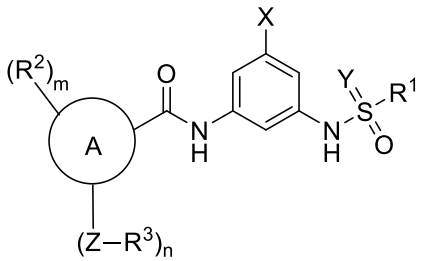
Thus, there is a need for DHX9 inhibitors as potential therapeutic agents for treating diseases or disorders that are responsive to DHX9 inhibition.

SUMMARY

The present disclosure provides compounds that are DHX9 inhibitors. In a first aspect, the present disclosure relates to compounds having the Formula I:



(I);

or a pharmaceutically acceptable salt thereof, wherein:

X is halo;

Y is O or NR^y;

R^y is H or C_{1-4}alkyl;

R^1 is C_{1-4}alkyl or C_{3-6}cycloalkyl; wherein the C_{1-4}alkyl or C_{3-6}cycloalkyl are each optionally and independently substituted with 1 to 3 halo or -OH,

Ring A is a C_{3-6}cycloalkyl, 4 to 6-membered monocyclic heterocyclyl, 6 to 10 membered bicyclic heterocyclyl; phenyl, 5 to 6-membered monocyclic heteroaryl, or 8 to 10-membered bicyclic heteroaryl;

m is 0 to 3;

n is 0 or 2;

each R^2 is independently selected from C_{1-4}alkyl, C_{3-6}cycloalkyl, halo, OR^{2a}, cyano, -$NR^{2b}R^{2c}$, -SO_2R^{2a}, -$C(O)R^{2d}$, and –$C(O)NR^{2b}R^{2c}$ wherein the C_{1-4}alkyl and C_{3-6}cycloalkyl are optionally substituted with 1 to 4 R^{2e}; or 2 R^2 together form oxo;

R^{2a} is H, C_{1-4}alkyl, C_{1-4}haloalkyl or C_{1-4}alkoxyC_{1-4}alkyl;

R^{2d} is H, C_{1-4}alkyl, C_{3-6}cycloalkyl, OR^{2a}, phenyl, 4 to 6-membered monocyclic heterocyclyl, 6 to 8-membered bicyclic heterocyclyl, or 5 to 6-membered monocyclic heteroaryl, wherein the C_{1-4}alkyl is optionally substituted with 1 to 3 halo and the 5- to 6-membered monocyclic heteroaryl is optionally substituted with 1 to 3 C_{1-4}alkyl, C_{1-4}haloalkyl, or phenyl;

R^{2b} and R^{2c} are each independently selected from H, C_{1-4}alkyl, C_{3-6}cycloalkyl, phenyl, 4 to 6-membered monocyclic heterocyclyl and 5 to 6-membered monocyclic heteroaryl,

R^{4b} and R^{4c} are each independently selected from H, phenyl, 4 to 6-membered monocyclic heterocyclyl, 5 to 6-membered monocyclic heteroaryl, and C_{1-4}alkyl optionally substituted with 1 to 4 R^{4d}; or R^{4b} and R^{4c} together with the nitrogen atom to which they are attached to form a 4 to 6-membered monocyclic heterocyclyl;

each R^{4d} is independently selected from halo, OR^{4f}, $-C(O)C_{1-4}$alkyl, $-C(O)NR^{4b}R^{4c}$, $-C(O)C_{1-4}$haloalkyl, $-C(O)OR^{4f}$, $-NR^{4b}R^{4c}$, phenyl, and 5 to 6-membered monocyclic heteroaryl, wherein the phenyl and 5 to 6-membered monocyclic heteroaryl are each optionally substituted with 1 to 3 R^{4g};

each R^{4e} is independently selected from halo, C_{1-4}alkyl, cyano, OR^{4f}, $-NR^{4b}R^{4c}$, $-C(O)H$, $-C(O)R^{4h}$, $-SO_2C_{1-3}$alkyl, and $-C(O)NR^{4b}R^{4c}$, wherein C_{1-4}alkyl is optionally substituted with 1 to 3 substitutes independently selected from halo, $-SO_2C_{1-3}$alkyl and $-C(O)NR^{4b}R^{4c}$; and $-C(O)NR^{4b}R^{4c}$; or two R^{4e} together form oxo;

R^{4f} is H, C_{1-4}alkyl, C_{1-4}haloalkyl, phenyl or 5 to 6-membered monocyclic heteroaryl, wherein the phenyl and 5 to 6-membered monocyclic heteroaryl are each optionally substituted with one to three halo;

each R^{4g} is independently selected from halo, OR^{4f}, C_{1-4}alkyl, C_{1-4}haloalkyl, halo, cyano, $-NR^{4b}R^{4c}$, $-C(O)H$, and $-C(O)OR^{4f}$; and

each R^{4h} is independently C_{1-4}alkyl, C_{3-6}cycloalkyl, C_{1-3}alkoxy or $–N(R^{4b})_2$.

The disclosure relates to pharmaceutical compositions comprising compounds of Formula (I) or pharmaceutically acceptable salts thereof, and a pharmaceutical carrier. Another aspect of the disclosure relates to a pharmaceutical composition comprising a compound as defined herein, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient

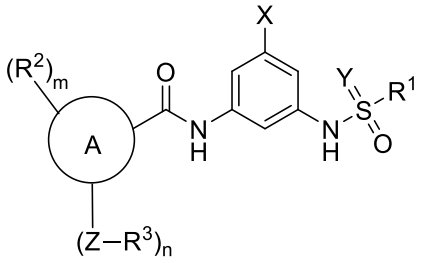
The present disclosure also provide a method of treating a disease or disorder that is responsive to inhibition of DHX9 in a subject comprising administering to said subject an effective amount of at least one compound described herein or a pharmaceutically acceptable salt thereof. In some examples, the method is for the treatment of cancer.

The present disclosure relates to the use of at least one compound described herein or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment of a disease or disorder responsive to inhibition of DHX9. Another aspect of the present disclosure relates to use of the compound as defined herein, or pharmaceutically acceptable salt thereof, or the pharmaceutical composition as defined herein, in the manufacture of a medicament for the treatment of a DHX9 mediated disease or

disorder in a subject. Also provided is a compound described herein or a pharmaceutically acceptable salt thereof for use in treating a disease or disorder responsive to inhibition of DHX9. Another aspect of the present disclosure relates to the compound as defined herein, or pharmaceutically acceptable salt thereof, or the pharmaceutical composition as defined herein, for use in treating a DHX9 mediated disease or disorder in a subject.

CLAIMS

1. A compound represented by Formula (I):



(I);

or a pharmaceutically acceptable salt thereof, wherein:

X is halo;

Y is O or NR^y;

R^y is H or C_{1-4}alkyl;

R^1 is C_{1-4}alkyl or C_{3-6}cycloalkyl; wherein the C_{1-4}alkyl or C_{3-6}cycloalkyl are each optionally and independently substituted with 1 to 3 halo or -OH;

Ring A is a C_{3-6}cycloalkyl, 4 to 6-membered monocyclic heterocyclyl, 6 to 10 membered bicyclic heterocyclyl; phenyl, 5 to 6-membered monocyclic heteroaryl, or 8 to 10-membered bicyclic heteroaryl;

m is 0 to 3;

n is 0 or 2;

each R^2 is independently selected from C_{1-4}alkyl, C_{3-6}cycloalkyl, halo, OR^{2a}, cyano, $-NR^{2b}R^{2c}$, $-SO_2R^{2a}$, $-C(O)R^{2d}$, and $–C(O)NR^{2b}R^{2c}$, wherein the C_{1-4}alkyl and C_{3-6}cycloalkyl are optionally substituted with 1 to 4 R^{2e}; or 2 R^2 together form oxo;

R^{2a} is H, C_{1-4}alkyl, C_{1-4}haloalkyl or C_{1-4}alkoxyC_{1-4}alkyl;

R^{2d} is H, C_{1-4}alkyl, C_{3-6}cycloalkyl, OR^{2a}, phenyl, 4 to 6-membered monocyclic heterocyclyl, 6 to 8-membered bicyclic heterocyclyl, or 5 to 6-membered monocyclic heteroaryl, wherein the C_{1-4}alkyl is optionally substituted with 1 to 3 halo and the 5- to 6-membered monocyclic heteroaryl is optionally substituted with 1 to 3 C_{1-4}alkyl, C_{1-4}haloalkyl, or phenyl;

R^{2b} and R^{2c} are each independently selected from H, C_{1-4}alkyl, C_{3-6}cycloalkyl, phenyl, 4 to 6-membered monocyclic heterocyclyl and 5 to 6-membered monocyclic heteroaryl, wherein the C_{1-4}alkyl is optionally substituted with 1 to 3 substituents independently selected from halo and C_{1-3}alkoxy; or R^{2b} and R^{2c}, together with the nitrogen to which they are attached form a 4 to 6 membered monocyclic heterocyclyl

or 6 to 10 membered bicyclic heterocyclyl; wherein the 4 to 6 membered monocyclic heterocyclyl or 6 to 10 membered bicyclic heterocyclyl are each optionally substituted with 1 to 3 R^{2d};

each R^{2e} is independently selected from halo, cyano, $NR^{2b}R^{2c}$, OR^{2a}, phenyl, and 4 to 6 membered monocyclic heterocyclyl;

Z is a bond, $-CH_2-$, -O-, -O-C_{1-4}alkylene-*, -C_{1-4}alkylene-O-*, -C(O)-, -C(O)O-*, -OC(O)-*, $-S(O)_2-$, $-S(O)_2N(Z^a)-$*, $-N(Z^a)S(O)_2-$*, $-N(Z^a)-$, $-N(Z^a)-C_{1-4}$alkylene-*, -C_{1-4}alkylene-$N(Z^a)$-*, -C(O)$N(Z^a)$-*, or -C(O)$N(Z^a)$-C_{1-3}alkylene-*, wherein * indicates the attachment point to R^3;

Z^a is H or C_{1-4}alkyl;

R^3 is C_{3-6}cycloalkyl, 7 to 10-membered bicyclic carbocyclyl, 4 to 6-membered monocyclic heterocyclyl, 6 to 10-membered bicyclic heterocyclyl, phenyl, 5 to 6-membered monocyclic heteroaryl, or 8 to 10-membered bicyclic heteroaryl, wherein the C_{3-6}cycloalkyl, 7 to 10-membered bicyclic carbocyclyl, 4 to 6-membered monocyclic heterocyclyl, 6 to 10-membered bicyclic heterocyclyl, phenyl, 5 to 6-membered monocyclic heteroaryl, or 8 to 10-membered bicyclic heteroaryl are each optionally and independently substituted with 1 to 4 R^4;

each R^4 is independently selected from C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, halo, OR^{4a}, cyano, $-NR^{4b}R^{4c}$, $-C(O)R^{4a}$, $-C(O)OR^{4a}$, $-C(O)NR^{4b}R^{4c}$, $-NR^{4b}C(O)R^{4a}$ - $NR^{4b}C(O)OR^{4a}$, $-NR^{4b}SO_2R^{4a}$, $-SR^{4a}$, $-S(O)R^{4a}$, $-SO_2R^{4a}$, $-SO_2NR^{4b}R^{4c}$, $-P(O)R^{4b}R^{4c}$, phenyl, 5 to 6-membered monocyclic heteroaryl, 4 to 6-membered monocyclic heterocyclyl, and 6 to 10-membered bicyclic heterocyclyl, wherein the C_{1-4}alkyl, C_{2-4}alkenyl, or C_{2-4}alkynyl is optionally substituted with 1 to 4 R^{4d}, and wherein the phenyl, 5 to 6-membered monocyclic heteroaryl, 4 to 6-membered monocyclic heterocyclyl and 6 to 10-membered bicyclic heterocyclyl are each optionally substituted with 1 to 3 R^{4e} and further optionally substituted with 1 or 2 oxo; or two R^4 together form oxo;

R^{4a} is H, C_{1-4}alkyl optionally substituted with 1 to 4 R^{4d}, $-NR^{4b}R^{4c}$, C_{3-6}cycloalkyl, 4 to 6-membered monocyclic heterocyclyl, phenyl, or 5 to 6-membered monocyclic heteroaryl; wherein the C_{3-6}cycloalkyl, 4 to 6-membered monocyclic heterocyclyl, phenyl or 5 to 6-membered monocyclic heteroaryl are each optionally and independently substituted with 1 to 3 R^{4e};

R^{4b} and R^{4c} are each independently selected from H, phenyl, 4 to 6-membered monocyclic heterocyclyl, 5 to 6-membered monocyclic heteroaryl, and C_{1-4}alkyl

optionally substituted with 1 to 4 R^{4d}; or R^{4b} and R^{4c} together with the nitrogen atom to which they are attached to form a 4 to 6-membered monocyclic heterocyclyl;

each R^{4d} is independently selected from halo, OR^{4f}, -C(O)C_{1-4}alkyl, -C(O)$NR^{4b}R^{4c}$, -C(O)C_{1-4}haloalkyl, -C(O)OR^{4f}, -$NR^{4b}R^{4c}$, phenyl, and 5 to 6-membered monocyclic heteroaryl, wherein the phenyl and 5 to 6-membered monocyclic heteroaryl are each optionally substituted with 1 to 3 R^{4g};

each R^{4e} is independently selected from halo, C_{1-4}alkyl, cyano, OR^{4f}, -$NR^{4b}R^{4c}$, -C(O)H, -C(O)R^{4h}, -SO_2C_{1-3}alkyl, and -C(O)$NR^{4b}R^{4c}$, wherein C_{1-4}alkyl is optionally substituted with 1 to 3 substitutes independently selected from halo, -SO_2C_{1-3}alkyl and -C(O)$NR^{4b}R^{4c}$; or two R^{4e} together form oxo;

R^{4f} is H, C_{1-4}alkyl, C_{1-4}haloalkyl, phenyl or 5 to 6-membered monocyclic heteroaryl, wherein the phenyl and 5 to 6-membered monocyclic heteroaryl are each optionally substituted with one to three halo;

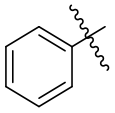
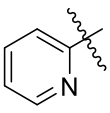
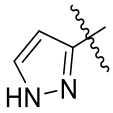
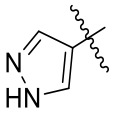
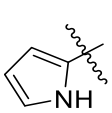
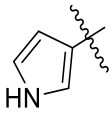
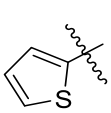
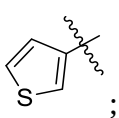
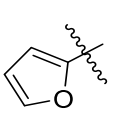
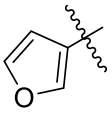
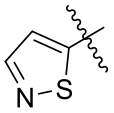
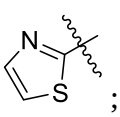
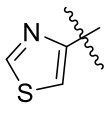
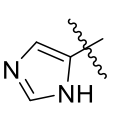
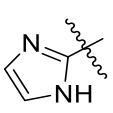
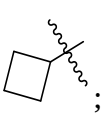
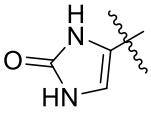
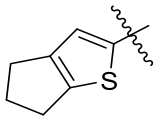
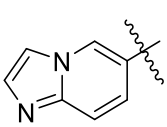
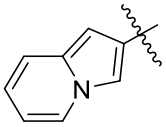
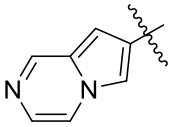
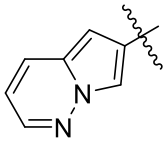
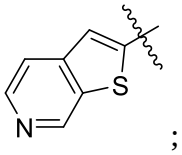
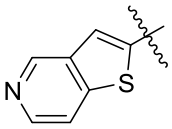
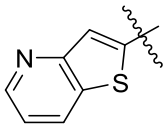
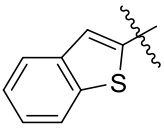
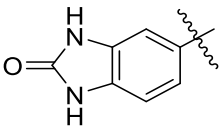
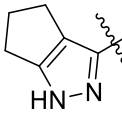
each R^{4g} is independently selected from halo, OR^{4f}, C_{1-4}alkyl, C_{1-4}haloalkyl, halo, cyano, -$NR^{4b}R^{4c}$, -C(O)H, and -C(O)OR^{4f}; and

each R^{4h} is independently C_{1-4}alkyl, C_{3-6}cycloalkyl, C_{1-3}alkoxy or $–N(R^{4b})_2$.

2. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein X is Cl, Br, or F, preferably wherein X is Cl.

3. The compound of claim 1 or 2, or a pharmaceutically acceptable salt thereof, wherein ring A is:

(i) selected from phenyl, thiophenyl, pyrrolyl, pyrazoyl, furanyl, isothiazoyl, thiazoyl, imidazoyl, cyclobutyl, benzofuranyl, 2-oxo-2,3-dihydro-1*H*-benzo[*d*]imidazolyl, imidazo[1,2-*a*]pyridin-6-yl, 1,4,5,6-tetrahydrocyclopenta[c]pyrazolyl, 2-oxo-2,3-dihydro-1*H*-imidazolyl, indolizinyl, pyrrolo[1,2-a]pyrimidinyl, pyrrolo[1,2-c]pyrimidinyl, pyrrolo[1,2-a]pyraziny, 5,6-dihydro-4H-cyclopenta[b]thiophenyl, 5-oxo-5H-thiazolo[3,2-a]pyridinyl, thieno[3,2-b]pyridinyl, thieno[3,2-c]pyridinyl, thieno[2,3-c]pyridinyl, benzothiophenyl, thieno[3,2-d]pyrimidinyl, pyrrolo[1,2-b]pyridazinyl, pyrrolo[1,2-a]pyrazinyl, pyrrolo[1,2-a]pyrimidinyl, pyrrolo[1,2-b] pyrimidinyl, pyrrolo[1,2-c]pyrimidinyl, 1-oxo-1,2-dihydropyrrolo[1,2-a]pyrazinyl, pyrrolo[2,1-f][1,2,4]triazinyl, 4,5,6,7-tetrahydrothieno[2,3-c]pyridinyl, 5,6-dihydro-4H-cyclopenta[b]thiophenyl, and 4,7-dihydro-5H-thieno[2,3-c]pyranyl;

(ii) represented by the following formula:  ;  ;  ;  ;  ;  ;  ;  ;  ;  ;  ;  ;  ;  ;  ;  ;  ;  ;  ;  ;  ;  ;  ;  ;  ;  ;  ;  ; 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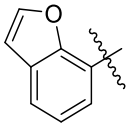
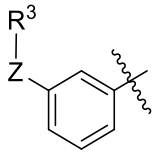
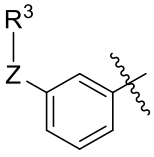
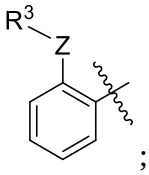
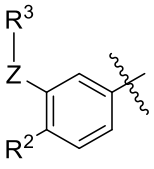
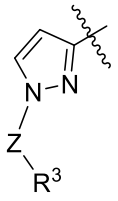
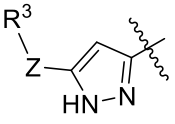
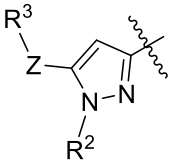
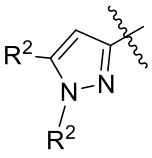
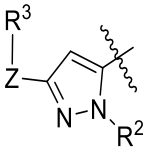
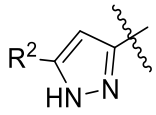
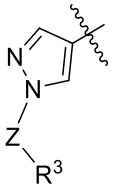


; each of which is substituted with 0 to 2 R^2 and 0 to 1 Z-R^3; or

(iii) represented by the following formula:  ;  ;

 ;  ;  ;  ;  ;  ;

 ;  ;  ; ; ; ;

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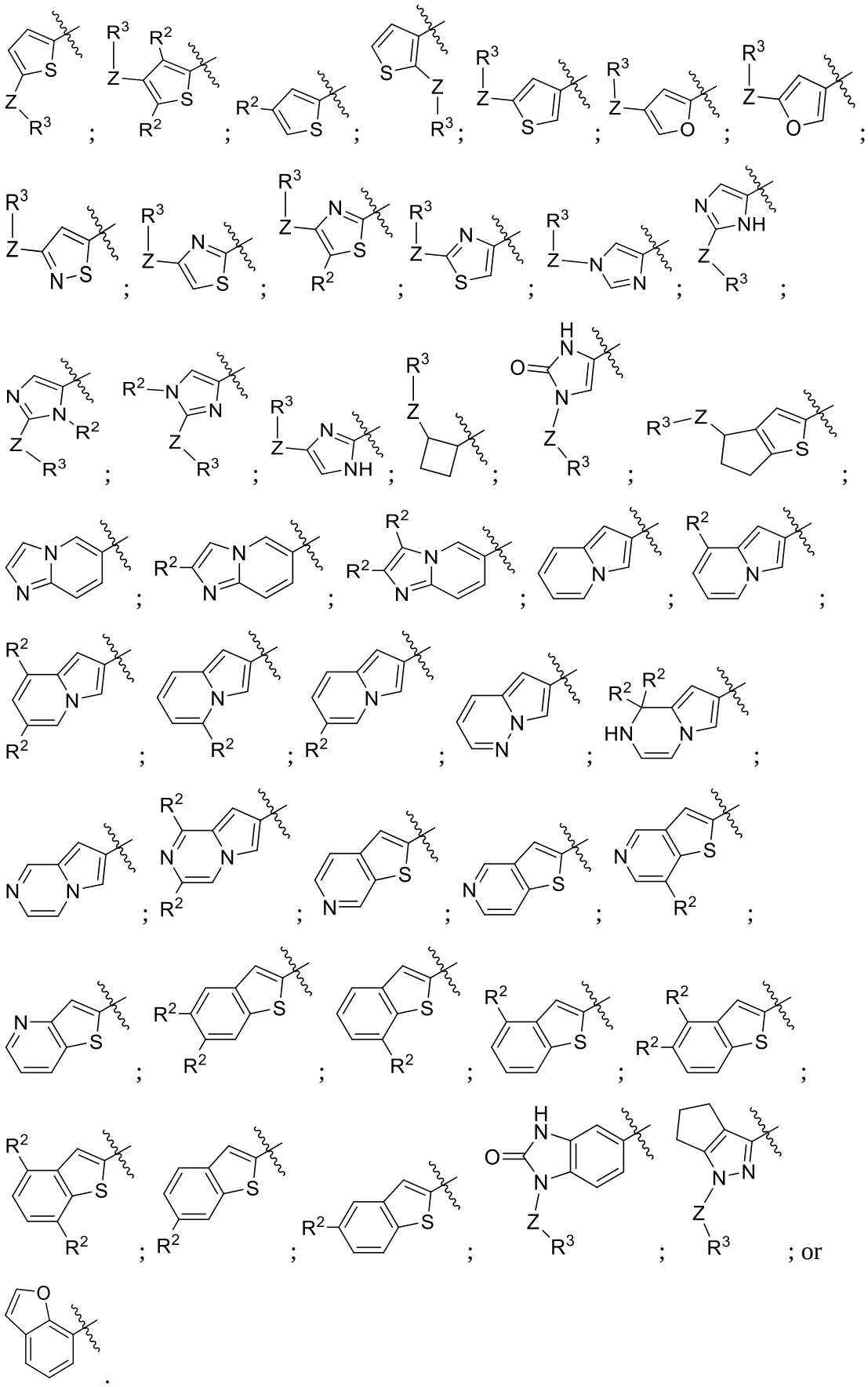

; or

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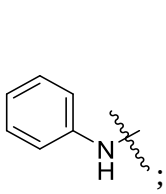
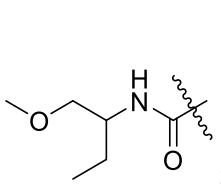
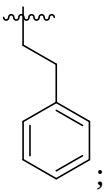
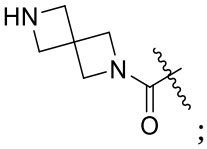
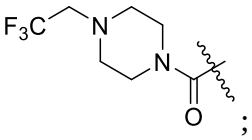
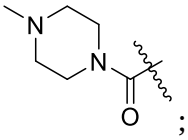
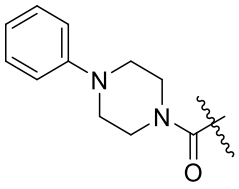
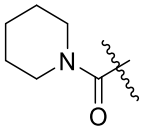
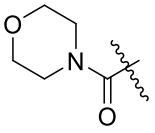
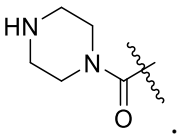
4. The compound of any one of claim 1 to 3, or a pharmaceutically acceptable salt thereof, wherein R^2 is selected from $–OCH_3$, cyclopropyl, $-CH_3$, $-CF_3$, $-CH_2CH_3$, $-CH(CH_3)_2$, $-CH(OH)CH_3$, $-C(CH_3)_2OH$, $-CH_2OCH_3$, $-CH_2OH$, $-CH_2CF_3$, $-CH_2CH_2OH$, $-CH_2CH_2CH_2OH$, $-CH_2CN$, $-CH_2CHF_2$, $-CH_2NH_2$, $-N(CH_3)_2$, $-SO_2CH_3$, cyano, halo, -C(O)OH, $-C(O)N(CH_3)_2$, and $–C(O)NHCH_3$, or the following structural formula: ; ; ; ; ; ; ; ; ; or .

5. The compound of any one of claims 1 to 4, or a pharmaceutically acceptable salt thereof, wherein:

(i) n is 1;

(ii) n is 1 and Z is a bond; or

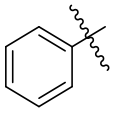
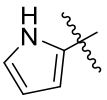
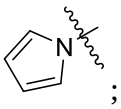
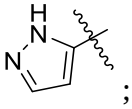
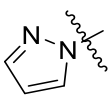
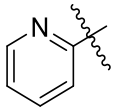
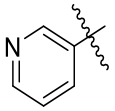
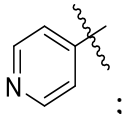
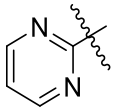
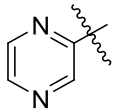
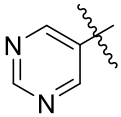
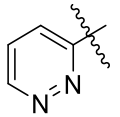
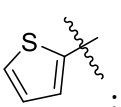
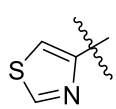
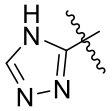
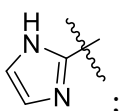
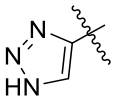
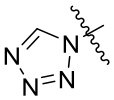
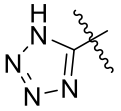
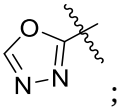
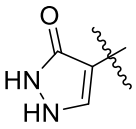
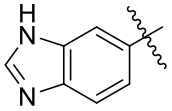
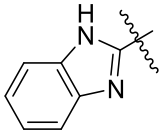
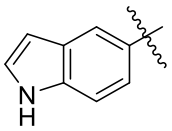
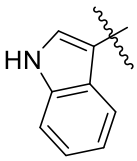
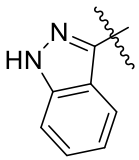
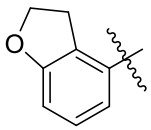
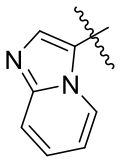
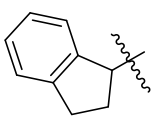
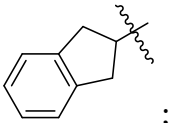
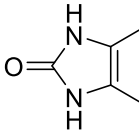
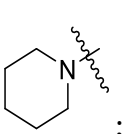
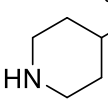
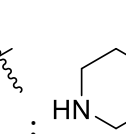
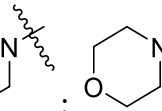
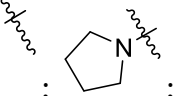
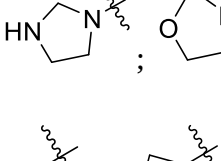
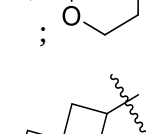
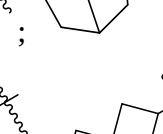
(iii) n is 1 and Z is $-CH_2-$, $-CH(CH_3)-$, -O-, -N(H)-, $-N(C_{1-4}alkyl)-$, or –C(O)NH-*, wherein * indicates the attachment point to R^3.

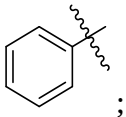
6. The compound of any one of claims 1 to 5, or a pharmaceutically acceptable salt thereof, wherein:

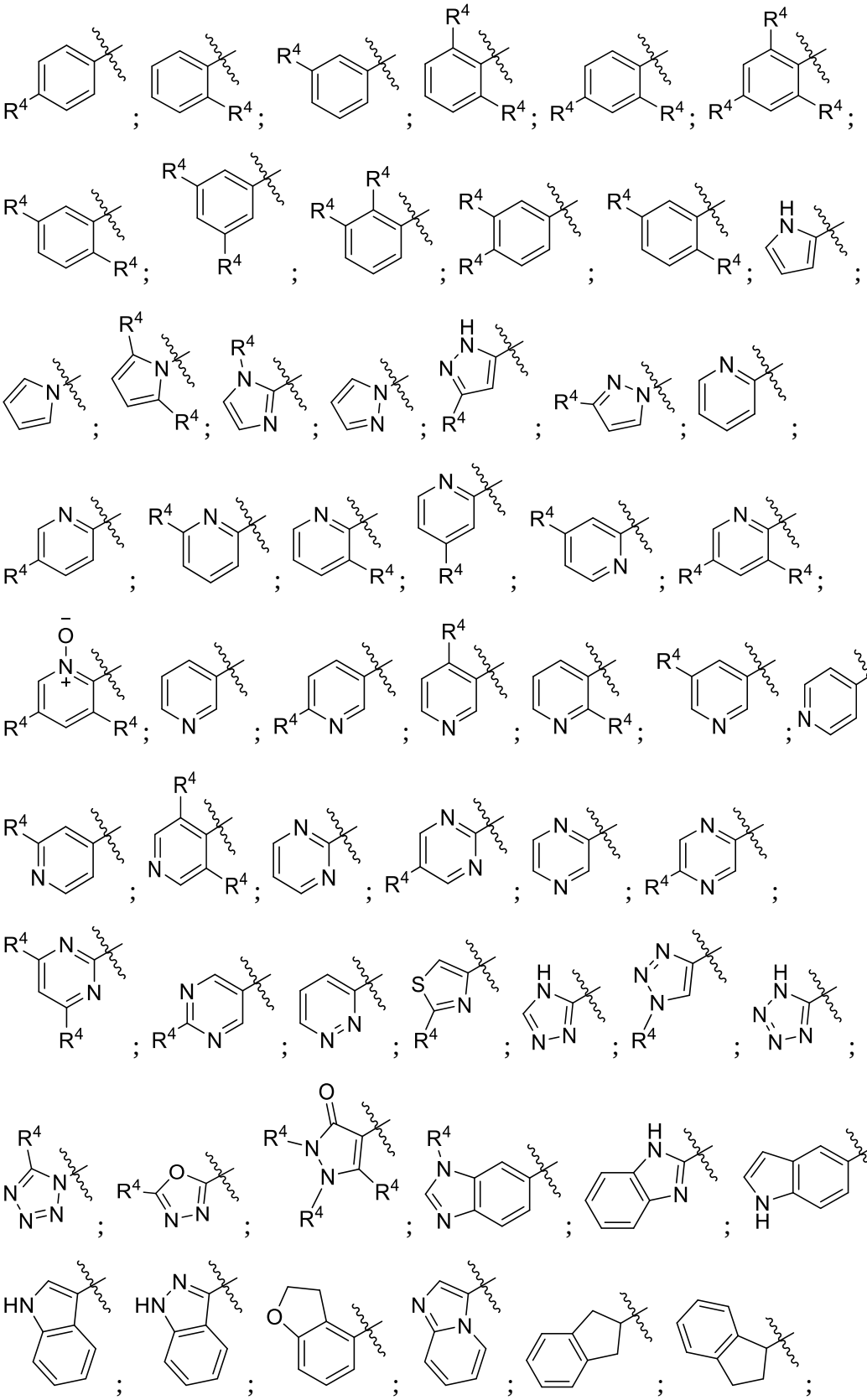
(i) R^3 is selected from cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, piperidinyl, piperazinyl, morpholinyl, pyrrolidinyl, phenyl, pyrrolyl, pyrazolyl, pyridyl, pyrimidyl, pyrazinyl, pyrazinyl, thiophenyl, tetrahydropyranyl, tetrahydrofuranyl, oxabicyclo[3.2.1]octanyl, thiazolyl, imidazoyl, triazolyl, tetrazolyl, oxadiazolyl, 3-oxo-2,3-dihydro-1H-pyrazoly, benzamidazolyl, indazolyl, indoyl, imidazolidinyl, azetidinyl, 2,3-dihydrobenzofuranyl, imidazo[1,2-a]pyridinyl, 2,3-dihydro-1H-indenyl, 2-oxo-2,3-dihydro-1H-benzo[d]imidazolyl, spiro[3.3]heptanyl,

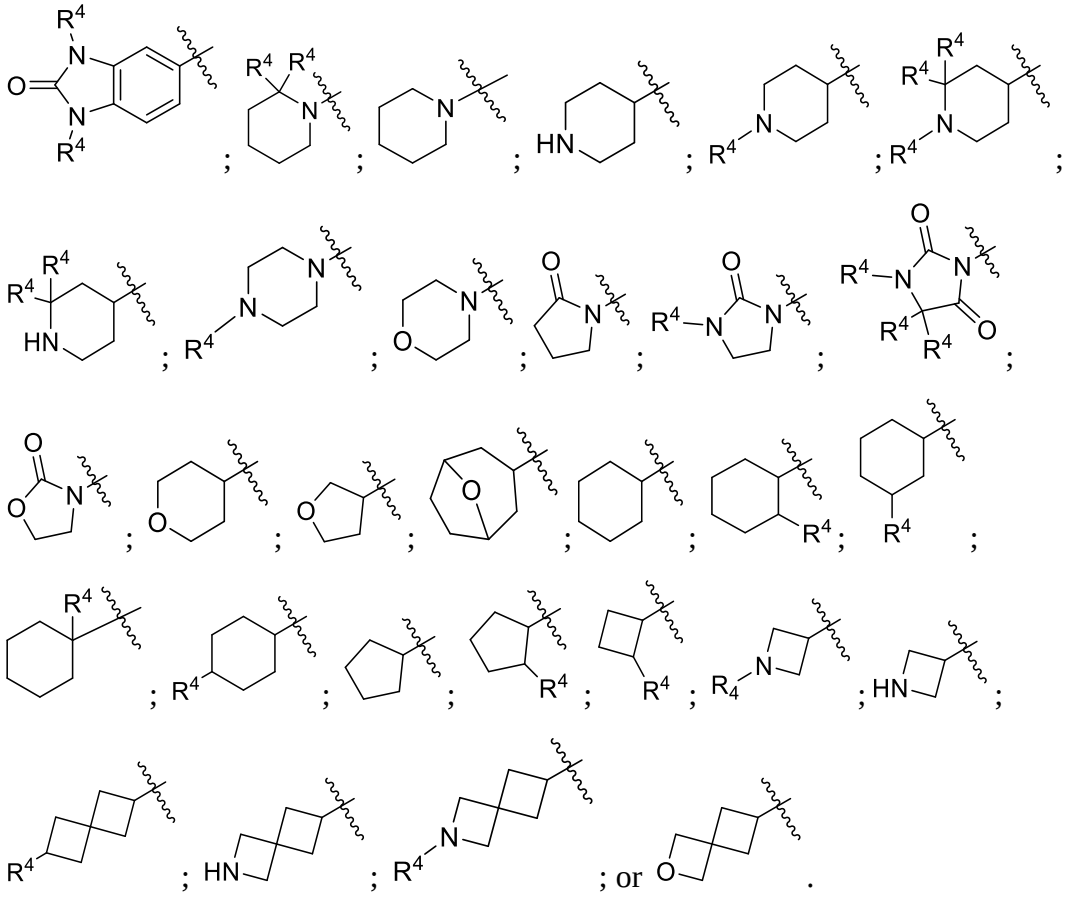
2-azaspiro[3.3]heptanyl, and 2-oxaspiro[3.3]heptanyl, each of which is optionally substituted with 1 to 3 R^4;

(ii) Z is $-CH_2-$ and R^3 is selected from thiophenyl, pyrrolyl, and 2-oxo-2,3-dihydro-1H-benzo[d]imidazolyl, each of which is optionally substituted with 1 to 2 R^4;

(iii) R^3 is represented by the following structural formula:  ;  ;  ;  ;  ;  ;  ;  ;  ;  ;  ;  ;  ;  ;  ;  ;  ;  ;  ;  ;  ;  ;  ;  ;  ;  ;  ;  ;  ;  ;  ;  ;  ;  ;  ;  ;  ;  ;  ;  ; ; ; ; ; ; ; ; ; ; ; ; ; ; ; ; each of which is optionally substituted with 1 to 3 R^4; or

(iv) R^3 is represented by the following structural formula:  ;





7. The compound of any one of claims 1 to 6, or a pharmaceutically acceptable salt thereof, wherein:

(i) R^4 is selected from C_{1-3}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, -OR^{4a}, -CN, -NH_2, -$NR^{4b}R^{4c}$, halo, -$C(O)R^{4a}$, -$NHC(O)R^{4a}$, -$NHC(O)OR^{4a}$, -$NR^{4b}SO_2R^{4a}$, -SR^{4a}, -$S(O)R^{4a}$, -SO_2R^{4a}, -$SO_2NR^{4b}R^{4c}$, -$P(O)R^{4b}R^{4c}$, -$C(O)O$-C_{1-4}alkyl, benzyl, phenyl, 5 to 6-membered monocyclic heteroaryl, 6 to 10-membered bicyclic heterocyclyl, and 4 to 6-membered monocyclic heterocyclyl, wherein the C_{1-3}alkyl, C_{2-4}alkenyl, or C_{2-4}alkynyl represented by R^4 is optionally substituted with 1 to 3 substituents independently selected from halo, phenyl, 5 to 6-membered monocyclic heteroaryl optionally substituted with 1 or 2 R^{4g}, and 4 to 6-membered monocyclic heterocyclyl optionally substituted with 1 or 2 R^{4g}, -$C(O)NR^{4b}R^{4c}$, -$C(O)R^{4a}$, and OR^{4f}; and the benzyl, phenyl, 5 to 6-membered monocyclic heteroaryl, 6 to 10-membered bicyclic heterocyclyl, and 4 to 6-membered monocyclic heterocyclyl represented by R^4 are each optionally substituted with 1 to 3 R^{4e} and further optionally substituted with one or two oxo, or two R^4 together form an oxo;

R^{4a} is H, C_{1-4}alkyl optionally substituted with 1 to 4 R^{4d}, -$NR^{4b}R^{4c}$, C_{3-6}cycloalkyl, phenyl, 4- to 6-membered monocyclic heterocyclyl, or 5 to 6-membered monocyclic heteroaryl, wherein the phenyl, 4- to 6-membered monocyclic heterocyclyl, and 5 to 6-membered monocyclic heteroaryl are optionally substituted with 1 to 3 R^{4e};

each R^{4b} is independently H or C_{1-4}alkyl;

R^{4c} is H, C_{1-4}alkyl optionally substituted with 1 to 4 R^{4d}, 4 to 6-membered monocyclic heterocyclyl, or 5 to 6-membered monocyclic heteroaryl;

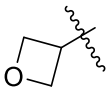
each R^{4d} is independently selected from halo, -OR^{4f}, C_{3-6}cycloalkyl, -C(O)OH, -$NR^{4b}R^{4c}$, phenyl, and 5 to 6-membered monocyclic heteroaryl, wherein the phenyl and 5 to 6-membered monocyclic heteroaryl are each optionally substituted with 1 to 3 substituents independently selected from C_{1-3}alkyl, C_{1-3}haloalkyl, halo, CN and OH;

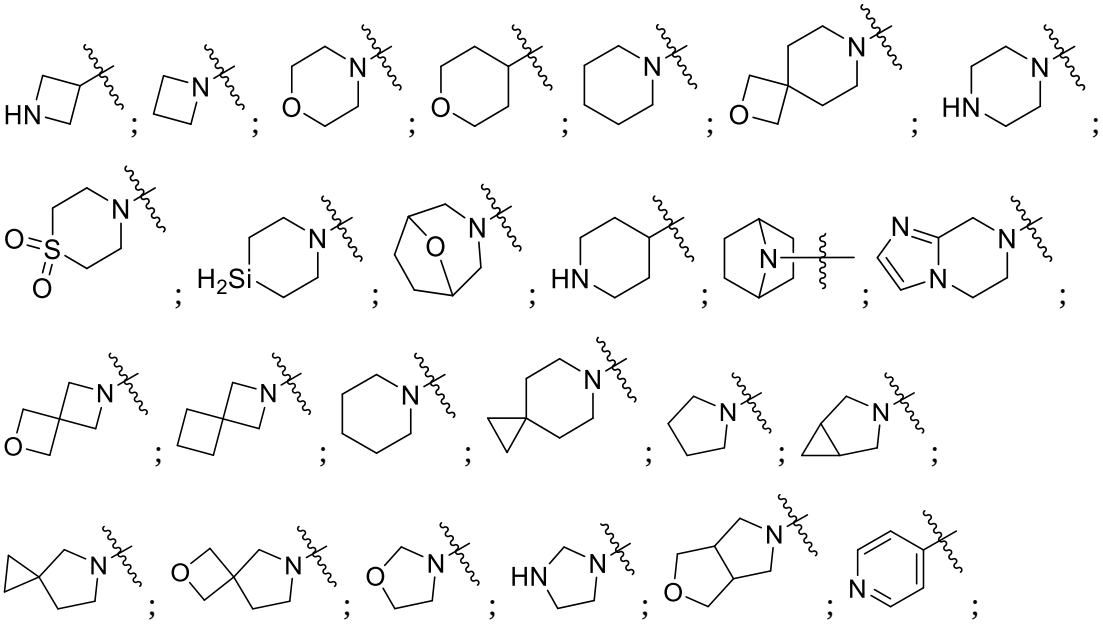
each R^{4e} is independently selected from halo,-OH, C_{1-4}alkyl, C_{1-4}haloalkyl, C_{1-4}alkoxy, –C(O)R^{4h}, -SO_2C_{1-3}alkyl, -C_{1-3}alkylSO_2C_{1-3}alkyl, -C(O)N(C_{1-3}alkyl)$_2$, and cyano; or two R^{4e} together form an oxo;

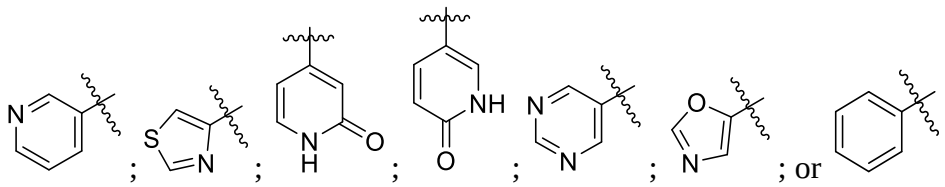
R^{4f} is H, C_{1-4}alkyl, phenyl or 5 to 6-membered monocyclic heteroaryl, wherein phenyl and 5 to 6-membered monocyclic heteroaryl are each optionally substituted with 1 to 3 halo;

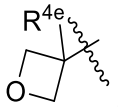
each R^{4g} is independently C_{1-3}alkyl or halo; and

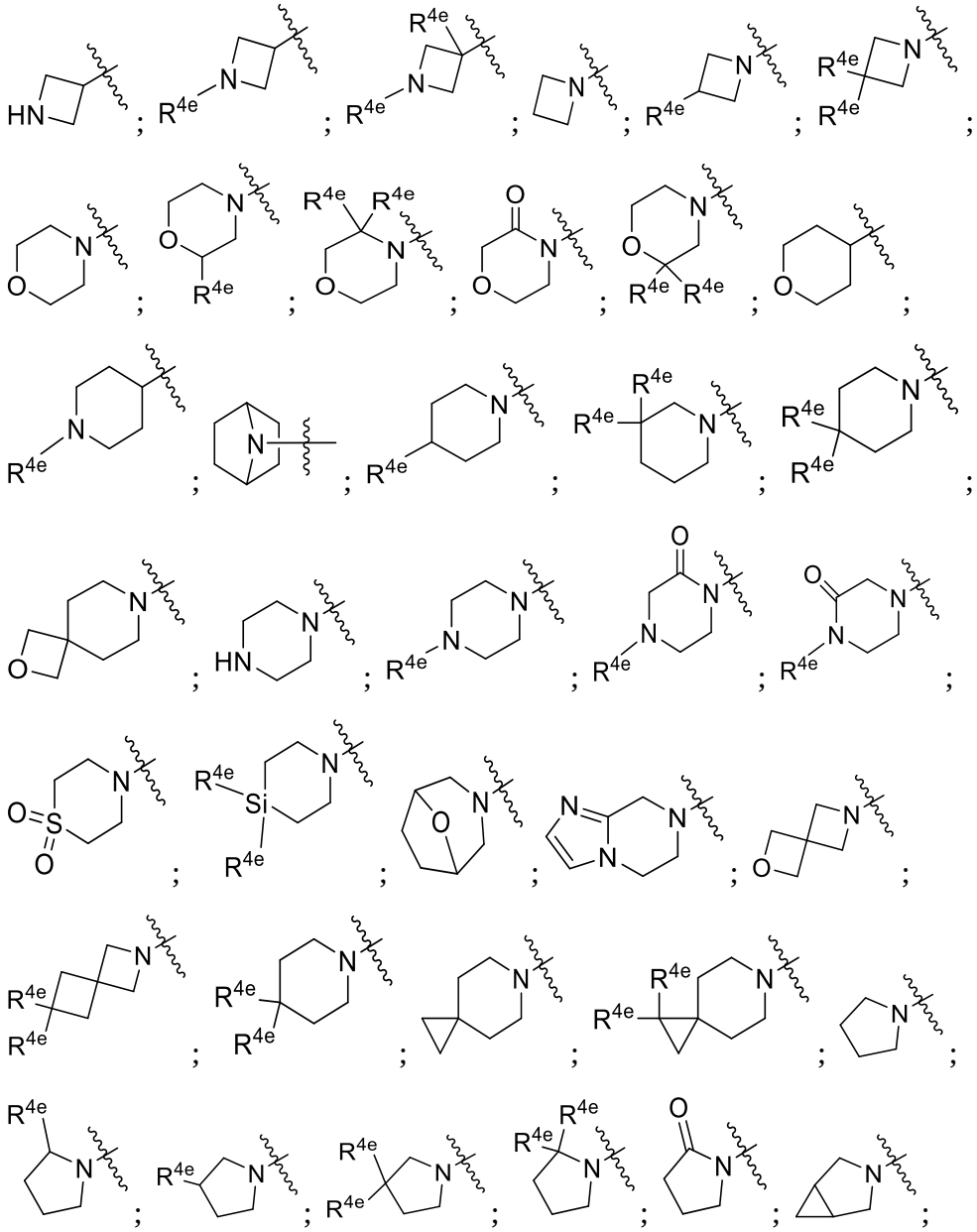
each R^{4h} is independently C_{1-4}alkyl, C_{3-6}cycloalkyl, C_{1-3}alkoxyl or –N(R^{4b})$_2$;

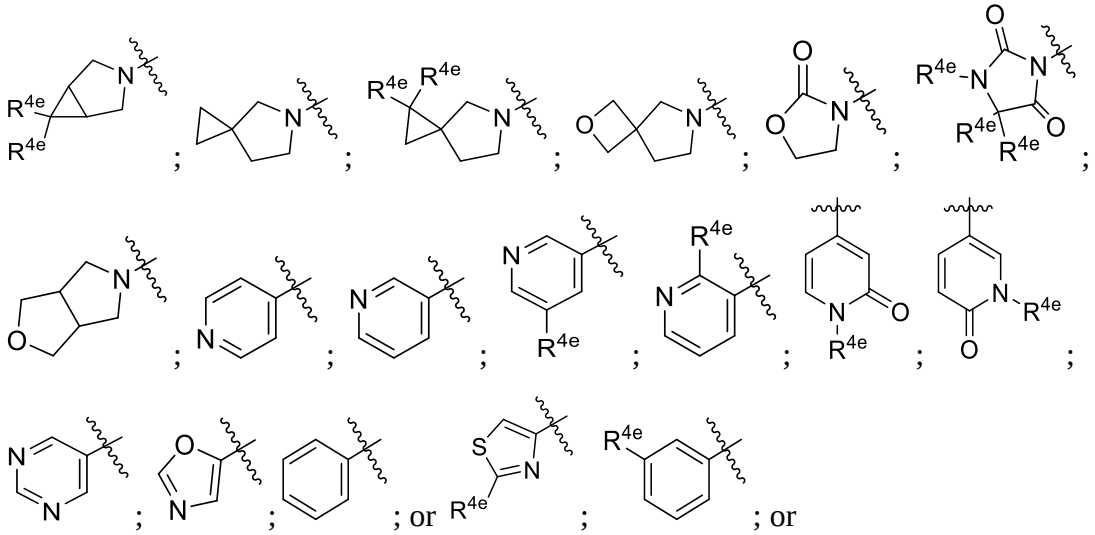
(ii) R^4 is represented by the following structural formula: ;



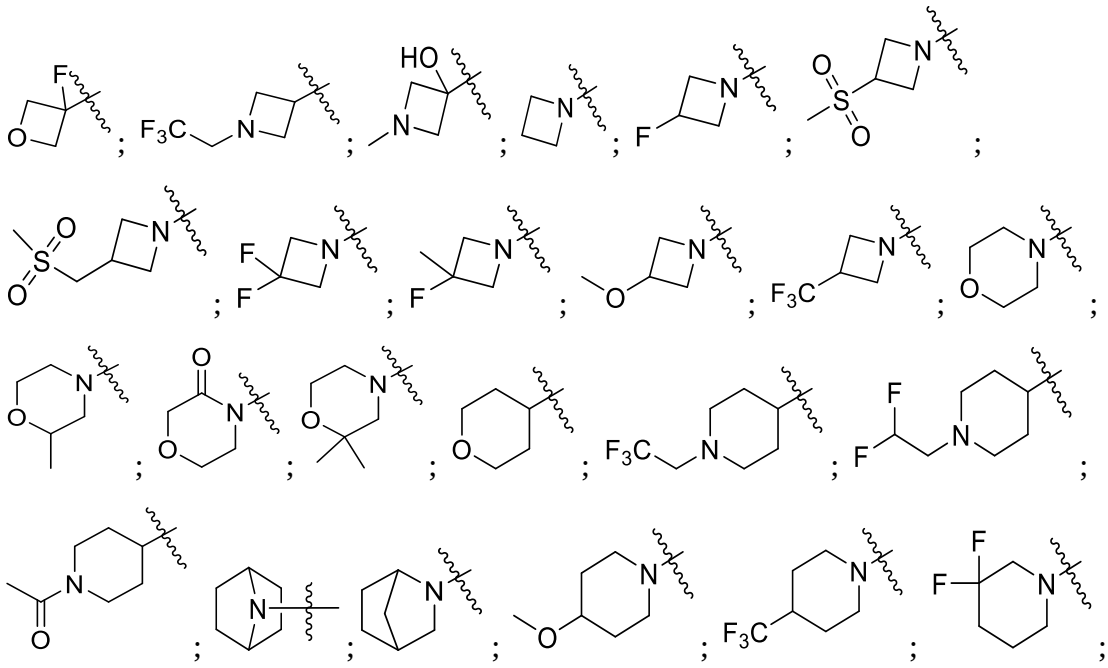

; each of which is optionally substituted with 1 to 3 R^{4e} and further optionally substituted with 1 or 2 oxo;

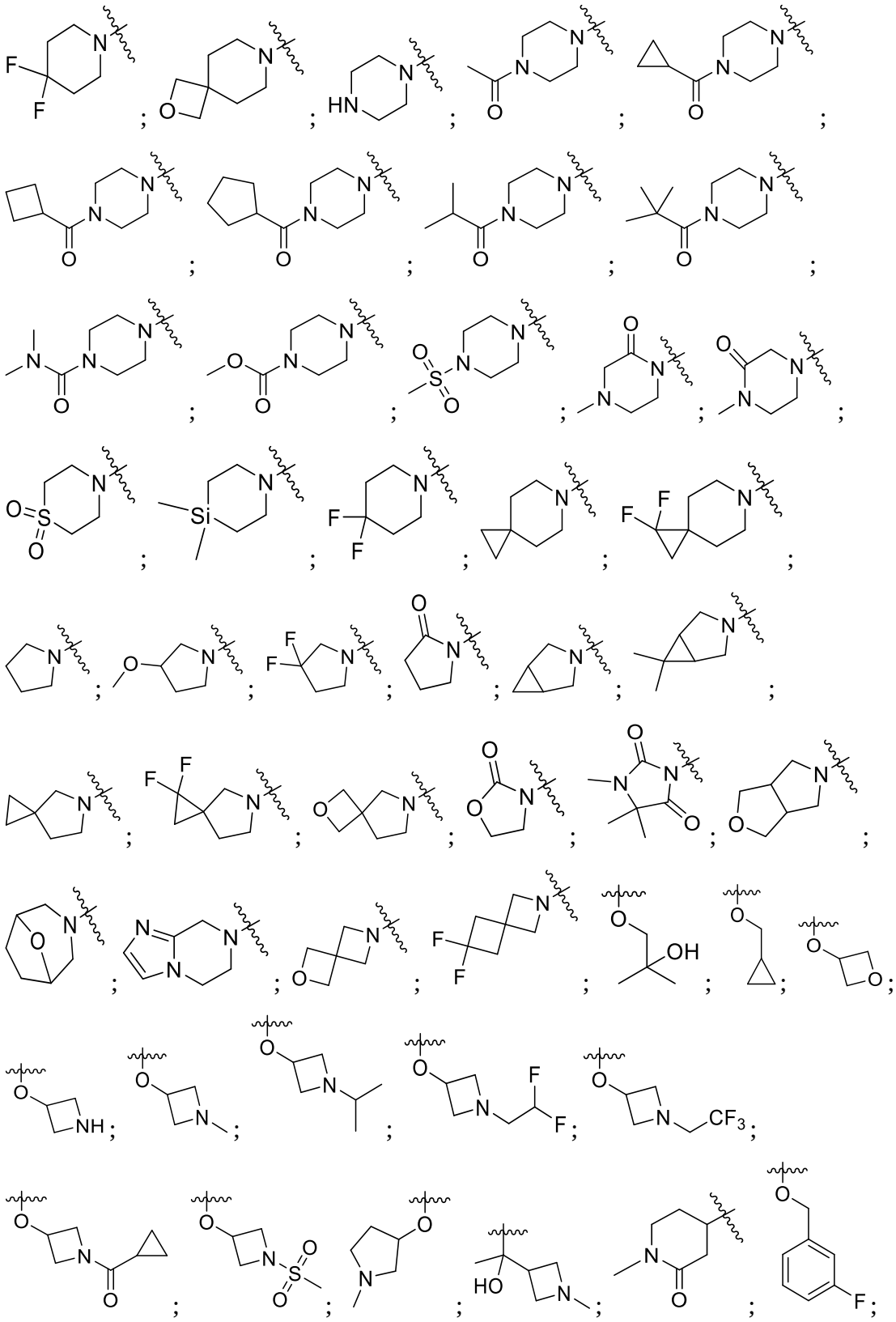
(iii) R^4 is represented by the following structural formula: ;

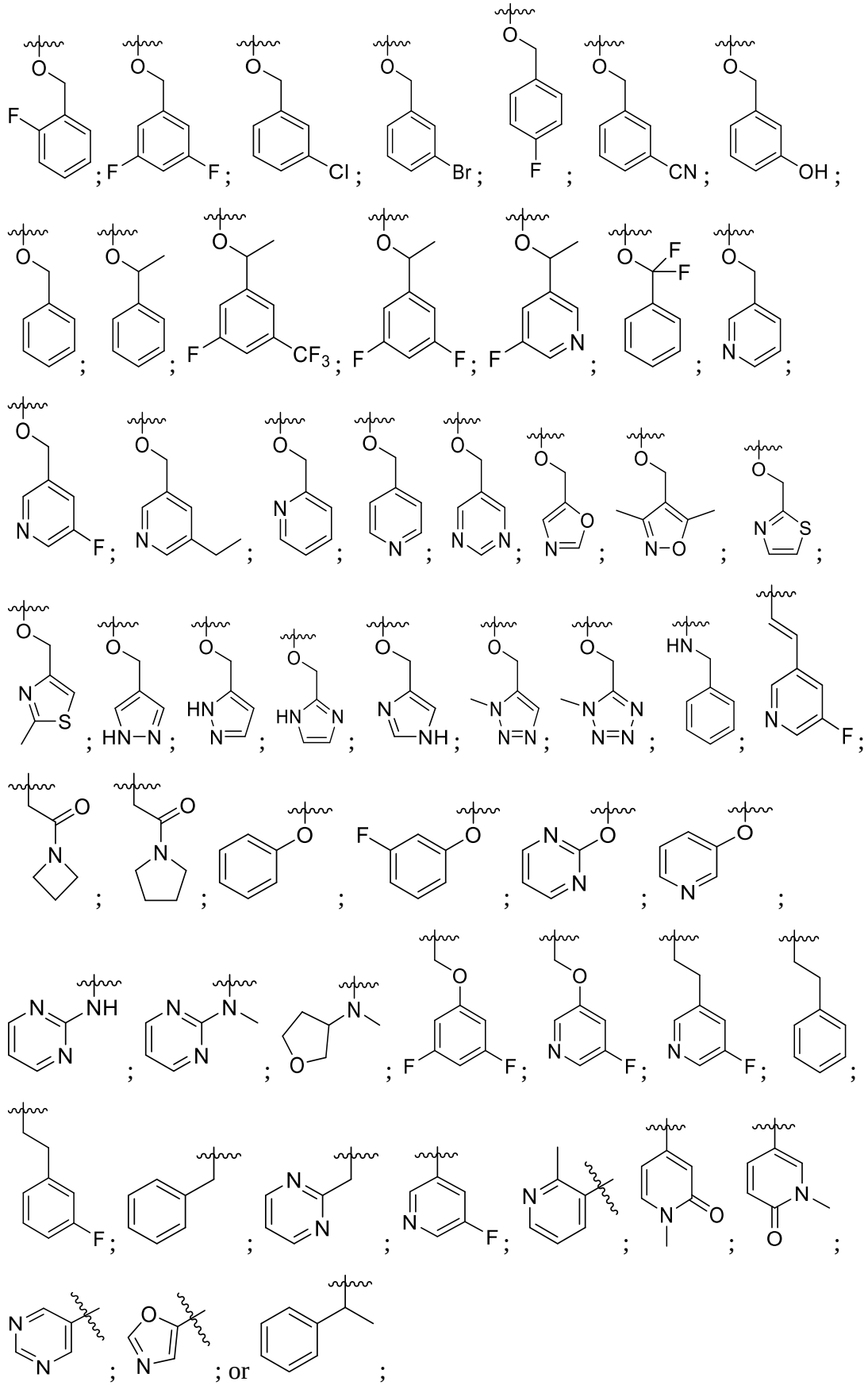




(iv) R^4 is –CH_3, CH_2OH, -CHF_2, -CF_3, -$CH(CF_3)OH$, -CH_2OCH_3, -CH_2CN, -CH_2CF_3, -CH_2CH_2OH, -$CH_2C(O)N(CH_3)_2$, -$C{\equiv}CC(CH_3)_2OH$, -OH, -OCH_3, -OCH_2CH_3, -$OCH_2CH_2OCH_3$, -$OCH(CH_3)_2$, -OCF_3, -$OCHF_2$, -OCH_2CF_3, -O-cyclopropyl, -O-cyclobutyl, -$OC(CH_3)_3$, -$OC(CH_3)_2CH_2OH$, -$OCH(CH_3)C(O)OH$, -$OC(CH_3)_2C(O)OH$, -$OCH(CH_3)CH_2OH$, -$OCH_2CH_2N(CH_3)_2$, -CN, -NH_2, -$NHCH_3$, halo, -C(O)H, -$C(O)CH(CH_3)_2$, -$C(O)OCH_3$, -C(O)O-*t*-butyl, -$N(CH_3)SO_2CH_3$, -$NHC(O)CH_3$, -NHC(O)cyclopropyl, -$NHC(O)OC(CH_3)_3$, -$C(O)CH_3$, -C(O)OH, -$C(O)NH_2$, -$C(O)NHCH_3$, -$C(O)N(CH_3)_2$, -$C(O)NC(CH_3)_3$, -SCH_3, -$S(O)CH_3$, -SO_2CH_3, -$SO_2N(CH_3)_2$, -$P(O)(CH_3)_2$, phenyl, or R^4 is represented by the following structural formula:





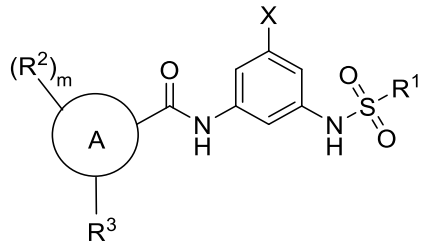


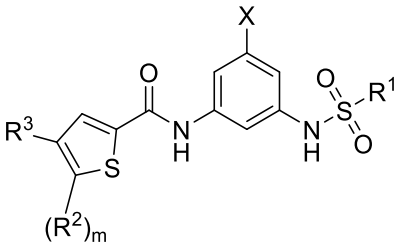
preferably, wherein:

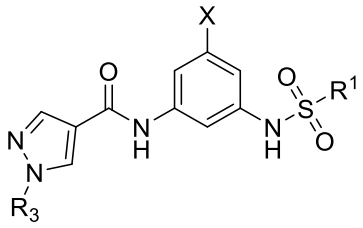
(a) each R^{4e} is independently –F, $–CH_3$, $-CF_3$, $-CH_2CHF_2$, $-CH_2CF_3$, $-CH_2SO_2CH_3$, -OH, $-OCH_3$, $-SO_2CH_3$, $–C(O)CH_3$, -C(O)cyclopropyl, -C(O)cyclobutyl, -C(O)cyclopentyl, $-C(O)CH(CH_3)_2$, $-C(O)C(CH_3)_3$ $–C(O)N(CH_3)_2$, $-C(O)OCH_3$, or cyano; or

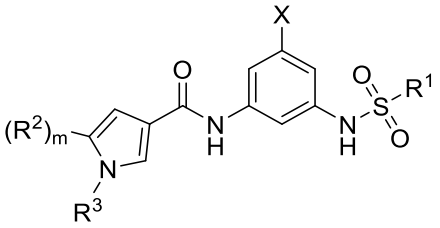
(b) R^{4e} is $–CH_3$, $–C(O)CH_3$, $-C(O)CH(CH_3)_2$ $–C(O)N(CH_3)_2$, or cyano.

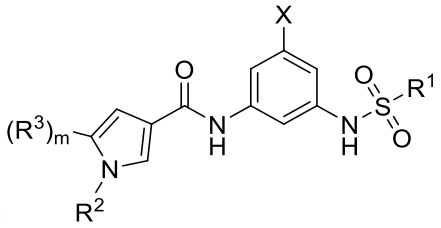
8. The compound of claim 1, wherein the compound is represented by Formula (V) , (IIB), (IIIA), (IVA) or (IVB):


(V);


(IIB);


(IIIA);


(IVA); or


(IVB);

or a pharmaceutically acceptable salt thereof, wherein:

X is Cl or Br;

R^1 is $-CH_3$ or $–CH_2CH_3$;

ring A is selected from phenyl, thiophenyl, pyrrolyl, pyrazolyl, furanyl, isothiazolyl, and imidazolyl;

m is 0 or 1;

each R^2 is independently selected from C_{1-3}alkyl and $-C(O)R^{2d}$, wherein the C_{1-3}alkyl is optionally substituted with R^{2g};

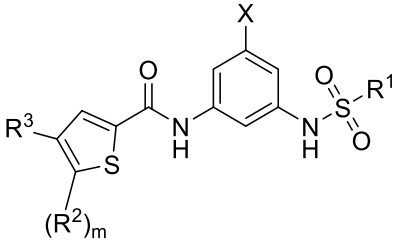
R^{2d} is 4 to 6-membered monocyclic heterocyclyl;

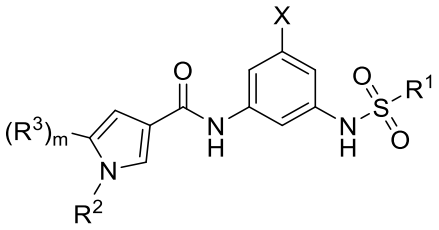
R^{2g} is cyano or OH;

R^3 is phenyl or 5 to 6-membered monocyclic heteroaryl, wherein the phenyl or 5 to 6-membered monocyclic heteroaryl are each optionally and independently substituted with 1 or 2 R^4;

each R^4 is independently selected from halo, C_{1-4}alkyl, -O-benzyl, -O-C_{1-3}alkyl, cyano, $-NH_2$, and 4 to 6-membered monocyclic heterocyclyl, wherein the benzyl is optionally substituted with 1 to 3 halo or C_{1-3}haloalkyl.

9. The compound of claim 8, wherein the compound is represented by Formula (IIB) or (IVB):


(IIB);


(IVB);

or a pharmaceutically acceptable salt thereof, wherein:

m is 1;

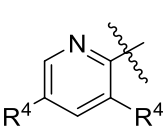
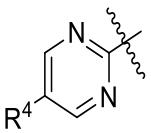
R^1 is $-CH_3$;

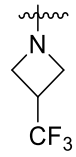
X is Cl;

R^2 is $-CH_3$;

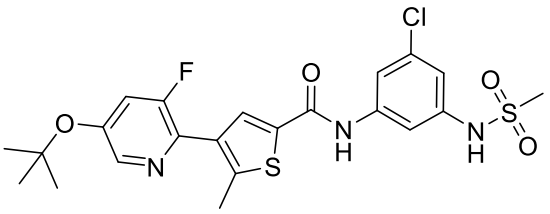
R^3 is pyrimidinyl or pyridinyl, each of which is optionally substituted with 1 or 2 R^4;

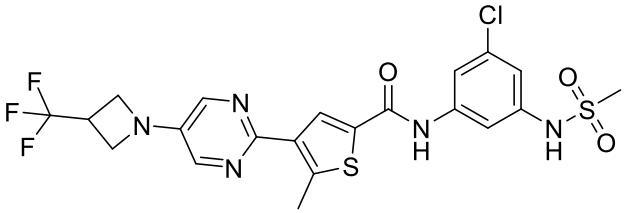
R^4 is halo, -OC_{1-3}alkyl, or 4- to 6-membered monocyclic heterocyclyl, wherein the 4- to 6-membered monocyclic heterocyclyl is optionally substituted with 1 or 2 halo or C_{1-3}haloalkyl.

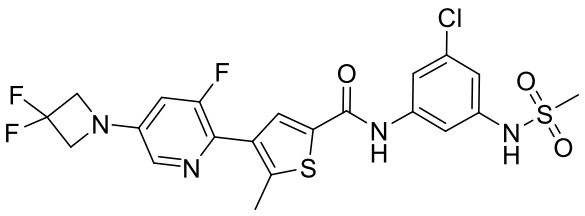
10. The compound of claim 9, or a pharmaceutically acceptable salt thereof, wherein R^3 is represented by the following structural formula:  ; or  .

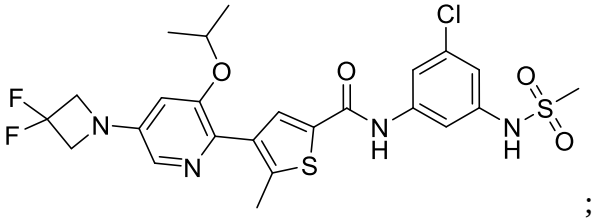
11. The compound of claim 9 or 10, or a pharmaceutically acceptable salt thereof, wherein each R^4 is independently –F, -$OCH(CH_3)_2$, or -$OC(CH_3)_3$, or R^4 is represented by the following structural formula: .

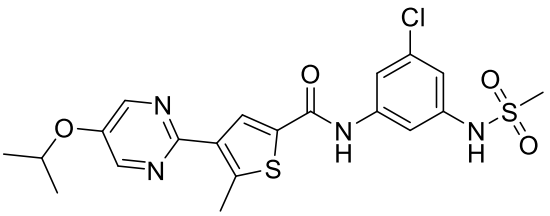
12. The compound of claim 1, wherein the compound is:

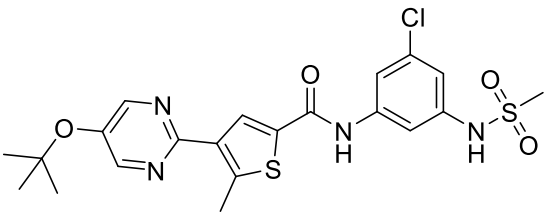
;

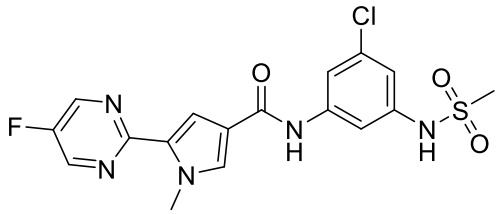
;

;

;

;

;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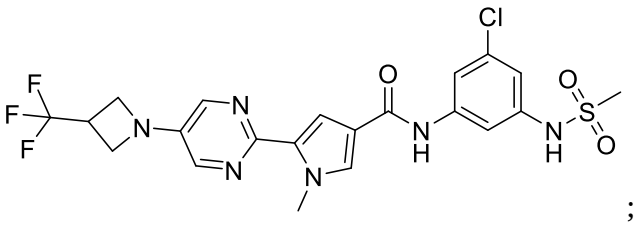
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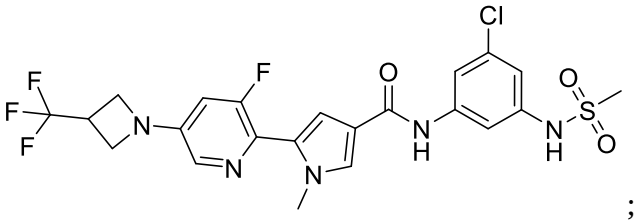
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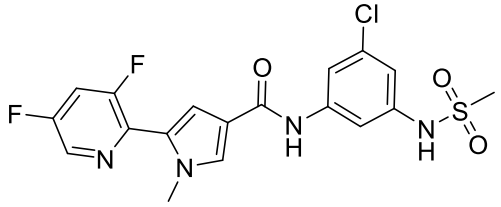
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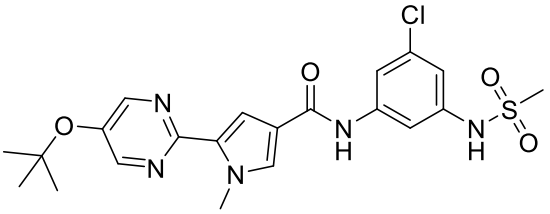
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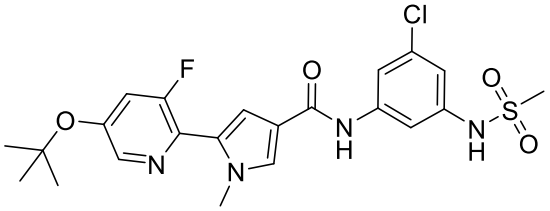
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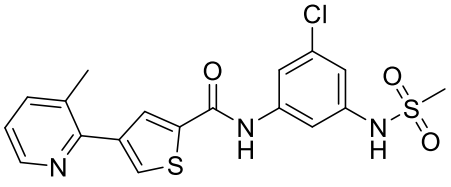
;

or a pharmaceutically acceptable salt thereof.

13. The compound of claim 1, wherein the compound is selected from any one of Examples 1-736, or a pharmaceutically acceptable salt thereof.

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

15. The compound of any one of claims 1 to 13, or pharmaceutically acceptable salt thereof, or the pharmaceutical composition of claim 14, for use in treating a DHX9 mediated disease or disorder in a subject.

16. Use of the compound of any one of claims 1 to 13, or pharmaceutically acceptable salt thereof, or the pharmaceutical composition of claim 14, in the manufacture of a medicament for the treatment of a DHX9 mediated disease or disorder in a subject.

17. The compound or pharmaceutical composition for use of claim 15 or the use of claim 16, wherein the disease or disorder is cancer, viral infection or autoimmune disease, preferably wherein the disease or disorder is cancer.

18. The compound or pharmaceutical composition for use or the use of claim 17, wherein the cancer is:

(i) selected from colorectal, endometrial, ovarian, gastric, hematopoietic, breast, brain, skin, lung, blood, prostate, head and neck, pancreatic, bladder, bone, soft-tissue, kidney, and liver cancer, preferably wherein the cancer is selected from colorectal, endometrial, ovarian, hematopoietic, and gastric cancer; or

(ii) Ewing's Sarcoma.

19. The compound or pharmaceutical composition for use or the use of claim 17 or 18, wherein:

(i) the cancer is a microsatellite instability (MSI) cancer, preferably wherein the cancer is a microsatellite instability-high (MSI-H) colorectal cancer; or

(ii) the cancer has mutations or defects in DNA mis-match repair (MMR), and/or mutations or defects in RNA splicing and the kinetochore complex.