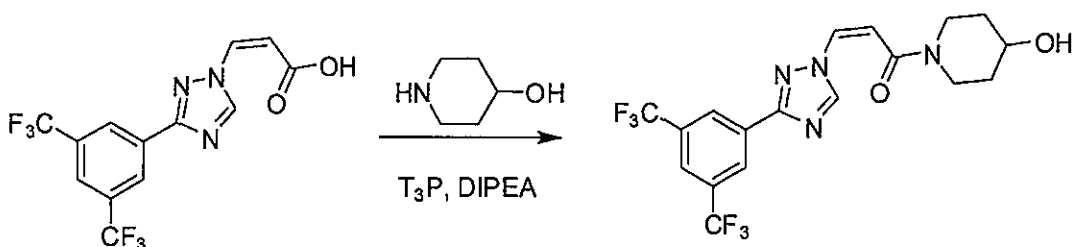


5

A 500-mL, 3-necked, round-bottomed flask was charged with a solution of (Z)-3-(3-(3,5-bis(trifluoromethyl)phenyl)-1H-1,2,4-triazol-1-yl)-N'-(pyridin-2-yl)acrylohydrazide (5.5 g) in Et₂O (250 mL). The solution was cooled to 5 °C, treated with HCl in 1,4-dioxane, allowed to warm to RT and stirred until completion, as shown by TLC analysis (about 1 h).

10 The solids were filtered on a Büchner funnel, washed with Et₂O and dried under vacuum to afford 5.5 g (yield: 92%) (Z)-3-(3-(3,5-bis(trifluoromethyl)phenyl)-1H-1,2,4-triazol-1-yl)-N'-(pyridin-2-yl)acrylohydrazide hydrochloride. ¹H NMR (400 MHz, DMSO-d₆) δ, 11.26 (s, 1H), 10.89 (s, 1H), 9.55 (s, 1H), 8.52 (s, 2H), 8.28 (s, 1H), 8.03-8.07 (m, 2H), 7.62-7.59 (d, J=10.4 Hz, 1H), 7.21-7.24 (m, 1H), 7.05-7.09 (m, 1H), 6.16-6.19 (d, J=10.4 Hz, 1H), LCMS
15 for C₁₈H₁₃F₆N₆O [M+H]⁺ 443.33; found 443.44 (RT 3.54 min, purity: 99.0%).

Example 4: Synthesis of (Z)-3-(3-(3,5-bis(trifluoromethyl)phenyl)-1H-1,2,4-triazol-1-yl)-1-(4-hydroxypiperidin-1-yl)prop-2-en-1-one ~~(1-5)~~.

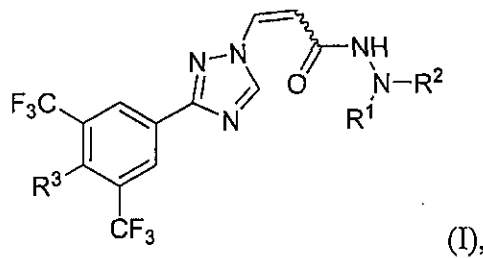


20 A 50-mL, 3-necked, round-bottomed flask was charged with a solution of (Z)-3-(3-(3,5-bis(trifluoromethyl)phenyl)-1H-1,2,4-triazol-1-yl)acrylic acid (0.20 g) in CH₂Cl₂ (10mL). Piperidin-4-ol (0.07 g, 1.2 eq.) was added and the solution was cooled to -60 °C for the addition of T3P (propyl phosphonic anhydride) (0.40 mL, 1.2 eq.) and DIPEA (0.19 mL, 2.0 eq.). The reaction mixture was stirred for 30 min before being poured into water (50 mL)
25 and extracted with CH₂Cl₂ (2 x 50 mL). The combined organic layers were washed with aqueous saturated brine (50 mL), dried over anhydrous MgSO₄, filtered, and concentrated under reduced pressure (25 °C, 20 mmHg). Purification by column chromatography using silica 60/120 and MeOH:CH₂Cl₂ as mobile phase. (desired compound started eluting using 3.0% MeOH/CH₂Cl₂) afforded 0.025 g (yield: 10%) of (Z)-3-(3-(3,5-

CLAIMS

What is claimed is:

1. A compound of structural formula I:



or a pharmaceutically acceptable salt thereof, wherein:

R¹ is selected from hydrogen and methyl;

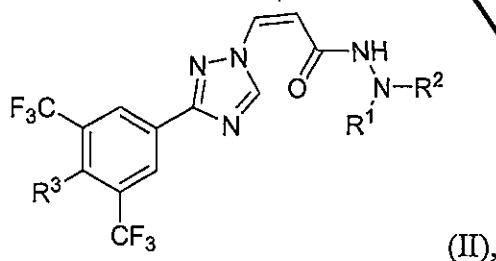
R² is selected from pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, pyrazin-2-yl, and quinoxalin-2-yl, pyrimidin-4-yl, 1,1-dioxotetrahydrothiophen-3-yl and cyclopropyl, wherein R² is optionally substituted with one or more substituents independently selected from methyl and halogen; or

R¹ and R² are taken together with their intervening atoms to form 4-hydroxypiperidin-1-yl, pyrrolidin-1-yl, azepan-1-yl, 4-benzylpiperazin-1-yl, 4-ethylpiperazin-1-yl, 3-hydroxyazetidin-1-yl, or morpholin-4-yl;

R³ is selected from hydrogen and halo; and

~ represents a single bond wherein a carbon-carbon double bond bound thereto is in an (*E*)- or (*Z*)-configuration.

2. The compound according to claim 1, wherein the compound is represented by structural formula II:



or a pharmaceutically acceptable salt thereof.

3. The compound of claim 2, wherein:

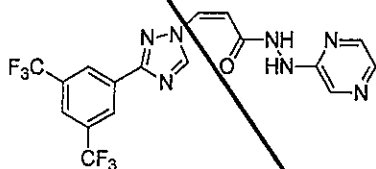
R¹ is selected from hydrogen and methyl; and

5 R^2 is selected from pyridin-2-yl, pyridin-4-yl, pyrazin-2-yl and pyrimidin-4-yl,
wherein R^2 is optionally substituted with a single substituent selected from methyl
and chloro; or

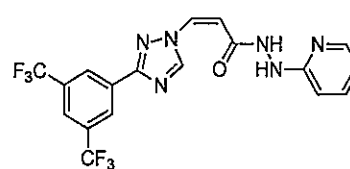
R^1 and R^2 are taken together to form 4-hydroxypiperidin-1-yl.

10 4. The compound of any one of Claims 1-3, wherein R^3 is hydrogen.

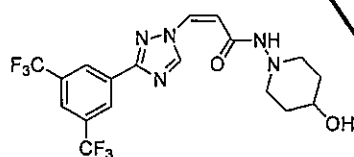
5. The compound according to claim 1, or a pharmaceutically acceptable salt thereof,
wherein the compound is represented by any one of the following structural formulas:



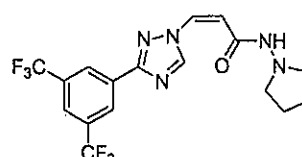
I-3,



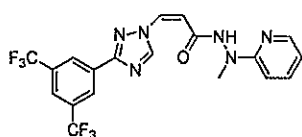
I-4,



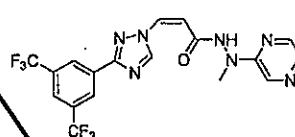
I-5,



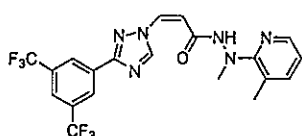
I-6,



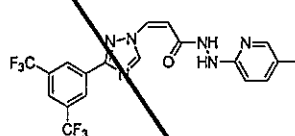
I-7,



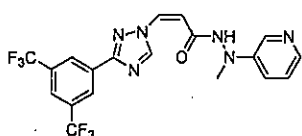
I-8,



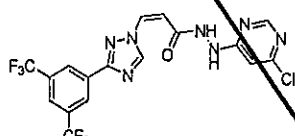
I-9,



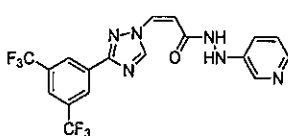
I-10,



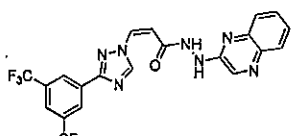
I-11,



I-12,

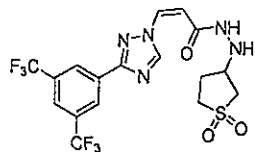


I-13,

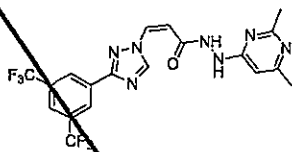


I-14,

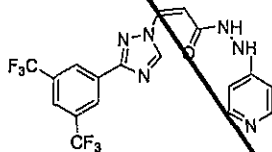
-115-



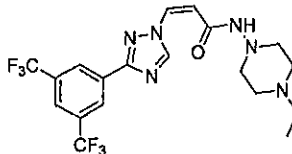
I-15,



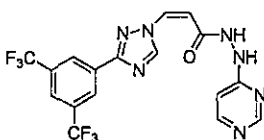
I-17,



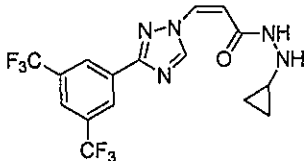
I-19,



I-21,

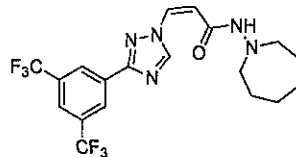


I-23,

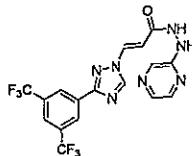


I-25

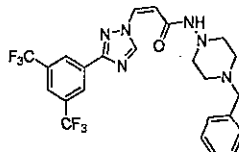
or



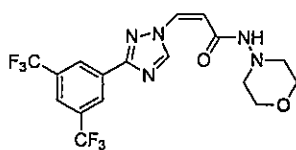
I-16,



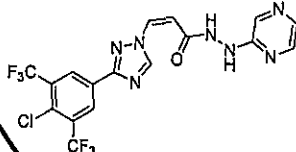
I-18,



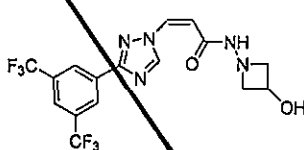
I-20,



I-22,



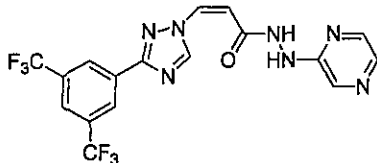
I-24,



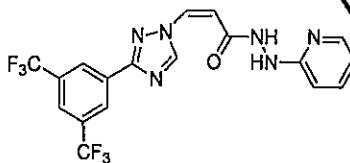
I-26.

5

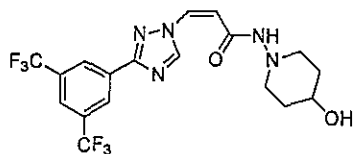
6. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein the compound is represented by any one of the following structural formulas:



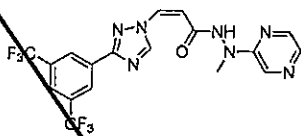
I-3,



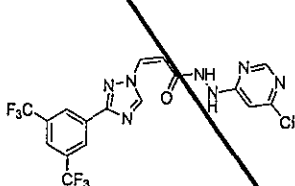
I-4,



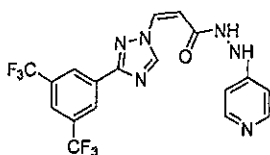
I-5,



I-8,

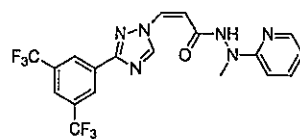


I-12,

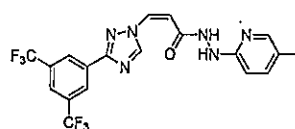


I-19

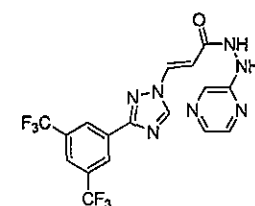
or



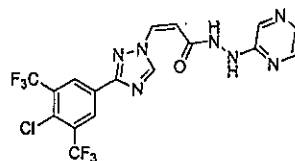
I-7,



I-10,



I-18,



I-24.

7. A composition comprising a compound of any one of claims 1-6, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.
8. The composition of Claim 7, further including a second therapeutic agent useful for treating cancer.
9. A method for treating a disorder associated with CRM1 activity comprising administering to a subject in need thereof a therapeutically effective amount of a composition according to claim 7.
10. The method according to claim 9, wherein the the disorder is selected from a proliferative disorder, an inflammatory disorder, an autoimmune disorder, a viral infection, an ophthalmological disorder, a neurodegenerative disorder, a disorder of

abnormal tissue growth, a disorder related to food intake, allergies, and a respiratory disorder.

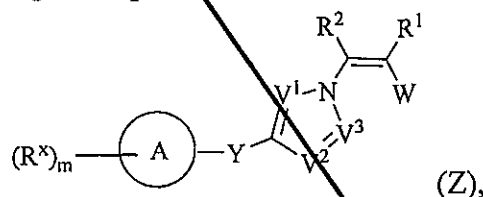
11. The method according to claim 10, wherein the disorder is cancer.

12. The method according to claim 11, wherein the composition is administered together with a second therapeutic useful for treating cancer.

13. A compound according to any one of Claims 1-6, or a pharmaceutically acceptable salt thereof, for use in treating a disorder associated with CRM1 activity in a subject in need thereof.

14. Use of a compound according to any one of Claims 1-6, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of a disorder associated with CRM1 activity.

15. A method for preparing a compound of formula Z:



or a pharmaceutically acceptable salt thereof, wherein:

Ring A is an optionally substituted ring selected from phenyl, an 8-10-membered bicyclic aryl ring, a 5-6-membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and an 8-10-membered bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

Y is a covalent bond or -L-;

L is a bivalent C₁₋₈ saturated or unsaturated, straight or branched, hydrocarbon radical, wherein one or two methylene units of L is optionally replaced by -NR-, -N(R)C(O)-, -C(O)N(R)-, -O-, -C(O)-, -OC(O)-, -C(O)O-, -S-, -SO-, -SO₂-, -C(S)-, -C(NOR)- or -C(NR)-;

each R is independently hydrogen or an optionally substituted group selected from C₁₋₆ aliphatic, phenyl, a 4-7-membered saturated or partially unsaturated

carbocyclic ring, a 4-7-membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6-membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or

two R groups on the same nitrogen are taken together with the nitrogen atom to which they are attached to form a 4-7-membered saturated or partially unsaturated heterocyclic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 5-6-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

each of V^1 , V^2 and V^3 is independently $C(R^y)$ or N;

each R^x and R^y is independently selected from $-R$, halogen, $-OR$, $-SR$, $-N(R)_2$, $-CN$, $-NO_2$, $-N_3$, $-SOR$, $-SO_2R$, $-SO_2NR$, $-C(O)R$, $-CO_2R$, $-C(O)OR$, $-C(O)N(R)_2$, $-NRC(O)R$, $-OC(O)R$, $-OC(O)N(R)_2$, $-NRC(O)OR$, $-NRC(O)NR_2$ and $-NRSO_2R$;

each R^1 and R^2 is independently hydrogen, deuterium, tritium or halogen;

W is $-CN$, haloalkyl, $-NO_2$ or $-C(=Z)R^3$;

Z is O, S, or NR;

R^3 is hydrogen, $-R$, $-OR$, $-SR$ or $-N(R^4)_2$;

each R^4 is independently $-R$, or

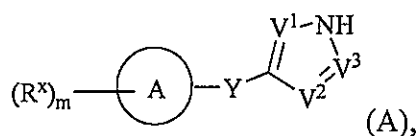
two R^4 on the same nitrogen are taken together with the nitrogen atom to which they are attached to form a 4-7-membered saturated or partially unsaturated heterocyclic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 5-6-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein the ring thereby formed is optionally substituted with $-(R^5)_n$;

each R^5 is independently selected from $-R$, halogen, $-OR$, $-SR$, $-N(R)_2$, $-CN$, $-NO_2$, $-N_3$, $-SOR$, $-SO_2R$, $-SO_2NR$, $-C(O)R$, $-CO_2R$, $-C(O)OR$, $-C(O)N(R)_2$, $-NRC(O)R$, $-OC(O)R$, $-OC(O)N(R)_2$, $-NRC(O)OR$, $-NRC(O)NR_2$ and $-NRSO_2R$;

and

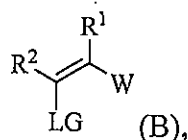
each m and n is independently an integer selected from 0, 1, 2, 3 and 4, comprising the steps of:

(a) providing a compound of formula A:



wherein each of Ring A, R^x , Y, V^1 , V^2 , V^3 and m is as defined above for the compound of formula Z; and

(b) reacting said compound of formula A with an olefin of formula B:



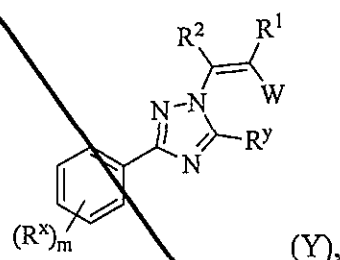
wherein:

LG is halogen, $-\text{OSO}_2\text{R}$ or $-\text{OSO}_2\text{CF}_3$; and

each of W, R, R^1 and R^2 is as defined above for the compound of formula Z;

in the presence of a sterically-hindered nucleophilic base to form a compound of formula Z.

16. A method for preparing a compound of formula Y:



or a pharmaceutically acceptable salt thereof, wherein:

each R^x and R^y is independently selected from $-\text{R}$, halogen, $-\text{OR}$, $-\text{SR}$, $-\text{N}(\text{R})_2$, $-\text{CN}$, $-\text{NO}_2$, $-\text{N}_3$, $-\text{SOR}$, $-\text{SO}_2\text{R}$, $-\text{SO}_2\text{NR}$, $-\text{C}(\text{O})\text{R}$, $-\text{CO}_2\text{R}$, $-\text{C}(\text{O})\text{OR}$, $-\text{C}(\text{O})\text{N}(\text{R})_2$, $-\text{NRC}(\text{O})\text{R}$, $-\text{OC}(\text{O})\text{R}$, $-\text{OC}(\text{O})\text{N}(\text{R})_2$, $-\text{NRC}(\text{O})\text{OR}$, $-\text{NRC}(\text{O})\text{NR}_2$ and $-\text{NRSO}_2\text{R}$;

each R is independently hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 4-7-membered saturated or partially unsaturated carbocyclic ring, a 4-7-membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6-membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or

two R groups on the same nitrogen are taken together with the nitrogen atom to which they are attached to form a 4-7-membered saturated or partially unsaturated heterocyclic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 5-6-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

each R^1 and R^2 is independently hydrogen, deuterium, tritium or halogen;

W is $-\text{CN}$, haloalkyl, $-\text{NO}_2$ or $-\text{C}(=\text{Z})\text{R}^3$;

Z is O, S, or NR;

R^3 is hydrogen, $-\text{R}$, $-\text{OR}$, $-\text{SR}$ or $-\text{N}(\text{R}^4)_2$;

each R^4 is independently $-\text{R}$, or

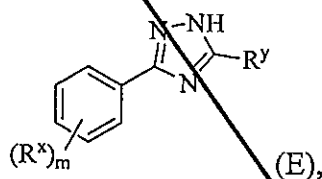
two R^4 on the same nitrogen are taken together with the nitrogen atom to which they are attached to form a 4-7-membered saturated or partially unsaturated heterocyclic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 5-6-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein the ring thereby formed is optionally substituted with $-(\text{R}^5)_n$;

each R^5 is independently selected from $-\text{R}$, halogen, $-\text{OR}$, $-\text{SR}$, $-\text{N}(\text{R})_2$, $-\text{CN}$, $-\text{NO}_2$, $-\text{N}_3$, $-\text{SOR}$, $-\text{SO}_2\text{R}$, $-\text{SO}_2\text{NR}$, $-\text{C}(\text{O})\text{R}$, $-\text{CO}_2\text{R}$, $-\text{C}(\text{O})\text{OR}$, $-\text{C}(\text{O})\text{N}(\text{R})_2$, $-\text{NRC}(\text{O})\text{R}$, $-\text{OC}(\text{O})\text{R}$, $-\text{OC}(\text{O})\text{N}(\text{R})_2$, $-\text{NRC}(\text{O})\text{OR}$, $-\text{NRC}(\text{O})\text{NR}_2$ and $-\text{NRSO}_2\text{R}$; and

each m and n is independently an integer selected from 0, 1, 2, 3 and 4;

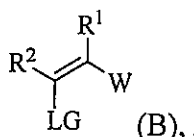
comprising the steps of:

(a) providing a compound of formula E:



wherein each of R^x , R^y and m is as defined above for the compound of formula Y; and

(b) reacting said compound of formula E with an olefin of formula B:



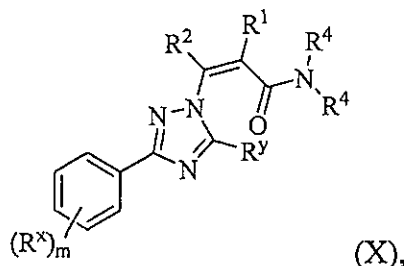
wherein:

LG is halogen, $-\text{OSO}_2\text{R}$ or $-\text{OSO}_2\text{CF}_3$; and

each of W, R, R^1 and R^2 is as defined above for the compound of formula Y,

in the presence of a sterically-hindered nucleophilic base to form the compound of formula Y.

17. A method for preparing a compound of formula X:



or a pharmaceutically acceptable salt thereof, wherein:

each R^x and R^y is independently selected from $-R$, halogen, $-OR$, $-SR$, $-N(R)_2$, $-CN$, $-NO_2$, $-N_3$, $-SOR$, $-SO_2R$, $-SO_2NR$, $-C(O)R$, $-CO_2R$, $-C(O)OR$, $-C(O)N(R)_2$, $-NRC(O)R$, $-OC(O)R$, $-OC(O)N(R)_2$, $-NRC(O)OR$, $-NRC(O)NR_2$ and $-NRSO_2R$;

each R is independently hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 4-7-membered saturated or partially unsaturated carbocyclic ring, a 4-7-membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6-membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or

two R groups on the same nitrogen are taken together with the nitrogen atom to which they are attached to form a 4-7-membered saturated or partially unsaturated heterocyclic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 5-6-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

each R^1 and R^2 is independently hydrogen, deuterium, tritium or halogen;

each R^4 is independently $-R$, or

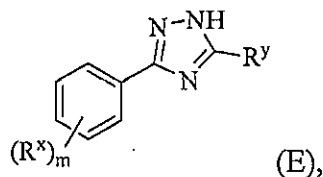
two R^4 on the same nitrogen are taken together with the nitrogen atom to which they are attached to form a 4-7-membered saturated or partially unsaturated heterocyclic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 5-6-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein the ring thereby formed is optionally substituted with $-(R^5)_n$;

each R^5 is independently selected from $-R$, halogen, $-OR$, $-SR$, $-N(R)_2$, $-CN$, $-NO_2$, $-N_3$, $-SOR$, $-SO_2R$, $-SO_2NR$, $-C(O)R$, $-CO_2R$, $-C(O)OR$, $-C(O)N(R)_2$, $-NRC(O)R$, $-OC(O)R$, $-OC(O)N(R)_2$, $-NRC(O)OR$, $-NRC(O)NR_2$ and $-NRSO_2R$; and

each m and n is independently an integer selected from 0, 1, 2, 3 and 4;

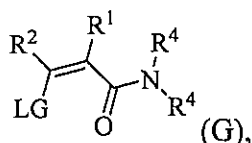
comprising the steps of:

(a) providing a compound of formula E:



wherein each of R^x , R^y and m is as defined above for the compound of formula X; and

(b) reacting said compound of formula E with an olefin of formula G:



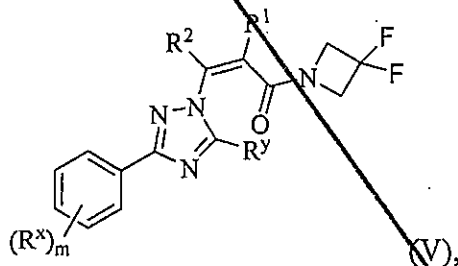
wherein:

LG is halogen, $-\text{OSO}_2\text{R}$ or $-\text{OSO}_2\text{CF}_3$; and

each of R , R^1 , R^2 and R^4 is as defined above for the compound of formula X,

in the presence of a sterically-hindered nucleophilic base to form the compound of formula X.

18. A method for preparing a compound of formula V:



or a pharmaceutically acceptable salt thereof, wherein:

each R^x and R^y is independently selected from $-\text{R}$, halogen, $-\text{OR}$, $-\text{SR}$, $-\text{N}(\text{R})_2$, $-\text{CN}$, $-\text{NO}_2$, $-\text{N}_3$, $-\text{SOR}$, $-\text{SO}_2\text{R}$, $-\text{SO}_2\text{NR}$, $-\text{C}(\text{O})\text{R}$, $-\text{CO}_2\text{R}$, $-\text{C}(\text{O})\text{OR}$, $-\text{C}(\text{O})\text{N}(\text{R})_2$, $-\text{NRC}(\text{O})\text{R}$, $-\text{OC}(\text{O})\text{R}$, $-\text{OC}(\text{O})\text{N}(\text{R})_2$, $-\text{NRC}(\text{O})\text{OR}$, $-\text{NRC}(\text{O})\text{NR}_2$ and $-\text{NRSO}_2\text{R}$;

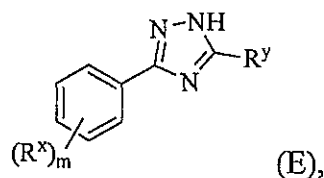
each R is independently hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 4-7-membered saturated or partially unsaturated carbocyclic ring, a 4-7-membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6-membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or

two R groups on the same nitrogen are taken together with the nitrogen atom to which they are attached to form a 4-7-membered saturated or partially unsaturated heterocyclic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 5-6-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

each R^1 and R^2 is independently hydrogen, deuterium, tritium or halogen; and m is an integer selected from 0, 1, 2, 3 and 4;

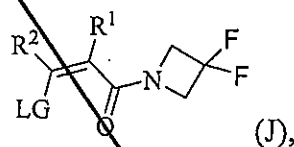
comprising the steps of:

(a) providing a compound of formula E:



wherein each of R^x , R^y and m is as defined above for the compound of formula V; and

(b) reacting said compound of formula E with an olefin of formula J:



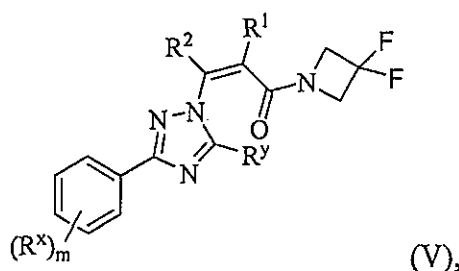
wherein:

LG is halogen, $-\text{OSO}_2\text{R}$ or $-\text{OSO}_2\text{CF}_3$, and

each of R , R^1 and R^2 is as defined above for the compound of formula V,

in the presence of a sterically-hindered nucleophilic base to form the compound of formula V.

19. A method for preparing a compound of formula V:



or a pharmaceutically acceptable salt thereof, wherein:

each R^x and R^y is independently selected from $-\text{R}$, halogen, $-\text{OR}$, $-\text{SR}$, $-\text{N}(\text{R})_2$, $-\text{CN}$, $-\text{NO}_2$, $-\text{N}_3$, $-\text{SOR}$, $-\text{SO}_2\text{R}$, $-\text{SO}_2\text{NR}$, $-\text{C}(\text{O})\text{R}$, $-\text{CO}_2\text{R}$, $-\text{C}(\text{O})\text{OR}$, $-\text{C}(\text{O})\text{N}(\text{R})_2$, $-\text{NRC}(\text{O})\text{R}$, $-\text{OC}(\text{O})\text{R}$, $-\text{OC}(\text{O})\text{N}(\text{R})_2$, $-\text{NRC}(\text{O})\text{OR}$, $-\text{NRC}(\text{O})\text{NR}_2$ and $-\text{NRSO}_2\text{R}$;

each R is independently hydrogen or an optionally substituted group selected from C₁₋₆ aliphatic, phenyl, a 4-7-membered saturated or partially unsaturated carbocyclic ring, a 4-7-membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6-membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or

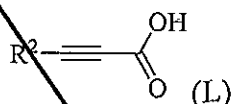
two R groups on the same nitrogen are taken together with the nitrogen atom to which they are attached to form a 4-7-membered saturated or partially unsaturated heterocyclic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 5-6-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

each R¹ and R² is independently hydrogen, deuterium, tritium or halogen; and

m is an integer selected from 0, 1, 2, 3 and 4;

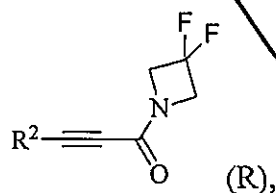
comprising the steps of:

(a) providing a compound of formula L:



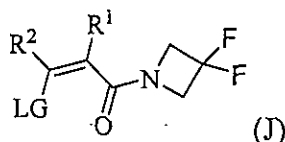
wherein R² is as defined above for the compound of formula V;

(b) reacting said compound of formula L with  to form a compound of formula R:



wherein R² is as defined above for the compound of formula V,

(c) reacting said compound of formula R to provide a compound of formula J:



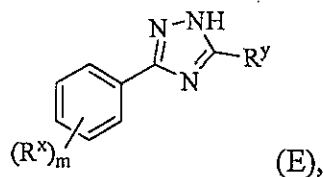
wherein:

LG is halogen, -OSO₂R or -OSO₂CF₃; and

each of R, R¹ and R² is as defined above for the compound of formula V; and

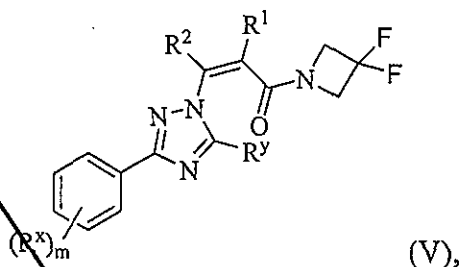
(d) reacting said compound of formula J with a compound of formula E:

-125-



wherein each of R^x , R^y and m is as defined above for the compound of formula V, in the presence of a sterically-hindered nucleophilic base to provide a compound of formula V.

20. A method for preparing a compound of formula V:



or a pharmaceutically acceptable salt thereof, wherein:

each R^x and R^y is independently selected from $-R$, halogen, $-OR$, $-SR$, $-N(R)_2$, $-CN$, $-NO_2$, $-N_3$, $-SOR$, $-SO_2R$, $-SO_2NR$, $-C(O)R$, $-CO_2R$, $-C(O)OR$, $-C(O)N(R)_2$, $-NRC(O)R$, $-OC(O)R$, $-OC(O)N(R)_2$, $-NRC(O)OR$, $-NRC(O)NR_2$ and $-NRSO_2R$;

each R is independently hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 4-7-membered saturated or partially unsaturated carbocyclic ring, a 4-7-membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 5-6-membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or

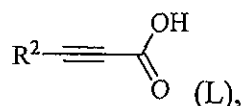
two R groups on the same nitrogen are taken together with the nitrogen atom to which they are attached to form a 4-7-membered saturated or partially unsaturated heterocyclic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 5-6-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

each R^1 and R^2 is independently hydrogen, deuterium, tritium or halogen; and m is an integer selected from 0, 1, 2, 3 and 4;

comprising the steps of:

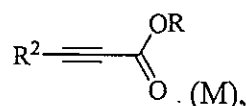
(a) providing a compound of formula L:

-126-



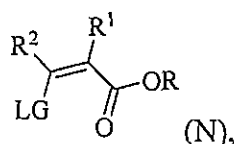
wherein R^2 is as defined above for the compound of formula V;

- (b) reacting said compound of formula L with an alcohol having the formula HO-R to form a compound of formula M:



wherein each of R and R^2 is as defined above for the compound of formula V;

- (c) reacting said compound of formula M to provide a compound of formula N:

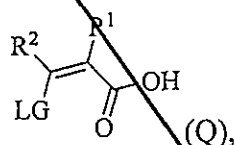


wherein:

LG is halogen, $-\text{OSO}_2\text{R}$ or $-\text{OSO}_2\text{CF}_3$; and

each of R, R^1 and R^2 is as defined above for the compound of formula V;

- (d) hydrolyzing said compound of formula N to form a compound of formula Q:

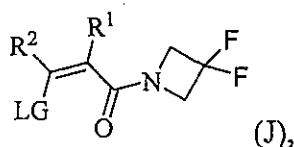


wherein:

LG is halogen, $-\text{OSO}_2\text{R}$ or $-\text{OSO}_2\text{CF}_3$; and

each of R, R^1 and R^2 is as defined above for the compound of formula V;

- (e) reacting said compound of formula Q with $\text{F}_2\text{C}_2\text{NH}$ to form a compound of formula J:

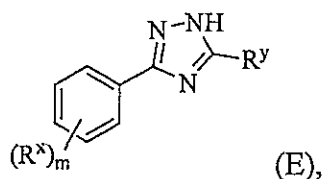


wherein:

LG is halogen, $-\text{OSO}_2\text{R}$ or $-\text{OSO}_2\text{CF}_3$; and

each of R, R^1 and R^2 is as defined above for the compound of formula V; and

- (f) reacting said compound of formula J with a compound of formula E:

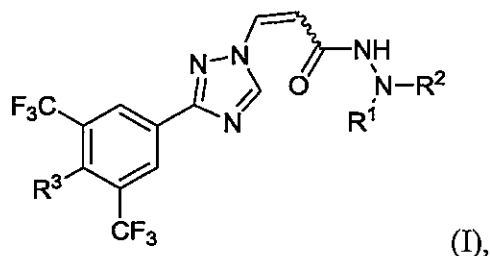


wherein each of R^x , R^y and m is as defined above for the compound of formula V, in the presence of a sterically-hindered nucleophilic base to provide the compound of formula V.

21. The method of any of claims 15 to 20, wherein the sterically-hindered nucleophilic base is selected from 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), 1,5-diazabicyclo[4.3.0]non-5-ene (DBN), 1,4-diazabicyclo(2.2.2)octane (DABCO), N,N-dicyclohexylmethylamine, 2,6-di-tert-butyl-4-methylpyridine, quinuclidine, 1,2,2,6,6-pentamethylpiperidine (PMP), 7-methyl-1,5,7-triazabicyclo(4.4.0)dec-5-ene (MTBD), triphenylphosphine, tri-*tert*-butylphosphine and tricyclohexylphosphine.
22. The method of claim 21, wherein the sterically-hindered nucleophilic base is selected from 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) and 1,4-diazabicyclo(2.2.2)octane (DABCO).
23. The method of claim 22, wherein the sterically-hindered nucleophilic base is 1,4-diazabicyclo(2.2.2)octane (DABCO).

CLAIMS

1. A compound of structural formula I:



or a pharmaceutically acceptable salt thereof, wherein:

R^1 is selected from hydrogen and methyl;

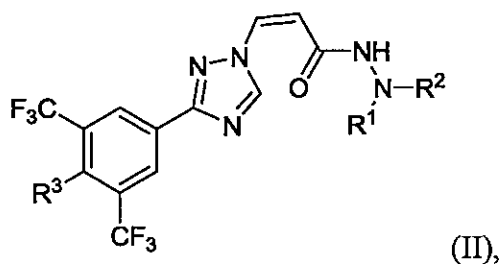
R^2 is selected from pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, pyrazin-2-yl, and quinoxalin-2-yl, pyrimidin-4-yl, 1,1-dioxotetrahydrothiophen-3-yl and cyclopropyl, wherein R^2 is optionally substituted with one or more substituents independently selected from methyl and halogen; or

R^1 and R^2 are taken together with their intervening atoms to form 4-hydroxypiperidin-1-yl, pyrrolidin-1-yl, azepan-1-yl, 4-benzylpiperazin-1-yl, 4-ethylpiperazin-1-yl, 3-hydroxyazetidin-1-yl, or morpholin-4-yl;

R^3 is selected from hydrogen and halo; and

~ represents a single bond wherein a carbon-carbon double bond bound thereto is in an (*E*)- or (*Z*)-configuration.

2. The compound according to claim 1, wherein the compound is represented by structural formula II:



or a pharmaceutically acceptable salt thereof.

3. The compound of claim 2, wherein:

R^1 is selected from hydrogen and methyl; and

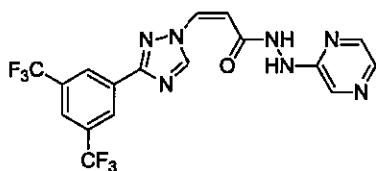
R^2 is selected from pyridin-2-yl, pyridin-4-yl, pyrazin-2-yl and pyrimidin-4-yl, wherein

R^2 is optionally substituted with a single substituent selected from methyl and chloro;

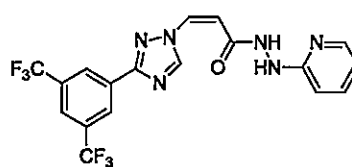
or

R^1 and R^2 are taken together to form 4-hydroxypiperidin-1-yl.

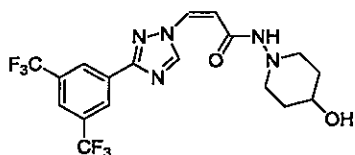
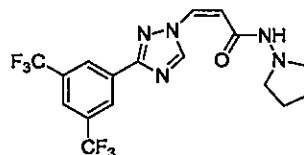
4. The compound of any one of Claims 1-3, wherein R^3 is hydrogen.
5. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein the compound is represented by any one of the following structural formulas:



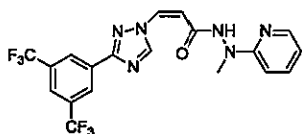
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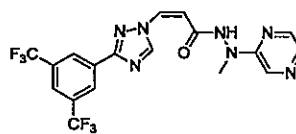
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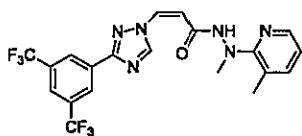
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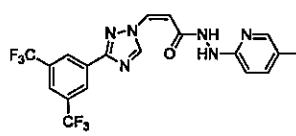
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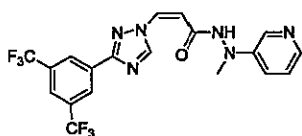
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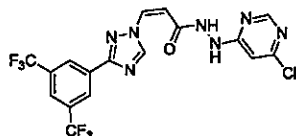
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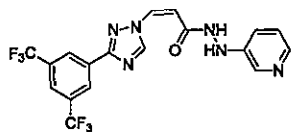
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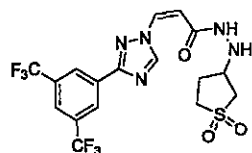
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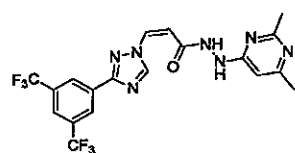
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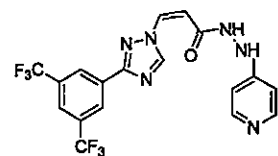
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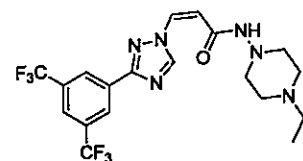
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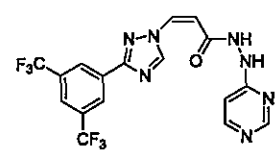
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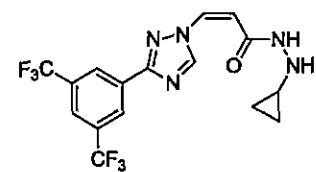
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I-21,

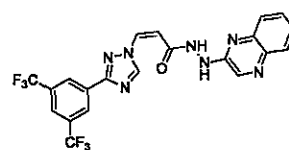


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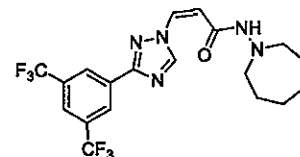


I-25

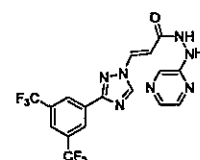
or



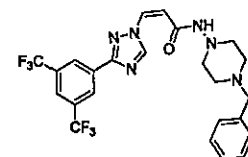
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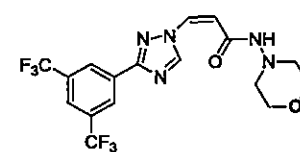
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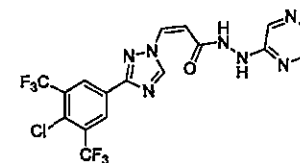
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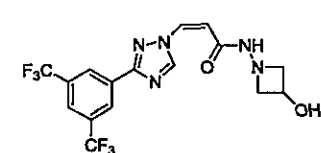
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I-22,

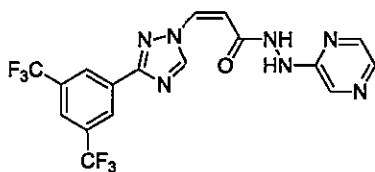


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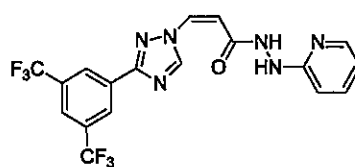


I-26.

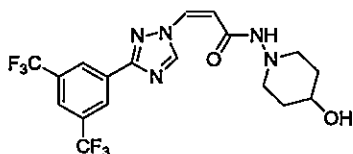
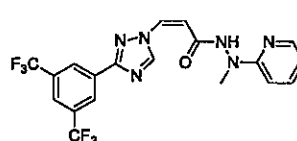
6. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein the compound is represented by any one of the following structural formulas:



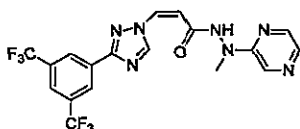
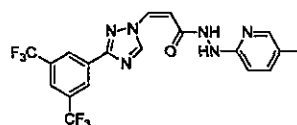
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I-4,

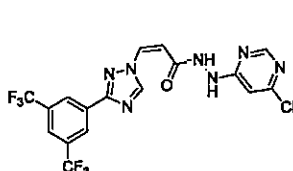
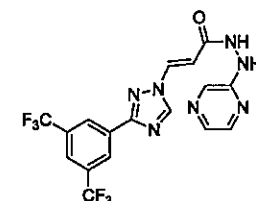


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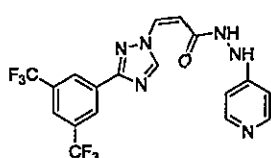
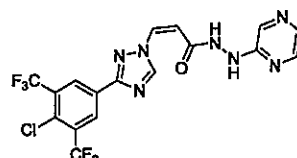
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I-10,



I-12,

I-18,



I-19

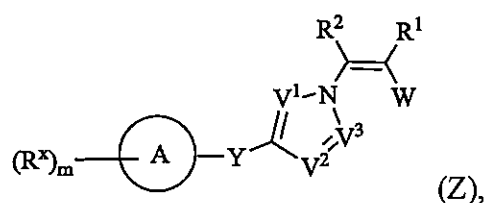
or

I-24.

7. A composition comprising a compound of any one of claims 1-6, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.
8. The composition of Claim 7, further including a second therapeutic agent useful for treating cancer.

9. A method for

preparing a compound of formula Z:



or a pharmaceutically acceptable salt thereof, wherein:

Ring A is an optionally substituted ring selected from phenyl, an 8-10-membered bicyclic aryl ring, a 5-6-membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and an 8-10-membered bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

Y is a covalent bond or $-L-$;

L is a bivalent C_{1-8} saturated or unsaturated, straight or branched, hydrocarbon radical, wherein one or two methylene units of L is optionally replaced by $-NR-$, $-N(R)C(O)-$, $-C(O)N(R)-$, $-O-$, $-C(O)-$, $-OC(O)-$, $-C(O)O-$, $-S-$, $-SO-$, $-SO_2-$, $-C(S)-$, $-C(NOR)-$ or $-C(NR)-$;

each R is independently hydrogen or an optionally substituted group selected from C₁₋₆ aliphatic, phenyl, a 4-7-membered saturated or partially unsaturated carbocyclic ring, a 4-7-membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6-membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or

two R groups on the same nitrogen are taken together with the nitrogen atom to which they are attached to form a 4-7-membered saturated or partially unsaturated heterocyclic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 5-6-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

each of V¹, V² and V³ is independently C(R^y) or N;

each R^x and R^y is independently selected from -R, halogen, -OR, -SR, -N(R)₂, -CN, -NO₂, -N₃, -SOR, -SO₂R, -SO₂NR, -C(O)R, -CO₂R, -C(O)OR, -C(O)N(R)₂, -NRC(O)R, -OC(O)R, -OC(O)N(R)₂, -NRC(O)OR, -NRC(O)NR₂ and -NRSO₂R;

each R¹ and R² is independently hydrogen, deuterium, tritium or halogen;

W is -C(O)N(R⁴)₂;

each R⁴ is independently -R, or

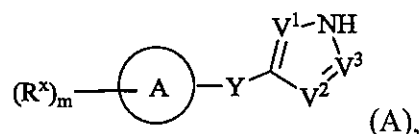
two R⁴ on the same nitrogen are taken together with the nitrogen atom to which they are attached to form a 4-7-membered saturated or partially unsaturated heterocyclic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 5-6-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein the ring thereby formed is optionally substituted with -(R⁵)_n;

each R⁵ is independently selected from -R, halogen, -OR, -SR, -N(R)₂, -CN, -NO₂, -N₃, -SOR, -SO₂R, -SO₂NR, -C(O)R, -CO₂R, -C(O)OR, -C(O)N(R)₂, -NRC(O)R, -OC(O)R, -OC(O)N(R)₂, -NRC(O)OR, -NRC(O)NR₂ and -NRSO₂R; and

each m and n is independently an integer selected from 0, 1, 2, 3 and 4;

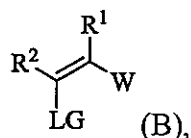
comprising the steps of:

(a) providing a compound of formula A:



wherein each of Ring A, R^x , Y, V^1 , V^2 , V^3 and m is as defined above for the compound of formula Z; and

(b) reacting said compound of formula A with an olefin of formula B:



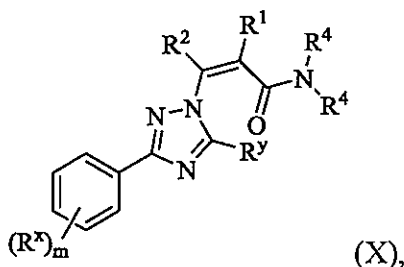
wherein:

LG is halogen, $-\text{OSO}_2\text{R}$ or $-\text{OSO}_2\text{CF}_3$; and

each of W, R, R^1 and R^2 is as defined above for the compound of formula Z;

in the presence of a sterically-hindered nucleophilic base to form a compound of formula Z.

10. The method of claim 9, wherein the compound of Formula Z is represented by a compound of formula X:



or a pharmaceutically acceptable salt thereof, wherein:

each R^x and R^y is independently selected from $-\text{R}$, halogen, $-\text{OR}$, $-\text{SR}$, $-\text{N}(\text{R})_2$, $-\text{CN}$, $-\text{NO}_2$, $-\text{N}_3$, $-\text{SOR}$, $-\text{SO}_2\text{R}$, $-\text{SO}_2\text{NR}$, $-\text{C}(\text{O})\text{R}$, $-\text{CO}_2\text{R}$, $-\text{C}(\text{O})\text{OR}$, $-\text{C}(\text{O})\text{N}(\text{R})_2$, $-\text{NRC}(\text{O})\text{R}$, $-\text{OC}(\text{O})\text{R}$, $-\text{OC}(\text{O})\text{N}(\text{R})_2$, $-\text{NRC}(\text{O})\text{OR}$, $-\text{NRC}(\text{O})\text{NR}_2$ and $-\text{NRSO}_2\text{R}$;

each R is independently hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 4-7-membered saturated or partially unsaturated carbocyclic ring, a 4-7-membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6-membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or

two R groups on the same nitrogen are taken together with the nitrogen atom to which they are attached to form a 4-7-membered saturated or partially unsaturated heterocyclic ring having 1-4 heteroatoms independently selected from nitrogen,

oxygen, and sulfur, or a 5-6-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

each R^1 and R^2 is independently hydrogen, deuterium, tritium or halogen;

each R^4 is independently $-R$, or

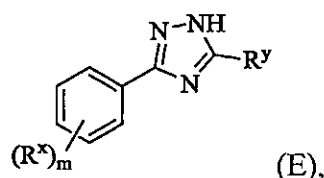
two R^4 on the same nitrogen are taken together with the nitrogen atom to which they are attached to form a 4-7-membered saturated or partially unsaturated heterocyclic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 5-6-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein the ring thereby formed is optionally substituted with $-(R^5)_n$;

each R^5 is independently selected from $-R$, halogen, $-OR$, $-SR$, $-N(R)_2$, $-CN$, $-NO_2$, $-N_3$, $-SOR$, $-SO_2R$, $-SO_2NR$, $-C(O)R$, $-CO_2R$, $-C(O)OR$, $-C(O)N(R)_2$, $-NRC(O)R$, $-OC(O)R$, $-OC(O)N(R)_2$, $-NRC(O)OR$, $-NRC(O)NR_2$ and $-NRSO_2R$; and

each m and n is independently an integer selected from 0, 1, 2, 3 and 4;

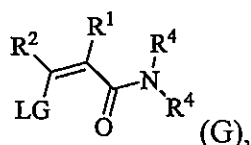
comprising the steps of:

(a) providing a compound of formula E:



wherein each of R^x , R^y and m is as defined above for the compound of formula X; and

(b) reacting said compound of formula E with an olefin of formula G:



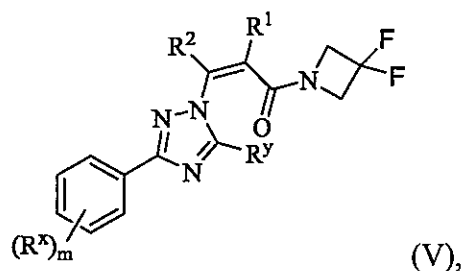
wherein:

LG is halogen, $-OSO_2R$ or $-OSO_2CF_3$; and

each of R , R^1 , R^2 and R^4 is as defined above for the compound of formula X,

in the presence of a sterically-hindered nucleophilic base to form the compound of formula X.

11. The method of claim 10, wherein the compound of formula X is represented by a compound of formula V:



or a pharmaceutically acceptable salt thereof, wherein:

each R^x and R^y is independently selected from $-R$, halogen, $-OR$, $-SR$, $-N(R)_2$, $-CN$, $-NO_2$, $-N_3$, $-SOR$, $-SO_2R$, $-SO_2NR$, $-C(O)R$, $-CO_2R$, $-C(O)OR$, $-C(O)N(R)_2$, $-NRC(O)R$, $-OC(O)R$, $-OC(O)N(R)_2$, $-NRC(O)OR$, $-NRC(O)NR_2$ and $-NRSO_2R$;

each R is independently hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 4-7-membered saturated or partially unsaturated carbocyclic ring, a 4-7-membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6-membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or

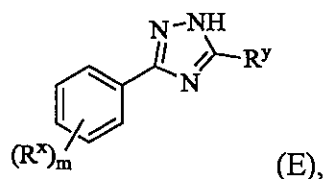
two R groups on the same nitrogen are taken together with the nitrogen atom to which they are attached to form a 4-7-membered saturated or partially unsaturated heterocyclic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 5-6-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

each R^1 and R^2 is independently hydrogen, deuterium, tritium or halogen; and

m is an integer selected from 0, 1, 2, 3 and 4;

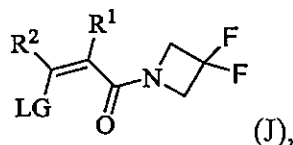
comprising the steps of:

- (a) providing a compound of formula E:



wherein each of R^x , R^y and m is as defined above for the compound of formula V; and

- (b) reacting said compound of formula E with an olefin of formula J:



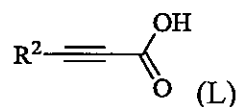
wherein:

LG is halogen, $-\text{OSO}_2\text{R}$ or $-\text{OSO}_2\text{CF}_3$; and

each of R , R^1 and R^2 is as defined above for the compound of formula V, in the presence of a sterically-hindered nucleophilic base to form the compound of formula V.

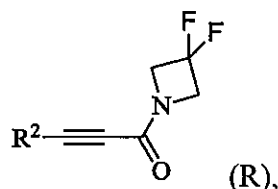
12. The method of claim **11**, further comprising the steps of:

(a) providing a compound of formula L:



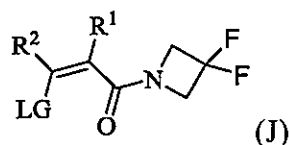
wherein R^2 is as defined for the compound of formula V;

(b) reacting said compound of formula L with  to form a compound of formula R:



wherein R^2 is as defined for the compound of formula V,

(c) reacting said compound of formula R to provide a compound of formula J:

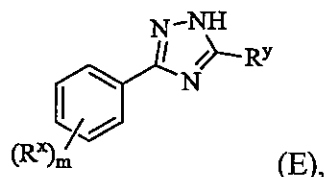


wherein:

LG is halogen, $-\text{OSO}_2\text{R}$ or $-\text{OSO}_2\text{CF}_3$; and

each of R , R^1 and R^2 is as defined for the compound of formula V; and

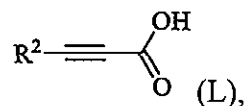
(d) reacting said compound of formula J with a compound of formula E:



wherein each of R^x , R^y and m is as defined for the compound of formula V, in the presence of a sterically-hindered nucleophilic base to provide a compound of formula V.

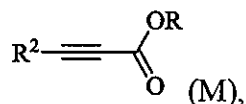
13. The method of claim 11, further comprising the steps of:

(a) providing a compound of formula L:



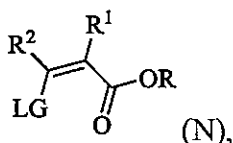
wherein R^2 is as defined for the compound of formula V;

(b) reacting said compound of formula L with an alcohol having the formula HO-R to form a compound of formula M:



wherein each of R and R^2 is as defined for the compound of formula V;

(c) reacting said compound of formula M to provide a compound of formula N:

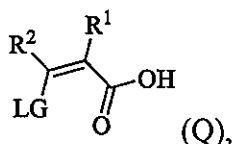


wherein:

LG is halogen, $-\text{OSO}_2\text{R}$ or $-\text{OSO}_2\text{CF}_3$; and

each of R, R^1 and R^2 is as defined for the compound of formula V;

(d) hydrolyzing said compound of formula N to form a compound of formula Q:

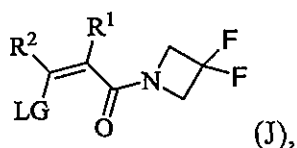


wherein:

LG is halogen, $-\text{OSO}_2\text{R}$ or $-\text{OSO}_2\text{CF}_3$; and

each of R, R^1 and R^2 is as defined for the compound of formula V;

(e) reacting said compound of formula Q with  to form a compound of formula J:

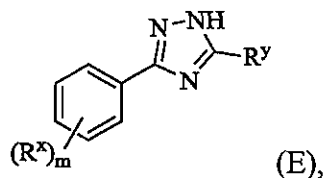


wherein:

LG is halogen, $-\text{OSO}_2\text{R}$ or $-\text{OSO}_2\text{CF}_3$; and

each of R , R^1 and R^2 is as defined for the compound of formula V; and

(f) reacting said compound of formula J with a compound of formula E:



wherein each of R^x , R^y and m is as defined for the compound of formula V, in the presence of a sterically-hindered nucleophilic base to provide the compound of formula V.

14. The method of any of claims 9 to 13, wherein the sterically-hindered nucleophilic base is selected from 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), 1,5-diazabicyclo[4.3.0]non-5-ene (DBN), 1,4-diazabicyclo(2.2.2)octane (DABCO), *N,N*-dicyclohexylmethylamine, 2,6-di-*tert*-butyl-4-methylpyridine, quinuclidine, 1,2,2,6,6-pentamethylpiperidine (PMP), 7-methyl-1,5,7-triazabicyclo(4.4.0)dec-5-ene (MTBD), triphenylphosphine, tri-*tert*-butylphosphine and tricyclohexylphosphine, preferably, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) and 1,4-diazabicyclo(2.2.2)octane (DABCO), more preferably 1,4-diazabicyclo(2.2.2)octane (DABCO).
15. The use of a compound according to any one of claims 1-6, or a pharmaceutically acceptable salt thereof, or a composition according to claim 7, for the manufacture of a medicament for the treatment of a disorder associated with CRM1 activity in a subject in need thereof.
16. The use of a compound according to any one of claims 1-6, or a pharmaceutically acceptable salt thereof, or a composition according to claim 7, for the manufacture of a medicament for the treatment of a disorder selected from a proliferative disorder, an inflammatory disorder, an autoimmune disorder, a viral infection, an ophthalmological disorder, a neurodegenerative disorder, a disorder of abnormal tissue growth, a disorder related to food intake, allergies, and a respiratory disorder.

17. The use of a compound according to any one of claims 1-6, or a pharmaceutically acceptable salt thereof, or a composition according to claim 7, for the manufacture of a medicament for a treatment where the proliferative disease is cancer.
18. The use of a compound according to any one of claims 1-6, or a pharmaceutically acceptable salt thereof, or a composition according to claim 7, together with a second therapeutic agent for the manufacture of a medicament which is administered for the treatment of cancer.
19. The use according to claim 17, wherein the cancer is a hematological cancer selected from a leukemia, a lymphoma or a myeloma or a solid tumor cancer selected from head and neck, prostate, breast, lung, ovarian, glioblastoma, squamous cell, colon and renal.