

HETEROAROMATIC COMPOUNDS AS BRUTON'S TYROSINE KINASE (BTK) INHIBITORS

APPLICATION DATA

This application claims benefit to US provisional application serial no. 61/681,684 filed August 10 2012.

5

BACKGROUND OF THE INVENTION

1. TECHNICAL FIELD

The present invention relates to novel compounds which inhibit BTK and their use as medicaments.

10

2. BACKGROUND INFORMATION

Members of the protein kinase family of human enzymes play important regulatory roles in a multitude of distinct signal transduction processes due to their post-translational modification of specific proteins via the addition of a phosphate group (Hunter, *Cell*, 1987 15 50, 823-829). Bruton's tyrosine kinase (BTK) is a member of the Tec family of tyrosine kinases and plays a critical role in B cell development, activation and antibody production.

The contribution of BTK to B cell biology is exemplified in the X-linked agammaglobulinemia (XLA) immunodeficiency in humans (reviewed in Lindvall, 20 Immunol Rev 2005, 203, 200-215 that display attenuated calcium signaling upon BCR engagement, lack mature B cells in periphery due to block between pro- and pre-B cells stage and have lower levels of circulating antibodies than normal healthy subjects. The outcome of recent clinical trials with B cell depleting anti-CD20 molecules in diseases such as rheumatoid arthritis (RA) and multiple sclerosis (MS) support the hypothesis that 25 B cells offer an important intervention node for controlling autoimmune disorders (Townsend et al. 2010). As such, attenuation of B cell activation and proliferation via inhibition of BTK may offer similar therapeutic benefit and is consistent with the demonstrated resistance of BTK-deficient mice to collagen induced arthritis (Jansson, 1993, Clin Exp Immunol 94, 459-xxx) and experimental autoimmune encephalitis

(Svensson et al. 2002 and Mangla et al 2004). Similarly, the clinical efficacy observed with a neutralizing antibody to the B cell stimulating factor BlyS supports a role for B cells in the pathophysiology of systemic lupus erythematosus (SLE) (La Cava 2010). Given the necessity for BTK for the production of autoantibodies, including anti-DNA antibodies, in
5 murine models of SLE (Steinberg et al., 1982; Golding et al., 1983; Scribner et al., 1987; Seldin et al., 1987; Satterthwaite et al., 1998; Takeshita et al., 1998; Whyburn et al., 2003), BTK inhibitors may offer therapeutic benefit to SLE patients.

Within myeloid cells, BTK signal transduction is necessary for the stimulated release of inflammatory cytokines such as TNF from stimulated monocytes (Horwood, J Exp Med,
10 2003, 1603-xxx) and for optimal actin cytoskeletal organization and lacunar bone resorption in isolated osteoclasts (Danks, 2011, J Bone and Mineral Research, 26, 182–192). Bone marrow derived mast cells lacking BTK exhibit impaired activation-induced degranulation and cytokine release (ref). Given the role of BTK in signal transduction processes across multiple cell types implicated in the pathogenesis of autoimmune and
15 allergic disorders, inhibition of BTK activity may provide clinical benefit in diseases such as RA, MS, SLE, asthma and allergic disorders.

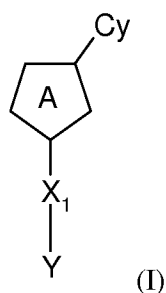
SUMMARY OF THE INVENTION

20 The invention comprises a novel class of heteroaromatic compounds and methods for making and using the same. These compounds are useful for the treatment of autoimmune and allergic disorders in that they exhibit good inhibitory effect upon BTK.

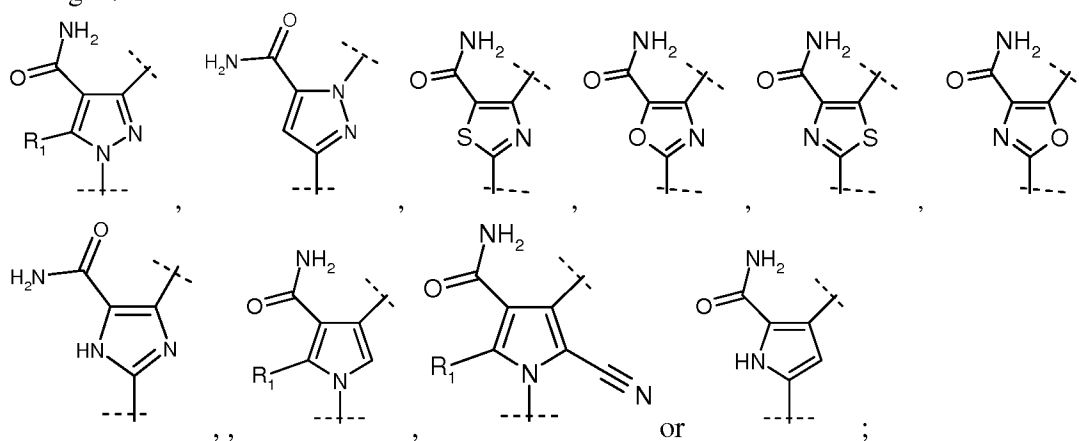
DETAILED DESCRIPTION OF THE INVENTION

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In a first generic embodiment, there is provided a compound of the formula (I)



A ring is:



R₁ is N(R₃)₂ or hydrogen;

Cy is aryl or heteroaryl each is substituted by R₂ and optionally substituted by halogen, halo C₁₋₄ alkyl, C₁₋₄ alkyl and C₁₋₄ alkoxy;

R_2 is chosen from:

10 L-Ar, C₁₋₆ alkyl and C₁₋₆ alkoxy, each Ar, C₁₋₆ alkyl and C₁₋₆ alkoxy are optionally substituted by halogen, halo C₁₋₄ alkyl, C₁₋₄ alkyl, R₃-S(O)_m-, -CN, -C(O)-N(R₃)₂ or C₁₋₄ alkoxy;

L is a linker chosen from a bond, O, >C(O) , $\text{-(CH}_2\text{)}_n\text{-}$, $\text{-O-(CH}_2\text{)}_n\text{-}$, $\text{-N(R}_3\text{)-}$, $\text{-N(R}_3\text{)-(CH}_2\text{)}_n\text{-}$, $\text{-(CH}_2\text{)}_n\text{-N(R}_3\text{)-}$, $\text{-C(O)-N(R}_3\text{)-}$, $\text{-C(O)-N(R}_3\text{)-(CH}_2\text{)}_n\text{-}$, $\text{-N(R}_3\text{)-C(O)-N(R}_3\text{)-}$, $\text{-N(R}_3\text{)-C(O)-}$,

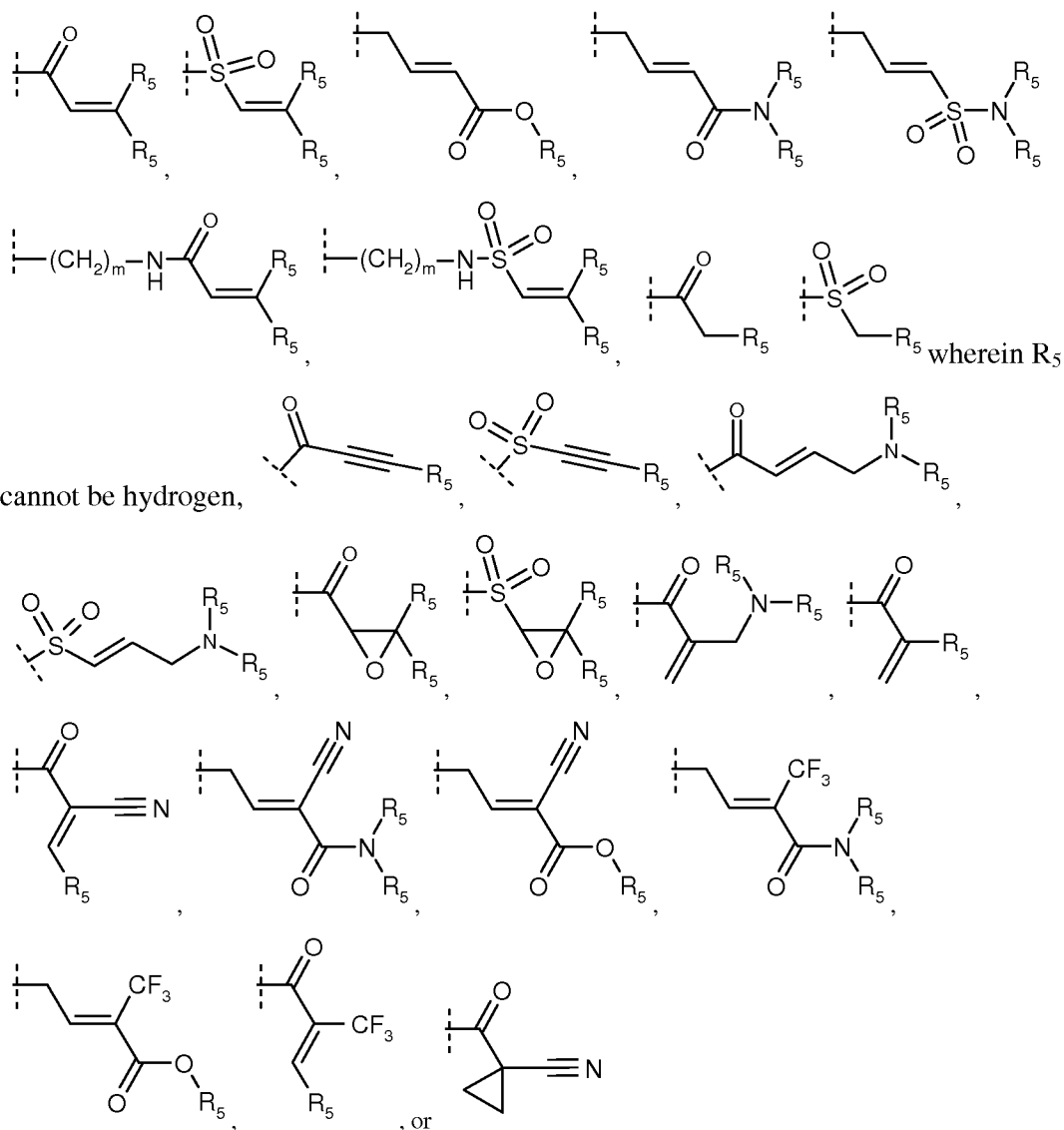
15 -S(O)_m-N(R₃)- and -N(R₃)-S(O)_m-, wherein the -CH₂- in each L can have 1-2 hydrogens replaced by C₁₋₃ alkyl, said C₁₋₃ alkyl groups can optionally cyclize to form a C₃₋₆ cycloalkyl ring;

Ar is carbocycle, heterocycyl or heteroaryl;

X₁ is a linker chosen from a bond, -(CH₂)_n-;

20 Y is chosen from C₇-C₁₀ spirocycle optionally containing 0-1 ring nitrogen atoms, a nitrogen containing mono- or bi-cyclic heterocycle, carbocycle, aryl, each substituted by one R₄;

R₄ is

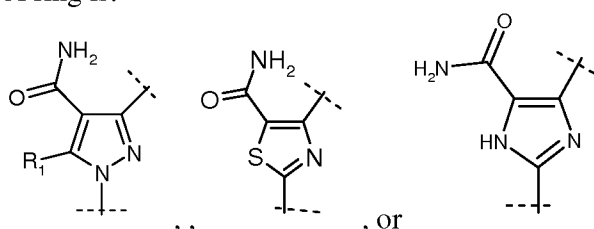


- each n is independently 1-4;
 each m is independently 0-2;
 10 each R₃ is independently chosen from hydrogen or C₁₋₄ alkyl;
 each R₅ is independently chosen from hydrogen, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₄ alkylC₁₋₄ alkoxy,
 -(CH₂)_n-heterocycle and heterocycle each heterocycle optionally substituted by halogen,
 OH and R₃-S(O)_m-;
 15 each group defined above for Cy, R₁-R₅, X₁ and Y can be where possible partially or fully

halogenated;
or a pharmaceutically acceptable salt thereof.

- 5 In a further embodiment, there is provided a compound of the formula (I) according to the embodiment herein-above and wherein

A ring is:



- 10 or a pharmaceutically acceptable salt thereof.

In a further embodiment, there is provided a compound of the formula (I) according to any of the embodiments herein-above and wherein

15

Cy is phenyl, pyridinyl, pyridazinyl, pyrimidinyl or pyrazinyl each is substituted by R_2 and optionally substituted by F, Cl or C_{1-4} alkoxy;

R_2 is chosen from:

- 20 L-Ar and C_{1-3} alkoxy, each Ar and C_{1-3} alkoxy are optionally substituted by F, Cl, C_{1-4} alkyl, $R_3-S(O)_2-$, -CN, -C(O)-NH(R_3) and C_{1-3} alkoxy;

L is a linker chosen from a bond, O, $>C(O)$, -CH₂-, -O-CH₂-, -NH-, -NH-CH₂-, -CH₂-NH-, -C(O)-NH-CH₂-, -NH-C(O)-NH- and -N(R_3)-S(O)_m-;

- 25 Ar is phenyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, benzoxazolyl, indolyl, isoindolyl, benzofuranyl, benzimidazolyl, benzothiazolyl, piperidinyl, piperazinyl or pyrrolidinyl

or a pharmaceutically acceptable salt thereof.

- 30 In a further embodiment, there is provided a compound of the formula (I) according to any of the embodiments herein-above and wherein

Cy is phenyl or pyridinyl, each is substituted by R₂ and optionally substituted by F, Cl or C₁₋₂ alkoxy;

R₂ is chosen from:

L-Ar and C₁₋₃ alkoxy, each Ar and C₁₋₃ alkoxy are optionally substituted by F, Cl, C₁₋₄ alkyl, CH₃-S(O)₂-, -CN, -C(O)-NH(R₃) and C₁₋₂ alkoxy;

L is a linker chosen from a bond, O, >C(O), -CH₂-, -O-CH₂-, -NH-, -NH-CH₂-, -CH₂-NH-, -C(O)-NH-CH₂-, -NH-C(O)-NH- and -N(R₃)-S(O)_m-;

Ar is phenyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, benzoxazolyl, indolyl, isoindolyl, benzofuranyl, benzimidazolyl, benzothiazolyl or piperidinyl

or a pharmaceutically acceptable salt thereof.

In a further embodiment, there is provided a compound of the formula (I) according to any of the embodiments herein-above and wherein

Cy is phenyl or pyridinyl, each is substituted by R₂ and optionally substituted by F, Cl or C₁₋₂ alkoxy;

R₂ is chosen from:

L-Ar and C₁₋₃ alkoxy, each Ar and C₁₋₃ alkoxy are optionally substituted by F, Cl, C₁₋₄ alkyl, CH₃-S(O)₂-, -CN, -C(O)-NH(CH₃) and C₁₋₂ alkoxy;

L is a linker chosen from a bond, O, >C(O), -CH₂-, -O-CH₂-, -NH-, -NH-CH₂-, -CH₂-NH-, -C(O)-NH-CH₂-, -NH-C(O)-NH- and -N(H)-S(O)₂-;

Ar is phenyl, pyridinyl, benzoxazolyl or piperidinyl

or a pharmaceutically acceptable salt thereof.

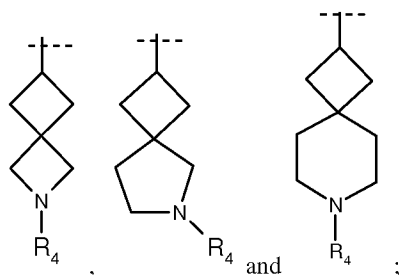
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In a further embodiment, there is provided a compound of the formula (I) according to any of the embodiments herein-above and wherein

X₁ is a linker chosen from a bond and -(CH₂)_n-;

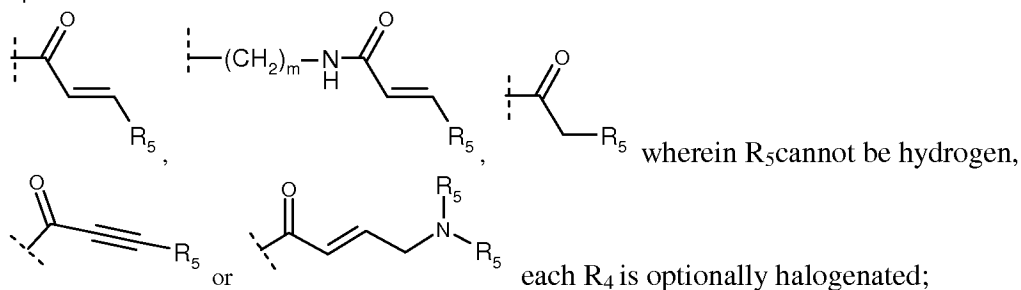
Y is chosen from:

a spirocycle chosen from



a heterocycle chosen from piperidinyl and pyrrolidinyl;
and phenyl each heterocycle or phenyl substituted by one R_4 ;

5 R_4 is



each R_5 is independently chosen from hydrogen, C_{1-3} alkyl, halo C_{1-3} alkyl, C_{1-3} alkyl C_{1-3}
10 alkoxy, $-CH_2$ -heterocycle and heterocycle each heterocycle optionally substituted by F, Cl, OH and $CH_3-S(O)_2-$ and each heterocycle chosen from pyrrolidinyl, piperidinyl, morpholinyl and 1,4-oxazepane,
or a pharmaceutically acceptable salt thereof.

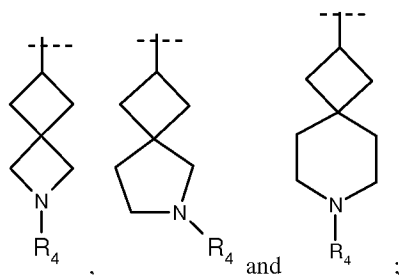
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In a further embodiment, there is provided a compound of the formula (I) according to any
of the embodiments herein-above and wherein

X_1 is a linker chosen from a bond and $-(CH_2)_n-$;

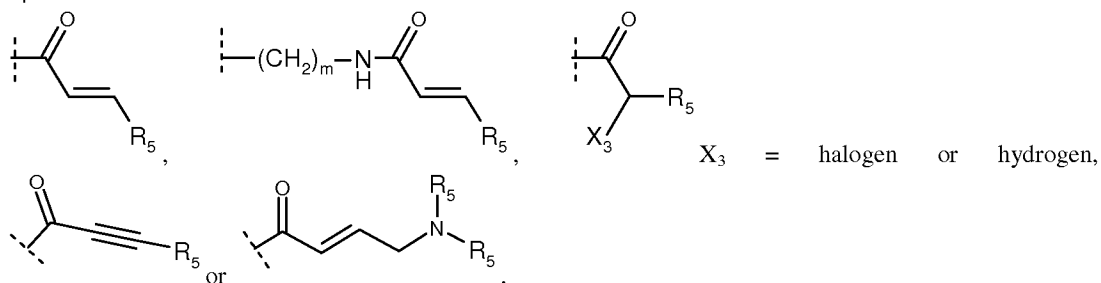
Y is chosen from:

20 a spirocycle chosen from



a heterocycle chosen from piperidinyl and pyrrolidinyl;
and phenyl each heterocycle or phenyl substituted by one R_4 ;

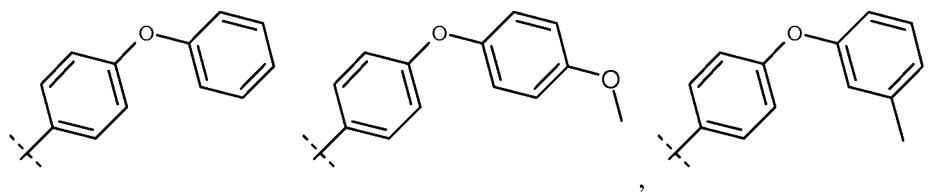
5 R_4 is

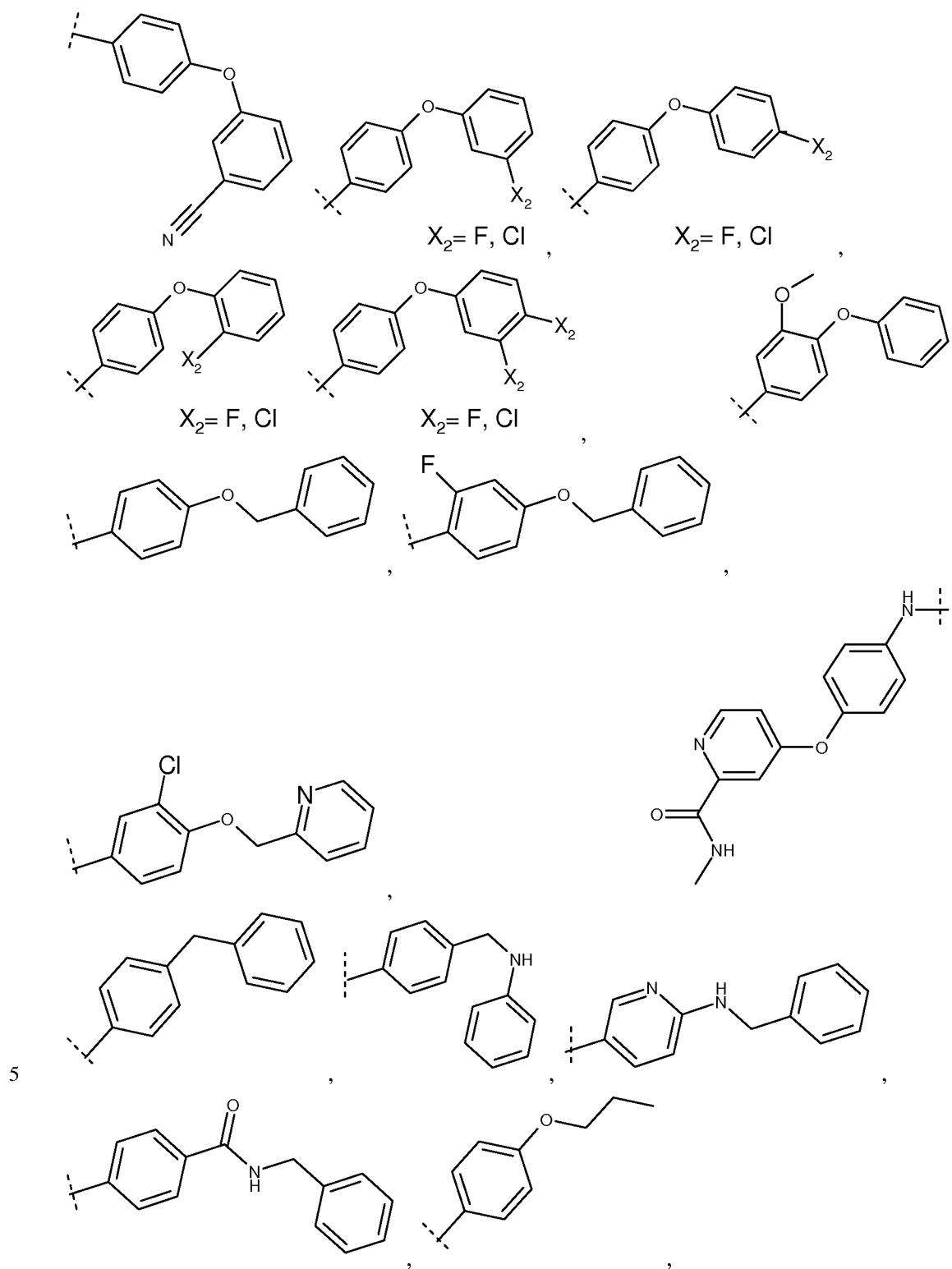


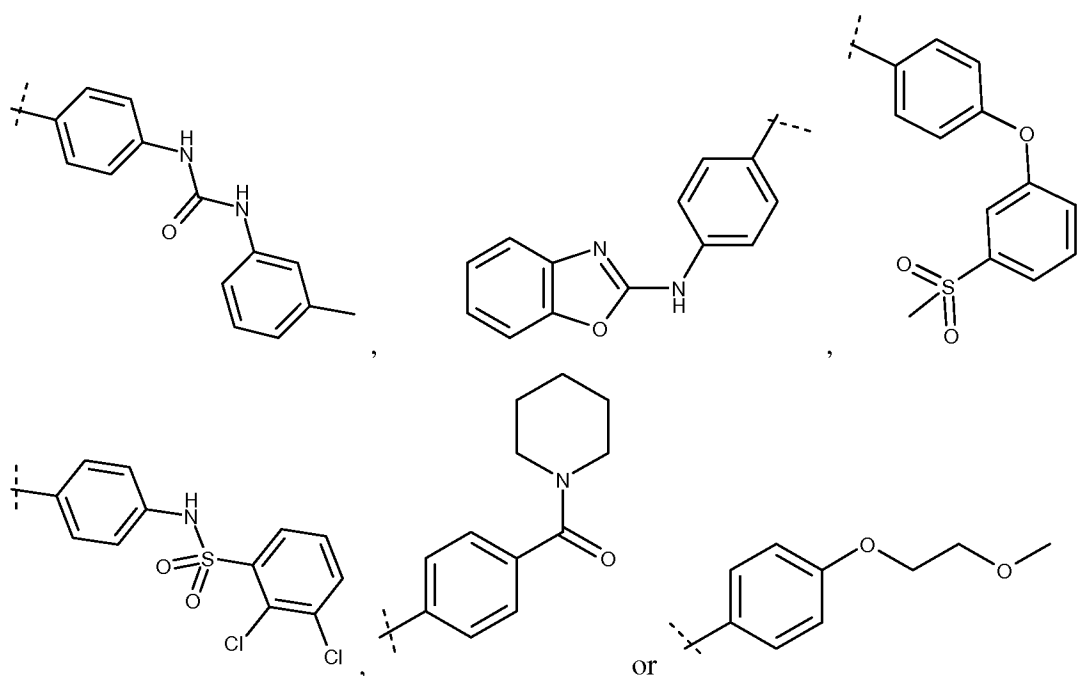
each R_5 is independently chosen from hydrogen, C_{1-3} alkyl, $-CF_3$, C_{1-3} alkyl C_{1-3} alkoxy, $-CH_2$ -heterocycle and heterocycle each heterocycle optionally substituted by F, Cl, OH and $CH_3-S(O)_2-$ and each heterocycle chosen from pyrrolidinyl, piperidinyl and 1,4-oxazepane,
10 or a pharmaceutically acceptable salt thereof.

In a further embodiment, there is provided a compound of the formula (I) according to any
15 of the embodiments herein-above and wherein

Cy is





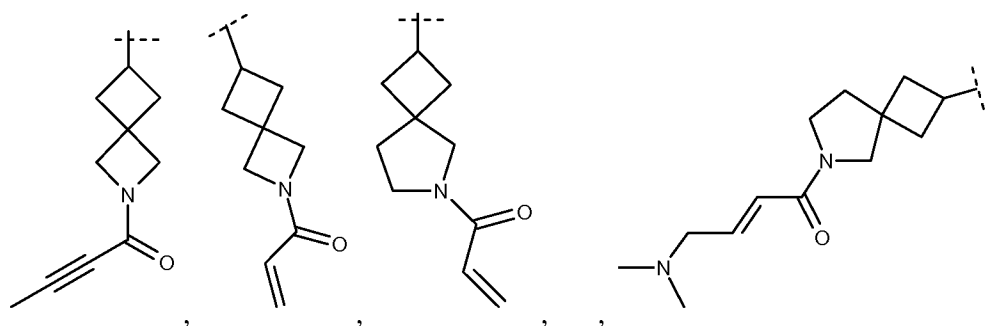


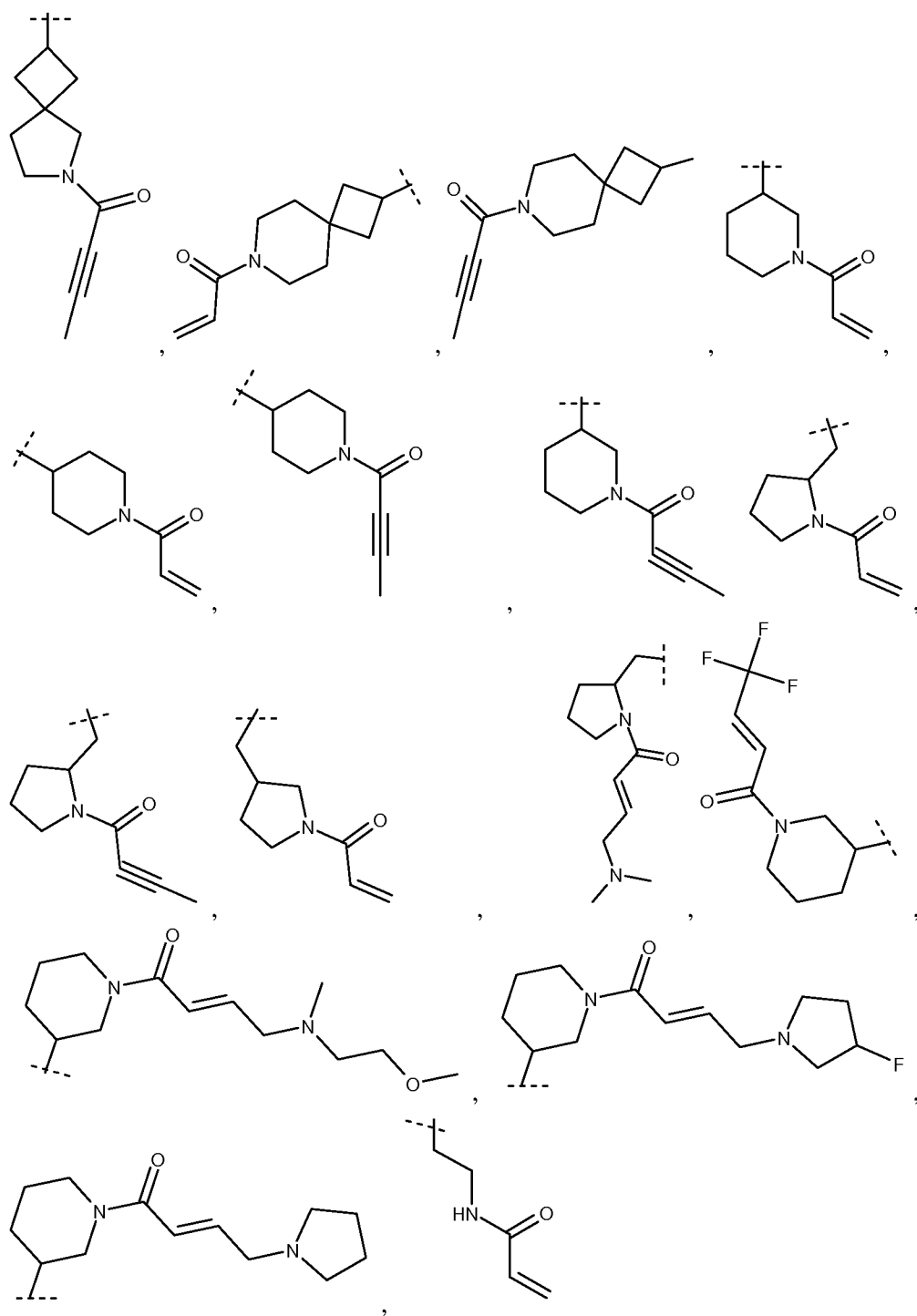
or a pharmaceutically acceptable salt thereof.

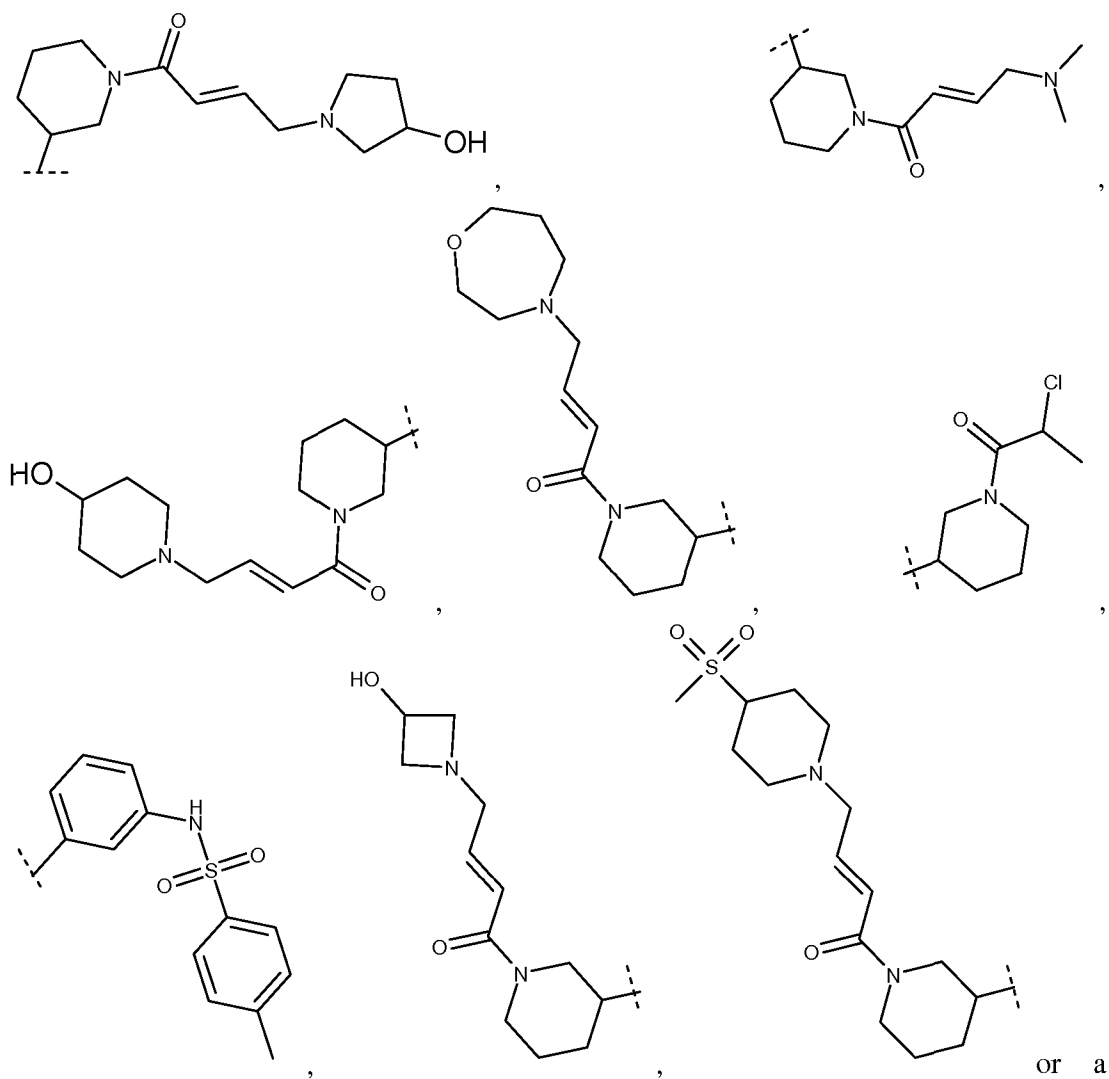
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In a further embodiment, there is provided a compound of the formula (I) according to any of the embodiments herein-above and wherein

X-Y =





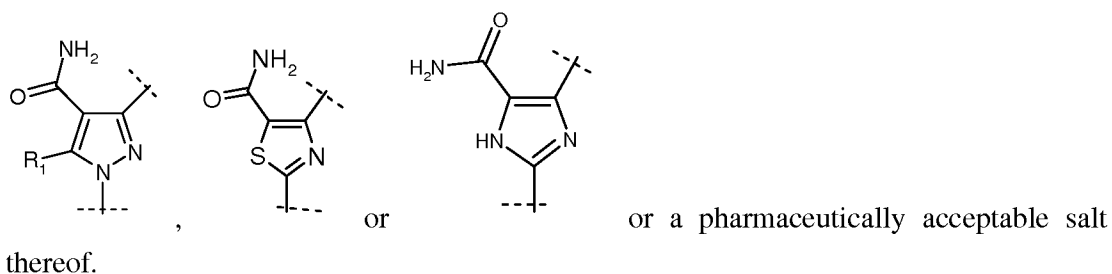


pharmaceutically acceptable salt thereof.

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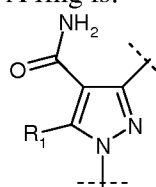
In a further embodiment, there is provided a compound of the formula (I) according to any of the embodiments herein-above and wherein

10 A ring is:



- 5 In a further embodiment, there is provided a compound of the formula (I) according to any of the embodiments herein-above and wherein

A ring is:

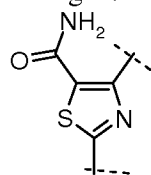


or a pharmaceutically acceptable salt thereof.

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In a further embodiment, there is provided a compound of the formula (I) according to any of the embodiments herein-above and wherein

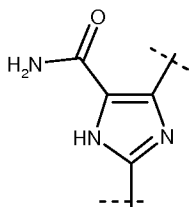
- 15 A ring is:



or a pharmaceutically acceptable salt thereof.

- 20 In a further embodiment, there is provided a compound of the formula (I) according to any of the embodiments herein-above and wherein

A ring is:



or a pharmaceutically acceptable salt thereof.

In a further embodiment, there is provided a compound of the formula (I) according to any of the embodiments herein-above and wherein

5

R_2 is

L-Ar;

L is a linker chosen from a bond, O, and $-O-(CH_2)_n-$;

n is 1-3;

10 Ar is carbocycle or heterocycle;

or a pharmaceutically acceptable salt thereof.

In a further embodiment, there is provided a compound of the formula (I) according to any of the embodiments hereinabove and wherein

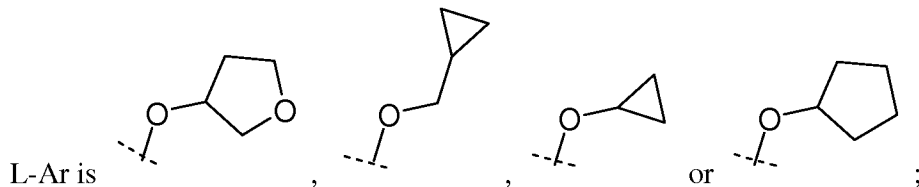
15 Ar is C_{3-5} cycloalkyl or tetrahydrofuranyl;

n = 1;

or a pharmaceutically acceptable salt thereof.

In a further embodiment, there is provided a compound of the formula (I) according to any of the embodiments herein-above and wherein

20

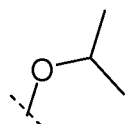


or a pharmaceutically acceptable salt thereof.

In a further embodiment, there is provided a compound of the formula (I) according to any of the embodiments herein-above and wherein

25

R_2 is:



, -OCH₂CH₃, -OCH₂CH₂CH₃, -OCH₃, -OCF₃ or -OCH₂CF₃;
or a pharmaceutically acceptable salt thereof.

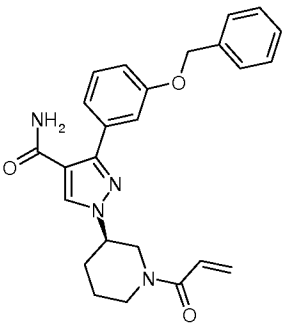
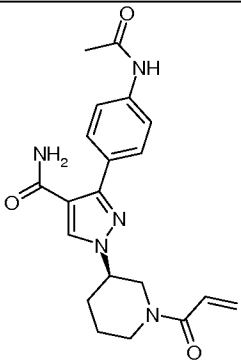
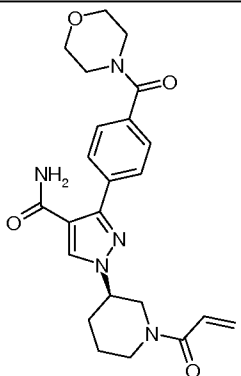
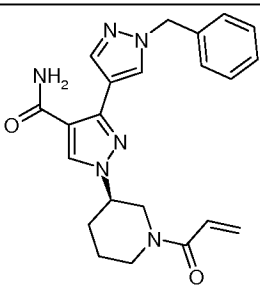
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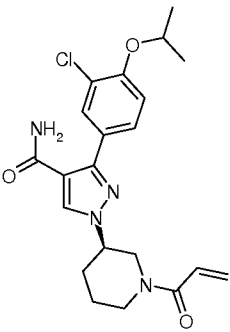
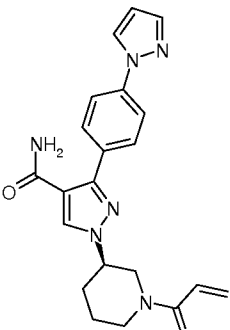
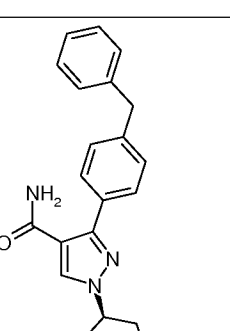
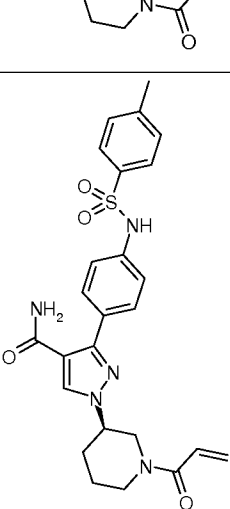
In another embodiment, the invention provides made compounds in Table I which can be made in view of the general schemes, examples and methods known in the art.

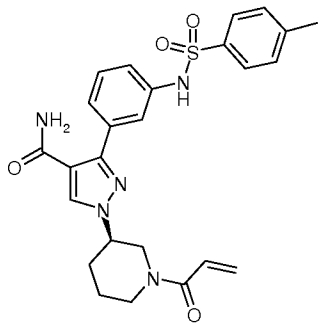
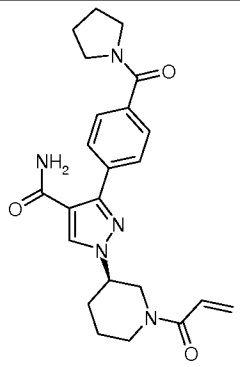
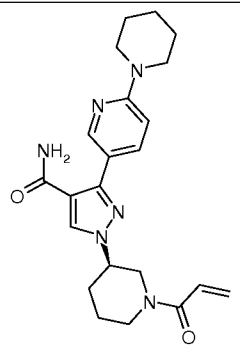
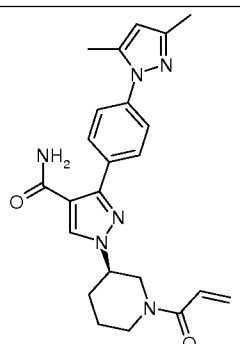
Table of compounds and Biological activity

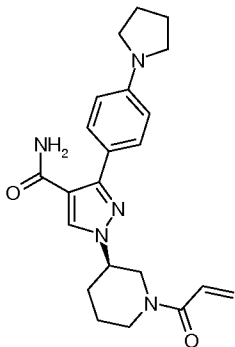
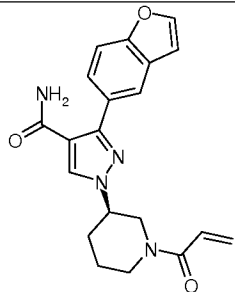
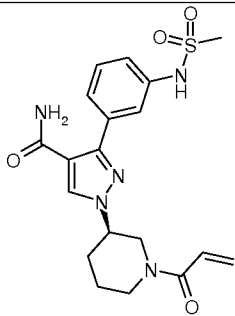
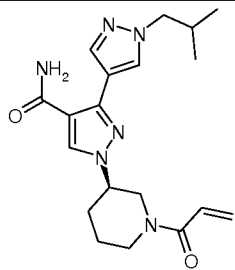
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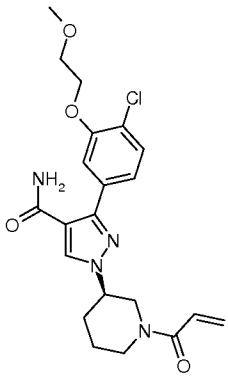
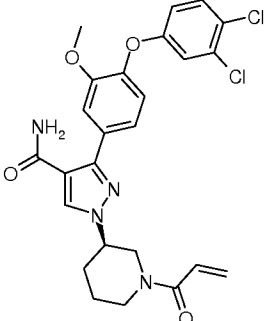
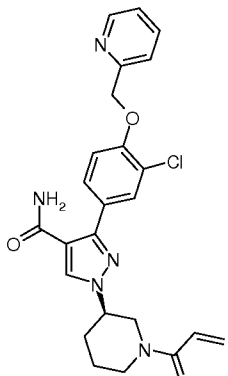
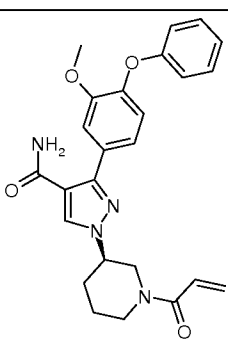
Example	Structure	BTK IC ₅₀ (nM)	HPLC Method	RT (min)	<i>m/z</i> [M+H] ⁺
1		2600	A	4.13	401.2
2		33	A	4.08	431.3

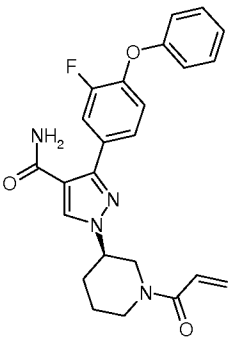
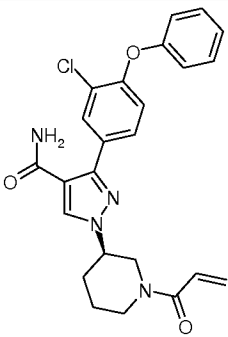
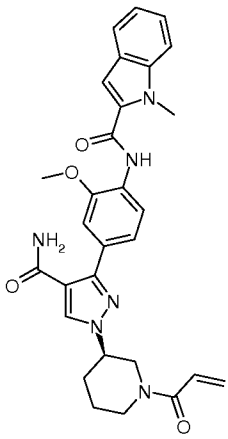
3		810	A	4.06	431.3
4		-	A	2.56	382.4
5		-	A	2.59	438.4
6		-	A	2.75	405.4

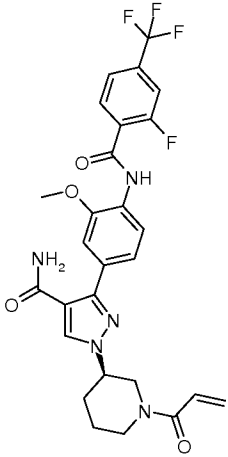
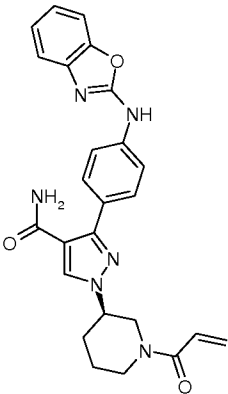
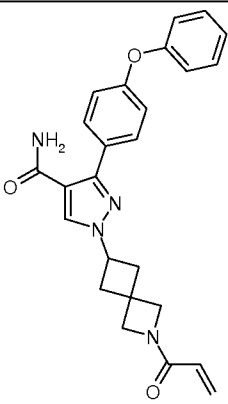
7		-	A	2.83	417.3
8		-	A	2.61	391.2
9		14	A	4.11	415.3
10		-	A	4.14	494.3

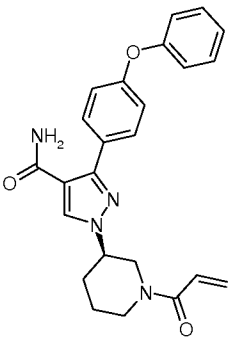
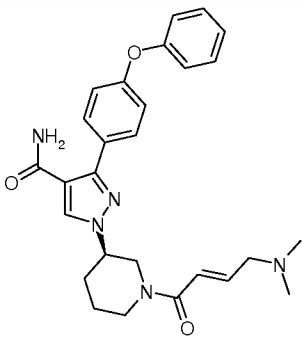
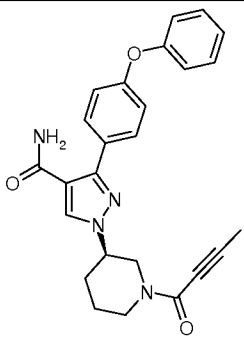
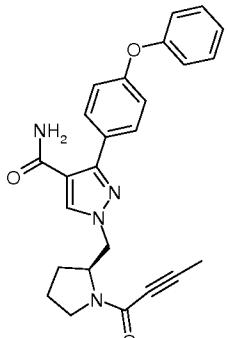
11		5500	A	2.80	494.2
12		-	A	2.67	422.3
13		-	A	2.56	409.3
14		7800	A	2.81	419.4

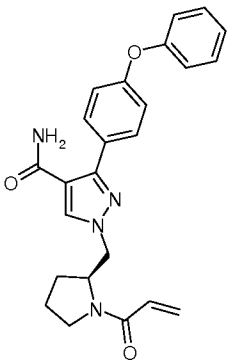
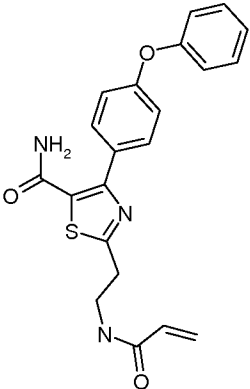
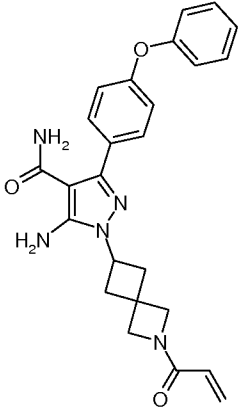
15		-	A	2.89	394.4
16		580	A	2.77	365.3
17		4800	A	2.60	418.4
18		-	A	2.72	371.4

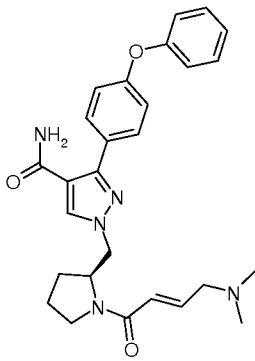
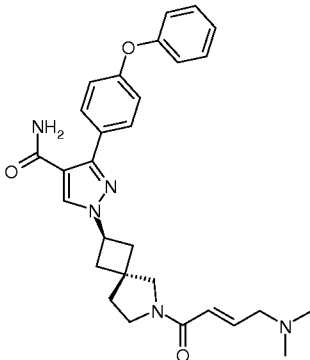
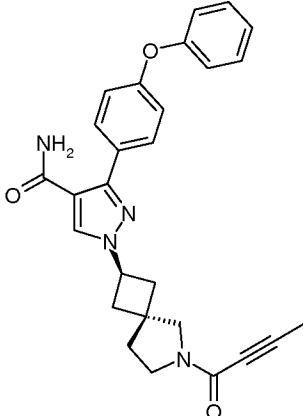
19		-	A	2.84	433.3
20		30	A	3.03	515.2
21		98	A	2.85	466.3
22		7.6	A	2.91	447.3

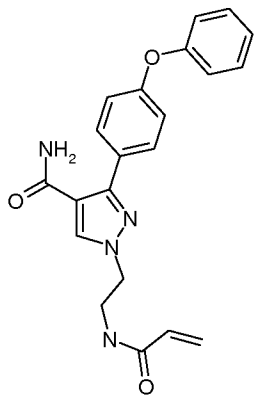
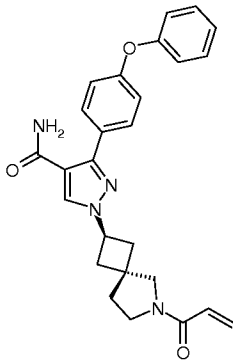
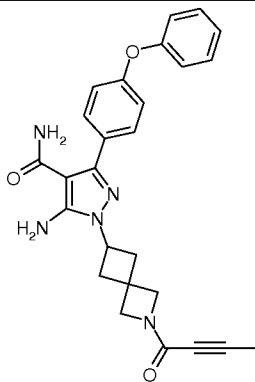
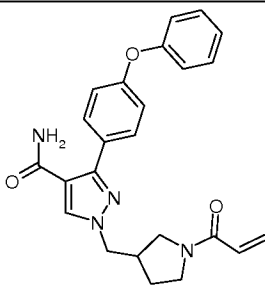
23		10	A	2.97	435.3
24		9.4	A	3.02	451.3
25		5.1	A	3.03	527.3

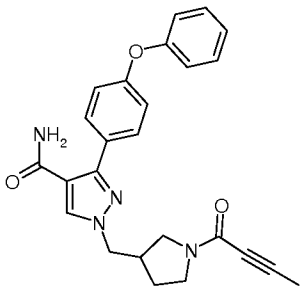
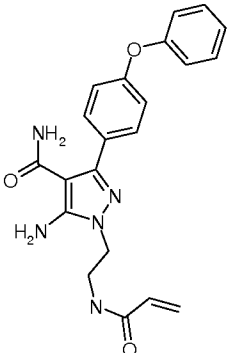
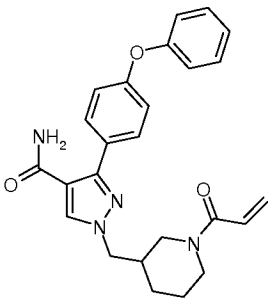
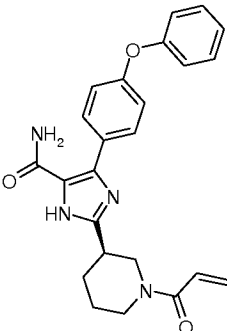
26		22	A	3.03	560.3
27		300	A	2.84	457.3
28		3.5	A	2.85	429.3

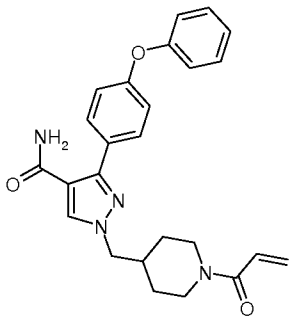
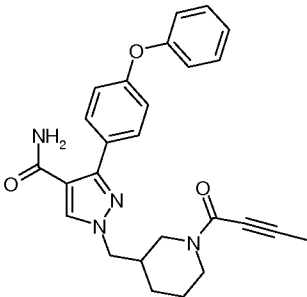
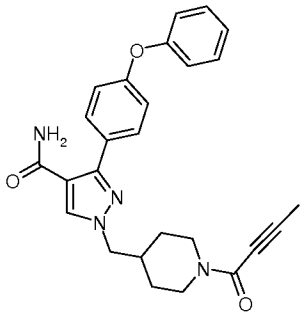
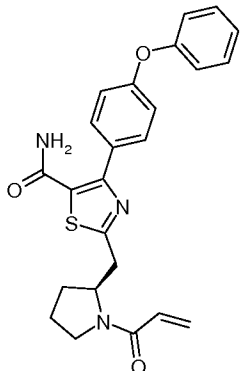
29		3.2	A	2.83	417.3
30		57	A	2.54	474.35
31		80	A	2.86	429.35
32		150	A	2.81	429.35

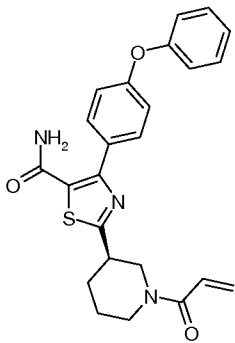
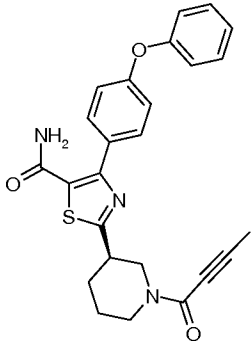
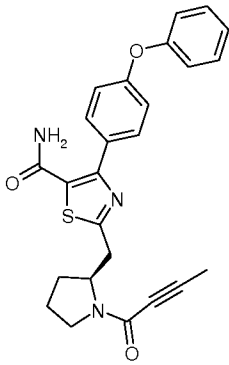
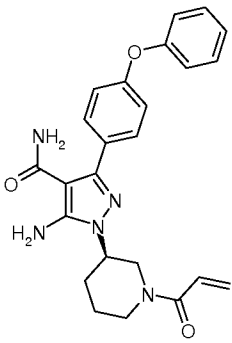
33		9.7	A	2.83	417.35
34		21	A	2.78	394.35
35		0.77	A	2.96	444.3

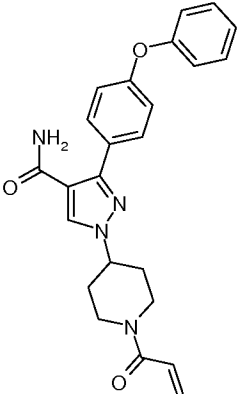
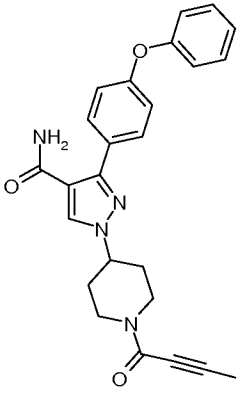
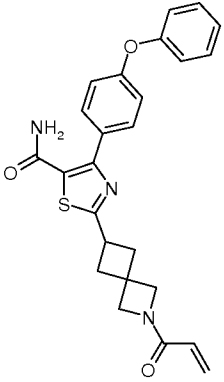
36		230	A	2.67	474.3
37		38	A	2.51	500.3
38		13	A	2.84	455.3

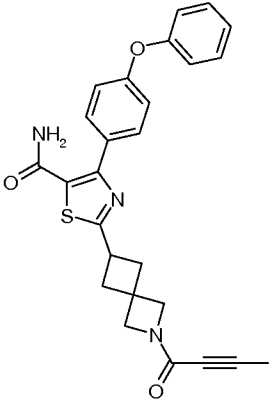
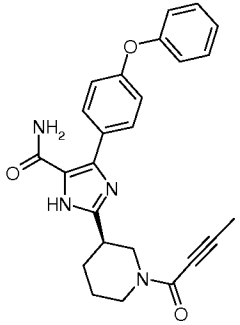
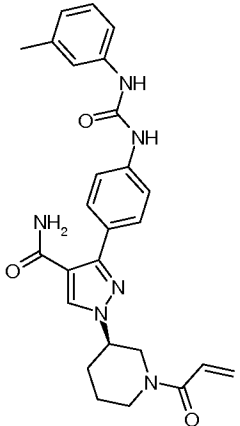
39		290	A	2.65	377.2
40		4.9	A	2.89	443.2
41		0.73	A	2.99	456.3
42		64	A	2.92	417.4

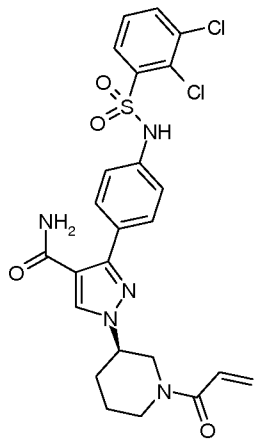
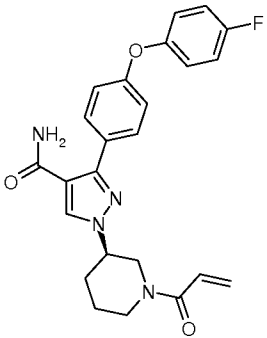
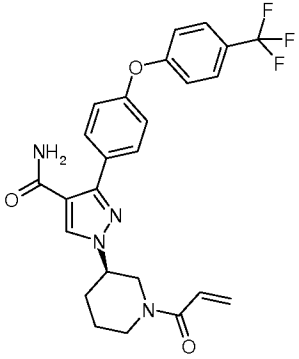
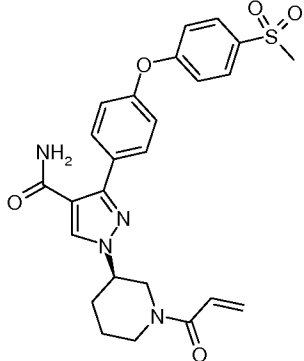
43		51	A	2.93	429.4
44		1	A	2.68	392.4
45		10	A	2.83	431.4
46		1.2	A	2.85	417.4

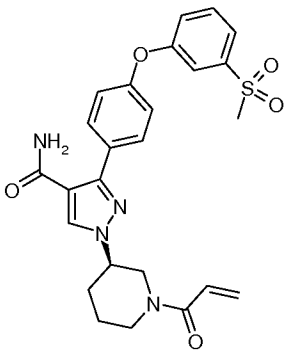
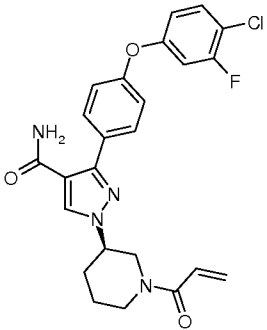
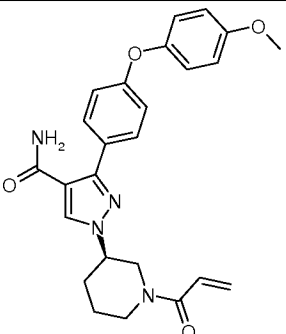
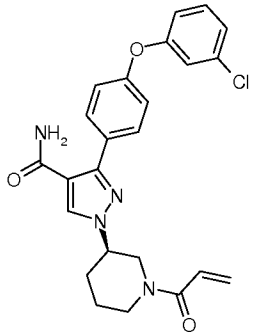
47		10	A	2.84	431.4
48		90	A	2.97	443.4
49		180	A	2.96	443.4
50		3	A	2.98	434.3

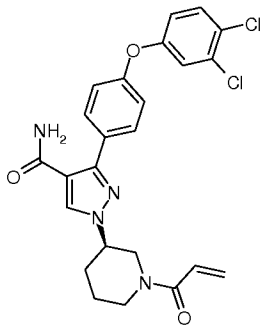
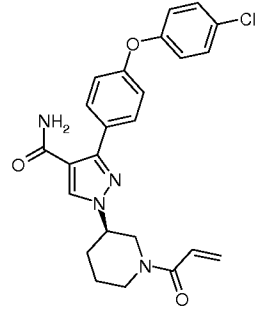
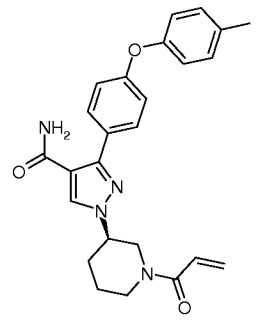
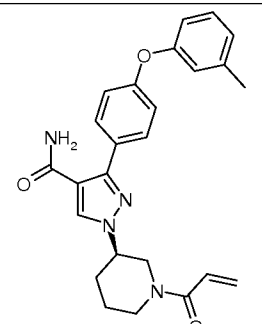
51		1.7	A	3.00	434.3
52		18	A	3.02	446.3
53		14	A	3.00	446.3
54		0.73	A	3.00	432.4

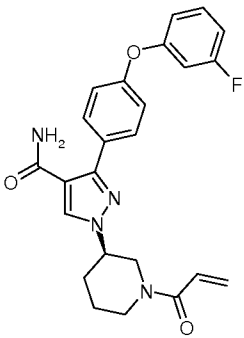
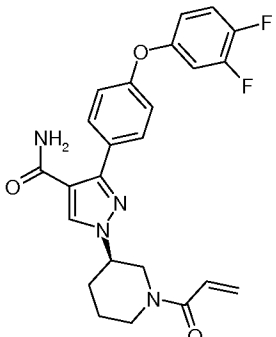
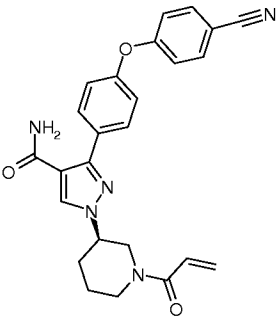
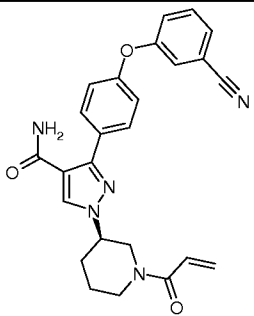
55		6.6	A	2.93	417.4
56		15	A	2.95	429.4
57		3.2	A	2.99	446.3

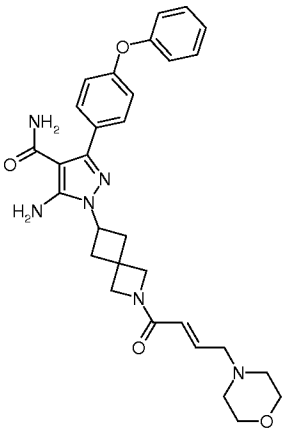
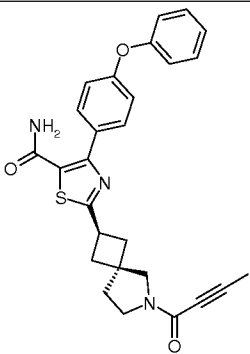
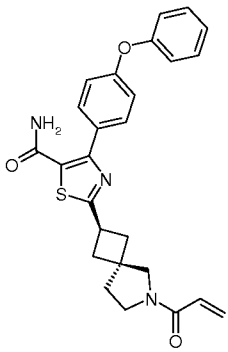
58		1.1	A	3.01	458.3
59		8.9	A	2.75	429.4
60		41	A	2.82	473.4

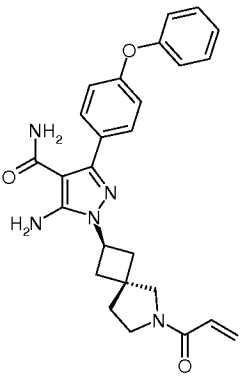
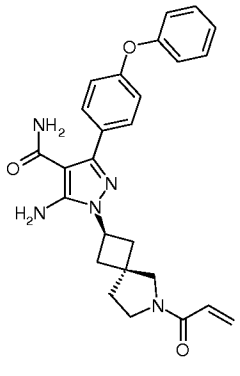
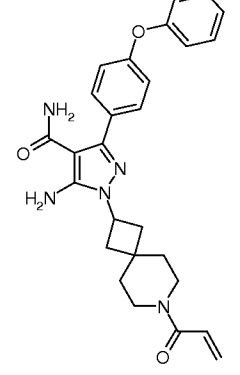
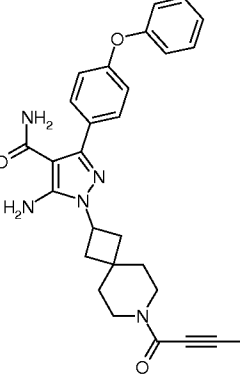
61		780	A	2.86	548.1
62		93	A	2.97	435.3
63		660	A	3.08	485.3
64		6500	A	2.79	495.1

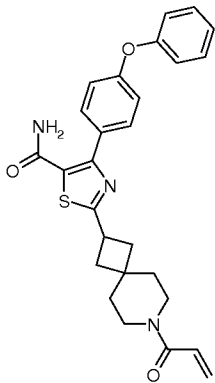
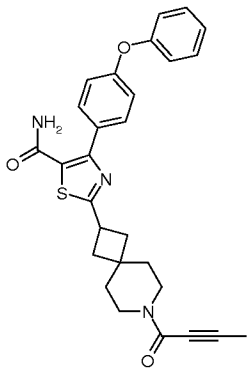
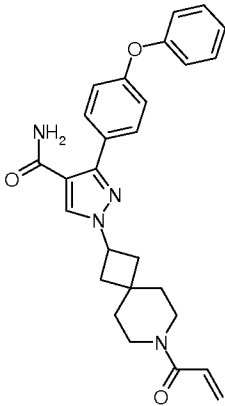
65		330	B	0.65	495.1
66		43	A	3.10	469.2
67		38	A	2.95	447.3
68		41	A	3.08	451.4

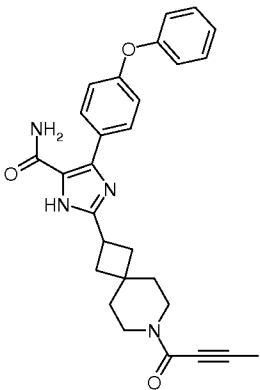
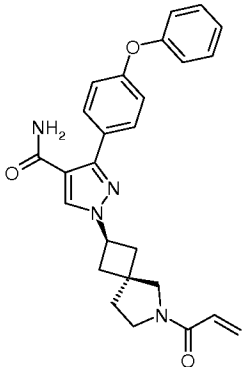
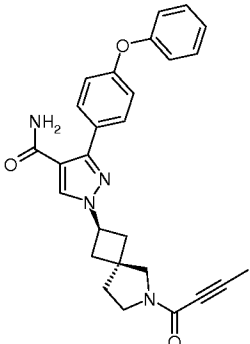
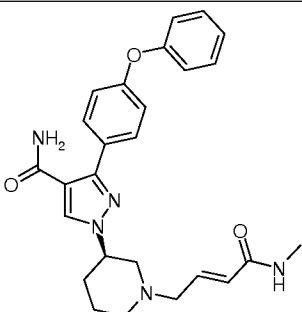
69		43	A	3.20	485.3
70		45	A	3.07	451.3
71		14	A	3.04	431.4
72		4	A	3.04	431.4

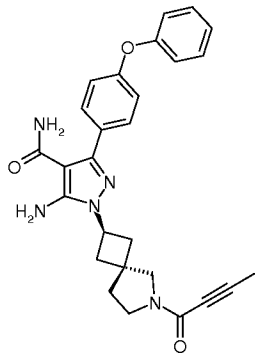
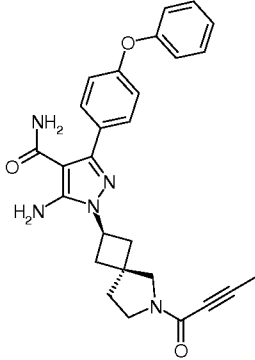
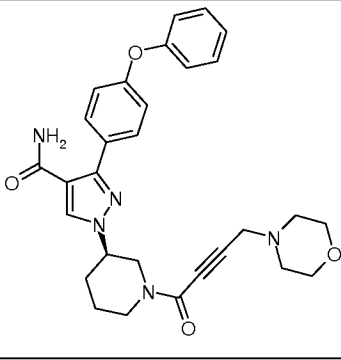
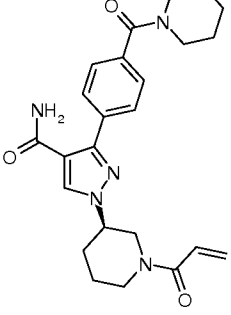
73		9.3	A	3.00	435.3
74		-	A	2.89	453.3
75		6600	A	2.91	442.3
76		61	A	2.92	442.4

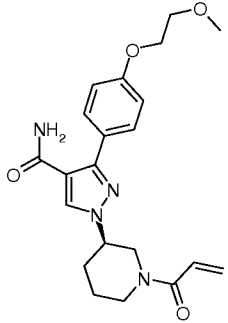
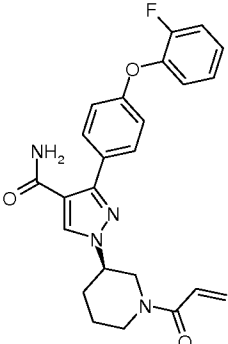
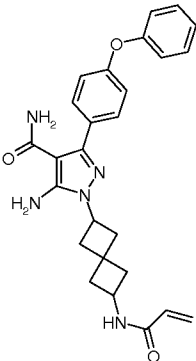
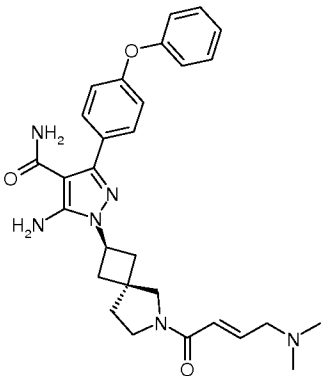
77		1.9	A	2.72	543.3
78		2.1	A	2.95	472.2
79		6.4	A	3.05	460.2

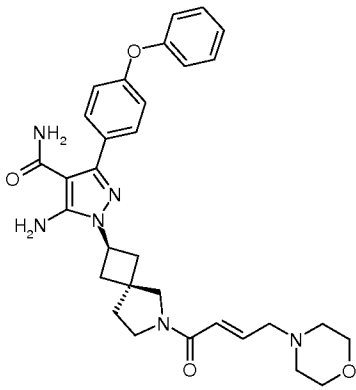
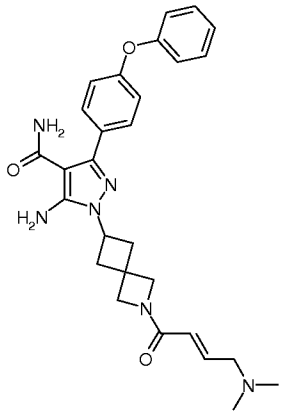
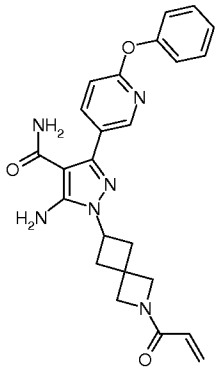
80		0.93	A	3.04	458.4
81		0.79	A	2.91	458.3
82		2	A	2.95	472.2
83		2.1	A	2.99	484.3

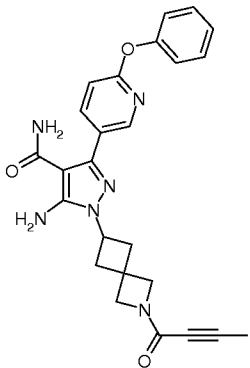
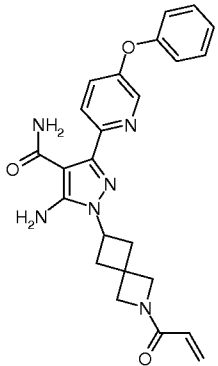
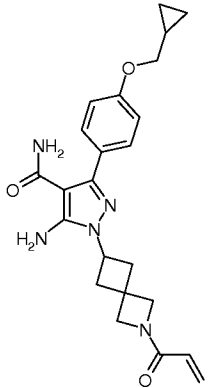
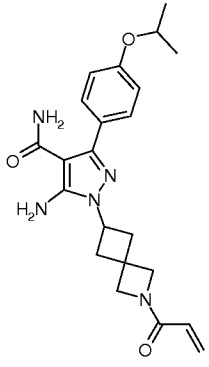
84		52	A	3.10	474.2
85		300	A	3.11	486.2
86		95	A	3.03	457.4

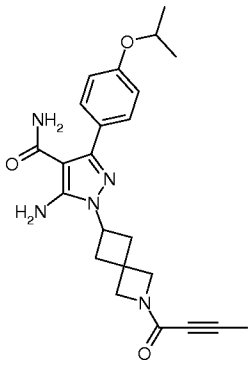
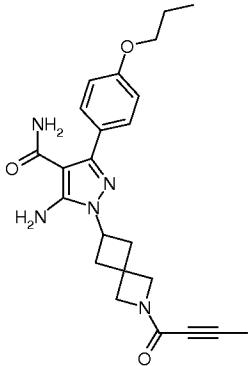
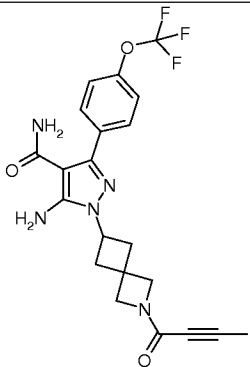
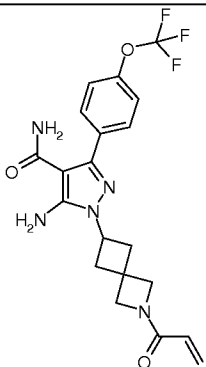
87		4.3	A	2.87	469.3
88		21	A	2.96	443.4
89		34	A	2.98	455.3
90		90	B	0.55	460.1

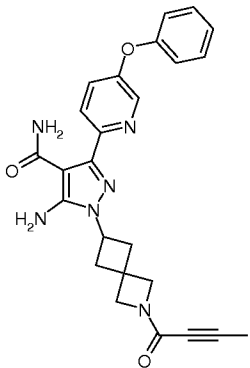
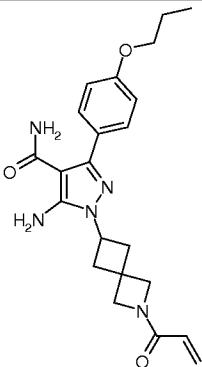
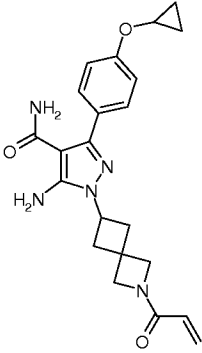
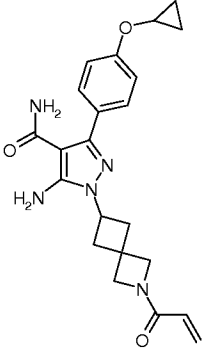
91		0.79	A	2.94	470.3
92		0.89	A	2.88	470.3
93		33	A	2.80	514.3
94		8200	A	2.75	436.3

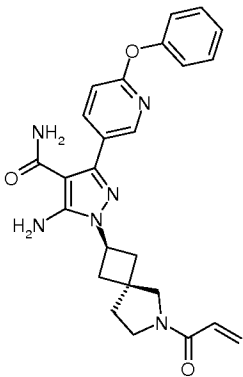
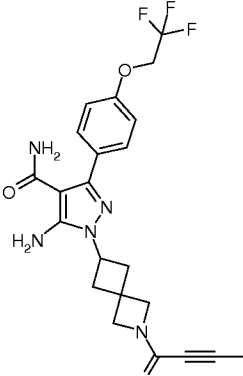
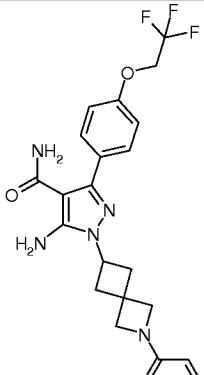
95		1600	A	2.71	399.3
96		4.8	A	2.95	435.3
97		0.8	A	2.93	458.3
98		0.7	A	2.69	515.4

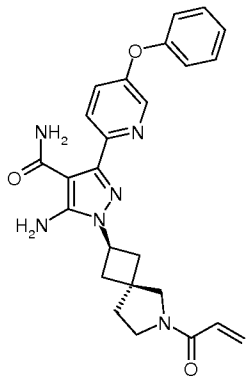
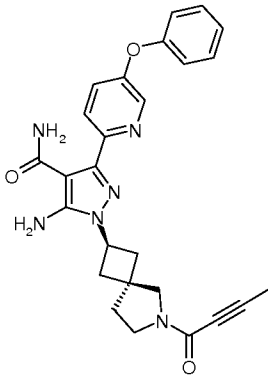
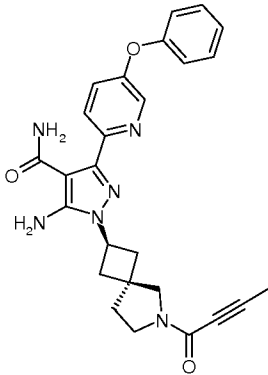
99		3.2	A	2.76	557.3
100		0.8	A	2.63	501.3
101		9.2	A	2.71	445.4

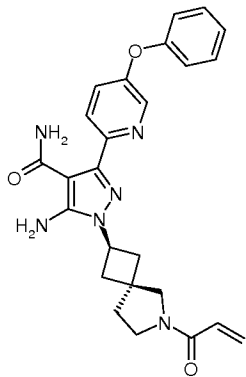
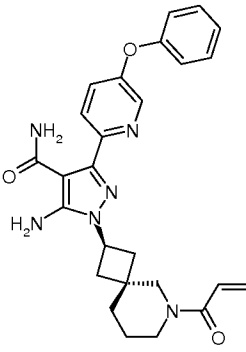
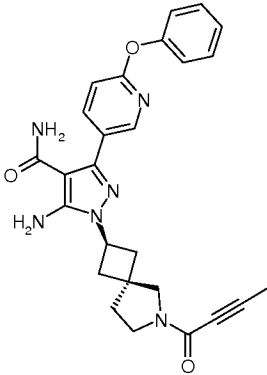
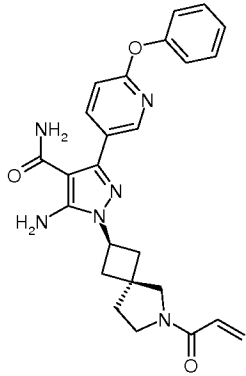
102		2.7	A	2.83	457.3
103		2.8	A	3.13	445.2
104		19	A	2.79	422.4
105		13	A	2.77	410.3

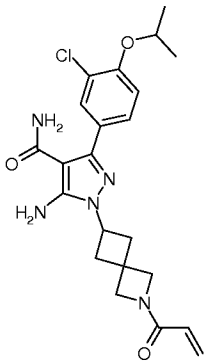
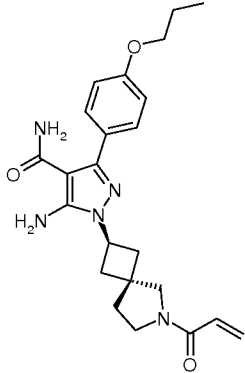
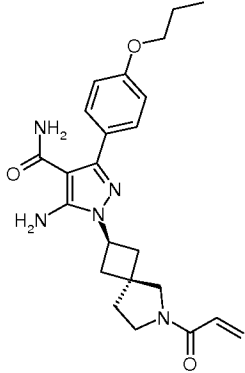
106		13	A	2.81	422.4
107		3.3	A	2.81	422.4
108		14	A	2.75	448.3
109		24	A	2.86	436.3

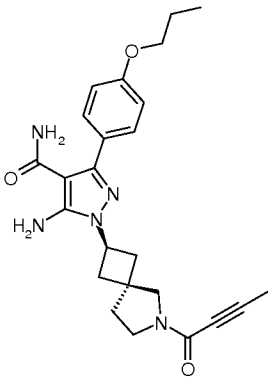
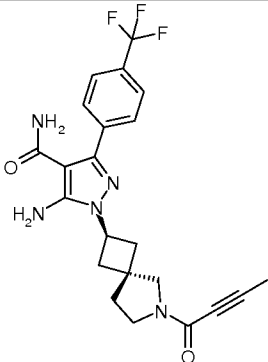
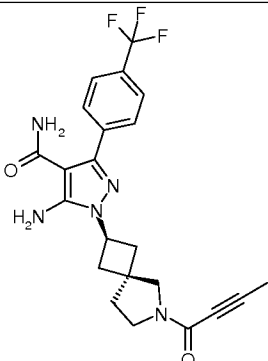
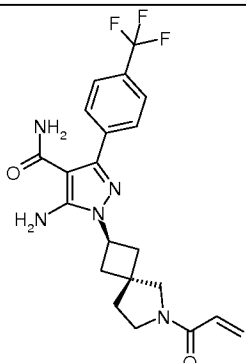
110		0.87	A	3.09	457.3
111		16	A	2.77	410.4
112		6.7	A	2.82	408.4
113		4.3	A	2.85	420.4

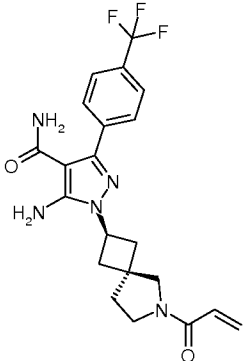
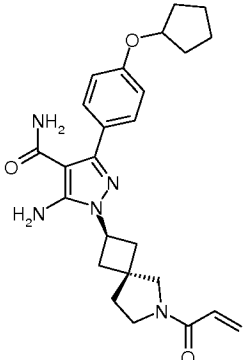
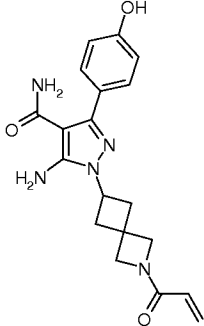
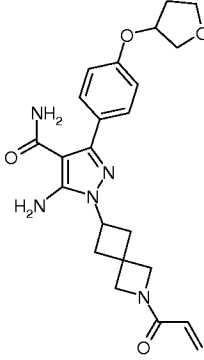
114		3.4	A	2.87	459.3
115		3.5	A	2.82	462.3
116		12	A	2.78	450.3

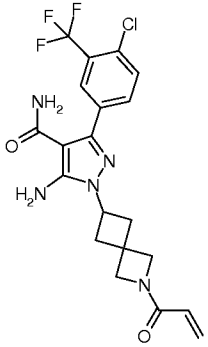
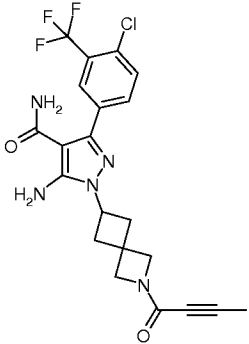
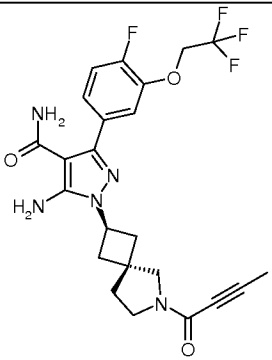
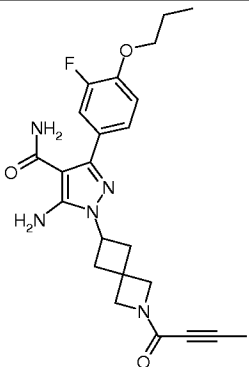
117		1.1	A	3.52	459.2
118		0.5	A	3.49	471.2
119		11	A	3.25	471.3

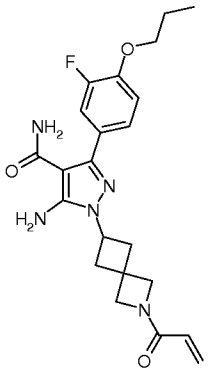
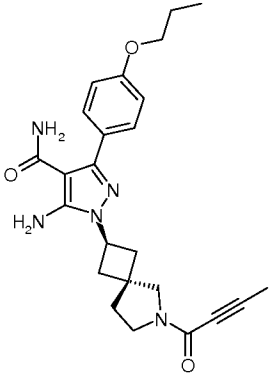
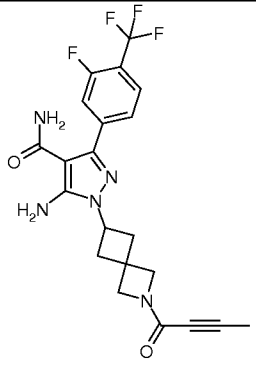
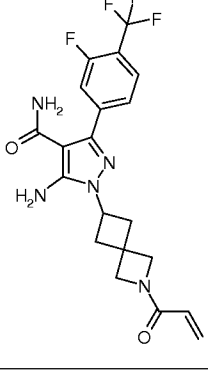
120		3.5	A	3.29	459.2
121		0.2	A	3.13	472.2
122		17	A	2.91	471.3
123		9.1	A	2.88	459.3

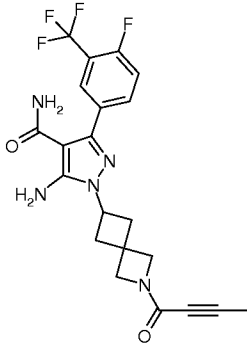
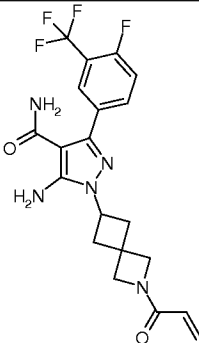
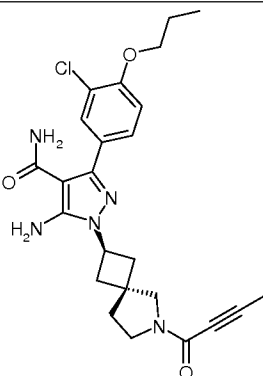
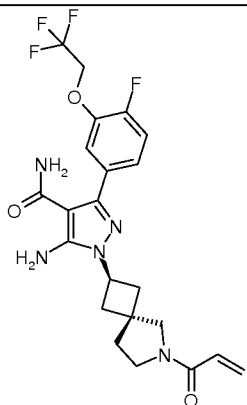
124		10	B	1.73	444.1
125		7.5	B	0.85	424.0
126		28	A	2.98	424.3

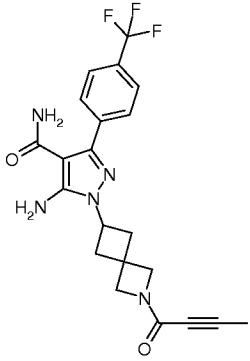
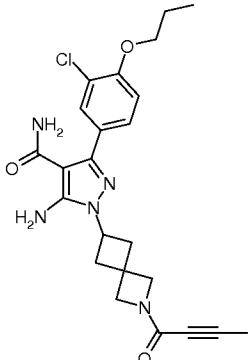
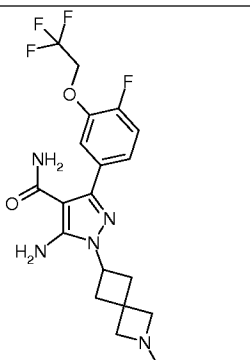
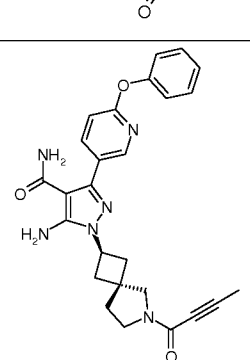
127		15	B	0.86	436
128		0.9	A	3.02	446.4
129		29	B	0.85	446.1
130		6.4	A	3	434.4

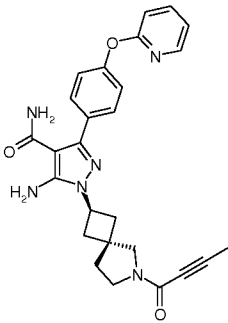
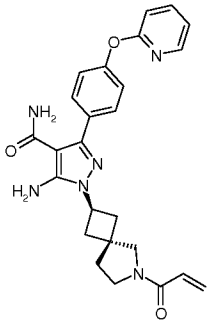
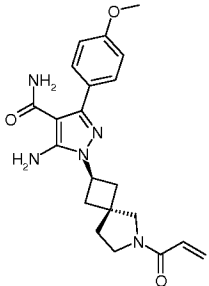
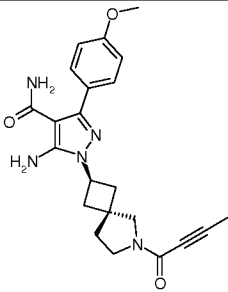
131		28	B	0.80	433.9
132		1.9	B	1.02	451.5
133		8.4	A	2.64	368.3
134		120	B	0.59	438.3

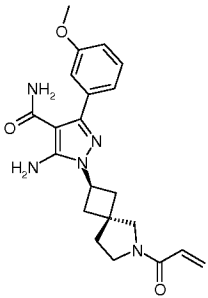
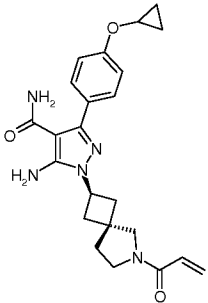
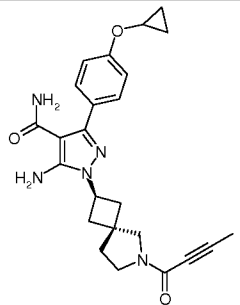
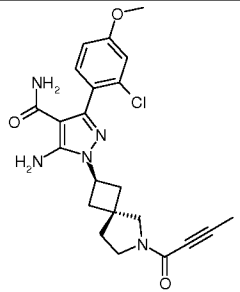
135		26	A	2.83	454.3
136		14	B	0.91	466
137		1.6	B	0.89	494.1
138		2.2	B	0.86	440.1

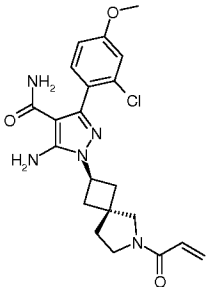
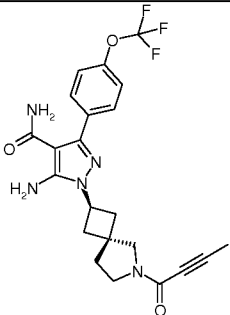
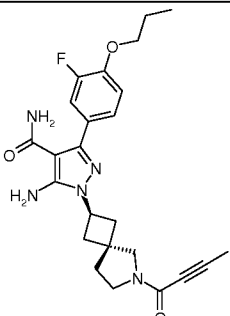
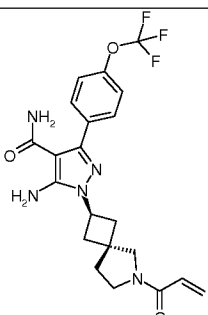
139		16	B	0.56	428.1
140		0.9	B	0.90	436.2
141		14	B	0.87	450.0
142		29	B	0.82	438.0

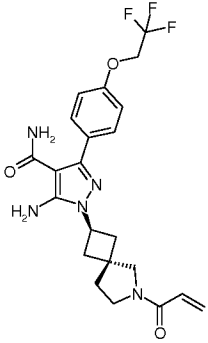
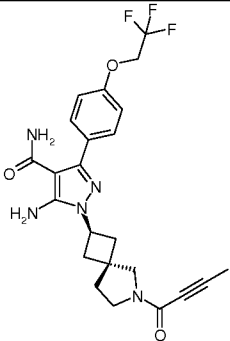
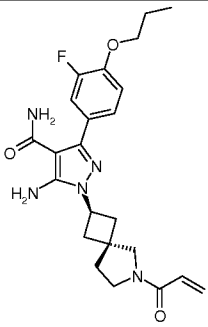
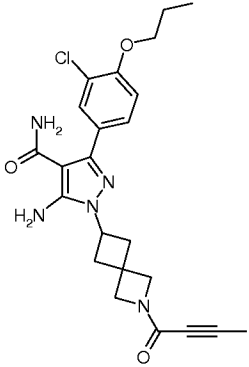
143		37	B	0.85	450.0
144		72	B	0.80	438.1
145		3.5	A	3.17	458.4
146		22	A	2.95	482.4

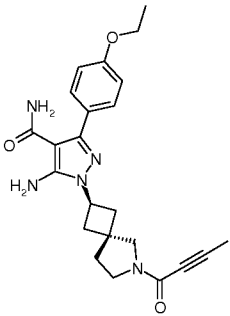
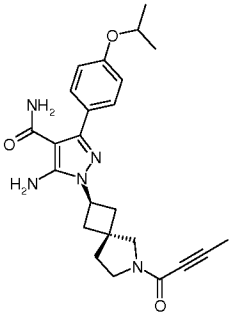
147		9.2	B	0.84	432.0
148		3.0	A	3.03	456.3
149		100	B	0.78	480.4
150		0.8	B	0.83	471.2

151		0.7	B	0.78	471.3
152		1.5	B	0.73	459.3
153		2.3	B	0.68	396.1
154		0.6	B	0.71	408.3

155		7.3	B	0.69	396.2
156		16	B	0.70	420.4 [M-H] ⁺
157		2.0	B	0.86	434.6
158		6.3	B	0.80	442.1

159		20	B	0.75	430.2
160		1.4	B	0.87	462.1
161		1.1	B	0.87	454.462.8
162		9.2	B	0.91	450.2

163		4.8	B	0.86	464.5
164		0.5	B	0.90	476.2
165		15	B	0.89	440.2 [M-H] ⁺ 443.2
166		6.6	B	1.06	420.3

167		0.9	B	0.75	422.2
168		1.2	B	0.84	436.3

or the pharmaceutically acceptable salts thereof.

The present invention further relates to metabolites, and prodrugs of compounds of the
5 formula (I).

The present invention further relates to a pharmaceutically acceptable salt of a compound of the formula (I) with inorganic or organic acids or bases.

In another aspect the invention relates to compounds of formula (I) – or the pharmaceutically acceptable salts thereof – as medicaments.

10 In another aspect the invention relates to compounds of formula (I) – or the pharmaceutically acceptable salts thereof – for use in a method for treatment of a patient.

In another aspect the invention relates to compounds of formula (I) – or the pharmaceutically acceptable salts thereof – for use in the treatment of autoimmune diseases and allergic disorders.

15 In another aspect the invention relates to the use of compounds of formula (I) – or the pharmaceutically acceptable salts thereof – for preparing a pharmaceutical composition for

the treatment of autoimmune diseases and allergic disorders.

In another aspect the invention relates to a method for the treatment of autoimmune diseases and allergic disorders comprising administering a therapeutically effective amount of a compound of formula (I) – or one of the pharmaceutically acceptable salts thereof – to
5 a patient.

In another aspect the invention relates to a pharmaceutical preparation containing as active substance one or more compounds of formula (I)– or the pharmaceutically acceptable salts thereof – optionally in combination with conventional excipients and/or carriers.

Definitions

10 Terms that are not specifically defined here have the meanings that are apparent to the skilled man in the light of the overall disclosure and the context as a whole.

As used herein, the following definitions apply, unless stated otherwise:

The use of the prefix C_{x-y}, wherein x and y each represent a natural number, indicates that the chain or ring structure or combination of chain and ring structure as a whole, specified
15 and mentioned in direct association, may consist of a maximum of y and a minimum of x carbon atoms.

Alkyl denotes monovalent, saturated hydrocarbon chains, which may be present in both straight-chain (unbranched) and branched form. If an alkyl is substituted, the substitution may take place independently of one another, by mono- or polysubstitution in each case,
20 on all the hydrogen-carrying carbon atoms.

For example, the term "C₁₋₅alkyl" includes for example H₃C-, H₃C-CH₂-, H₃C-CH₂-CH₂-, H₃C-CH(CH₃)-, H₃C-CH₂-CH₂-CH₂-, H₃C-CH₂-CH(CH₃)-, H₃C-CH(CH₃)-CH₂-, H₃C-C(CH₃)₂-, H₃C-CH₂-CH₂-CH₂-CH₂-, H₃C-CH₂-CH₂-CH(CH₃)-, H₃C-CH₂-CH(CH₃)-CH₂-, H₃C-CH(CH₃)-CH₂-CH₂-, H₃C-CH₂-C(CH₃)₂-, H₃C-C(CH₃)₂-CH₂-, H₃C-CH(CH₃)-
25 CH(CH₃)- and H₃C-CH₂-CH(CH₂CH₃)-.

Further examples of alkyl are methyl (Me; -CH₃), ethyl (Et; -CH₂CH₃), 1-propyl (*n*-propyl; *n*-Pr; -CH₂CH₂CH₃), 2-propyl (*i*-Pr; *iso*-propyl; -CH(CH₃)₂), 1-butyl (*n*-butyl; *n*-Bu; -CH₂CH₂CH₂CH₃), 2-methyl-1-propyl (*iso*-butyl; *i*-Bu; -CH₂CH(CH₃)₂), 2-butyl (*sec*-butyl; *sec*-Bu; -CH(CH₃)CH₂CH₃), 2-methyl-2-propyl (*tert*-butyl; *t*-Bu; -C(CH₃)₃), 1-

pentyl (*n*-pentyl; $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 2-pentyl ($-\text{CH}(\text{CH}_3)\text{CH}_2\text{CH}_2\text{CH}_3$), 3-pentyl
 ($-\text{CH}(\text{CH}_2\text{CH}_3)_2$), 3-methyl-1-butyl (*iso*-pentyl; $-\text{CH}_2\text{CH}_2\text{CH}(\text{CH}_3)_2$), 2-methyl-2-butyl
 ($-\text{C}(\text{CH}_3)_2\text{CH}_2\text{CH}_3$), 3-methyl-2-butyl ($-\text{CH}(\text{CH}_3)\text{CH}(\text{CH}_3)_2$), 2,2-dimethyl-1-propyl
 (*neo*-pentyl; $-\text{CH}_2\text{C}(\text{CH}_3)_3$), 2-methyl-1-butyl ($-\text{CH}_2\text{CH}(\text{CH}_3)\text{CH}_2\text{CH}_3$), 1-hexyl (*n*-hexyl;
 5 $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 2-hexyl ($-\text{CH}(\text{CH}_3)\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 3-hexyl
 ($-\text{CH}(\text{CH}_2\text{CH}_3)(\text{CH}_2\text{CH}_2\text{CH}_3)$), 2-methyl-2-pentyl ($-\text{C}(\text{CH}_3)_2\text{CH}_2\text{CH}_2\text{CH}_3$), 3-methyl-2-
 pentyl ($-\text{CH}(\text{CH}_3)\text{CH}(\text{CH}_3)\text{CH}_2\text{CH}_3$), 4-methyl-2-pentyl ($-\text{CH}(\text{CH}_3)\text{CH}_2\text{CH}(\text{CH}_3)_2$),
 3-methyl-3-pentyl ($-\text{C}(\text{CH}_3)(\text{CH}_2\text{CH}_3)_2$), 2-methyl-3-pentyl ($-\text{CH}(\text{CH}_2\text{CH}_3)\text{CH}(\text{CH}_3)_2$),
 2,3-dimethyl-2-butyl ($-\text{C}(\text{CH}_3)_2\text{CH}(\text{CH}_3)_2$), 3,3-dimethyl-2-butyl ($-\text{CH}(\text{CH}_3)\text{C}(\text{CH}_3)_3$),
 10 2,3-dimethyl-1-butyl ($-\text{CH}_2\text{CH}(\text{CH}_3)\text{CH}(\text{CH}_3)\text{CH}_3$), 2,2-dimethyl-1-butyl
 ($-\text{CH}_2\text{C}(\text{CH}_3)_2\text{CH}_2\text{CH}_3$), 3,3-dimethyl-1-butyl ($-\text{CH}_2\text{CH}_2\text{C}(\text{CH}_3)_3$), 2-methyl-1-pentyl
 ($-\text{CH}_2\text{CH}(\text{CH}_3)\text{CH}_2\text{CH}_2\text{CH}_3$), 3-methyl-1-pentyl ($-\text{CH}_2\text{CH}_2\text{CH}(\text{CH}_3)\text{CH}_2\text{CH}_3$), 1-heptyl
 (*n*-heptyl), 2-methyl-1-hexyl, 3-methyl-1-hexyl, 2,2-dimethyl-1-pentyl,
 2,3-dimethyl-1-pentyl, 2,4-dimethyl-1-pentyl, 3,3-dimethyl-1-pentyl, 2,2,3-trimethyl-1-
 15 butyl, 3-ethyl-1-pentyl, 1-octyl (*n*-octyl), 1-nonyl (*n*-nonyl); 1-decyl (*n*-decyl) etc.

By the terms propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl etc. without any further definition are meant saturated hydrocarbon groups with the corresponding number of carbon atoms, wherein all isomeric forms are included.

The above definition for alkyl also applies if alkyl is a part of another (combined) group
 20 such as for example C_{x-y} alkylamino or C_{x-y} alkoxy.

Unlike alkyl, alkenyl consists of at least two carbon atoms, wherein at least two adjacent
 carbon atoms are joined together by a C-C double bond and a carbon atom can only be part
 of one C-C double bond. If in an alkyl as hereinbefore defined having at least two carbon
 atoms, two hydrogen atoms on adjacent carbon atoms are formally removed and the free
 25 valencies are saturated to form a second bond, the corresponding alkenyl is formed.

Alkenyl may optionally be present in the *cis* or *trans* or *E* or *Z* orientation with regard to the double bond(s).

Unlike alkyl, alkynyl consists of at least two carbon atoms, wherein at least two adjacent
 carbon atoms are joined together by a C-C triple bond. If in an alkyl as hereinbefore

defined having at least two carbon atoms, two hydrogen atoms in each case at adjacent carbon atoms are formally removed and the free valencies are saturated to form two further bonds, the corresponding alkynyl is formed.

Haloalkyl (haloalkenyl, haloalkynyl) is derived from the previously defined alkyl (alkenyl, alkynyl) by replacing one or more hydrogen atoms of the hydrocarbon chain independently of one another by halogen atoms, which may be identical or different. If a haloalkyl (haloalkenyl, haloalkynyl) is to be further substituted, the substitutions may take place independently of one another, in the form of mono- or polysubstitutions in each case, on all the hydrogen-carrying carbon atoms.

10 Examples of haloalkyl (haloalkenyl, haloalkynyl) are -CF₃, -CHF₂, -CH₂F, -CF₂CF₃, -CHFCH₂CF₃, -CH₂CF₃, -CF₂CH₃, -CHFCH₃, -CF₂CF₂CF₃, -CF₂CH₂CH₃, -CF=CF₂, -CCl=CH₂, -CBr=CH₂, -C≡C-CF₃, -CHFCH₂CH₃, -CHFCH₂CF₃ etc.

Halogen relates to fluorine, chlorine, bromine and/or iodine atoms.

Cycloalkyl is made up of the subgroups monocyclic hydrocarbon rings, bicyclic
15 hydrocarbon rings and spiro-hydrocarbon rings. The systems are saturated. In bicyclic
hydrocarbon rings two rings are joined together so that they have at least two carbon atoms
together.

If a cycloalkyl is to be substituted, the substitutions may take place independently of one another, in the form of mono- or polysubstitutions in each case, on all the hydrogen-carrying carbon atoms. Cycloalkyl itself may be linked as a substituent to the molecule via every suitable position of the ring system.

Examples of cycloalkyl are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl.

Corresponding groups are an example:



Spirocycle is a spiro-hydrocarbon ring one carbon atom (spiroatom) belongs to two rings together.

Aryl denotes mono-, bi- or tricyclic carbocycles with at least one aromatic carbocycle.

- 5 Preferably, it denotes a monocyclic group with six carbon atoms (phenyl) or a bicyclic group with nine or ten carbon atoms (two six-membered rings or one six-membered ring with a five-membered ring), wherein the second ring may also be aromatic or, however, may also be saturated or partially saturated.

- 10 If an aryl is to be substituted, the substitutions may take place independently of one another, in the form of mono- or polysubstitutions in each case, on all the hydrogen-carrying carbon atoms. Aryl itself may be linked as a substituent to the molecule via every suitable position of the ring system.

Examples of aryl are phenyl and naphthyl.

- 15 The above definition of aryl also applies if aryl is part of another (combined) group as for example in arylamino, aryloxy or arylalkyl.

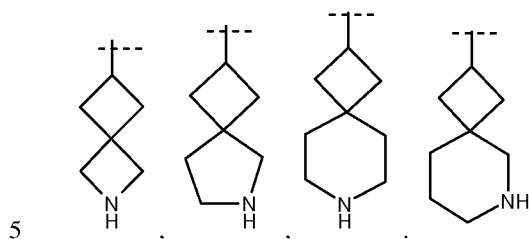
- 20 Heterocyclyl denotes ring systems, which are derived from the previously defined cycloalkyl or spirocycle by replacing one or more of the groups -CH₂- independently of one another in the hydrocarbon rings by the groups -O-, -S- or -NH-, wherein a total of not more than five heteroatoms may be present, at least one carbon atom may be present between two oxygen atoms and between two sulphur atoms or between one oxygen and one sulphur atom and the ring as a whole must have chemical stability. Heteroatoms may optionally be present in all the possible oxidation stages (sulphur → sulfoxide -SO-, sulphone -SO₂-; nitrogen → N-oxide).

25

If a heterocyclyl is substituted, the substitutions may take place independently of one another, in the form of mono- or polysubstitutions in each case, on all the hydrogen-carrying carbon and/or nitrogen atoms. Heterocyclyl itself may be linked as a substituent to

the molecule via every suitable position of the ring system.

Examples of heterocyclyl are tetrahydrofuranyl, tetrahydropyranyl, piperidinyl, piperazinyl, pyrrolidinyl, morpholinyl, or the following heterocyclic spirocycles



Heteroaryl denotes monocyclic heteroaromatic rings or polycyclic rings with at least one heteroaromatic ring, which compared with the corresponding aryl or cycloalkyl, instead of one or more carbon atoms, one or more identical or different heteroatoms, selected independently of one another from among nitrogen, sulphur and oxygen, wherein the resulting group must be chemically stable. The prerequisite for the presence of heteroaryl is a heteroatom and a heteroaromatic system.

If a heteroaryl is to be substituted, the substitutions may take place independently of one another, in the form of mono- or polysubstitutions in each case, on all the hydrogen-carrying carbon and/or nitrogen atoms. Heteroaryl itself may be linked as a substituent to the molecule via every suitable position of the ring system, both carbon and nitrogen.

Examples of heteroaryl are, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, benzoxazolyl, indolyl, isoindolyl, benzofuranyl, benzimidazolyl, benzothiazolyl, and the like.

Heteroatoms may optionally be present in all the possible oxidation stages (sulphur → sulfoxide -SO-, sulphone -SO₂-; nitrogen → N-oxide).

Carbocycles include hydrocarbon rings containing from three to twelve carbon atoms. These carbocycles may be either aromatic either aromatic or non-aromatic ring systems. The non-aromatic ring systems may be mono- or polyunsaturated. Preferred carbocycles include but are not limited to cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, cycloheptanyl, cycloheptenyl, phenyl, indanyl, indenyl, benzocyclobutanyl, dihydronaphthyl, tetrahydronaphthyl, naphthyl, decahydronaphthyl,

benzocycloheptanyl and benzocycloheptenyl.

All cyclic and acyclic systems defined in this section hereinabove shall be understood to be optionally partially or fully halogenated where possible and unless otherwise indicated.

- 5 Stereochemistry/solvates/hydrates: Unless specifically indicated, throughout the specification and appended claims, a given chemical formula or name shall encompass tautomers and all stereo, optical and geometrical isomers (*e.g.* enantiomers, diastereomers, *E/Z* isomers, etc.) and racemates thereof as well as mixtures in different proportions of the separate enantiomers, mixtures of diastereomers, or mixtures of any of the foregoing forms
- 10 where such isomers and enantiomers exist, as well as salts, including pharmaceutically acceptable salts thereof. The compounds and salts of the invention can exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol and the like. In general, the solvated forms such as hydrates are considered equivalent to the unsolvated forms for the purposes of the invention.
- 15 Salts: The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgement, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, and commensurate with a reasonable benefit/risk ratio.
- 20 As used herein "pharmaceutically acceptable salts" refers to derivatives of the disclosed compounds wherein the parent compound is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like.
- 25 For example, such salts include acetates, ascorbates, benzenesulphonates, benzoates, besylates, bicarbonates, bitartrates, bromides/hydrobromides, Ca-edetates/edetates, camsylates, carbonates, chlorides/hydrochlorides, citrates, edisylates, ethane disulphonates, estolates esylates, fumarates, gluceptates, gluconates, glutamates, glycolates, glycolylarsnates, hexylresorcinates, hydrabamines, hydroxymaleates,

hydroxynaphthoates, iodides, isothionates, lactates, lactobionates, malates, maleates, mandelates, methanesulphonates, mesylates, methylbromides, methylnitrates, methylsulphates, mucates, napsylates, nitrates, oxalates, pamoates, pantothenates, phenyl acetates, phosphates/diphosphates, polygalacturonates, propionates, salicylates, stearates, subacetates, succinates, sulphonamides, sulphates, tannates, tartrates, teoclates, toluenesulphonates, triethiodides, ammonium, benzathines, chlorprocaines, cholines, diethanolamines, ethylenediamines, meglumines and procaines.

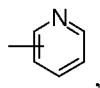
Further pharmaceutically acceptable salts can be formed with cations from metals like aluminium, calcium, lithium, magnesium, potassium, sodium, zinc and the like (also see Pharmaceutical salts, Birge, S.M. et al., J. Pharm. Sci., (1977), 66, 1-19).

The pharmaceutically acceptable salts of the present invention can be synthesised from the parent compound which contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base form of these compounds with a sufficient amount of the appropriate base or acid in water or in an organic diluent like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile, or a mixture thereof.

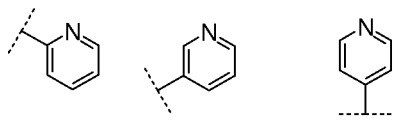
Salts of other acids than those mentioned above which for example are useful for purifying or isolating the compounds of the present invention (*e.g.* trifluoroacetates), also comprise a part of the invention.

Some abbreviated notations and their structure correspondences are listed below:

In a representation such as for example



the solid line means that the ring system may be attached to the molecule via the carbon atom 1, 2 or 3, and is thus equivalent to the following representation



By a therapeutically effective amount for the purposes of this invention is meant a quantity

of substance that is capable of obviating symptoms of illness or alleviating these symptoms, or which prolong the survival of a treated patient.

List of abbreviations

Ac	Acetyl
ACN	Acetonitrile
aq	Aqueous
ATP	adenosine triphosphate
Bn	Benzyl
Bu	Butyl
Boc	tert-butyloxycarbonyl
cat	Catalyst
conc	concentrated
d	day(s)
TLC	thin layer chromatography
DIEA	<i>N,N</i> -diisopropylethylamine
DMAP	4- <i>N,N</i> -dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	<i>N,N</i> -dimethylformamide
DMSO	Dimethylsulphoxide
dppf	1,1'-bis(diphenylphosphino)ferrocene
EDC	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
ESI	electron spray ionization
Et	Ethyl
Et ₂ O	diethyl ether
EtOAc	ethyl acetate
EtOH	Ethanol
h	hour(s)
HATU	O-(7-azabenzotriazol-1-yl)- <i>N,N,N',N'</i> -tetramethyl-uronium hexafluorophosphate

Hep	Heptane
HPLC	high performance liquid chromatography
<i>i</i>	Iso
LC	liquid chromatography
LiHMDS	lithium bis(trimethylsilyl)amide
sln.	Solution
mCPBA	3-Chloroperoxybenzoic acid
Me	Methyl
MeOH	Methanol
min	Minutes
MPLC	medium pressure liquid chromatography
MS	mass spectrometry
NBS	<i>N</i> -bromo-succinimide
NIS	<i>N</i> -iodo-succinimide
NMM	<i>N</i> -methylmorpholine
NMP	<i>N</i> -methylpyrrolidone
NP	normal phase
n.a.	not available
PBS	phosphate-buffered saline
Ph	Phenyl
Pr	Propyl
Pyr	Pyridine
rac	Racemic
R _f (R _f)	retention factor
RP	reversed phase
RT	Retention time (HPLC)
rt	ambient temperature
TBAF	tetrabutylammonium fluoride
TBDMS	tert-butyldimethylsilyl

TBME	tert-butylmethylether
TBTU	O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyl-uronium tetrafluoroborate
tBu	tert-butyl
TEA	Triethylamine
temp.	Temperature
<i>tert</i>	Tertiary
Tf	Triflate
TFA	trifluoroacetic acid
THF	Tetrahydrofuran
TMS	Trimethylsilyl
TRIS	tris(hydroxymethyl)-aminomethane
Ts	<i>p</i> -Tosyl
TsOH	<i>p</i> -toluenesulphonic acid
UV	Ultraviolet

Features and advantages of the present invention will become apparent from the following detailed examples which illustrate the fundamentals of the invention by way of example without restricting its scope:

5

Preparation of the compounds according to the invention

General Synthetic Methods

Optimum reaction conditions and reaction times may vary depending on the particular reactants used. Unless otherwise specified, solvents, temperatures, pressures and other
 10 reaction conditions may be readily selected by one of ordinary skill in the art. Specific procedures are provided in the Synthetic Examples section. Intermediates and products may be purified by chromatography on silica gel, recrystallization and/or reverse phase HPLC (RHPLC). Discrete enantiomers may be obtained by resolution of racemic products using chiral HPLC. RHPLC purification methods used anywhere from 0-100% acetonitrile

in water containing 0.1% formic acid or 0.1% TFA and used one of the following columns:

- a) Waters Sunfire OBD C18 5 μ m 30x150 mm column
- b) Waters XBridge OBD C18 5 μ m 30x150 mm column
- c) Waters ODB C8 5 μ m 19x150 mm column.
- 5 d) Waters Atlantis ODB C18 5 μ m 19x50 mm column.
- e) Waters Atlantis T3 OBD 5 μ m 30x100 mm column
- f) Phenomenex Gemini Axia C18 5 μ m 30x100 mm column

HPLC Methods:

Analytical LC/MS Analysis Method A:

- 10 Column : Thermo Scientific, Aquasil C18, 50 x 2.1 mm, 5 μ m column

Gradient:

Time(min)	0.1% Formic Acid in Water	0.1% Formic Acid in CAN	Flow(ml/min)
0	90	10	0.5
0.5	90	10	0.5
1.5	1	99	0.5
2.5	1	99	0.5
3.3	90	10	0.5
4.0	90	10	0.5

Analytical LC/MS Analysis Method B:

Column: Waters BEH 2.1x50mm C18 1.7 μ m column

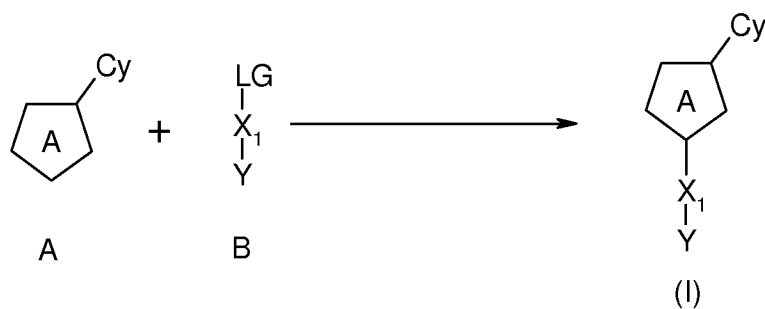
Gradient:

Time(min)	95%Water/5%ACN(0.05%TFA)	ACN(0.05%TFA)	Flow(ml/min)
0	90	10	0.8
1.19	0	100	0.8
1.7	0	100	0.8

- 5 The compounds according to the invention are prepared by the methods of synthesis described hereinafter in which the substituents of the general formulae have the meanings given hereinbefore. These methods are intended as an illustration of the invention without restricting its subject matter and the scope of the compounds claimed to these examples. Where the preparation of starting compounds is not described, they are commercially
- 10 obtainable or may be prepared analogously to known compounds or methods described herein. Substances described in the literature are prepared according to the published methods of synthesis.

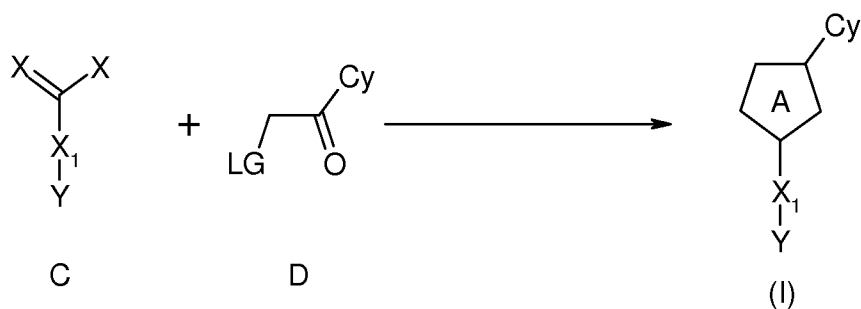
Compounds of formula I may be prepared as shown in Scheme Ia and Ib below.

Scheme 1a:



In scheme Ia, a heterocycle **A** is treated with a suitable base and reacted with an X₁-Y group containing a leaving group (LG) **B** to afford the compound of general formula (I).

Scheme 1b:

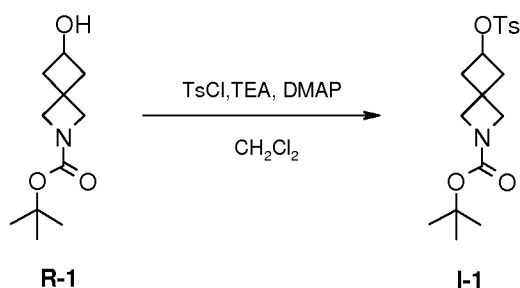


- 5 In scheme Ib, **C** (where X = O, N, S, or NH₂) is condensed with **D** to afford the compound of general formula (I).

Synthetic Examples

10 **Method 1**

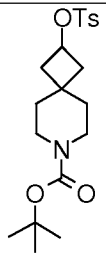
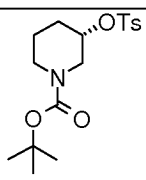
Synthesis of Intermediate I-1



A solution of **R-1** (5.0 g, 23 mmol) in CH₂Cl₂ is treated with TEA (6.5 mL, 47 mmol) and DMAP (0.57 g, 4.7 mmol). The mixture is stirred for 24 h then concentrated in vacuo.

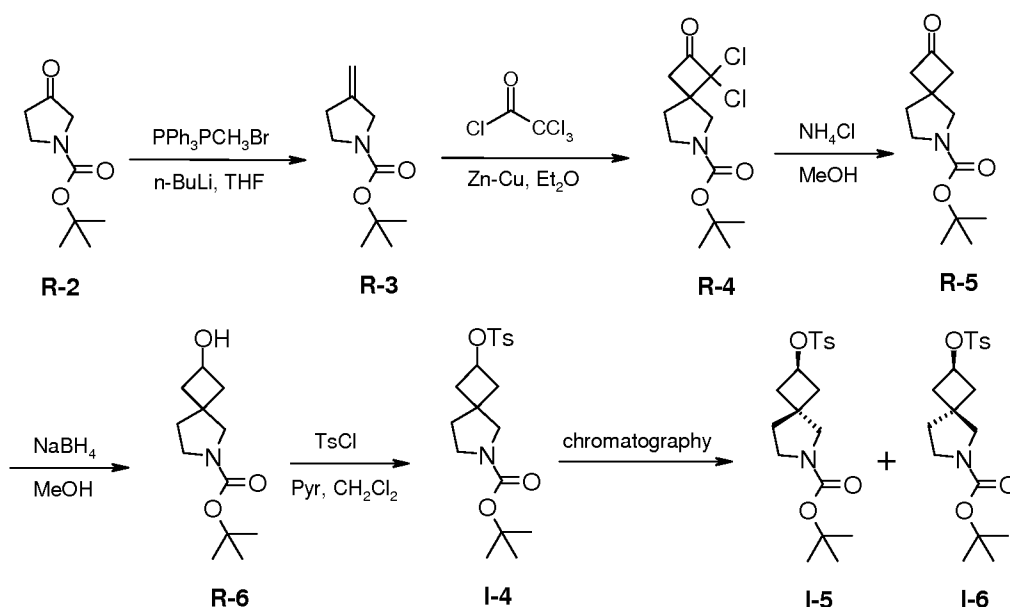
- 15 The residue is dissolved in EtOAc and washed with saturated aqueous ammonium chloride and brine. The organics are collected and volatiles are removed in vacuo. The crude residue is triturated with Et₂O and solid filtered and collected to afford **I-1** (5.6 g, 65%) *m/z* 367.9 [M⁺].

The following intermediates were prepared in a similar manner

Structure	Intermediate	<i>m/z</i>
	I-2	396.3 [M+H]
	I-3	356.0 [M+H]

5 Method 2

Synthesis of Intermediate I-4 and separation of diastereomers I-5 and I-6.



To a solution of $\text{PPh}_3\text{CH}_2\text{Br}$ (578 g, 1.62 mol) in THF (3.5 L) is added a solution of $n\text{-BuLi}$ (600 mL, 1.5 mol) at -78°C under N_2 . The mixture is stirred at 0°C for 1 h then **R-2** (200 g, 1.08 mol) in THF (2.0 L) is added to the reaction mixture at 0°C . The mixture is
 5 allowed to warm to ambient temperature, stirred for 1 h, then poured into H_2O and extracted with EtOAc . The organic layers are washed with brine, dried with Na_2SO_4 , concentrated and purified by flash chromatography (SiO_2 , Hep to 25% EtOAc in Hep) to give compound **R-3** (70 g, 36%).

10 To a solution of **R-3** (20 g, 109 mmol) in Et_2O (150 mL) is added Zn-Cu (56.2 g, 436 mmol) at 10°C under N_2 . Trichloroacetyl chloride (39.7 g, 218 mmol) in DME (150 mL) is added. The mixture is allowed to warm to ambient temperature and stirred for 2 days. The mixture is treated with aqueous NaHCO_3 and extracted with EtOAc . The organic layers are washed with brine, dried with Na_2SO_4 , concentrated and purified by flash chromatography
 15 (SiO_2 , Hep to 25% EtOAc in Hep) to give **R-4** (11 g, 34%).

To a solution of **R-4** (35.5 g, 121 mmol) in saturated NH_4Cl (64.7 g, 1.21 mol) in MeOH (400 mL) is added Zn (79.1 g, 1.21 mol). The mixture is stirred at ambient temperature for

8 h. The mixture is treated with H₂O and extracted with EtOAc. The organic layers are washed with brine, dried with Na₂SO₄, concentrated and purified by flash chromatography (SiO₂, Hep to 25%EtOAc in Hep) to afford **R-5** (19 g, 69%).

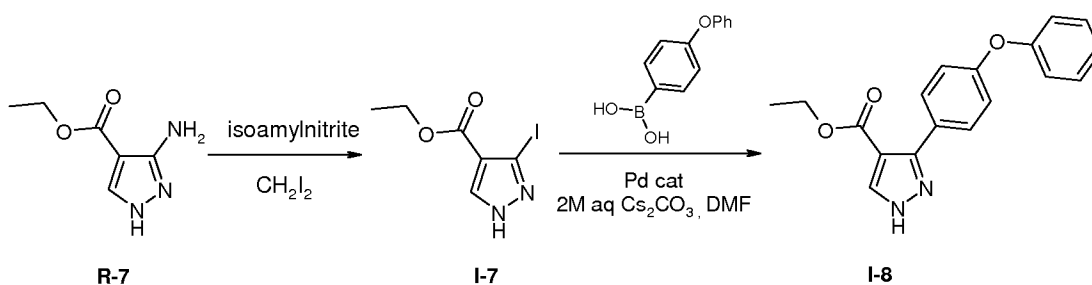
- 5 To the mixture of **R-5** (19 g, 84.3 mmol) in THF (200 mL) is added NaBH₄ (12.8 g, 337.2 mmol) at 0°C and then stirred at ambient temperature for 6 h. The mixture is treated with MeOH and H₂O, then extracted with EtOAc. The organic layers are washed with brine, dried with Na₂SO₄, concentrated and purified by flash chromatography (SiO₂, Hep to 50%EtOAc in Hep) to yield **R-6** (12 g, 63%).

10

- To the mixture of **R-6** (22 g, 96.8 mmol) and pyridine (23.2 g, 290.4 mmol) in CH₂Cl₂ (300 mL) is added TsCl (27.7 g, 145.2 mmol) at 0 °C and then stirred at ambient temperature overnight. The mixture is treated with H₂O and extracted with EtOAc. The organic layers are washed with brine, dried with Na₂SO₄, concentrated and purified by
- 15 flash chromatography (SiO₂, Hep to 40%EtOAc in Hep) to give **I-4** (26.6 g, 72%) *m/z* 382.2 [M+H]. **I-4** is separated by flash chromatography (SiO₂, Hep to 40%EtOAc in Hep) to give diastereomers **I-5** (*m/z* 382.2 [M+H]) and **I-6** (*m/z* 382.2 [M+H]).

Method 3

20 **Synthesis of Intermediate I-8**



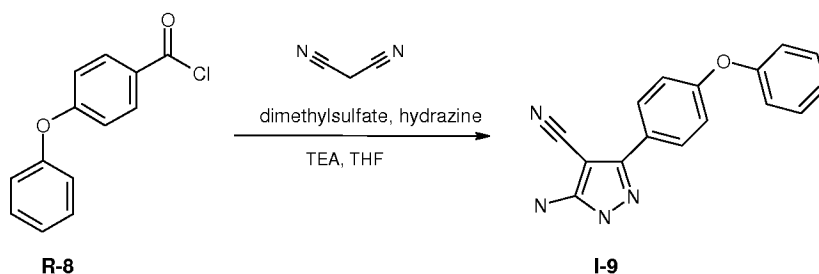
To a solution of **R-7** (15.0 g, 97 mmol) in CH_2I_2 (350 mL) is added isoamyl nitrite (58.7 g, 580 mmol). The solution is stirred for 15 min at ambient temperature then heated at 70° C for 2 h. The mixture is cooled to ambient temperature then partitioned between EtOAc and aqueous sodium bisulfite. The organics are collected, dried over MgSO_4 , filtered, and concentrated in vacuo. The crude is purified by flash chromatography (SiO_2 , Hep to 50%EtOAc in Hep) to give the **I-7** (13.1 g, 51%) m/z 266.8 [M+H].

A solution of **I-7** (2.0 g, 7.5 mmol), 4-phenoxyphenylboronic acid (2.0 g, 9.3 mmol), and bis(di-tert-butyl(4-dimethylaminophenyl)phosphine) dichloropalladium(II) (1.5 g, 2.1 mmol) in DMF (20 mL) and 2M aqueous Cs_2CO_3 (10 mL) is heated at 120° C for 2h. The mixture is cooled to ambient temperature then partitioned between EtOAc and aqueous NH_4Cl . The organics are collected, dried over MgSO_4 , filtered, and concentrated in vacuo. The crude is purified by flash chromatography (SiO_2 , 10-30% EtOAc in Hep) to give **I-8** (1.6 g, 69%). m/z 309.1 [M+H]

15

Method 4

Synthesis of Intermediate I-9



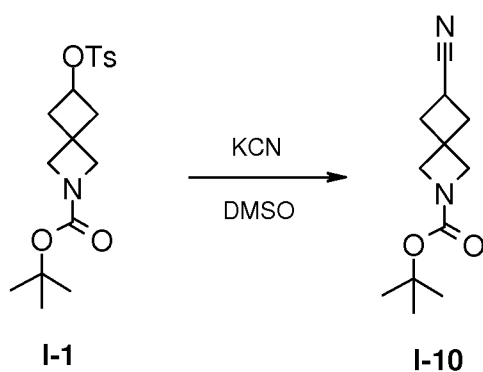
To malonitrile (7.55 g, 114 mmol) in THF (200 mL) at 0° C is added sodium hydride (60% dispersion in mineral oil, 4.57 g, 114 mmol) slowly under a stream of nitrogen. After 10 min **R-8** (27 g, 115 mmol) is added and the ice bath removed. The mixture is stirred at ambient temperature for 1.5h then dimethylsulfate is added then heated at reflux for 2 h. The mixture is cooled to ambient temperature then triethylamine and hydrazine are added.

The mixture is heated at reflux for 2 h then concentrated in vacuo, diluted with water, and extracted with 10% MeOH in EtOAc. The organics are collected, dried over MgSO₄, filtered and concentrated. The crude is purified by flash chromatography (SiO₂, 0-100% EtOAc in Hep) to afford **I-9** (5.7 g, 18%). *m/z* 277.5 [M+H]

5

Method 5

Synthesis of Intermediate I-10



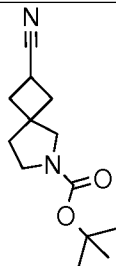
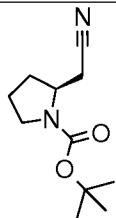
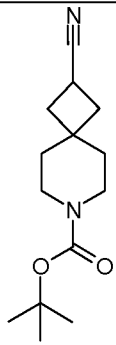
To a solution of **I-1** (200 mg, 0.54 mmol) in DMSO (2.5 mL) was added KCN (71 mg, 1.1 mmol). The mixture was heated at 100° C for 18 h then cooled to ambient temperature and partitioned between EtOAc and water. The organics were collected, dried over MgSO₄, filtered and concentrated in vacuo to afford **I-10** (quant, 120 mg). *m/z* 223.1 [M+H]

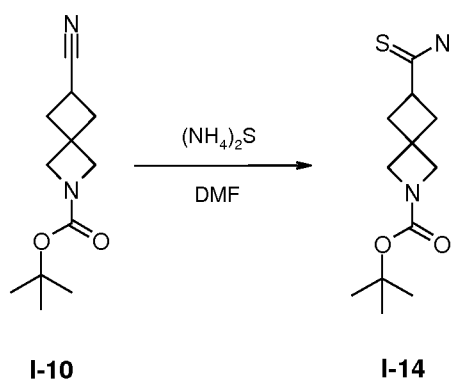
10

The following intermediates were prepared in a similar manner

15

Structure	Intermediate	<i>m/z</i>
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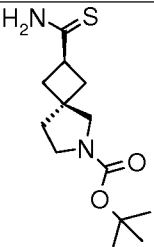
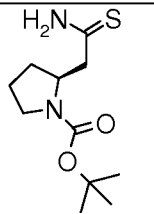
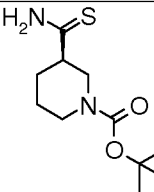
	I-11	181.0 [M-tBu]
	I-12	211.1 [M+H]
	I-13	195.4 [M-tBu]

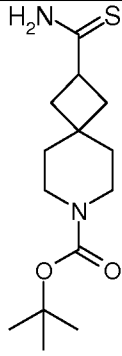
Method 6**Synthesis of Intermediate I-14**

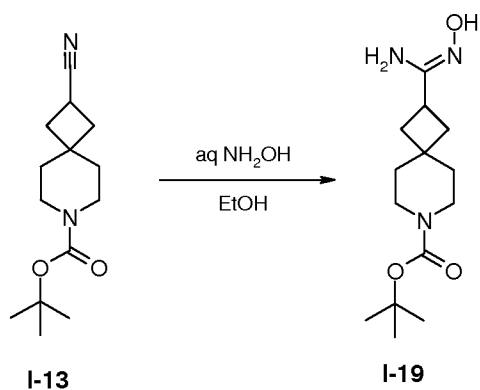
To a solution of **I-10** (250 mg, 1.1 mmol) in DMF (2 mL) is added 20% (w/w) aqueous (NH₄)₂S (2 mL, 5.9 mmol). The mixture is stirred at ambient temperature for 17 h then diluted with water. The resulting white solid is filtered and collected to give **I-14** (160 mg, 55%). *m/z* 257.0 [M+H]

5

The following intermediates were prepared in a similar manner

Structure	Intermediate	<i>m/z</i>
	I-15	271.1 [M+H]
	I-16	189.0 [M-tBu]
	I-17	245.0 [M+H]

	I-18	285.1 [M+H]
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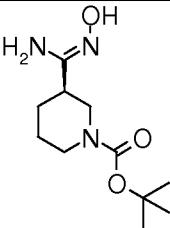
Method 7**Synthesis of Intermediate I-19**

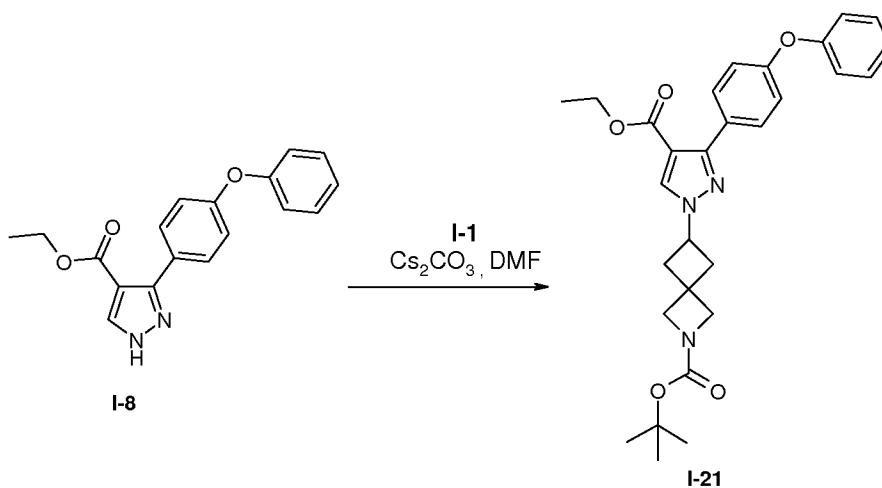
- 5 A solution of **I-13** (422 mg, 1.69 mmol) in EtOH (8.4 mL) is treated with 50% (w/w) aqueous hydroxylamine (1.1 mL, 16.9 mmol). The solution is heated at 70° C for 2 h then volatiles are removed in vacuo to afford **I-19** (478 mg, quant) m/z 284.1 [M+H].

The following intermediates were prepared in similar manner

10

Structure	Intermediate	m/z
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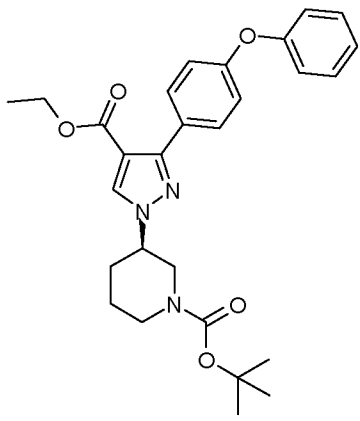
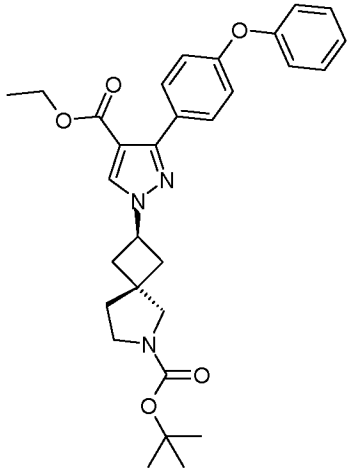
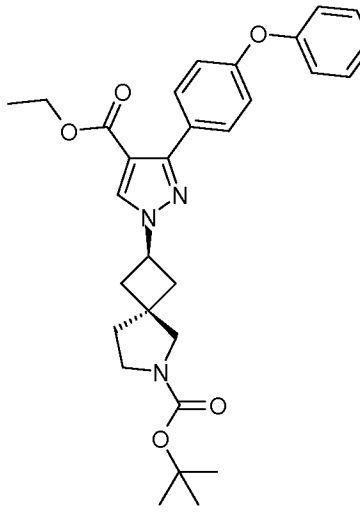
	I-20	244.1 [M+H]
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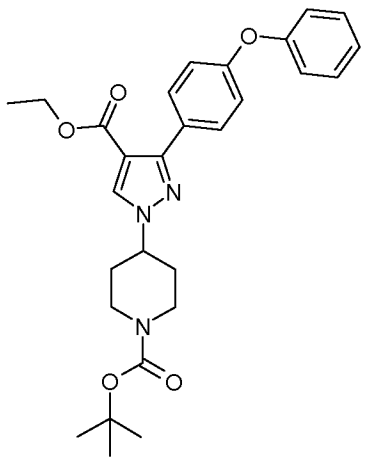
Method 8**Synthesis of Intermediate I-21**

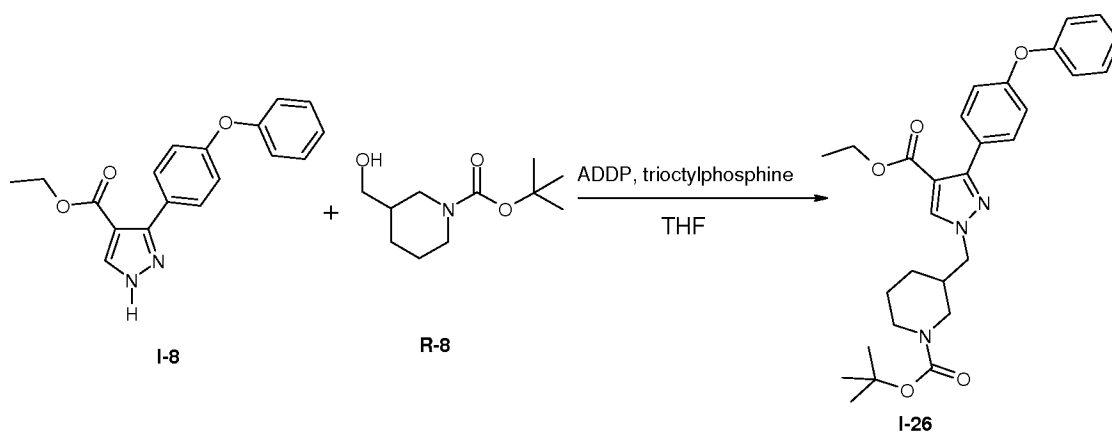
- 5 To a solution of **I-8** (200 mg, 0.65 mmol) and Cs_2CO_3 (423 mg, 1.30 mmol) in DMF (3 mL) is added **I-1** (262 mg, 0.71 mmol). The mixture is heated at 60° C for 18 h then concentrated in vacuo. The residue is purified by flash chromatography (SiO_2 , Hep to 50% EtOAc in Hep) to give **I-21** (217 mg, 66%) m/z 504.2 [M+H].

- 10 The following intermediates were prepared in similar fashion:

Structure	Intermediate	m/z
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	I-22	492.2 [M+H]
	I-23	518.2 [M+H]
	I-24	518.2 [M+H]

	I-25	NA
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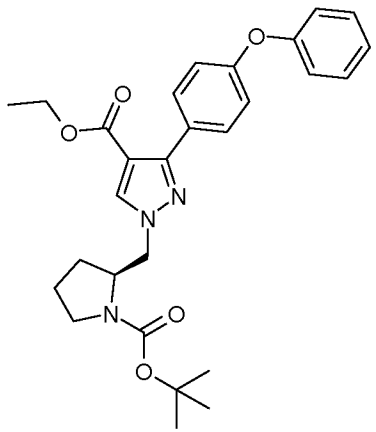
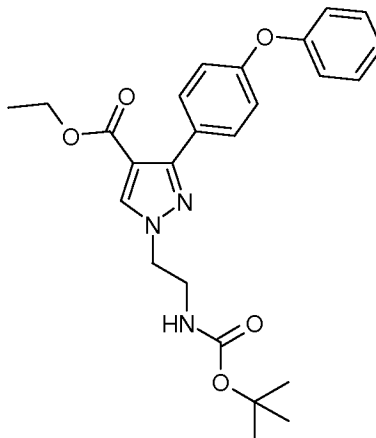
Method 9**Synthesis of Intermediate I-26**

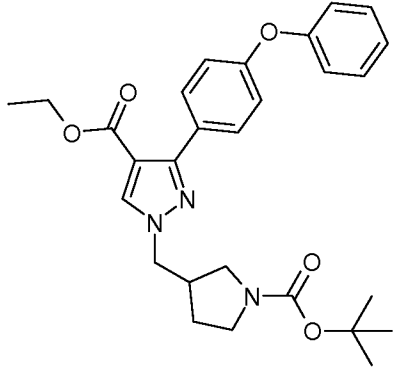
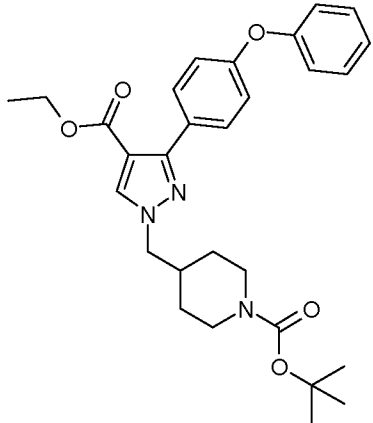
5

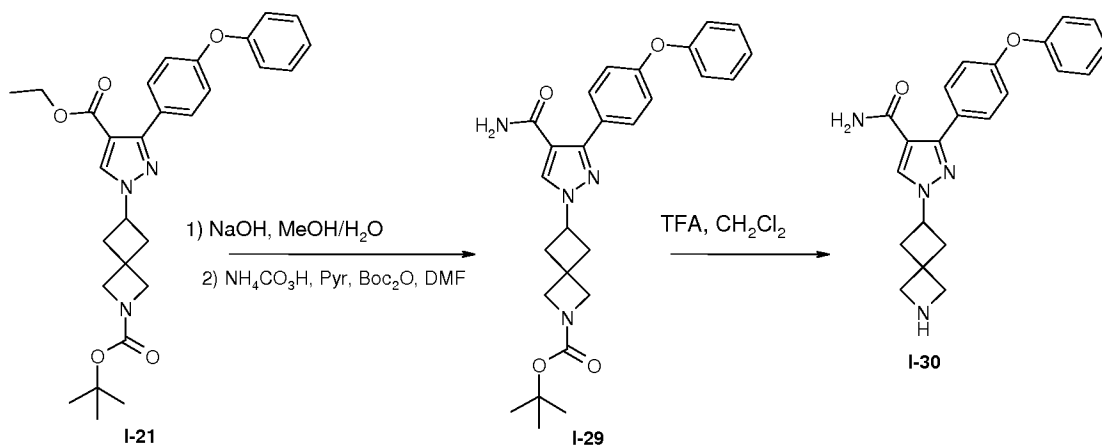
To a solution of **I-6** (800 mg, 2.6 mmol) in THF (40 mL) is added **R-8** (650 mg, 3.0 mmol), tri-*n*-octyl phosphine (3.0 g, 8.0 mmol), and ADDP (1,1'-(azodicarbonyl)dipiperidine) (2.1 g, 8.2 mmol). The mixture is stirred for 48 h then concentrated in vacuo. The residue is partitioned between saturated aqueous NH₄Cl and EtOAc. The organics are washed with brine, dried over Na₂SO₄, filtered, and concentrated in vacuo. The crude is purified by flash chromatography (SiO₂, Hep to 30%EtOAc in Hep)

to give **I-24** (1.1 g, 84%) m/z 506.1 [M+H].

The following intermediates are prepared in similar fashion:

Structure	Intermediate	m/z
	I-25	NA
	I-26	NA

	I-27	417.9 [M+H]
	I-28	NA

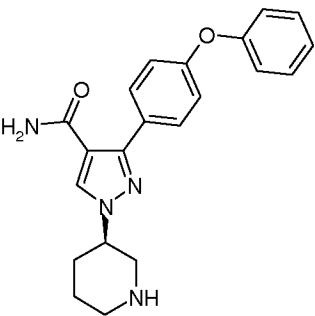
Method 10**Synthesis of Intermediate I-30**

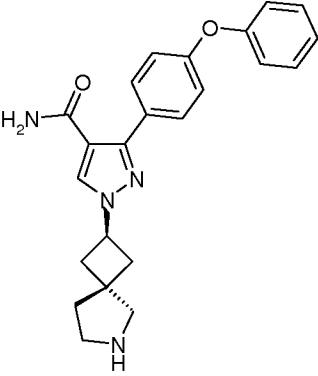
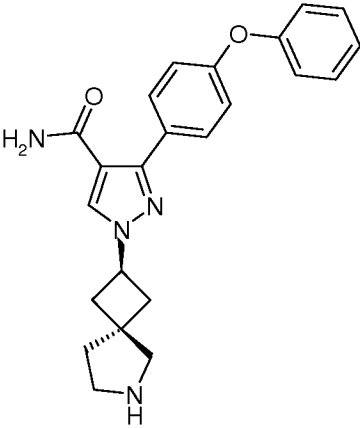
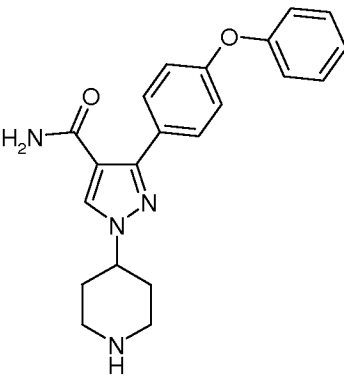
A solution of **I-21** (260 mg, 0.52 mmol) in 1:1 dioxane/water (8 mL) is treated with LiOH (120 mg, 5.0 mmol). The mixture is heated at reflux for 2 h then volatiles are removed in vacuo. The residue is acidified to pH = 4 with 2M aqueous HCl, extracted with EtOAc, washed with brine, dried over Na₂SO₄, filtered, and concentrated in vacuo. The residue is dissolved in DMF (4 mL) and treated with pyridine (80 uL, 1.0 mmol) and Boc anhydride (80 mg, 1.0 mmol). The solution is stirred for 10 min then ammonium bicarbonate (95 mg, 1.2 mmol) is added. The mixture is stirred for 16 h then volatiles are removed in vacuo. The residue is partitioned between EtOAc and saturated aqueous NH₄Cl. The organics are washed with brine, dried over Na₂SO₄, filtered, and concentrated in vacuo. The residue is purified by flash chromatography (SiO₂, 20-80%EtOAc in Hep, then 20%MeOH in CH₂Cl₂) to give **I-29** (180 mg, 75%) *m/z* 475.0 [M+H].

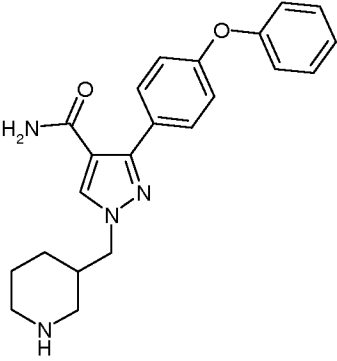
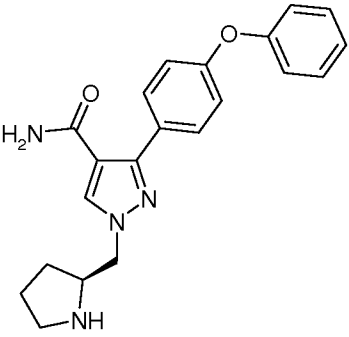
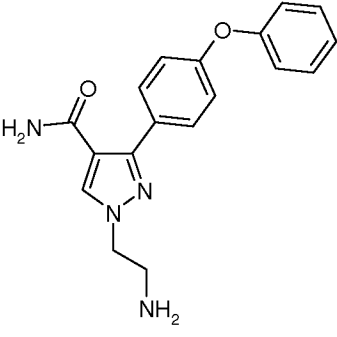
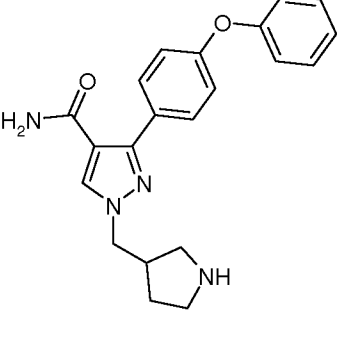
To a stirred solution of **I-29** (180 mg, 0.38 mmol) in CH₂Cl₂ (3 mL) is added TFA (2 mL). The solution is stirred at ambient temperature for 3 h then volatiles are removed in vacuo. The residue is partitioned between saturated aqueous NaHCO₃ and EtOAc. The organics are collected, dried over Na₂SO₄, filtered, and concentrated in vacuo to afford **I-30** (130 mg, 92%) *m/z* 375.0 [M+H].

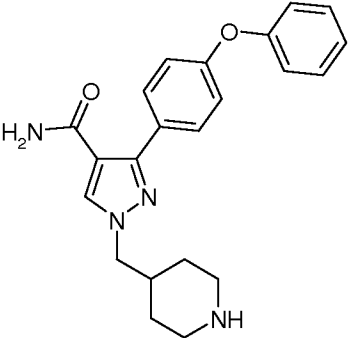
The following intermediates were prepared in similar fashion:

20

Structure	Intermediate	<i>m/z</i>
	I-31	

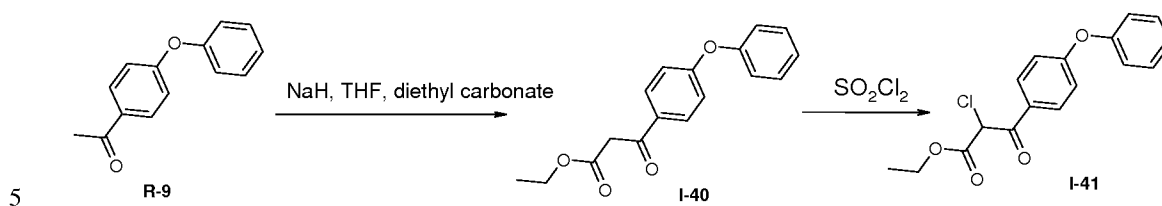
	I-32	
	I-33	
	I-34	

	I-35	
	I-36	
	I-37	
	I-38	

	I-39	NA
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Method 11

Synthesis of Intermediate I-41



To a solution of **R-9** (5.00 g, 23.6 mmol) in THF (50 mL) is added a 60% dispersion of sodium hydride in mineral oil (1.41 g, 35.1 mmol). The mixture is stirred for 5 min at ambient temperature then diethyl carbonate (5.7 mL, 47.4 mmol). The reaction is stirred for 30 min at ambient temperature then heated at reflux for 2 h. The mixture is cooled to ambient temperature then partitioned between saturated aqueous NH_4Cl and EtOAc. The organics are collected and concentrated in vacuo to afford a residue that is purified by flash chromatography (SiO_2 , Hep to 70%EtOAc in Hep) to give **I-40** (6.2 g, 93%) m/z 285.1 [M+H].

10

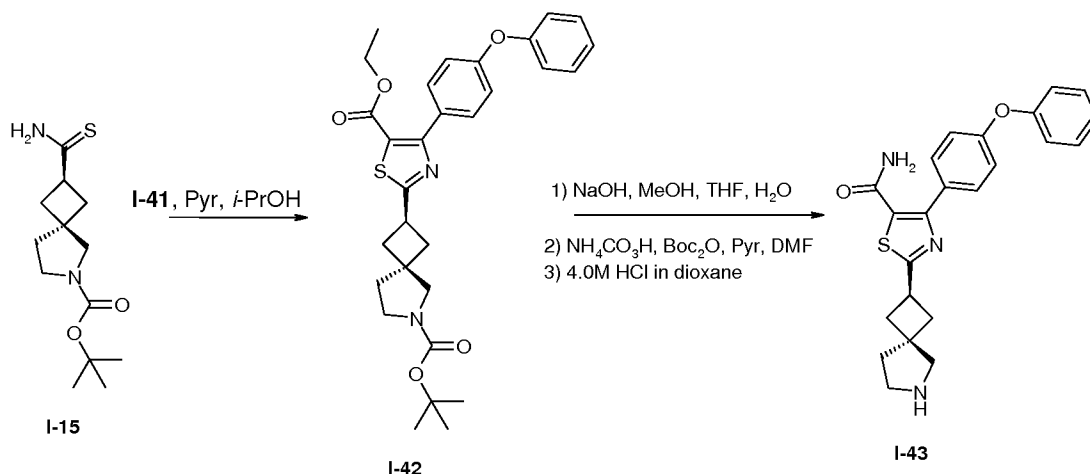
15

To a cold (0°C) solution of **I-40** (5.2 g, 18.3 mmol) in CH_2Cl_2 (46 mL) is added SO_2Cl_2 (1.5 mL, 18.3 mmol). The mixture is allowed to warm to ambient temperature and stirred

for 30 min then treated with water, extracted with CH₂Cl₂, dried over Na₂SO₄, filtered, and concentrated in vacuo to afford **I-41** (quant) *m/z* 318.9 [M+H].

Method 12

5 Synthesis of Intermediate I-43



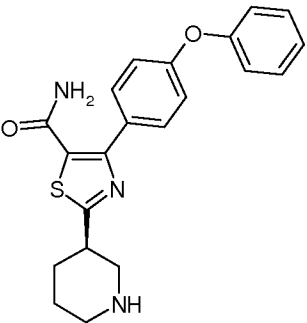
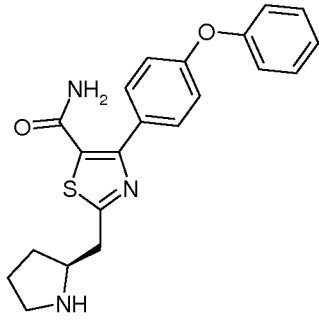
A solution of **I-15** (400 mg, 1.48 mmol) and **I-41** (943 mg, 2.96 mmol) in *i*-PrOH (15 mL) is treated with pyridine (0.36 mL, 4.44 mmol). The mixture is heated at 60° C for 3 days then volatiles are removed in vacuo. The residue is purified by flash chromatography (SiO₂, Hep to 40%EtOAc in Hep) to give **I-42** (240 mg, 30%) *m/z* 535.2 [M+H].

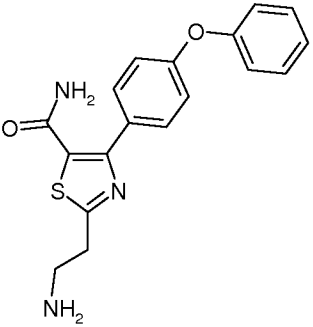
A solution of **I-42** (240 mg, 0.45 mmol) in MeOH (3 mL), THF (1 mL), and 5M aqueous NaOH (0.5 mL) is heated at 60° C for 3 h. The mixture is cooled to ambient temperature then acidified to pH=1 with 6M aqueous HCl. The mixture is extracted with CH₂Cl₂ then filtered through a phase separator® then volatiles are removed in vacuo. The residue is dissolved in DMF (2 mL) and treated with pyridine (324 mg, 4.1 mmol), Boc anhydride (327 mg, 0.45 mmol), followed by ammonium bicarbonate (215 mg, 2.72 mmol). The mixture is stirred for 3 h then volatiles are removed in vacuo to afford a residue that is purified by flash chromatography (SiO₂, CH₂Cl₂ to 5%MeOH in CH₂Cl₂). The purified

material is dissolved in CH₂Cl₂ (5 mL) and treated with 4.0M HCl in dioxane (1.1 mL). The mixture is stirred for 1 h then volatiles are removed in vacuo to afford a residue that is purified by flash chromatography (SiO₂, CH₂Cl₂ to 20%MeOH in CH₂Cl₂ containing 2.5%TEA) to give **I-43** (134 mg, 73%) *m/z* 405.9 [M+H].

5

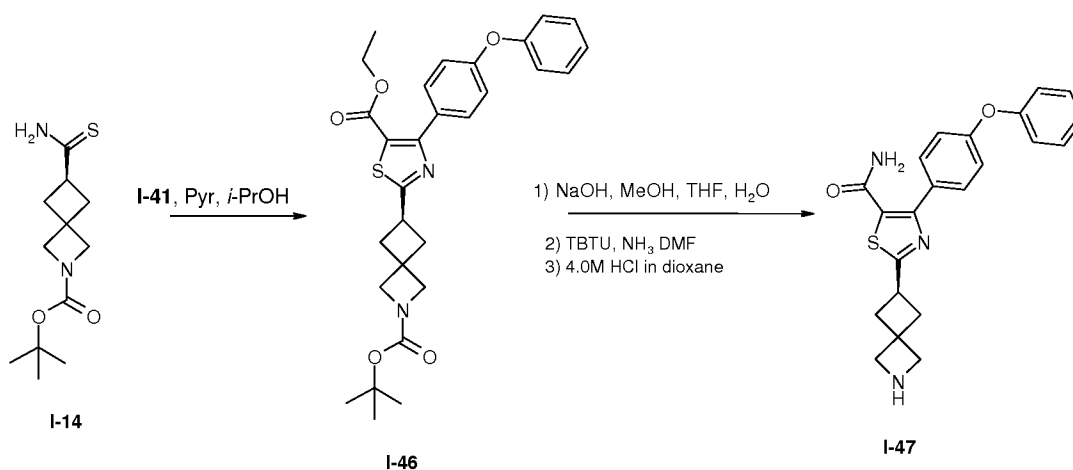
The following compounds are made in similar fashion:

Structure	Intermediate	<i>m/z</i>
	I-44	380.8 [M+H]
	I-45	380.4 [M+H]

	I-46	NA
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Method 13**Synthesis of Intermediate I-46**

5



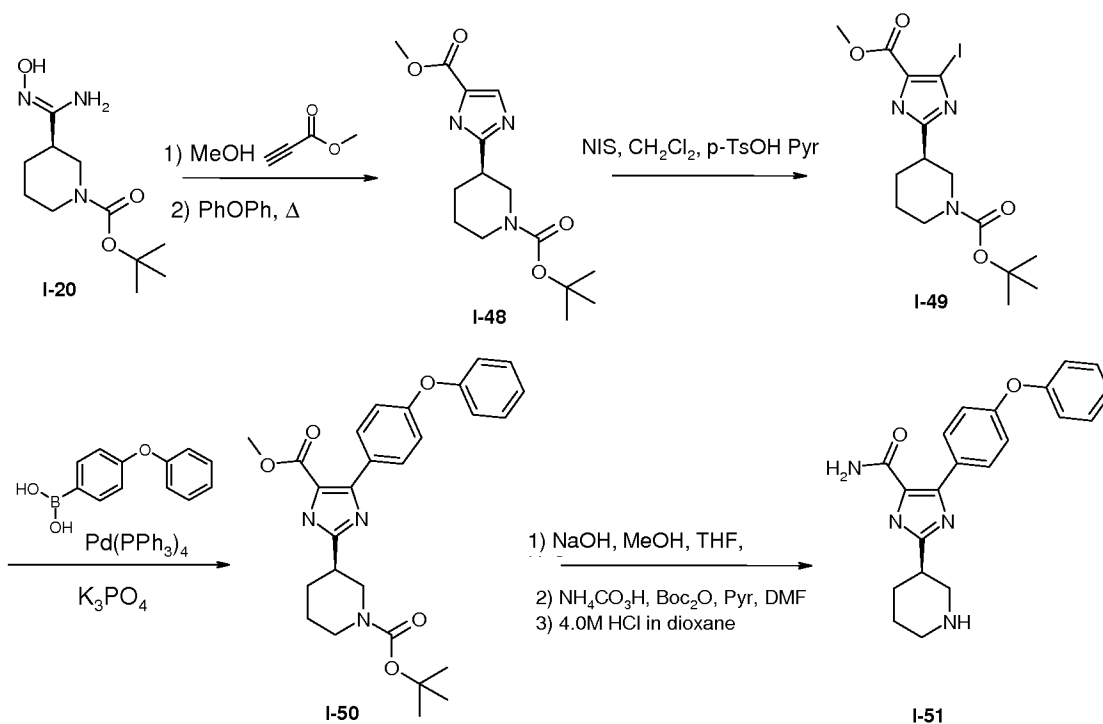
To a solution of **I-14** (160 mg, 0.62 mmol) and **I-41** (298 mg, 0.94 mmol) in *i*-PrOH (6.2 mL) is added pyridine (0.15 mL, 1.9 mmol). The solution is heated at 70° C for 24h then volatiles are removed in vacuo. The crude is purified by flash chromatography (SiO₂, Hep to 40%EtOAc in Hep) to give **I-46** (144 mg, 44%) m/z 521.2 [M+H].

A solution of **I-46** (144 mg, 0.28 mmol) in MeOH (2 mL) and 3M aqueous NaOH (2 mL) is heated at 65° C for 3 h then cooled to ambient temperature. The solid is filtered,

collected, and dried then dissolved in DMF (2 mL) and treated with TBTU (71 mg, 0.22 mmol). The mixture is stirred for 15 min then treated with 7M ammonia in MeOH (7 mL). The mixture is stirred for 20 min then volatiles are removed in vacuo. The residue is partitioned between water and EtOAc and organics are collected and concentrated. The crude is purified by flash chromatography (Hep to EtOAc). The resulting compound is dissolved in CH₂Cl₂ (2 mL) and treated with TFA (1 mL). The reaction mixture is stirred for 2 h then volatiles are removed in vacuo. The crude is partitioned between CH₂Cl₂ and 10% (w/w) aqueous Na₂CO₃ and CH₂Cl₂. The organics are collected and filtered through a phase separator® to afford after removal of the volatiles **I-47** (58 mg, 53%) *m/z* 392.1 [M+H].

Method 14

Synthesis of Intermediate I-51



A solution of **I-20** (500 mg, 2.1 mmol) and methyl propiolate (0.35 mL, 4.1 mmol) in

MeOH (10 mL) is heated at 65° C for 4 h. The mixture is concentrated in vacuo then dissolved in diphenyl ether (2 mL) and heated at 200° C for 1 h. The mixture is cooled to ambient temperature then purified by flash chromatography (SiO₂, Hep to EtOAc) to give **I-48** (317 mg, 50%) *m/z* 310.2 [M+H].

5

To a solution of **I-48** (317 mg, 1.0 mmol) and *p*-TsOH Pyr (461 mg, 2.1 mmol) in CH₂Cl₂ (5 mL) is added NIS (461 mg, 2.1 mmol). The mixture is stirred in the dark at ambient temperature for 24 h. The mixture is treated with saturated aqueous Na₂SO₃ then filtered through a phase separator. The organics are collected and concentrated in vacuo to afford
10 a residue that is purified by flash chromatography (SiO₂, Hep to 80%EtOAc in Hep) to afford **I-49** (339 mg, 76%) *m/z* 436.0 [M+H].

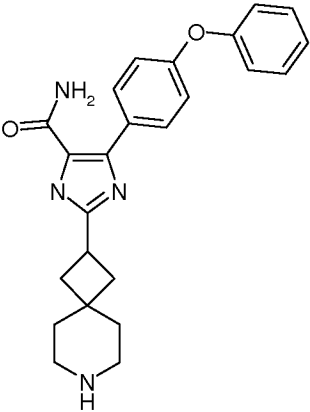
A mixture of **I-49** (339 mg, 0.78 mmol), 4-phenoxyphenylboronic acid (333 mg, 1.56 mmol), and tetrakis(triphenylphosphine)palladium(0) (90 mg, 0.078 mmol), and K₃PO₄
15 (827 mg, 3.89 mmol) in dioxane (4 mL) is heated at 100° C in the microwave for 45 min. The mixture is cooled and concentrated in vacuo to afford a residue that is purified by flash chromatography (SiO₂, Hep to 80%EtOAc in Hep) to afford **I-50** (302 mg, 81%) *m/z* 478.2 [M+H].

20 A solution of **I-50** (372 mg, 0.78 mmol) in MeOH (1.5 mL), THF (1 mL), and 3M aqueous NaOH (3 mL) is heated at ambient temperature for 20 h then acidified to pH=5 with concentrated aqueous HCl. The volatiles are removed in vacuo and residue triturated with a mixture of CH₂Cl₂ and MTBE. The solid is filtered, collected, and dried. The solid is dissolved in DMF (2 mL) and treated with pyridine (0.1 mL, 1.2 mmol), Boc anhydride
25 (69 mg, 0.87 mmol), followed by ammonium bicarbonate (96 mg, 1.2 mmol). The mixture is stirred for 16 h then partitioned between water and CH₂Cl₂. The mixture is filtered through a phase separator® and organics are concentrated in vacuo to afford a residue that is purified by flash chromatography (SiO₂, CH₂Cl₂ to 5%MeOH in CH₂Cl₂). The purified material is dissolved in CH₂Cl₂ (2 mL) and treated with 4.0M HCl in dioxane (4 mL). The

mixture is stirred for 2 h then volatiles are removed in vacuo to afford a residue that is purified by trituration with MTBE:EtOAc to give **I-51** (75 mg, 22%) m/z 393.1 [M+H].

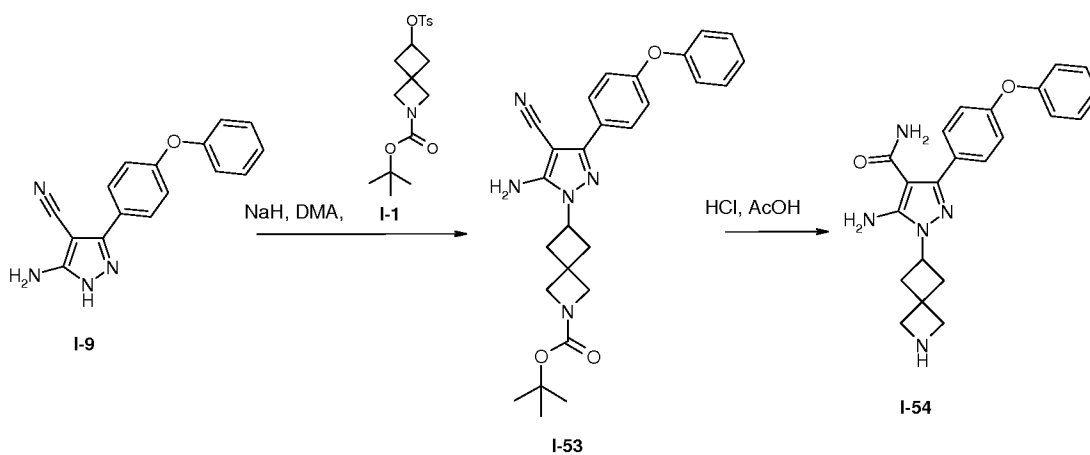
The following intermediate is prepared in similar fashion:

5

Structure	Intermediate	m/z
	I-52	403.2 [M+H]

Method 15

Synthesis of Intermediate I-54

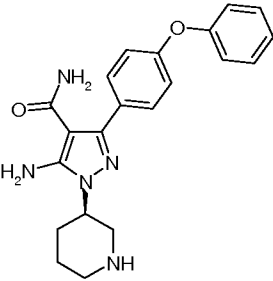
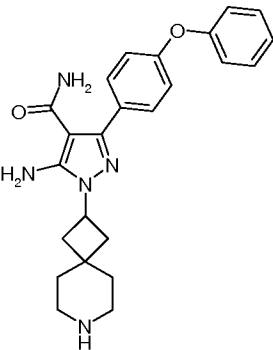


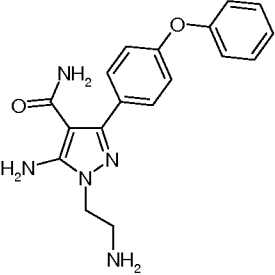
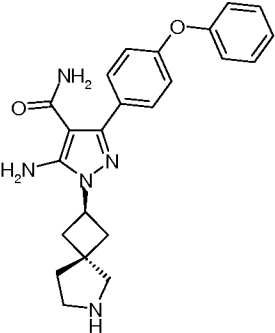
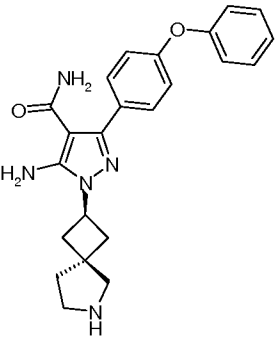
- 10 To a solution of **I-9** (1.50 g, 5.4 mmol) in DMF (20 mL) is added sodium hydride (60% dispersion in mineral oil, 0.26 g, 6.5 mmol). The mixture is stirred for 5 min then **I-1**

(2.39 g, 6.5 mmol) is added. The mixture is heated at 70 ° C for 18 h then cooled to ambient temperature. The mixture is partitioned between EtOAc and water then organics are collected, dried over Na₂SO₄, filtered, and concentrated in vacuo. The residue is purified by flash chromatography (SiO₂, Hep to 70%EtOAc in Hep) to afford **I-53** (1.2 g, 47%) *m/z* 472.2 [M+H].

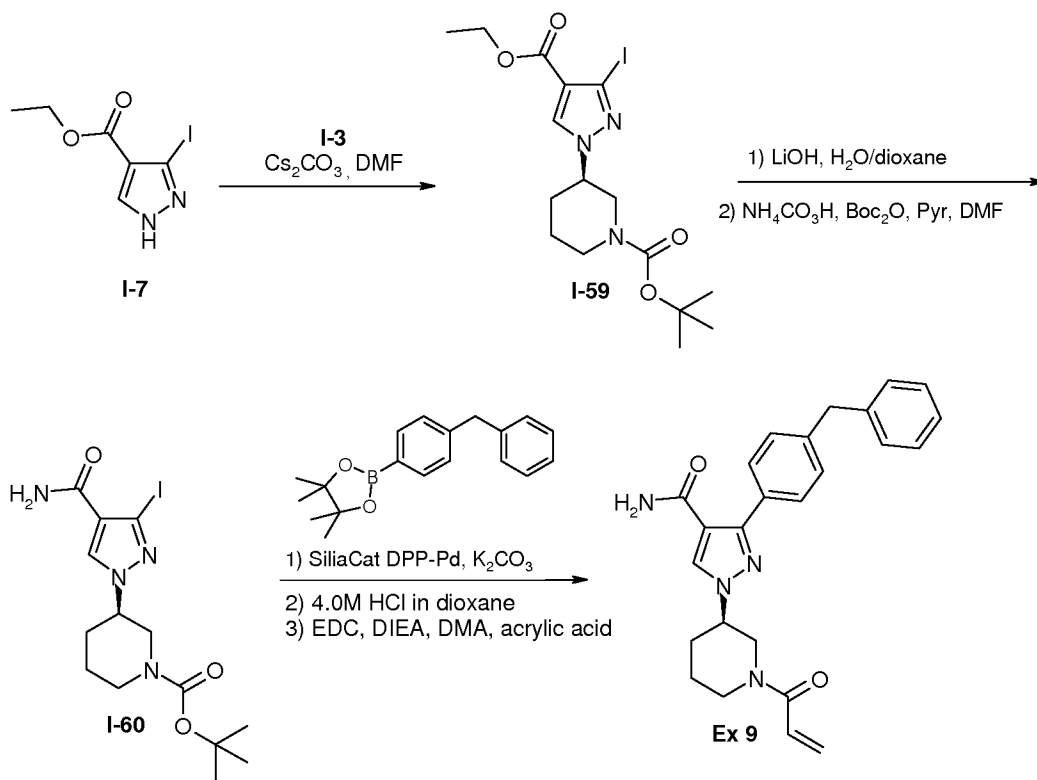
A solution of **I-53** (1.00 g, 2.2 mmol) in AcOH (5 mL) and Concentrated aqueous HCl (1 mL) is heated at 90° C for 10 h. The mixture is cooled to ambient temperature then poured into ice. The mixture is basified to pH 9-10 by addition of ammonium hydroxide then extracted with EtOAc, washed with brine, dried over Na₂SO₄, filtered, and concentrated in vacuo. The residue is purified by RHPLC to afford **I-54** (0.39 g, 48%) *m/z* 390.1 [M+H].

The following intermediates are prepared in similar fashion:

Structure	Intermediate	<i>m/z</i>
	I-54	378.1 [M+H]
	I-55	418.2 [M+H]

	I-56	
	I-57	404.1 [M+H]
	I-58	404.1 [M+H]

Method 16**Synthesis of Example 9**



To a solution of **I-7** (2.00 g, 7.5 mmol) in DMF (20 mL) is added Cs_2CO_3 (4.9 g, 15 mmol) and **I-3** (4.0 g, 11 mmol). The reaction mixture is heated at 60° C for 24 h then cooled to ambient temperature. The mixture is partitioned between EtOAc and water. The organics are collected, washed with water, dried over MgSO_4 , filtered, and concentrated in vacuo. The crude is purified by flash chromatography (SiO_2 , Hep to 30%EtOAc in Hep) to afford **I-59** (2.10 g, 62%) m/z 445.0 [M+H].

To a solution of **I-59** (7.00 g, 15.6 mmol) in 1:1 dioxane:water (50 mL) is added LiOH (3.00 g, 125 mmol). The reaction mixture was heated at reflux for 2h then volatiles are removed in vacuo. The residue is acidified with aqueous 2 N HCl to pH = 4 then diluted with EtOAc, washed with brine, dried over Na_2SO_4 , filtered, and concentrated in vacuo. The residue is dissolved in DMF (30 mL) and treated with Boc anhydride (2.22 g, 28 mmol) followed by ammonium bicarbonate (2.21 g, 28 mmol) and pyridine (2.2 mL, 28 mmol). The mixture is stirred for 16 h then volatiles are removed in vacuo. The residue is

partitioned between EtOAc and saturated aqueous NH₄Cl then organics are collected, washed with brine, dried over Na₂SO₄, filtered, and concentrated in vacuo. The crude is purified by flash chromatography (SiO₂, 20-80%EtOAc in Hep, then 20%MeOH in CH₂Cl₂) to afford **I-60** (3.8 g, 61%) *m/z* 421.0 [M+H]

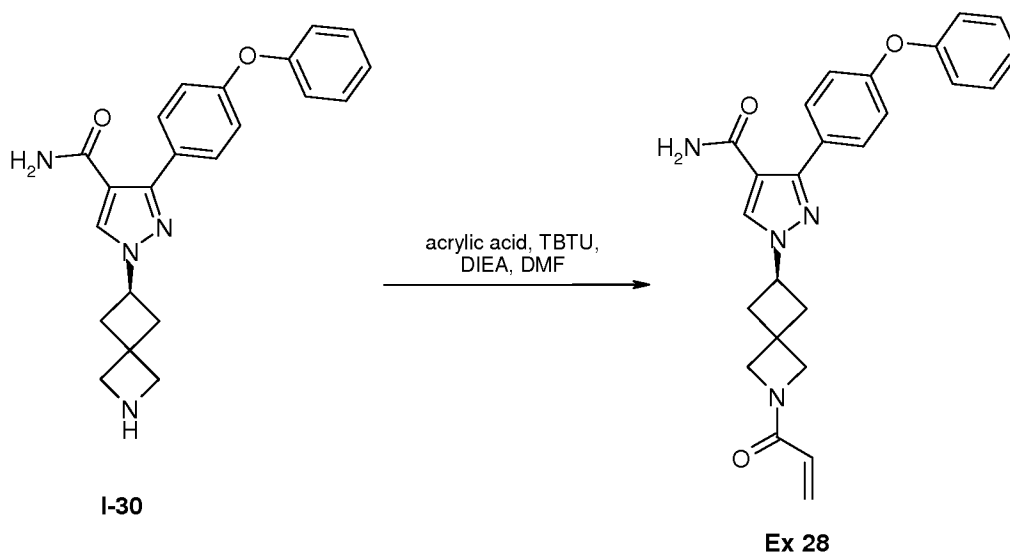
5

To a solution of 4-benzylphenylboronic acid pinacol ester (47 mg, 0.16 mmol) in DME (1 mL) is added a solution of **I-19** (45 mg, 0.11 mmol) in DME (1 mL). To this solution is added aqueous 1 M K₂CO₃ (1 mL) and SiliaCat DPP-Pd (50 mg, 0.01 mmol). The mixture is heated at 100° C for 16 h then concentrated in vacuo. The crude was purified by RHPLC
10 to afford a residue that is dissolved in DCE and treated with 4.0M HCl in dioxane (0.5 mL). The mixture is stirred for 16 h then volatiles are removed in vacuo. To the residue is added a solution of acrylic acid (7.7 mg, 0.11 mmol), EDC (23 mg, 0.12 mmol), and DIEA (35 uL, 0.20 mmol) in DMA (0.8 mL). The reaction mixture is stirred for 4 h then volatiles were removed in vacuo to afford a residue that was purified by RHPLC to afford
15 example **9** (12 mg, 26%).

The following compounds were prepared in a similar manner:

Examples **1-8, 10-27, 94-96**

20 **Method 17****Synthesis of Example 28**



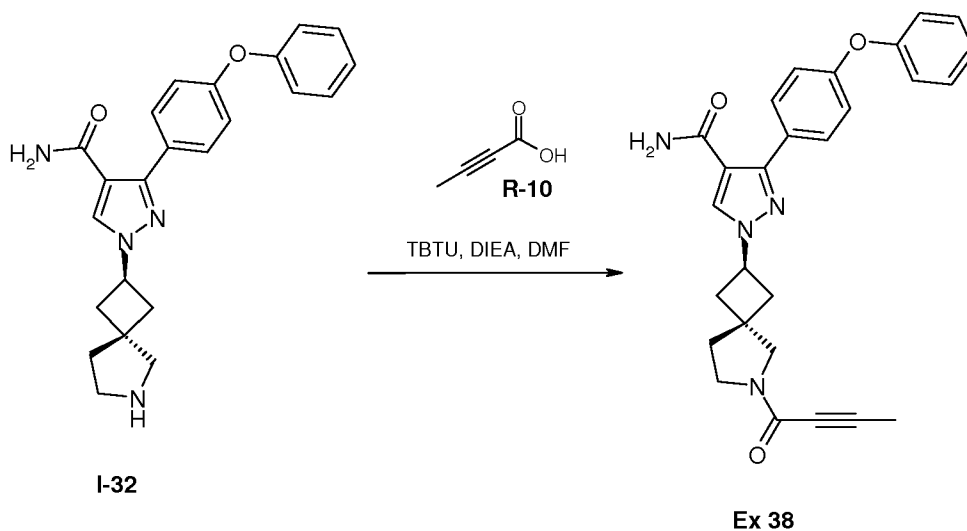
To a solution of **I-30** (75 mg, 0.20 mmol) in DMF (2 mL) is added DIEA (0.3 mL), TBTU (96 mg, 0.30 mmol), and acrylic acid (22 mg, 0.30 mmol). The mixture is stirred for 12 h at ambient temperature then treated with water. The mixture is extracted with EtOAc, dried over Na₂SO₄, filtered, and concentrated in vacuo. The crude is purified by flash chromatography (30 to 90%EtOAc in Hep) to give example **28** (36 mg, 42%).

The following compounds are prepared in similar fashion:

10 Examples **29, 33, 39, 42, 45, 47, 55, 88**

Method 18

Synthesis of Example 38



To a solution of **I-32** (70 mg, 0.18 mmol) in DMF (3 mL) is added DIEA (1 mL), TBTU (116 mg, 0.36 mmol), and **R-10** (17 mg, 0.20 mmol). The mixture is stirred for 12 h at ambient temperature then treated with water. The mixture is extracted with EtOAc, dried
 5 over Na₂SO₄, filtered, and concentrated in vacuo. The crude is purified by RHPLC to give example **38** (38 mg, 46%).

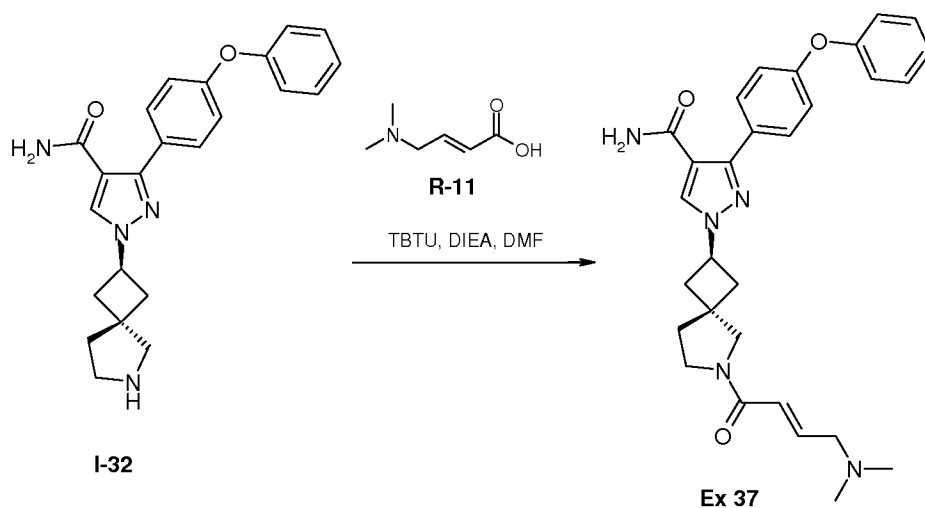
The following compounds are prepared in similar fashion:

Examples **31, 32, 43, 48, 49, 56**

10

Method 19

Synthesis of Example 37



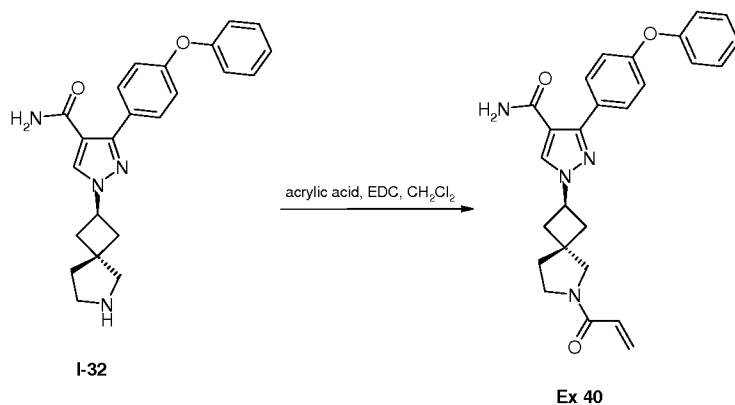
To a solution of **I-32** (25 mg, 0.064 mmol) in DMF (2 mL) is added DIEA (0.4 mL), TBTU (32 mg, 0.080 mmol), and **R-11** (10 mg, 0.080 mmol). The mixture is stirred for 12 h at ambient temperature then treated with water. The mixture is extracted with EtOAc, dried over Na₂SO₄, filtered, and concentrated in vacuo. The crude is purified by flash chromatography (SiO₂, 30 to 70%EtOAc in Hep) to give example **37** (5 mg, 16%).

The following compounds are prepared in similar fashion:

10 Examples **30, 36**

Method 20

Synthesis of Example 40



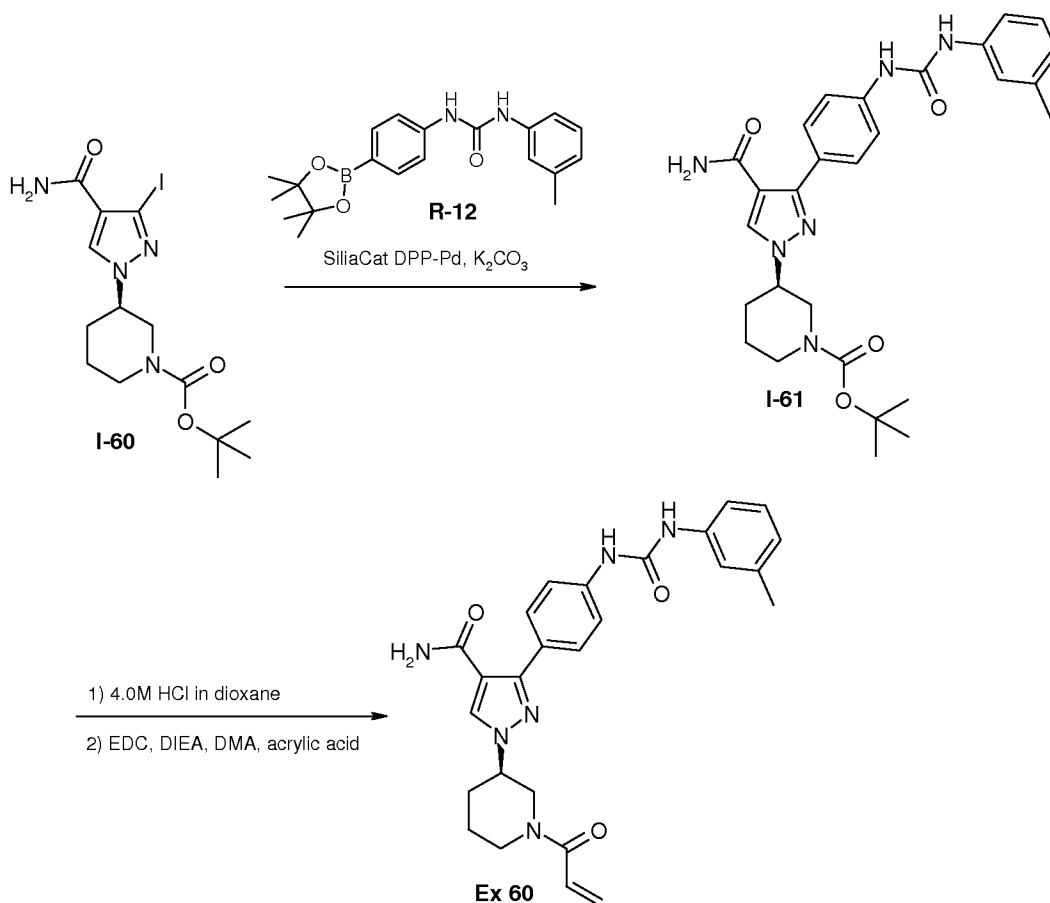
To a solution of **I-32** (100 mg, 0.26 mmol) in CH_2Cl_2 (2 mL) is added EDC (60 mg, 0.31 mmol) followed by acrylic acid (22 mg, 0.31 mmol). The mixture is stirred at ambient temperature for 1 h then directly purified by flash chromatography (SiO_2 , CH_2Cl_2 to 5% MeOH in CH_2Cl_2) to give example **40** (15 mg, 13%).

The following compounds were made in similar fashion:

Examples **86, 89** (**R-10** used instead of acrylic acid)

10 Method 21

Synthesis of Example 60



To a solution of **I-60** (43 mg, 0.10 mmol) in DME (2 mL) is added **R-12** (65 mg, 0.18 mmol), SiliaCat DPP-Pd (50 mg, 0.01 mmol), and potassium carbonate (500 mg). The mixture is heated at 140° C in a microwave for 2 h then concentrated in vacuo. The crude is purified by flash chromatography (SiO₂, 0 to 4% MeOH in CH₂Cl₂) to give **I-61** (38 mg, 72%) *m/z* 519.2 [M+H].

I-61 (38 mg, 0.073 mmol) is dissolved in CH₂Cl₂ (2 mL) and treated with 4.0M HCl in dioxane (3 mL). The mixture is stirred for 2 h at ambient temperature then volatiles are removed in vacuo. The residue is dissolved in CH₂Cl₂ (2 mL) and treated with acrylic acid (5 mg, 0.073 mmol) and EDC (14 mg, 0.073 mmol). The mixture is stirred for 1 h at

ambient temperature then partitioned between water and CH_2Cl_2 . The mixture is filtered through a phase separator® and organics are collected and concentrated in vacuo. The crude is purified by flash chromatography (SiO_2 , CH_2Cl_2 to 8% MeOH in CH_2Cl_2) to give example **60** (13 mg, 57%).

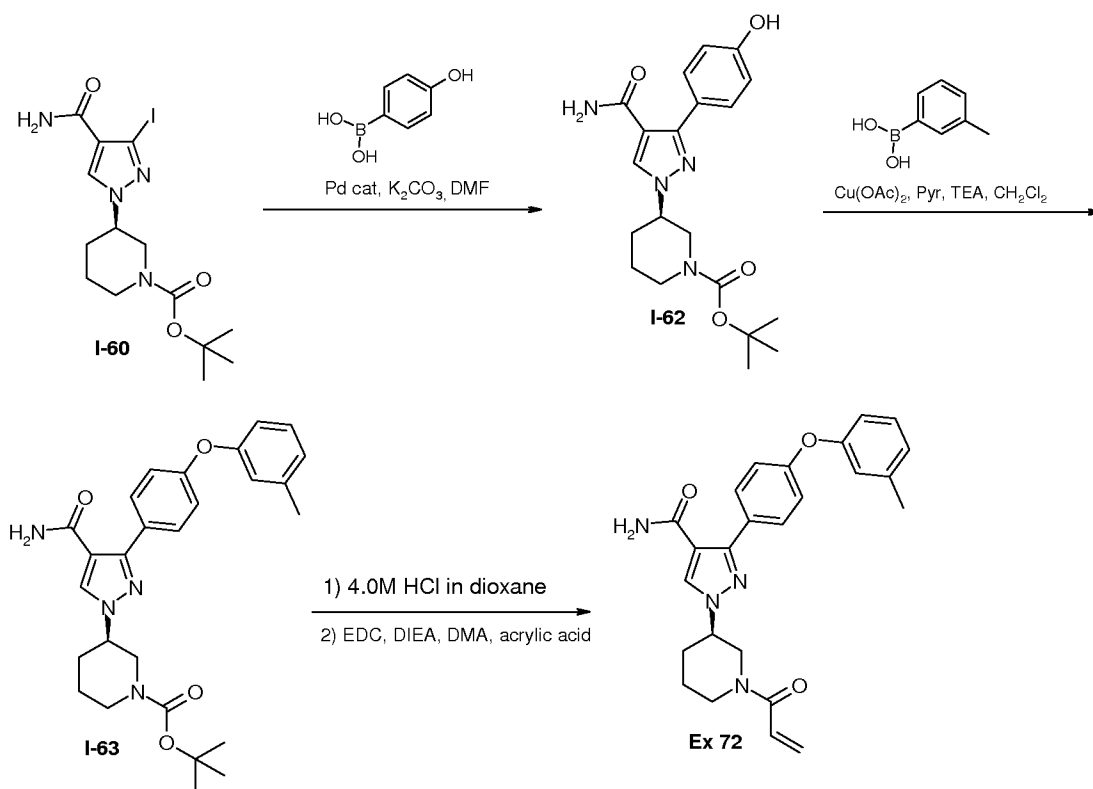
5

The following compound was made in similar fashion:

Example 61

Method 22

10 Synthesis of Example 72



A flask is charged with **I-60** (4.0 g, 9.5 mmol), 4-hydroxyphenylboronic acid (1.9 g, 14

mmol), bis(di-*tert*-butyl(4-dimethylaminophenyl)phosphine)dichloropalladium(II) (0.67 g, 0.95 mmol), potassium carbonate (2.5 g, 18 mmol) and treated with DMF (40 mL) and water (10 mL). The mixture is heated in the microwave at 140° C for 90 min. The mixture is cooled to ambient temperature then treated with saturated aqueous NH₄Cl, extracted with EtOAc, dried over Na₂SO₄, filtered, and concentrated in vacuo. The crude is purified by flash chromatography (SiO₂, 20 to 50% EtOAc in Hep) to give **I-62** (2.0 g, 54%) *m/z* [M+H].

To a solution of **I-62** (90 mg, 0.23 mmol) in CH₂Cl₂ (7 mL) is added 3-tolylboronic acid (95 mg, 0.70 mmol), Cu(OAc)₂ (300 mg), pyridine (1 mL), TEA (1 mL), and molecular sieves (4Å). The mixture is stirred at ambient temperature open to air for 12 h. The mixture was filtered through a silica gel pad and volatiles from the filtrate are removed in vacuo. The crude is purified by RHPLC to afford **I-63** (61 mg, 55%) *m/z* 477.1 [M+H].

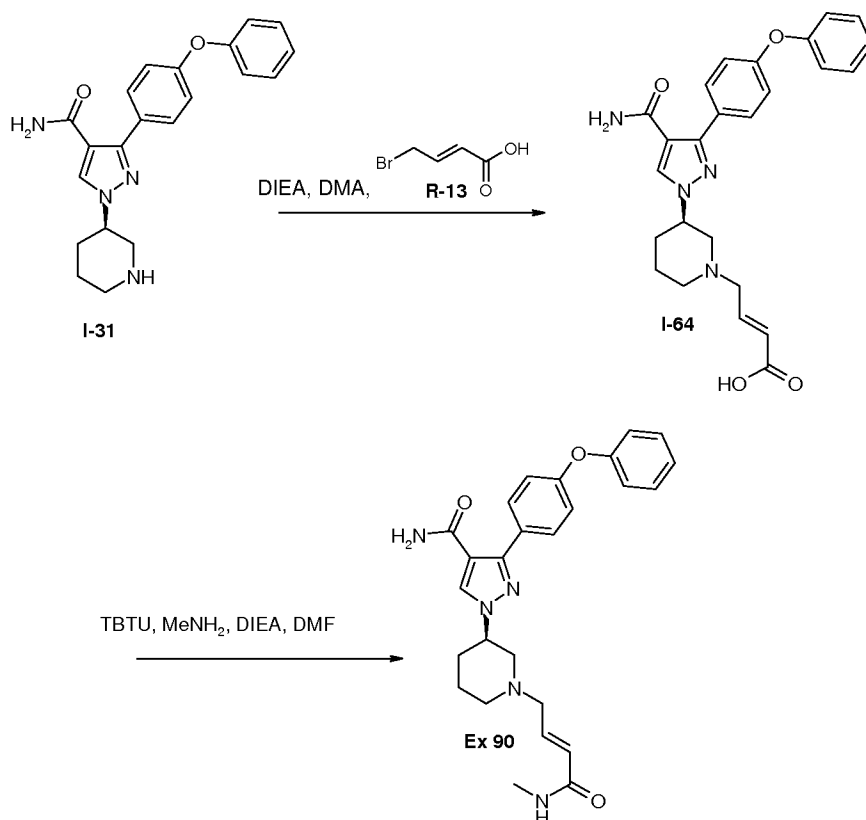
To a solution of **I-63** (55 mg, 0.115 mmol) in CH₂Cl₂ (3 mL) is added TFA (1 mL). The mixture is stirred at ambient temperature for 2 h then treated with saturated aqueous Na₂CO₃. The layers are separated and volatiles from the organics are removed in vacuo to afford a residue. The residue is dissolved in DMF (4 mL) and treated with acrylic acid (0.6 mL) and EDC (38 mg, 0.25 mmol). The mixture is stirred at ambient temperature 12 h then directly purified by RHPLC to give example **72** (17 mg, 34%).

The following compounds are prepared in similar fashion:

Examples **62-71, 73-76**

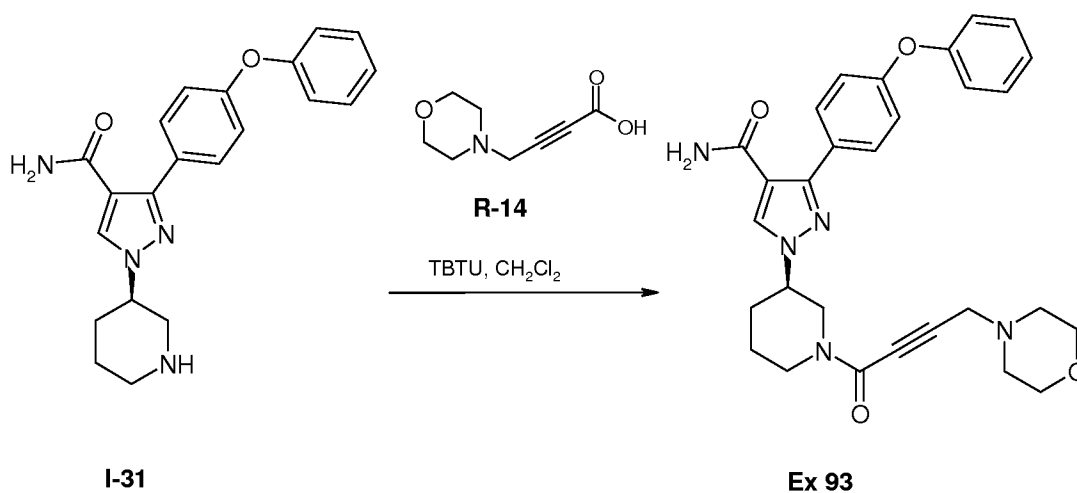
25 Method 23

Synthesis of Example 90



To a solution of **I-31** (0.20 g, 0.55 mmol) in DMA (3 mL) is added DIEA (0.15 mL, 0.86 mmol) and **R-13** (0.12 g, 0.71 mmol). The mixture is heated at 50 °C for 18 h then cooled to ambient temperature. The mixture is partitioned between water and EtOAc. The organics are collected, dried over Na₂SO₄, filtered, and concentrated in vacuo. The crude is purified by RHPLC to afford **I-64** (0.15 g, 62%) *m/z* 447.1 [M+H].

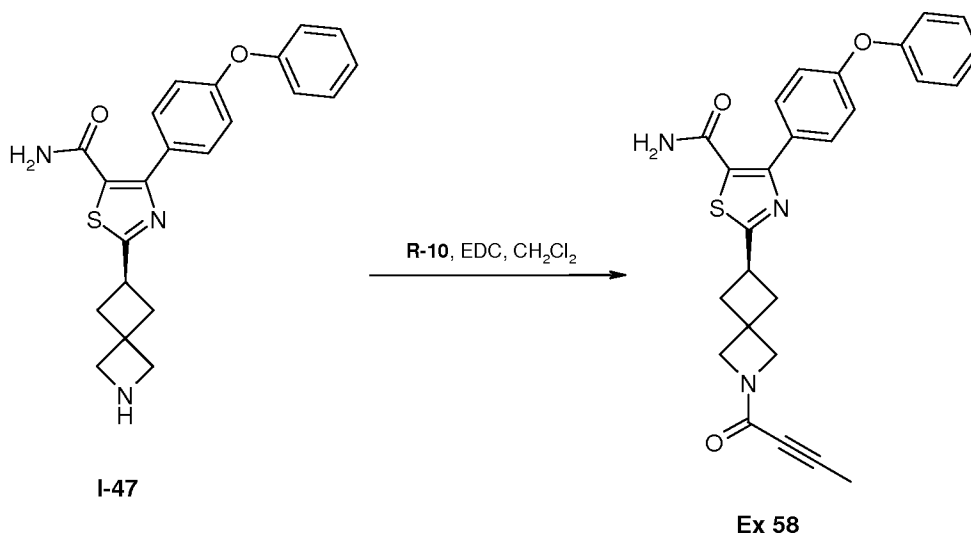
To a solution of **I-64** (70 mg, 0.16 mmol) in DMF (2 mL) is added TBTU (60 mg, 0.19 mmol) and DIEA (0.06 mL, 0.19 mmol). The mixture is stirred for 5 min then treated with a 2.0M solution of methylamine in THF (0.24 mL, 0.47 mmol). The mixture is stirred at ambient temperature for 16 h then treated with saturated aqueous ammonium chloride. The mixture is extracted with EtOAc, dried over Na₂SO₄, filtered, and concentrated in vacuo. The crude is purified by RHPLC to afford example **90** (7 mg, 10%).

Method 24**Synthesis of Example 93**

- 5 To a solution of **I-31** (100 mg, 0.28 mmol) in CH_2Cl_2 (5 mL) is added TBTU (91 mg, 0.28 mmol) and **R-14** (prepared according to *J. Med. Chem.* **2001**, 44, 2719-2734, 70 mg, 0.41 mmol). The mixture is stirred at ambient temperature over night then filtered and purified by flash chromatography (SiO_2 , CH_2Cl_2 to 10% MeOH with 1% ammonium hydroxide) to give example **93** (58 mg, 41%).

10

Method 25**Synthesis of Example 58**



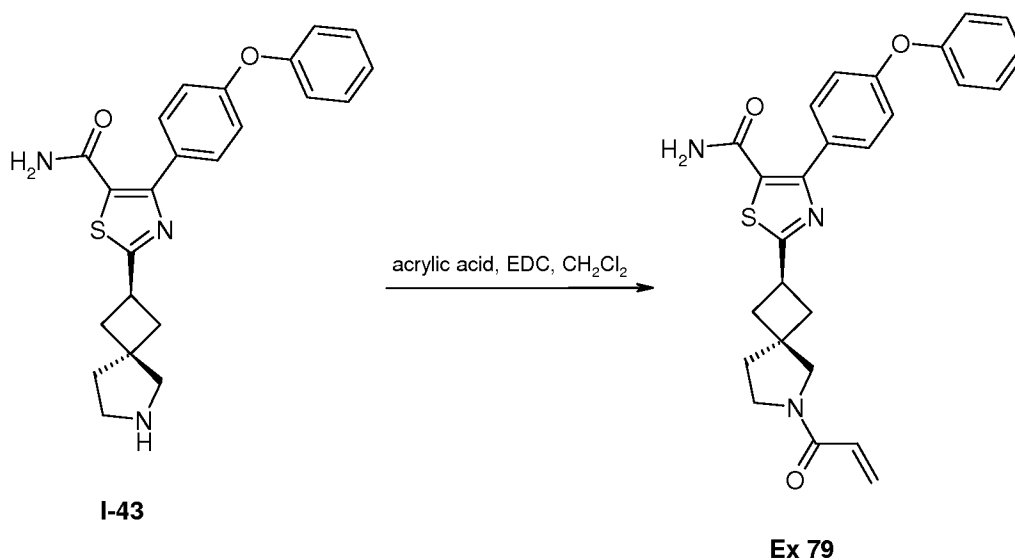
To a solution of **I-47** (29 mg, 0.074 mmol) in CH_2Cl_2 (2 mL) is added EDC (92 mg, 0.38 mmol) and **R-10** (20 mg, 0.24 mmol). The mixture is stirred at ambient temperature for 1 h then partitioned between water and CH_2Cl_2 . The mixture is filtered through a phase separator® and organics are collected and concentrated in vacuo. The crude is purified by flash chromatography (SiO_2 , 20 to 100% EtOAc in Hep) to give example **58** (23 mg, 68%).

The following compounds are made in similar fashion:

10 Examples **78, 85, 52, 53**

Method 26

Synthesis of Example 79



To a solution of **I-43** (65 mg, 0.16 mmol) in CH_2Cl_2 (2 mL) is added EDC (37 mg, 0.19 mmol) followed by acrylic acid (14 mg, 0.19 mmol). The mixture is stirred at ambient temperature for 1 h then directly purified by flash chromatography (SiO_2 , CH_2Cl_2 to 5% MeOH in CH_2Cl_2) to give example **79** (14 mg, 19%).

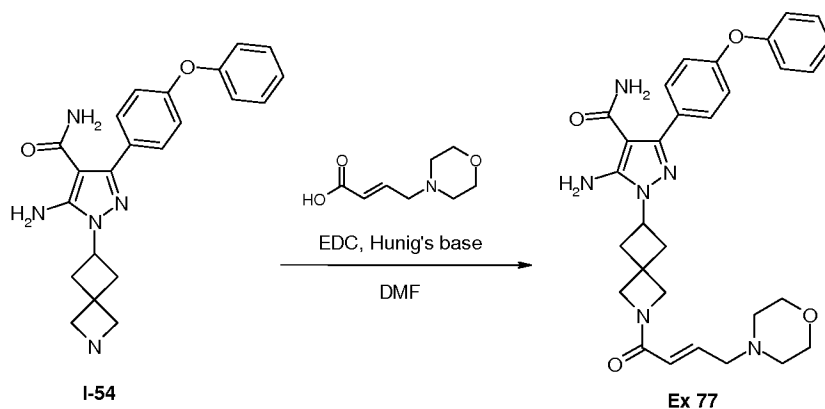
The following compounds were made in similar fashion:

Examples **34**, **50**, **51**, **57**, **84**

10

Method 27

Synthesis of Example 77



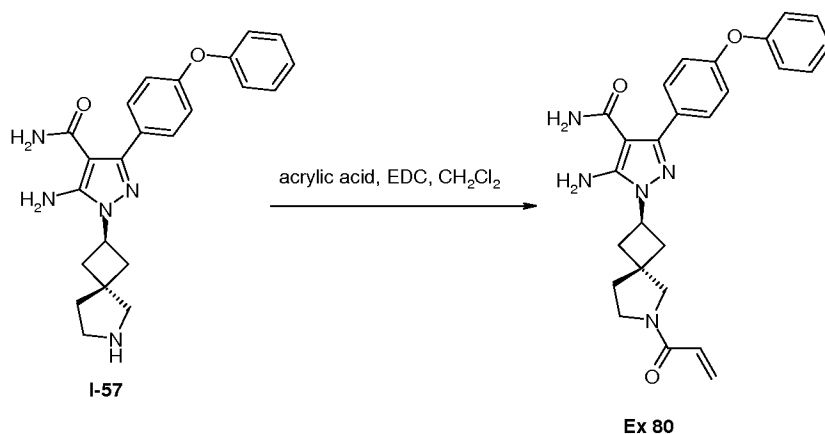
A solution of morpholine (35 mg, 0.4 mmol), (E)-4-bromo-but-2-enoic acid (79 mg, 0.48 mmol), and Hunig's base (0.21 mL, 1.2 mmol) in DMF (2 mL) is stirred for 18 h. To this mixture is added EDC (71 mg, 0.37 mmol). The mixture is stirred for 5 min then treated with **I-54** (120 mg, 0.31 mmol) and stirred for 18 h. Saturated aqueous ammonium chloride is added (4 mL) and mixture is extracted with EtOAc, dried over sodium sulphate, concentrated, and then purified by preparative TLC (SiO₂, 30% MeOH in EtOAc) to provide example **77** (64 mg, 38%).

The following compounds are made in similar fashion:

Examples **98-100**

Method 28

Synthesis of Example 80



To a solution of **I-57** (200 mg, 0.51 mmol) in DMF (2 mL) is treated with DIEA (150 mg, 1.1 mmol), EDC (130 mg, 0.67 mmol), followed by acrylic acid (0.05 mL, 0.67 mmol). The solution is stirred for 16 h then treated with saturated aqueous ammonium chloride. The mixture is extracted with EtOAc, dried over Na₂SO₄, filtered, and concentrated in vacuo. The crude is purified by flash chromatography (SiO₂, EtOAc to 10%MeOH in EtOAc) to afford example **80** (52 mg, 23%).

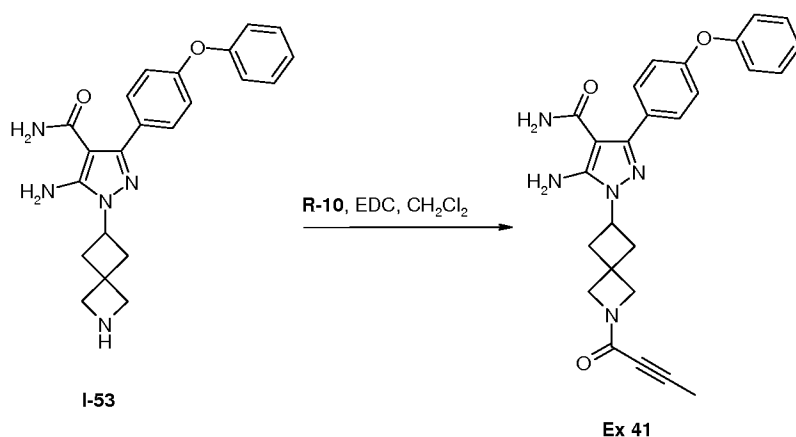
The following compounds are prepared in similar fashion:

Examples **35**, **44**, **54**, **81**, **82**

10

Method 29

Synthesis of Example 41



To a solution of **I-53** (100 mg, 0.26 mmol) in DMF (2 mL) is added EDC (54 mg, 0.28 mmol) and **R-10** (23 mg, 0.28 mmol). The mixture is stirred at ambient temperature for 16 h then partitioned between saturated aqueous ammonium chloride and EtOAc. The organics are collected, dried over Na₂SO₄, filtered, and concentrated. The crude is purified by flash chromatography (SiO₂, EtOAc to 10%MeOH in EtOAc) to give example **41** (24 mg, 21%).

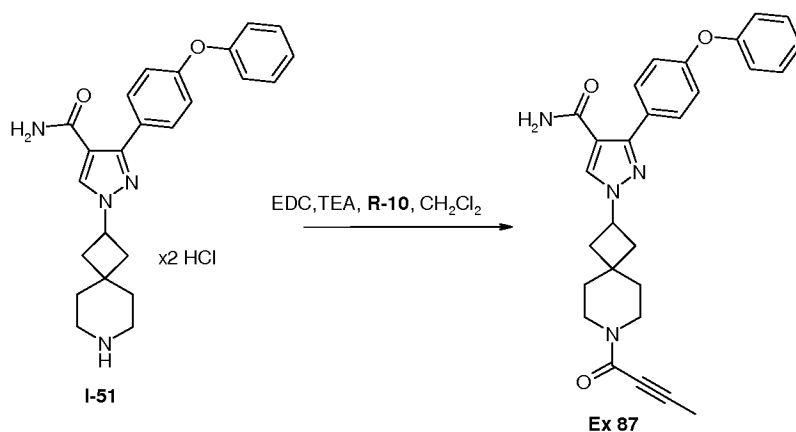
20

The following compounds are prepared in similar fashion:

Examples **83**, **91**, **92**

Method 30

5 Synthesis of Example 87



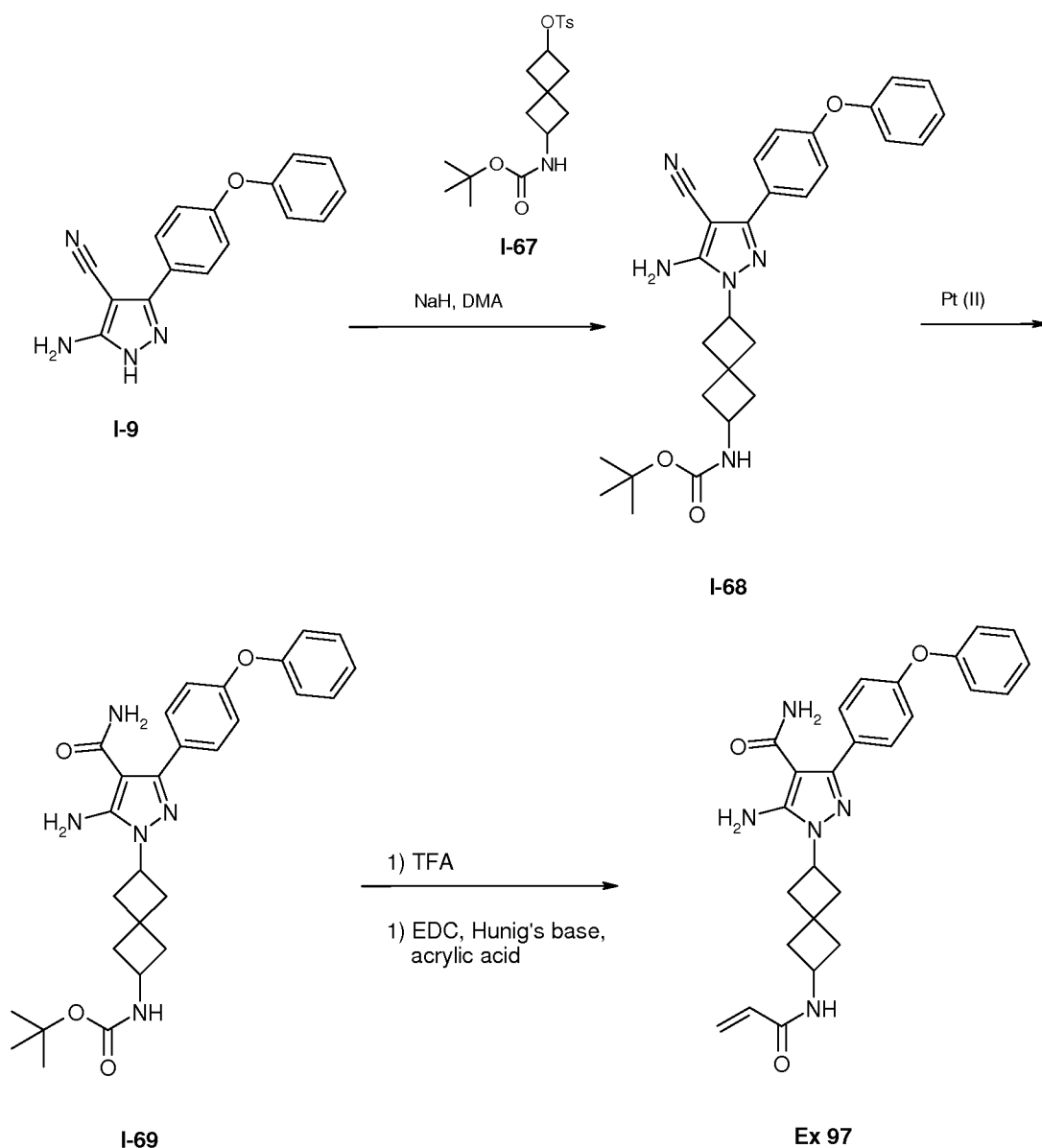
To a solution of the bis HCl salt of **I-51** (55 mg, 0.12 mmol) in CH_2Cl_2 (1.7 mL) is added TEA (29 mg, 0.29 mmol), EDC (34 mg, 0.17 mmol), and **R-10** (15 mg, 0.17 mmol). The mixture is stirred at ambient temperature for 2 h then partitioned between water and CH_2Cl_2 then filtered through a phase separator®. The organics are collected and concentrated in vacuo to afford a residue that is purified by flash chromatography (SiO_2 , CH_2Cl_2 to 45% MeOH in CH_2Cl_2) to afford example **87** (25 mg, 46%).

The following compounds were prepared in similar fashion:

15 Examples **59**, **46** (acrylic acid used instead of **R-10**)

Method 31

Synthesis of Example 97



To a suspension of NaH (60% dispersion in mineral oil, 160 mg, 4.0 mmol) in DMF (5 mL) is added **I-9** (0.93 g, 3.35 mmol). After 5 min of stirring, a solution of **I-67** (1.28 g, 3.35 mmol) in DMF (5 mL) is added. The mixture is heated at 70 °C overnight then cooled to ambient temperature and partitioned between EtOAc and water. The organics are collected and washed with water and brine, dried, and concentrated in vacuo. The crude is purified by flash chromatography (SiO₂, 0-70% EtOAc in Heptane) to afford **I-68**

5

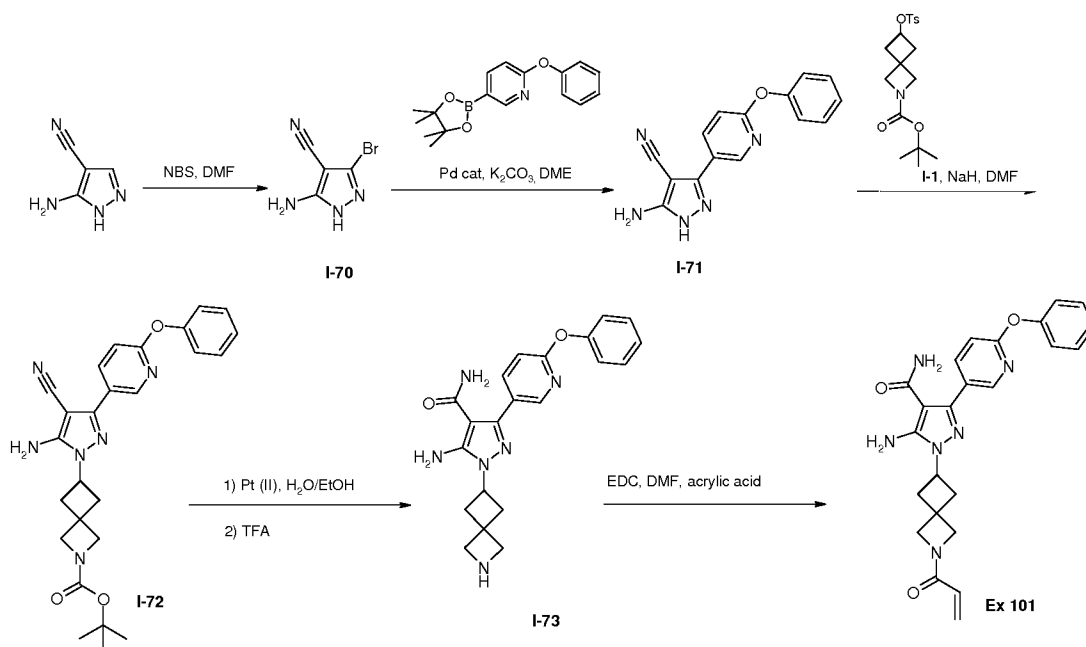
(0.59 g, 37%) m/z 486.7 [M+H].

I-68 (0.59 g, 1.22 mmol) is diluted with EtOH (1 mL) and water (0.5 mL) and Hydrido(dimethylphosphinous acid kP) [hydrogen bis(dimethylphosphinito-kP)] platinum (II) (0.07 g, 0.163 mmol) is added. The mixture is heated at 80 °C overnight then
5 concentrated in vacuo. The residue is dissolved in CH₂Cl₂ then filtered and concentrated to afford **I-69** (0.28 g, 45%) m/z 504.7 [M+H].

I-69 (50 mg, 0.1 mmol) is dissolved in CH₂Cl₂ (0.8 mL) and TFA (0.08 mL). The mixture is stirred for 3 h then partitioned between CH₂Cl₂ and aqueous saturated NaHCO₃. Organics are combined and concentrated to give a residue that is treated with a prestirred
10 (15 min) solution of acrylic acid (10 µL, 0.13 mmol), EDC (3.5 mg, 0.18 mmol), and Hunig's base (70 µL, 0.38 mmol) in DMF (1.0 mL). The mixture is stirred overnight then diluted with aqueous saturated ammonium chloride and extracted with EtOAc. The organics are combined, washed with brine, dried over Na₂SO₄, filtered, and concentrated in vacuo. The crude is purified by flash chromatography (SiO₂) to afford example **97** (5 mg,
15 88%).

Method 32

Synthesis of Example 101



To a solution of 3-amino-4-cyanopyrazole (100 g, 0.9 mol) in DMF (1 L) is added NBS (197.5 g, 1.1 mol) and mixture is stirred for 10 h at ambient temperature. The mixture is concentrated in vacuo then dissolved in EtOAc and washed with brine (8 x). The organics are collected and concentrated in vacuo to afford **I-70** (50 g, 29%) m/z 187.0 [M+].

A vial is charged with **I-70** (1.0 g, 5.35 mmol), 2-phenoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-pyridine (2.07 g, 6.95 mmol), tetrakis(triphenylphosphine) palladium (0) (0.62 g, 0.535 mmol) and dissolved in aqueous potassium carbonate (10 mL, 2.0 M) and DME (6 mL). The mixture is heated at 130 °C for 3 h in a microwave. The mixture is filtered then diluted with water, extracted with EtOAc, dried over sodium sulphate, filtered, and concentrated in vacuo. The residue is purified by flash chromatography (SiO₂, 0-100%EtOAc in heptanes) to give **I-71** (1.18 g, 80%) m/z 278.0 [M+H].

Sodium hydride (60% dispersion in mineral oil, 100 mg, 2.5 mmol) is added to a solution of **I-71** (530 mg, 1.9 mmol) in DMF (7.5 mL). The mixture is stirred for 5 min then treated with **I-1** (840 mg, 2.3 mmol) and heated at 70 °C for 18 h. The solution is cooled to

ambient temperature then partitioned between EtOAc and water. Organics are collected, dried, filtered, and concentrated in vacuo to afford a residue that is purified by flash chromatography (SiO₂, 0-100%EtOAc in heptanes) to give **I-72** (310 mg, 35%) *m/z* 473.2 [M+H].

- 5 **I-72** (0.31 g, 0.66 mmol) is diluted with EtOH (5 mL) and water (0.5 mL) and Hydrido(dimethylphosphinous acid kP) [hydrogen bis(dimethylphosphinito-kP)] platinum (II) (28 mg, 0.066 mmol) is added. The mixture is heated at 80 °C overnight then concentrated in vacuo. The residue is dissolved in CH₂Cl₂ then filtered and concentrated to afford a residue that is dissolved in TFA (5 mL) and stirred for 3 h at ambient temperature
- 10 then concentrated in vacuo. The residue is dissolved in MeOH and passed through an Agilent Stratospheres PL-HCO₃ MP SPE cartridge and concentrated in vacuo to afford **I-73** (0.25 g, 98%) *m/z* 391.2 [M+H].

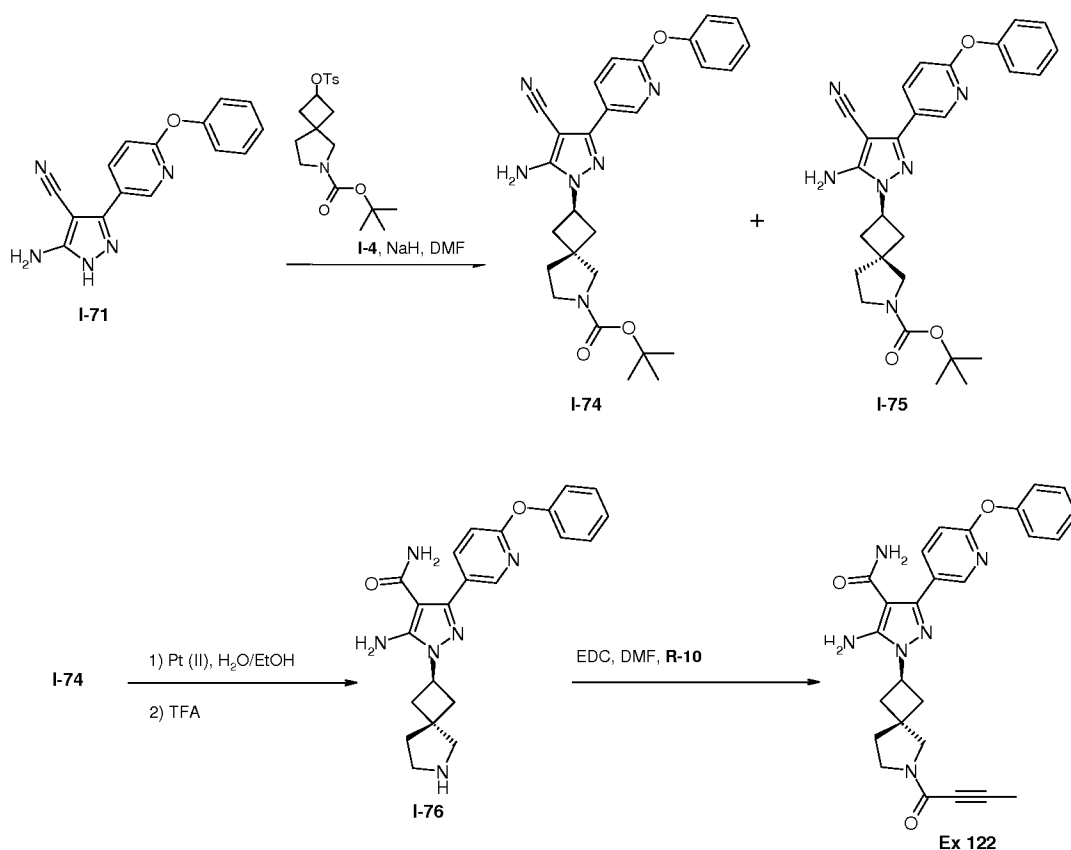
- I-73** (110 mg, 0.28 mmol) is treated with a prestirred (15 min) solution of acrylic acid (21 μL, 0.13 mmol) and EDC (65 mg, 0.34 mmol) in DMF (2.0 mL). The mixture is stirred
- 15 overnight then diluted with aqueous saturated ammonium chloride and extracted with EtOAc. The organics are combined, washed with brine, dried over Na₂SO₄, filtered, and concentrated in vacuo. The crude is purified by flash chromatography (SiO₂, 10%MeOH in EtOAc) to afford example **101** (32 mg, 26%).

The following compounds are made in similar fashion:

- 20 Examples **102-103, 110**

Method 33

Synthesis of Example 122



To a solution of **I-71** (1.1 g, 3.97 mmol) in DMF (20 mL) is added NaH (60% dispersion in mineral oil, 190 mg, 4.76 mmol). The mixture is stirred for 5 min then treated with **I-4** (1.82 g, 4.76 mmol) and heated at 70 °C for 18 h. The mixture is cooled then partitioned between EtOAc and water. Organics are collected, dried over Na₂SO₄, filtered, and concentrated in vacuo to give a residue that is purified by flash chromatography (SiO₂, 0-80% EtOAc in heptanes) to give **I-74** (520 mg, 27%) *m/z* 487.3 [M+H] and **I-75** (500 mg, 26%) *m/z* 487.3 [M+H].

I-74 (250 mg, 0.514 mmol) is diluted with EtOH (5 mL) and water (0.5 mL) and Hydrido(dimethylphosphinous acid kP) [hydrogen bis(dimethylphosphinito-kP)] platinum (II) (22 mg, 0.051 mmol) is added. The mixture is heated at 80 °C overnight then concentrated in vacuo. The residue is dissolved in CH₂Cl₂ then filtered and concentrated to afford a residue that is dissolved in TFA (5 mL) and stirred for 3 h at ambient temperature

then concentrated in vacuo. The residue is dissolved in MeOH and passed through an Agilent Stratospheres PL-HCO₃ MP SPE cartridge and concentrated in vacuo to afford **I-76** (0.206 g, 98%) *m/z* 405.3 [M+H].

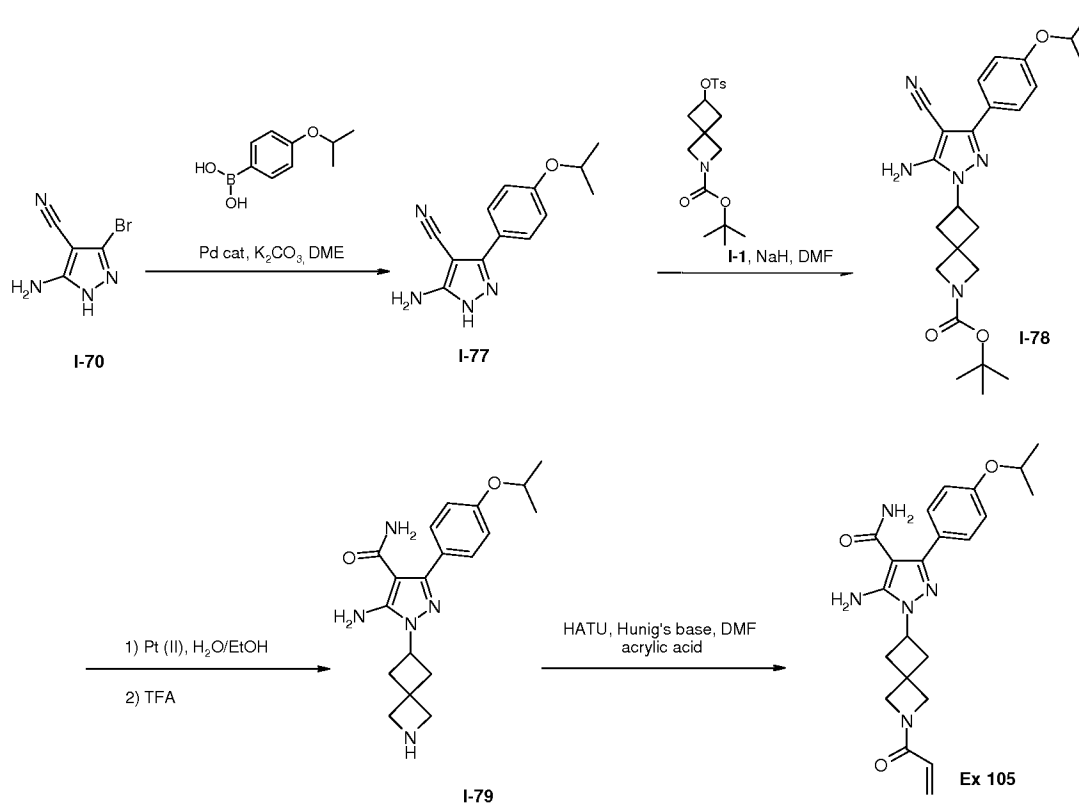
I-76 (254 mg, 0.63 mmol) is treated with a prestirred (15 min) solution of **R-10** (69 mg, 0.82 mmol) and EDC (144 mg, 0.75 mmol) in DMF (2.0 mL). The mixture is stirred overnight then diluted with aqueous saturated ammonium chloride and extracted with EtOAc. The organics are combined, washed with brine, dried over Na₂SO₄, filtered, and concentrated in vacuo. The crude is purified by flash chromatography (SiO₂, 10%MeOH in EtOAc) to afford example **122** (48 mg, 16%).

10 The following compounds are made in similar fashion:

Examples **114**, **117-120**, **123**, **150-152**

Method 34

Synthesis of Example 104



A vial is charged with **I-70** (0.50 g, 2.67 mmol), 4-isopropoxyboronic acid (0.58 g, 3.21 mmol), tetrakis(triphenylphosphine) palladium (0) (0.43 g, 0.37 mmol) and dissolved in aqueous potassium carbonate (4 mL, 2.0 M) and DME (3 mL). The mixture is heated at 130 °C for 3 h in a microwave. The mixture is filtered then diluted with water, extracted with EtOAc, dried over sodium sulphate, filtered, and concentrated in vacuo. The residue is purified by flash chromatography (SiO_2 , 0-80%EtOAc in heptanes) to give **I-77** (0.473 g, 73%) m/z 243.5 [M+H].

Sodium hydride (60% dispersion in mineral oil, 55 mg, 1.37 mmol) is added to a solution of **I-77** (300 mg, 1.24 mmol) in DMF (5 mL). The mixture is stirred for 5 min then treated with **I-1** (550 mg, 1.47 mmol) and heated at 70 °C for 18 h. The solution is cooled to ambient temperature then partitioned between EtOAc and water. Organics are collected, dried, filtered, and concentrated in vacuo to afford a residue that is purified by flash chromatography (SiO_2 , 0-100%EtOAc in heptanes) to give **I-78** (200 mg, 37%) m/z 438.6

[M+H].

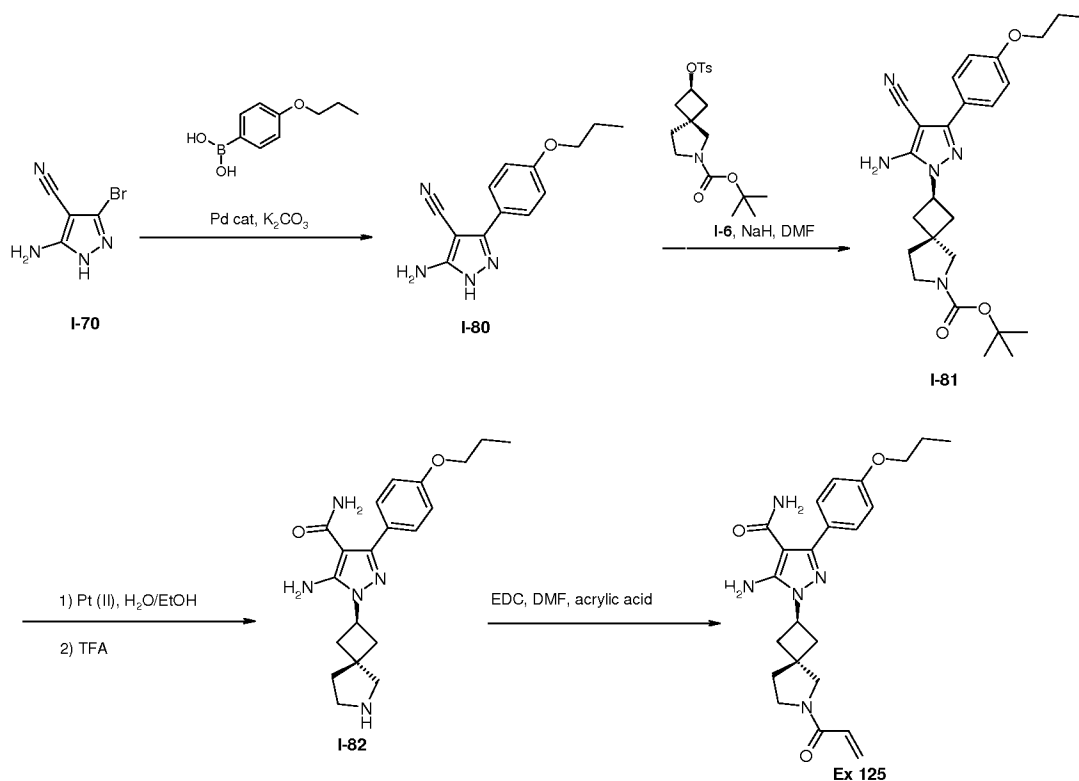
I-78 (190 mg, 0.43 mmol) is diluted with EtOH (4 mL) and water (2 mL) and Hydrido(dimethylphosphinous acid kP) [hydrogen bis(dimethylphosphinito-kP)] platinum (II) (11 mg, 0.026 mmol) is added. The mixture is heated at 80 °C overnight then concentrated in vacuo. The residue is dissolved in CH₂Cl₂ then filtered and concentrated to afford a residue that is dissolved in CH₂Cl₂ (5 mL) and TFA (1 mL) and stirred overnight at ambient temperature then concentrated in vacuo. The residue is dissolved in MeOH and passed through an Agilent Stratospheres PL-HCO₃ MP SPE cartridge and concentrated in vacuo to afford **I-79** (110 mg, 71%).

I-79 (40 mg, 0.11 mmol) and acrylic acid (10 mg, 0.14 mmol) in DMF (5 mL) is treated with HATU (88 mg, 0.17 mmol) and Hunig's base (60 µL, 0.34 mmol) in DMF (2.0 mL). The mixture is stirred overnight then concentrated in vacuo. The crude is purified by RHPLC to afford example **105** (25 mg, 54%).

The following compounds are made in similar fashion:

Examples **104**, **106-109**, **111-113**, **115-116**, **124**, **133**, **134-136**, **138-139**, **141-144**, **147-149**, **166**

Method 35



A vial is charged with **I-70** (0.45 g, 2.41 mmol), 4-*n*-propoxyboronic acid (0.48 g, 2.65 mmol), tetrakis(triphenylphosphine) palladium (0) (0.28 g, 0.24 mmol) and dissolved in aqueous potassium carbonate (4.8 mL, 2.0 M) and dioxane (2 mL). The mixture is heated at 130 °C overnight. The mixture is filtered then diluted with water, extracted with EtOAc, dried over sodium sulphate, filtered, and concentrated in vacuo. The residue is purified by flash chromatography (SiO₂, 0-6% MeOH in CH₂Cl₂) to give **I-80** (0.400 g, 69%) *m/z* 242.4 [M⁺].

Sodium hydride (60% dispersion in mineral oil, 33 mg, 0.82 mmol) is added to a solution of **I-80** (200 mg, 0.74 mmol) in DMF (5 mL). The mixture is stirred for 5 min then treated with **I-6** (318 mg, 0.82 mmol) and heated at 70 °C for 18 h. The mixture is concentrated in vacuo and purified by flash chromatography (SiO₂, 35% EtOAc in heptanes) to give **I-81** (130 mg, 39%) *m/z* 452.9 [M+H].

I-81 (130 mg, 0.29 mmol) is diluted with EtOH (1.5 mL) and water (0.5 mL) and

Hydrido(dimethylphosphinous acid kP) [hydrogen bis(dimethylphosphinito-kP)] platinum (II) (13 mg, 0.029 mmol) is added. The mixture is heated at 80 °C overnight then concentrated in vacuo. The residue is dissolved in EtOAc then filtered and concentrated to afford a residue that is dissolved in CH₂Cl₂ (1 mL) and TFA (1 mL) and stirred for 1 h at
5 ambient temperature then concentrated in vacuo. The residue is dissolved in MeOH and passed through an Agilent Stratospheres PL-HCO₃ MP SPE cartridge and concentrated in vacuo to afford **I-82** (80 mg, 84%).

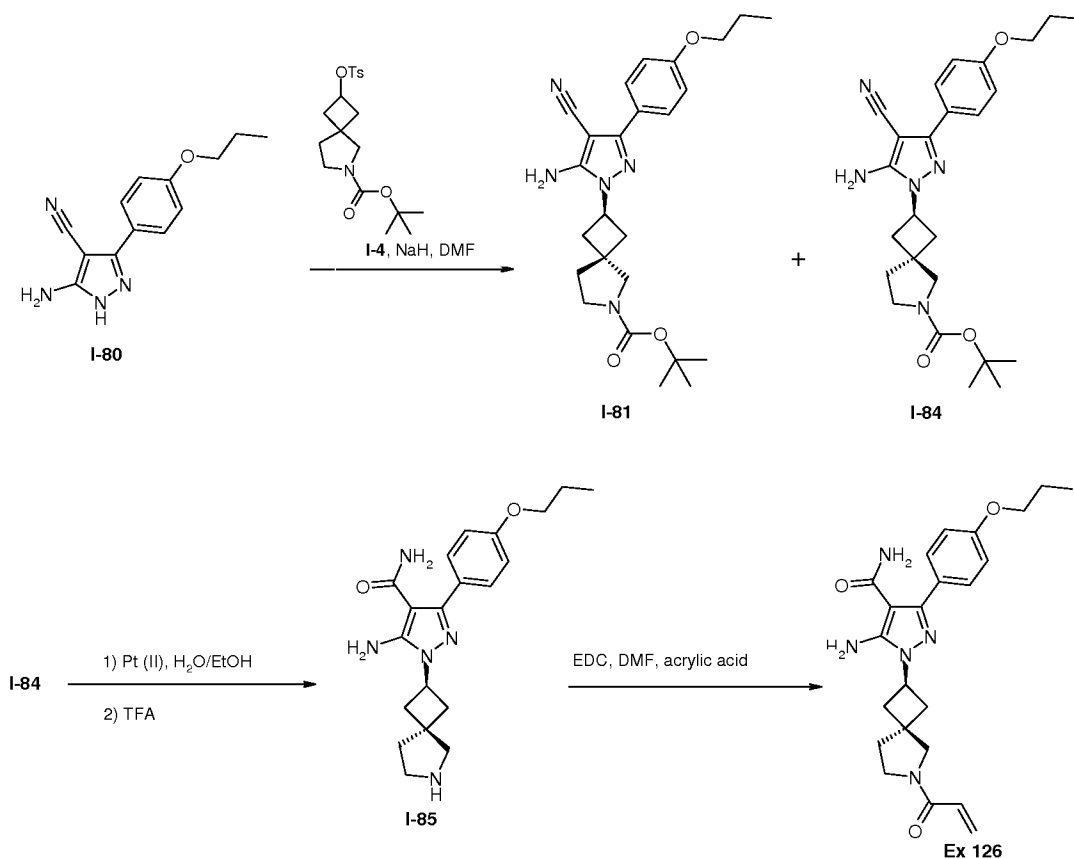
I-82 (130 mg, 0.35 mmol) is treated with a prestirred (15 min) solution of acrylic acid (30 mg, 0.42 mmol) and EDC (81 mg, 0.42 mmol) in DMF (2.0 mL). The mixture is stirred
10 overnight then diluted with aqueous saturated ammonium chloride and extracted with EtOAc. The organics are combined, dried over Na₂SO₄, filtered, and concentrated in vacuo. The crude is purified by RHPLC to afford example **125** (30 mg, 20%).

The following compounds are made in similar fashion:

Examples **130, 132, 145-146, 153, 155-156, 159, 162-163, 165**

15 **Method 36**

Synthesis of Example 126



Sodium hydride (60% dispersion in mineral oil, 80 mg, 2.02 mmol) is added to a solution of **I-80** (445 mg, 1.84 mmol) in DMF (5 mL). The mixture is stirred for 5 min then treated with **I-4** (770 mg, 2.02 mmol) and heated at 70 °C for 18 h. The mixture is diluted with saturated aqueous ammonium chloride, extracted with EtOAc, dried over Na₂SO₄, filtered, and concentrated in vacuo. The residue is purified by flash chromatography (SiO₂, 0-6% MeOH in CH₂Cl₂) to give **I-81** (200 mg, 24%) and **I-84** (300 mg, 36%) *m/z* 452.5 [M+H].

I-84 (300 mg, 0.66 mmol) is diluted with EtOH (1.5 mL) and water (0.5 mL) and Hydrido(dimethylphosphinous acid kP) [hydrogen bis(dimethylphosphinito-kP)] platinum (II) (28 mg, 0.066 mmol) is added. The mixture is heated at 80 °C for 72 h then concentrated in vacuo. The residue is dissolved in EtOAc then filtered and concentrated to afford a residue that is dissolved in CH₂Cl₂ (1 mL) and TFA (1 mL) and stirred for 1 h at

ambient temperature then concentrated in vacuo. The residue is dissolved in MeOH and passed through an Agilent Stratospheres PL-HCO₃ MP SPE cartridge and concentrated in vacuo to afford **I-85** (270 mg).

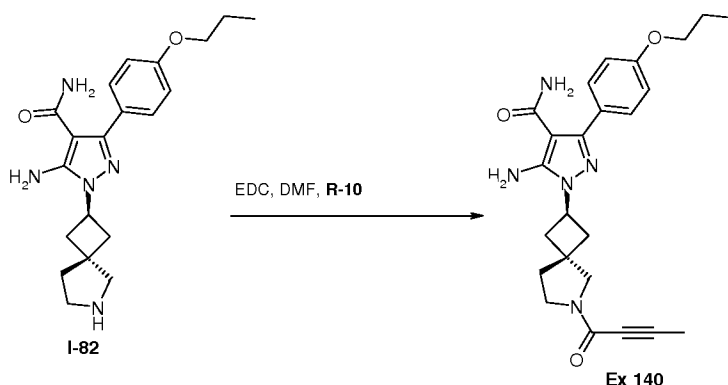
I-85 (80 mg, 0.22 mmol) is treated with a prestirred (15 min) solution of acrylic acid (19 mg, 0.26 mmol) and EDC (50 mg, 0.26 mmol) in DMF (2.0 mL). The mixture is stirred overnight then diluted with aqueous saturated ammonium chloride and extracted with EtOAc. The organics are combined, dried over Na₂SO₄, filtered, and concentrated in vacuo. The crude is purified by RHPLC to afford example **126** (7 mg, 8%).

The following compounds are made in similar fashion:

10 Examples **131**

Method **37**

Synthesis of Example **140**



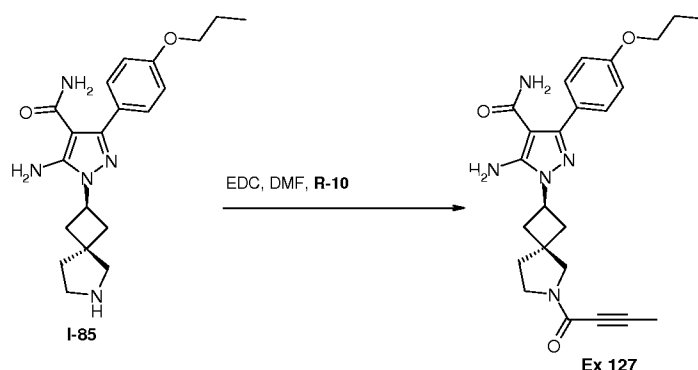
I-82 (80 mg, 0.22 mmol) is treated with a prestirred (15 min) solution of **R-10** (24 mg, 0.28 mmol) and EDC (50 mg, 0.26 mmol) in DMF (2.0 mL). The mixture is stirred overnight then diluted with aqueous saturated ammonium chloride and extracted with EtOAc. The organics are combined, dried over Na₂SO₄, filtered, and concentrated in vacuo. The crude is purified by RHPLC to afford example **140** (14 mg, 15%).

The following compounds are made in similar fashion:

Example **128**, **137**, **154**, **157-158**, **160-161**, **164**, **167-168**

Method 38

Synthesis of Example 127



5

I-85 (70 mg, 0.19 mmol) is treated with a prestirred (15 min) solution of **R-10** (21 mg, 0.25 mmol) and EDC (44 mg, 0.23 mmol) in DMF (2.0 mL). The mixture is stirred overnight then diluted with aqueous saturated ammonium chloride and extracted with EtOAc. The organics are combined, dried over Na₂SO₄, filtered, and concentrated in vacuo. The crude is purified by RHPLC to afford example **127** (13 mg, 16%).

10

The following compounds are made in similar fashion:

Example **129**

Description of Biological Properties

BTK Assay

15 An HTRF assay (Cisbio KinEASE-TK cat # 62TK0PEC) was performed to quantitate the ability of test compounds to inhibit BTK mediated phosphorylation of substrate. Assays were assembled in 384 well plates where 6nM of full-length human His-tagged BTK (Life

Technologies cat # PV3587) and test compound at varying concentrations were preincubated for 15 minutes at 28°C. Then, 1uM of TK substrate-biotin and 30uM ATP were added and incubated for an additional 30 minutes at 28°C. Phosphorylation was detected by adding 62.5nM Streptavidin-XL665 and TK-Antibody Cryptate diluted 1:100
 5 in HTRF detection buffer (Cisbio cat # 62SDBRDF) and incubated for 60 minutes at RT. The plate was read on an Envision plate reader and the fluorescence is measured at 620nm (cryptate) and 665nm (XL665). A ratio is calculated (665/620) and converted to POC relative to control and blank wells.

Assay buffer:

10 50mM HEPES (Invitrogen #15630), 0.01% Brij-35 (sigma #B4184), 10mM MgCl₂ (Sigma M1028), 1mM EGTA (Ambion AM9262) and 100uM sodium orthovanadate (Sigma S6508), 1mM DTT (Sigma D5545) and 10nM supplement enzyme buffer (Cisbio cat# 61SEBALB).

15 Preferred compounds for the treatment of autoimmune disorders exhibit selective inhibition of BTK over other kinases such as EGFR. The compounds described herein show a range of selectivities against EGFR as measured in cellular assays (BTK activity measured by CD69 expression in primary CD19⁺ cells; EGFR activity measured by EGFR phosphorylation in A431 cells). See Table II.

20

Table II

Example	B-cell CD69 IC₅₀ (nM)	A431 p-EGFR IC₅₀ (nM)
54	1.2	6.6
46	2.0	120
161	2.1	400
164	1.5	420
41	1	430
81	0.9	790
160	4.5	1200
78	2.5	1800

165	10	3700
107	8.2	4200
28	9	4700
163	15	5200
112	41	5800
113	24	6300
115	7.8	6400
40	20	>10000
106	30	>10000
158	58	>10000

Inhibition of B-cell activation measured by CD69 expression

Primary CD19⁺ cells were purified from healthy frozen peripheral blood mononuclear cells (AllCells, Emeryville, CA) and negatively selected by magnetic separation, >97% purity (Stemcell Technologies, Vancouver, CA). Cells were collected and plated in a 96 flat bottom plate at a concentration of 2×10^5 /well in RPMI media containing 10% FBS, rested for 1 hour at 37°C. Cells were treated with inhibitor in duplicates or vehicle control in 1% DMSO final concentration for 1 hour at 37°C, 5% CO₂. Cells were then stimulated with 12.5ug/ml Goat F(ab')₂ anti-human IgD (SouthernBiotech, Birmingham, AL) for 18-24 hours at 37 °C, 5% CO₂. Cells were collected and stained for APC-CD19, clone HIB19 and PE-CD69, clone FN50 (antibodies purchased from BD Bioscience, San Jose, CA). B cells were analyzed by flow cytometry using a BD LSRII or BD FACsCanto Flow Cytometer. Viable cells were gated, and CD69 percentage was determined using FlowJo software.

15

Inhibition of EGFR autophosphorylation in A431 human epithelial cells stimulated with epithelial growth factor

A431cells (ATCC # CRL-1555 FZ) are thawed and plated in DMEM containing 10% FBS in a 384-well tissue culture treated plate at 15,000 cells/well. After incubating for 24 hours

at 37 °C, 5 % CO₂, the cells are treated with test compound (1% DMSO final concentration) and incubated for 16 hours at 37 °C, 5 % CO₂. EGF (Millipore, 01-107) is added at a final concentration of 60 ng/mL and incubated for 10 minutes. The medium is removed, the cells are lysed, and phospho EGFR is measured (Meso Scale Diagnostics, N31CB-1).

Therapeutic Use

On the basis of their biological properties the compounds of formula (I) according to the invention, or their tautomers, racemates, enantiomers, diastereomers, mixtures thereof and the salts of all the above-mentioned forms are suitable for treating autoimmune and allergic disorders in that they exhibit good inhibitory effect upon BTK.

Such diseases include for example: rheumatoid arthritis, systemic lupus erythematosus, scleroderma, asthma, allergic rhinitis, allergic eczema, B cell lymphoma, multiple sclerosis, juvenile rheumatoid arthritis, juvenile idiopathic arthritis, inflammatory bowel disease, graft versus host disease, psoriatic arthritis, ankylosing spondylitis and uveitis.

The compounds of formula (I) may be used on their own or in combination with other active substances according to the invention, optionally also in combination with other pharmacologically active substances.

Suitable preparations include for example tablets, capsules, suppositories, solutions – particularly solutions for injection (s.c., i.v., i.m.) and infusion – elixirs, emulsions or dispersible powders. The content of the pharmaceutically active compound(s) should be in the range from 0.1 to 90 wt.-%, preferably 0.5 to 50 wt.-% of the composition as a whole, *i.e.* in amounts which are sufficient to achieve the dosage range specified below. The doses specified may, if necessary, be given several times a day.

Suitable tablets may be obtained, for example, by mixing the active substance(s) with known excipients, for example inert diluents such as calcium carbonate, calcium phosphate or lactose, disintegrants such as corn starch or alginic acid, binders such as starch or
5 gelatine, lubricants such as magnesium stearate or talc and/or agents for delaying release, such as carboxymethyl cellulose, cellulose acetate phthalate, or polyvinyl acetate. The tablets may also comprise several layers.

Coated tablets may be prepared accordingly by coating cores produced analogously to the
10 tablets with substances normally used for tablet coatings, for example collidone or shellac, gum arabic, talc, titanium dioxide or sugar. To achieve delayed release or prevent incompatibilities the core may also consist of a number of layers. Similarly the tablet coating may consist of a number of layers to achieve delayed release, possibly using the excipients mentioned above for the tablets.

15

Syrups or elixirs containing the active substances or combinations thereof according to the invention may additionally contain a sweetener such as saccharine, cyclamate, glycerol or sugar and a flavour enhancer, *e.g.* a flavouring such as vanillin or orange extract. They may also contain suspension adjuvants or thickeners such as sodium carboxymethyl
20 cellulose, wetting agents such as, for example, condensation products of fatty alcohols with ethylene oxide, or preservatives such as p-hydroxybenzoates.

Solutions for injection and infusion are prepared in the usual way, *e.g.* with the addition of isotonic agents, preservatives such as p-hydroxybenzoates, or stabilisers such as alkali
25 metal salts of ethylenediamine tetraacetic acid, optionally using emulsifiers and/or dispersants, whilst if water is used as the diluent, for example, organic solvents may optionally be used as solvating agents or dissolving aids, and transferred into injection vials or ampoules or infusion bottles.

Capsules containing one or more active substances or combinations of active substances may for example be prepared by mixing the active substances with inert carriers such as lactose or sorbitol and packing them into gelatine capsules.

- 5 Suitable suppositories may be made for example by mixing with carriers provided for this purpose such as neutral fats or polyethyleneglycol or the derivatives thereof.

Excipients which may be used include, for example, water, pharmaceutically acceptable organic solvents such as paraffins (*e.g.* petroleum fractions), vegetable oils (*e.g.* groundnut
10 or sesame oil), mono- or polyfunctional alcohols (*e.g.* ethanol or glycerol), carriers such as *e.g.* natural mineral powders (*e.g.* kaolins, clays, talc, chalk), synthetic mineral powders (*e.g.* highly dispersed silicic acid and silicates), sugars (*e.g.* cane sugar, lactose and glucose), emulsifiers (*e.g.* lignin, spent sulphite liquors, methylcellulose, starch and polyvinylpyrrolidone) and lubricants (*e.g.* magnesium stearate, talc, stearic acid and
15 sodium lauryl sulphate).

The preparations are administered by the usual methods, preferably by oral or transdermal route, most preferably by oral route. For oral administration the tablets may of course contain, apart from the above-mentioned carriers, additives such as sodium citrate, calcium
20 carbonate and dicalcium phosphate together with various additives such as starch, preferably potato starch, gelatine and the like. Moreover, lubricants such as magnesium stearate, sodium lauryl sulphate and talc may be used at the same time for the tableting process. In the case of aqueous suspensions the active substances may be combined with various flavour enhancers or colourings in addition to the excipients mentioned above.

25

For parenteral use, solutions of the active substances with suitable liquid carriers may be used.

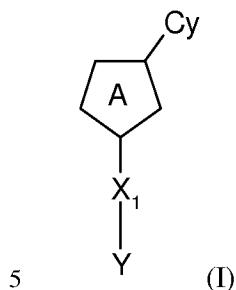
The dosage for intravenous use is from 1 – 1000 mg per hour, preferably between 5 and 500 mg per hour.

However, it may sometimes be necessary to depart from the amounts specified, depending
5 on the body weight, the route of administration, the individual response to the drug, the
nature of its formulation and the time or interval over which the drug is administered.
Thus, in some cases it may be sufficient to use less than the minimum dose given above,
whereas in other cases the upper limit may have to be exceeded. When administering large
amounts it may be advisable to divide them up into a number of smaller doses spread over
10 the day.

All patent and non-patent documents or literature cited in this application are herein
incorporated by reference in their entirety.

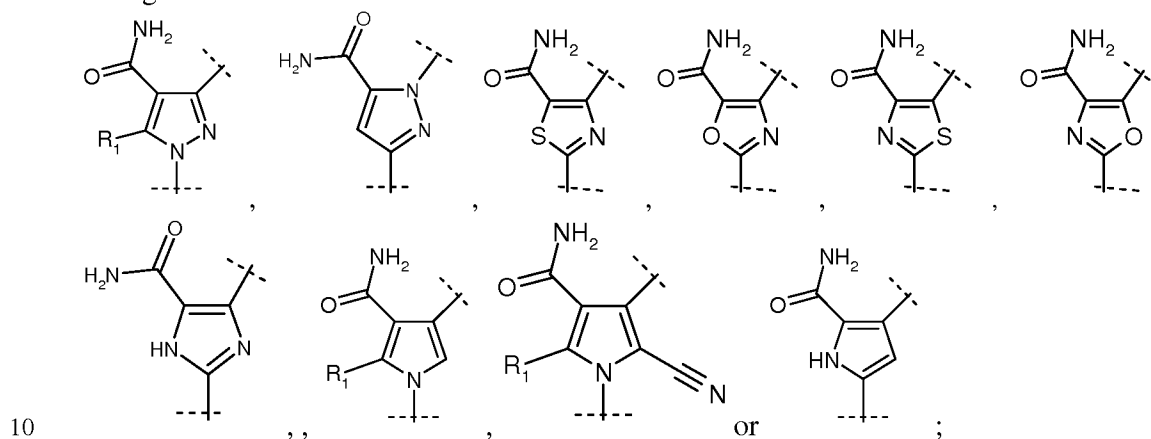
Claims

1. A compound of the formula (I)



wherein

A ring is:



R_1 is $N(R_3)_2$ or hydrogen;

Cy is aryl or heteroaryl each is substituted by R_2 and optionally substituted by halogen, halo C_{1-4} alkyl, C_{1-4} alkyl and C_{1-4} alkoxy;

R_2 is chosen from:

15 L-Ar, C_{1-6} alkyl and C_{1-6} alkoxy, each Ar, C_{1-6} alkyl and C_{1-6} alkoxy are optionally substituted by halogen, halo C_{1-4} alkyl, C_{1-4} alkyl, $R_3-S(O)_m$ -, -CN, -C(O)- $N(R_3)_2$ or C_{1-4} alkoxy;

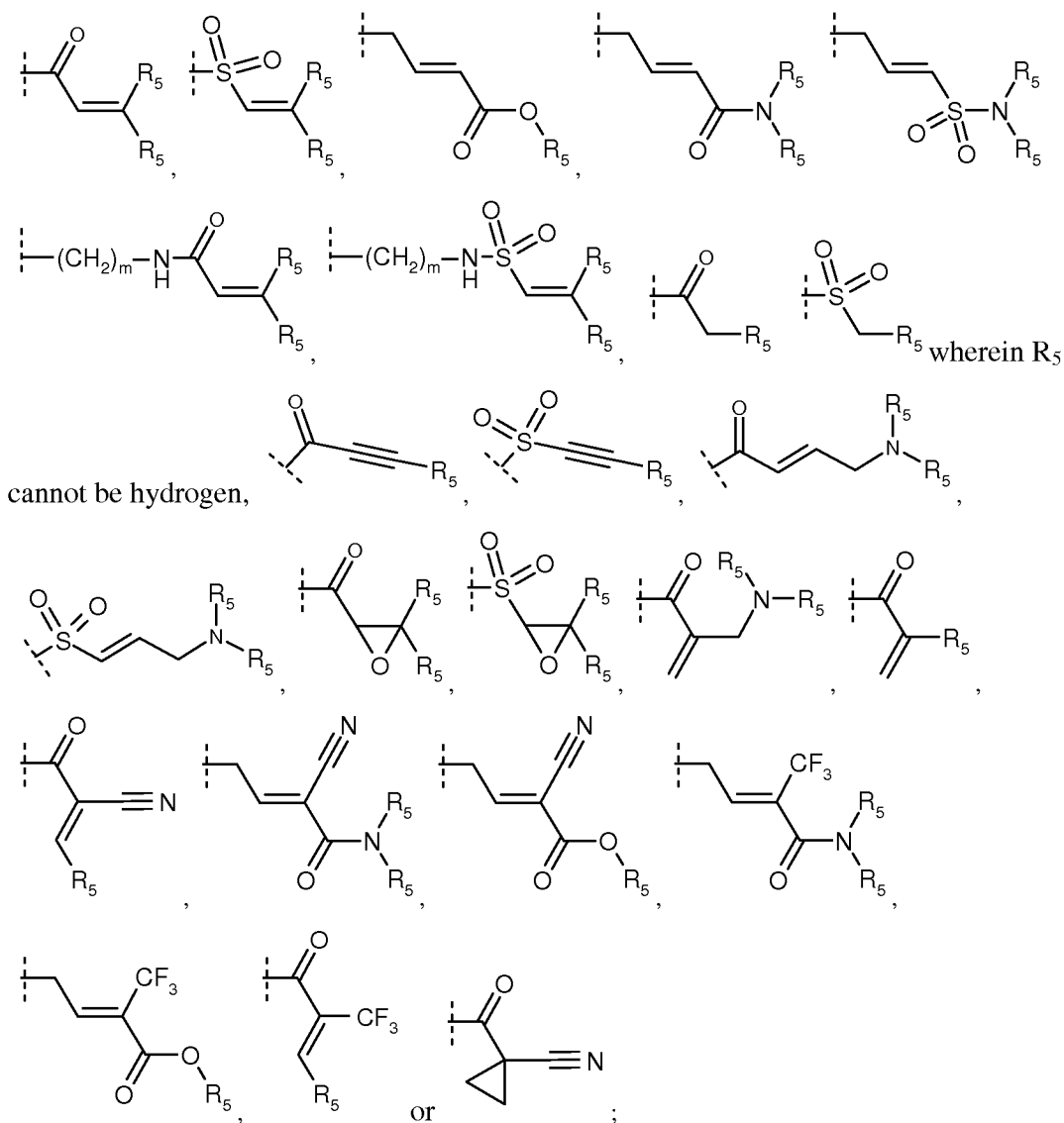
L is a linker chosen from a bond, O, $>C(O)$ -, $-(CH_2)_n$ -, $-O-(CH_2)_n$ -, $-N(R_3)$ -, $-N(R_3)-(CH_2)_n$ -, $-(CH_2)_n-N(R_3)$ -, $-C(O)-N(R_3)$ -, $-C(O)-N(R_3)-(CH_2)_n$ -, $-N(R_3)-C(O)-N(R_3)$ -, $-N(R_3)-C(O)$ -,
 20 $-S(O)_m-N(R_3)$ - and $-N(R_3)-S(O)_m$ -, wherein the $-CH_2-$ in each L can have 1-2 hydrogens replaced by C_{1-3} alkyl, said C_{1-3} alkyl groups can optionally cyclize to form a C_{3-6} cycloalkyl ring;

Ar is carbocycle, heterocycyl or heteroaryl;

X₁ is a linker chosen from a bond, -(CH₂)_n;

Y is chosen from C₇-C₁₀ spirocycle optionally containing 0-1 ring nitrogen atoms, a nitrogen containing mono- or bi-cyclic heterocycle, carbocycle, aryl, each substituted by one R₄;

R₄ is



each n is independently 1-4;

each m is independently 0-2;

each R₃ is independently chosen from hydrogen or C₁₋₄ alkyl;

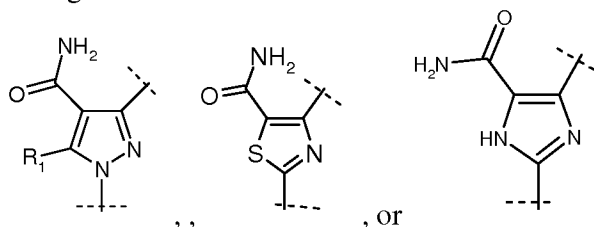
each R_5 is independently chosen from hydrogen, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} alkyl C_{1-4} alkoxy, $-(CH_2)_n$ -heterocycle and heterocycle each heterocycle optionally substituted by halogen, OH or $R_3-S(O)_m$;

- each group defined above for Cy, R_1 - R_5 , X_1 and Y can be where possible partially or fully
 5 halogenated;
 or a pharmaceutically acceptable salt thereof.

2. The compound according to claim 1 and wherein

10

A ring is:



or a pharmaceutically acceptable salt thereof.

15

3. The compound according to claim 2 and wherein

Cy is phenyl, pyridinyl, pyridazinyl, pyrimidinyl or pyrazinyl each is substituted by R_2 and optionally substituted by F, Cl or C_{1-4} alkoxy;

20 R_2 is chosen from:

L-Ar and C_{1-3} alkoxy, each Ar and C_{1-3} alkoxy are optionally substituted by F, Cl, C_{1-4} alkyl, $R_3-S(O)_2$ -, -CN, -C(O)-NH(R_3) or C_{1-3} alkoxy;

L is a linker chosen from a bond, O, $>C(O)$ -, $-CH_2$ -, $-O-CH_2$ -, $-NH$ -, $-NH-CH_2$ -, $-CH_2-NH$ -, $-C(O)-NH-CH_2$ -, $-NH-C(O)-NH$ - and $-N(R_3)-S(O)_m$;

25 Ar is phenyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, benzoxazolyl, indolyl, isoindolyl, benzofuranyl, benzimidazolyl, benzothiazolyl, piperidinyl, piperazinyl or pyrrolidinyl

or a pharmaceutically acceptable salt thereof.

30

4. The compound according to claim 3 and wherein

Cy is phenyl or pyridinyl, each is substituted by R_2 and optionally substituted by F, Cl or C_{1-2} alkoxy;

R_2 is chosen from:

L-Ar and C_{1-3} alkoxy, each Ar and C_{1-3} alkoxy are optionally substituted by F, Cl, C_{1-4} alkyl, $CH_3-S(O)_2-$, $-CN$, $-C(O)-NH(R_3)$ or C_{1-2} alkoxy;

L is a linker chosen from a bond, O, $>C(O)$, $-CH_2-$, $-O-CH_2-$, $-NH-$, $-NH-CH_2-$, $-CH_2-NH-$, $-C(O)-NH-CH_2-$, $-NH-C(O)-NH-$ and $-N(R_3)-S(O)_m-$;

Ar is phenyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, benzoxazolyl, indolyl, isoindolyl, benzofuranyl, benzimidazolyl, benzothiazolyl or piperidinyl

or a pharmaceutically acceptable salt thereof.

5. The compound according to claim 4 and wherein

Cy is phenyl or pyridinyl, each is substituted by R_2 and optionally substituted by F, Cl or C_{1-2} alkoxy;

R_2 is chosen from:

L-Ar and C_{1-3} alkoxy, each Ar and C_{1-3} alkoxy are optionally substituted by F, Cl, C_{1-4} alkyl, $CH_3-S(O)_2-$, $-CN$, $-C(O)-NH(CH_3)$ or C_{1-2} alkoxy;

L is a linker chosen from a bond, O, $>C(O)$, $-CH_2-$, $-O-CH_2-$, $-NH-$, $-NH-CH_2-$, $-CH_2-NH-$, $-C(O)-NH-CH_2-$, $-NH-C(O)-NH-$ and $-N(H)-S(O)_2-$;

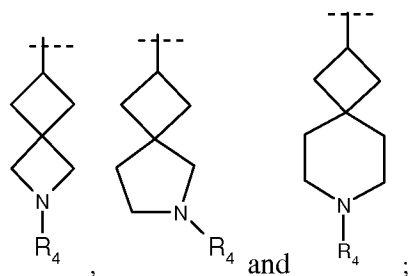
Ar is phenyl, pyridinyl, benzoxazolyl or piperidinyl
or a pharmaceutically acceptable salt thereof.

6. The compound according to claim 5 and wherein

X_1 is a linker chosen from a bond and $-(CH_2)_n-$;

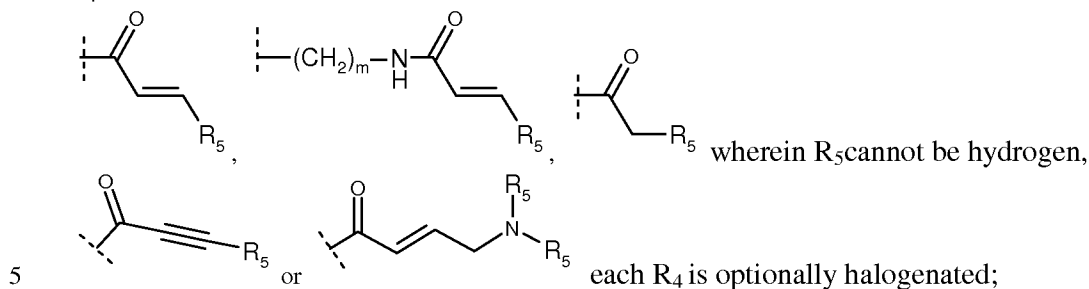
Y is chosen from:

a spirocycle chosen from



a heterocycle chosen from piperidinyl and pyrrolidinyl;
and phenyl each heterocycle or phenyl substituted by one R₄;

R₄ is



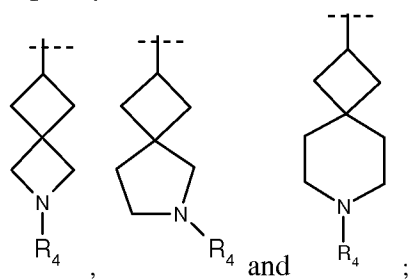
each R₅ is independently chosen from hydrogen, C₁₋₃ alkyl, halo C₁₋₃ alkyl, C₁₋₃ alkylC₁₋₃ alkoxy, -CH₂-heterocycle and heterocycle each heterocycle optionally substituted by F, Cl, OH and CH₃-S(O)₂- and each heterocycle chosen from pyrrolidinyl, piperidinyl,
10 morpholinyl and 1,4-oxazepane,
or a pharmaceutically acceptable salt thereof.

7. The compound according to claim 6 and wherein

15 X₁ is a linker chosen from a bond and -(CH₂)_n;

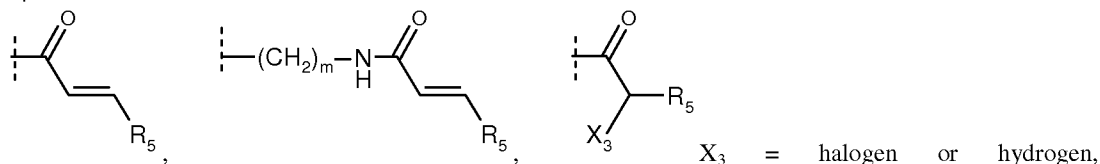
Y is chosen from:

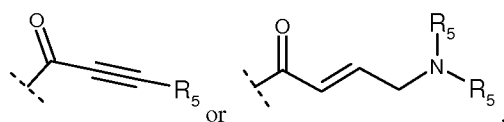
a spirocycle chosen from



20 a heterocycle chosen from piperidinyl and pyrrolidinyl;
and phenyl each heterocycle or phenyl substituted by one R₄;

R₄ is

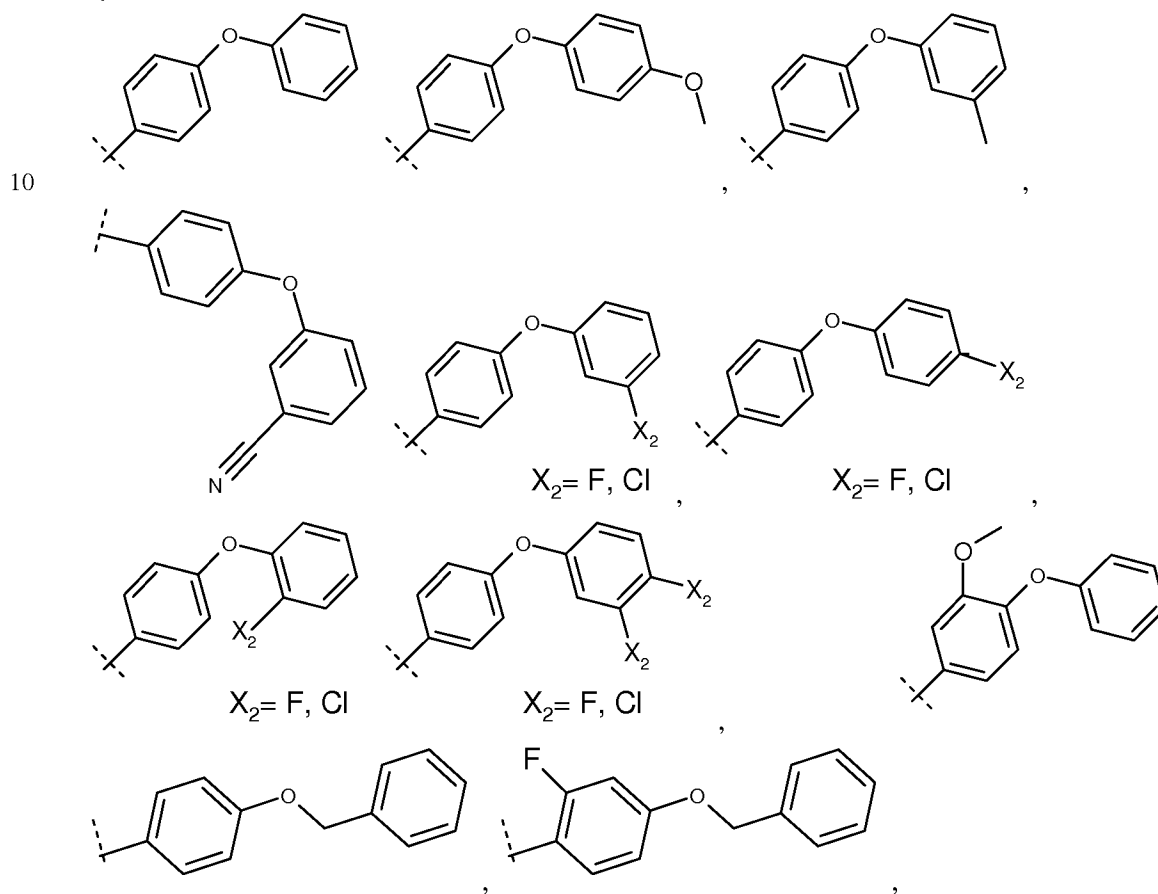


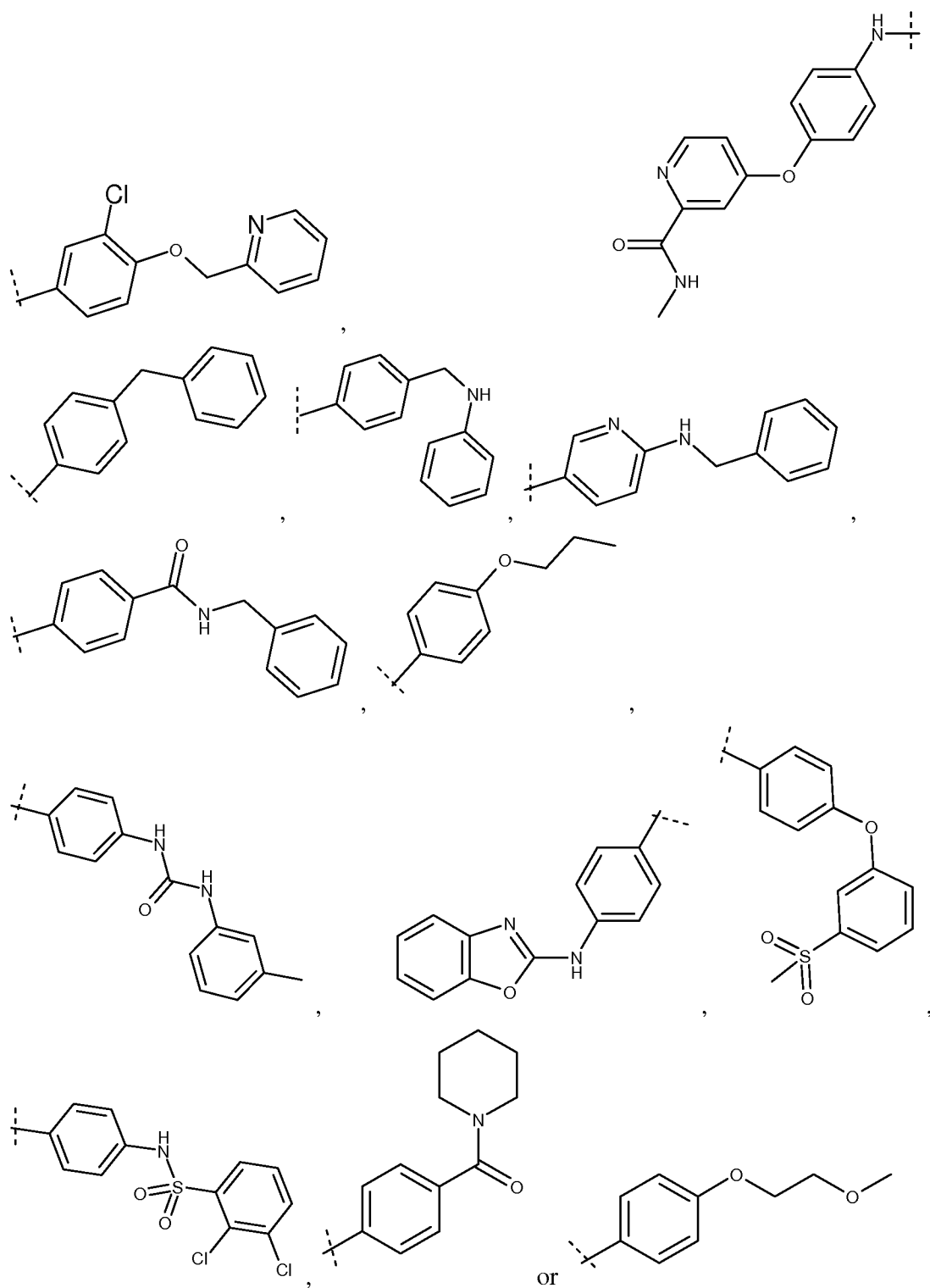


each R_5 is independently chosen from hydrogen, C_{1-3} alkyl, $-CF_3$, C_{1-3} alkyl C_{1-3} alkoxy, $-CH_2$ -heterocycle and heterocycle each heterocycle optionally substituted by F, Cl, OH and $CH_3-S(O)_2-$ and each heterocycle chosen from pyrrolidinyl, piperidinyl and 1,4-oxazepane,
 5 or a pharmaceutically acceptable salt thereof.

8. The compound according to claim 1 and wherein

Cy is

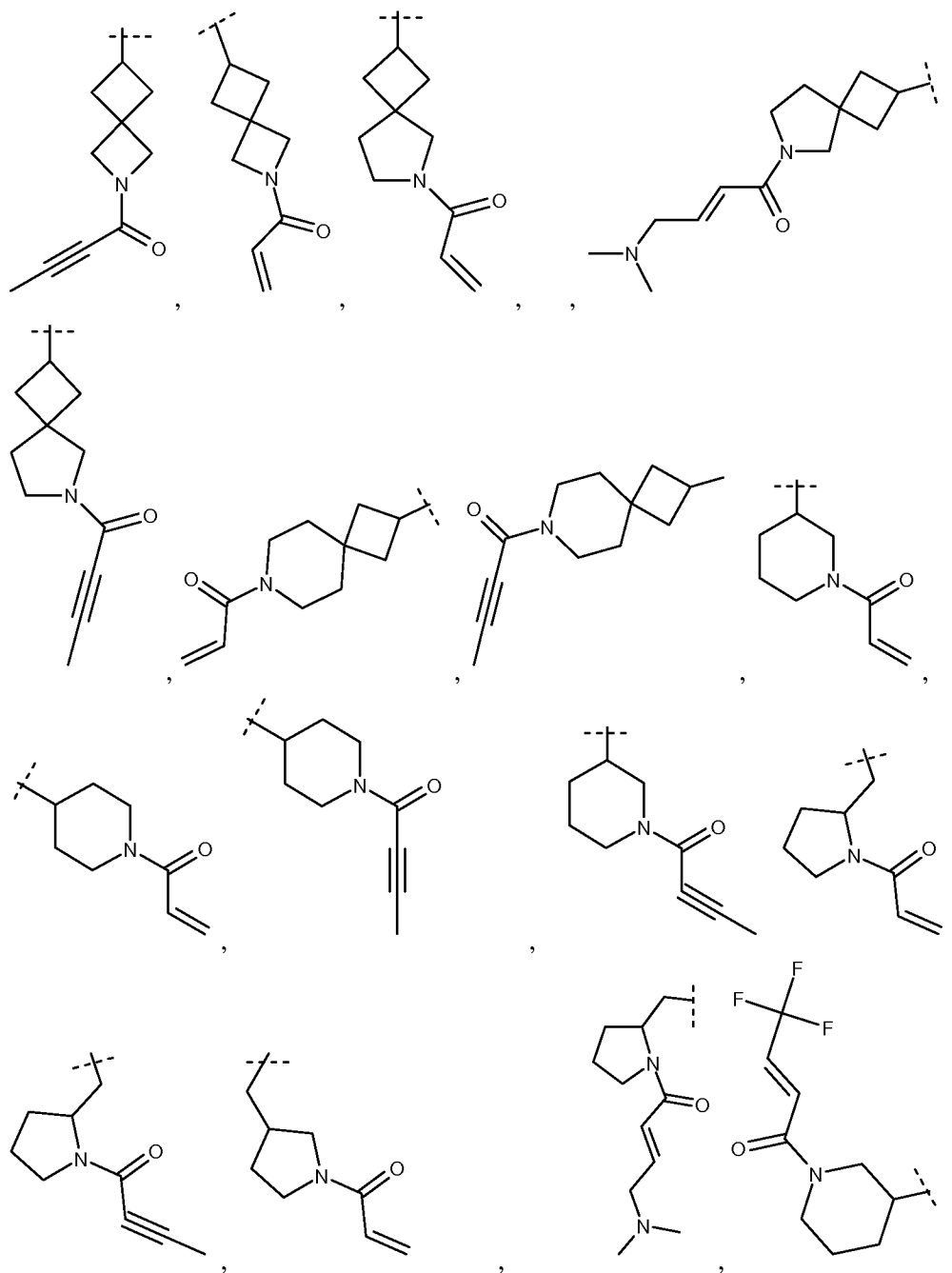




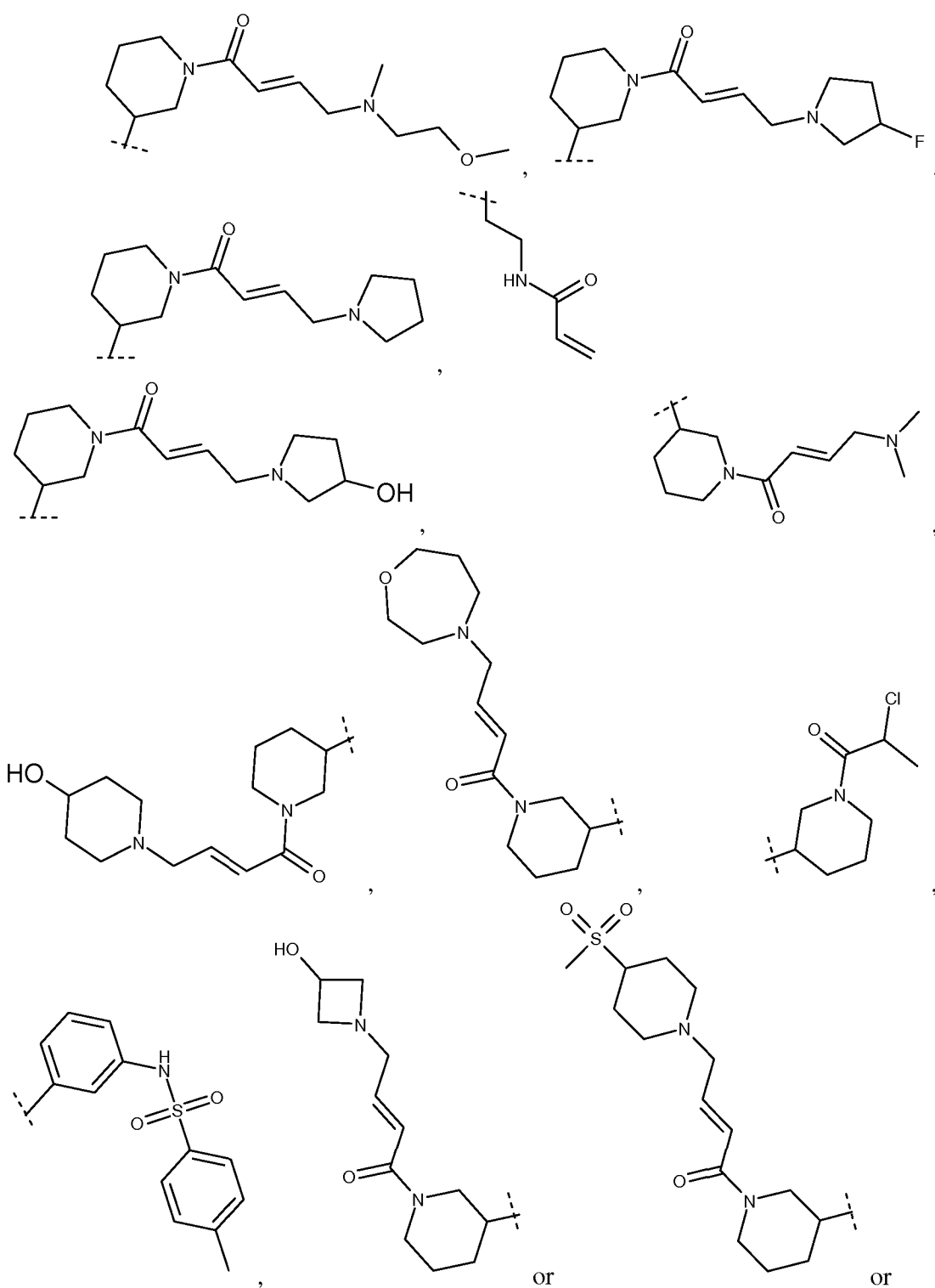
or a pharmaceutically acceptable salt thereof.

9. The compound according to claim 8 and wherein

X-Y =



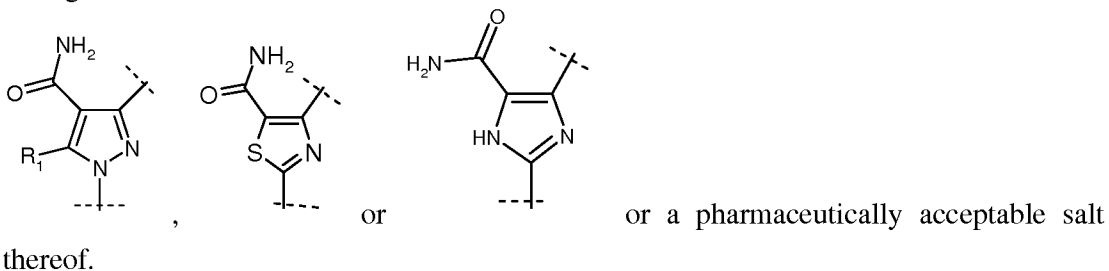
5



a pharmaceutically acceptable salt thereof.

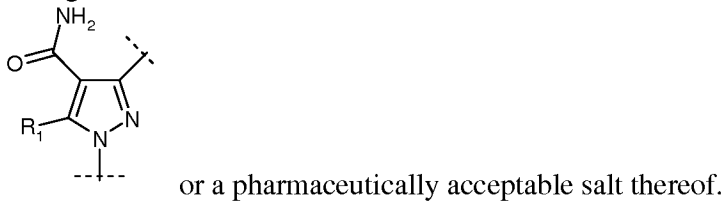
10. The compound according to claim 9 and wherein

A ring is:



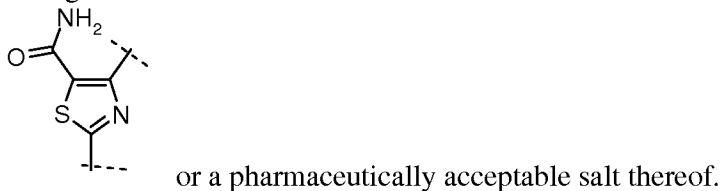
11. The compound according to claim 9 and wherein

A ring is:



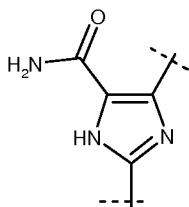
12. The compound according to claim 9 and wherein

A ring is:



13. The compound according to claim 9 and wherein

A ring is:



or a pharmaceutically acceptable salt thereof.

14. The compound according to claim 2 and wherein

5 R_2 is

L-Ar;

L is a linker chosen from a bond, O, and $-O-(CH_2)_n-$;

n is 1-3;

Ar is carbocycle or heterocycle.

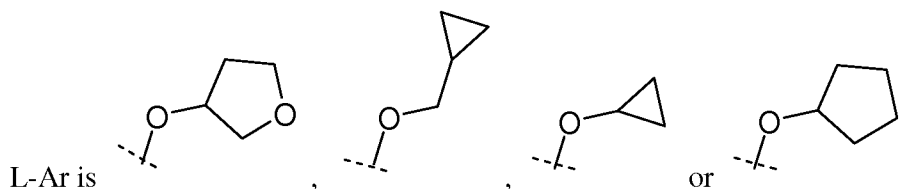
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15. The compound according to claim 14 and wherein

Ar is C_{3-5} cycloalkyl or tetrahydrofuranyl;

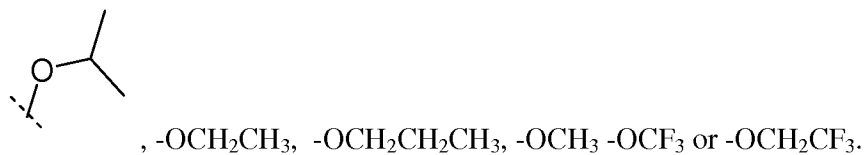
n = 1.

15 16. The compound according to claim 15 and wherein

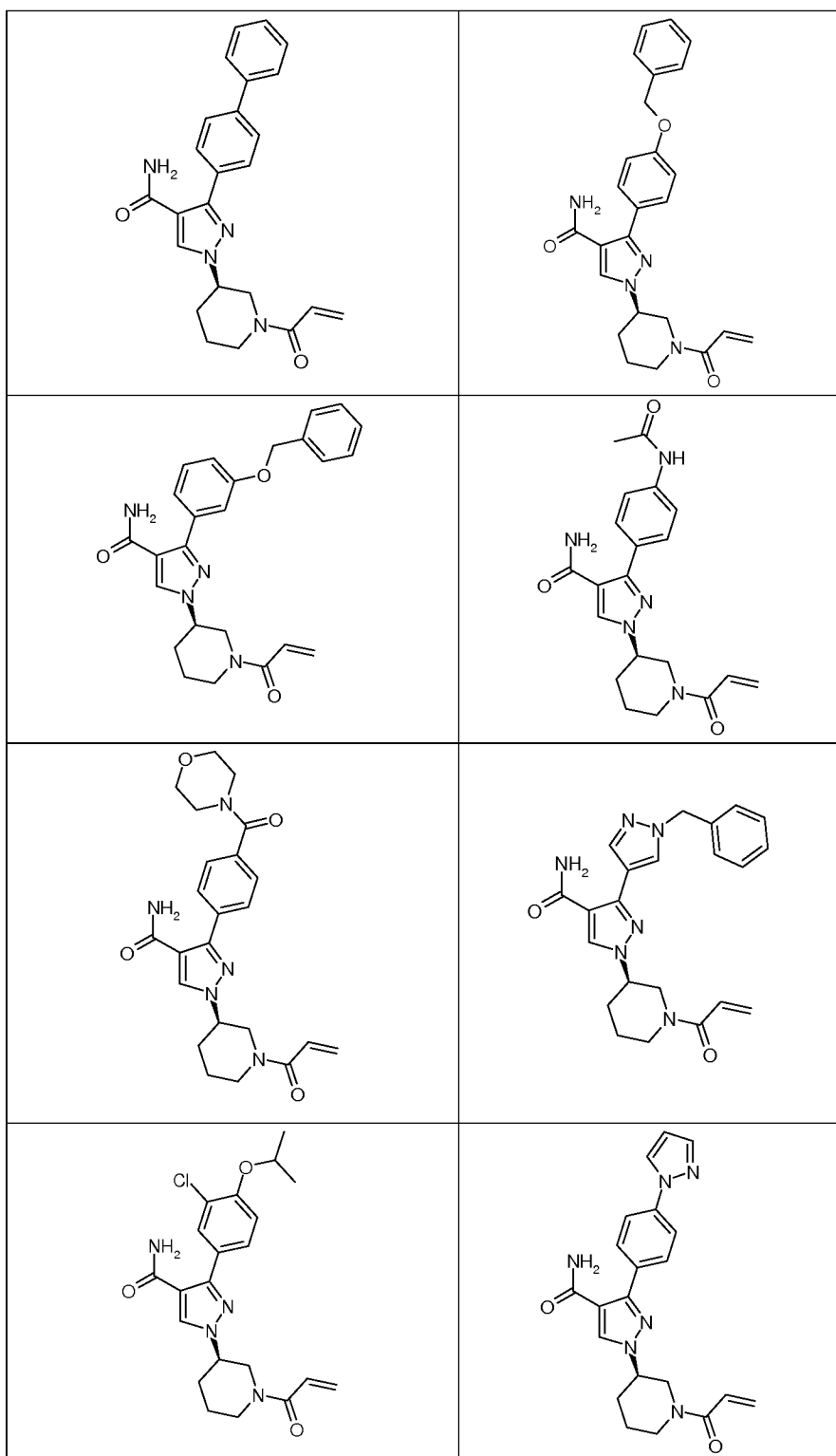


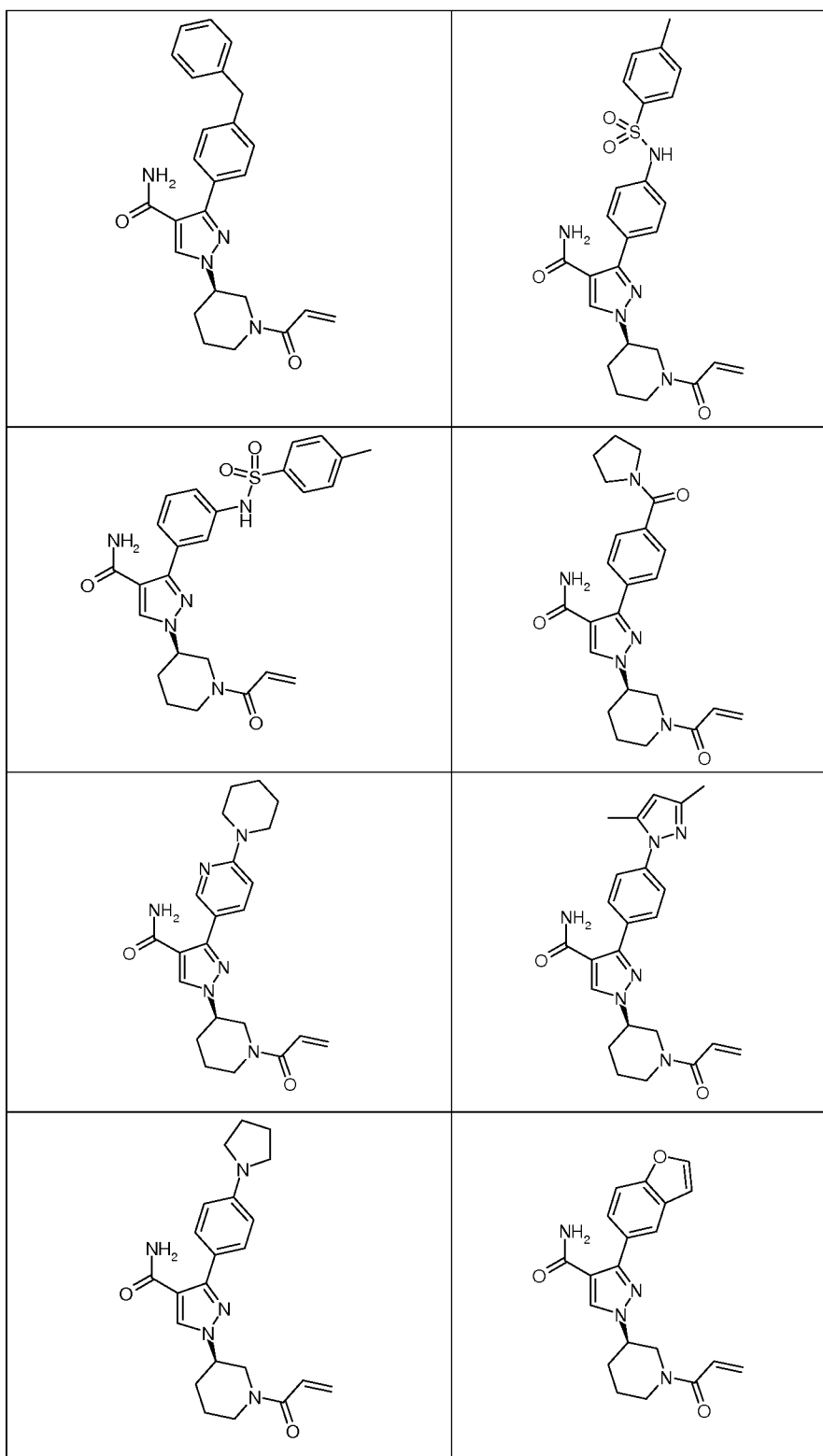
17. The compound according to claim 2 and wherein

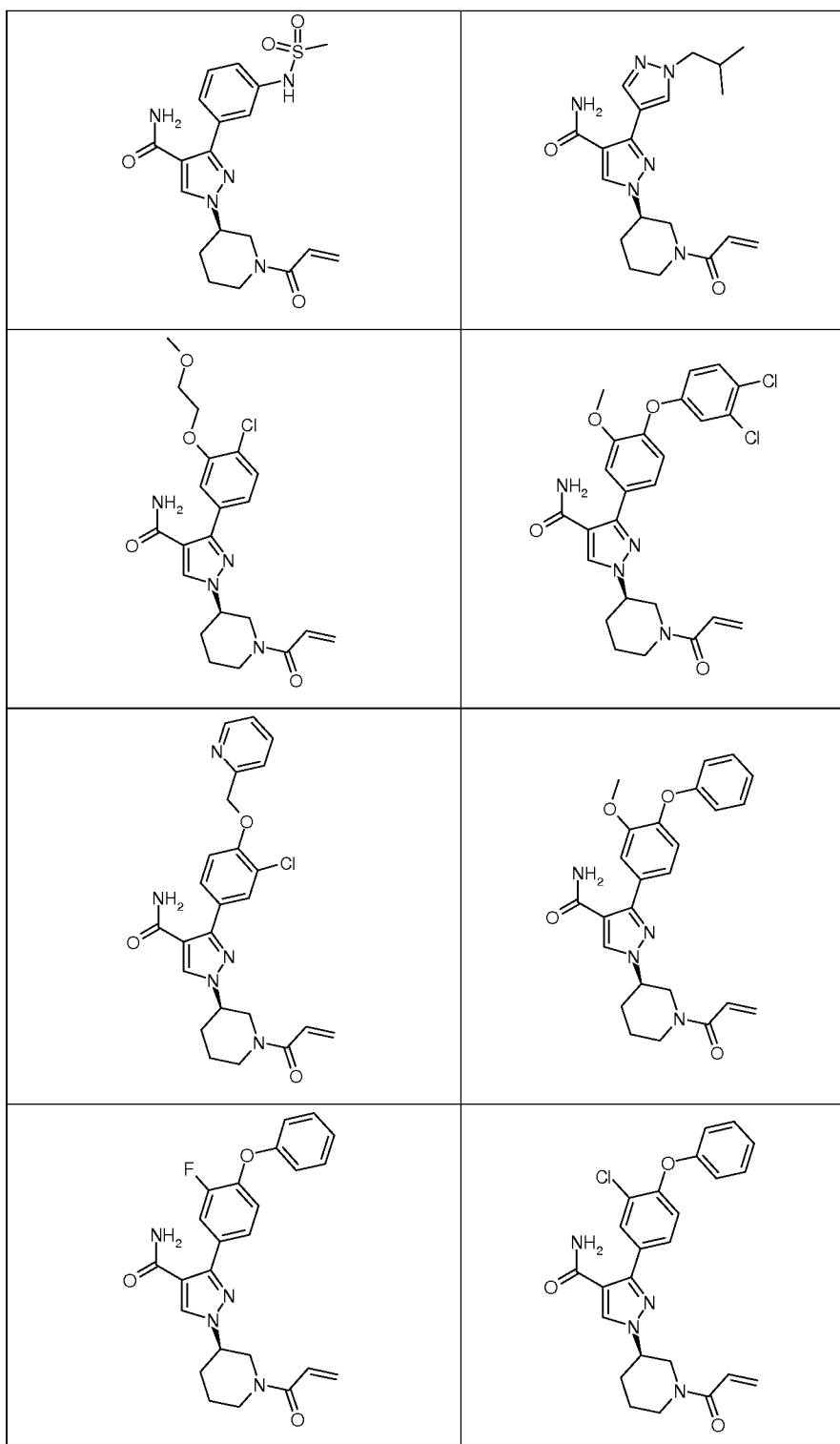
20 R_2 is:

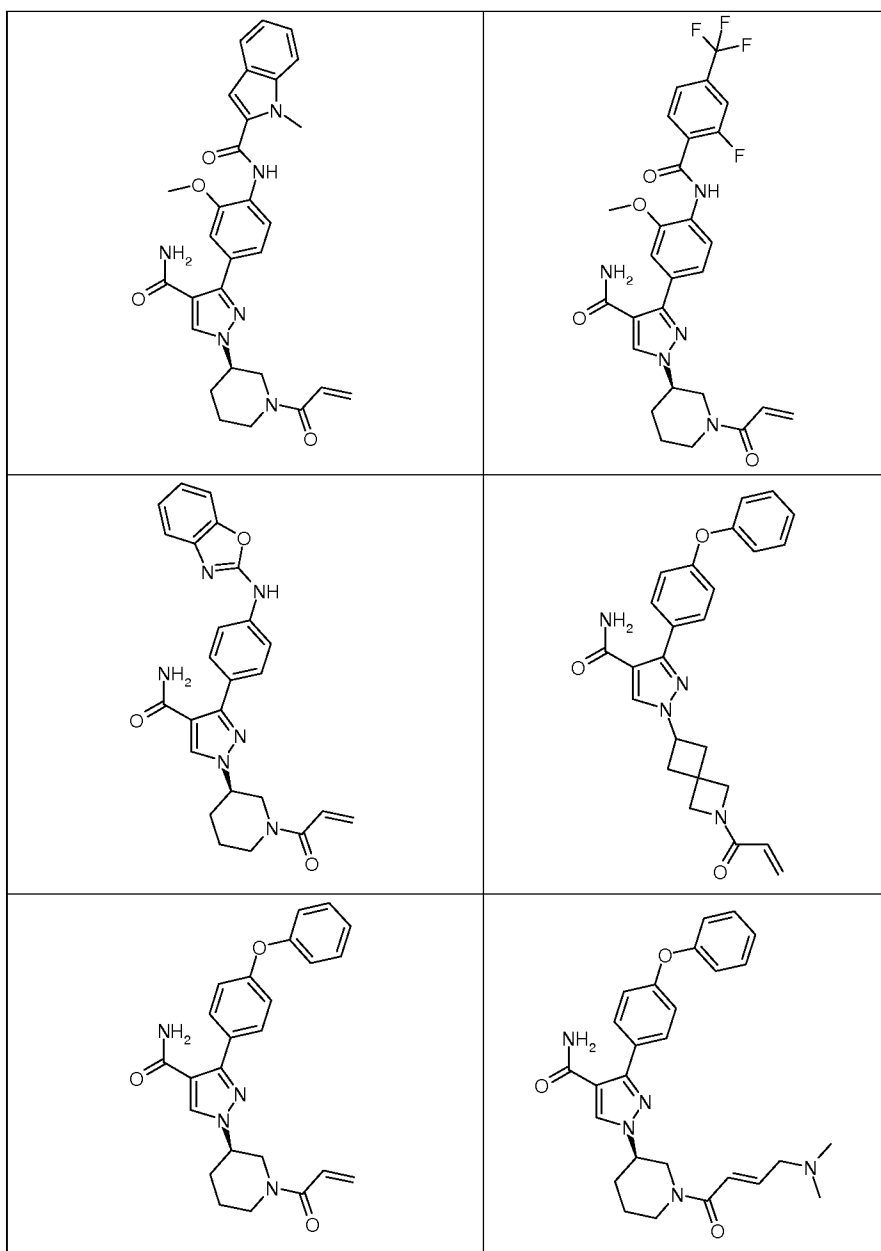


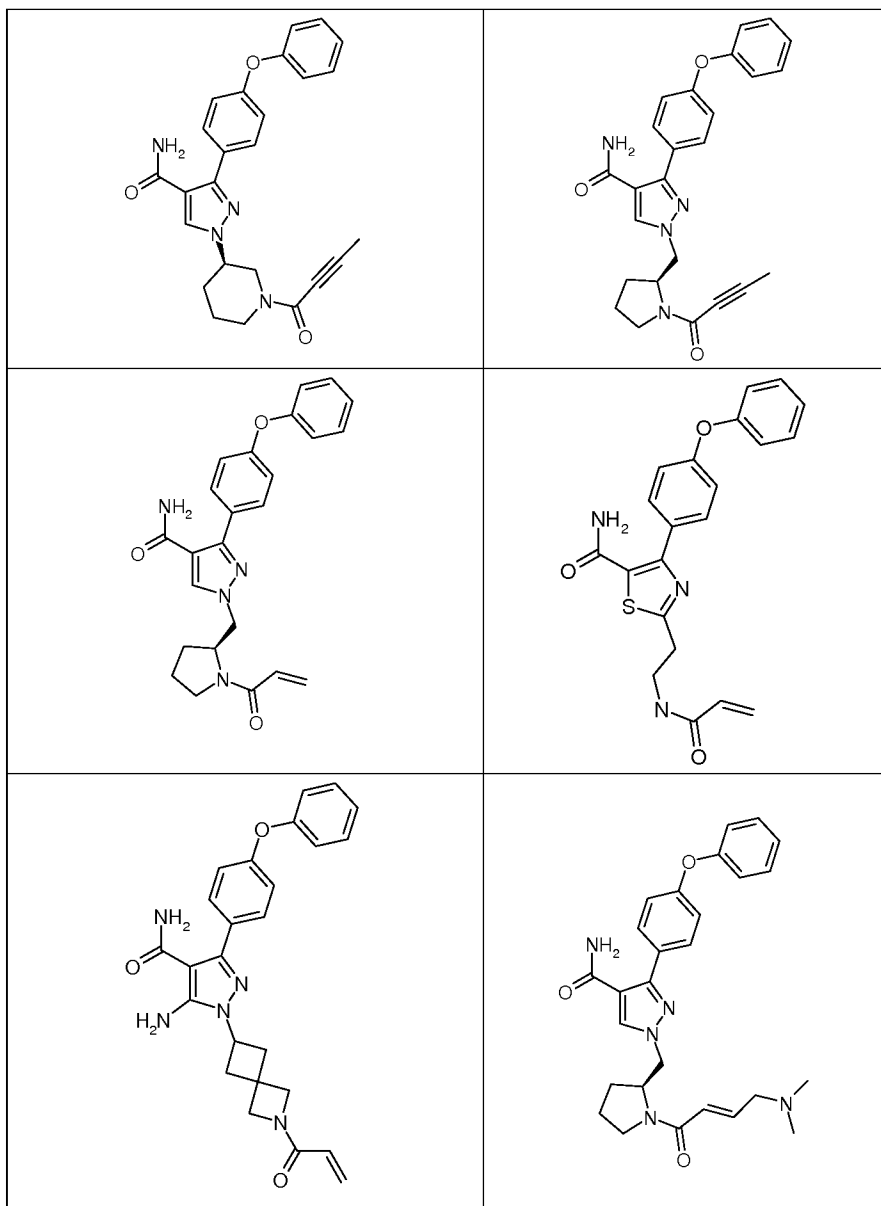
25 18. A compound chosen from:

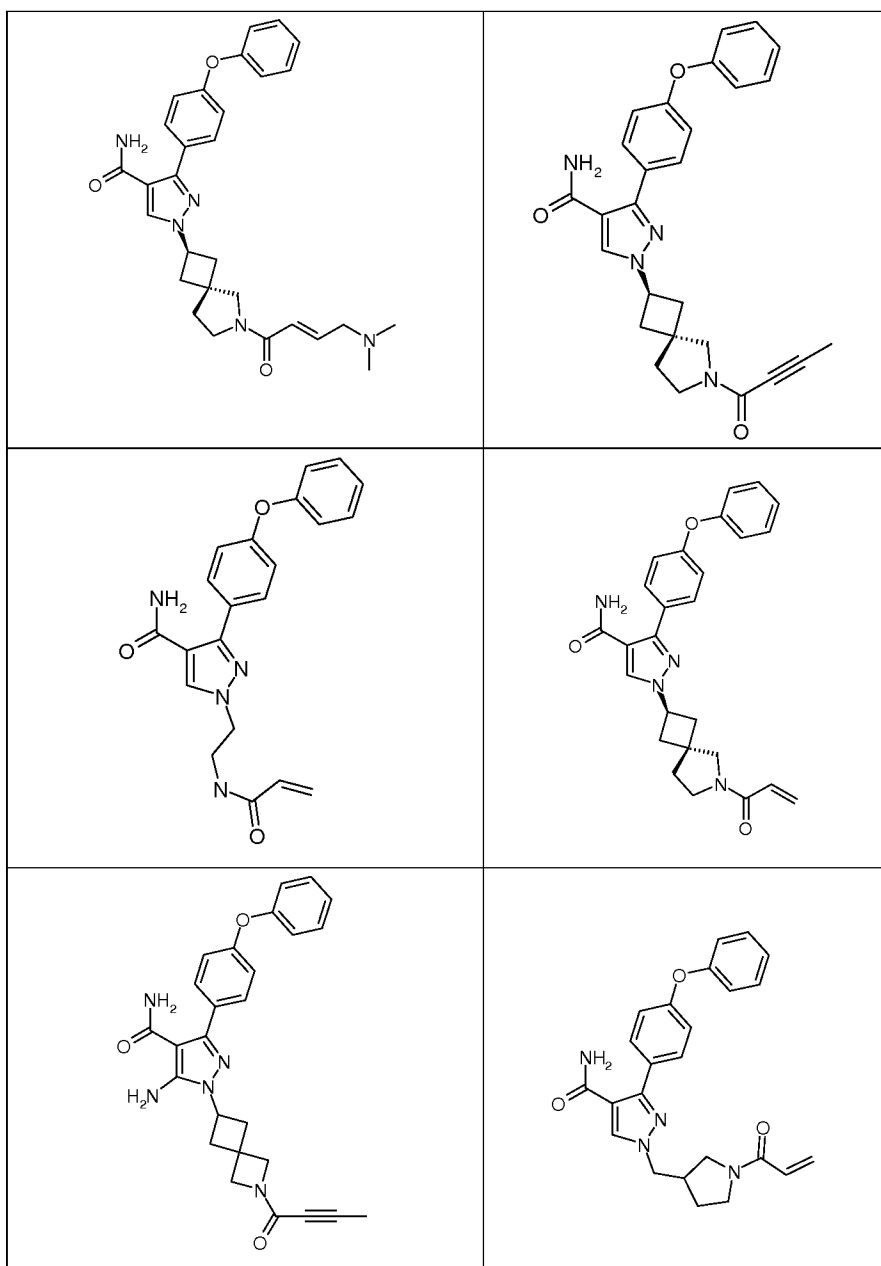


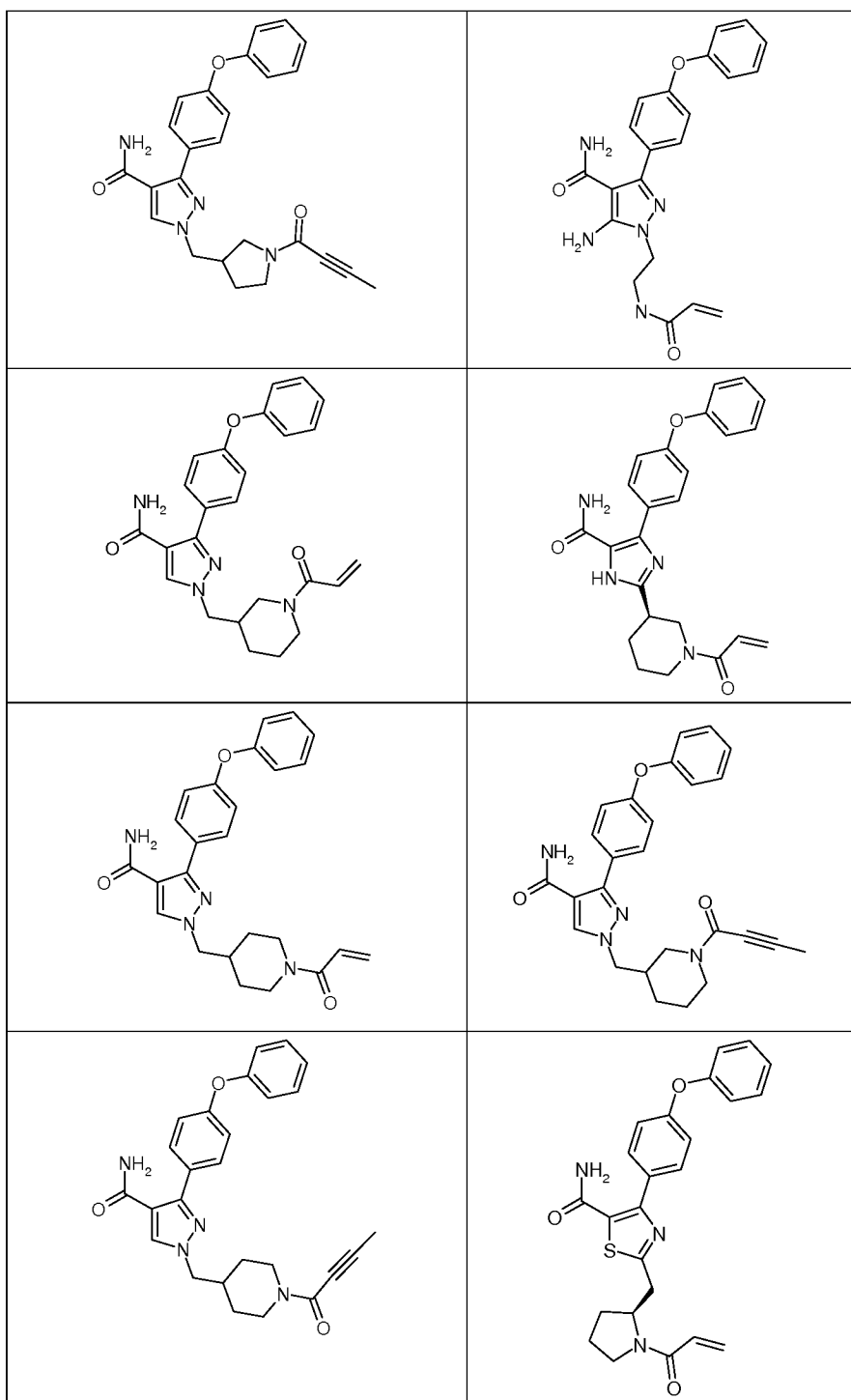


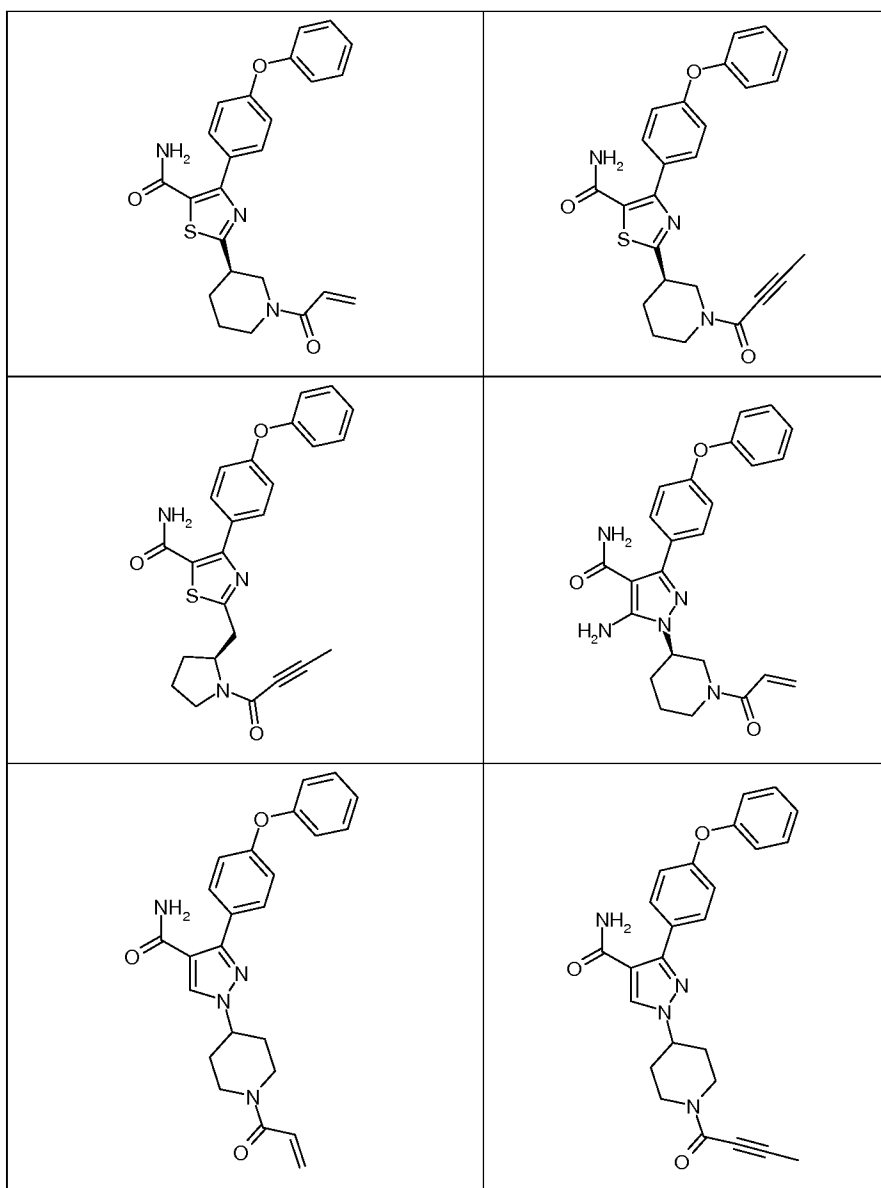


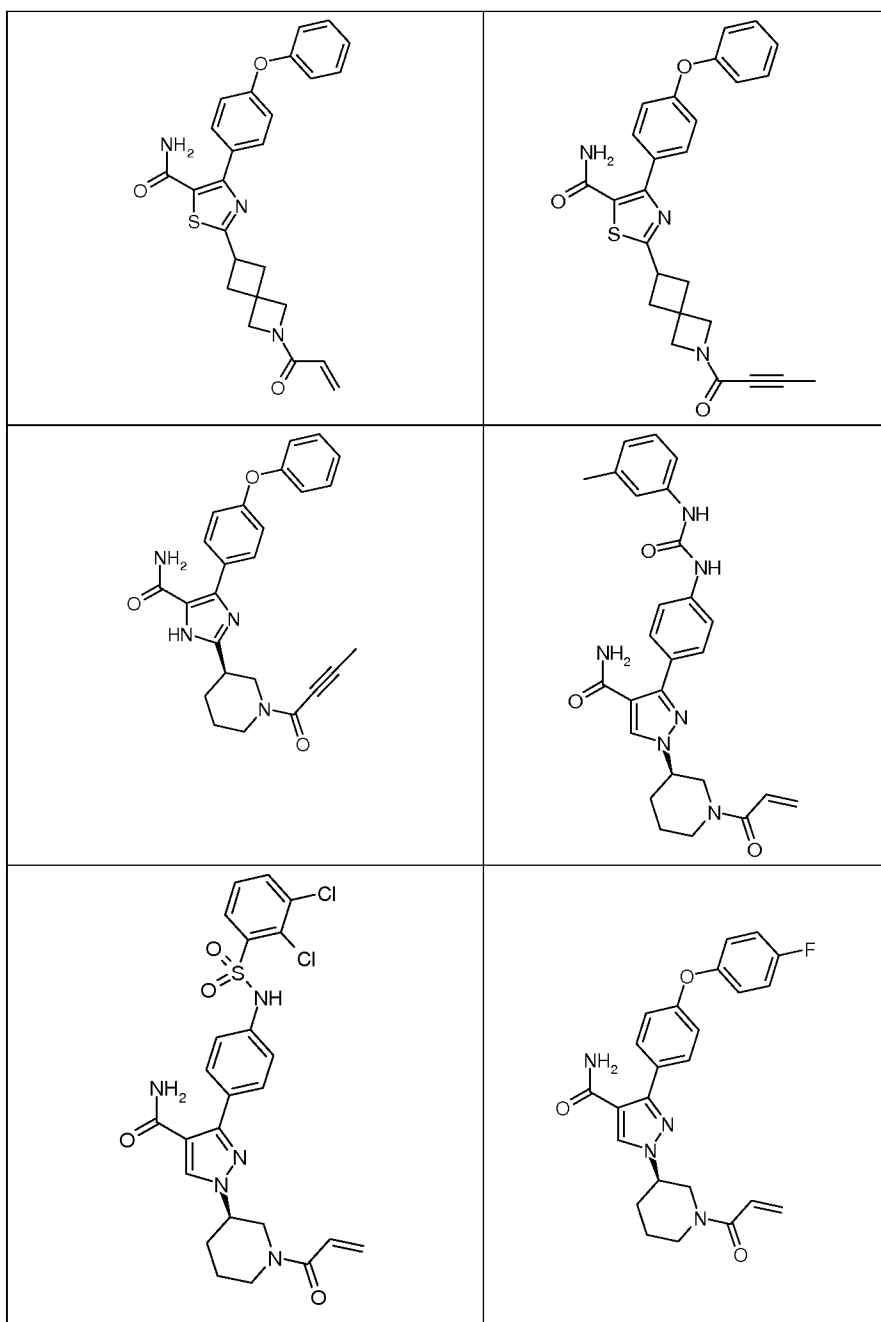


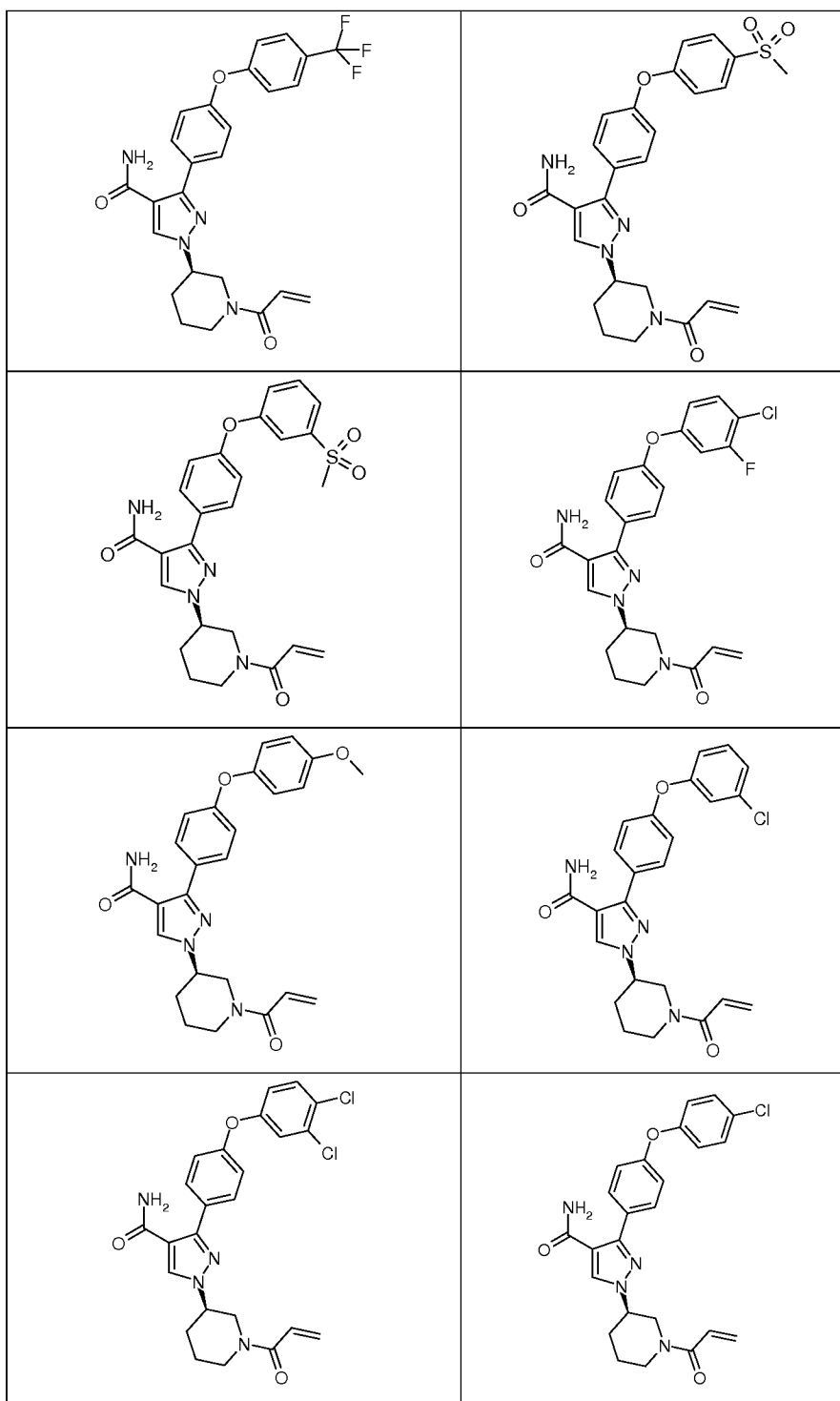


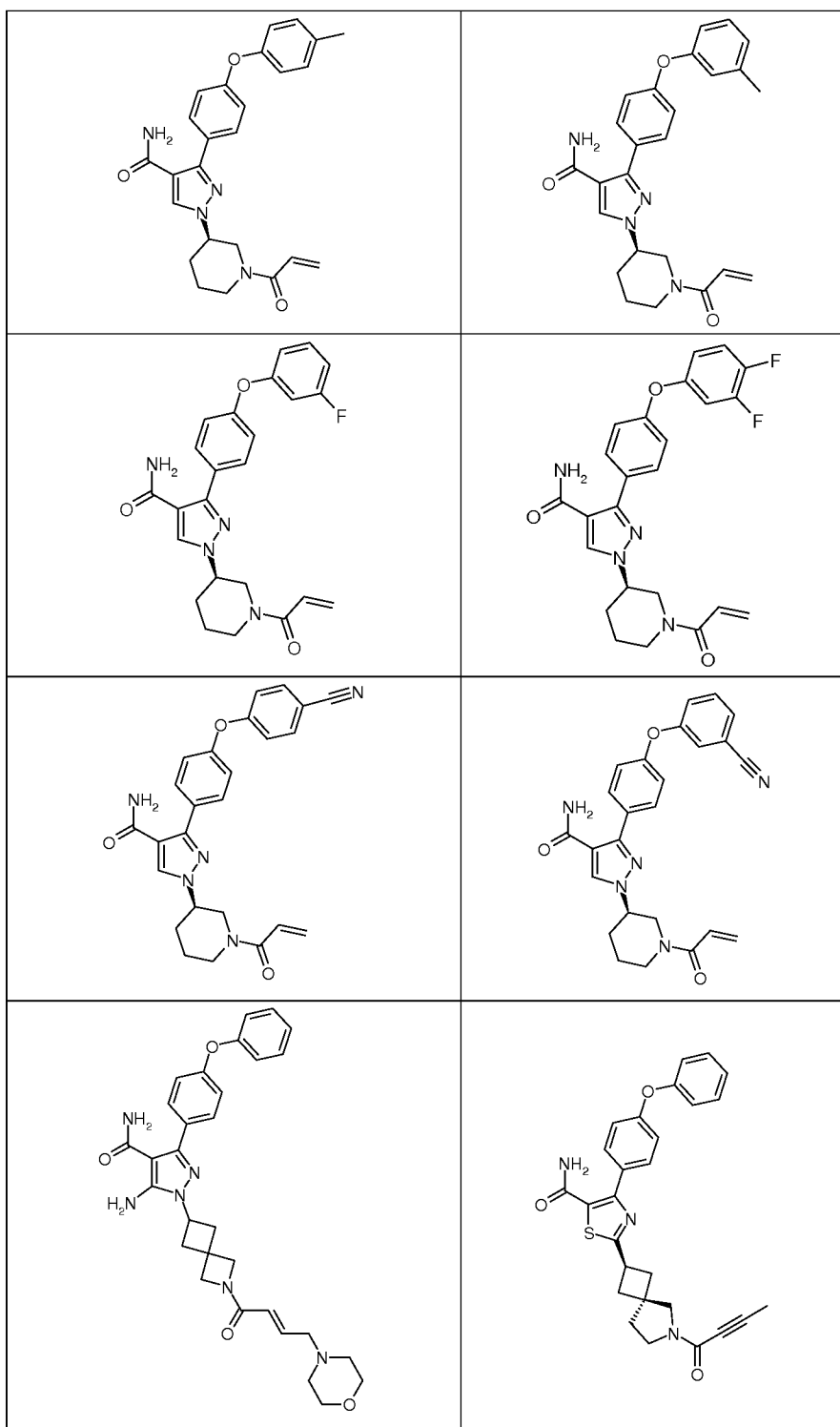


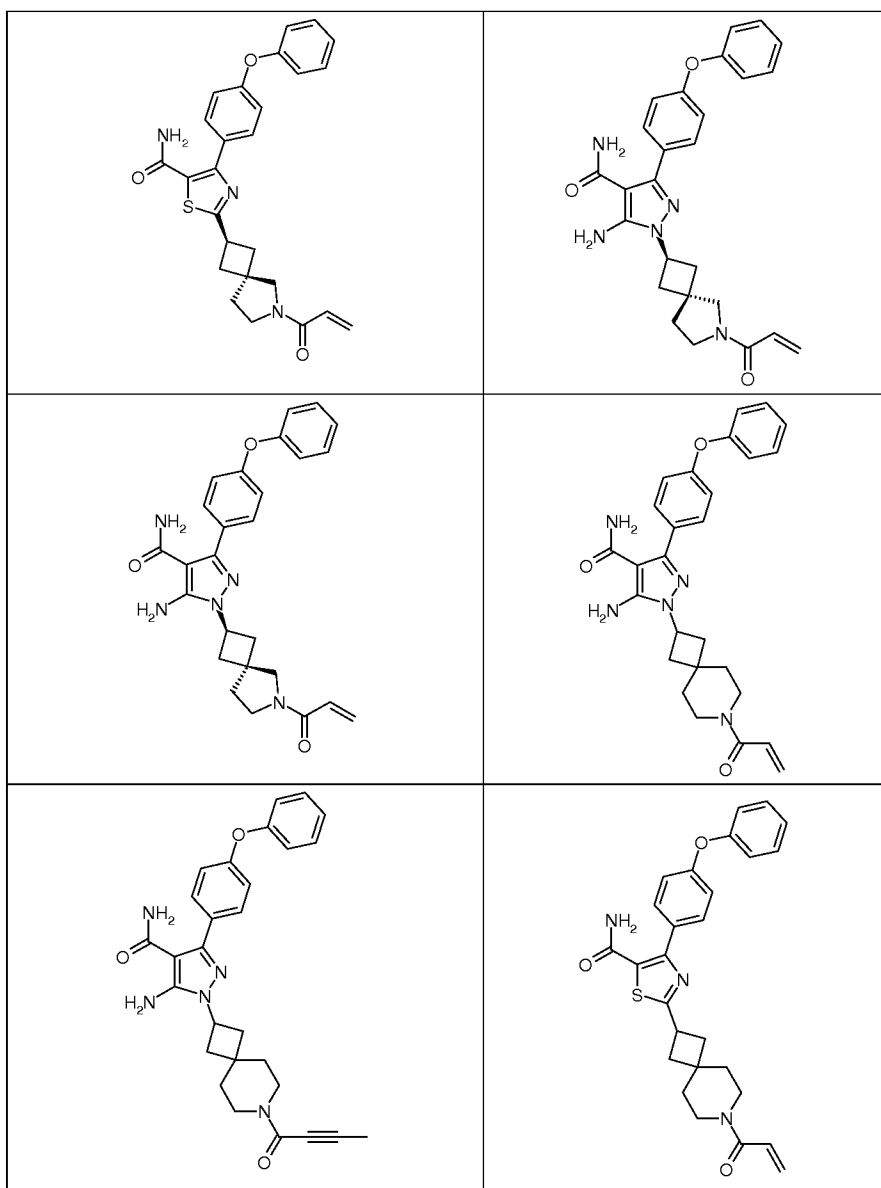


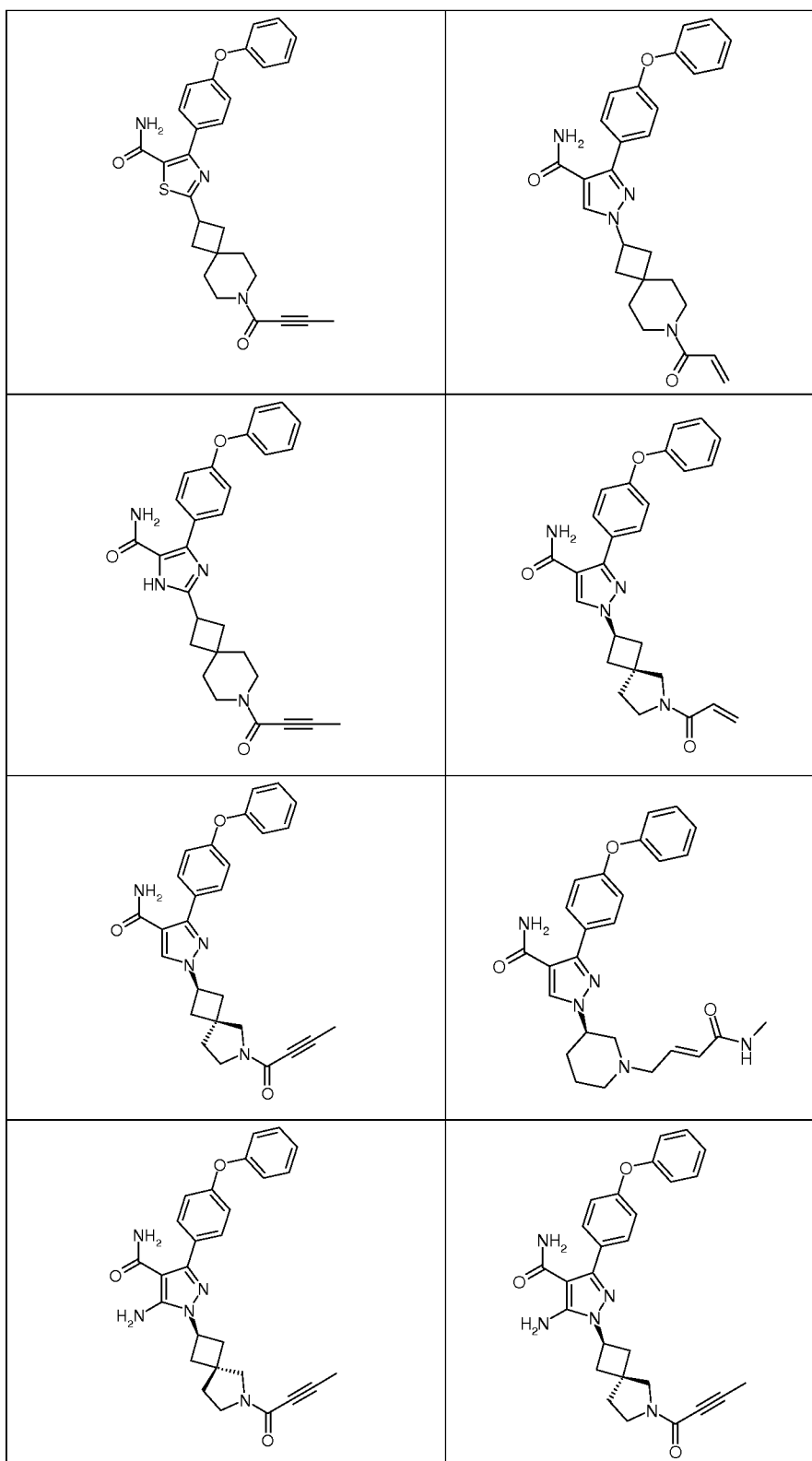


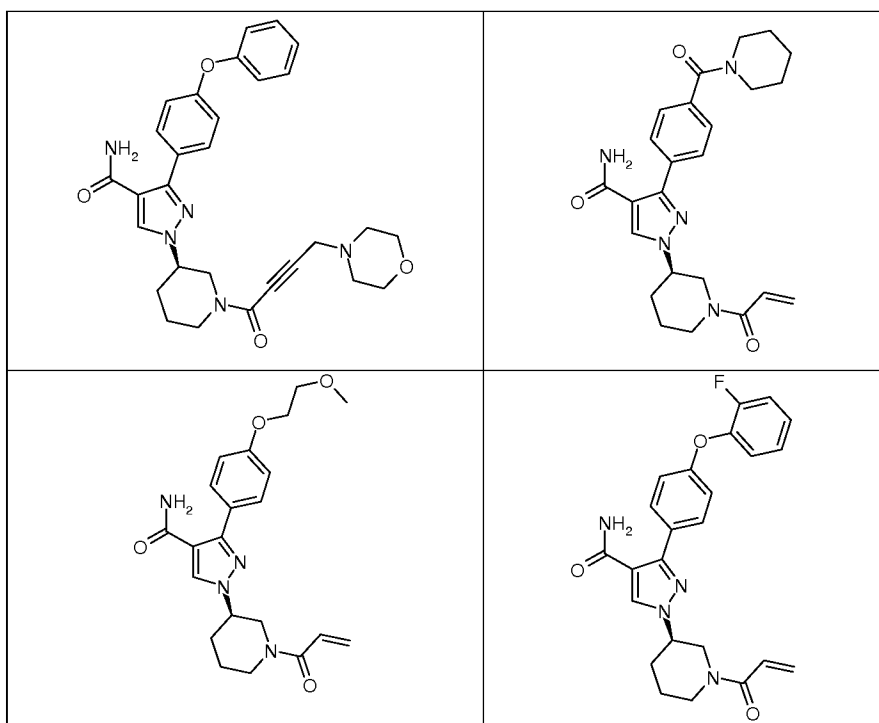






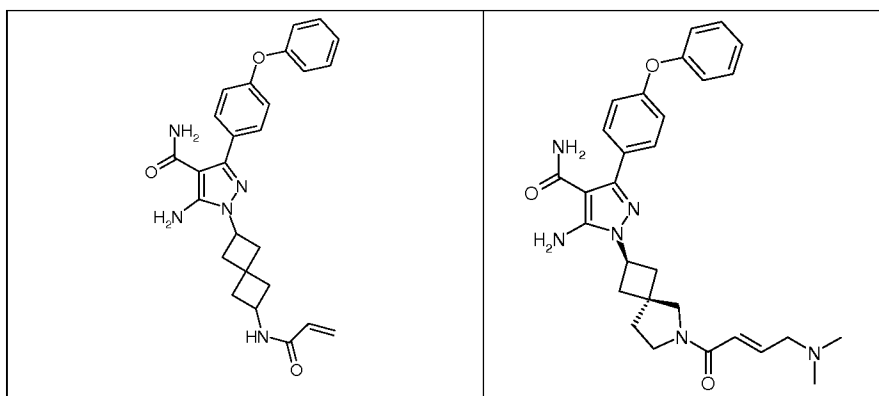


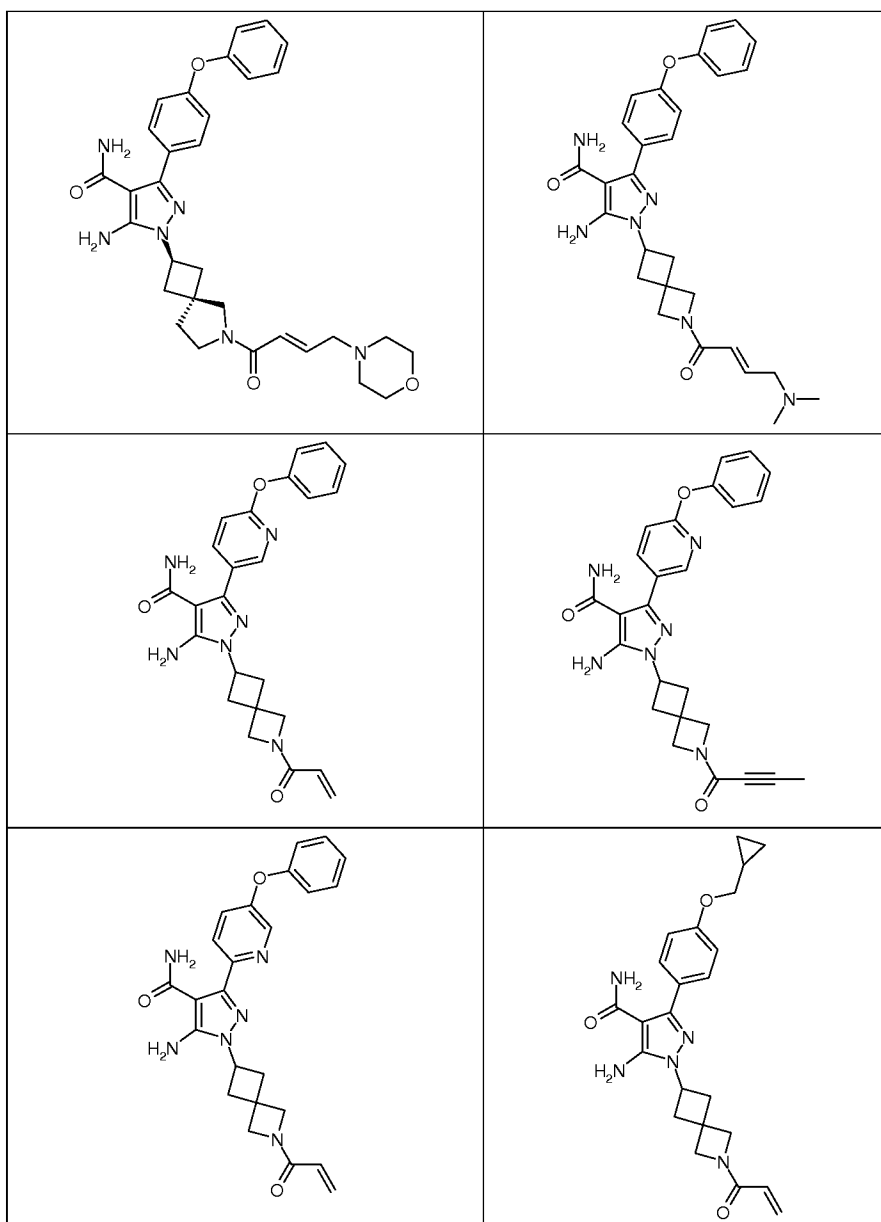


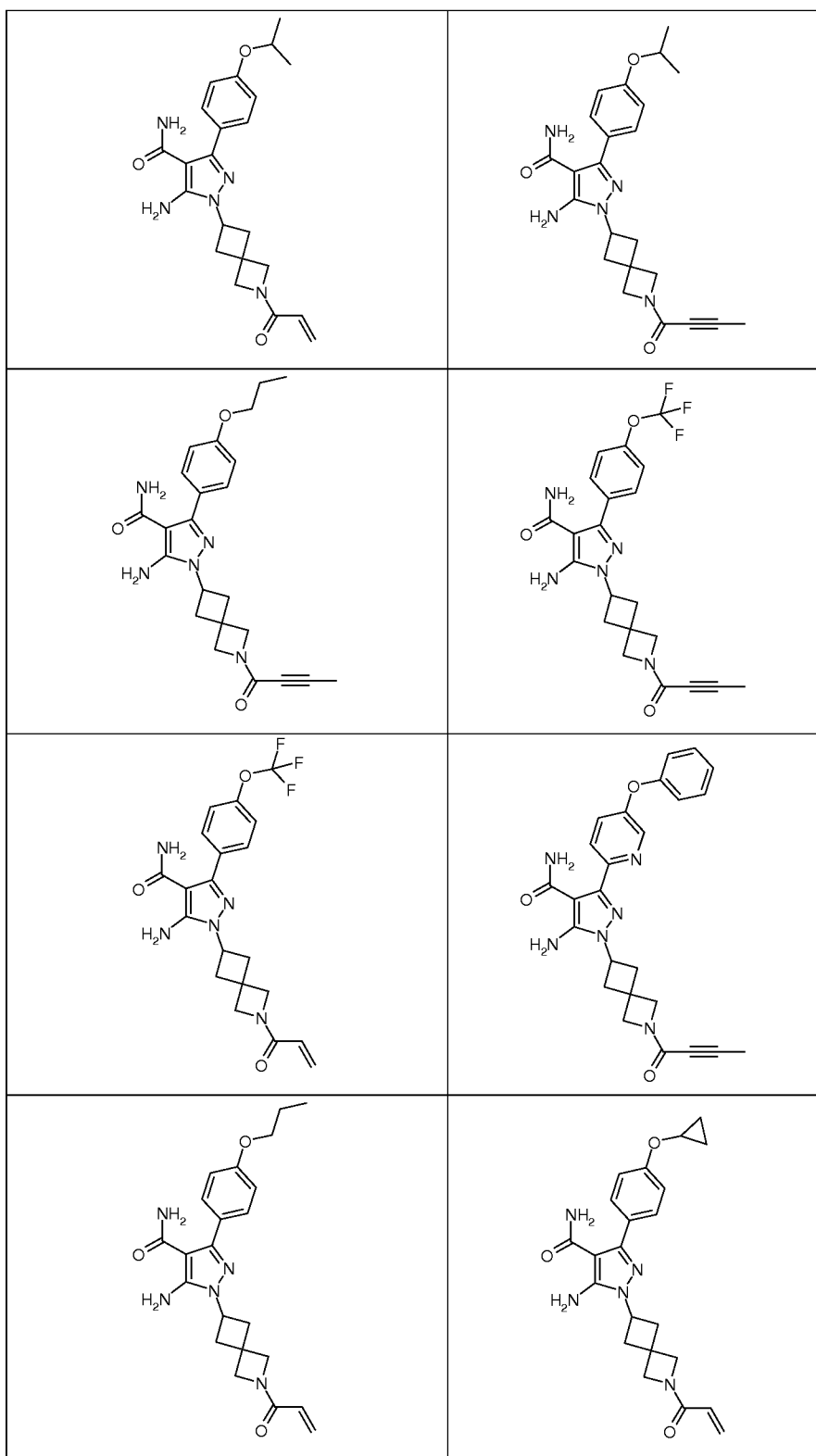


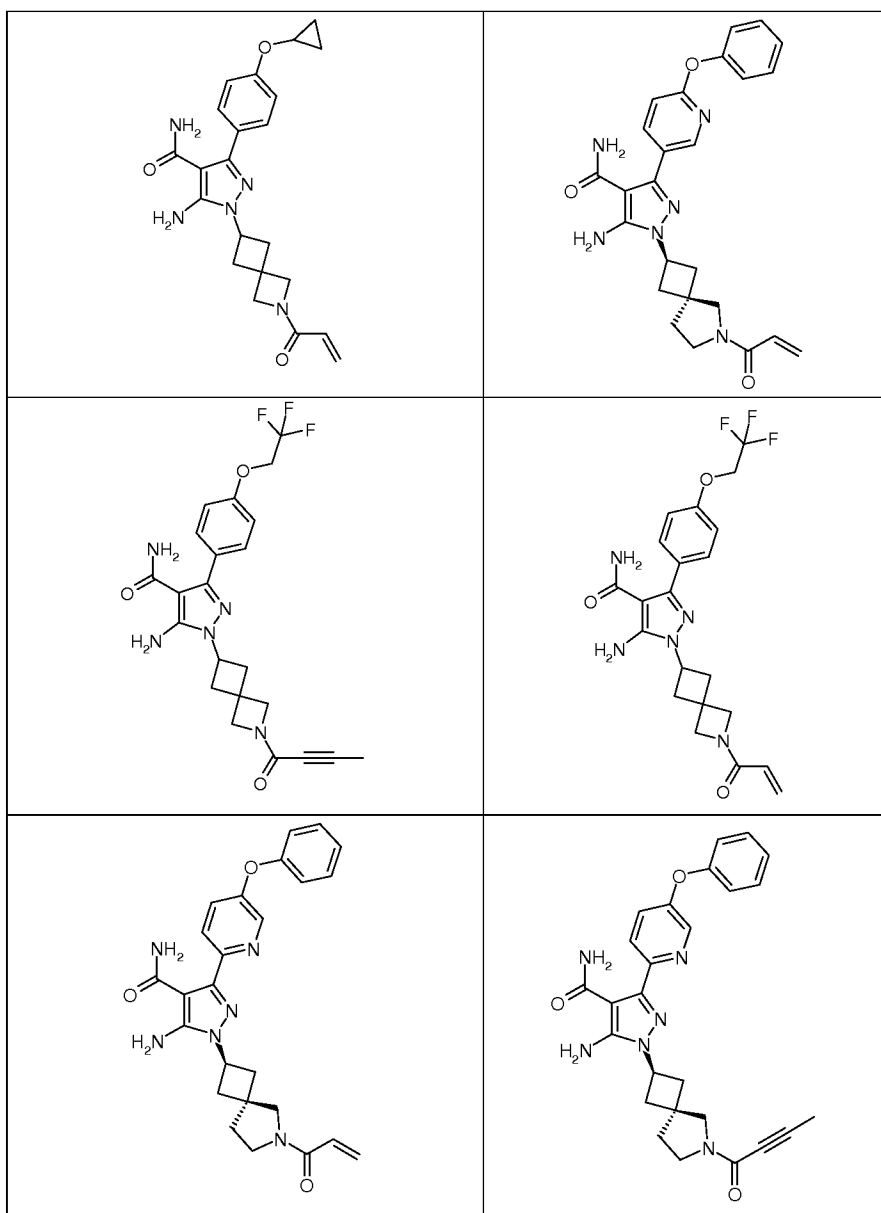
or the pharmaceutically acceptable salts thereof.

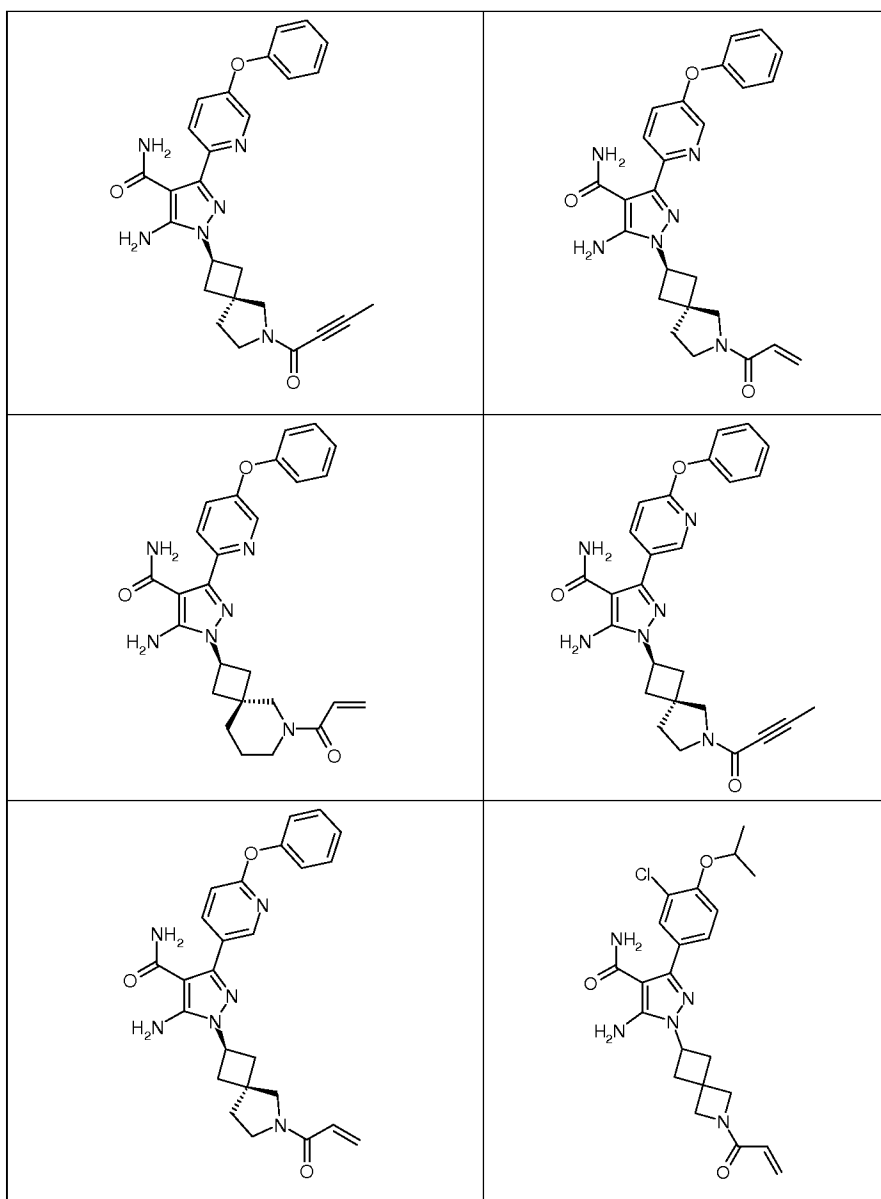
5 19. A compound chosen from:

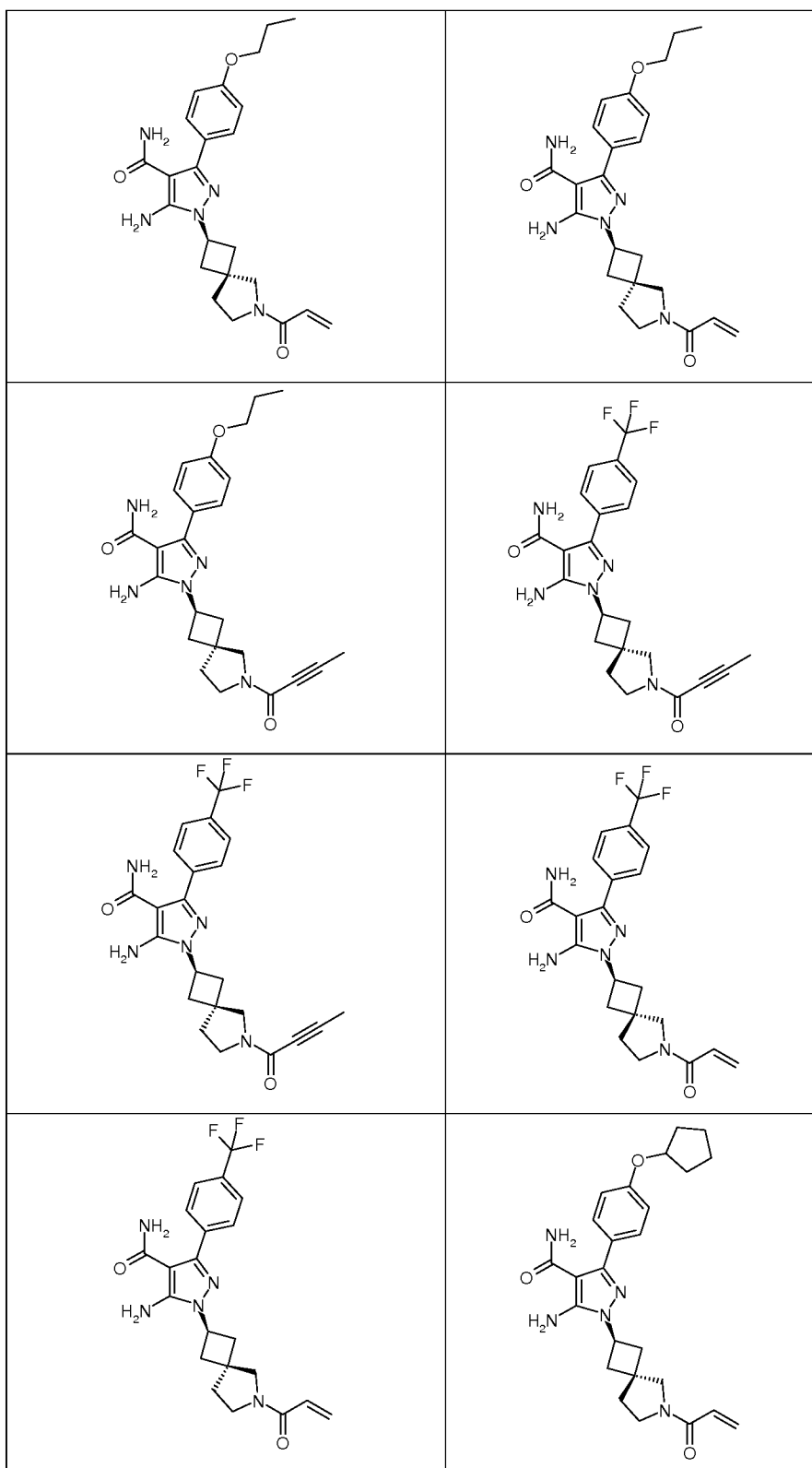


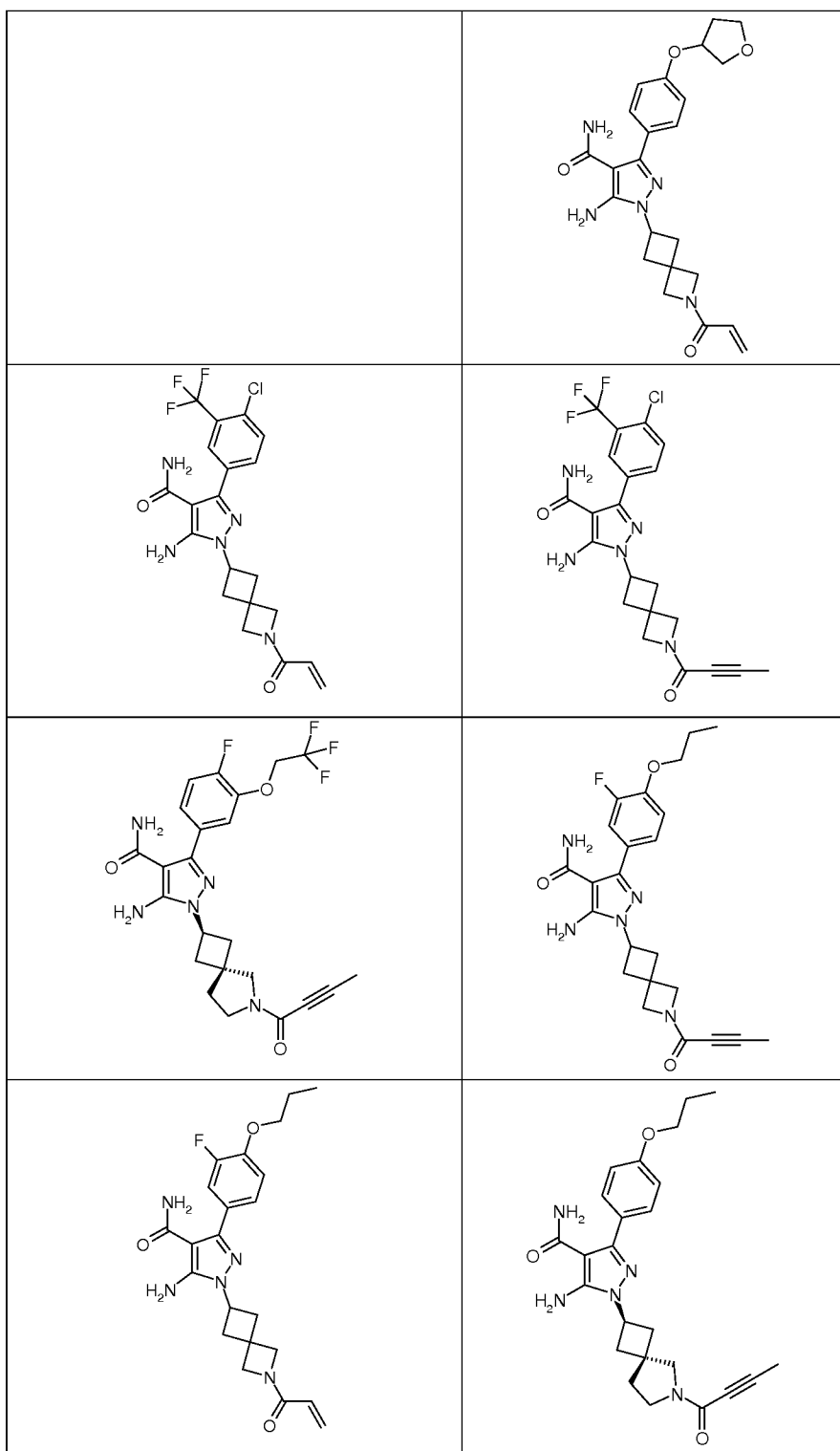


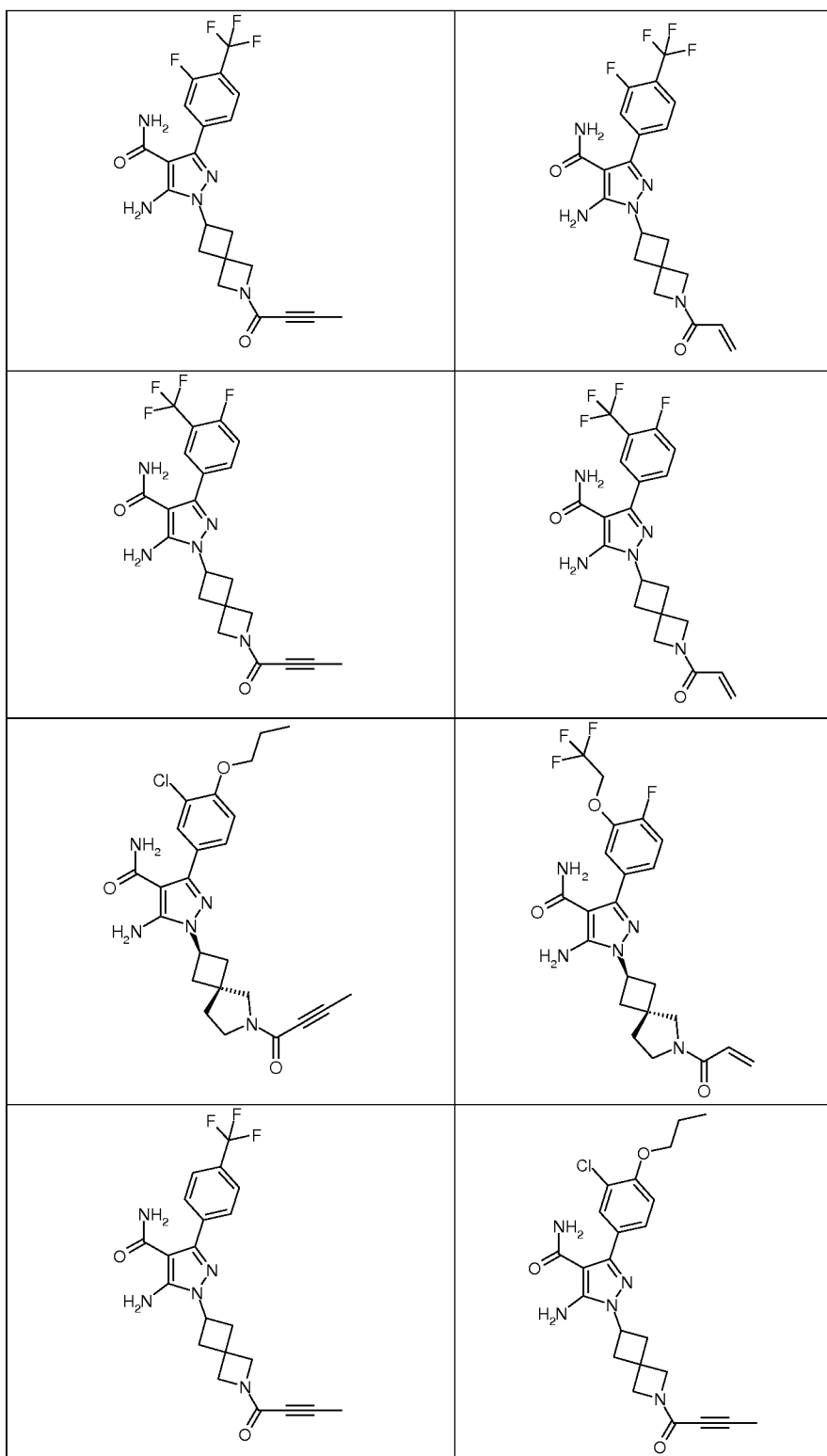


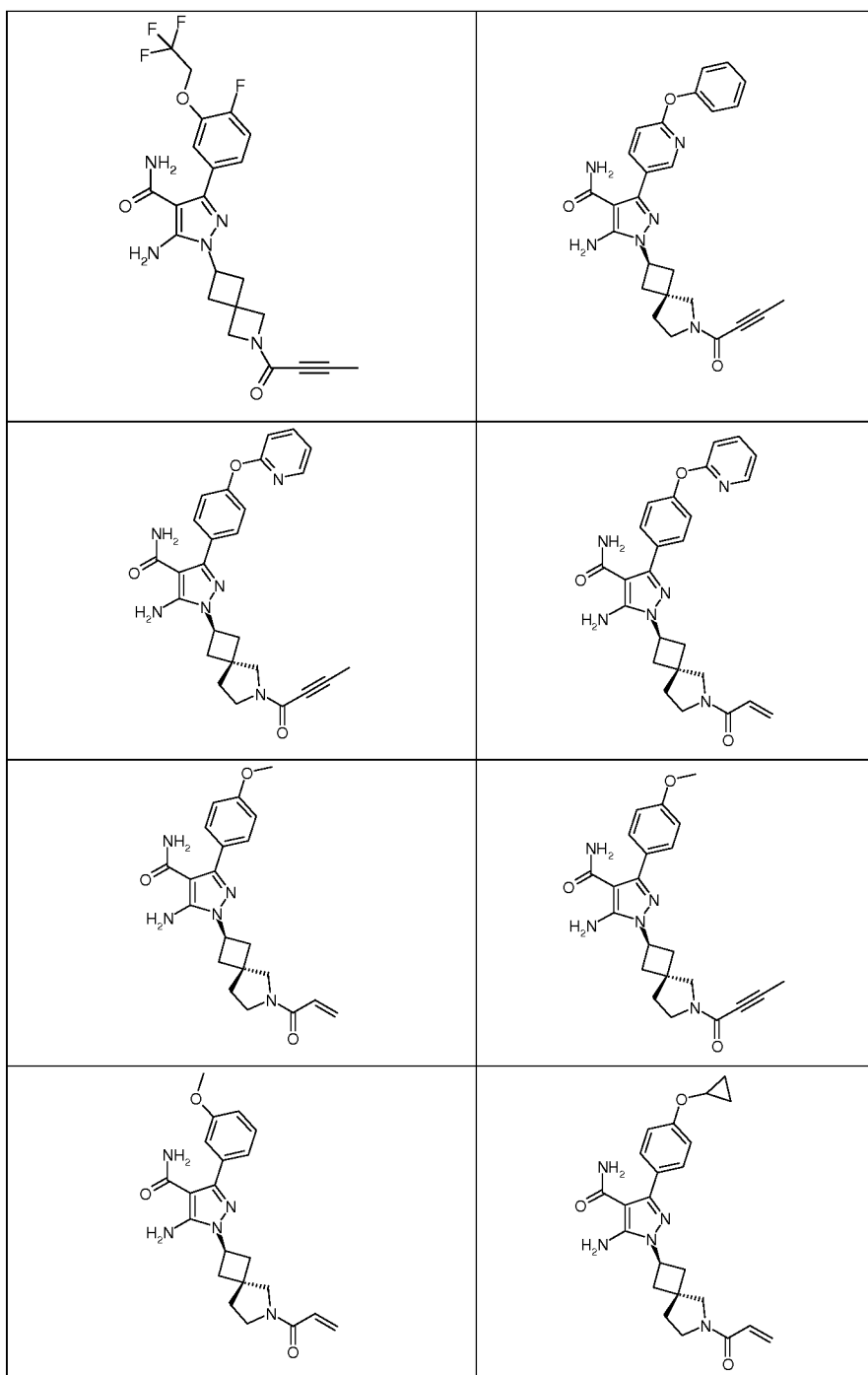


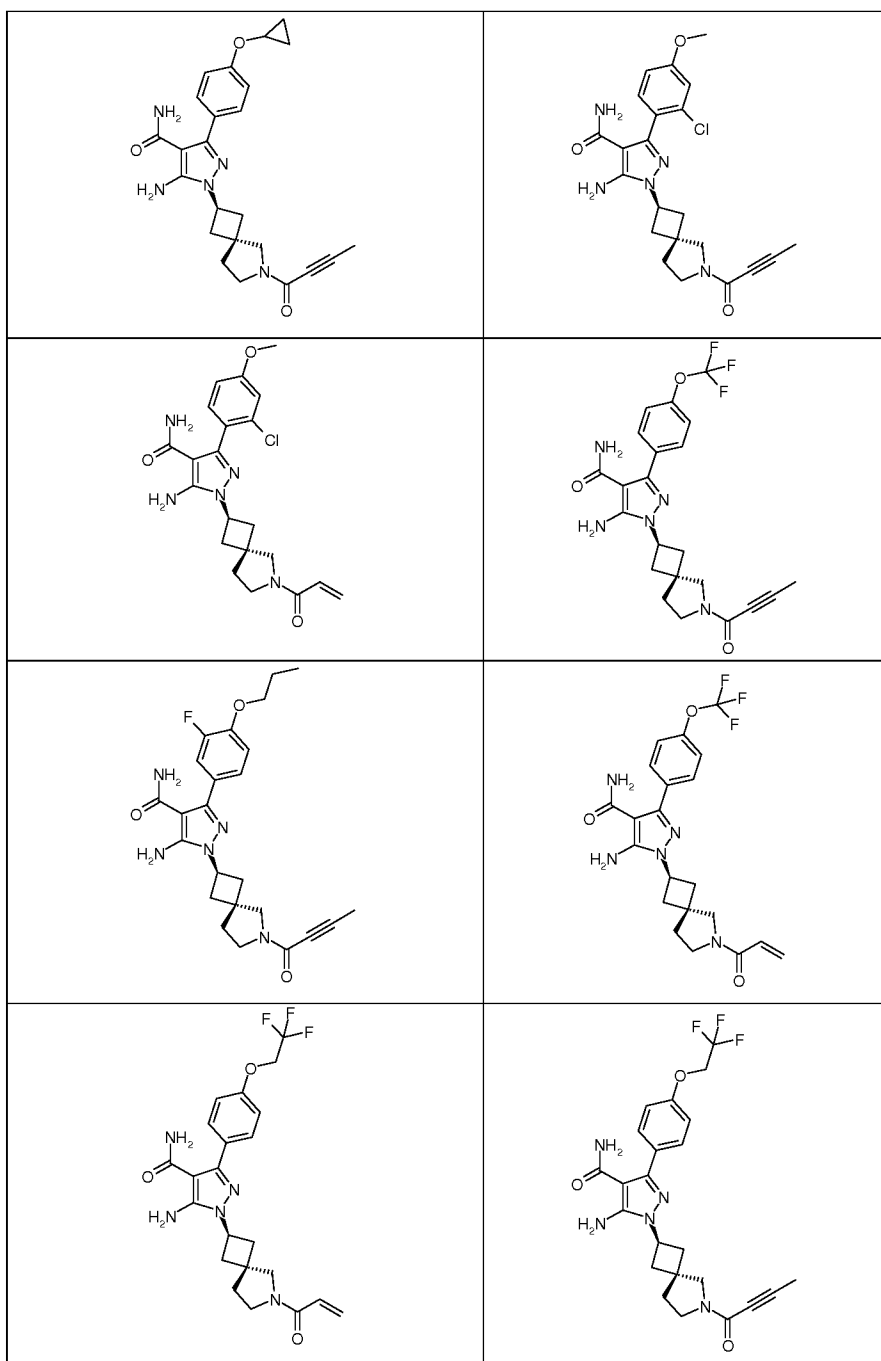


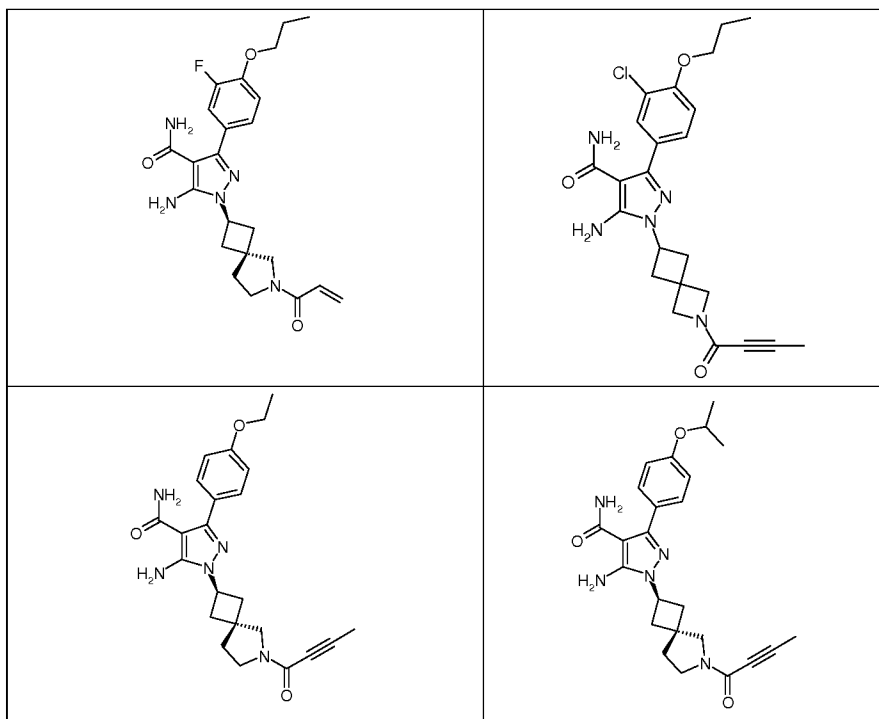












or the pharmaceutically acceptable salts thereof.

20. A pharmaceutical composition comprising a therapeutically effective amount of a
5 compound according to claim 1 or a pharmaceutically acceptable salt thereof.

21. A method of treating a disease chosen from rheumatoid arthritis, systemic lupus
erythromatosis, scleroderma, asthma, allergic rhinitis, allergic eczema, B cell lymphoma,
multiple sclerosis, juvenile rheumatoid arthritis, juvenile idiopathic arthritis, inflammatory
10 bowel disease, graft versus host disease, psoriatic arthritis, ankylosing spondylitis and
uveitis, comprising administering to a patient a therapeutically effective amount of a
compound according to claim 1 or a pharmaceutically acceptable salt thereof.