combined profile of safe, effective and convenient treatment of inflammatory and/or autoimmune disease, without the disadvantages possessed by prior agents. United States Application Publication US 2014/0162983 discloses certain Compositions and Methods for the Production of Pyrimidine and Pyridine Compounds with BTK Inhibitory Activity, and recites the compounds as useful in treating a number of diseases including cancer, lupus, allergic disorders, Sjogren's disease and rheumatoid arthritis.

Summary

In an aspect of the present disclosure, there is provided a compound of the formula:



wherein:

D is -CR²- or N,

Q is O or NH,

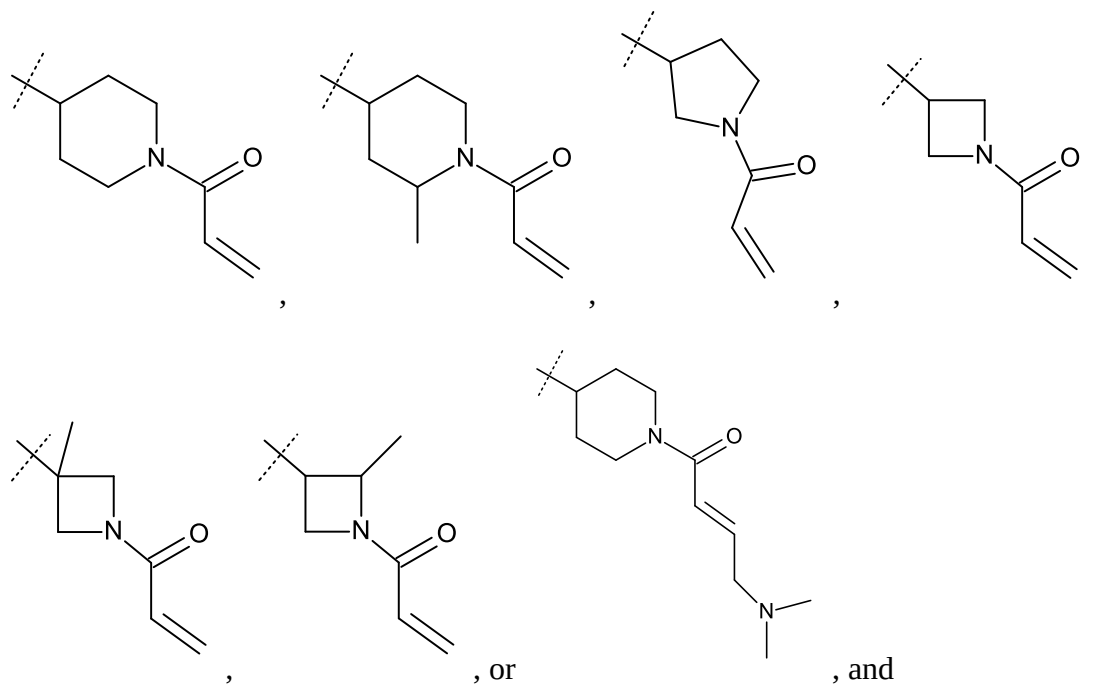
X is -CH- or N,

R¹ is -H, -Cl, -F, -CN, -CH₃, -CF₃, -OCHF₂, -OCH₃, -OCF₃, or -C≡CH,

R² is -H, -F or -OCF₃,

R³ is -H, -Cl or -F,

R⁴ is



R⁵ is -H or -F,

or a pharmaceutically acceptable salt thereof.

In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising a compound disclosed herein, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, diluent or excipient.

In a further aspect of the present disclosure, there is provided a use of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating Rheumatoid Arthritis.

In another aspect of the present disclosure, there is provided a use of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating Systemic Lupus Erythematosus.

In a further aspect of the present disclosure, there is provided a use of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating Multiple Sclerosis.

In another aspect of the present disclosure, there is provided a use of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating Sjögren's Syndrome.

In a further aspect of the present disclosure, there is provided a use of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating Pemphigus.

In another aspect of the present disclosure, there is provided a compound disclosed herein, or a pharmaceutically acceptable salt thereof, for use in therapy.

In a further aspect of the present disclosure, there is provided a compound disclosed herein, or a pharmaceutically acceptable salt thereof, for use in the treatment of Rheumatoid Arthritis.

In another aspect of the present disclosure, there is provided a compound disclosed herein, or a pharmaceutically acceptable salt thereof, for use in the treatment of Systemic Lupus Erythematosus.

In a further aspect of the present disclosure, there is provided a compound disclosed herein, or a pharmaceutically acceptable salt thereof, for use in the treatment of Multiple Sclerosis.

In another aspect of the present disclosure, there is provided a compound disclosed herein, or a pharmaceutically acceptable salt thereof, for use in the treatment of Pemphigus.

In a further aspect of the present disclosure, there is provided a use of 1-[4-[[5-[2-(3-chlorophenoxy)pyrimidin-5-yl]-3-pyridyl]amino]-1-piperidyl]prop-2-en-1-one in the manufacture of a medicament for treating Rheumatoid Arthritis.

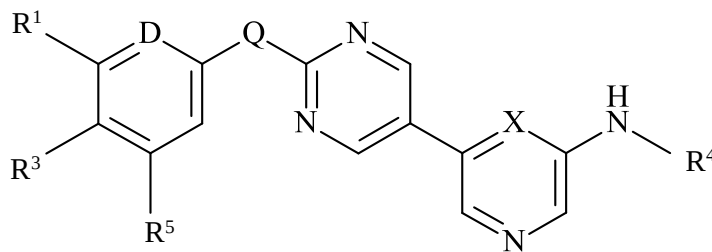
In another aspect of the present disclosure, there is provided a use of 1-[4-[[5-[2-(3-chlorophenoxy)pyrimidin-5-yl]-3-pyridyl]amino]-1-piperidyl]prop-2-en-1-one in the manufacture of a medicament for treating treating Systemic Lupus Erythematosus.

In a further aspect of the present disclosure, there is provided a use of 1-[4-[[5-[2-(3-chlorophenoxy)pyrimidin-5-yl]-3-pyridyl]amino]-1-piperidyl]prop-2-en-1-one in the manufacture of a medicament for treating Multiple Sclerosis.

Description

The present invention provides alternative compounds which are useful in treatment of autoimmune diseases such as RA, MS, and/or SLE. In addition, the compounds provided address the need for treatment of BTK mediated conditions with improved efficacy, and side effect and/or tolerability profiles. The compounds of the present invention are BTK inhibitors, and demonstrate potent BTK inhibition with favorable selectivity relative to other TEC tyrosine kinases. As such, compounds of the present invention are believed to be useful for the treatment of conditions in which BTK signaling plays a role, such as RA, MS, and/or SLE.

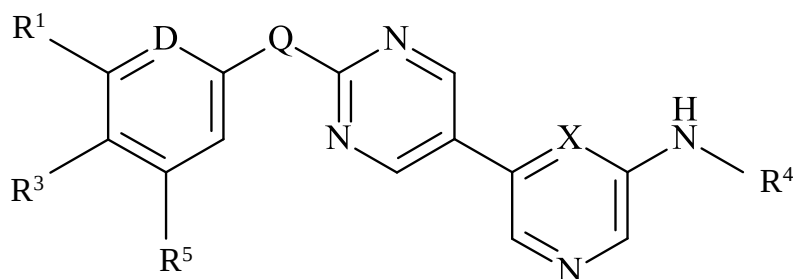
The present invention provides a compound of the formula:



Formula I

We claim:

1. A compound of the formula:



wherein:

5 D is $-CR^2-$ or N,

Q is O or NH,

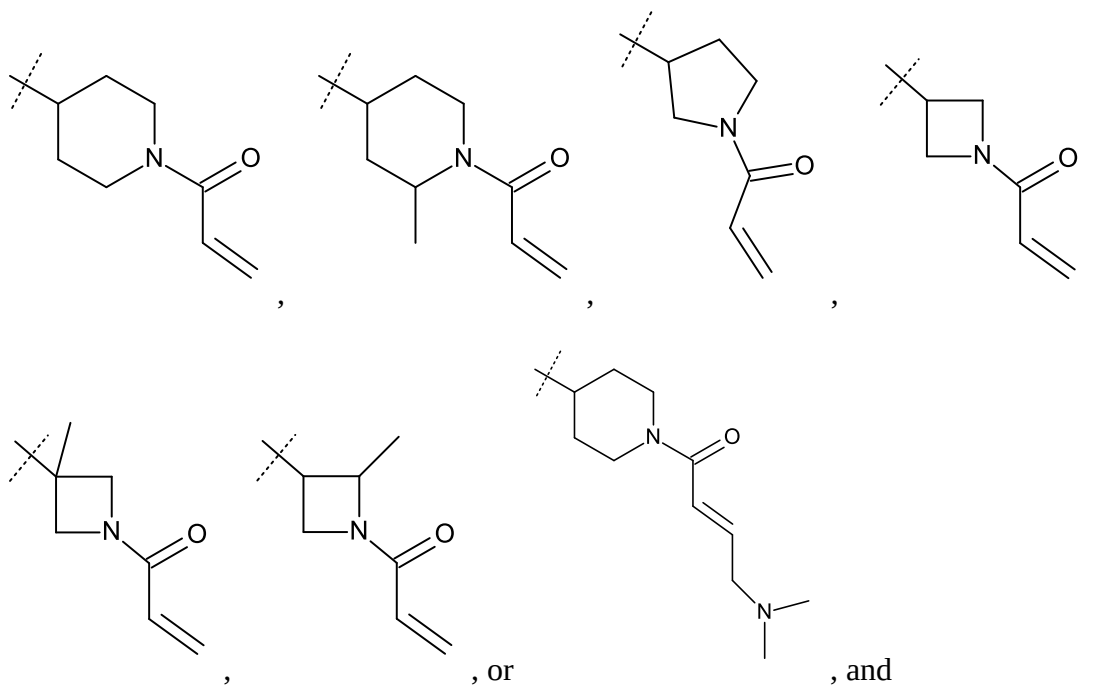
X is $-CH-$ or N,

R^1 is $-H$, $-Cl$, $-F$, $-CN$, $-CH_3$, $-CF_3$, $-OCHF_2$, $-OCH_3$, $-OCF_3$, or $-C\equiv CH$,

R^2 is $-H$, $-F$ or $-OCF_3$,

10 R^3 is $-H$, $-Cl$ or $-F$,

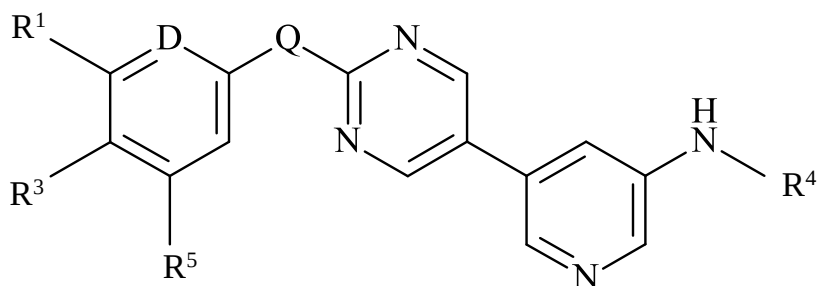
R^4 is



R^5 is $-H$ or $-F$,

or a pharmaceutically acceptable salt thereof.

2. A compound of claim 1 wherein D is $-\text{CR}^2-$, R^1 is $-\text{Cl}$, R^3 is $-\text{H}$, and R^5 is $-\text{H}$, or a pharmaceutically acceptable salt thereof.
3. A compound of claim 1 of the formula:



5

wherein:

D is $-\text{CR}^2-$ or N,

Q is O or NH,

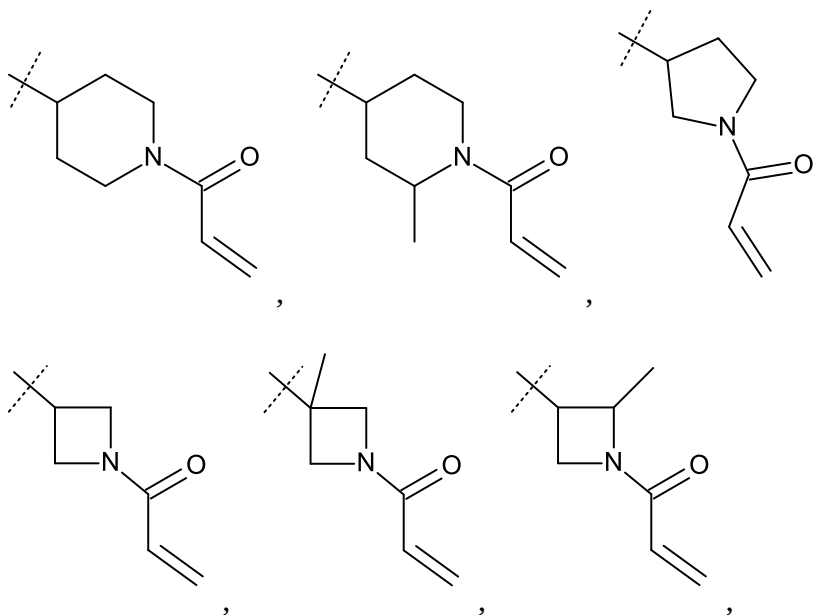
R^1 is $-\text{H}$, $-\text{Cl}$, $-\text{F}$, $-\text{CN}$, $-\text{CH}_3$, $-\text{CF}_3$, $-\text{OCHF}_2$, $-\text{OCH}_3$, $-\text{OCF}_3$, or $-\text{C}\equiv\text{CH}$,

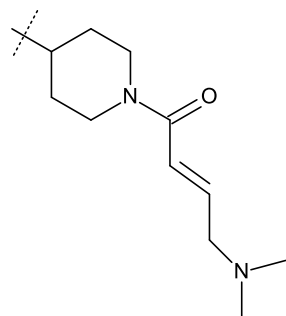
10

R^2 is $-\text{H}$, $-\text{F}$ or $-\text{OCF}_3$,

R^3 is $-\text{H}$, $-\text{Cl}$ or $-\text{F}$,

R^4 is



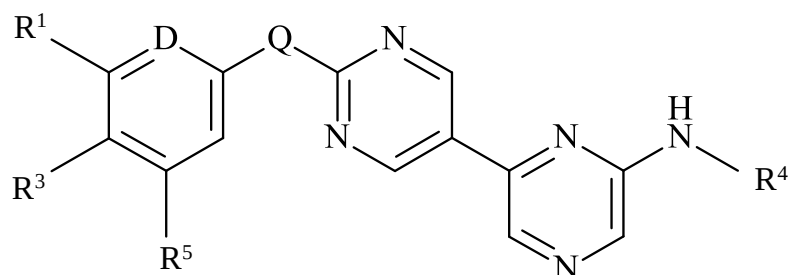


or , and

R^5 is $-H$ or $-F$,

or a pharmaceutically acceptable salt thereof.

4. The compound of claim 3 wherein D is $-CR^2-$, R^1 is $-Cl$, R^3 is $-H$, and R^5 is $-H$, or a pharmaceutically acceptable salt thereof.
5. A compound of claim 1 of the formula:



wherein:

D is $-CR^2-$ or N,

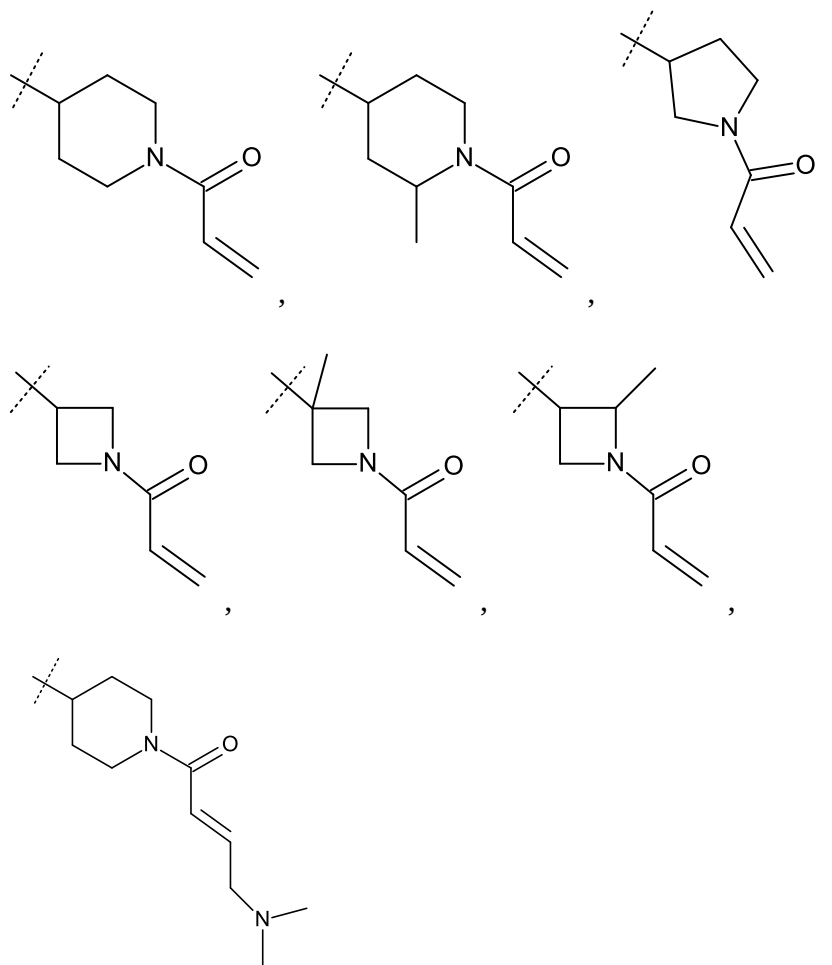
Q is O or NH,

R^1 is $-H$, $-Cl$, $-F$, $-CN$, $-CH_3$, $-CF_3$, $-OCHF_2$, $-OCH_3$, $-OCF_3$, or $-C\equiv CH$,

R^2 is $-H$, $-F$ or $-OCF_3$,

R^3 is $-H$, $-Cl$ or $-F$,

R^4 is



or
, and

R^5 is $-H$ or $-F$,

5 or a pharmaceutically acceptable salt thereof.

6. The compound of claim 5 wherein D is $-CR^2-$, R^1 is $-Cl$, R^3 is $-H$, and R^5 is $-H$, or a pharmaceutically acceptable salt thereof.

7. The compound of claim 1 selected from the group consisting of:

- 10 1-[3-[[5-[2-(3-chloro-2-fluoro-phenoxy)pyrimidin-5-yl]-3-pyridyl]amino]azetidin-1-yl]prop-2-en-1-one;
3-[5-[5-[(1-prop-2-enoylazetidin-3-yl)amino]-3-pyridyl]pyrimidin-2-yl]oxybenzonitrile;

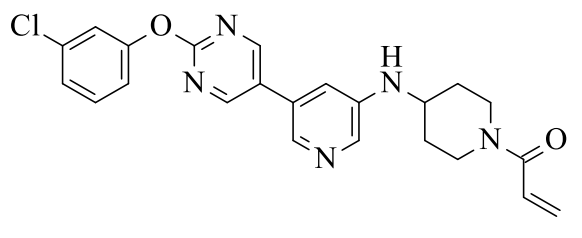
- 1-[3-[[5-[2-[3-(difluoromethoxy)phenoxy]pyrimidin-5-yl]-3-pyridyl]amino]azetidin-1-yl]prop-2-en-1-one;
- 1-[(3S)-3-[[5-[2-[3-(difluoromethoxy)phenoxy]pyrimidin-5-yl]-3-pyridyl]amino]pyrrolidin-1-yl]prop-2-en-1-one;
- 5 1-[(3S)-3-[[5-[2-(3-chlorophenoxy)pyrimidin-5-yl]-3-pyridyl]amino]pyrrolidin-1-yl]prop-2-en-1-one;
- 1-[3-[[5-[2-(3-chlorophenoxy)pyrimidin-5-yl]-3-pyridyl]amino]azetidin-1-yl]prop-2-en-1-one;
- 10 1-[3-[[5-[2-[3-(trifluoromethyl)phenoxy]pyrimidin-5-yl]-3-pyridyl]amino]azetidin-1-yl]prop-2-en-1-one;
- 1-[3-[[5-[2-[3-(difluoromethoxy)-4-fluoro-phenoxy]pyrimidin-5-yl]-3-pyridyl]amino]azetidin-1-yl]prop-2-en-1-one;
- 1-[3-[[5-[2-[3-(trifluoromethoxy)phenoxy]pyrimidin-5-yl]-3-pyridyl]amino]azetidin-1-yl]prop-2-en-1-one;
- 15 1-[3-[[5-[2-(3-fluorophenoxy)pyrimidin-5-yl]-3-pyridyl]amino]azetidin-1-yl]prop-2-en-1-one;
- 1-[3-[[5-[2-(3-chlorophenoxy)pyrimidin-5-yl]-3-pyridyl]amino]-3-methylazetidin-1-yl]prop-2-en-1-one;
- 1-[3-[[5-[2-(3-chloro-4-fluoro-phenoxy)pyrimidin-5-yl]-3-pyridyl]amino]azetidin-1-yl]prop-2-en-1-one;
- 20 1-[3-[[5-[2-(3-ethynylphenoxy)pyrimidin-5-yl]-3-pyridyl]amino]azetidin-1-yl]prop-2-en-1-one;
- 1-[3-[[5-[2-(3-chloroanilino)pyrimidin-5-yl]-3-pyridyl]amino]azetidin-1-yl]prop-2-en-1-one;
- 25 (S)-1-(3-((5-(2-((3-(difluoromethoxy)phenyl)amino)pyrimidin-5-yl)pyridin-3-yl)amino)pyrrolidin-1-yl)prop-2-en-1-one;
- 1-{(3S)-3-[(5-{2-[(6-methylpyridin-2-yl)amino]pyrimidin-5-yl}pyridin-3-yl)amino]pyrrolidin-1-yl}prop-2-en-1-one;

- 1-[3-[[5-[2-[3-(trifluoromethyl)anilino]pyrimidin-5-yl]-3-pyridyl]amino]azetidin-1-yl]prop-2-en-1-one;
- 1-[4-[[5-[2-(3-chloroanilino)pyrimidin-5-yl]-3-pyridyl]amino]-1-piperidyl]prop-2-en-1-one;
- 5 1-[4-[[5-[2-[(6-methyl-2-pyridyl)amino]pyrimidin-5-yl]-3-pyridyl]amino]-1-piperidyl]prop-2-en-1-one;
- 1-[4-[[5-[2-[[6-(trifluoromethyl)-2-pyridyl]amino]pyrimidin-5-yl]-3-pyridyl]amino]-1-piperidyl]prop-2-en-1-one;
- 10 1-[4-[[5-[2-(2-pyridylamino)pyrimidin-5-yl]-3-pyridyl]amino]-1-piperidyl]prop-2-en-1-one;
- (E)-1-[4-[[5-[2-(3-chloroanilino)pyrimidin-5-yl]-3-pyridyl]amino]-1-piperidyl]-4-(dimethylamino)but-2-en-1-one;
- 1-[3-[[6-[2-[3-(difluoromethoxy)phenoxy]pyrimidin-5-yl]pyrazin-2-yl]amino]azetidin-1-yl]prop-2-en-1-one;
- 15 1-[3-[[6-[2-(3-fluorophenoxy)pyrimidin-5-yl]pyrazin-2-yl]amino]azetidin-1-yl]prop-2-en-1-one;
- 1-[3-[[6-[2-[3-(trifluoromethyl)phenoxy]pyrimidin-5-yl]pyrazin-2-yl]amino]azetidin-1-yl]prop-2-en-1-one;
- 1-[3-[[6-[2-[3-(trifluoromethoxy)phenoxy]pyrimidin-5-yl]pyrazin-2-yl]amino]azetidin-1-yl]prop-2-en-1-one;
- 20 1-[3-[[6-(2-phenoxy)pyrimidin-5-yl]pyrazin-2-yl]amino]azetidin-1-yl]prop-2-en-1-one;
- 1-[3-[[6-[2-(3-chlorophenoxy)pyrimidin-5-yl]pyrazin-2-yl]amino]-3-methylazetidin-1-yl]prop-2-en-1-one;
- 25 1-[3-[[6-[2-(3,5-difluorophenoxy)pyrimidin-5-yl]pyrazin-2-yl]amino]azetidin-1-yl]prop-2-en-1-one;
- 1-[3-[[6-[2-(3-chlorophenoxy)pyrimidin-5-yl]pyrazin-2-yl]amino]azetidin-1-yl]prop-2-en-1-one;

- 1-[(2S,3R)-3-[[6-[2-(3-chlorophenoxy)pyrimidin-5-yl]pyrazin-2-yl]amino]-2-methyl-azetidin-1-yl]prop-2-en-1-one, Isomer 1;
- 1-[(3S)-3-[[6-[2-[3-(trifluoromethoxy)anilino]pyrimidin-5-yl]pyrazin-2-yl]amino]pyrrolidin-1-yl]prop-2-en-1-one;
- 5 1-[(3S)-3-[[6-[2-(3-chloroanilino)pyrimidin-5-yl]pyrazin-2-yl]amino]pyrrolidin-1-yl]prop-2-en-1-one;
- 1-3-[[6-[2-(3-chloro-4-fluoro-anilino)pyrimidin-5-yl]pyrazin-2-yl]amino]azetidin-1-yl]prop-2-en-1-one;
- 1-[(3S)-3-[[6-[2-[2-(trifluoromethoxy)anilino]pyrimidin-5-yl]pyrazin-2-yl]amino]pyrrolidin-1-yl]prop-2-en-1-one;
- 10 1-3-[[6-[2-[3-(trifluoromethoxy)anilino]pyrimidin-5-yl]pyrazin-2-yl]amino]azetidin-1-yl]prop-2-en-1-one;
- 1-4-[[6-[2-[3-(difluoromethoxy)phenoxy]pyrimidin-5-yl]pyrazin-2-yl]amino]-1-piperidyl]prop-2-en-1-one;
- 15 1-[(3S)-3-[[6-[2-[3-(difluoromethoxy)anilino]pyrimidin-5-yl]pyrazin-2-yl]amino]pyrrolidin-1-yl]prop-2-en-1-one;
- 1-3-[[6-[2-[(6-methyl-2-pyridyl)amino]pyrimidin-5-yl]pyrazin-2-yl]amino]azetidin-1-yl]prop-2-en-1-one;
- 1-3-[[6-[2-(4-chlorophenoxy)pyrimidin-5-yl]pyrazin-2-yl]amino]azetidin-1-yl]prop-2-en-1-one;
- 20 1-3-[[6-[2-(3-methoxyphenoxy)pyrimidin-5-yl]pyrazin-2-yl]amino]azetidin-1-yl]prop-2-en-1-one;
- 1-3-[[6-[2-[2-(trifluoromethoxy)anilino]pyrimidin-5-yl]pyrazin-2-yl]amino]azetidin-1-yl]prop-2-en-1-one;
- 25 1-4-[[6-[2-(3-chlorophenoxy)pyrimidin-5-yl]pyrazin-2-yl]amino]-1-piperidyl]prop-2-en-1-one;
- (E)-1-4-[[6-[2-(3-chlorophenoxy)pyrimidin-5-yl]pyrazin-2-yl]amino]-1-piperidyl]-4-(dimethylamino)but-2-en-1-one;

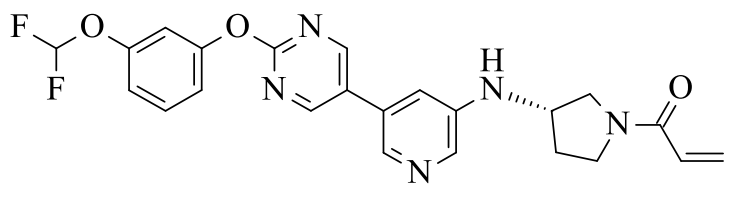
(E)-1-[4-[[6-[2-(3-chloroanilino)pyrimidin-5-yl]pyrazin-2-yl]amino]-1-piperidyl]-
4-(dimethylamino)but-2-en-1-one; and
1-[4-[[5-[2-(3-chloroanilino)pyrimidin-5-yl]-3-pyridyl]amino]-2-methyl-1-
piperidyl]prop-2-en-1-one,
5 or a pharmaceutically acceptable salt thereof.

8. The compound of claim 1 which is:



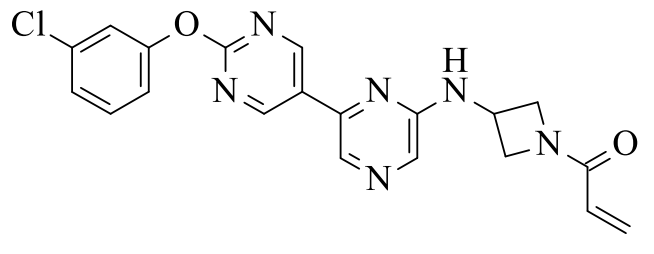
or a pharmaceutically acceptable salt thereof.

10 9. The compound of claim 1 which is:

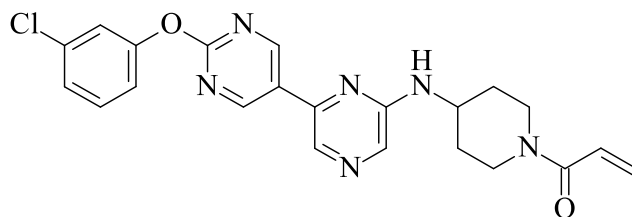


or a pharmaceutically acceptable salt thereof.

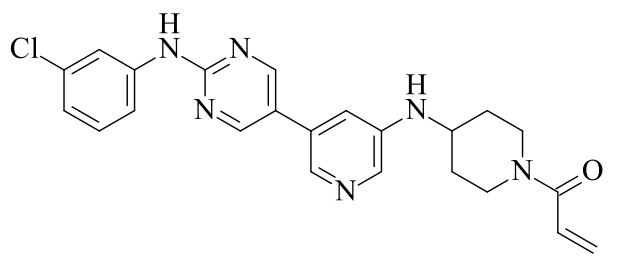
10. The compound of claim 1 which:



15 11. The compound of claim 1 which:

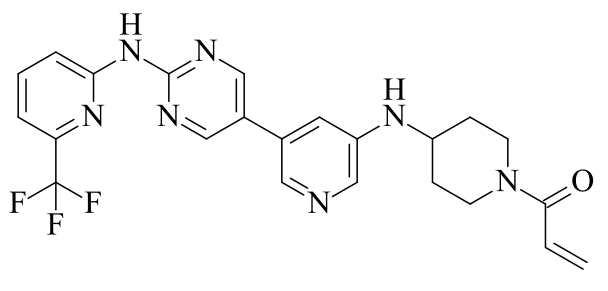


12. The compound of claim 1 which is:



or a pharmaceutically acceptable salt thereof.

5 13. The compound of claim 1 which is:



or a pharmaceutically acceptable salt thereof.

14. A pharmaceutical composition comprising a compound according to any one of claims 1 to 13, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, diluent or excipient.

15. Use of a compound according to any one of claims 1 to 13, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating Rheumatoid Arthritis.

16. Use of a compound according to any one of claims 1 to 13, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating Systemic Lupus Erythematosus.

17. Use of a compound according to any one of claims 1 to 13, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating Multiple Sclerosis.
- 5 18. Use of a compound according to any one of claims 1 to 13, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating Sjögren's Syndrome.
19. Use of a compound according to any one of claims 1-9, or 12-13, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating Pemphigus.
- 10 20. A compound as claimed in any one of claims 1-13, or a pharmaceutically acceptable salt thereof, for use in therapy.
21. A compound as claimed in any one of claims 1-9, or 12-13, or a pharmaceutically acceptable salt thereof, for use in the treatment of Rheumatoid Arthritis.
22. A compound as claimed in any one of claims 1-9, or 12-13, or a pharmaceutically acceptable salt thereof, for use in the treatment of Systemic Lupus Erythematosus.
- 15 23. A compound as claimed in any one of claims 1-9, or 12-13, or a pharmaceutically acceptable salt thereof, for use in the treatment of Multiple Sclerosis.
24. A compound as claimed in any one of claims 1-9, or 12-13, or a pharmaceutically acceptable salt thereof, for use in the treatment of Pemphigus.
- 20 25. Use of 1-[4-[[5-[2-(3-chlorophenoxy)pyrimidin-5-yl]-3-pyridyl]amino]-1-piperidyl]prop-2-en-1-one in the manufacture of a medicament for treating Rheumatoid Arthritis.
26. Use of 1-[4-[[5-[2-(3-chlorophenoxy)pyrimidin-5-yl]-3-pyridyl]amino]-1-piperidyl]prop-2-en-1-one in the manufacture of a medicament for treating treating Systemic Lupus Erythematosus.
- 25 27. Use of 1-[4-[[5-[2-(3-chlorophenoxy)pyrimidin-5-yl]-3-pyridyl]amino]-1-piperidyl]prop-2-en-1-one in the manufacture of a medicament for treating Multiple Sclerosis.