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| [19] | INTELLECTUAL PROPERTY PHILIPPINES | | | |
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| [22] | Publication Date: | 20/4/2015 | | |
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| [22] | Date Filed: | 10/2/2015 | | |
| [54] | Title: | HETEROAROMATIC COMPOUNDS AS BRUTON'S TYROSINE KINASE (BTK) INHIBITORS | | |
| [71] | Applicant(s): | BOEHRINGER INGELHEIM INT | | |
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| [30] | Priority Data: | 10/8/2012 US201261681684P | | |
| [51] | International Class 8: | A61K 31/415 20060101AFI20180709BHPH; A61K 31/4155 20060101ALI20180709BHPH; A61K 31/426 20060101ALI20180709BHPH; A61K 31/427 20060101ALI20180709BHPH; A61K 31/4439 20060101ALI20180709BHPH; A61K 31/5377 20060101ALI20180709BHPH; C07D 403/06 20060101ALI20180709BHPH; C07D 405/14 20060101ALI20180709BHPH; C07D 417/04 20060101ALI20180709BHPH; C07D 417/06 20060101ALI20180709BHPH; C07D 231/38 20060101ALI20180709BHPH; C07D 277/56 20060101ALI20180709BHPH; C07D 401/04 20060101ALI20180709BHPH; C07D 401/06 20060101ALI20180709BHPH; C07D 401/14 20060101ALI20180709BHPH; C07D 403/04 20060101ALI20180709BHPH; A61P 27/02 20060101ALI20180709BHPH; A61P 29/00 20060101ALI20180709BHPH; A61P 35/02 20060101ALI20180709BHPH; A61P 37/06 20060101ALI20180709BHPH; A61P 37/08 20060101ALI20180709BHPH; A61P 43/00 20060101ALI20180709BHPH; A61P 1/04 20060101ALI20180709BHPH; A61P 11/02 20060101ALI20180709BHPH; A61P 11/06 20060101ALI20180709BHPH; A61P 17/00 20060101ALI20180709BHPH; A61P 17/04 20060101ALI20180709BHPH; A61P 19/02 20060101ALI20180709BHPH; | | |
| [57] | Abstract: | The present invention encompasses compounds of the formula (I) wherein the groups A, Cy, X1 and Y are defined herein, which are suitable for the treatment of | | |

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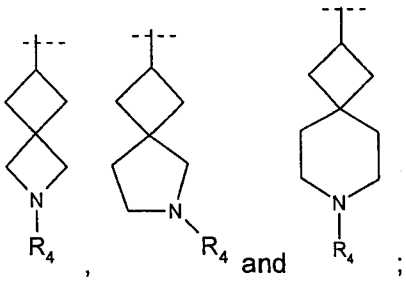
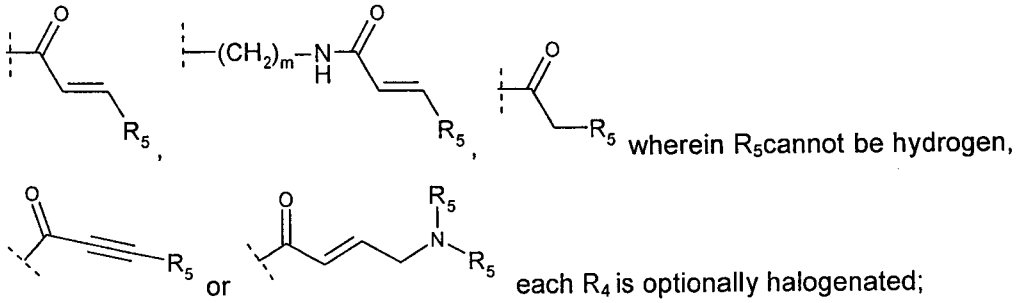
| | | diseases related to BTK, process of making, pharmaceutical preparations which contain compounds and their methods of use. |



a heterocycle chosen from piperidinyl and pyrrolidinyl;

and phenyl each heterocycle or phenyl substituted by one $R_4$;

$R_4$ is



wherein $R_5$cannot be hydrogen, each $R_4$ is optionally halogenated;

each $R_5$ is independently chosen from hydrogen, $C_{1-3}$ alkyl, halo $C_{1-3}$ alkyl, $C_{1-3}$ 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, morpholinyl and 1,4-oxazepane,

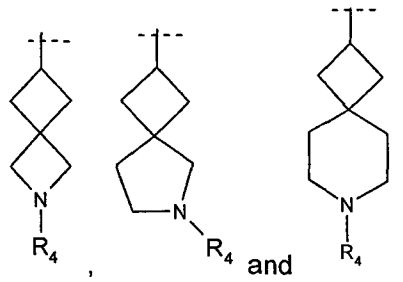
or a pharmaceutically acceptable salt thereof.

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

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

Y is chosen from:

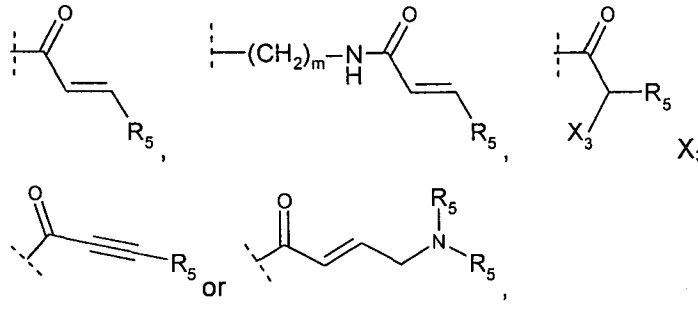
a spirocycle chosen from



a heterocycle chosen from piperidinyl and pyrrolidinyl;

and phenyl each heterocycle or phenyl substituted by one $R_4$;

$R_4$ is

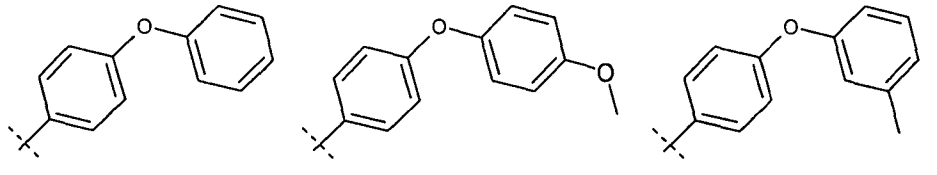


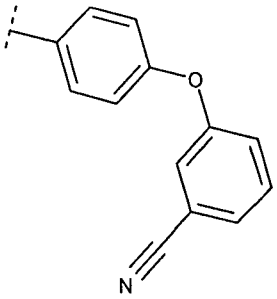
$X_3$ = halogen or hydrogen,

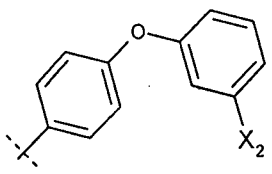
each $R_5$ is independently chosen from hydrogen, $C_{1-3}$ alkyl, $-CF_3$, $C_{1-3}$ alkyl$C_{1-3}$ alkoxy, $-CH_2$-heterocycle and heterocycle each heterocycle optionally substituted by F, Cl, OH and $CH_3$-$S(O)_2$- and each heterocycle chosen from pyrrolidinyl, piperidinyl and 1,4-oxazepane, or a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

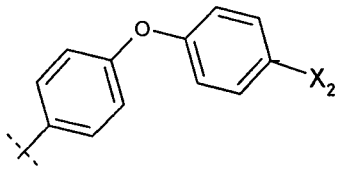
Cy is



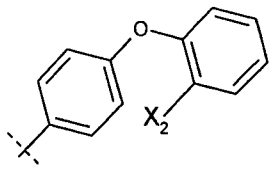




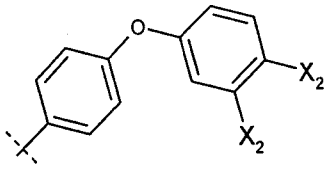
$X_2$= F, Cl ,



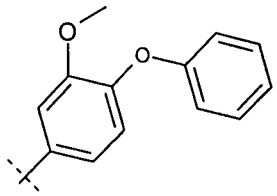
$X_2$= F, Cl ,



$X_2$= F, Cl



$X_2$= F, Cl



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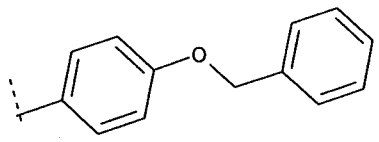

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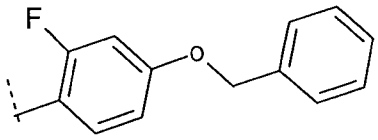

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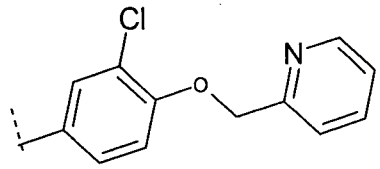

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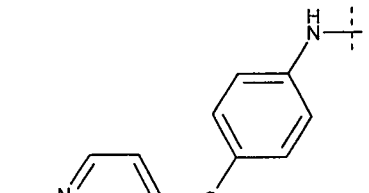

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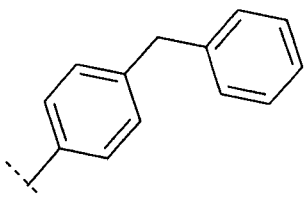

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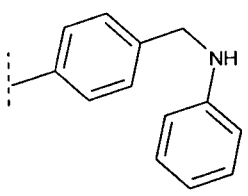

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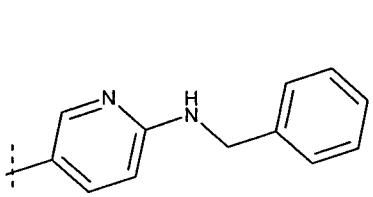

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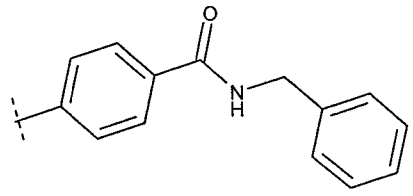

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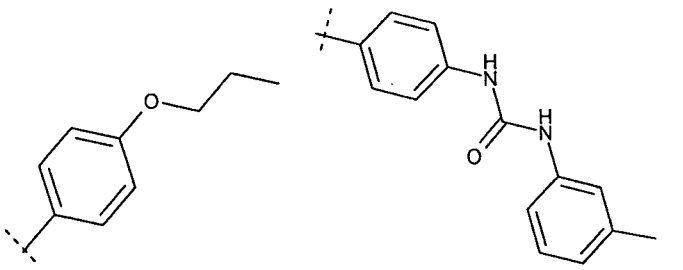
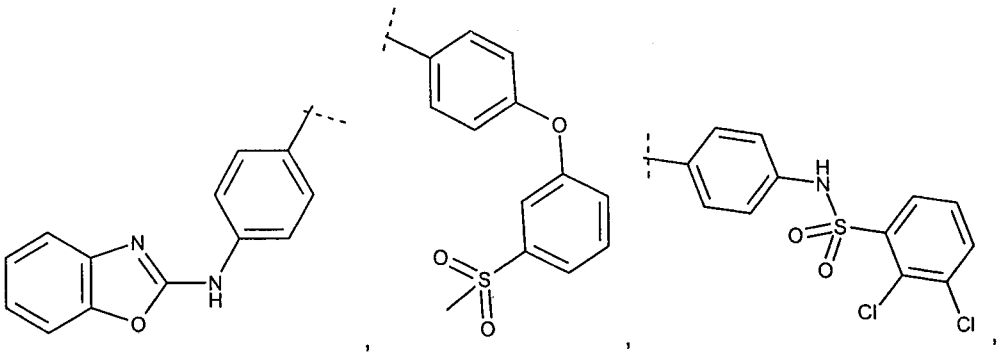
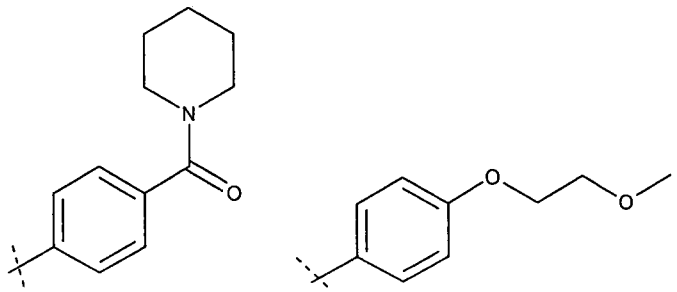






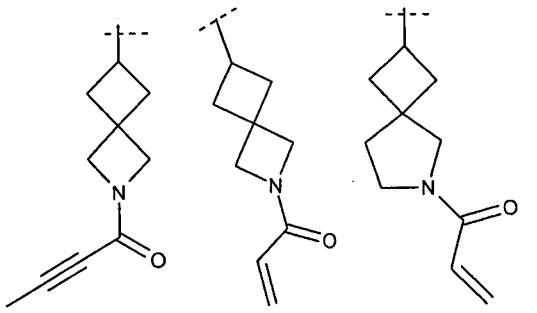
or

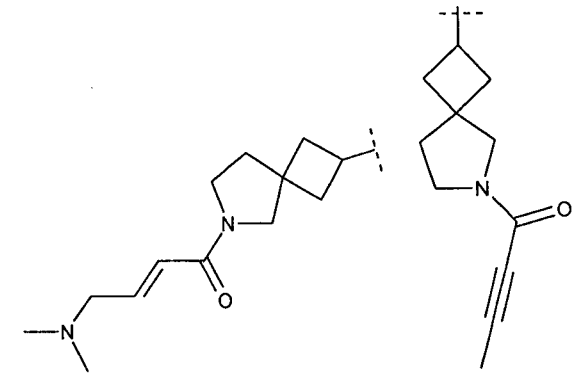


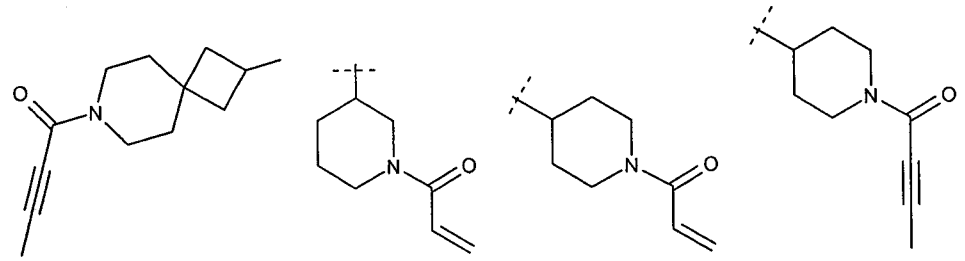
or a pharmaceutically acceptable salt thereof.

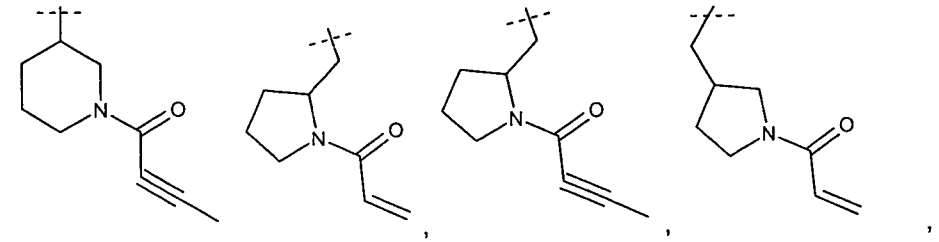
In a further embodiment, there is provided a compound of the formula (I) according to any of the embodiments herein-above and wherein

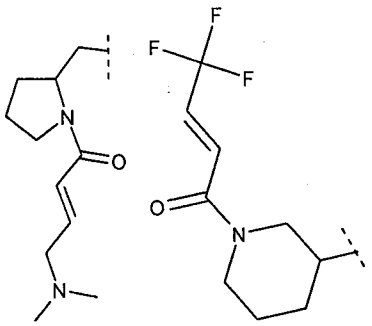
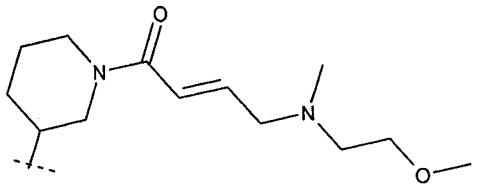
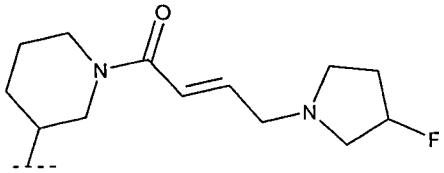
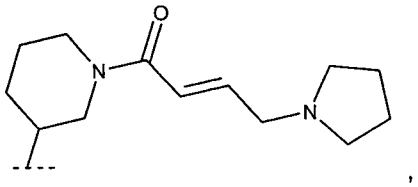
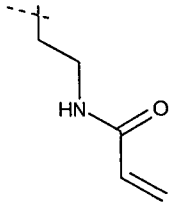
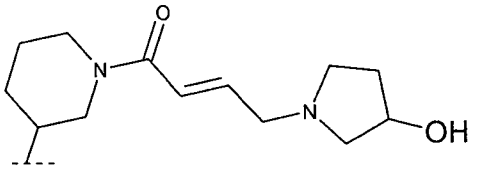
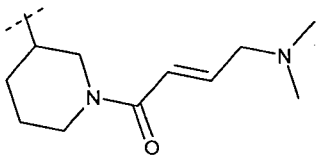
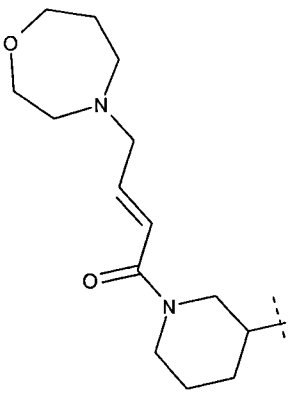
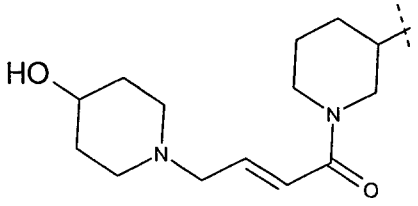
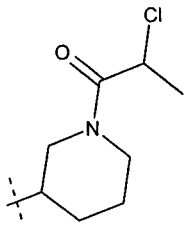
X-Y =

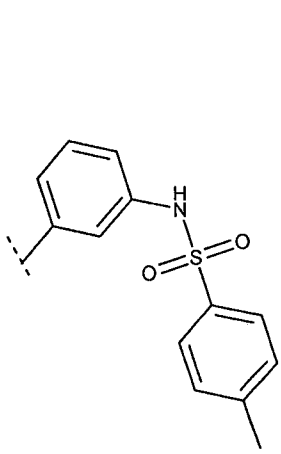
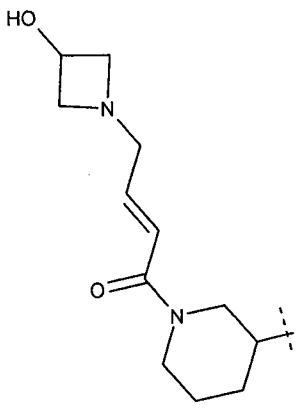
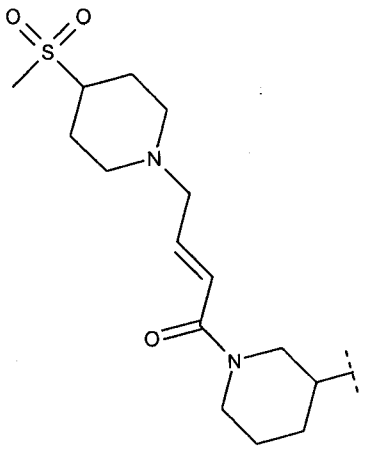






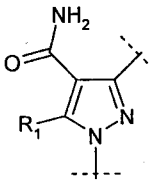
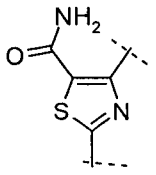
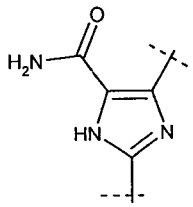





or a pharmaceutically acceptable salt thereof.

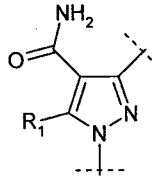
In a further embodiment, there is provided a compound of the formula (I) according to any of the embodiments herein-above and wherein

A ring is:




or a pharmaceutically acceptable salt thereof.

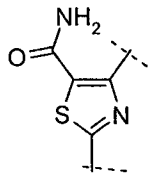
In a further embodiment, there is provided a compound of the formula (I) according to any of the embodiments herein-above and wherein

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

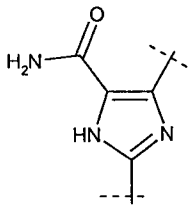
A ring is:



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

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

$R_2$ 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;

or a pharmaceutically acceptable salt thereof.

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

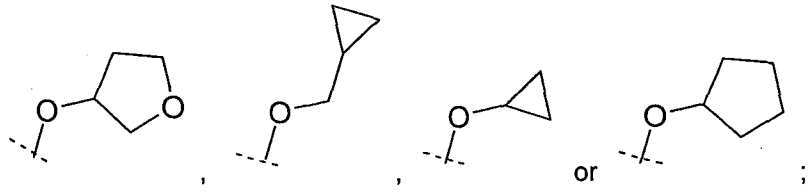
of the embodiments hereinabove and wherein

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

n = 1;

or a pharmaceutically acceptable salt thereof.

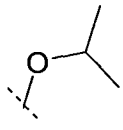
In a further embodiment, there is provided a compound of the formula (I) according to any of the embodiments herein-above and wherein

L-Ar 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

$R_2$ is:

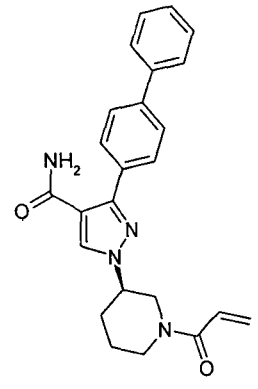
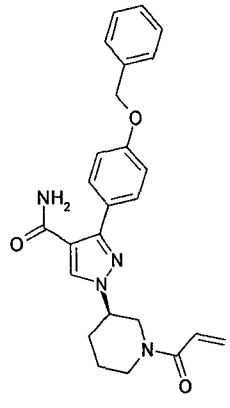
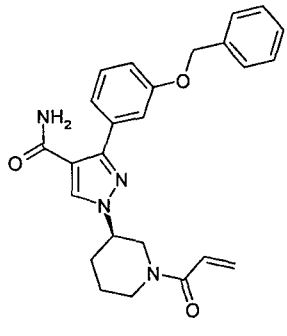
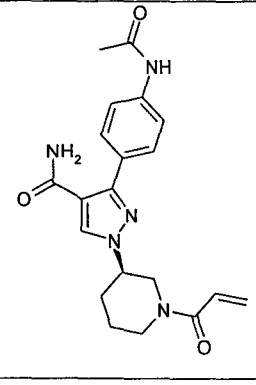
 , $-OCH_2CH_3$, $-OCH_2CH_2CH_3$, $-OCH_3$, $-OCF_3$ or $-OCH_2CF_3$;

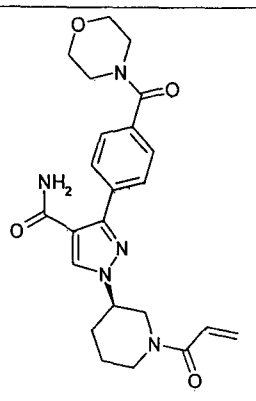
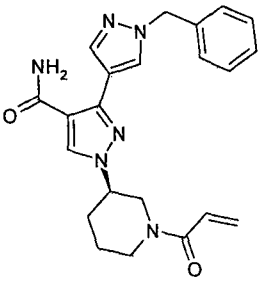
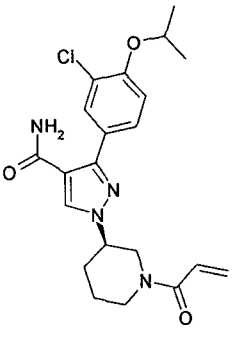
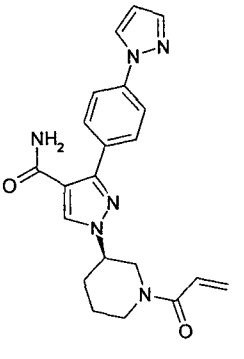
or a pharmaceutically acceptable salt thereof.

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

| Example | Structure | BTK IC50 (nM) | HPLC Method | RT (min) | *m/z*[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 |

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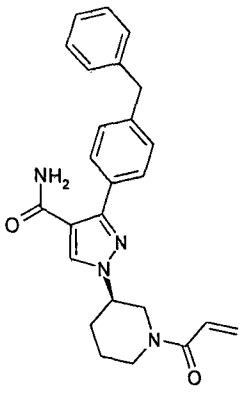
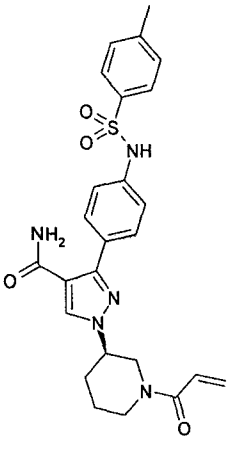
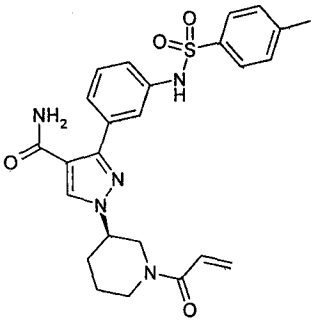
|---|---|---|---|---|---|
| 9 |  | 14 | A | 4.11 | 415.3 |
| 10 |  | - | A | 4.14 | 494.3 |
| 11 |  | 5500 | A | 2.80 | 494.2 |

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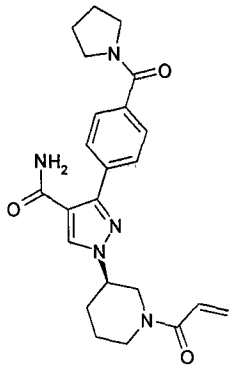
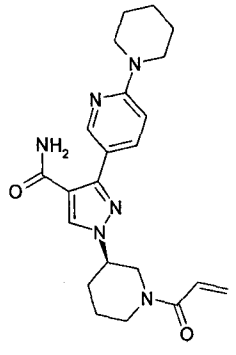
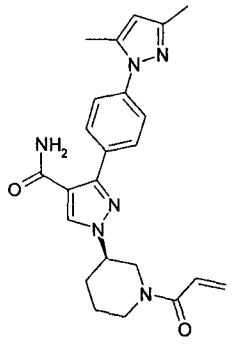
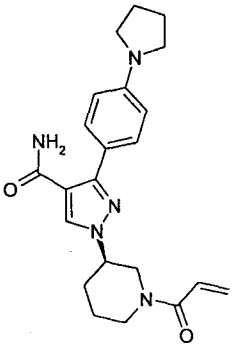
|---|---|---|---|---|---|
| 12 |  | - | A | 2.67 | 422.3 |
| 13 |  | - | A | 2.56 | 409.3 |
| 14 |  | 7800 | A | 2.81 | 419.4 |
| 15 |  | - | A | 2.89 | 394.4 |

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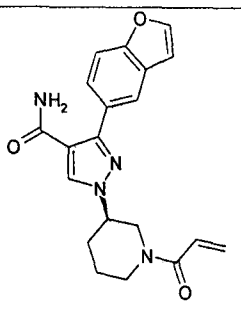
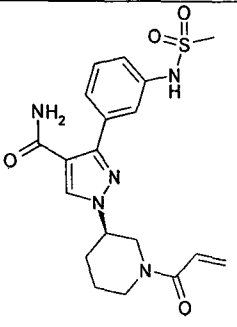
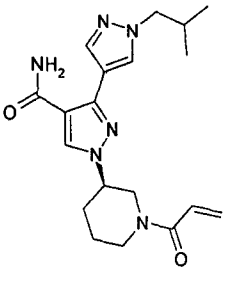
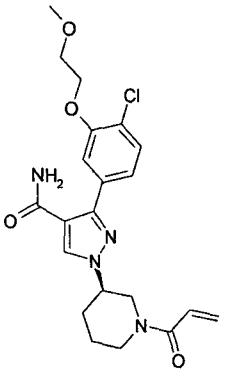
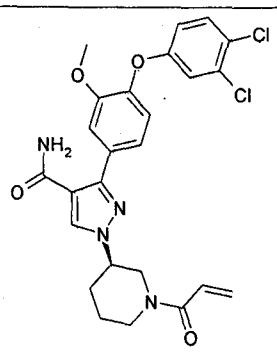
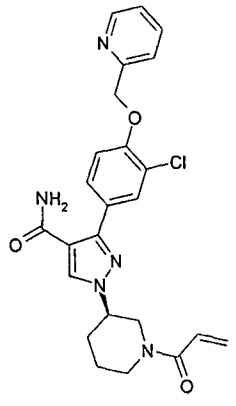
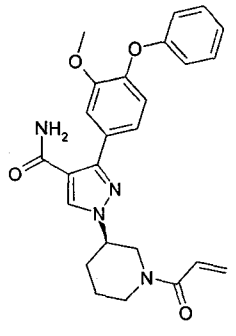
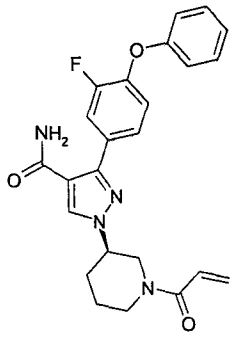
|---|---|---|---|---|---|
| 16 |  | 580 | A | 2.77 | 365.3 |
| 17 |  | 4800 | A | 2.60 | 418.4 |
| 18 |  | - | A | 2.72 | 371.4 |
| 19 |  | - | A | 2.84 | 433.3 |

| | | | | | |
|---|---|---|---|---|---|
| 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 |

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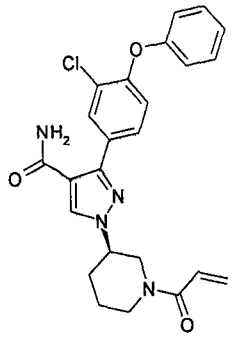
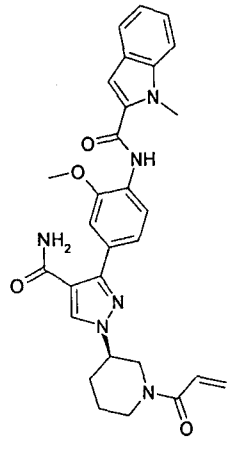
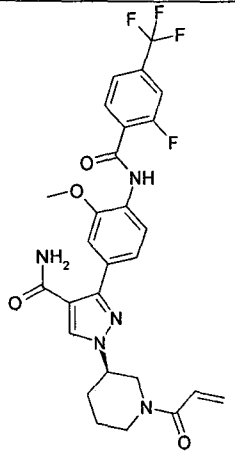
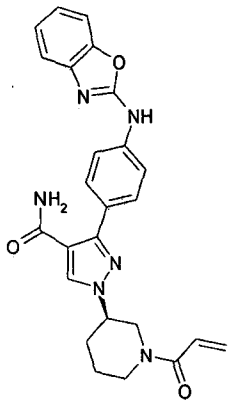
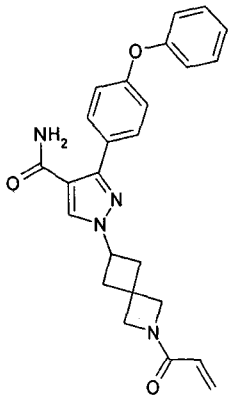
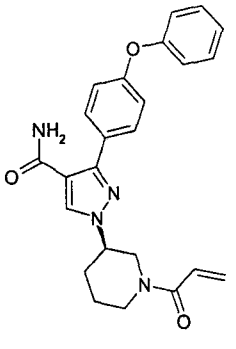
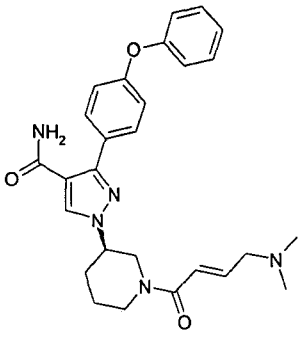
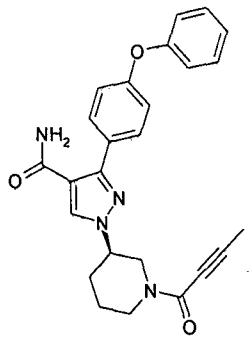
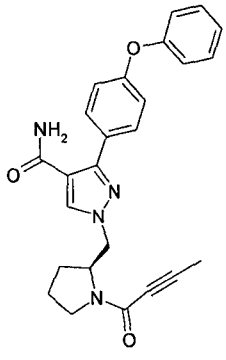
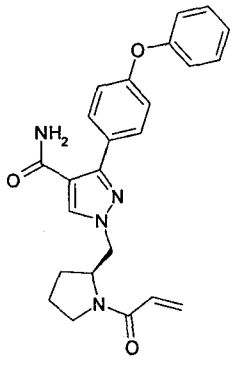
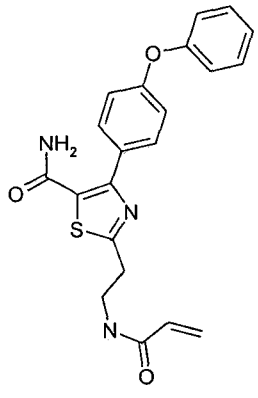
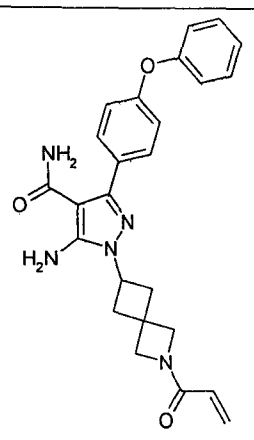
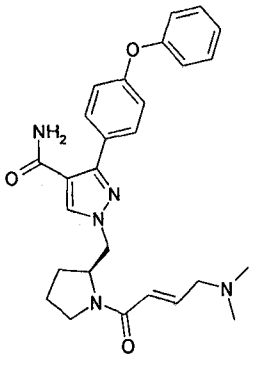
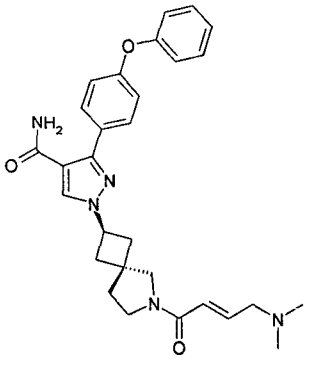
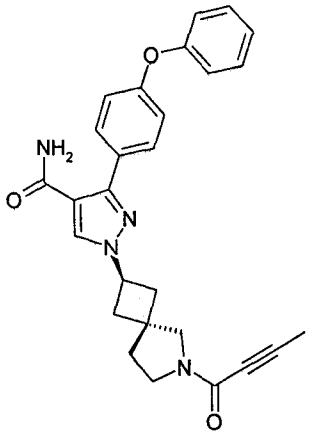
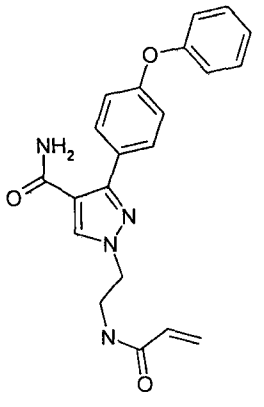
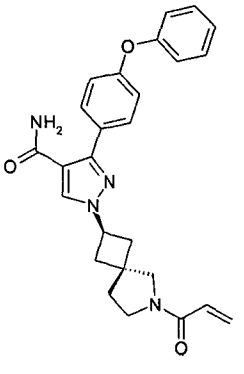
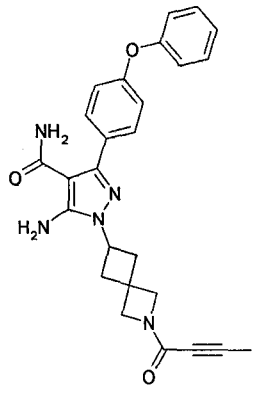
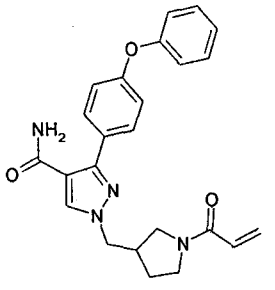
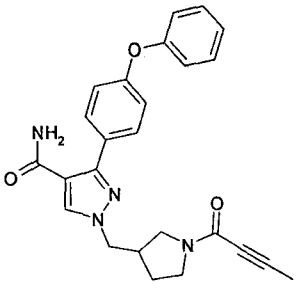
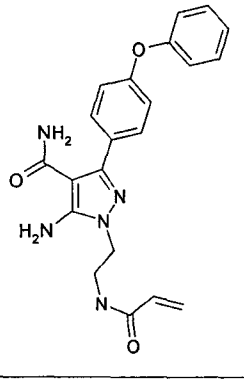
|---|---|---|---|---|---|
| 24 |  | 9.4 | A | 3.02 | 451.3 |
| 25 |  | 5.1 | A | 3.03 | 527.3 |
| 26 |  | 22 | A | 3.03 | 560.3 |

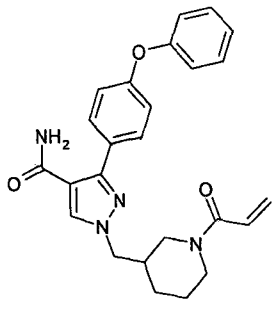
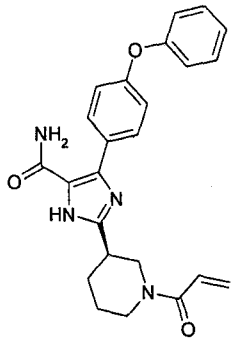
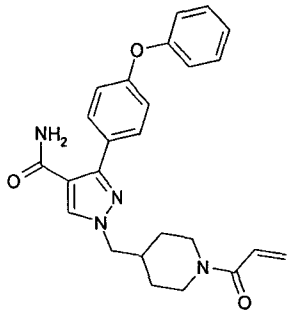
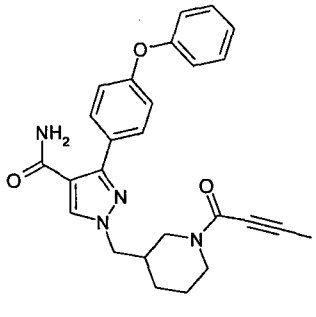
| | | | | | |
|---|---|---|---|---|---|
| 27 |  | 300 | A | 2.84 | 457.3 |
| 28 |  | 3.5 | A | 2.85 | 429.3 |
| 29 |  | 3.2 | A | 2.83 | 417.3 |
| 30 |  | 57 | A | 2.54 | 474.35 |

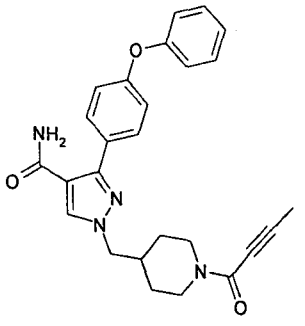
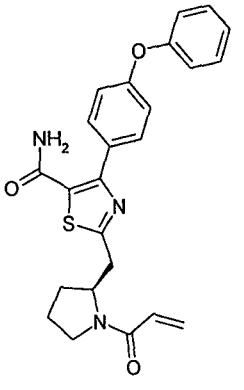
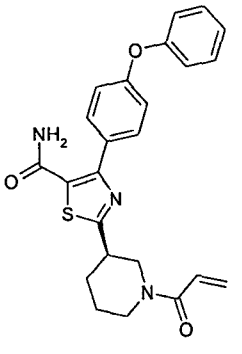
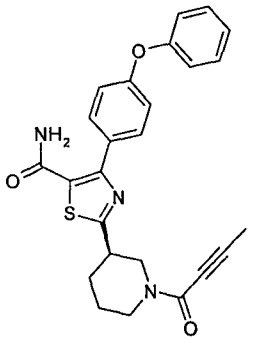
| | | | | | |
|---|---|---|---|---|---|
| 31 |  | 80 | A | 2.86 | 429.35 |
| 32 |  | 150 | A | 2.81 | 429.35 |
| 33 |  | 9.7 | A | 2.83 | 417.35 |
| 34 |  | 21 | A | 2.78 | 394.35 |

| | | | | | |
|---|---|---|---|---|---|
| 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 |

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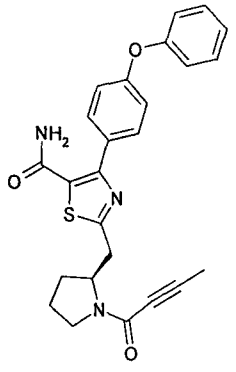
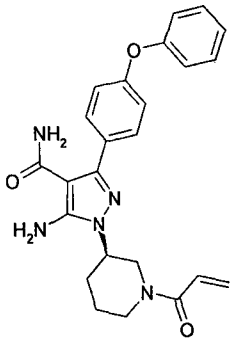
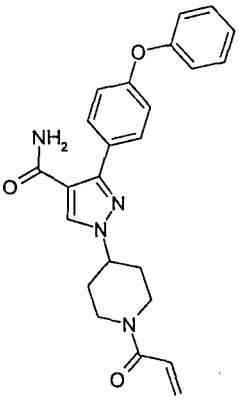
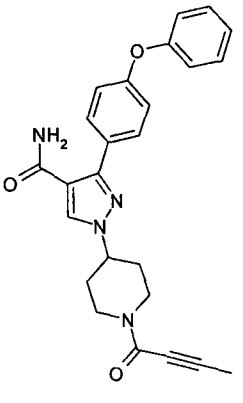
| 53 |  | 14 | A | 3.00 | 446.3 |
| 54 |  | 0.73 | A | 3.00 | 432.4 |
| 55 |  | 6.6 | A | 2.93 | 417.4 |
| 56 |  | 15 | A | 2.95 | 429.4 |

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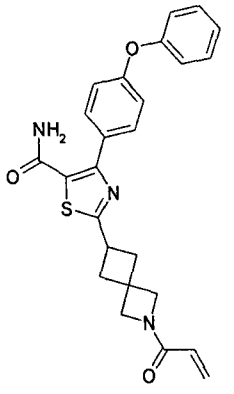
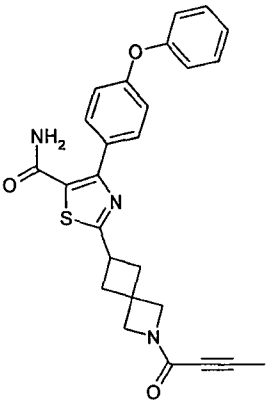
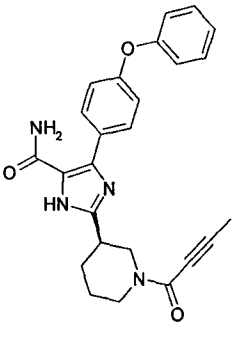
| 57 |  | 3.2 | A | 2.99 | 446.3 |
| 58 |  | 1.1 | A | 3.01 | 458.3 |
| 59 |  | 8.9 | A | 2.75 | 429.4 |

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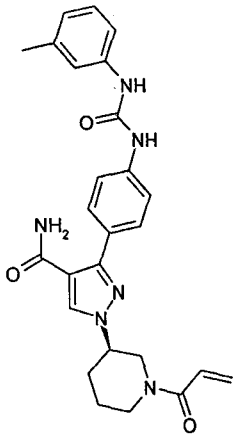
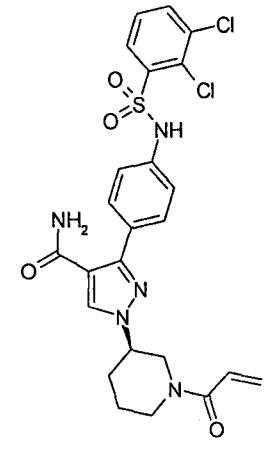
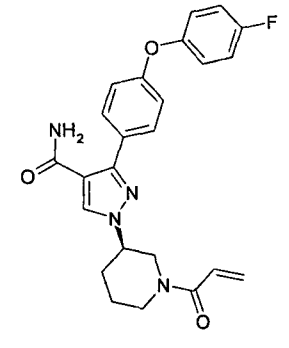
| 60 |  | 41 | A | 2.82 | 473.4 |
| 61 |  | 780 | A | 2.86 | 548.1 |
| 62 |  | 93 | A | 2.97 | 435.3 |

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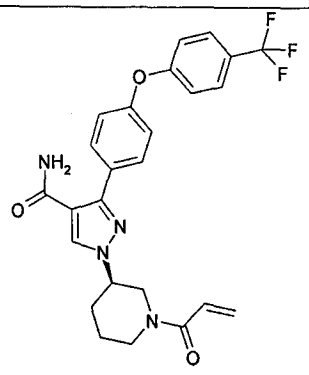
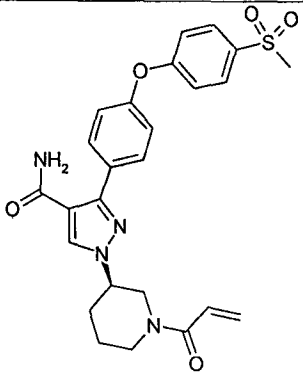
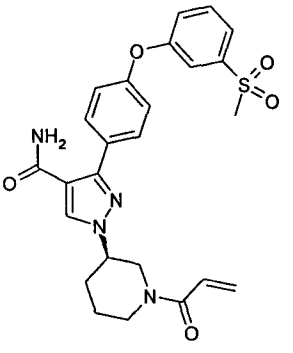
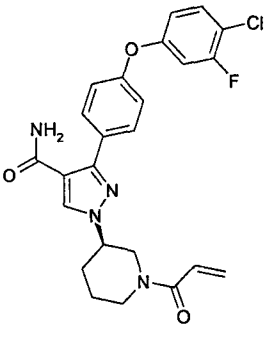
| 63 |  | 660 | A | 3.08 | 485.3 |
| 64 |  | 6500 | A | 2.79 | 495.1 |
| 65 |  | 330 | B | 0.65 | 495.1 |
| 66 |  | 43 | A | 3.10 | 469.2 |

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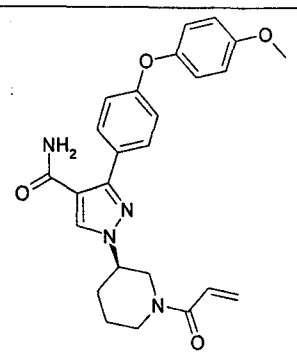
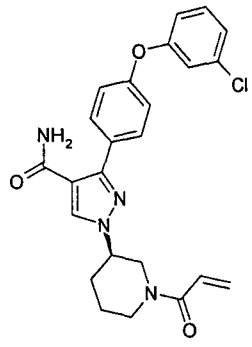
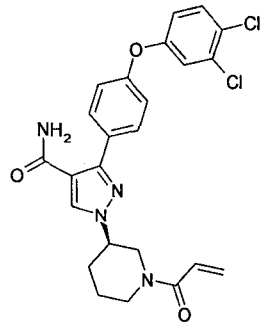
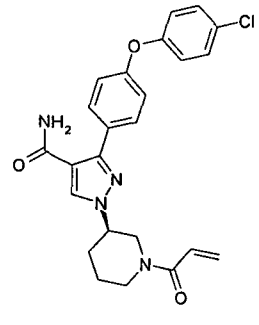
| 67 |  | 38 | A | 2.95 | 447.3 |
| 68 |  | 41 | A | 3.08 | 451.4 |
| 69 |  | 43 | A | 3.20 | 485.3 |
| 70 |  | 45 | A | 3.07 | 451.3 |

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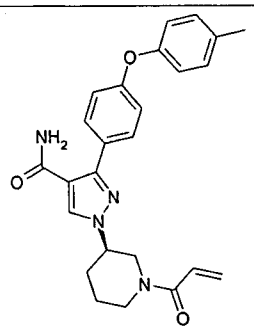
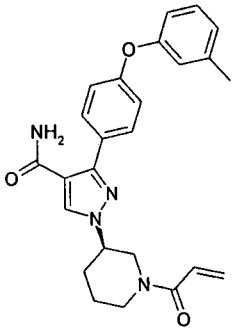
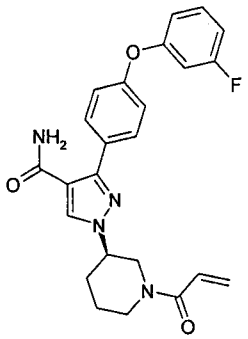
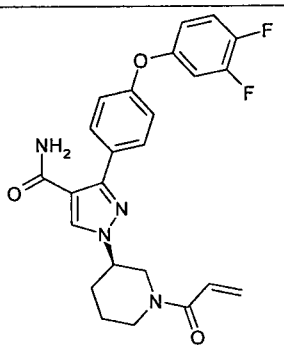
| 71 |  | 14 | A | 3.04 | 431.4 |
| 72 |  | 4 | A | 3.04 | 431.4 |
| 73 |  | 9.3 | A | 3.00 | 435.3 |
| 74 |  | - | A | 2.89 | 453.3 |

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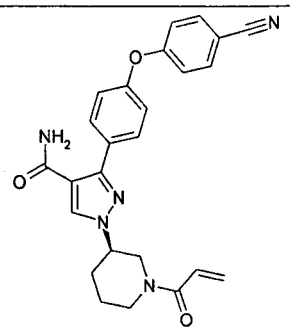
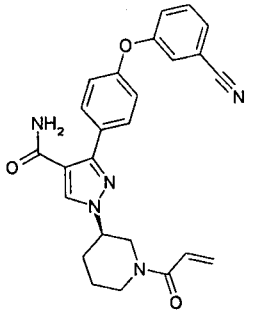
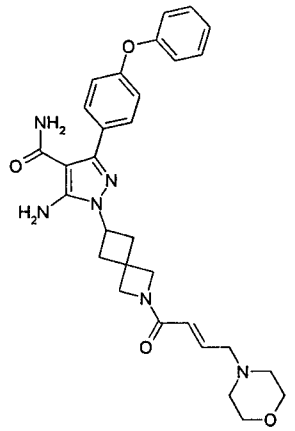
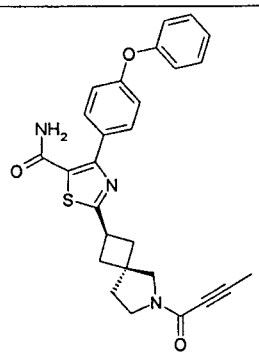
| 75 |  | 6600 | A | 2.91 | 442.3 |
| 76 |  | 61 | A | 2.92 | 442.4 |
| 77 |  | 1.9 | A | 2.72 | 543.3 |
| 78 |  | 2.1 | A | 2.95 | 472.2 |

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



## BACKGROUND OF THE INVENTION

### 1. TECHNICAL FIELD

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

### 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 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, 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 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

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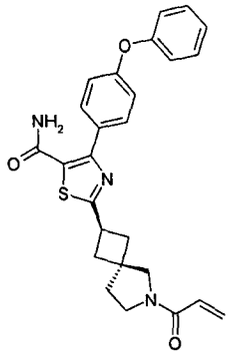
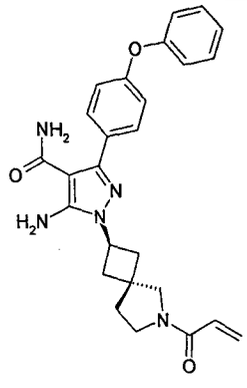
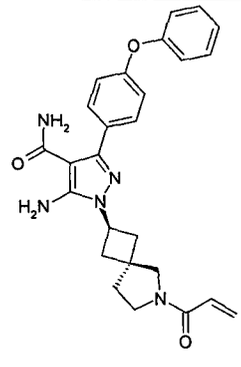
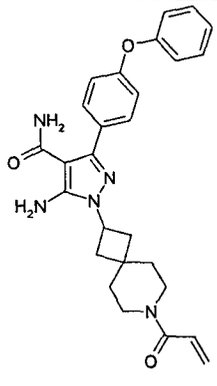
| 79 |  | 6.4 | A | 3.05 | 460.2 |
| 80 |  | 0.93 | A | 3.04 | 458.4 |
| 81 |  | 0.79 | A | 2.91 | 458.3 |
| 82 |  | 2 | A | 2.95 | 472.2 |

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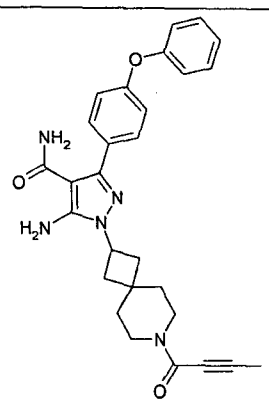
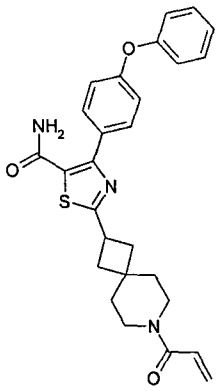
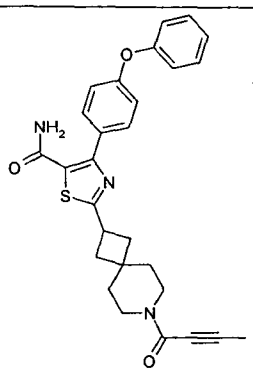
| 83 |  | 2.1 | A | 2.99 | 484.3 |
| 84 |  | 52 | A | 3.10 | 474.2 |
| 85 |  | 300 | A | 3.11 | 486.2 |

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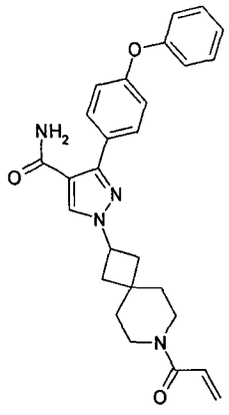
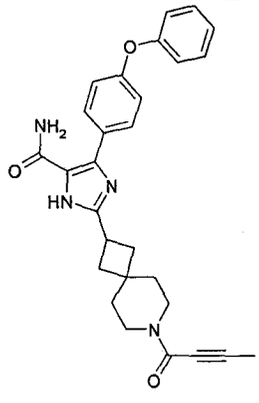
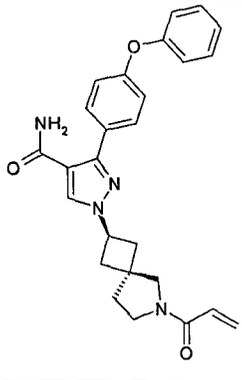
| 86 |  | 95 | A | 3.03 | 457.4 |
| 87 |  | 4.3 | A | 2.87 | 469.3 |
| 88 |  | 21 | A | 2.96 | 443.4 |

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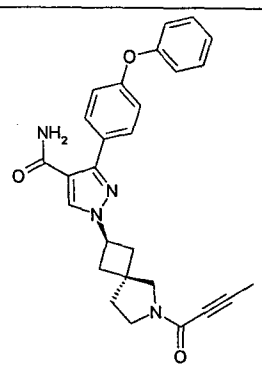
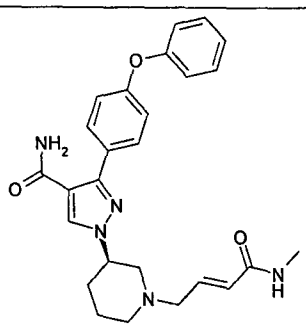
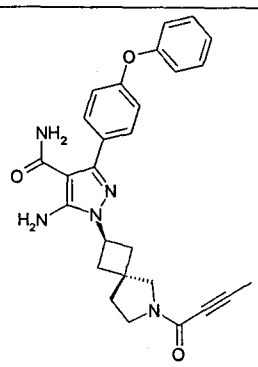
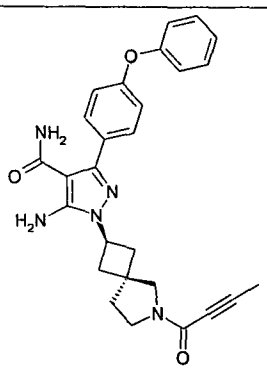
| 89 |  | 34 | A | 2.98 | 455.3 |
| 90 |  | 90 | B | 0.55 | 460.1 |
| 91 |  | 0.79 | A | 2.94 | 470.3 |
| 92 |  | 0.89 | A | 2.88 | 470.3 |

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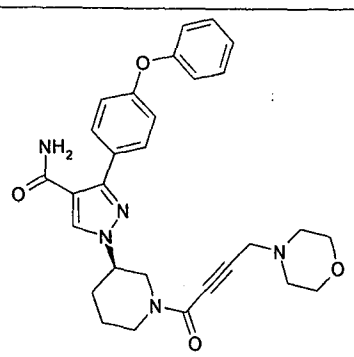
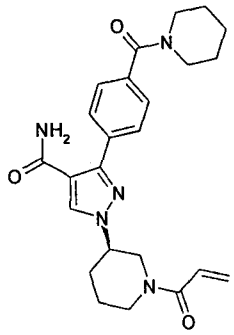
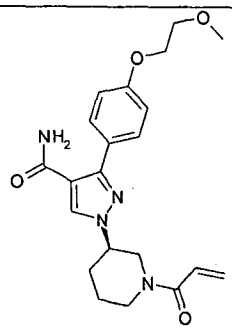
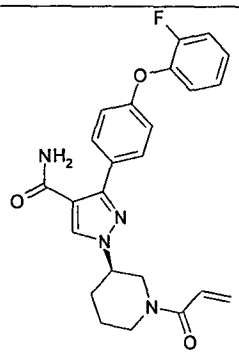
| 93 |  | 33 | A | 2.80 | 514.3 |
| 94 |  | 8200 | A | 2.75 | 436.3 |
| 95 |  | 1600 | A | 2.71 | 399.3 |
| 96 |  | 4.8 | A | 2.95 | 435.3 |

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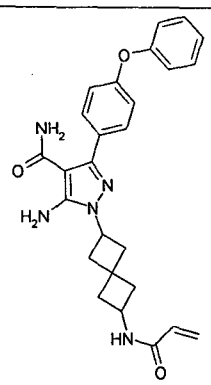
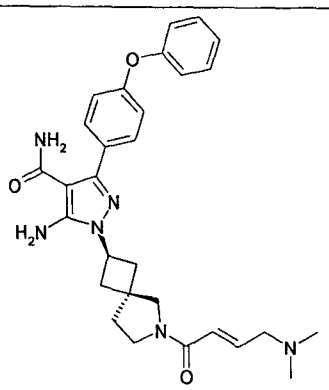
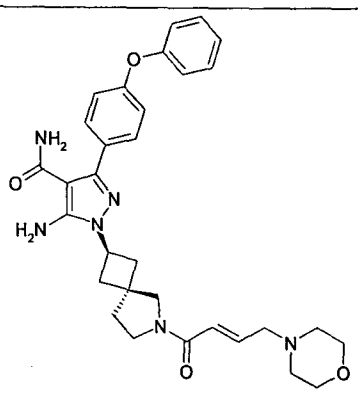
| 97 |  | 0.8 | A | 2.93 | 458.3 |
| 98 |  | 0.7 | A | 2.69 | 515.4 |
| 99 |  | 3.2 | A | 2.76 | 557.3 |

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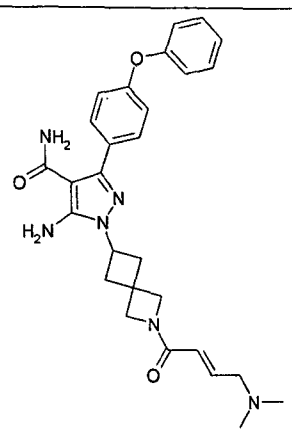
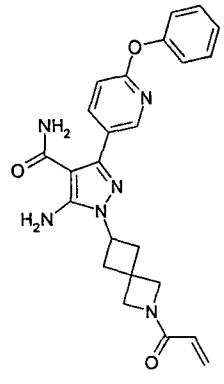
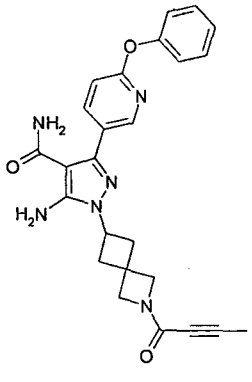
| 100 |  | 0.8 | A | 2.63 | 501.3 |
| 101 |  | 9.2 | A | 2.71 | 445.4 |
| 102 |  | 2.7 | A | 2.83 | 457.3 |

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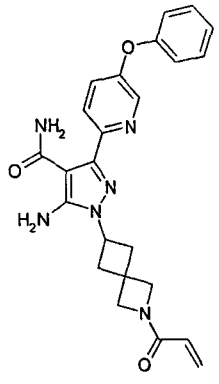
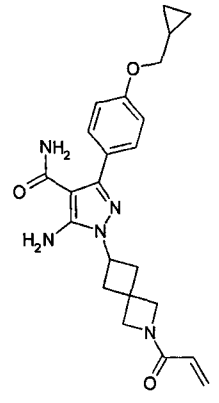
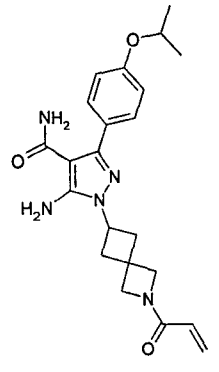
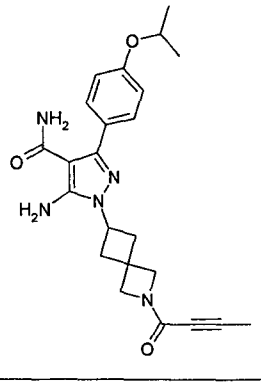
| 103 |  | 2.8 | A | 3.13 | 445.2 |
| 104 |  | 19 | A | 2.79 | 422.4 |
| 105 |  | 13 | A | 2.77 | 410.3 |
| 106 |  | 13 | A | 2.81 | 422.4 |

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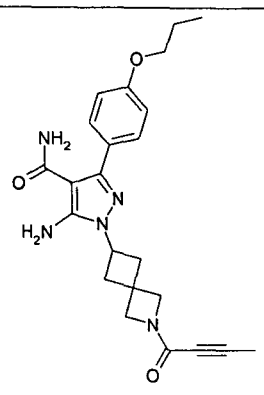
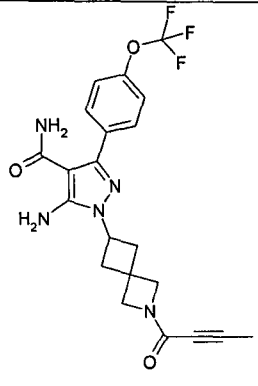
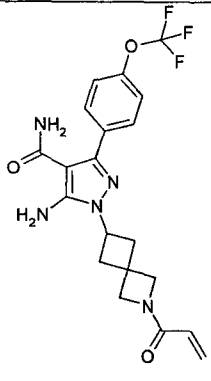
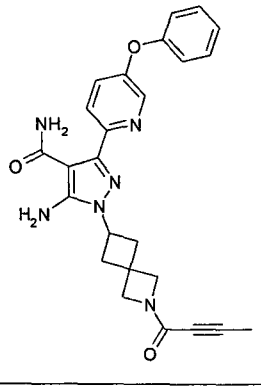
| 107 |  | 3.3 | A | 2.81 | 422.4 |
| 108 |  | 14 | A | 2.75 | 448.3 |
| 109 |  | 24 | A | 2.86 | 436.3 |
| 110 |  | 0.87 | A | 3.09 | 457.3 |

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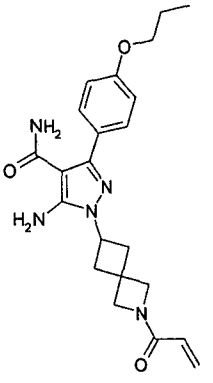
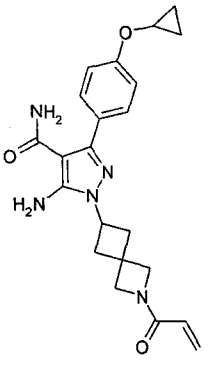
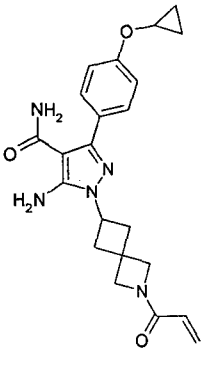
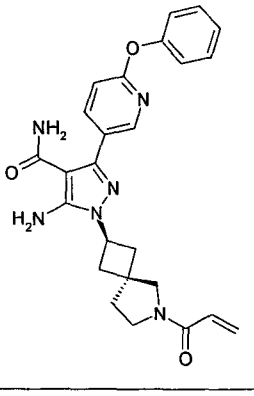
| 111 |  | 16 | A | 2.77 | 410.4 |
| 112 |  | 6.7 | A | 2.82 | 408.4 |
| 113 |  | 4.3 | A | 2.85 | 420.4 |
| 114 |  | 3.4 | A | 2.87 | 459.3 |

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 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.

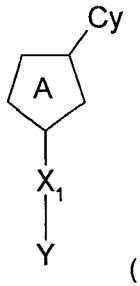
Within myeloid cells, BTK signal transduction is necessary for the stimulated release of inflammatory cytokines such as TNF from stimulated monocytes (Horwood, J Exp Med, 2003, 1603-xxx) and for optimal actin cytoskeletal organization and lacunar bone resorption in isolated osteoclasts (Danks, 2011, 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 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

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

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




(I)

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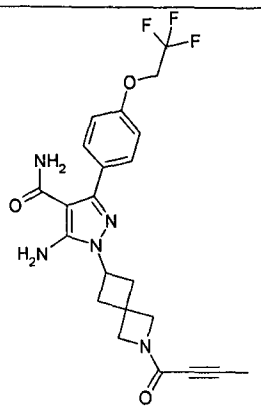
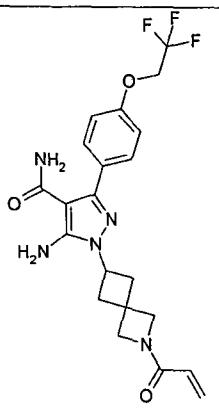
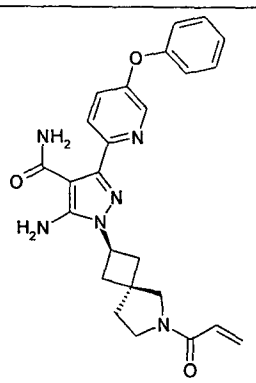
| 115 |  | 3.5 | A | 2.82 | 462.3 |
| 116 |  | 12 | A | 2.78 | 450.3 |
| 117 |  | 1.1 | A | 3.52 | 459.2 |

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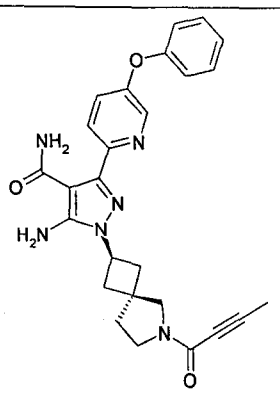
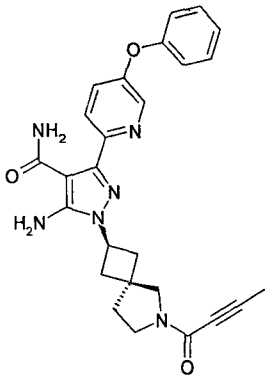
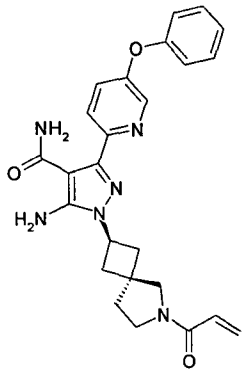
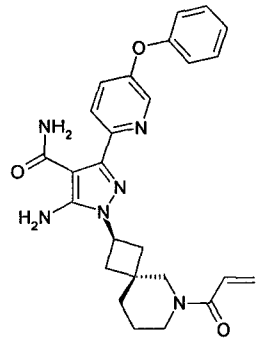
| 118 |  | 0.5 | A | 3.49 | 471.2 |
| 119 |  | 11 | A | 3.25 | 471.3 |
| 120 |  | 3.5 | A | 3.29 | 459.2 |
| 121 |  | 0.2 | A | 3.13 | 472.2 |

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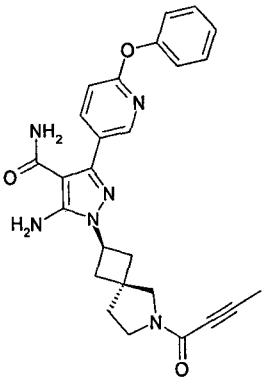
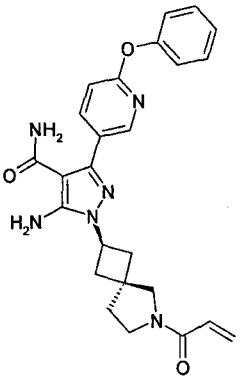
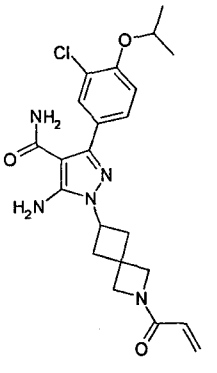
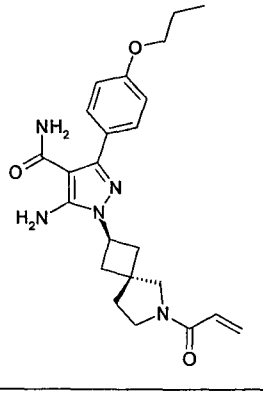
| 122 |  | 17 | A | 2.91 | 471.3 |
| 123 |  | 9.1 | A | 2.88 | 459.3 |
| 124 |  | 10 | B | 1.73 | 444.1 |
| 125 |  | 7.5 | B | 0.85 | 424.0 |

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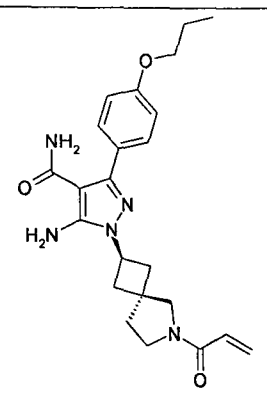
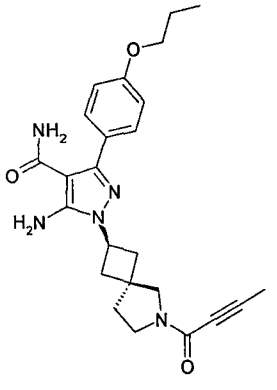
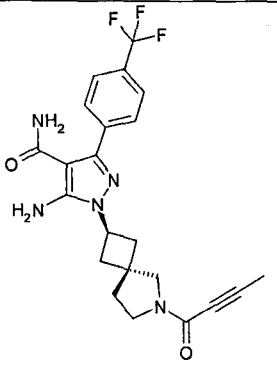
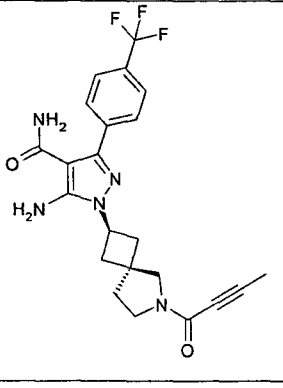
| 126 |  | 28 | A | 2.98 | 424.3 |
| 127 |  | 15 | B | 0.86 | 436 |
| 128 |  | 0.9 | A | 3.02 | 446.4 |
| 129 |  | 29 | B | 0.85 | 446.1 |

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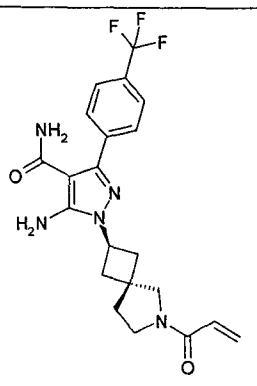
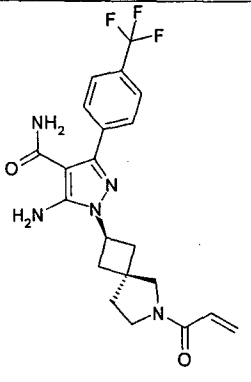
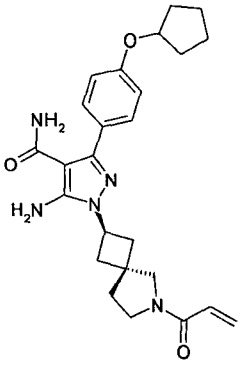
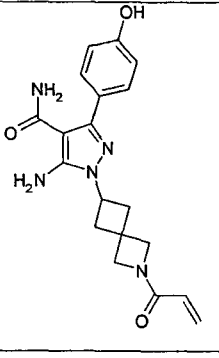
| 130 |  | 6.4 | A | 3 | 434.4 |
| 131 |  | 28 | B | 0.80 | 433.9 |
| 132 |  | 1.9 | B | 1.02 | 451.5 |
| 133 |  | 8.4 | A | 2.64 | 368.3 |

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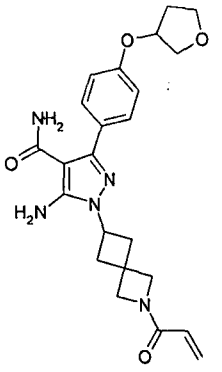
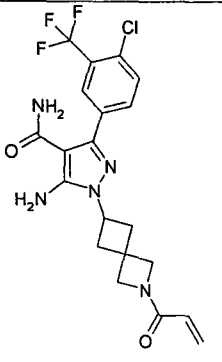
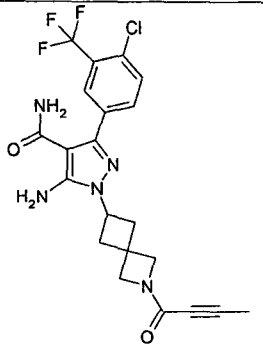
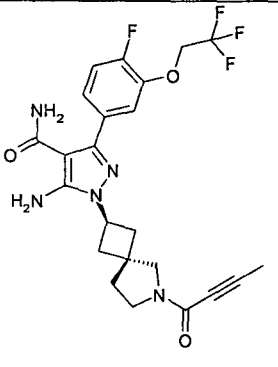
| 134 |  | 120 | B | 0.59 | 438.3 |
| 135 |  | 26 | A | 2.83 | 454.3 |
| 136 |  | 14 | B | 0.91 | 466 |
| 137 |  | 1.6 | B | 0.89 | 494.1 |

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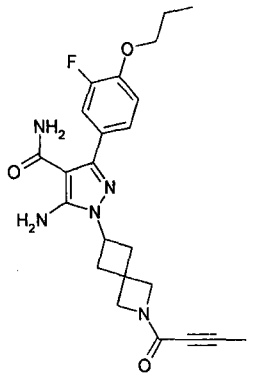
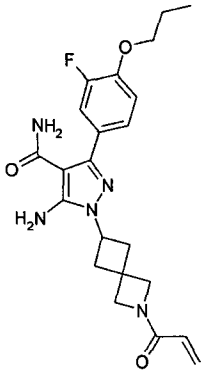
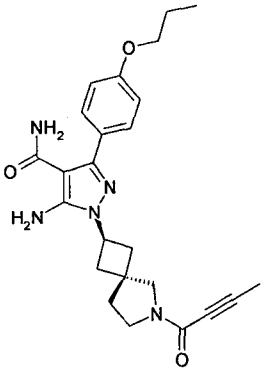
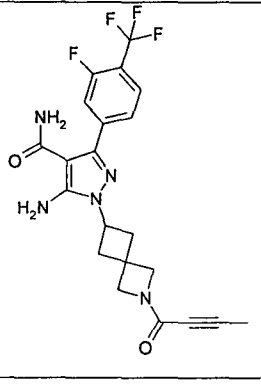
| 138 |  | 2.2 | B | 0.86 | 440.1 |
| 139 |  | 16 | B | 0.56 | 428.1 |
| 140 |  | 0.9 | B | 0.90 | 436.2 |
| 141 |  | 14 | B | 0.87 | 450.0 |

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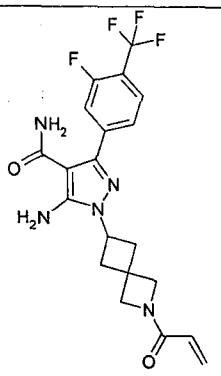
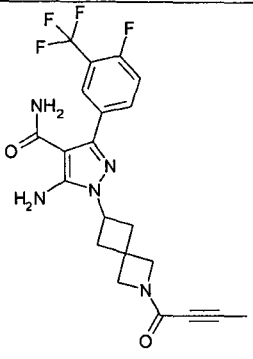
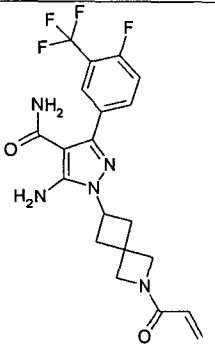
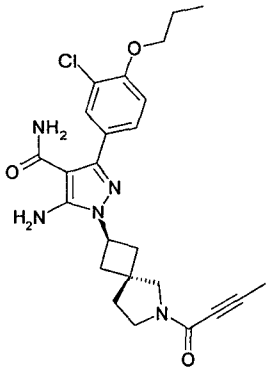
| 142 |  | 29 | B | 0.82 | 438.0 |
| 143 |  | 37 | B | 0.85 | 450.0 |
| 144 |  | 72 | B | 0.80 | 438.1 |
| 145 |  | 3.5 | A | 3.17 | 458.4 |

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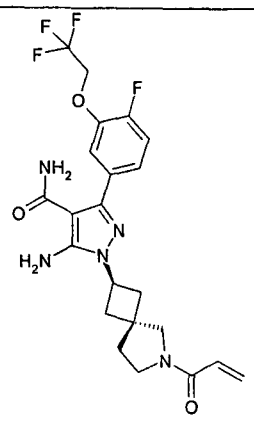
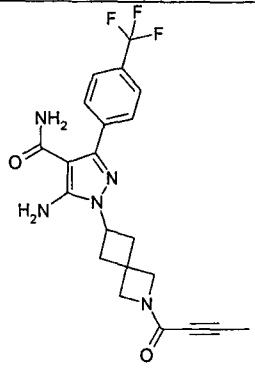
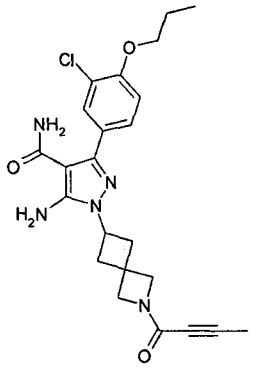
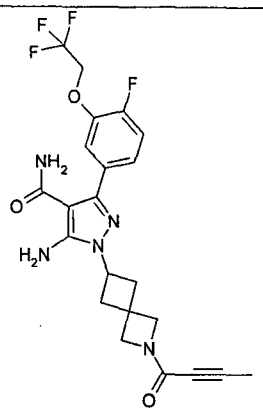
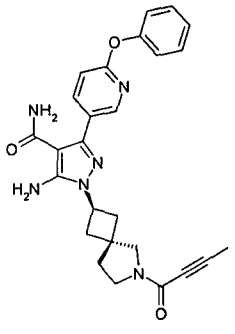
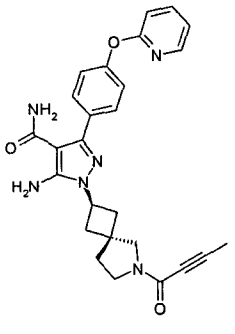
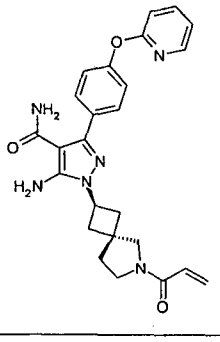
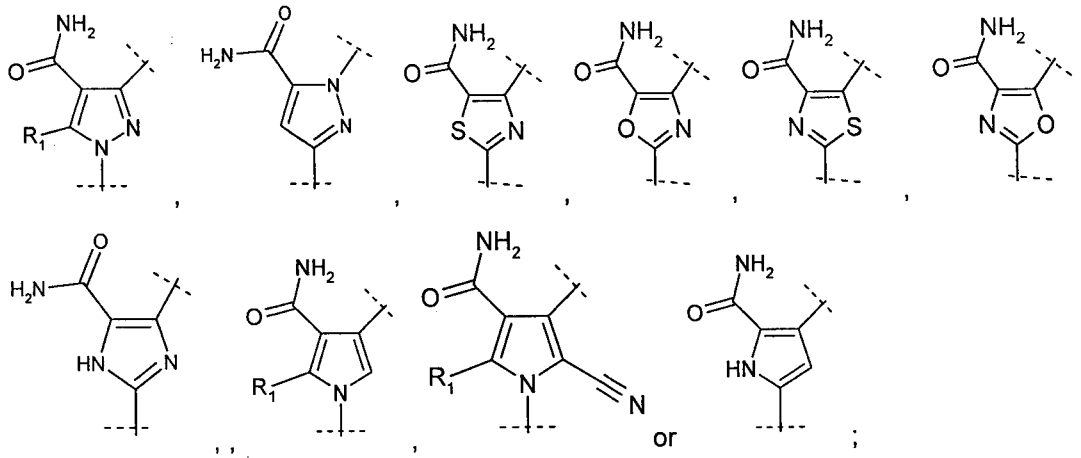
| 146 |  | 22 | A | 2.95 | 482.4 |
| 147 |  | 9.2 | B | 0.84 | 432.0 |
| 148 |  | 3.0 | A | 3.03 | 456.3 |

| | | | | | |
|---|---|---|---|---|---|
| 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 |

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:

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;

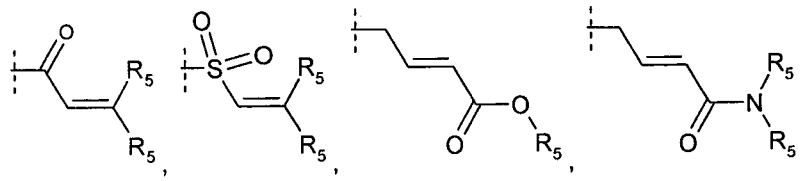
L is a linker chosen from a bond, O, >C(O), -$(CH_2)_n$-, -O-$(CH_2)_n$-, -$N(R_3)$-, -$N(R_3)$-$(CH_2)_n$-, -$(CH_2)_n$-$N(R_3)$-, -C(O)-$N(R_3)$-, -C(O)-$N(R_3)$-$(CH_2)_n$-,-$N(R_3)$-C(O)-$N(R_3)$-, -$N(R_3)$-C(O)-, -$S(O)_m$-$N(R_3)$- and -$N(R_3)$-$S(O)_m$-, wherein the -$CH_2$- in each L can have 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;

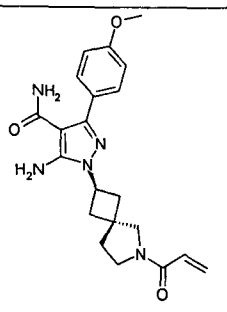
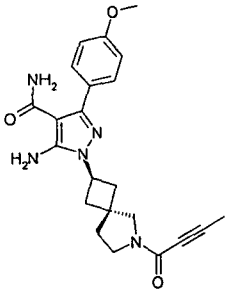
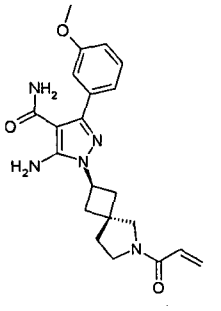
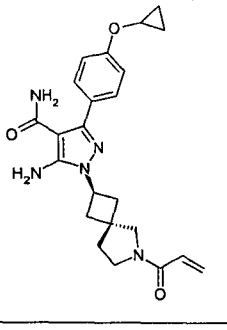
Ar is carbocycle, heterocycyl or heteroaryl;

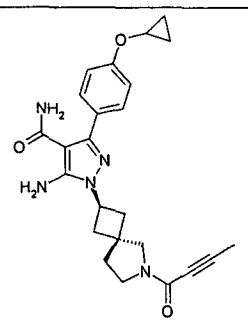
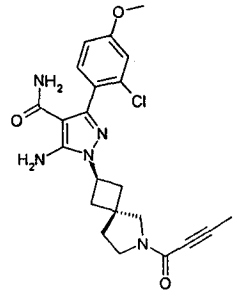
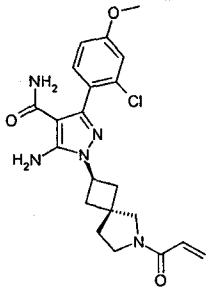
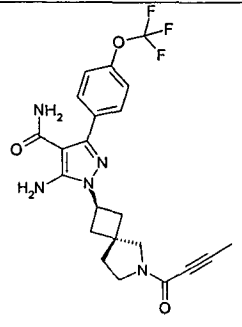
$X_1$ is a linker chosen from a bond, -$(CH_2)_n$-;

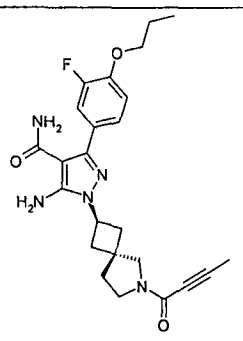
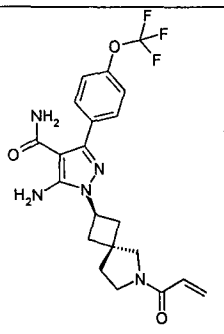
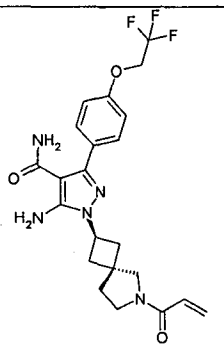
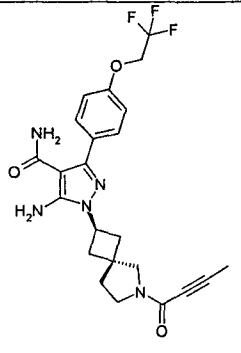
Y is chosen from $C_7$-$C_{10}$ spirocycle optionally containing 0-1 ring nitrogen atoms, a nitrogen containing mono- or bi-cyclic heterocycle, carbocycle, aryl, each substituted by one $R_4$;

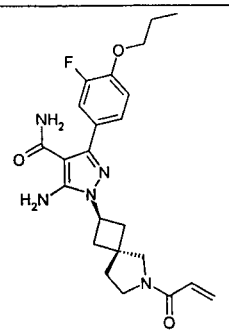
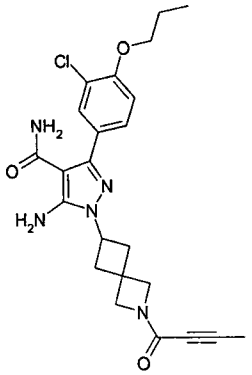
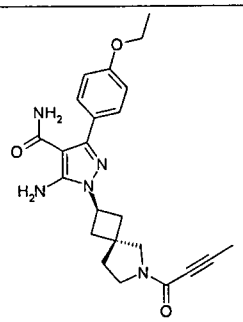
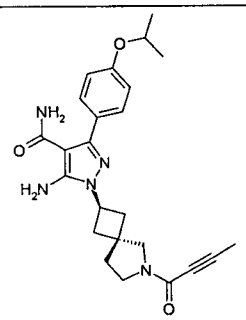
$R_4$ is



| | | | | | |
|---|---|---|---|---|---|
| 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<br>.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

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.

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.

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 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

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 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, on all the hydrogen-carrying carbon atoms.

For example, the term "$C_{1-5}$alkyl" includes for example $H_3C$-, $H_3C-CH_2$-, $H_3C-CH_2-CH_2$-, $H_3C-CH(CH_3)$-, $H_3C-CH_2-CH_2-CH_2$-, $H_3C-CH_2-CH(CH_3)$-, $H_3C-CH(CH_3)-CH_2$-, $H_3C-C(CH_3)_2$-, $H_3C-CH_2-CH_2-CH_2-CH_2$-, $H_3C-CH_2-CH_2-CH(CH_3)$-, $H_3C-CH_2-CH(CH_3)-CH_2$-, $H_3C-CH(CH_3)-CH_2-CH_2$-, $H_3C-CH_2-C(CH_3)_2$-, $H_3C-C(CH_3)_2-CH_2$-, $H_3C-CH(CH_3)-CH(CH_3)$- and $H_3C-CH_2-CH(CH_2CH_3)$-.

Further examples of alkyl are methyl (Me; $-CH_3$), ethyl (Et; $-CH_2CH_3$), 1-propyl (*n*-propyl; *n*-Pr; $-CH_2CH_2CH_3$), 2-propyl (*i*-Pr; *iso*-propyl; $-CH(CH_3)_2$), 1-butyl (*n*-butyl; *n*-Bu; $-CH_2CH_2CH_2CH_3$), 2-methyl-1-propyl (*iso*-butyl; *i*-Bu; $-CH_2CH(CH_3)_2$), 2-butyl (*sec*-butyl; *sec*-Bu; $-CH(CH_3)CH_2CH_3$), 2-methyl-2-propyl (*tert*-butyl; *t*-Bu; $-C(CH_3)_3$), 1-pentyl (*n*-pentyl; $-CH_2CH_2CH_2CH_2CH_3$), 2-pentyl ($-CH(CH_3)CH_2CH_2CH_3$), 3-pentyl ($-CH(CH_2CH_3)_2$), 3-methyl-1-butyl (*iso*-pentyl; $-CH_2CH_2CH(CH_3)_2$), 2-methyl-2-butyl ($-C(CH_3)_2CH_2CH_3$), 3-methyl-2-butyl ($-CH(CH_3)CH(CH_3)_2$), 2,2-dimethyl-1-propyl (*neo*-pentyl; $-CH_2C(CH_3)_3$), 2-methyl-1-butyl ($-CH_2CH(CH_3)CH_2CH_3$), 1-hexyl (*n*-hexyl; $-CH_2CH_2CH_2CH_2CH_2CH_3$), 2-hexyl ($-CH(CH_3)CH_2CH_2CH_2CH_3$), 3-hexyl ($-CH(CH_2CH_3)(CH_2CH_2CH_3)$), 2-methyl-2-pentyl ($-C(CH_3)_2CH_2CH_2CH_3$), 3-methyl-2-pentyl ($-CH(CH_3)CH(CH_3)CH_2CH_3$), 4-methyl-2-pentyl ($-CH(CH_3)CH_2CH(CH_3)_2$), 3-methyl-3-pentyl ($-C(CH_3)(CH_2CH_3)_2$), 2-methyl-3-pentyl ($-CH(CH_2CH_3)CH(CH_3)_2$), 2,3-dimethyl-2-butyl ($-C(CH_3)_2CH(CH_3)_2$), 3,3-dimethyl-2-butyl ($-CH(CH_3)C(CH_3)_3$), 2,3-dimethyl-1-butyl ($-CH_2CH(CH_3)CH(CH_3)CH_3$), 2,2-dimethyl-1-butyl ($-CH_2C(CH_3)_2CH_2CH_3$), 3,3-dimethyl-1-butyl ($-CH_2CH_2C(CH_3)_3$), 2-methyl-1-pentyl ($-CH_2CH(CH_3)CH_2CH_2CH_3$), 3-methyl-1-pentyl ($-CH_2CH_2CH(CH_3)CH_2CH_3$), 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-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 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 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.

Examples of haloalkyl (haloalkenyl, haloalkynyl) are $-CF_3$, $-CHF_2$, $-CH_2F$, $-CF_2CF_3$, $-CHFCF_3$, $-CH_2CF_3$, $-CF_2CH_3$, $-CHFCH_3$, $-CF_2CF_2CF_3$, $-CF_2CH_2CH_3$, $-CF=CF_2$, $-CCl=CH_2$, $-CBr=CH_2$, $-C\equiv C-CF_3$, $-CHFCH_2CH_3$, $-CHFCH_2CF_3$ etc.

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

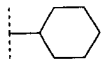
Cycloalkyl is made up of the subgroups monocyclic hydrocarbon rings, bicyclic hydrocarbon rings and spiro-hydrocarbon rings. The systems are saturated. In bicyclic hydrocarbon rings two rings are joined together so that they have at least two carbon atoms together.

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:

cyclohexyl 

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. 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.

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.

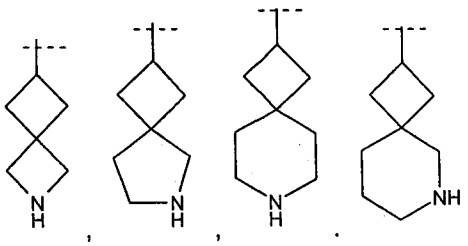
Examples of aryl are phenyl and naphthyl.

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

Heterocyclyl denotes ring systems, which are derived from the previously defined cycloalkyl or spirocycle by replacing one or more of the groups $-CH_2-$ 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 → sulphoxide -SO-, sulphone $-SO_2-$; nitrogen → N-oxide).

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 → sulphoxide -SO-, sulphone -$SO_2$-; 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.

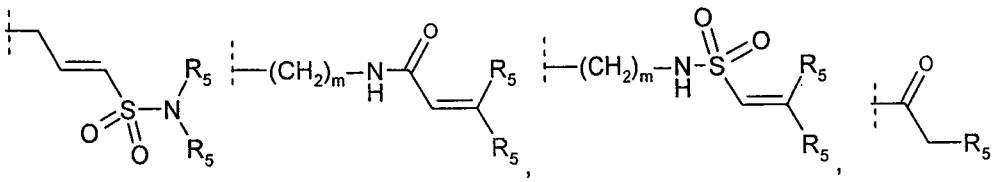
All cyclic and acyclic systems defined in this section hereinabove shall be understood to be optionally partially or fully halogenated where possible and unless otherwise indicated.

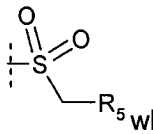
Stereochemistry/solvates/hydrates: Unless specifically indicated, throughout the specification and appended claims, a given chemical formula or name shall encompass tautomers and all stereo, optical and geometrical isomers (*e.g.* enantiomers, diastereomers, *E*/*Z* isomers, etc.) and racemates thereof as well as mixtures in different proportions of the separate enantiomers, mixtures of diastereomers, or mixtures of any of the foregoing forms 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.

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.

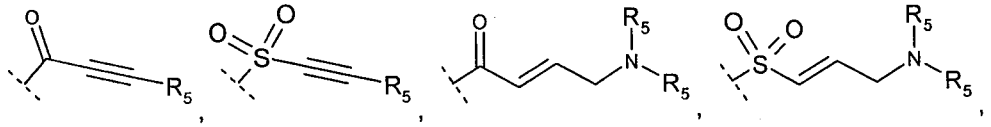
As used herein "pharmaceutically acceptable salts" refers to derivatives of the disclosed compounds wherein the parent compound is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like.

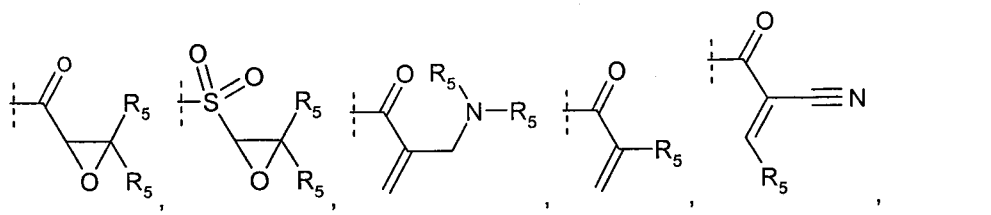
For example, such salts include acetates, ascorbates, benzenesulphonates, benzoates, besylates, bicarbonates, bitartrates, bromides/hydrobromides, Ca-edetates/edetates, camsylates, carbonates, chlorides/hydrochlorides, citrates, edisylates, ethane disulphonates, estolates esylates, fumarates, gluceptates, gluconates, glutamates, glycolates, glycollylarsnilates, hexylresorcinates, hydrabamines, hydroxymaleates,

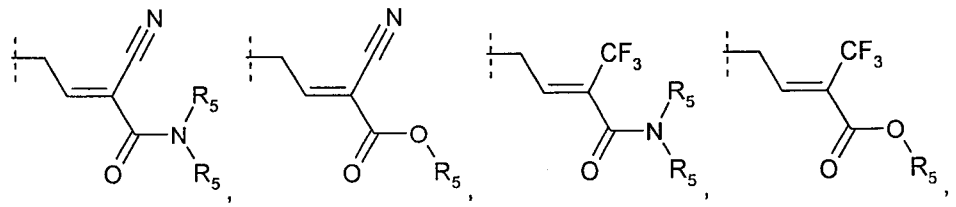


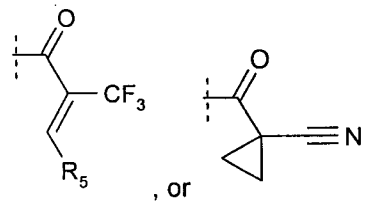


wherein $R_5$ cannot be hydrogen,









, or

each n is independently 1-4;

each m is independently 0-2;

each $R_3$ is independently chosen from hydrogen or $C_{1-4}$ 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 and $R_3$-$S(O)_m$-;

each group defined above for Cy, $R_1$-$R_5$, $X_1$ and Y can be where possible partially or fully halogenated;

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, sulphamides, sulphates, tannates, tartrates, teoclates, toluenesulphonates, triethiodides, ammonium, benzathines, chloroprocaines, cholines, diethanolamines, ethylenediamines, meglumines and procaines.

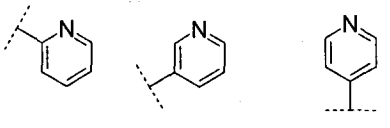
Further pharmaceutically acceptable salts can be formed with cations from metals like aluminium, calcium, lithium, magnesium, potassium, sodium, zinc and the like (also see Pharmaceutical salts, Birge, S.M. et al., J. Pharm. Sci., (1977), 66, 1-19).

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 | *N,N*-di*iso*propylethylamine |
| DMAP | 4-*N,N*-dimethylaminopyridine |
| DME | 1,2-dimethoxyethane |
| DMF | *N,N*-dimethylformamide |
| DMSO | Dimethylsulphoxide |
| dppf | 1.1´-bis(diphenylphosphino)ferrocene |
| EDC | 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide |
| ESI | electron spray ionization |
| Et | Ethyl |
| $Et_2O$ | diethyl ether |
| EtOAc | ethyl acetate |
| EtOH | Ethanol |
| h | hour(s) |
| HATU | O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyl-uronium hexafluorophosphate |
| Hep | Heptane |
| HPLC | high performance liquid chromatography |
| *i* | Iso |
| LC | liquid chromatography |
| LiHMDS | lithium bis(trimethylsilyl)amide |

| | |
|---|---|
| sln. | Solution |
| mCPBA | 3-Chloroperoxbenzoic acid |
| Me | Methyl |
| MeOH | Methanol |
| min | Minutes |
| MPLC | medium pressure liquid chromatography |
| MS | mass spectrometry |
| NBS | *N*-bromo-succinimide |
| NIS | *N*-iodo-succinimide |
| NMM | *N*-methylmorpholine |
| NMP | *N*-methylpyrrolidone |
| NP | normal phase |
| n.a. | not available |
| PBS | phosphate-buffered saline |
| Ph | Phenyl |
| Pr | Propyl |
| Pyr | Pyridine |
| rac | Racemic |
| Rf ($R_f$) | 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 |
| *tert* | Tertiary |
| Tf | Triflate |

| | |
|---|---|
| TFA | trifluoroacetic acid |
| THF | Tetrahydrofuran |
| TMS | Trimethylsilyl |
| TRIS | tris(hydroxymethyl)-aminomethane |
| Ts | *p*-Tosyl |
| TsOH | *p*-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:

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 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 µm 30x150 mm column

b) Waters XBridge OBD C18 5 µm 30x150 mm column

c) Waters ODB C8 5 µm 19x150 mm column.

d) Waters Atlantis ODB C18 5 µm 19x50 mm column.

e) Waters Atlantis T3 OBD 5 µm 30x100 mm column

f) Phenomenex Gemini Axia C18 5 µm 30x100 mm column

HPLC Methods:

Analytical LC/MS Analysis Method A:

Column : Thermo Scientific, Aquasil C18, 50 x 2.1 mm, 5 µm 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 µm column

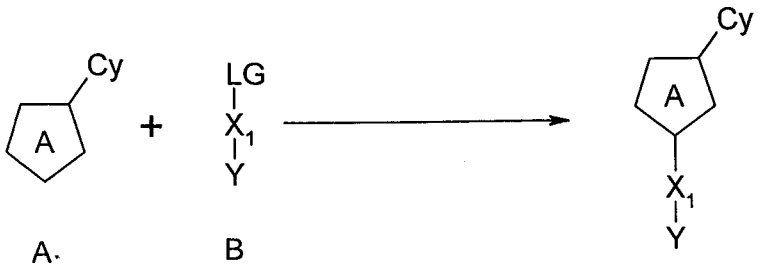
Gradient:

| 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 |

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 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.

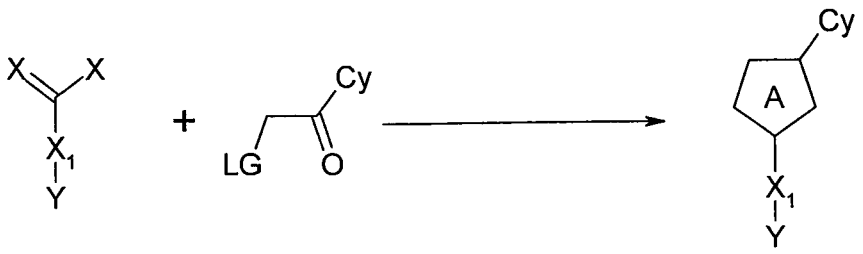
Scheme 1a:




A. B (I)

In scheme Ia, a heterocycle **A** is treated with a suitable base and reacted with an $X_1$-Y group containing a leaving group (LG) **B** to afford the compound of general formula (I).

Scheme 1b:



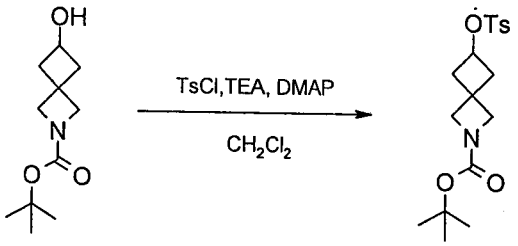

C D (I)

In scheme Ib, **C** (where X = O, N, S, or $NH_2$) is condensed with **D** to afford the compound of general formula (I).

Synthetic Examples

**Method 1**

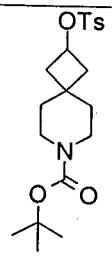
**Synthesis of Intermediate I-1**

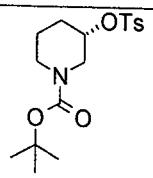



**R-1** **I-1**

A solution of **R-1** (5.0 g, 23 mmol) in $CH_2Cl_2$ 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. 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 $Et_2O$ and solid filtered and collected to afford **I-1** (5.6 g, 65%) *m/z* 367.9 [M+].

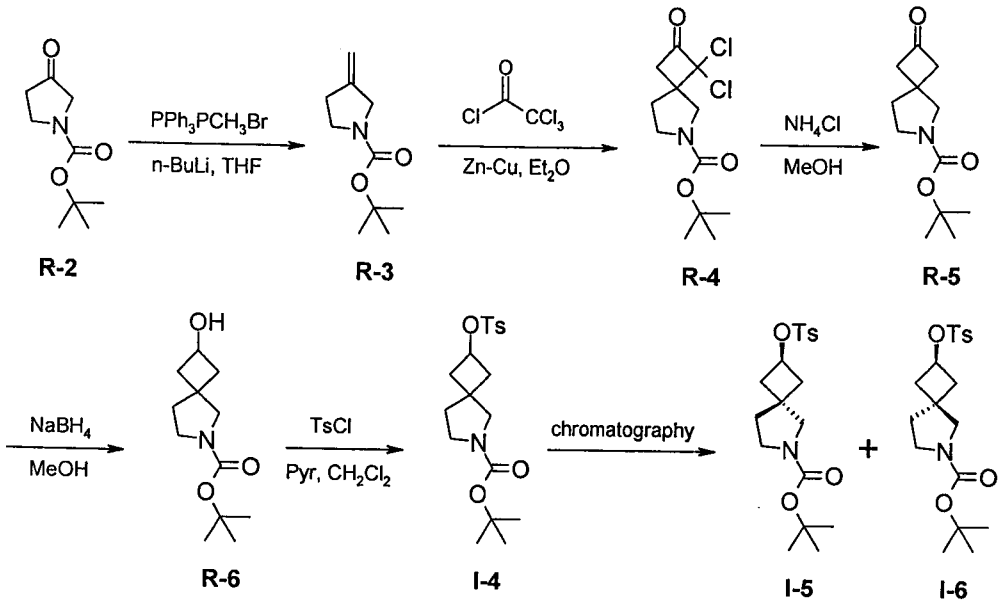
The following intermediates were prepared in a similar manner

| Structure | Intermediate | *m/z* |
|---|---|---|
|  | **I-2** | 396.3 [M+H] |

| | | |
|---|---|---|
|  | I-3 | 356.0 [M+H] |

**Method 2**

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




To a solution of $PPh_3CH_3Br$ (578 g, 1.62 mol) in THF (3.5 L) is added a solution of n-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 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%).

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 ($SiO_2$, Hep to 25%EtOAc in Hep) to give **R-4** (11 g, 34%).

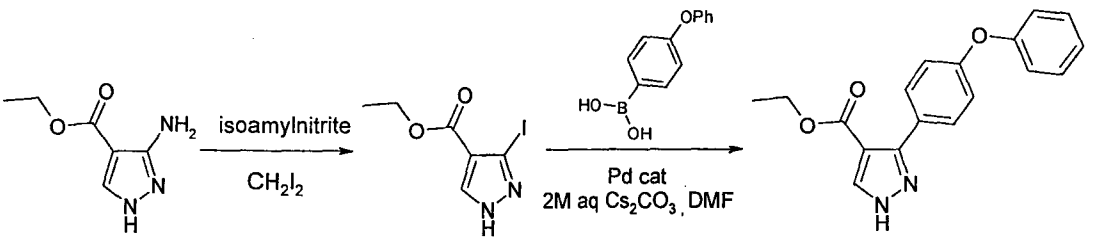
To a solution of **R-4** (35.5 g, 121 mmol) in saturated $NH_4Cl$ (64.7 g, 1.21 mol) in MeOH (400 mL) is added Zn (79.1 g, 1.21 mol). The mixture is stirred at ambient temperature for 8 h. The mixture is treated with $H_2O$ and extracted with EtOAc. The organic layers are washed with brine, dried with $Na_2SO_4$, concentrated and purified by flash chromatography ($SiO_2$, Hep to 25%EtOAc in Hep) to afford **R-5** (19 g, 69%).

To the mixture of **R-5** (19 g, 84.3 mmol) in THF (200 mL) is added $NaBH_4$ (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 $H_2O$, then 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 50%EtOAc in Hep) to yield **R-6** (12 g, 63%).

To the mixture of **R-6** (22 g, 96.8 mmol) and pyridine (23.2 g, 290.4 mmol) in $CH_2Cl_2$ (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 $H_2O$ 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 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 ($SiO_2$, 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**

**Synthesis of Intermediate I-8**



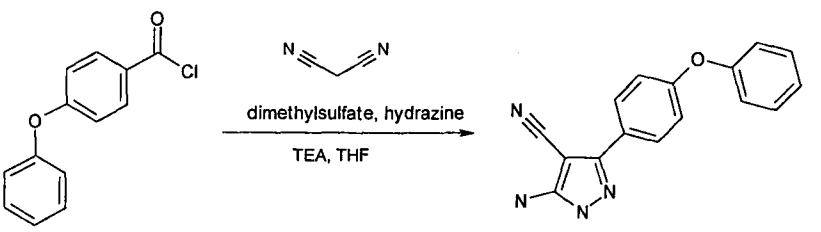

R-7 I-7 I-8

To a solution of **R-7** (15.0 g, 97 mmol) in $CH_2I_2$ (350 mL) is added isoamylnitrite (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)phosphin e) 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]

**Method 4**

**Synthesis of Intermediate I-9**

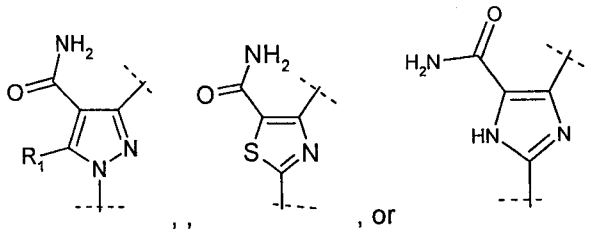



R-8 I-9

or a pharmaceutically acceptable salt thereof.

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

A ring is:



, , , or

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, 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:

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), -$CH_2$-, -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, piperidinyl, piperazinyl or pyrrolidinyl

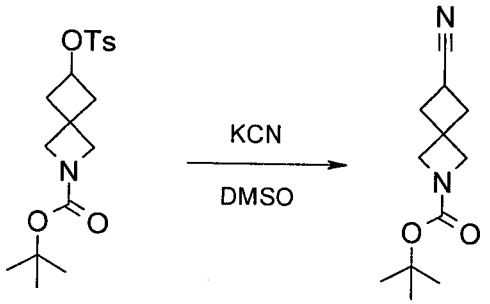
or a pharmaceutically acceptable salt thereof.

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

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 $MgSO_4$, filtered and concentrated. The crude is purified by flash chromatography ($SiO_2$, 0-100% EtOAc in Hep) to afford **I-9** (5.7 g, 18%). *m/z* 277.5 [M+H]

**Method 5**

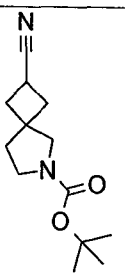
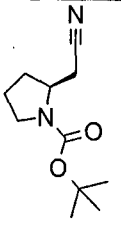
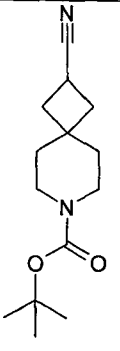
**Synthesis of Intermediate I-10**




**I-1** **I-10**

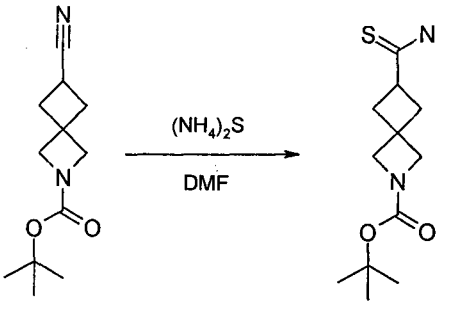
To a solution of **I-1** (200 mg, 0.54 mmol) in DMSO (2.5 mL) was added KCN (71 mg, 1.1 mmol). The mixture was heated at 100° C for 18 h then cooled to ambient temperature and partitioned between EtOAc and water. The organics were collected, dried over $MgSO_4$, filtered and concentrated in vacuo to afford **I-10** (quant, 120 mg). *m/z* 223.1 [M+H]

The following intermediates were prepared in a similar manner

| Structure | Intermediate | *m/z* |
|---|---|---|
|  | **I-11** | 181.0 [M-tBu] |
|  | **I-12** | 211.1 [M+H] |
|  | **I-13** | 195.4 [M-tBu] |

**Method 6**

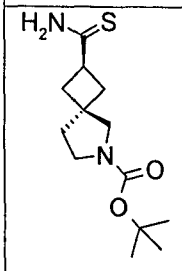
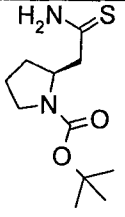
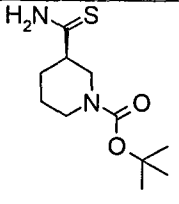
**Synthesis of Intermediate I-14**

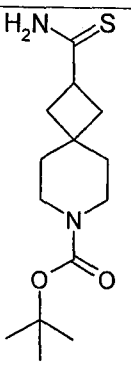



**I-10** **I-14**

To a solution of **I-10** (250 mg, 1.1 mmol) in DMF (2 mL) is added 20% (w/w) aqueous $(NH_4)_2S$ (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]

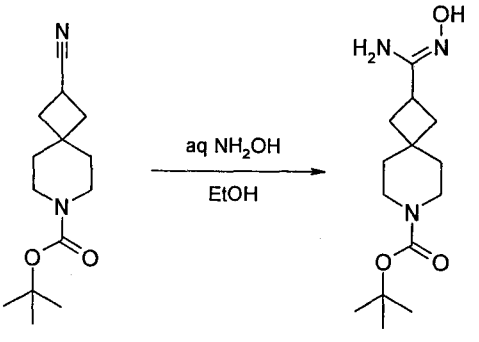
The following intermediates were prepared in a similar manner

| Structure | Intermediate | *m/z* |
|---|---|---|
|  | **I-15** | 271.1 [M+H] |
|  | **I-16** | 189.0 [M-tBu] |
|  | **I-17** | 245.0 [M+H] |

| | | |
|---|---|---|
|  | **I-18** | 285.1 [M+H] |

**Method 7**

**Synthesis of Intermediate I-19**

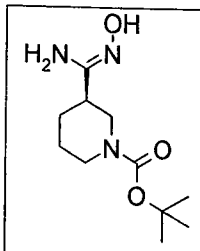



**I-13** **I-19**

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].

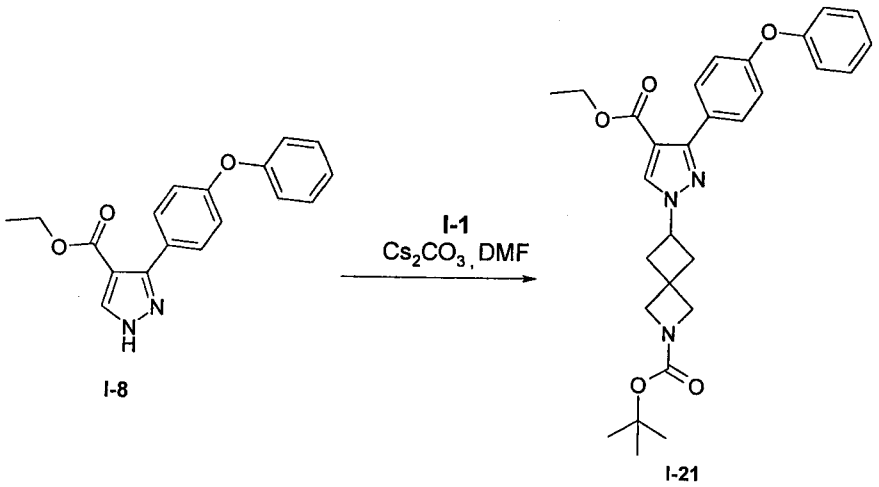
The following intermediates were prepared in similar manner

| Structure | Intermediate | *m/z* |
|---|---|---|

| | | |
|---|---|---|
|  | **I-20** | 244.1 [M+H] |

**Method 8**

**Synthesis of Intermediate I-21**

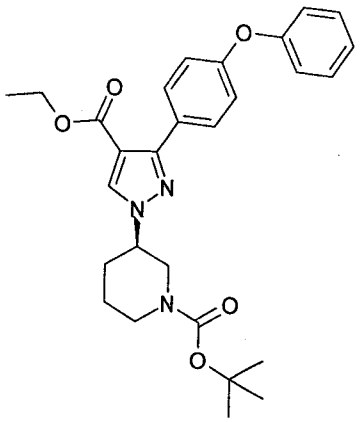
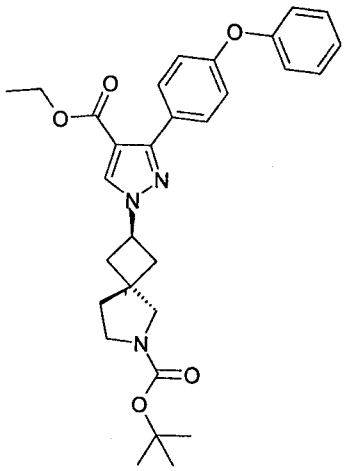
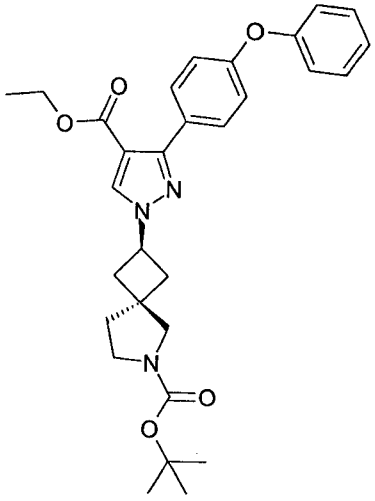


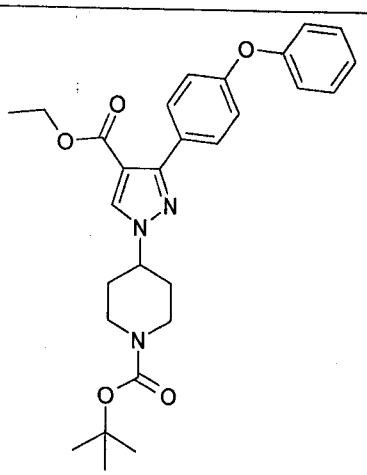

**I-8** **I-21**

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].

The following intermediates were prepared in similar fashion:

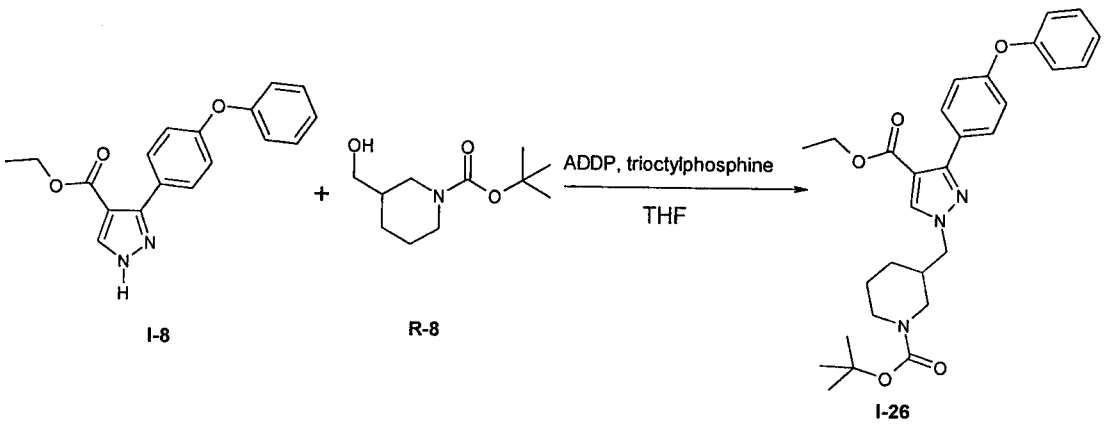
| Structure | Intermediate | *m/z* |
|---|---|---|

| | | |
|---|---|---|
|  | **I-22** | 492.2 [M+H] |
|  | **I-23** | 518.2 [M+H] |
|  | **I-24** | 518.2 [M+H] |

| | | |
|---|---|---|
|  | **I-25** | NA |

**Method 9**

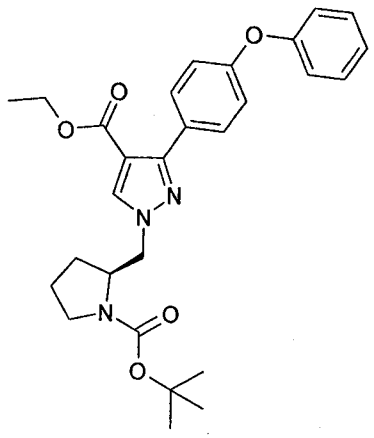
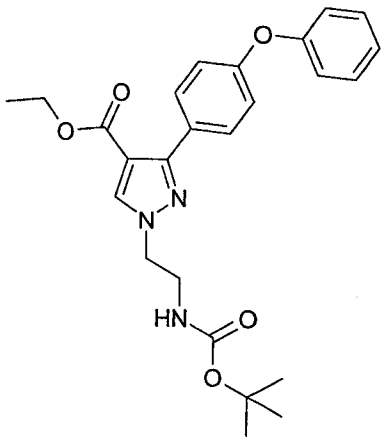
**Synthesis of Intermediate I-26**

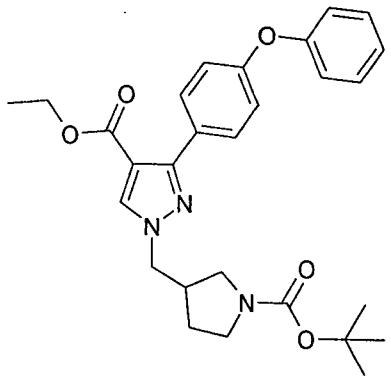
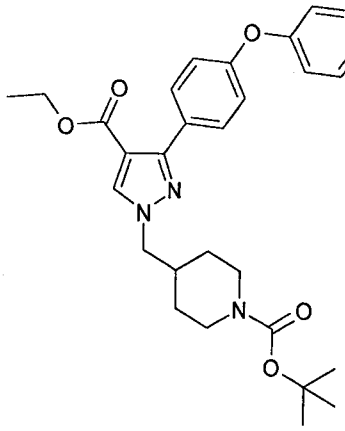



**I-8** **R-8** **I-26**

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 $NH_4Cl$ and EtOAc. The organics are washed with brine, dried over $Na_2SO_4$, filtered, and concentrated in vacuo. The crude is purified by flash chromatography ($SiO_2$, Hep to 30%EtOAc in Hep) to give **I-24** (1.1 g, 84%) *m/z* 506.1 [M+H].

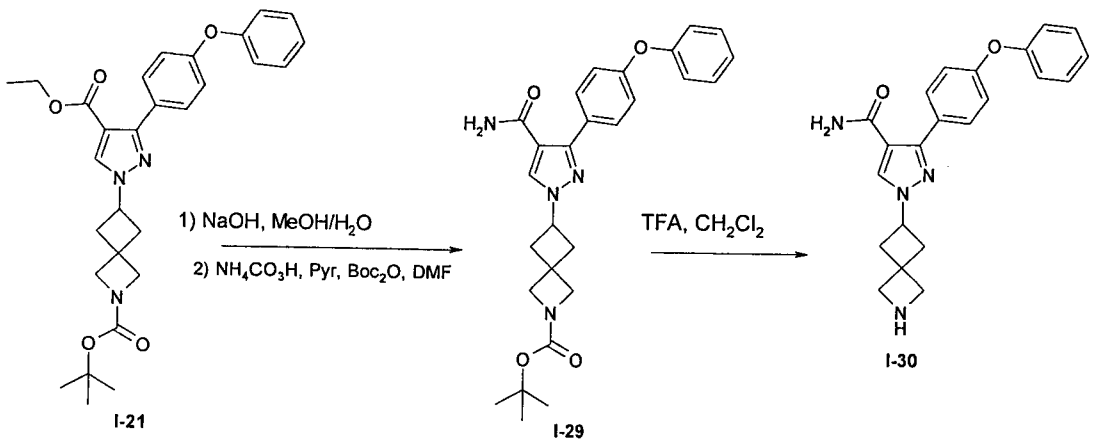
The following intermediates are prepared in similar fashion:

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

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

**Method 10**

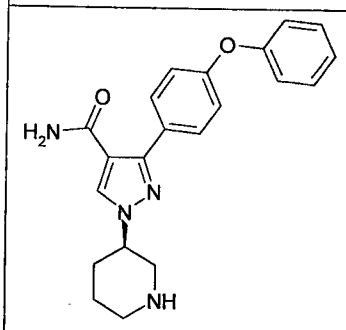
**Synthesis of Intermediate I-30**



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 $Na_2SO_4$, 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 $NH_4Cl$. The organics are washed with brine, dried over $Na_2SO_4$, filtered, and concentrated in vacuo. The residue is purified by flash chromatography ($SiO_2$, 20-80%EtOAc in Hep, then 20%MeOH in $CH_2Cl_2$) 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 $CH_2Cl_2$ (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 $NaHCO_3$ and EtOAc. The organics are collected, dried over $Na_2SO_4$, 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:

| Structure | Intermediate | *m/z* |
|---|---|---|
|  | **I-31** | |

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($R_3$) and $C_{1-2}$ 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.

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 $R_2$ 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($CH_3$) and $C_{1-2}$ 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

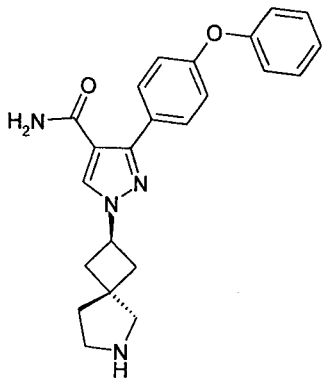
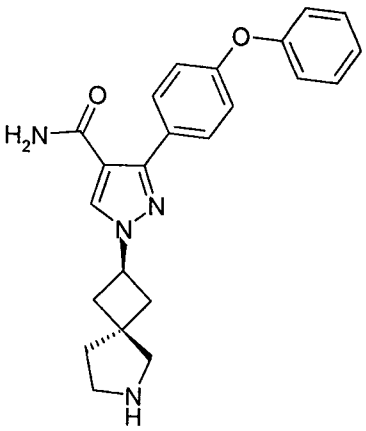
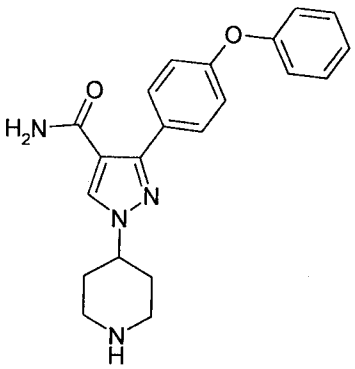
or a pharmaceutically acceptable salt thereof.

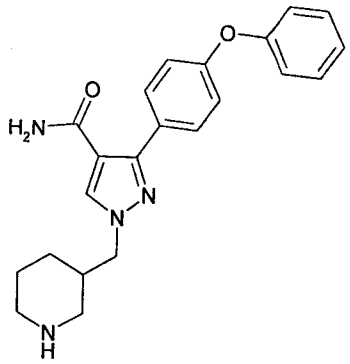
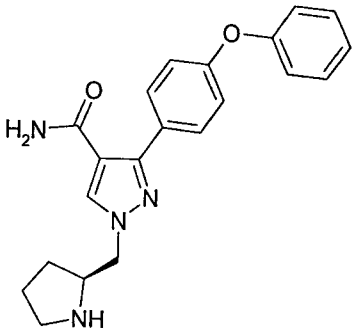
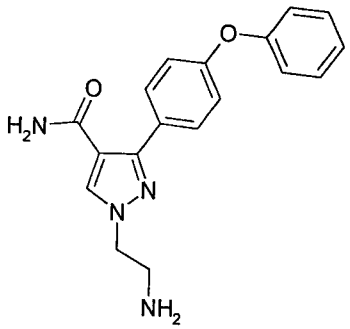
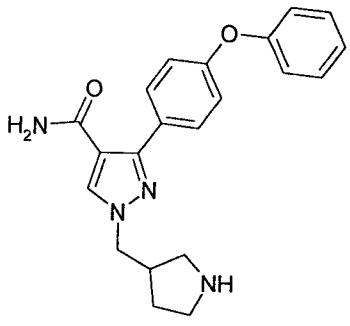
In a further embodiment, there is provided a compound of the formula (I) according to any of the embodiments herein-above and wherein

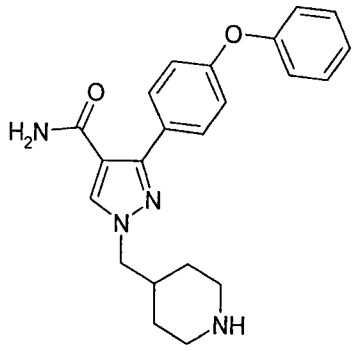
$X_1$ is a linker chosen from a bond and -$(CH_2)_n$-;

Y is chosen from:

a spirocycle chosen from

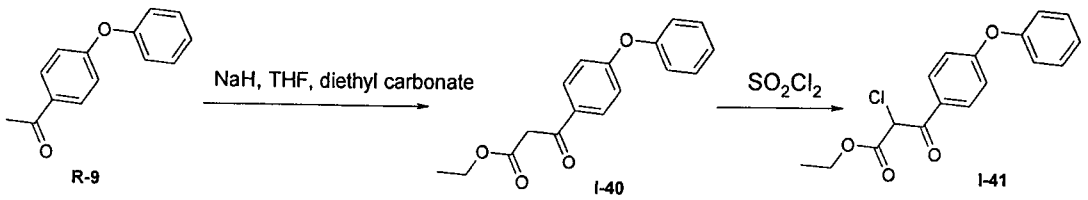
| | | |
|---|---|---|
|  | **I-32** | |
|  | **I-33** | |
|  | **I-34** | |

| | | |
|---|---|---|
|  | **I-35** | |
|  | **I-36** | |
|  | **I-37** | |
|  | **I-38** | |

| | | |
|---|---|---|
|  | **I-39** | NA |

**Method 11**

**Synthesis of Intermediate I-41**

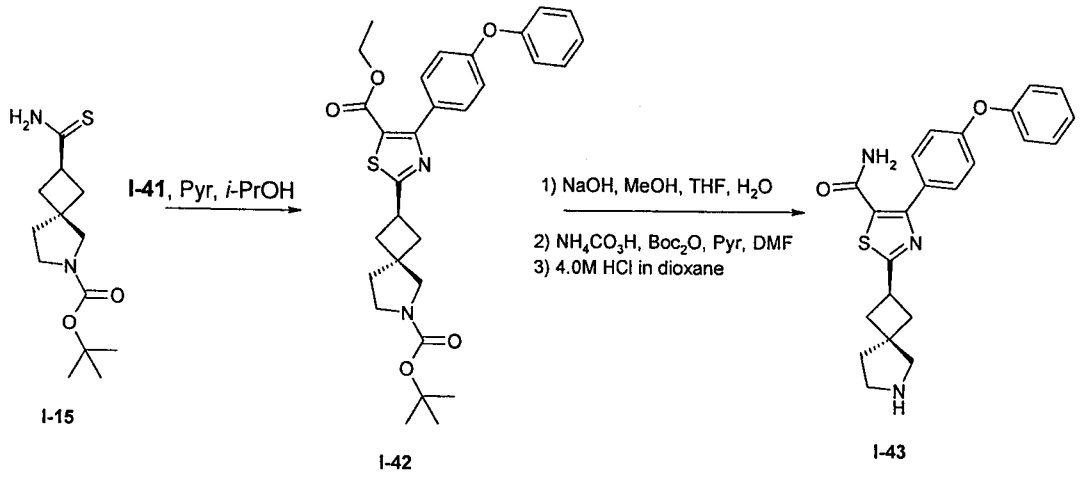



To a solution of **R-9** (5.00 g, 23.6 mmol) in THF (50 mL) is added a 60% dispersion of sodium hydride in mineral oil (1.41 g, 35.1 mmol). The mixture is stirred for 5 min at ambient temperature then diethyl carbonate (5.7 mL, 47.4 mmol). The reaction is stirred for 30 min at ambient temperature then 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].

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 $CH_2Cl_2$, dried over $Na_2SO_4$, filtered, and concentrated in vacuo to afford **I-41** (quant) *m/z* 318.9 [M+H].

**Method 12**

**Synthesis of Intermediate I-43**

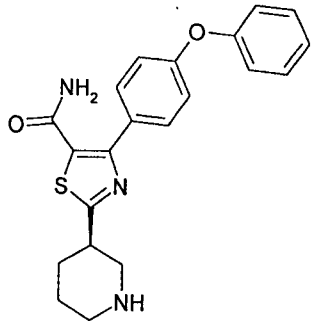
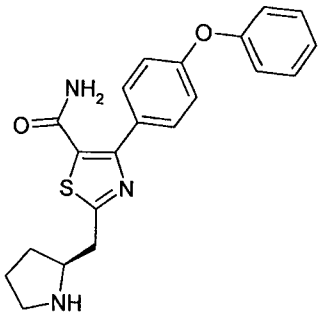
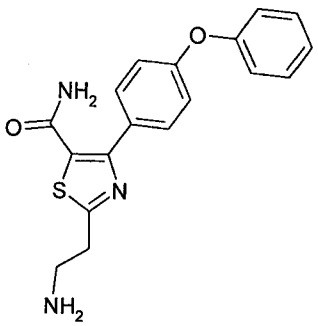



I-15 I-42 I-43

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 ($SiO_2$, Hep to 40%EtOAc in Hep) to give **I-42** (240 mg, 30%) *m/z* 535.2 [M+H].

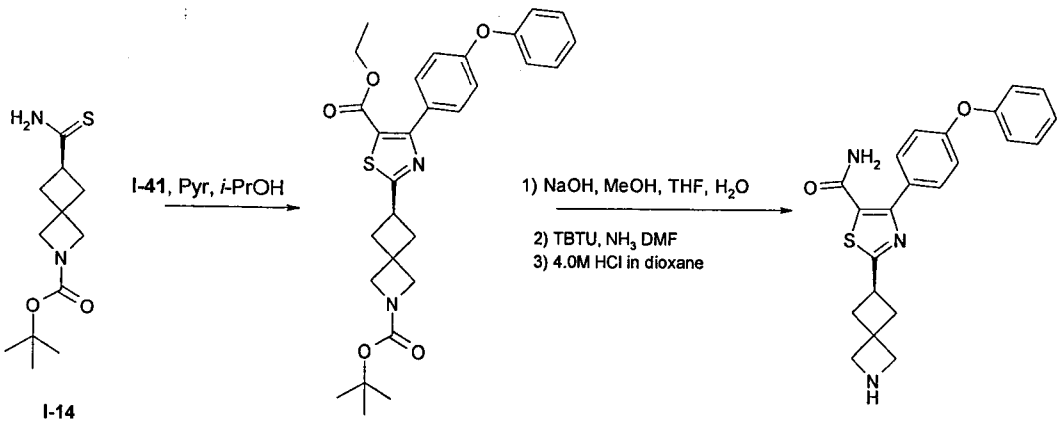
A solution of **I-42** (240 mg, 0.45 mmol) in MeOH (3 mL), THF (1 mL), and 5M aqueous NaOH (0.5 mL) is heated at 60° C for 3 h. The mixture is cooled to ambient temperature then acidified to pH=1 with 6M aqueous HCl. The mixture is extracted with $CH_2Cl_2$ then filtered through a phase separator® then 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 ($SiO_2$, $CH_2Cl_2$ to 5%MeOH in $CH_2Cl_2$). The purified material is dissolved in $CH_2Cl_2$ (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 ($SiO_2$, $CH_2Cl_2$ to 20%MeOH in $CH_2Cl_2$ containing 2.5%TEA) to give **I-43** (134 mg, 73%) *m/z* 405.9 [M+H].

The following compounds are made in similar fashion:

| Structure | Intermediate | *m/z* |
|---|---|---|
|  | **I-44** | 380.8 [M+H] |
|  | **I-45** | 380.4 [M+H] |
|  | **I-46** | NA |

**Method 13**

**Synthesis of Intermediate I-46**



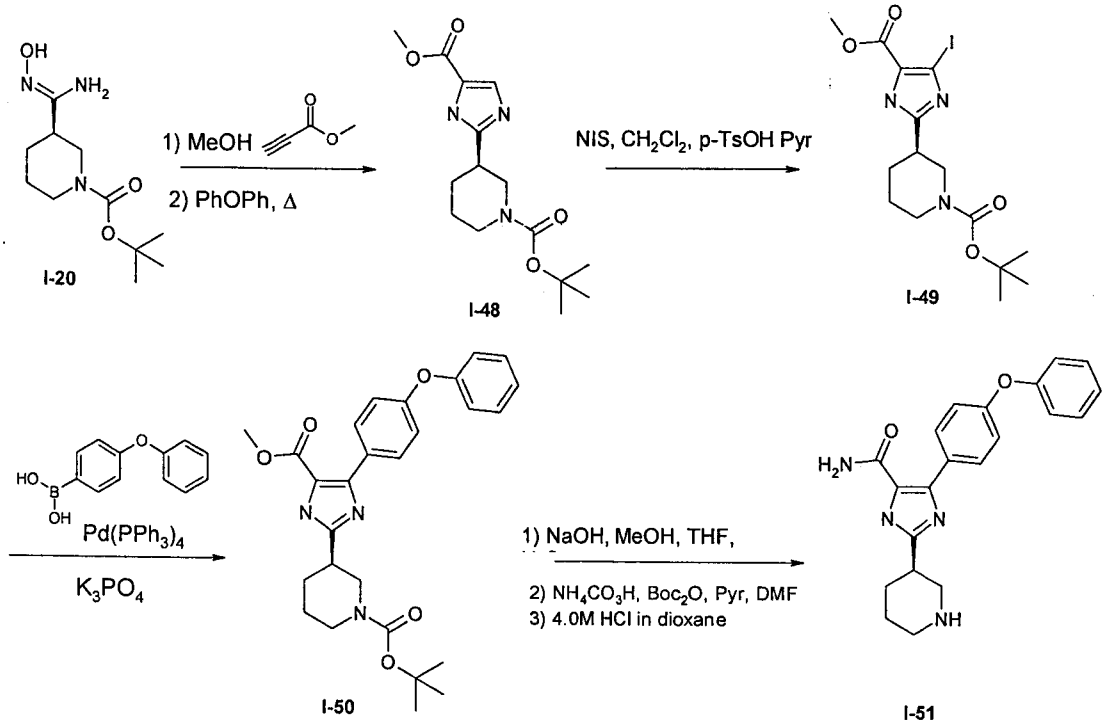

I-14 I-46 I-47

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 ($SiO_2$, 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 $CH_2Cl_2$ (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 $CH_2Cl_2$ and 10% (w/w) aqueous $Na_2CO_3$ and $CH_2Cl_2$. 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**




I-20 I-48 I-49 I-50 I-51

A solution of **I-20** (500 mg, 2.1 mmol) and methyl propriolate (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 ($SiO_2$, Hep to EtOAc) to give **I-48** (317 mg, 50%) *m/z* 310.2 [M+H].

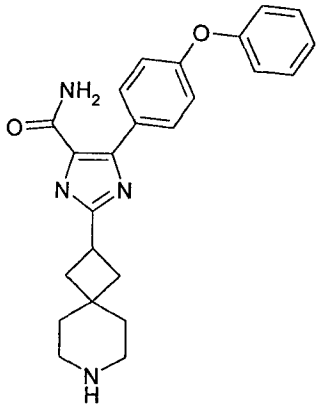
To a solution of **I-48** (317 mg, 1.0 mmol) and *p*-TsOH Pyr (461 mg, 2.1 mmol) in $CH_2Cl_2$ (5 mL) is added NIS (461 mg, 2.1 mmol). The mixture is stirred in the dark at ambient temperature for 24 h. The mixture is treated with saturated aqueous $Na_2SO_3$ then filtered through a phase separator. The organics are collected and concentrated in vacuo to afford a residue that is purified by flash chromatography ($SiO_2$, 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-phenoxylphenylboronic acid (333 mg, 1.56 mmol), and tetrakis(triphenylphosphine)palladium(0) (90 mg, 0.078 mmol), and $K_3PO_4$ (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 ($SiO_2$, Hep to 80%EtOAc in Hep) to afford **I-50** (302 mg, 81%) *m/z* 478.2 [M+H].

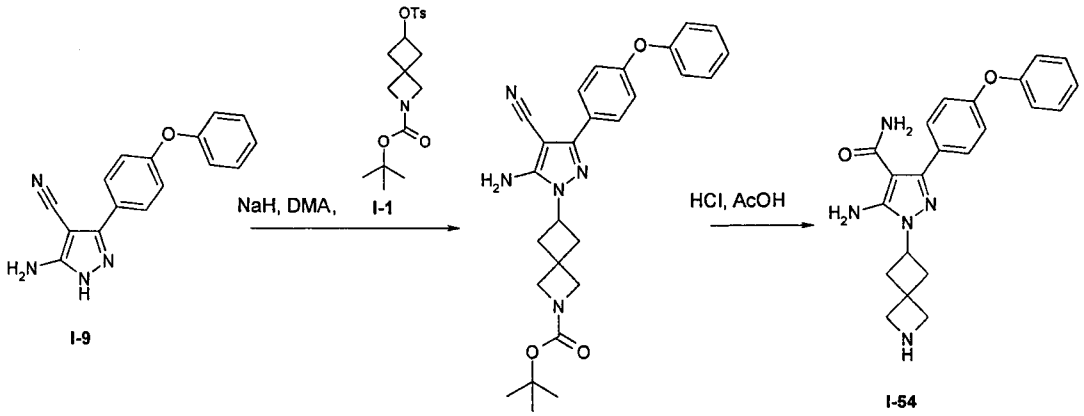
A solution of **I-50** (372 mg, 0.78 mmol) in MeOH (1.5 mL), THF (1 mL), and 3M aqueous NaOH (3 mL) is heated at ambient temperature for 20 h then acidified to pH=5 with concentrated aqueous HCl. The volatiles are removed in vacuo and residue triturated with a mixture of $CH_2Cl_2$ and MTBE. The solid 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 (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 $CH_2Cl_2$. The mixture is filtered through a phase separator® and organics are concentrated in vacuo to afford a residue that is purified by flash chromatography ($SiO_2$, $CH_2Cl_2$ to 5%MeOH in $CH_2Cl_2$). The purified material is dissolved in $CH_2Cl_2$ (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:

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

**Method 15**

**Synthesis of Intermediate I-54**

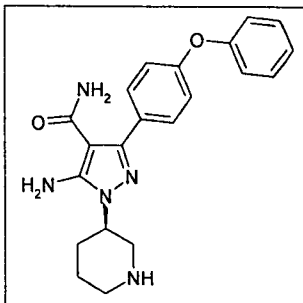
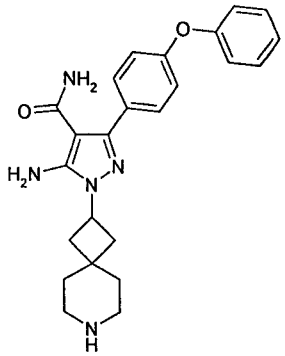
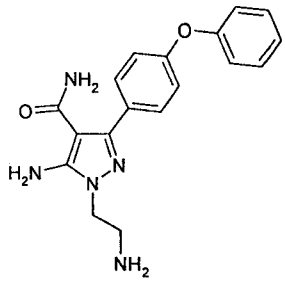
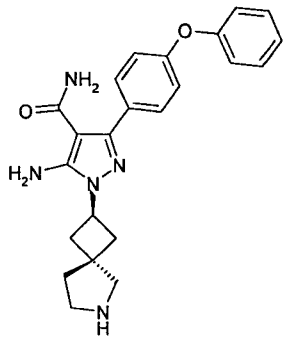



To a solution of **I-9** (1.50 g, 5.4 mmol) in DMF (20 mL) is added sodium hydride (60%dispersion in mineral oil, 0.26 g, 6.5 mmol). The mixture is stirred for 5 min then **I-1** (2.39 g, 6.5 mmol) is added. The mixture is heated at 70 ° C for 18 h then cooled to ambient temperature. The mixture is partitioned between EtOAc and water then organics are collected, dried over $Na_2SO_4$, filtered, and concentrated in vacuo. The residue is purified by flash chromatography ($SiO_2$, 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 $Na_2SO_4$, 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].

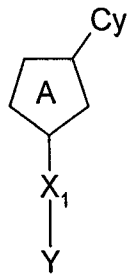
The following intermediates are prepared in similar fashion:

| Structure | Intermediate | *m/z* |
|---|---|---|

| | | |
|---|---|---|
|  | **I-54** | 378.1 [M+H] |
|  | **I-55** | 418.2 [M+H] |
|  | **I-56** | |
|  | **I-57** | 404.1 [M+H] |

Claims

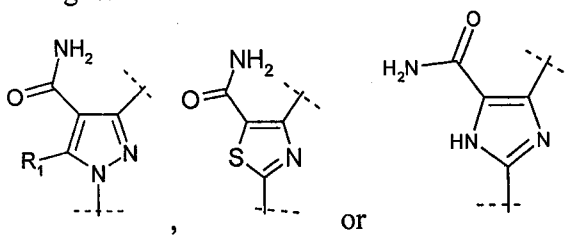
1. A compound of the formula (I)



(I)

wherein

A ring is:



;

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

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:

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 -$N(R_3)$-$S(O)_m$-;

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

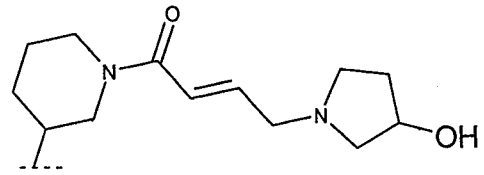
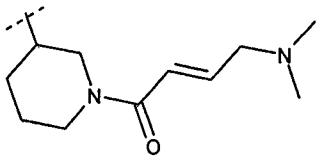
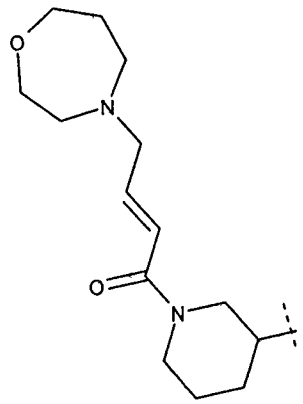
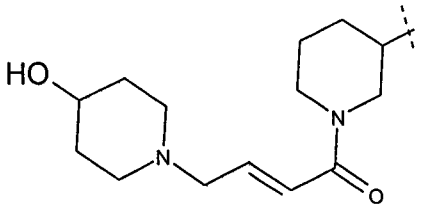
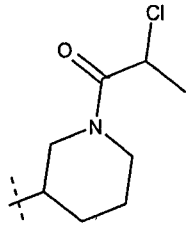
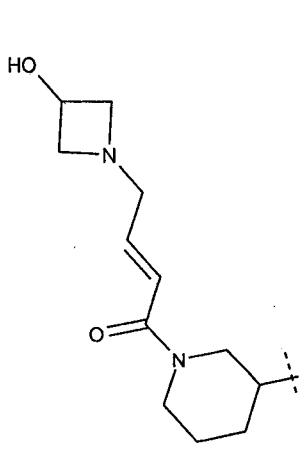
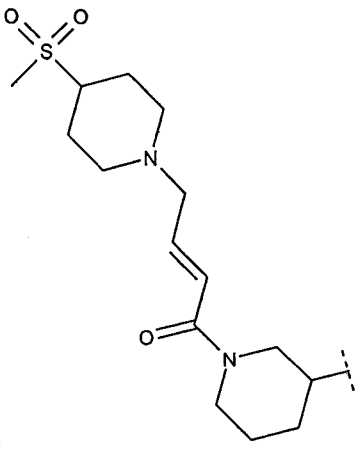
$X_1$ is a linker chosen from a bond, -$(CH_2)_n$-;

each n is independently 1-4;

each m is independently 0-2;

each $R_3$ is independently chosen from hydrogen or $C_{1-4}$ alkyl;

Y is chosen from:

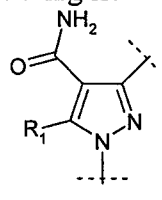








or or

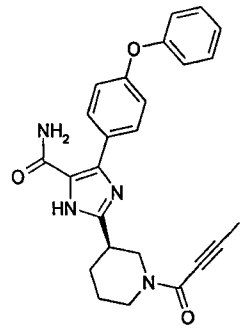
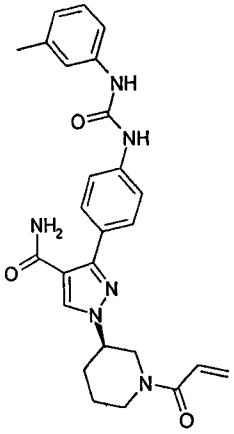
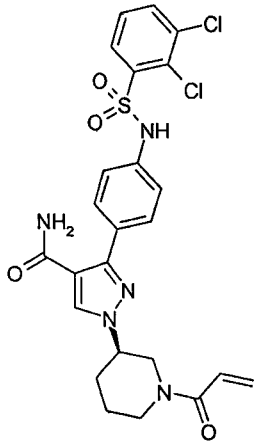
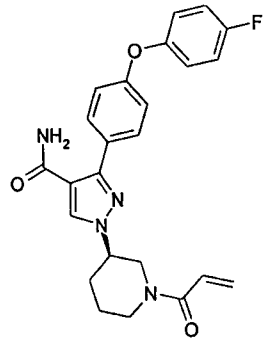
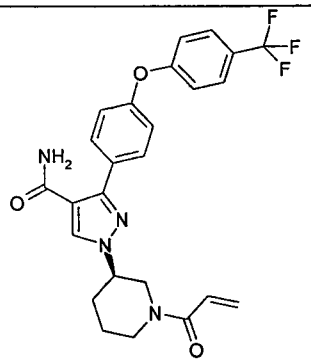
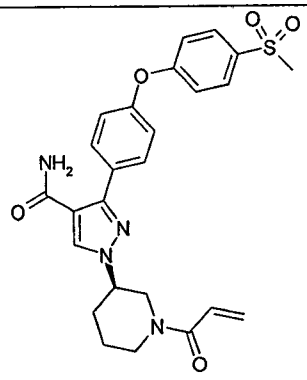
a pharmaceutically acceptable salt thereof.

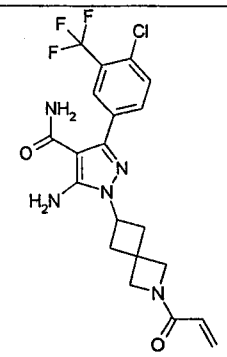
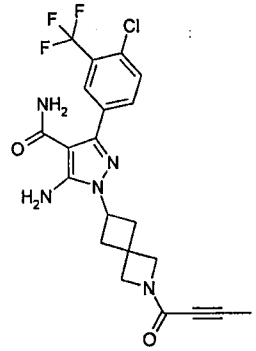
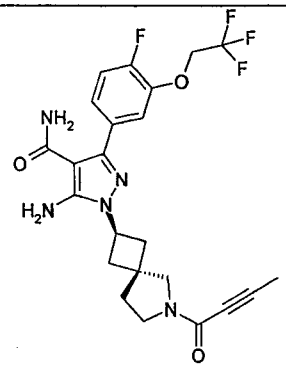
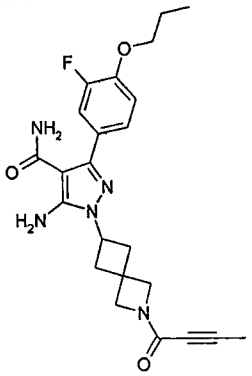
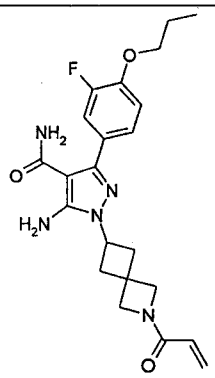
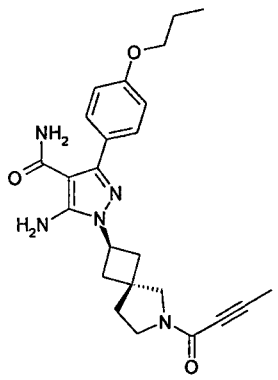
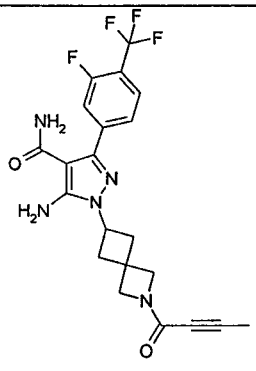
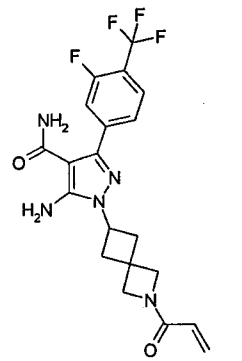
5. The compound according to claim 1 and wherein

A ring is:



or a pharmaceutically acceptable salt thereof.

| | |
|---|---|
|  |  |
|  |  |
|  |  |

| | |
|---|---|
|  |  |
|  |  |
|  |  |
|  |  |