

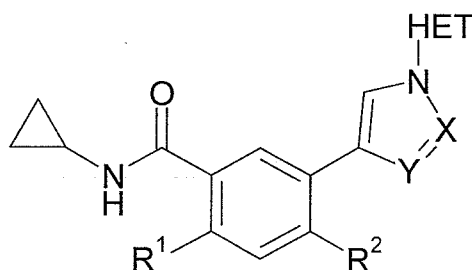
Mutations in NOD2 have been linked to multiple diseases. Activating mutations have been linked to Early Onset Sarcoidosis (Kanazawa et al., 2005) and Blau syndrome (Miceli-Richard et al., 2001) which affect skin, joints, and eyes. These activating mutations result in increased basal NF- κ B activity (Kanazawa et al., 2005). Loss-of-function mutations in the NOD2 LRR are linked to Crohn's Disease (Ogura et al. 2001; Hugot et al. 2001; Hampe et al. 2001; Hampe 2002; Lesange 2002). In addition, polymorphisms in NOD1 have been linked to atopy (Weidinger et al. 2005) and asthma (Hysi et al. 2005). Additional studies in cellular and in vivo mouse models have suggested a role for NOD1 and NOD2 signaling in a variety of diseases such as Graft vs. Host Disease, Arthritis, Multiple Sclerosis, and Diabetic Nephropathy (Peaneck et al. 2009; Saha et al. 2009; Vieira et al. 2012; Rosenzweig et al. 2010; Joosten et al. 2008; Shaw et al. 2011; Du et al. 2013). Small molecule inhibitors of RIP2 kinase (RIPK2) are disclosed in US2013/0023532 A1 but appear to have limited potency.

Pharmacological inhibition of RIPK2 by a potent and selective small molecule inhibitor will attenuate pro-inflammatory signaling through the bacterial sensing pathways initiated by NOD1 and NOD2 stimulation. This reduction in inflammatory signaling will provide therapeutic benefit in a variety of autoinflammatory diseases. Thus, there is a need for potent inhibitors of RIPK2 for pharmaceutical purposes.

BRIEF SUMMARY

The present disclosure provides novel heteroaryl carboxamide series of compounds which inhibit the receptor-interacting serine/threonine protein kinase 2 (RIPK2) and are thus useful for treating a variety of diseases and disorders that are mediated or sustained through the activity of RIPK2 including inflammatory, cardiometabolic and cardiovascular diseases and cancer.

In one aspect of the present disclosure, there is provided a compound of Formula (I):



I

or pharmaceutically acceptable salts thereof, wherein:

X is N and **Y** is CH; or

X is CH and **Y** is N;

HET is a 5-membered heteroaryl ring containing one to three heteroatoms selected from nitrogen and sulfur, wherein each heteroaryl ring is optionally substituted with one to two substituents groups independently selected from **R³** and **R⁴**; or

HET is a 5-membered heteroaryl ring containing one to three heteroatoms selected from nitrogen and sulfur, wherein each heteroaryl ring is substituted with two substituents groups selected from **Rᵃ** and **Rᵇ**, wherein **Rᵃ** and **Rᵇ** together with the atoms to which they are attached form a 5-6 membered heterocyclic or heteroaryl ring which may be optionally substituted with one to two substituents selected from **R³** and **R⁴**;

R¹ is hydrogen or F;

R² is C₁₋₃ alkyl or Cl;

R³ and **R⁴** are each independently selected from:

- (a) -H,
- (b) -O R⁵,
- (c) -O- C₁₋₆alkyl-O- C₁₋₃ alkyl,

- (d) $-O-C_{3-6}$ cycloalkyl,
- (e) $-C(O)R^5$,
- (f) C_{1-6} alkyl optionally substituted with one to three $-OH$, fluorine, heterocyclyl optionally substituted with oxo, C_{3-6} cycloalkyl, $-CO_2R^5$, $-O-C_{1-6}$ alkyl, aryl, $-N(R^5)(R^6)$, or $-C(O)N(R^5)(R^6)$,
- (g) C_{3-6} cycloalkyl optionally substituted with one to three $-OH$, one to three fluorine, C_{1-6} alkyl, $-OC_{1-6}$ alkyl, C_{1-6} alkyl- OC_{1-6} alkyl, C_{1-6} alkyl- OH , CF_3 , $-OC_{3-6}$ cycloalkyl, $-CO_2H$, $-CO_2R^5$, C_{3-6} cycloalkyl, 5-6 membered heteroaryl, C_{3-6} heterocyclyl, $N(R^5)(R^6)$, or $-C(O)N(R^5)(R^6)$,
- (h) $-CO_2R^5$,
- (i) $-C(O)N(R^5)(R^6)$,
- (j) $-S(O)_2N(R^5)(R^6)$,
- (k) $-S(O)_n-R^5$,
- (l) a 5-6 membered heteroaryl group optionally substituted with one to three groups selected from C_{1-6} alkyl, C_{3-6} cycloalkyl, halogen, $-CF_3$, $-OH$, $-(CH_2)_nCO_2R^5$, $-C(O)N(R^5)(R^6)$, $-N(R^5)(R^6)$, $-NH-SO_2C_{1-6}$ alkyl, C_{1-6} alkoxyl, C_{1-6} alkyl- $O-C_{1-3}$ alkyl, C_{1-6} alkylhydroxyl, C_{1-3} alkyl-CN, oxo, phenyl optionally substituted with halogen and $-S(O)_nC_{1-6}$ alkyl,
- (m) 4-10 membered monocyclic, bicyclic or spirocyclic heterocyclyl group containing N, S or O, wherein each heterocycle is optionally substituted with with 1-3 substituents selected from 3-6 membered heterocyclic ring, halogen, $-C_{1-3}$ alkyl, $-C_{1-3}$ alkyl $-O-C_{1-3}$ alkyl and $-C_{1-3}$ alkyl- $C(O)N(R^5)(R^6)$,
- (n) aryl,
- (o) $-N(R^5)(R^6)$;

R^5 and R^6 are each independently selected from $-H$, 4-6 membered heterocyclyl, $-C(O)-C_{1-3}$ alkyl $-C(O)-C_{1-3}$ cycloalkyl and $-(C_{1-6})$ alkyl, wherein each R^5 and R^6 is independently optionally substituted with $-OH$, C_{3-6} cycloalkyl, $-C_{1-3}$ alkyl, $-O-C_{1-3}$ alkyl, $-NH-C_{1-3}$ alkyl or $-N-(C_{1-3}-alkyl)_2$; or

R^5 and R^6 together with the nitrogen atom to which they are attached form a 4-6 membered heterocyclic ring optionally substituted with methyl; and

n is 0, 1, or 2.

In another aspect of the present disclosure, there is provided a pharmaceutically acceptable salt of a compound as defined herein.

In yet another aspect of the present disclosure, there is provided a pharmaceutical composition comprising the compound as defined herein, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable carrier.

This disclosure also relates to pharmaceutical compositions comprising these compounds, methods of using these compounds in the treatment of various diseases and disorders, processes for preparing these compounds and intermediates useful in these processes.

In one embodiment of the disclosure, a compound of this disclosure has good binding potency.

In another embodiment of the disclosure, a compound this disclosure exhibits good cellular potency.

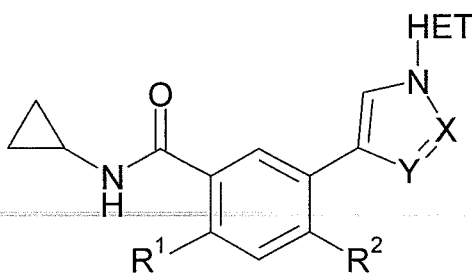
In yet another embodiment, a compound of this disclosure exhibits good stability.

In another embodiment, a compound of this disclosure exhibits good cell permeability.

In another aspect of the present disclosure, there is provided a use of compound as defined herein, for the manufacture of a medicament for the treatment of an autoimmune disease or allergic disorder.

DETAILED DESCRIPTION OF THE INVENTION

In its broadest embodiment, the present invention relates compounds of formula I:



I

or pharmaceutically acceptable salts thereof, wherein:

X is N and **Y** is CH; or

X is CH and **Y** is N;

HET is a 5-membered heteroaryl ring containing one to three heteroatoms selected from nitrogen and sulfur, wherein each heteroaryl ring is optionally substituted with one to two substituents groups independently selected from **R³** and **R⁴**; or

HET is a 5-membered heteroaryl ring containing one to three heteroatoms selected from nitrogen and sulfur, wherein each heteroaryl ring is substituted with two substituents groups selected from **R^a** and **R^b**, wherein **R^a** and **R^b** together with the atoms to which they are attached form a 5-6 membered heterocyclic or heteroaryl ring which may be optionally substituted with one to two substituents selected from **R³** and **R⁴**;

R¹ is hydrogen or F;

substituted with --OH , C_{3-6} cycloalkyl, $\text{--C}_{1-3}\text{alkyl}$, $\text{--O--C}_{1-3}\text{alkyl}$, $\text{--NH--C}_{1-3}\text{alkyl}$ or $\text{--N--(C}_{1-3}\text{alkyl)}_2$; or

R^5 and R^6 together with the nitrogen atom to which they are attached form a 4-6 membered heterocyclic ring optionally substituted with methyl; and

n is 0, 1, or 2.

2. The compound according to claim 1 or a pharmaceutically acceptable salt thereof, wherein:

X is N and Y is CH; or

X is CH and Y is N;

Het is a 5-membered heteroaryl ring selected from pyrazolyl, imidazolyl, thiazolyl and thiadiazolyl, wherein each heteroaryl ring is optionally substituted with one to two substituents groups independently selected from R^3 and R^4 ; or

Het is a 5-membered heteroaryl ring selected from pyrazolyl and imidazolyl, wherein each heteroaryl ring is substituted with two substituents groups selected from R^a and R^b , wherein R^a and R^b together with the atoms to which they are attached form a 5-6 membered heterocyclic or heteroaryl ring which may be optionally substituted with one to two substituents selected from R^3 and R^4 ;

R^1 is hydrogen or F;

R^2 is C_{1-3} alkyl or Cl;

R^3 and R^4 are each independently selected from:

- (a) --H ,
- (b) --OR^5 ,
- (c) $\text{--O--C}_{1-6}\text{alkyl--O--C}_{1-3}\text{alkyl}$
- (d) $\text{--O--C}_{3-6}\text{ cycloalkyl}$,
- (e) --C(O)R^5 ,

(f) C₁₋₆alkyl optionally substituted with one to three –OH, fluorine, heterocyclyl optionally substituted with oxo, C₃₋₆ cycloalkyl, –CO₂R⁵, –O– C₁₋₆alkyl, aryl, –N(R⁵)(R⁶), or –C(O)N(R⁵)(R⁶),

(g) C₃₋₆ cycloalkyl optionally substituted with one to three –OH, one to three fluorine, C₁₋₆alkyl, –OC₁₋₆alkyl, C₁₋₆alkyl–OC₁₋₆alkyl, C₁₋₆alkyl–OH, CF₃, –OC₃₋₆cycloalkyl, –CO₂H, –CO₂R⁵, C₃₋₆cycloalkyl, 5-6 membered heteroaryl, C₃₋₆ heterocyclyl, N(R⁵)(R⁶), or –C(O)N(R⁵)(R⁶),

(h) –CO₂R⁵,

(i) –C(O)N(R⁵)(R⁶),

(j) –S(O)₂N(R⁵)(R⁶),

(k) –S(O)_n–R⁵

(l) a 5-6 membered heteroaryl group optionally substituted with one to three groups selected from C₁₋₆alkyl, C₃₋₆cycloalkyl, halogen, –CF₃, –OH, –(CH₂)_nCO₂R⁵, –C(O)N(R⁵)(R⁶), –N(R⁵)(R⁶), –NH–SO₂C₁₋₆alkyl, C₁₋₆alkoxyl, C₁₋₆alkyl–O– C₁₋₃ alkyl, C₁₋₆alkylhydroxyl, C₁₋₃alkyl–CN, oxo, phenyl optionally substituted with halogen and –S(O)_nC₁₋₆alkyl,

(m) 4-10 membered monocyclic, bicyclic or spirocyclic heterocyclyl group containing N, S or O, wherein each heterocycle is optionally substituted with 1-3 substituents selected from 3-6 membered heterocyclic ring, halogen, C₁₋₃alkyl, and C₁₋₃alkyl–C(O)N(R⁵)(R⁶),

(n) aryl,

(o)– N(R⁵)(R⁶);

R⁵ and R⁶ are each independently selected from –H, 4-6 membered heterocyclyl, –C(O)–C₁₋₃ alkyl –C(O)–C₁₋₃ cycloalkyl and –(C₁–C₆)alkyl optionally substituted with –OH, C₃₋₆ cycloalkyl, –NH–C₁₋₃ alkyl or –N–(C₁₋₃–alkyl)₂; or

R⁵ and R⁶ together with the nitrogen atom to which they are attached form a 5-6 membered heterocyclic ring optionally substituted with methyl; and

n is 0 or 2 .

3. The compound according to claim 1 or a pharmaceutically acceptable salt thereof, wherein:

HET is a 5-membered heteroaryl ring selected from pyrazolyl, imidazolyl, thiazolyl and thiadiazolyl, wherein each heteroaryl ring is optionally substituted with one to two substituents groups independently selected from **R**³ and **R**⁴;

R³ and **R**⁴ are each independently selected from:

- (a) -H,
- (b) -O R⁵,
- (c) -O- C₁₋₆alkyl-O- C₁₋₃ alkyl
- (d) -O-C₃₋₆ cycloalkyl,
- (e) -C(O)R⁵,
- (f) C₁₋₆alkyl optionally substituted with one to three -OH, fluorine, heterocyclyl optionally substituted with oxo, C₃₋₆ cycloalkyl, -CO₂R⁵, -O- C₁₋₆alkyl, aryl, -N(R⁵)(R⁶), or -C(O)N(R⁵)(R⁶),
- (g) C₃₋₆ cycloalkyl optionally substituted with one to three -OH, one to three fluorine, C₁₋₆alkyl, -OC₁₋₆alkyl, C₁₋₆alkyl-OC₁₋₆alkyl, C₁₋₆alkyl-OH, CF₃, -OC₃₋₆cycloalkyl, -CO₂H, -CO₂R⁵, C₃₋₆cycloalkyl, 5-6 membered heteroaryl, C₃₋₆heterocyclyl, N(R⁵)(R⁶), or -C(O)N(R⁵)(R⁶),
- (h) -CO₂R⁵,
- (i) -C(O)N(R⁵)(R⁶),
- (j) -S(O)₂N(R⁵)(R⁶),
- (k) -S(O)_n-R⁵
- (l) a 5-6 membered heteroaryl group optionally substituted with one to three groups selected from C₁₋₆alkyl, C₃₋₆cycloalkyl, halogen, -CF₃, -OH, -(CH₂)_nCO₂R⁵, -C(O)N(R⁵)(R⁶), -N(R⁵)(R⁶), -NH-SO₂C₁₋₆alkyl, C₁₋₆alkoxyl, C₁₋₆alkyl-O- C₁₋₃ alkyl, C₁₋₆alkylhydroxyl, C₁₋₃alkyl-CN, oxo, phenyl optionally substituted with halogen and -S(O)_nC₁₋₆alkyl,

(m) 4-10 membered monocyclic, bicyclic or spirocyclic heterocyclyl group containing N, S or O, wherein each heterocycle is optionally substituted with 1-3 substituents selected from 3-6 membered heterocyclic ring, halogen, C₁₋₃alkyl, and C₁₋₃alkyl- C(O)N(R⁵)(R⁶),

(n) aryl,

(o)- N(R⁵)(R⁶);

R⁵ and R⁶ are each independently selected from -H, 4-6 membered heterocyclyl, -C(O)-C₁₋₃ alkyl -C(O)-C₁₋₃ cycloalkyl and -(C₁-C₆)alkyl optionally substituted with -OH, C₃₋₆ cycloalkyl, -NH-C₁₋₃ alkyl or -N-(C₁₋₃-alkyl)₂; or

R⁵ and R⁶ together with the nitrogen atom to which they are attached form a 5-6 membered heterocyclic ring optionally substituted with methyl; and

n is 0 or 2 .

4. The compound according to claim 1 or a pharmaceutically acceptable salt thereof, wherein:

HET is a 5-membered heteroaryl ring selected from pyrazolyl and imidazolyl, wherein each heteroaryl ring is substituted with two substituents groups selected from **R^a** and **R^b**; wherein **R^a** and **R^b** together with the atoms to which they are attached form a 5-6 membered heterocyclic or heteroaryl ring which may be optionally substituted with one to two substituents selected from **R³** and **R⁴**;

R³ and **R⁴** are each independently selected from:

(a) -H,

(b) -O R⁵,

(c) -O- C₁₋₆alkyl-O- C₁₋₃ alkyl

(d) -O-C₃₋₆ cycloalkyl,

(e) -C(O)R⁵,

(f) C₁₋₆alkyl optionally substituted with one to three -OH, fluorine, heterocyclyl optionally substituted with oxo, C₃₋₆ cycloalkyl, -CO₂R⁵, -O- C₁₋₆alkyl, aryl, -N(R⁵)(R⁶), or -C(O)N(R⁵)(R⁶),

- (g) C₃₋₆ cycloalkyl optionally substituted with one to three –OH, one to three fluorine, C₁₋₆alkyl, –OC₁₋₆alkyl, C₁₋₆alkyl–OC₁₋₆alkyl, C₁₋₆alkyl–OH, CF₃, –OC₃₋₆cycloalkyl, –CO₂H, –CO₂R⁵, C₃₋₆cycloalkyl, 5-6 membered heteroaryl, C₃₋₆ heterocyclyl, N(R⁵)(R⁶), or –C(O)N(R⁵)(R⁶),
- (h) –CO₂R⁵,
- (i) –C(O)N(R⁵)(R⁶),
- (j) –S(O)₂N(R⁵)(R⁶),
- (k) –S(O)_n–R⁵
- (l) a 5-6 membered heteroaryl group optionally substituted with one to three groups selected from C₁₋₆alkyl, C₃₋₆cycloalkyl, halogen, –CF₃, –OH, –(CH₂)_nCO₂R⁵, –C(O)N(R⁵)(R⁶), –N(R⁵)(R⁶), –NH–SO₂C₁₋₆alkyl, C₁₋₆alkoxyl, C₁₋₆alkyl–O–C₁₋₃alkyl, C₁₋₆alkylhydroxyl, C₁₋₃alkyl–CN, oxo, phenyl optionally substituted with halogen and –S(O)_nC₁₋₆alkyl,
- (m) 4-10 membered monocyclic, bicyclic or spirocyclic heterocyclyl group containing N, S or O, wherein each heterocycle is optionally substituted with 1-3 substituents selected from 3-6 membered heterocyclic ring, halogen, C₁₋₃alkyl, and C₁₋₃alkyl–C(O)N(R⁵)(R⁶),
- (n) aryl,
- (o) –N(R⁵)(R⁶);

R⁵ and R⁶ are each independently selected from –H, 4-6 membered heterocyclyl, –C(O)–C₁₋₃alkyl, –C(O)–C₁₋₃cycloalkyl and –(C₁₋₆)alkyl optionally substituted with –OH, C₃₋₆cycloalkyl, –NH–C₁₋₃alkyl or –N–(C₁₋₃alkyl)₂; or

R⁵ and R⁶ together with the nitrogen atom to which they are attached form a 6 membered heterocyclic ring optionally substituted with methyl; and

n is 0 or 2 .

5. The compound according to claim 1 or a pharmaceutically acceptable salt thereof, wherein: **HET** is pyrazolyl optionally substituted with one to two substituents groups selected from **R**³ and **R**⁴.

6. The compound according to claim 1 or a pharmaceutically acceptable salt thereof, wherein:

HET is a 5-membered heteroaryl ring selected from pyrazolyl and imidazolyl, wherein each heteroaryl ring is substituted with two substituents groups selected from **R^a** and **R^b**; wherein **R^a** and **R^b** together with the atoms to which they are attached form a 5-6 membered heteroaryl ring such that **HET** is a bicyclic heteroaryl ring selected from imidazopyridine and pyrazolopyridine which may be optionally substituted one to two substituents selected from **R³** and **R⁴**.

7. The compound according to claim 1 or a pharmaceutically acceptable salt thereof, wherein:

X is N;

Y is CH;

R¹ is F;

R² is selected from methyl and Cl;

HET is selected from imidazopyridine and pyrazolopyridine which may be optionally substituted one to two substituents selected from **R³** and **R⁴**;

R³ and **R⁴** are each independently selected from:

(a) -H,

(b) -O R⁵,

(c) -O- C₁₋₆alkyl-O- C₁₋₃ alkyl

(d) -O-C₃₋₆ cycloalkyl,

(e) -C(O)R⁵,

(f) C₁₋₆alkyl optionally substituted with one to three -OH, fluorine, heterocyclyl optionally substituted with oxo, C₃₋₆ cycloalkyl, -CO₂R⁵, -O- C₁₋₆alkyl, aryl, -N(R⁵)(R⁶), or -C(O)N(R⁵)(R⁶),

(g) C₃₋₆ cycloalkyl optionally substituted with one to three -OH, one to three fluorine, C₁₋₆alkyl, -OC₁₋₆alkyl, C₁₋₆alkyl-OC₁₋₆alkyl, C₁₋₆alkyl-OH, CF₃, -OC₃₋₆cycloalkyl, -CO₂H, -CO₂R⁵, C₃₋₆cycloalkyl, 5-6 membered heteroaryl, C₃₋₆ heterocyclyl, N(R⁵)(R⁶), or -C(O)N(R⁵)(R⁶),

(h) $-\text{CO}_2\text{R}^5$,

(i) $-\text{C}(\text{O})\text{N}(\text{R}^5)(\text{R}^6)$,

(j) $-\text{S}(\text{O})_2\text{N}(\text{R}^5)(\text{R}^6)$,

(k) $-\text{S}(\text{O})_2-\text{R}^5$

(l) a 5-6 membered heteroaryl group optionally substituted with one to three groups selected from C_{1-6} alkyl, C_{3-6} cycloalkyl, halogen, $-\text{CF}_3$, $-\text{OH}$, $-(\text{CH}_2)\text{CO}_2\text{R}^5$, $-\text{C}(\text{O})\text{N}(\text{R}^5)(\text{R}^6)$, $-\text{N}(\text{R}^5)(\text{R}^6)$, $-\text{NH}-\text{SO}_2\text{C}_{1-6}$ alkyl, C_{1-6} alkoxyl, C_{1-6} alkyl-O- C_{1-3} alkyl, C_{1-6} alkylhydroxyl, C_{1-3} alkyl-CN, oxo, phenyl optionally substituted with halogen and $-\text{S}(\text{O})_2\text{C}_{1-6}$ alkyl,

(m) 4-10 membered monocyclic, bicyclic or spirocyclic heterocyclyl group containing N, S or O, wherein each heterocycle is optionally substituted with 1-3 substituents selected from 3-6 membered heterocyclic ring, halogen, C_{1-3} alkyl, or C_{1-3} alkyl- $\text{C}(\text{O})\text{N}(\text{R}^5)(\text{R}^6)$,

(n) aryl,

(o) $-\text{N}(\text{R}^5)(\text{R}^6)$;

R^5 and R^6 are each independently selected from $-\text{H}$, 4-6 membered heterocyclyl, $-\text{C}(\text{O})-\text{C}_{1-3}$ alkyl $-\text{C}(\text{O})-\text{C}_{1-3}$ cycloalkyl and $-(\text{C}_1-\text{C}_6)$ alkyl optionally substituted with $-\text{OH}$, C_{3-6} cycloalkyl, $-\text{NH}-\text{C}_{1-3}$ alkyl or $-\text{N}-(\text{C}_{1-3}\text{-alkyl})_2$; or

R^5 and R^6 together with the nitrogen atom to which they are attached form a 6 membered heterocyclic ring optionally substituted with methyl.

8. The compound according to claim 1 or a pharmaceutically acceptable salt thereof, wherein:

X is N;

Y is CH;

R¹ is F;

R² is selected from methyl and Cl;

HET is imidazopyridine which may be optionally substituted with one to two substituents selected from **R**³ and **R**⁴;

R^3 and R^4 are each independently selected from:

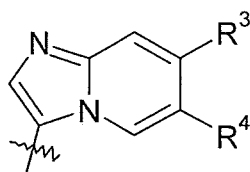
- (a) $-H$,
- (b) $-O R^5$,
- (c) $-O-C_{1-6}alkyl-O-C_{1-3} alkyl$
- (d) $-O-C_{3-6} cycloalkyl$,
- (e) $-C(O)R^5$,
- (f) $C_{1-6}alkyl$ optionally substituted with one to three $-OH$, fluorine, heterocyclyl optionally substituted with oxo, $C_{3-6} cycloalkyl$, $-CO_2R^5$, $-O-C_{1-6}alkyl$, aryl, $-N(R^5)(R^6)$,
or $-C(O)N(R^5)(R^6)$,
- (g) $C_{3-6} cycloalkyl$ optionally substituted with one to three $-OH$, one to three fluorine, $C_{1-6}alkyl$, $-OC_{1-6}alkyl$, $C_{1-6}alkyl-OC_{1-6}alkyl$, $C_{1-6}alkyl-OH$, CF_3 , $-OC_{3-6}cycloalkyl$, $-CO_2H$, $-CO_2R^5$, $C_{3-6}cycloalkyl$, 5-6 membered heteroaryl, $C_{3-6} heterocyclyl$, $N(R^5)(R^6)$,
or $-C(O)N(R^5)(R^6)$,
- (h) $-CO_2R^5$,
- (i) $-C(O)N(R^5)(R^6)$,
- (j) $-S(O)_2N(R^5)(R^6)$,
- (k) $-S(O)_2-R^5$
- (l) a 5-6 membered heteroaryl group optionally substituted with one to three groups selected from $C_{1-6}alkyl$, $C_{3-6}cycloalkyl$, halogen, $-CF_3$, $-OH$, $-(CH_2) CO_2R^5$, $-C(O)N(R^5)(R^6)$, $-N(R^5)(R^6)$, $-NH-SO_2C_{1-6}alkyl$, $C_{1-6}alkoxyl$, $C_{1-6}alkyl-O-C_{1-3} alkyl$, $C_{1-6}alkylhydroxyl$, $C_{1-3}alkyl-CN$, oxo, phenyl optionally substituted with halogen and $-S(O)_2C_{1-6}alkyl$,
- (m) 6 membered monocyclic heterocyclyl group containing N wherein the heterocycle is optionally substituted with 1-3 substituents selected from 3-6 membered heterocyclic ring, halogen, $C_{1-3}alkyl$, and $C_{1-3}alkyl-C(O)N(R^5)(R^6)$,
- (n) aryl,
- (o) $-N(R^5)(R^6)$;

R^5 and R^6 are each independently selected from $-H$, 4-6 membered heterocyclyl, $-C(O)-C_{1-3} alkyl$, $-C(O)-C_{1-3} cycloalkyl$ and $-(C_1-C_6)alkyl$ optionally substituted with $-OH$, $C_{3-6} cycloalkyl$, $-NH-C_{1-3} alkyl$ or $-N-(C_{1-3}alkyl)_2$; or

R⁵ and R⁶ together with the nitrogen atom to which they are attached form a 6 membered heterocyclic ring optionally substituted with methyl.

9. The compound according to claim 7 or a pharmaceutically acceptable salt thereof, wherein:

HET is :



optionally substituted one to two substituents selected from **R³ and R⁴**;

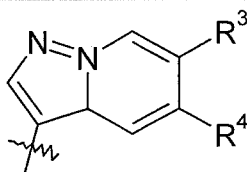
R³ and R⁴ are each independently selected from:

- (a) -H,
- (b) -O R⁵,
- (c) -O- C₁₋₆alkyl-O- C₁₋₃ alkyl
- (d) -O-C₃₋₆ cycloalkyl,
- (e) -C(O)R⁵,
- (f) C₁₋₆alkyl optionally substituted with one to three -OH, fluorine, heterocyclyl optionally substituted with oxo, C₃₋₆ cycloalkyl, -CO₂R⁵, -O- C₁₋₆alkyl, aryl, -N(R⁵)(R⁶), or -C(O)N(R⁵)(R⁶),
- (g) C₃₋₆ cycloalkyl optionally substituted with one to three -OH, one to three fluorine, C₁₋₆alkyl, -OC₁₋₆alkyl, C₁₋₆alkyl-OC₁₋₆alkyl, C₁₋₆alkyl-OH, CF₃, -OC₃₋₆cycloalkyl, -CO₂H, -CO₂R⁵, C₃₋₆cycloalkyl, 5-6 membered heteroaryl, C₃₋₆ heterocyclyl, N(R⁵)(R⁶), or -C(O)N(R⁵)(R⁶),
- (h) -CO₂R⁵,
- (i) -C(O)N(R⁵)(R⁶),
- (j) -S(O)₂N(R⁵)(R⁶),
- (k) -S(O)₂-R⁵
- (l) a 5-6 membered heteroaryl group optionally substituted with one to three groups selected from C₁₋₆alkyl, C₃₋₆cycloalkyl, halogen, -CF₃, -OH, -(CH₂) CO₂R⁵, -C(O)N(R⁵)(R⁶), -

$N(R^5)(R^6)$, $-NH-SO_2C_{1-6}alkyl$, $C_{1-6}alkoxyl$, $C_{1-6}alkyl-O-$ $C_{1-3}alkyl$, $C_{1-6}alkylhydroxyl$, $C_{1-3}alkyl-CN$, oxo, phenyl optionally substituted with halogen and $-S(O)_2C_{1-6}alkyl$,
 (m) 4-10 membered monocyclic, bicyclic or spirocyclic heterocyclyl group containing N, S or O, wherein each heterocycle is optionally substituted with 1-3 substituents selected from 3-6 membered heterocyclic ring, halogen, $C_{1-3}alkyl$, and $C_{1-3}alkyl-C(O)N(R^5)(R^6)$,
 (n) aryl,
 (o) $-N(R^5)(R^6)$;

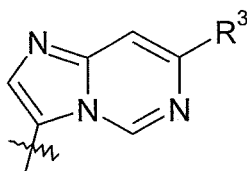
R^5 and R^6 are each independently selected from $-H$, 4-6 membered heterocyclyl, $-C(O)-C_{1-3}alkyl$, $-C(O)-C_{1-3}cycloalkyl$ and $-(C_1-C_6)alkyl$ optionally substituted with $-OH$, $C_{3-6}cycloalkyl$, $-NH-C_{1-3}alkyl$ or $-N-(C_{1-3}alkyl)_2$; or
 R^5 and R^6 together with the nitrogen atom to which they are attached form a 6 membered heterocyclic ring optionally substituted with methyl.

10. The compound according to claim 7 or a pharmaceutically acceptable salt thereof, wherein:
HET is :



optionally substituted one to two substituents selected from R^3 and R^4 .

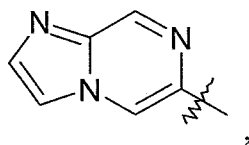
11. The compound according to claim 1 or a pharmaceutically acceptable salt thereof, wherein:
HET is :



optionally substituted with R^3 ,

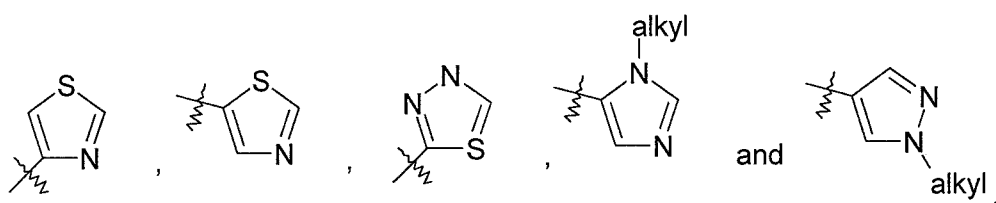
or

HET is :



or

HET is selected from:



12. The compound according to claim 1 or a pharmaceutically acceptable salt thereof, wherein:

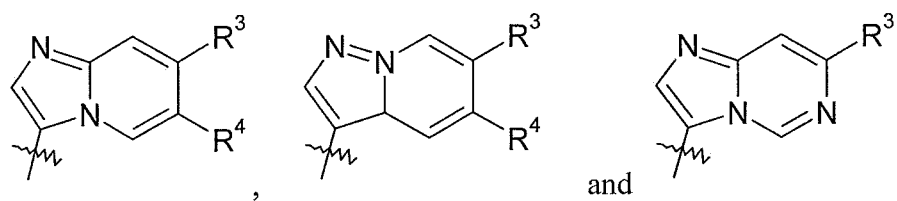
X is N;

Y is CH;

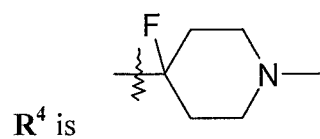
R¹ is F;

R² is methyl;

HET is :

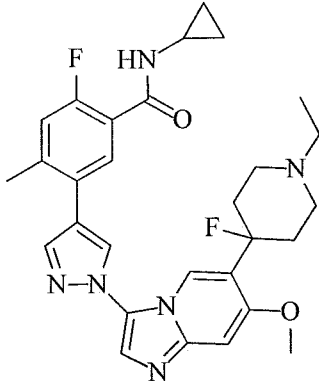


R^3 is methoxy; and

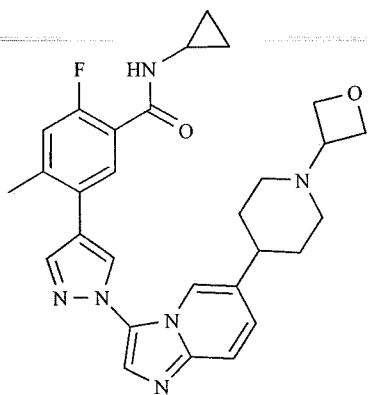


13. The compound according to claim 1, namely a compound selected from the group consisting of:

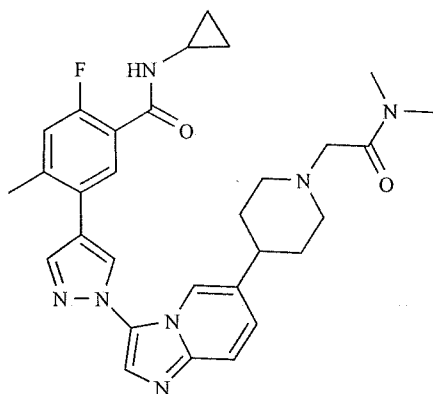
Example	Structure	Example	Structure
1		54	

Example	Structure	Example	Structure
		101	

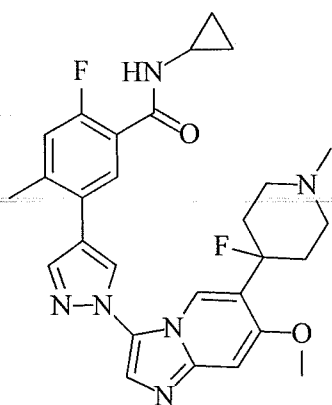
14. The compound according to any one of claims 1 and 13 having the structure:



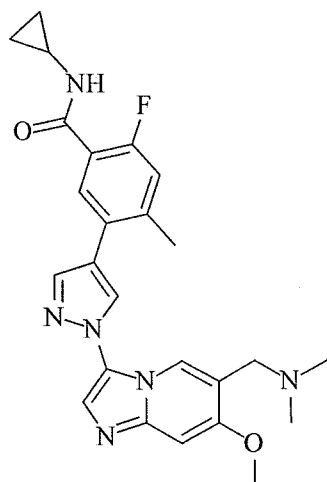
15. The compound according to any one of claims 1 and 13 having the structure:



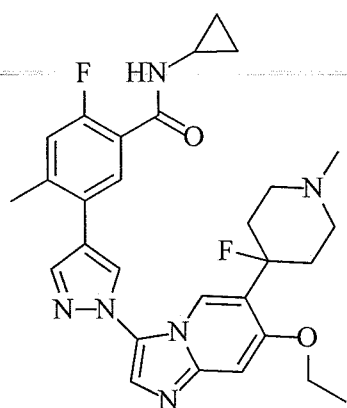
16. The compound according to any one of claims 1 and 13 having the structure:



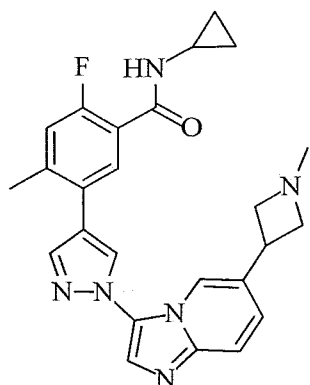
17. The compound according to any one of claims 1 and 13 having the structure:



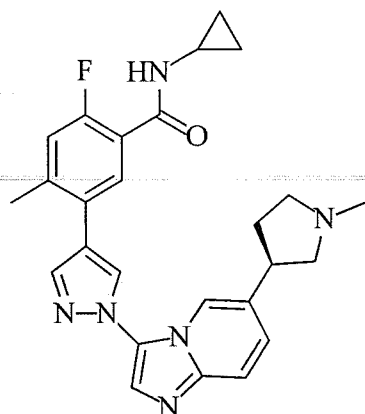
18. The compound according to any one of claims 1 and 13 having the structure:



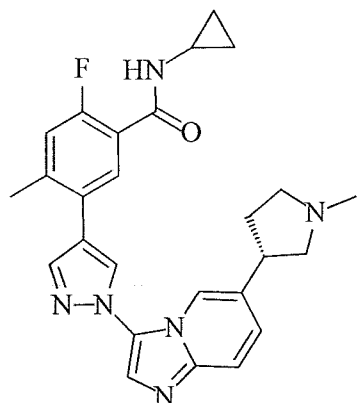
19. The compound according to any one of claims 1 and 13 having the structure:



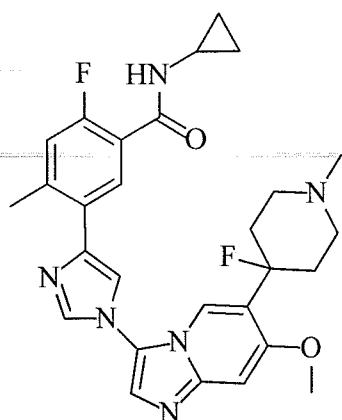
20. The compound according to any one of claims 1 and 13 having the structure:



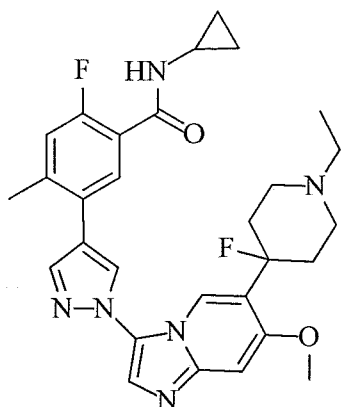
21. The compound according to any one of claims 1 and 13 having the structure:



22. The compound according to any one of claims 1 and 13 having the structure:



23. The compound according to any one of claims 1 and 13 having the structure:



24. A pharmaceutically acceptable salt of a compound according to any one of claims 13 to 23.
25. A pharmaceutical composition comprising the compound according to claim 1, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable carrier.
26. Use of a compound according to any one of claims 1 to 24 for the manufacture of a medicament for the treatment of an autoimmune disease or allergic disorder.
27. Use of the compound according to claim 26 for the manufacture of a medicament for the treatment of an autoimmune disease or allergic disorder selected from rheumatoid arthritis, psoriasis, systemic lupus erythematosus, lupus nephritis, scleroderma, asthma, Chronic Obstructive Pulmonary Disease (COPD), allergic rhinitis, allergic eczema, multiple sclerosis, juvenile rheumatoid arthritis, juvenile idiopathic arthritis, type I diabetes, inflammatory bowel disease, graft versus host disease, psoriatic arthritis, reactive arthritis, ankylosing spondylitis, Crohn's disease, ulcerative colitis, uveitis and non-radiographic spondyloarthropathy.