Protein kinases are a large multigene family consisting of more than 500 proteins which play a critical role in the development and treatment of a number of human diseases in oncology, neurology and immunology. The Tec kinases are non-receptor tyrosine kinases which consists of five members (Tec (tyrosine kinase expressed in hepatocellular carcinoma), Btk (Bruton's tyrosine kinase), Itk (interleukin-2 (IL-2)-inducible T-cell kinase; also known as Emt or Tsk), Rlk (resting lymphocyte kinase; also known as Txk) and Bmx (bone -marrow tyrosine kinase gene on chromosome X; also known as Etk)) and are primarily expressed in haematopoietic cells, although expression of Bmx and Tec has been detected in endothelial and liver cells. Tec kinases (Itk, Rlk and Tec) are expressed in T cell and are all activated downstream of the T-cell finvolved in regulating B cell activation, proliferation, and differentiation. More specifically, Btk contains a PH domain that binds phosphatidylinositol (3,4,5)-trisphosphate (PIP3). PIP3 binding induces Btk to phosphorylate phospholipase C (PLCy), which in turn hydrolyzes PIP2 to produce two secondary messengers, inositol triphosphate (IP3) and diacylglycerol (DAG), which activate protein kinase PKC, which then induces additional B-cell signaling. Mutations that disable Btk enzymatic activity result in XLA syndrome (X-linked agammaglobulinemia), a primary immunodeficiency. Because Tec kinases play critical roles in both B-cell and T-cell signaling, Tec kinases are targets of interest for autoimmune disorders.

Given that Btk plays an important role in B-cell signalling, there is a great need to develop chimeric compounds capable of activating the ubiquitination and degradation of Btk proteins. It is an object of the present disclosure to provide new compounds, methods, compositions and methods of manufacture that are useful for the selective degradation of Btk protein *in vivo* via the ubiquitin-proteasome pathway (UPP).

SUMMARY

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

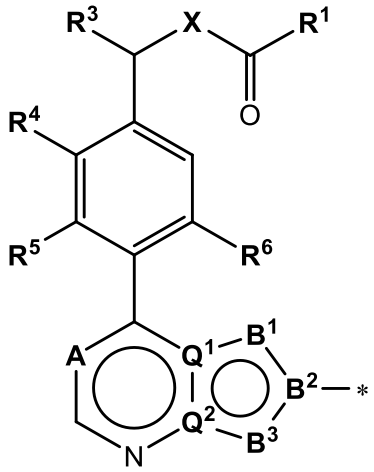
BTK—L—DSM (A) ,

or a pharmaceutically acceptable salt thereof, wherein:

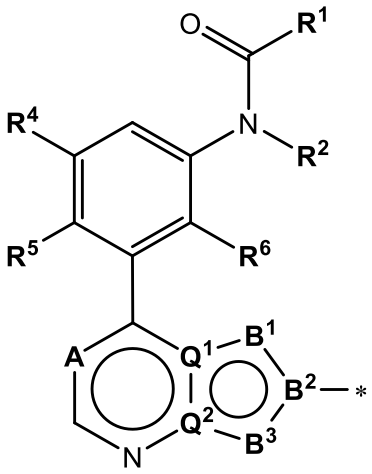
DSM is a degradation signaling moiety that is covalently attached to the linker L;

L is a linker that covalently attaches BTK to DSM; and

BTK is a Btk binding moiety represented by Formula (I) or Formula (II) that is covalently attached to linker L:



(I)



(II) ,

or a pharmaceutically acceptable salt thereof, wherein:

A is selected from CR^7 and N;

B^1 is selected from CR^8, N, and NR^8;

B^2 is C or N;

B^3 is selected from CR^8, N, NR^8 and S;

one of Q^1 and Q^2 is N, and the other one is C; or both of Q^1 and Q^2 are C;

X is selected from O and NR^2;

R^1 is selected from $-N(R^{1a})_2$, C_{1-10} alkyl, 3- to 7-membered monocyclic carbocyclyl, 3- to 7-membered monocyclic heterocyclyl, 7- to 10-membered bicyclic carbocyclyl, and 7- to 10-membered bicyclic heterocyclyl; wherein the C_{1-10} alkyl, 3- to 7-membered monocyclic carbocyclyl, 3- to 7-membered monocyclic heterocyclyl, 7- to 10-membered bicyclic carbocyclyl, and 7- to 10-membered bicyclic heterocyclyl represented by R^1 are each optionally substituted with one or more R^{10};

R^{1a}, for each occurrence, is independently selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6}alkynyl, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl represented by R^{1a} are each optionally substituted with one or more R^{10}; or alternatively two R^{1a}, taken together with their intervening atoms, form a 3- to 7-membered monocyclic heterocyclyl which is optionally substituted with one or more R^{10};

R^{10}, for each occurrence, is independently selected from H, halogen, $-OR^{10a}$, $-S(O)_2R^{10a}$, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 3- to 7-membered monocyclic carbocyclyl, and 4- to 6-membered monocyclic heterocyclyl; wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 3- to 7-membered monocyclic carbocyclyl, and 4- to 6-membered monocyclic heterocyclyl represented by R^{10} are each optionally substituted with one or more R^{15};

or alternatively two R^{10}, taken together with their intervening atoms, form a Ring A that is selected from 3- to 7-membered monocyclic carbocyclyl, 3- to 7-membered monocyclic heterocyclyl, 7- to 10-membered bicyclic carbocyclyl, and 7- to 10-membered bicyclic heterocyclyl, wherein the Ring A is optionally substituted with one or more R^{15};

R^{10a}, for each occurrence, is independently selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 3- to 7-membered monocyclic carbocyclyl, and 4- to 6-membered monocyclic heterocyclyl;

R^{15}, for each occurrence, is independently selected from C_{1-6} alkyl, halogen, -CN, 3- to 7-membered monocyclic carbocyclyl and $-OR^{15a}$; wherein the C_{1-6} alkyl and 3- to 7-membered monocyclic carbocyclyl represented by R^{15} is optionally substituted with one or more R^{15a}; or two R^{15}, taken together with their intervening atom, form 3- to 7- membered monocyclic carbocyclyl or 4- to 6-membered monocyclic heterocyclyl;

R^{15a} is selected from H, halogen and C_{1-6} alkyl optionally substituted with at least one halogen;

R^2 is selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

R^3 is selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, $-C(O)N(R^{3a})_2$, $-C(O)OR^{3a}$, and $-C(O)R^{3a}$, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6}alkynyl represented by R^3 are each optionally substituted with one or more R^{30};

R^{3a}, for each occurrence, is independently selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl represented by R^{3a} are each optionally substituted with one or more R^{30};

R^{30}, for each occurrence, is independently selected from halogen, $-OR^{30a}$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 3- to 7-membered monocyclic carbocyclyl, and 4- to 6-membered monocyclic heterocyclyl;

R^{30a} is selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 3- to 6-membered monocyclic carbocyclyl, and 4- to 6-membered monocyclic heterocyclyl;

or alternatively R^1 and R^2, taken together with their intervening atoms, form a Ring B that is selected from 3- to 7-membered monocyclic heterocyclyl and 7- to 14-membered bicyclic heterocyclyl; wherein the Ring B is optionally substituted with one or more R^{200};

or alternatively R^2 and R^3, taken together with their intervening atoms, form a Ring C that is selected from 3- to 7-membered monocyclic heterocyclyl and 7- to 10-membered bicyclic heterocyclyl; wherein the Ring C is optionally substituted with one or more R^{200};

R^{200}, for each occurrence, is independently selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 3- to 7-membered monocyclic carbocyclyl, 4- to 6-membered monocyclic heterocyclyl, halogen, -CN, $-C(O)R^{200a}$, $-C(O)_2R^{200a}$; $-C(O)N(R^{200a})_2$, $-N(R^{200a})_2$, $-N(R^{200a})C(O)R^{200a}$, -

$N(R^{200a})C(O)_2R^{200a}$, $-N(R^{200a})C(O)N(R^{200a})_2$, $-N(R^{200a})S(O)_2R^{200a}$, $-OR^{200a}$, $-OC(O)R^{200a}$, $-OC(O)N(R^{200a})_2$, $-SR^{200a}$, $-S(O)R^{200a}$, $-S(O)_2R^{200a}$, $-S(O)N(R^{200a})_2$, $-S(O)_2N(R^{200a})_2$; wherein the C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, 3- to 7-membered monocyclic carbocyclyl, 4- to 6-membered monocyclic heterocyclyl represented by R^{200} are each optionally substituted with one or more R^{250}; or two R^{200} taken together with their intervening atom, form 4- to 6- membered monocyclic heterocyclyl or 3- to 7-membered monocyclic carbocyclyl, each of which is optionally substituted with one or more R^{250};

R^{200a}, for each occurrence, is independently selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 3- to 7-membered monocyclic carbocyclyl, and 4- to 6-membered monocyclic heterocyclyl, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 3- to 7-membered monocyclic carbocyclyl, and 4- to 6-membered monocyclic heterocyclyl represented by R^{200a} are each optionally substituted with one or more R^{250};

R^{250}, for each occurrence, is independently selected from C_{1-6} alkyl, halogen and $–OR^{250a}$;

R^{250a} is H or C_{1-6} alkyl;

R^4 is selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 3- to 7-membered monocyclic carbocyclyl, 4- to 6-membered monocyclic heterocyclyl, halogen, $-NO_2$, -CN, $-OR^{4a}$, $-SR^{4a}$, $-N(R^{4a})_2$, $-C(O)R^{4a}$, $-C(O)OR^{4a}$, $-S(O)R^{4a}$, $-S(O)_2R^{4a}$, $-C(O)N(R^{4a})_2$, $-SO_2N(R^{4a})_2$, $-OC(O)R^{4a}$, $-N(R)C(O)R^{4a}$, $-N(R)C(O)OR^{4a}$,$-N(R)SO_2R^{4a}$, and $-OC(O)N(R^{4a})_2$; wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 3- to 7-membered monocyclic carbocyclyl, and 4- to 6-membered monocyclic heterocyclyl represented by R^4 are each optionally substituted with one or more R^{40};

R^{4a} is H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 3- to 7-membered monocyclic carbocyclyl, and 4- to 6-membered monocyclic heterocyclyl, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 3- to 7-membered monocyclic carbocyclyl and 4- to 6-membered monocyclic heterocyclyl represented by R^{4a} are each optionally substituted with one or more R^{40};

R^{40}, for each occurrence, is independently selected from halogen, $-OR^{40a}$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 3- to 7-membered monocyclic carbocyclyl, and 4- to 6-membered monocyclic heterocyclyl; wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 3- to 7-membered monocyclic carbocyclyl, and 4- to 6-membered monocyclic heterocyclyl represented by R^{40} are each optionally substituted with one or more R^{45};

R^{40a} is H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 3- to 7-membered monocyclic carbocyclyl, and 4- to 6-membered monocyclic heterocyclyl, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 3- to 7-membered monocyclic carbocyclyl, and 4- to 6-membered monocyclic heterocyclyl are each optionally substituted with one or more R^{45};

R^{45}, for each occurrence, is independently selected from C_{1-6} alkyl, halogen and $–OR^{45a}$;

R^{45a} is H or C_{1-6} alkyl;

or alternatively R^3 and R^4, taken together with their intervening atoms form Ring D that is selected from 5- to 7-membered monocyclic carbocyclyl and 5- to 7-membered monocyclic heterocyclyl having 1-2 heteroatoms independently selected from O, N and S; wherein the Ring D is optionally substituted with one or more R^{300};

R^{300}, for each occurrence, is independently selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 3- to 7-membered monocyclic carbocyclyl, 4- to 6-membered monocyclic heterocyclyl, halogen, $-C(O)R^{300a}$, $-OR^{300a}$, and $-S(O)_2R^{300a}$; wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 3- to 7-membered monocyclic carbocyclyl, and 4- to 6-membered monocyclic heterocyclyl represented by R^{300} are each optionally substituted with one or more R^{350};

R^{300a} is selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 3- to 7-membered monocyclic carbocyclyl, and 4- to 6-membered monocyclic heterocyclyl, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 3- to 7-membered monocyclic carbocyclyl, and 4- to 6-membered monocyclic heterocyclyl represented by R^{300a} are each optionally substituted with one or more R^{350};

R^{350}, for each occurrence, is independently selected from C_{1-6} alkyl, halogen, -CN, $-C(O)R^{350a}$, $-C(O)N(R^{350a})_2$, $-C(R^{350a})_2N(R^{350a})_2$, and $-OR^{350a}$;

R^{350a}, for each occurrence, is independently H or C_{1-6} alkyl optionally substituted with one to three halogen, or two R^{350a} together with the N atom from which they are attached form 4- to 6-membered monocyclic heterocyclyl with 1-2 heteroatoms selected from N and O;

R^5 is selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halogen, and $-OR^{5a}$; wherein the C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl represented by R^5 are optionally substituted with one or more halogen;

R^{5a} is selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 3- to 7-membered monocyclic carbocyclyl, and 4- to 6-membered monocyclic heterocyclyl, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 3- to 6-membered monocyclic carbocyclyl represented by R^{5a} are each optionally substituted with one or more halogen;

R^6 is selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halogen, $-OR^{6a}$; wherein the C_{1-6} alkyl, C_{2-6} alkenyl and C_{2-6} alkynyl represented by R^6 are each optionally substituted with one or more halogen;

R^{6a} is H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 3- to 6-membered monocyclic carbocyclyl, and 4- to 6-membered monocyclic heterocyclyl, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 3- to 6-membered monocyclic carbocyclyl and 4- to 6-membered monocyclic heterocyclyl represented by R^{6a} are each optionally substituted with one or more halogen;

R^7 is selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, -CN, -OR^{7a}, -$C(O)N(R^{7a})_2$, -$C(O)OR^{7a}$, and -$C(O)R^{7a}$; wherein the C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl represented by R^7 are each optionally substituted one or more R^{70};

R^{7a}, for each occurrence, is independently selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 3- to 7-membered monocyclic carbocyclyl, and 4- to 6-membered monocyclic heterocyclyl, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 3- to 7-membered monocyclic carbocyclyl and 4- to 6-membered monocyclic heterocyclyl represented by R^{7a} are each optionally substituted with one or more R^{70};

R^{70}, for each occurrence, is independently selected from halogen, -OR^{70a}, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 3- to 7-membered monocyclic carbocyclyl, and 4- to 6-membered monocyclic heterocyclyl; wherein the C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, 3- to 7-membered monocyclic carbocyclyl and 4- to 6-membered monocyclic heterocyclyl represented by R^{70} are optionally substituted with one or more R^{75};

R^{70a} is selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 3- to 7-membered monocyclic carbocyclyl, and 4- to 6-membered monocyclic heterocyclyl, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 3- to 7-membered monocyclic carbocyclyl, and 4- to 6-membered monocyclic heterocyclyl represented by R^{70a} are each optionally substituted one or more R^{75};

R^{75}, for each occurrence, is independently selected from C_{1-6} alkyl, halogen and –OR^{75a};

R^{75a} is H or C_{1-6} alkyl;

R^8, for each occurrence, is independently selected from H, halogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, -CN, -$C(O)R^{8a}$, -$C(O)_2R^{8a}$, -$C(O)N(R^{8a})_2$, -$N(R^{8a})_2$, -$N(R^{8a})C(O)R^{8a}$, -$N(R^{8a})C(O)_2R^{8a}$, -$N(R^{8a})C(O)N(R^{8a})_2$, -$N(R^{8a})S(O)_2R^{8a}$, -OR^{8a}, -$OC(O)R^{8a}$, -$OC(O)N(R^{8a})_2$, -SR^{8a}, -$S(O)R^{8a}$, -$S(O)_2R^{8a}$, -$S(O)N(R^{8a})_2$, -$S(O)_2N(R^{8a})_2$, 3- to 7-membered monocyclic carbocyclyl, 4- to 6- membered monocyclic heterocyclyl, and 7- to 10-membered bicyclic heterocyclyl; wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 3- to 7-membered monocyclic carbocyclyl, 4- to 6-membered monocyclic heterocyclyl and 7- to 10-membered bicyclic heterocyclyl represented by R^8 are each optionally substituted with one or more R^{80};

R^{8a}, for each occurrence, is independently selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 3- to 7-membered monocyclic carbocyclyl, and 4- to 6- membered monocyclic heterocyclyl, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 3- to 7-membered monocyclic carbocyclyl, and 4- to 6- membered monocyclic heterocyclyl represented by R^{8a} are each optionally substituted with one or more R^{80}; or two R^{8a}, taken together with their intervening atom, form 4- to 6- membered monocyclic heterocyclyl optionally substituted with one or more R^{80};

R^{80}, for each occurrence, is independently selected from halogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, -CN, $-C(O)R^{80a}$, $-C(O)_2R^{80a}$, $-C(O)N(R^{80a})_2$, $-N(R^{80a})_2$, $-N(R^{80a})C(O)R^{80a}$, $-N(R^{80a})C(O)_2R^{80a}$, $-N(R^{80a})C(O)N(R^{80a})_2$, $-N(R^{80a})S(O)_2R^{80a}$, $-OR^{80a}$, $-OC(O)R^{80a}$, $-OC(O)N(R^{80a})_2$, $-SR^{80a}$, $-S(O)R^{80a}$, $-S(O)_2R^{80a}$, $-S(O)N(R^{80a})_2$, $-S(O)_2N(R^{80a})_2$, 3- to 7-membered monocyclic carbocyclyl, and 4- to 6-membered monocyclic heterocyclyl; wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 3- to 7-membered monocyclic carbocyclyl, and 4- to 6-membered monocyclic heterocyclyl represented by R^{80} are each optionally substituted with one or more R^{85}; or two R^{80} together the carbon atom from which they are attached form an oxo group (-C=O)-);

R^{80a}, for each occurrence, is independently selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 3- to 6-membered monocyclic carbocyclyl, and 4- to 6-membered monocyclic heterocyclyl; wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6}alkynyl, 3- to 6-membered monocyclic carbocyclyl, and 4- to 6-membered monocyclic heterocyclyl represented by R^{80a} are each optionally substituted with one or more R^{85};

R^{85}, for each occurrence, is independently C_{1-6} alkyl, halogen and $–OR^{85a}$;

R^{85a} is H or C_{1-6} alkyl; and

—* represents a bond to the linker L.

In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising a compound as disclosed herein or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

In yet another aspect of the present disclosure, there is provided a use of a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition as disclosed herein, in the manufacture of a medicament for treating a disorder responsive to degradation and/or inhibition of Bruton's tyrosine kinase in a subject, optionally

wherein the disorder is an autoimmune disorder, rheumatoid arthritis, systemic lupus erythematosus, atopic dermatitis, or cancer, preferably,

wherein the autoimmune disorder is multiple sclerosis and wherein the cancer is leukemia or lymphoma.

In a further aspect of the present disclosure, there is provided a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition as disclosed herein, for use in therapy.

A first example of the present disclosure is a compound of Formula (A):

BTK—L—DSM (A) ,

or a pharmaceutically acceptable salt thereof, wherein:

DSM is a degradation signaling moiety that is covalently attached to the linker L,

L is a linker that covalently attaches BTK to DSM; and

BTK is a Btk binding moiety represented by Formula (I) or Formula (II) that is covalently attached to linker L:

heterocyclyl represented by R^8 are each optionally substituted with one or more (*e.g.*, 1 to 6, 1 to 3, or 1, 2, 3, 4, 5, or 6) R^{80};

R^{8a}, for each occurrence, is independently selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 3- to 7-membered monocyclic carbocyclyl, and 4- to 6- membered monocyclic heterocyclyl, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 3- to 7-membered monocyclic carbocyclyl, and 4- to 6- membered monocyclic heterocyclyl represented by R^{8a} are each optionally substituted with one or more (*e.g.*, 1 to 6, 1 to 3, or 1, 2, 3, 4, 5, or 6) R^{80}; or two R^{8a}, taken together with their intervening atom, form 4- to 6- membered monocyclic heterocyclyl optionally substituted with one or more (*e.g.*, 1 to 6, 1 to 3, or 1, 2, 3, 4, 5, or 6) R^{80};

R^{80}, for each occurrence, is independently selected from halogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, -CN, $-C(O)R^{80a}$, $-C(O)_2R^{80a}$, $-C(O)N(R^{80a})_2$, $-N(R^{80a})_2$, $-N(R^{80a})C(O)R^{80a}$, $-N(R^{80a})C(O)_2R^{80a}$, $-N(R^{80a})C(O)N(R^{80a})_2$, $-N(R^{80a})S(O)_2R^{80a}$, $-OR^{80a}$, $-OC(O)R^{80a}$, $-OC(O)N(R^{80a})_2$, $-SR^{80a}$, $-S(O)R^{80a}$, $-S(O)_2R^{80a}$, $-S(O)N(R^{80a})_2$, $-S(O)_2N(R^{80a})_2$, 3- to 7-membered monocyclic carbocyclyl, and 4- to 6-membered monocyclic heterocyclyl; wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 3- to 7-membered monocyclic carbocyclyl, and 4- to 6-membered monocyclic heterocyclyl represented by R^{80} are each optionally substituted with one or more (*e.g.*, 1 to 6, 1 to 3, or 1, 2, 3, 4, 5, or 6) R^{85}; or two R^{80} together the carbon atom from which they are attached form an oxo group (-C=O)-);

R^{80a}, for each occurrence, is independently selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6}alkynyl, 3- to 6-membered monocyclic carbocyclyl, and 4- to 6-membered monocyclic heterocyclyl; wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6}alkynyl, 3- to 6-membered monocyclic carbocyclyl, and 4- to 6-membered monocyclic heterocyclyl represented by R^{80a} are each optionally substituted with one or more (*e.g.*, 1 to 6, 1 to 3, or 1, 2, 3, 4, 5, or 6) R^{85};

R^{85}, for each occurrence, is independently C_{1-6} alkyl, halogen and $–OR^{85a}$;

R^{85a} is H or C_{1-6} alkyl; and

—* represents a bond to the linker L.

In another example, the present disclosure provides methods of treating a disorder responsive to modulation of Btk activity and/or degradation of Btk in a subject comprising administering to the subject an effective amount of at least one compound described herein. The present disclosure also includes the use of at least one compound described herein, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment of a disorder responsive to modulation of Btk activity and/or degradation of Btk. Also provided are compounds described herein, or pharmaceutically acceptable salts thereof, for use in treating a disorder responsive to modulation of Btk activity and/or degradation of Btk. Methods of

making the compounds described herein and any synthetic intermediates are also included in the present disclosure.

Other features or advantages will be apparent from the following detailed description of several examples, and also from the appended claims.

DETAILED DESCRIPTION

Compounds or pharmaceutically acceptable salts thereof as described herein are capable of activating the selective ubiqitination of Btk proteins via the ubiquitin-proteasome pathways (UPP) and cause degradation of Btk proteins. In some embodiments, compounds or pharmaceutically acceptable salts thereof as described herein can modulate Btk activities.

I. DEFINITIONS

Compounds are described using standard nomenclature. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in the art to which this invention belongs.

The terms“a” and “an” do not denote a limitation of quantity, but rather denote the presence of at least one of the referenced item. Recitation of ranges of values are merely intended to serve as a shorthand method of referring individually to each separate value falling within the range, unless otherwise indicated herein, and each separate value is incorporated into the specification as if it were individually recited herein. The endpoints of all ranges are included within the range and independently combinable. All methods described herein can be performed in a suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of examples, or exemplary language (e.g.,“such as”), is intended merely to better illustrate the invention and does not pose a limitation on the scope of the invention unless otherwise claimed.

As used herein, the term "alkyl" refers to a fully saturated branched or unbranched hydrocarbon moiety. In some embodiments, the alkyl comprises 1 to 20 carbon atoms, 1 to 10 carbon atoms, 1 to 8 carbon atoms, 1 to 6 carbon atoms, or 1 to 4 carbon atoms. In some embodiments, an alkyl comprises from 6 to 20 carbon atoms. Representative examples of alkyl include, but are not limited to, methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, tert-butyl, n-pentyl, isopentyl, neopentyl, or n-hexyl.

"Alkenyl" refers to an unsaturated hydrocarbon group which may be linear or branched and has at least one carbon-carbon double bond. In some embodiments, alkenyl groups have 2 to 20 carbon atoms, 2 to 10 carbon atoms or 2-6 carbon atoms. The alkenyl group may contain 1, 2

CLAIMS

What is claimed is:

1. A compound of Formula (A):

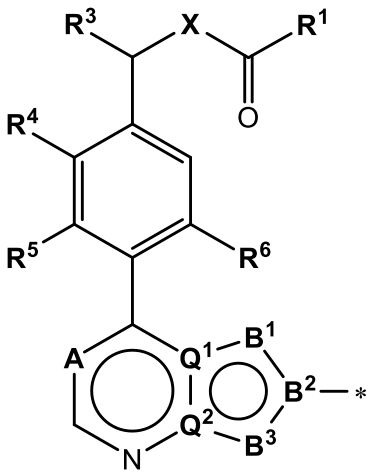
BTK—L—DSM (A) ,

or a pharmaceutically acceptable salt thereof, wherein:

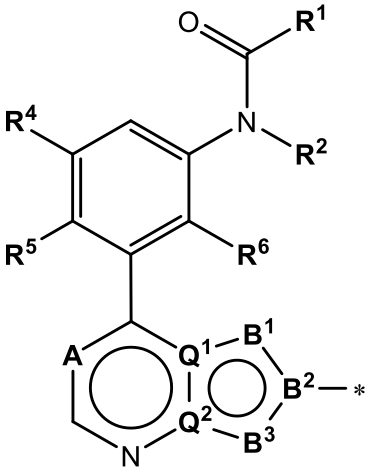
DSM is a degradation signaling moiety that is covalently attached to the linker L;

L is a linker that covalently attaches BTK to DSM; and

BTK is a Btk binding moiety represented by Formula (I) or Formula (II) that is covalently attached to linker L:



(I)



(II) ,

or a pharmaceutically acceptable salt thereof, wherein:

A is selected from CR^7 and N;

B^1 is selected from CR^8, N, and NR^8;

B^2 is C or N;

B^3 is selected from CR^8, N, NR^8 and S;

one of Q^1 and Q^2 is N, and the other one is C; or both of Q^1 and Q^2 are C;

X is selected from O and NR^2;

R^1 is selected from $-N(R^{1a})_2$, $C_{1\text{-}10}$ alkyl, 3- to 7-membered monocyclic carbocyclyl, 3- to 7-membered monocyclic heterocyclyl, 7- to 10-membered bicyclic carbocyclyl, and 7- to 10-membered bicyclic heterocyclyl; wherein the $C_{1\text{-}10}$ alkyl, 3- to 7-membered monocyclic carbocyclyl, 3- to 7-membered monocyclic heterocyclyl, 7- to 10-membered bicyclic carbocyclyl, and 7- to 10-membered bicyclic heterocyclyl represented by R^1 are each optionally substituted with one or more R^{10};

R^{1a}, for each occurrence, is independently selected from H, $C_{1\text{-}6}$ alkyl, $C_{2\text{-}6}$ alkenyl,

C_{2-6}alkynyl, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl represented by R^{1a} are each optionally substituted with one or more R^{10}; or alternatively two R^{1a}, taken together with their intervening atoms, form a 3- to 7-membered monocyclic heterocyclyl which is optionally substituted with one or more R^{10};

R^{10}, for each occurrence, is independently selected from H, halogen, -OR^{10a}, -$S(O)_2R^{10a}$, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 3- to 7-membered monocyclic carbocyclyl, and 4- to 6-membered monocyclic heterocyclyl; wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 3- to 7-membered monocyclic carbocyclyl, and 4- to 6-membered monocyclic heterocyclyl represented by R^{10} are each optionally substituted with one or more R^{15};

or alternatively two R^{10}, taken together with their intervening atoms, form a Ring A that is selected from 3- to 7-membered monocyclic carbocyclyl, 3- to 7-membered monocyclic heterocyclyl, 7- to 10-membered bicyclic carbocyclyl, and 7- to 10-membered bicyclic heterocyclyl, wherein the Ring A is optionally substituted with one or more R^{15};

R^{10a}, for each occurrence, is independently selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 3- to 7-membered monocyclic carbocyclyl, and 4- to 6-membered monocyclic heterocyclyl;

R^{15}, for each occurrence, is independently selected from C_{1-6} alkyl, halogen, -CN, 3- to 7-membered monocyclic carbocyclyl and -OR^{15a}; wherein the C_{1-6} alkyl and 3- to 7-membered monocyclic carbocyclyl represented by R^{15} is optionally substituted with one or more R^{15a}; or two R^{15}, taken together with their intervening atom, form 3- to 7- membered monocyclic carbocyclyl or 4- to 6-membered monocyclic heterocyclyl;

R^{15a} is selected from H, halogen and C_{1-6} alkyl optionally substituted with at least one halogen;

R^2 is selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

R^3 is selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, -$C(O)N(R^{3a})_2$, -$C(O)OR^{3a}$, and -$C(O)R^{3a}$, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6}alkynyl represented by R^3 are each optionally substituted with one or more R^{30};

R^{3a}, for each occurrence, is independently selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl represented by R^{3a} are each optionally substituted with one or more R^{30};

R^{30}, for each occurrence, is independently selected from halogen, -OR^{30a}, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 3- to 7-membered monocyclic carbocyclyl, and 4- to 6-membered monocyclic heterocyclyl;

R^{30a} is selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 3- to 6-membered

monocyclic carbocyclyl, and 4- to 6-membered monocyclic heterocyclyl;

or alternatively R^1 and R^2, taken together with their intervening atoms, form a Ring B that is selected from 3- to 7-membered monocyclic heterocyclyl and 7- to 14-membered bicyclic heterocyclyl; wherein the Ring B is optionally substituted with one or more R^{200};

or alternatively R^2 and R^3, taken together with their intervening atoms, form a Ring C that is selected from 3- to 7-membered monocyclic heterocyclyl and 7- to 10-membered bicyclic heterocyclyl; wherein the Ring C is optionally substituted with one or more R^{200};

R^{200}, for each occurrence, is independently selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 3- to 7-membered monocyclic carbocyclyl, 4- to 6-membered monocyclic heterocyclyl, halogen, -CN, $-C(O)R^{200a}$, $-C(O)_2R^{200a}$; $-C(O)N(R^{200a})_2$, $-N(R^{200a})_2$, $-N(R^{200a})C(O)R^{200a}$, $-N(R^{200a})C(O)_2R^{200a}$, $-N(R^{200a})C(O)N(R^{200a})_2$, $-N(R^{200a})S(O)_2R^{200a}$, $-OR^{200a}$, $-OC(O)R^{200a}$, $-OC(O)N(R^{200a})_2$, $-SR^{200a}$, $-S(O)R^{200a}$, $-S(O)_2R^{200a}$, $-S(O)N(R^{200a})_2$, $-S(O)_2N(R^{200a})_2$; wherein the C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, 3- to 7-membered monocyclic carbocyclyl, 4- to 6-membered monocyclic heterocyclyl represented by R^{200} are each optionally substituted with one or more R^{250}; or two R^{200} taken together with their intervening atom, form 4- to 6- membered monocyclic heterocyclyl or 3- to 7-membered monocyclic carbocyclyl, each of which is optionally substituted with one or more R^{250};

R^{200a}, for each occurrence, is independently selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 3- to 7-membered monocyclic carbocyclyl, and 4- to 6-membered monocyclic heterocyclyl, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 3- to 7-membered monocyclic carbocyclyl, and 4- to 6-membered monocyclic heterocyclyl represented by R^{200a} are each optionally substituted with one or more R^{250};

R^{250}, for each occurrence, is independently selected from C_{1-6} alkyl, halogen and $–OR^{250a}$;

R^{250a} is H or C_{1-6} alkyl;

R^4 is selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 3- to 7-membered monocyclic carbocyclyl, 4- to 6-membered monocyclic heterocyclyl, halogen, $-NO_2$, -CN, $-OR^{4a}$, $-SR^{4a}$, $-N(R^{4a})_2$, $-C(O)R^{4a}$, $-C(O)OR^{4a}$, $-S(O)R^{4a}$, $-S(O)_2R^{4a}$, $-C(O)N(R^{4a})_2$, $-SO_2N(R^{4a})_2$, $-OC(O)R^{4a}$, $-N(R)C(O)R^{4a}$, $-N(R)C(O)OR^{4a}$,$-N(R)SO_2R^{4a}$, and $-OC(O)N(R^{4a})_2$; wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 3- to 7-membered monocyclic carbocyclyl, and 4- to 6-membered monocyclic heterocyclyl represented by R^4 are each optionally substituted with one or more R^{40};

R^{4a} is H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 3- to 7-membered monocyclic carbocyclyl, and 4- to 6-membered monocyclic heterocyclyl, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 3- to 7-membered monocyclic carbocyclyl and 4- to 6-membered monocyclic heterocyclyl represented by R^{4a} are each optionally substituted with one or more R^{40};

R^{40}, for each occurrence, is independently selected from halogen, -OR^{40a}, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 3- to 7-membered monocyclic carbocyclyl, and 4- to 6-membered monocyclic heterocyclyl; wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 3- to 7-membered monocyclic carbocyclyl, and 4- to 6-membered monocyclic heterocyclyl represented by R^{40} are each optionally substituted with one or more R^{45};

R^{40a} is H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 3- to 7-membered monocyclic carbocyclyl, and 4- to 6-membered monocyclic heterocyclyl, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 3- to 7-membered monocyclic carbocyclyl, and 4- to 6-membered monocyclic heterocyclyl are each optionally substituted with one or more R^{45};

R^{45}, for each occurrence, is independently selected from C_{1-6} alkyl, halogen and –OR^{45a};

R^{45a} is H or C_{1-6} alkyl;

or alternatively R^3 and R^4, taken together with their intervening atoms form Ring D that is selected from 5- to 7-membered monocyclic carbocyclyl and 5- to 7-membered monocyclic heterocyclyl having 1-2 heteroatoms independently selected from O, N and S; wherein the Ring D is optionally substituted with one or more R^{300};

R^{300}, for each occurrence, is independently selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 3- to 7-membered monocyclic carbocyclyl, 4- to 6-membered monocyclic heterocyclyl, halogen, -$C(O)R^{300a}$, -OR^{300a}, and -$S(O)_2R^{300a}$; wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 3- to 7-membered monocyclic carbocyclyl, and 4- to 6-membered monocyclic heterocyclyl represented by R^{300} are each optionally substituted with one or more R^{350};

R^{300a} is selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 3- to 7-membered monocyclic carbocyclyl, and 4- to 6-membered monocyclic heterocyclyl, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 3- to 7-membered monocyclic carbocyclyl, and 4- to 6-membered monocyclic heterocyclyl represented by R^{300a} are each optionally substituted with one or more R^{350};

R^{350}, for each occurrence, is independently selected from C_{1-6} alkyl, halogen, -CN, -$C(O)R^{350a}$, -$C(O)N(R^{350a})_2$, -$C(R^{350a})_2N(R^{350a})_2$, and –$OR^{350a}$;

R^{350a}, for each occurrence, is independently H or C_{1-6} alkyl optionally substituted with one to three halogen, or two R^{350a} together with the N atom from which they are attached form 4- to 6-membered monocyclic heterocyclyl with 1-2 heteroatoms selected from N and O;

R^5 is selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halogen, and -OR^{5a}; wherein the C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl represented by R^5 are optionally substituted with one or more halogen;

R^{5a} is selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 3- to 7-membered

monocyclic carbocyclyl, and 4- to 6-membered monocyclic heterocyclyl, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 3- to 6-membered monocyclic carbocyclyl represented by R^{5a} are each optionally substituted with one or more halogen;

R^6 is selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halogen, $-OR^{6a}$; wherein the C_{1-6} alkyl, C_{2-6} alkenyl and C_{2-6} alkynyl represented by R^6 are each optionally substituted with one or more halogen;

R^{6a} is H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 3- to 6-membered monocyclic carbocyclyl, and 4- to 6-membered monocyclic heterocyclyl, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 3- to 6-membered monocyclic carbocyclyl and 4- to 6-membered monocyclic heterocyclyl represented by R^{6a} are each optionally substituted with one or more halogen;

R^7 is selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, -CN, $-OR^{7a}$, $-C(O)N(R^{7a})_2$, $-C(O)OR^{7a}$, and $-C(O)R^{7a}$; wherein the C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl represented by R^7 are each optionally substituted one or more R^{70};

R^{7a}, for each occurrence, is independently selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 3- to 7-membered monocyclic carbocyclyl, and 4- to 6-membered monocyclic heterocyclyl, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 3- to 7-membered monocyclic carbocyclyl and 4- to 6-membered monocyclic heterocyclyl represented by R^{7a} are each optionally substituted with one or more R^{70};

R^{70}, for each occurrence, is independently selected from halogen, $-OR^{70a}$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 3- to 7-membered monocyclic carbocyclyl, and 4- to 6-membered monocyclic heterocyclyl; wherein the C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, 3- to 7-membered monocyclic carbocyclyl and 4- to 6-membered monocyclic heterocyclyl represented by R^{70} are optionally substituted with one or more R^{75};

R^{70a} is selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 3- to 7-membered monocyclic carbocyclyl, and 4- to 6-membered monocyclic heterocyclyl, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 3- to 7-membered monocyclic carbocyclyl, and 4- to 6-membered monocyclic heterocyclyl represented by R^{70a} are each optionally substituted one or more R^{75};

R^{75}, for each occurrence, is independently selected from C_{1-6} alkyl, halogen and $–OR^{75a}$;

R^{75a} is H or C_{1-6} alkyl;

R^8, for each occurrence, is independently selected from H, halogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, -CN, $-C(O)R^{8a}$, $-C(O)_2R^{8a}$, $-C(O)N(R^{8a})_2$, $-N(R^{8a})_2$, $-N(R^{8a})C(O)R^{8a}$, $-N(R^{8a})C(O)_2R^{8a}$, $-N(R^{8a})C(O)N(R^{8a})_2$, $-N(R^{8a})S(O)_2R^{8a}$, $-OR^{8a}$, $-OC(O)R^{8a}$, $-OC(O)N(R^{8a})_2$, $-SR^{8a}$, $-S(O)R^{8a}$, $-S(O)_2R^{8a}$, $-S(O)N(R^{8a})_2$, $-S(O)_2N(R^{8a})_2$, 3- to 7-membered monocyclic carbocyclyl, 4- to 6- membered monocyclic heterocyclyl, and 7- to 10-membered bicyclic

heterocyclyl; wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 3- to 7-membered monocyclic carbocyclyl, 4- to 6-membered monocyclic heterocyclyl and 7- to 10-membered bicyclic heterocyclyl represented by R^8 are each optionally substituted with one or more R^{80};

R^{8a}, for each occurrence, is independently selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 3- to 7-membered monocyclic carbocyclyl, and 4- to 6- membered monocyclic heterocyclyl, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 3- to 7-membered monocyclic carbocyclyl, and 4- to 6- membered monocyclic heterocyclyl represented by R^{8a} are each optionally substituted with one or more R^{80}; or two R^{8a}, taken together with their intervening atom, form 4- to 6- membered monocyclic heterocyclyl optionally substituted with one or more R^{80};

R^{80}, for each occurrence, is independently selected from halogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, -CN, $-C(O)R^{80a}$, $-C(O)_2R^{80a}$, $-C(O)N(R^{80a})_2$, $-N(R^{80a})_2$, $-N(R^{80a})C(O)R^{80a}$, $-N(R^{80a})C(O)_2R^{80a}$, $-N(R^{80a})C(O)N(R^{80a})_2$, $-N(R^{80a})S(O)_2R^{80a}$, $-OR^{80a}$, $-OC(O)R^{80a}$, $-OC(O)N(R^{80a})_2$, $-SR^{80a}$, $-S(O)R^{80a}$, $-S(O)_2R^{80a}$, $-S(O)N(R^{80a})_2$, $-S(O)_2N(R^{80a})_2$, 3- to 7-membered monocyclic carbocyclyl, and 4- to 6-membered monocyclic heterocyclyl; wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 3- to 7-membered monocyclic carbocyclyl, and 4- to 6-membered monocyclic heterocyclyl represented by R^{80} are each optionally substituted with one or more R^{85}; or two R^{80} together the carbon atom from which they are attached form an oxo group (-C=O)-);

R^{80a}, for each occurrence, is independently selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 3- to 6-membered monocyclic carbocyclyl, and 4- to 6-membered monocyclic heterocyclyl; wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6}alkynyl, 3- to 6-membered monocyclic carbocyclyl, and 4- to 6-membered monocyclic heterocyclyl represented by R^{80a} are each optionally substituted with one or more R^{85};

R^{85}, for each occurrence, is independently C_{1-6} alkyl, halogen and $–OR^{85a}$;

R^{85a} is H or C_{1-6} alkyl; and

—* represents a bond to the linker L.

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

(a)

(i) A is N, Q^1 is C, and Q^2 is N;

(ii) A is CH, Q^1 is C, and Q^2 is C;

(iii) A is CH, Q^1 is N, and Q^2 is C; or

(iv) A is CH, Q^1 is C, and Q^2 is N;

and/or

(b)

(i) B^1 is CH, B^2 is C, and B^3 is CH;

(ii) B^1 is CH, B^2 is C, and B^3 is S;

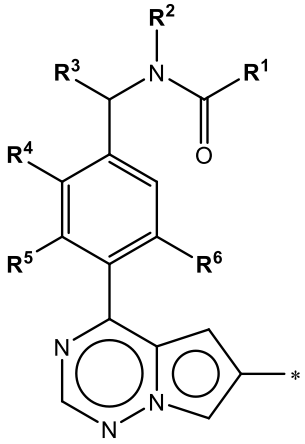
(iii) B^1 is N, B^2 is C, and B^3 is CH;

(iv) B^1 is CH, B^2 is C, and B^3 is NR^8;

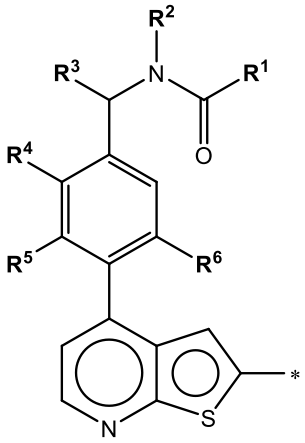
(v) B^1 is N, B^2 is N, and B^3 is CH; or

(vi) B^1 is CH, B^2 is N, and B^3 is N.

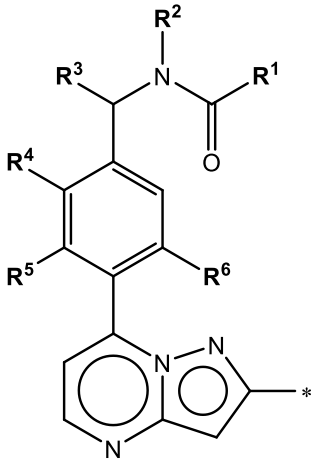
3. The compound of claim 1, wherein BTK in formula (A) is a Btk binding moiety represented by one of the following formulae:



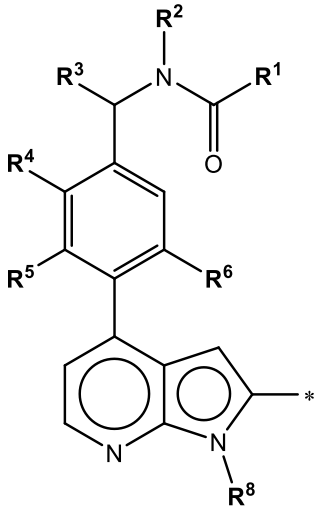
(IA) ,



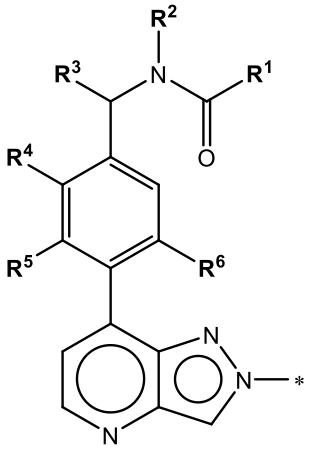
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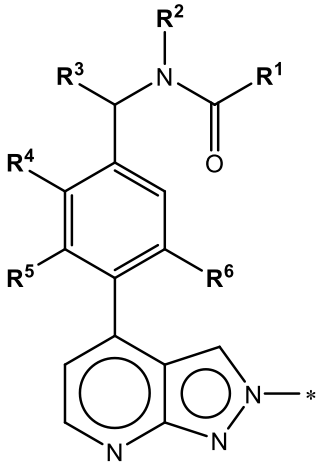
(IC) ,



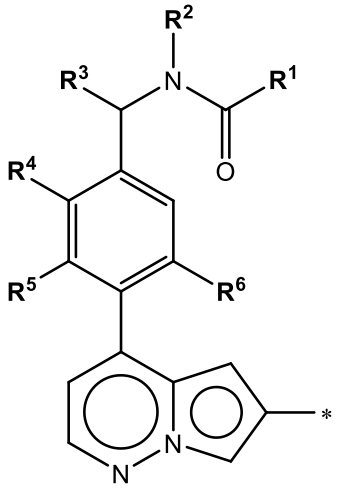
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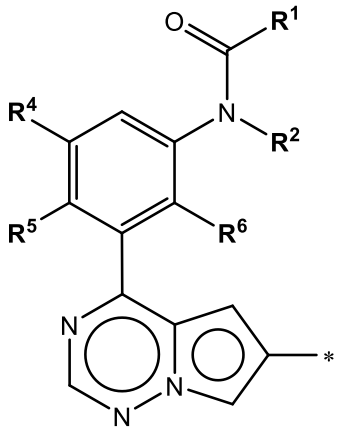


(IE) ,



(IF) ,



(IG) and  (IIA) ,

or a pharmaceutically acceptable salt thereof, preferably wherein BTK in formula (A) is a Btk binding moiety represented by formula (IA) or (IC) or a pharmaceutically acceptable salt thereof.

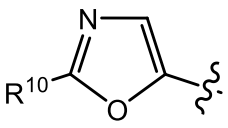
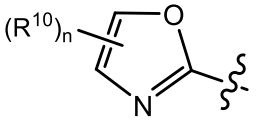
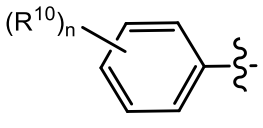
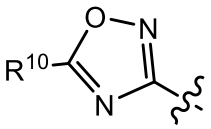
4. The compound of any one of claims 1-3, or a pharmaceutically acceptable salt thereof, wherein R^1 is:

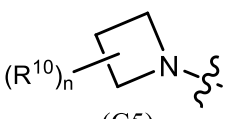
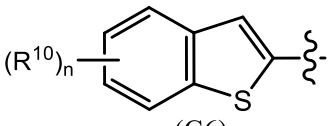
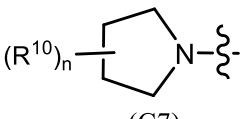
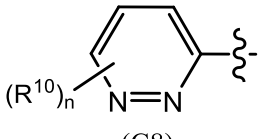
(i) selected from a C_{1-6} alkyl, 3- to 6-membered monocyclic or bicyclic carbocyclyl, 4- to 6-membered saturated monocyclic heterocyclyl, 5- to 6-membered monocyclic heteroaryl, and 9- to 10-membered bicyclic heteroaryl; wherein the C_{1-6} alkyl, phenyl, monocyclic or bicyclic C_{3-7} cycloalkyl, 4- to 6-membered saturated heterocyclyl, 5- to 6-membered monocyclic heteroaryl, and 9-to 10-membered bicyclic heteroaryl represented by R^1 are each optionally substituted with one or more R^{10};

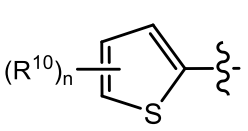
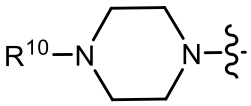
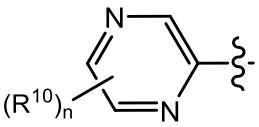
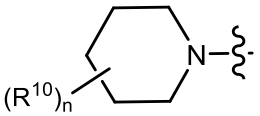
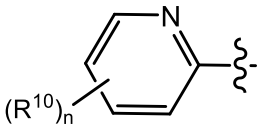
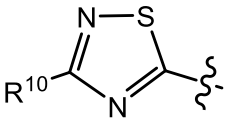
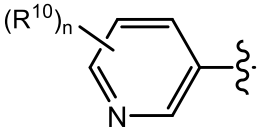
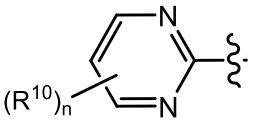
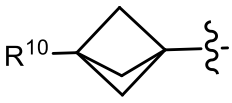
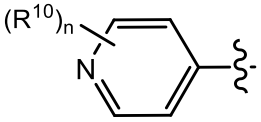
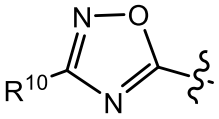
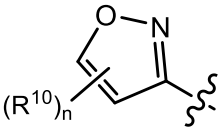
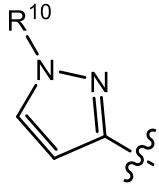
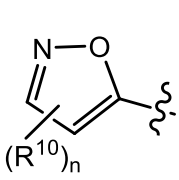
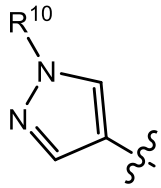
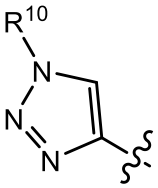
(ii) 5-membered monocyclic heteroaryl optionally substituted with one to three R^{10};

(iii) methyl, butyl, pentyl, phenyl, bicyclo[1.1.1]pentanyl, azetidinyl, isoxazolyl, 1,2,4-oxadiazolyl, oxazolyl, pyrazolyl, triazolyl, piperidinyl, piperazinyl, pyrazinyl, pyridinyl, pyrimidinyl, pyrrolidinyl, pyridazinyl, 1,2,4-thiadiazolyl, thiophenyl, or benzothiophenyl, each of which is optionally substituted with one to three R^{10}; or

(iv) represented by one of the following formulae:


(C1) ,

(C2) ,

(C3) ,

(C4) ,


(C5) ,

(C6) ,

(C7) ,

(C8) ,


(C9),

(C10),

(C11),

(C12),

(C13),

(C14),

(C15),

(C16),

(C17),

(C18),

(C19),

(C22),

(C23),

(C24),

(C25) or

(C26), wherein n represents an integer ranging from 0 to 3.

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

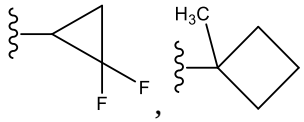
(i) R^{10}, for each occurrence, is independently selected from halogen, $-OR^{10a}$, $-S(O)_2R^{10a}$, C_{1-6} alkyl, and 3- to 7-membered monocyclic carbocyclyl, wherein the C_{1-6} alkyl and 3- to 7-membered monocyclic carbocyclyl represented by R^{10} are each optionally substituted with one or more R^{15}; or alternatively two R^{10}, taken together with their intervening atoms, form a 5- to 7-membered monocyclic carbocyclyl that is optionally substituted with one or more R^{15};

R^{10a}, for each occurrence, is H or C_{1-6} alkyl;

R^{15}, for each occurrence, is independently selected from C_{1-6} alkyl, halogen, $-OR^{15a}$, and 3- to 7-membered monocyclic carbocyclyl; wherein the C_{1-6} alkyl and the 3- to 7-membered monocyclic carbocyclyl represented by R^{15} is optionally substituted with one or more R^{15a}; and

R^{15a} is selected from H, halogen and C_{1-6} alkyl optionally substituted with at least one halogen; or

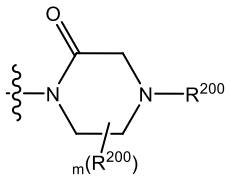
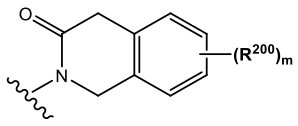
(ii) R^{10}, for each occurrence, is independently selected from Cl, F, $-CH_3$, $-CF_3$, $-CH_2-CH_3$, $-CH(CH_3)_2$, $-CHF_2$, $-C(CH_3)F_2$, $-CH_2-CF_3$, $-CH_2-C(CH_3)_3$, $-OCH_3$, $-C(CH_3)_3$, $-O-CH(CH_3)_2$, $-O-C(CH_3)_3$, $-O-CH_2-C(CH_3)_3$, $-C(CH_3)_2OH$, -cyclopropyl–CF_3, $-CH_2-$

cyclopropyl–CF_3, , and -$S(O)_2$–CH_3; or alternatively two R^{10}, taken together with their intervening atoms, form a cyclohexane.

6. The compound of any one of claims 1-5, or a pharmaceutically acceptable salt thereof, wherein R^2 is H or C_{1-3} alkyl, preferably wherein R^2 is H.

7. The compound of any one of claims 1-3, or a pharmaceutically acceptable salt thereof, wherein

(i) R^1 and R^2, taken together with their intervening atoms, form the Ring B that is selected from 3- to 7-membered monocyclic heterocyclyl and 9- to 10-membered bicyclic heterocyclyl; wherein the Ring B is optionally substituted with one to three R^{200}, preferably wherein the Ring B is represented by the following formula:

, or ,

wherein m is 0, 1, 2 or 3; and

(ii) R^{200} is halo or C_{1-6} alkyl optionally substituted with one to three halogen.

8. The compound of claim 1 or 2, or a pharmaceutically acceptable salt thereof, wherein X is O.

9. The compound of claim 8, or a pharmaceutically acceptable salt thereof, wherein R^1 is

(i) a 4- to 6-membered monocyclic heterocyclyl that is optionally substituted with one to three R^{10}; or

(ii) pyrrolidinyl, piperidinyl or piperazinyl, each of which is optionally substituted with one or three R^{10},

optionally, wherein:

(i) R^{10} for each occurrence is independently -OR^{10a} or C_{1-6} alkyl optionally substituted with one to three halogen; and R^{10a} is C_{1-6} alkyl; or

(ii) R^{10} is selected from –CH_2–$C(CH_3)_3$, -CH_2–CF_3 and -O–$C(CH_3)_3$.

10. The compound of any one of claims 1-9, or a pharmaceutically acceptable salt thereof, wherein:

(i) R^3 is H or C_{1-4} alkyl, preferably wherein R^3 is H;

(ii) R^4 is selected from:

(a) H, C_{1-6} alkyl, C_{3-6} cycloalkyl, halogen and $-OR^{4a}$; and R^{4a} is H, C_{1-6} alkyl or C_{1-6} haloalkyl; or

(b) H, F, Cl, $-CH_3$, $-CH(CH_3)_2$ and $-OCH_3$; and/or

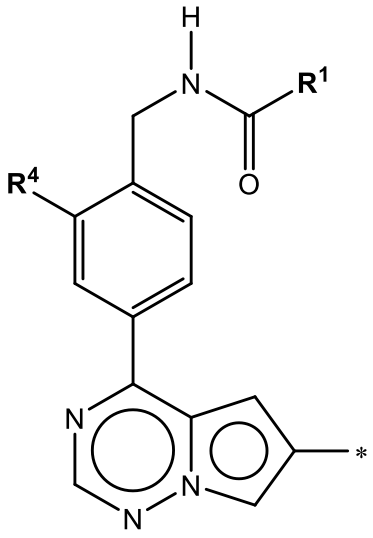
(iii) R^3 and R^4 together with their intervening atoms form Ring D that is a 7-membered monocyclic heterocyclyl having 1 heteroatom selected from N and O, and Ring D is optionally substituted with R^{300}, preferably wherein Ring D is oxepane or azepane, optionally substituted with R^{300} and R^{300} is C_{1-6} alkyl, 3- to 7-membered monocyclic carbocyclyl, or 4- to 6-membered monocyclic heterocyclyl.

11. The compound of any one of claims 1-10, or a pharmaceutically acceptable salt thereof, wherein:

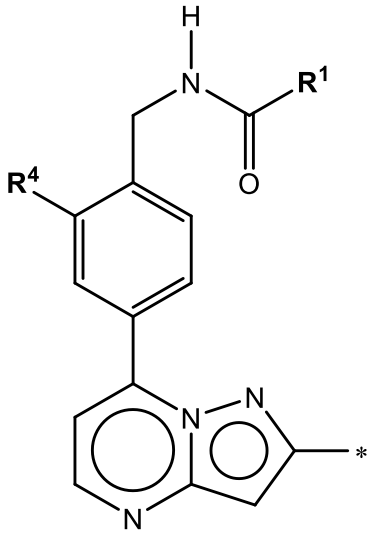
(i) R^5 is H, C_{1-4} alkyl or halogen, preferably wherein R^5 is H; and/or

(ii) R^6 is H, C_{1-4} alkyl or halogen, preferably wherein R^6 is H, $-CH_3$, or F.

12. The compound of claim 1, wherein BTK in formula (A) is a Btk binding moiety represented by Formula (III) or Formula (IV):



(III)



(IV) ,

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is phenyl, 4- to 6-membered saturated monocyclic heterocyclyl, or 5- or 6-membered heteroaryl, each of which is optionally substituted with 1 to 3 R^{10};

R^{10}, for each occurrence, is independently selected from halogen, -OR^{10a}, -$S(O)_2R^{10a}$, C_{1-6} alkyl and C_{3-6} cycloalkyl, wherein the C_{1-6} alkyl and C_{3-6} cycloalkyl are optionally substituted with one to three R^{15}, or alternatively two R^{10}, taken together with their intervening atoms, form a 5- to 7-membered monocyclic carbocyclyl that is optionally substituted with one to three R^{15};

R^{10a}, for each occurrence, is H or C_{1-6} alkyl;

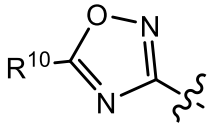
R^{15}, for each occurrence, is independently selected from C_{1-6} alkyl, halogen, -OR^{15a}, and C_{3-6} cycloalkyl; wherein the C_{1-6} alkyl and the C_{3-6} cycloalkyl represented by R^{15} is optionally substituted with one to three R^{15a};

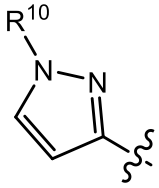
R^{15a} is selected from H, halogen and C_{1-3} alkyl optionally substituted with one to three halogen.

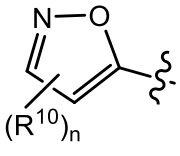
13. The compound of claim 12, or a pharmaceutically acceptable salt thereof, wherein R^1 is

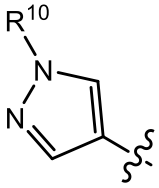
(i) phenyl, isoxazolyl, 1,2,4-oxadiazolyl, pyrazolyl, triazolyl or azetidinyl, each of which is optionally substituted with 1 to 3 R^{10}; or

(ii) represented by the following formula:

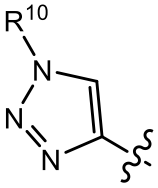

(C4)

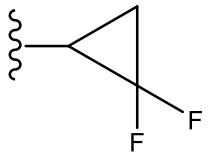

(C23)


(C24)


(C25)

or

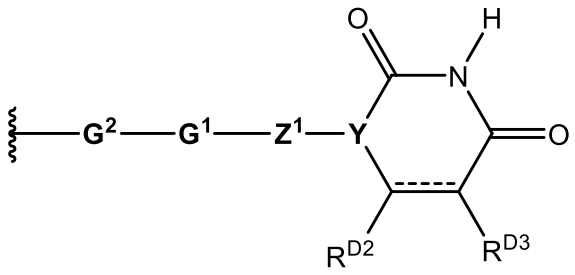

(C26),

wherein R^{10} is C_{1-4} alkyl, C_{1-4} haloalkyl or C_{3-6} cycloalkyl optionally substituted with 1 to 3 halogen, and n is 0 or 1, optionally, wherein R^{10} is -$C(CH_3)_3$ or .

14. The compound of claim 12 or 13, or a pharmaceutically acceptable salt thereof, wherein R^4 is C_{1-3} alkyl or halogen, preferably wherein R^4 is –CH_3 or F.

15. The compound of any one of claims 1-14, or a pharmaceutically acceptable salt thereof, wherein DSM is

(i) a degradation signaling moiety of formula (D):



(D)

,

wherein:

represents a bond to the linker L;

----- represents an optional double bond;

Y is CR^{D1} or N;

Z^1 is selected from bond, $-NR^{D6}-$, -O-, $-CH_2-$, $*–C(O)–CH_2–‡$, $*-C_{1-8}$ alkyl-$NR^{D6}-‡$, $*-NR^{D6}-C_{1-8}$ alkyl-‡, ; wherein *– represents a bond to G^1, and ‡– represents a bond to Y;

G^1 is selected from bond, 3- to 7-membered monocyclic carbocyclyl, 5- to 6-membered monocyclic heterocyclyl, 9- to 14-membered bicyclic or tricyclic heterocyclyl; wherein the 3- to 7-membered monocyclic carbocyclyl, 5- to 6-membered monocyclic heterocyclyl, 9- to 14-membered bicyclic or tricyclic heterocyclyl represented by G^1 are each optionally substituted with one or more R^{D4};

G^2 is selected from bond, $-NR^{D6}-$, -C(O)-, $*–NR^{D6}–C_{1-4}$ alkyl–‡, $*–NR^{D6}–C_{1-4}$ alkyl–O-‡, 3- to 7-membered monocyclic carbocyclyl, Het, $*-NR^{D6}$-Het-‡, and *-Het-C_{1-4} alkyl–‡; wherein *– represents a bond to the linker L, and ‡– represents a bond to G^1; and wherein the 3- to 7-membered monocyclic carbocyclyl and Het represented by G^2 are each optionally substituted with one or more R^{D5};

Het is 4- to 7-membered monocyclic heterocyclyl or 9- to 11-membered bicyclic heterocyclyl,

R^{D1}, R^{D2} and R^{D3} are each independently H or C_{1-6} alkyl;

or alternatively R^{D1} and R^{D3}, taken together with their intervening atoms when the optional double bond is not present, form a 4- to 6-membered carbocyclyl;

R^{D4} is, for each occurrence, independently selected from H, halogen, oxo, C_{1-4} alkyl, C_{1-4}haloalkyl, and C_{1-4} alkoxy; or alternatively two R^{D4}, taken together with their intervening atoms, form a 4- to 6-membered monocyclic heterocyclyl; and

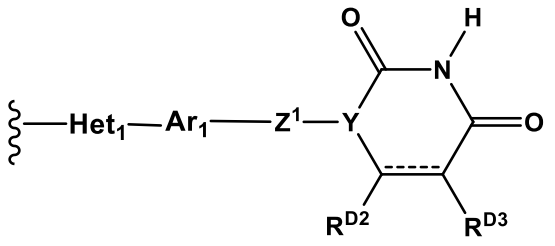
R^{D5} is, for each occurrence, independently selected from H, halogen, OH, C_{1-4} alkyl, C_{1-4}haloalkyl and C_{1-4} alkoxy; or alternatively two R^{D5}, taken together with their intervening

atoms, form a 3- to 6-membered monocyclic carbocyclyl or 4- to 6-membered monocyclic heterocyclyl;

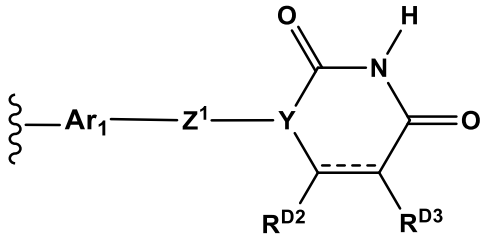
R^{D6} is H or C_{1-3} alkyl,

provided at least one of Z^1, G^1 and G^2 is not a bond; or

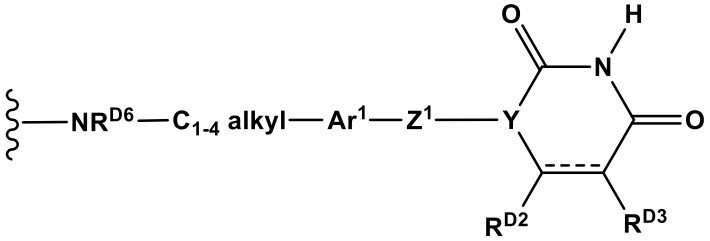
(ii) a degradation signaling moiety of formula (D-I), (D-II), (D-III) or (D-IV):



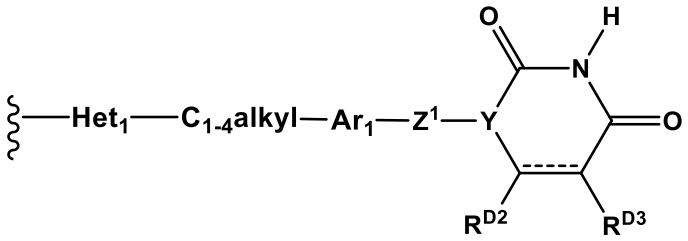
(D-I),



(D-II),



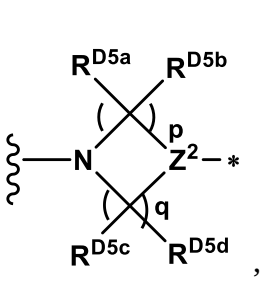
(D-III), or



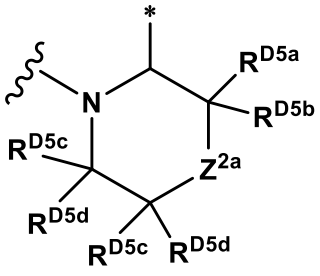
(D-IV),

wherein:

Het_1 is represented by the following formula:



, or



,

wherein * indicates the connection point to Ar_1 in formula (D-I) or the C_{1-4}alkyl group in formula (D-IV);

p is 1 or 2;

q is 1, 2 or 3;

Z^2 is CH or N;

Z^{2a} is CH_2 or O;

R^{D5a} and R^{D5b}, for each occurrence, are each independently H, C_{1-4} alkyl, halogen, OH or C_{1-4} alkoxy; or R^{D5a} and R^{D5b} together with the carbon atom from which they are attached from a C_{3-6} cycloalkyl;

R^{D5c} and R^{D5d}, for each occurrence, are each independently H, C_{1-4} alkyl, halogen, OH or C_{1-4} alkoxy; or R^{D5a} and R^{D5c} together form $–(CH_2)_t$-;

t is 1, 2 or 3;

Ar_1 is phenyl, phenyl fused with 5- to 7-membered heterocyclyl, naphthalenyl fused with 5- to 7-membered heterocyclyl, 5- to 6-membered monocyclic heteroaryl or 9- to 10-membered bicyclic heteroaryl, wherein the phenyl, phenyl fused with 5- to 7-membered heterocyclyl, 5- to 6-membered monocyclic heteroaryl and 9- to 10-membered bicyclic heteroaryl are each optionally substituted with 1 to 3 R^{D4};

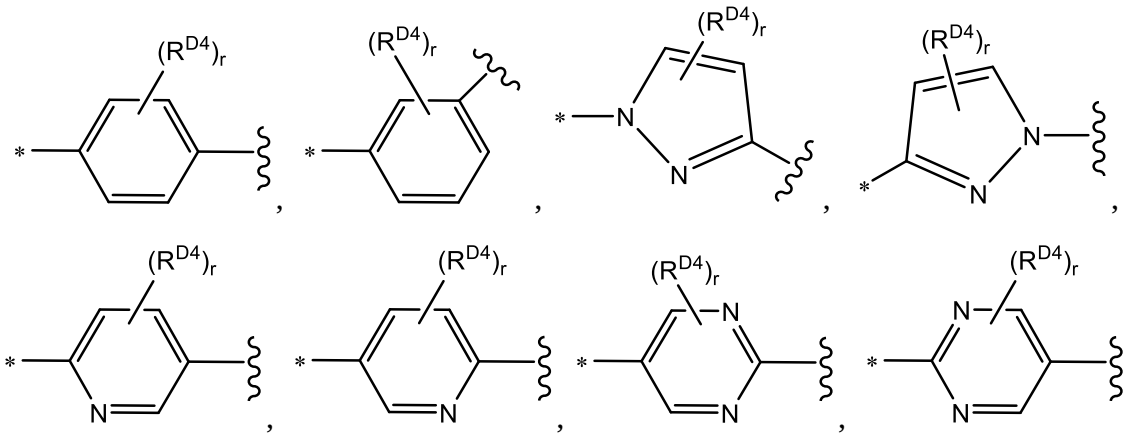
Z^1 is a bond, NR^{D6}, or O;

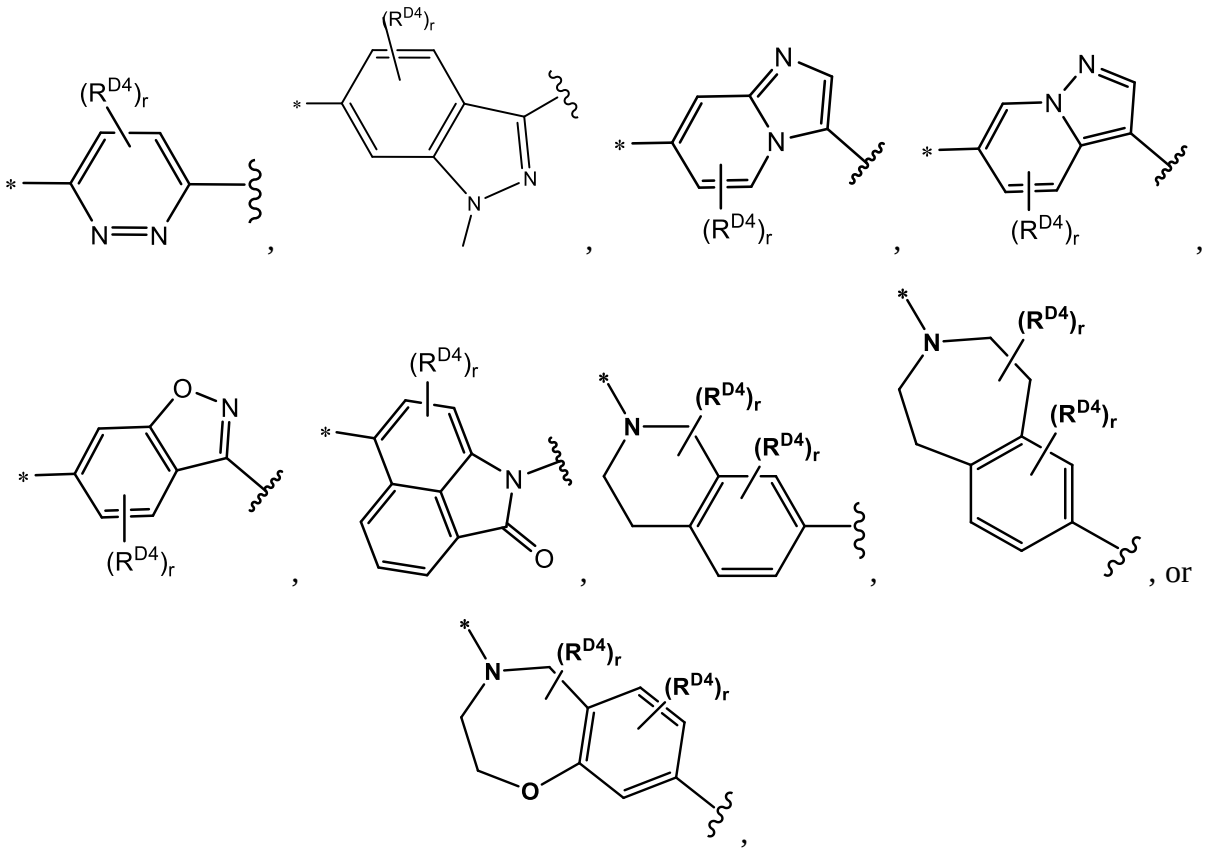
R^{D6} is H or C_{1-4} alkyl.

16. The compound of claim 15, or a pharmaceutically acceptable salt thereof, wherein Ar_1 is

(i) phenyl, pyrazol, pyrazolo-pyridinyl, pyridinyl, pyrimidinyl, pyridazinyl, benzoisoxazolyl, benzo[*cd*]indol-2(1*H*)-onyl, imidazo-pyridinyl or indazolyl, each or which is optionally substituted with 1 to 3 R^{D4};

(ii) represented by the following formula:





wherein:

* — represents a bond to Het_1; ~— represents a bond to Z^1;

R^{D4}, for each occurrence, is independently selected from C_{1-4} alkyl, C_{1-4} haloalkyl, halogen and C_{1-4} alkoxy, preferably wherein R^{D4}, for each occurrence, is independently selected from $-CH_3$, F, Cl, CF_3, and $-OCH_3$; and

r is 0, 1 or 2.

17. The compound of claim 15 or 16, or a pharmaceutically acceptable salt thereof, wherein:

(i) p is 1 and q is 1;

(ii) p is 2 and q is 2; or

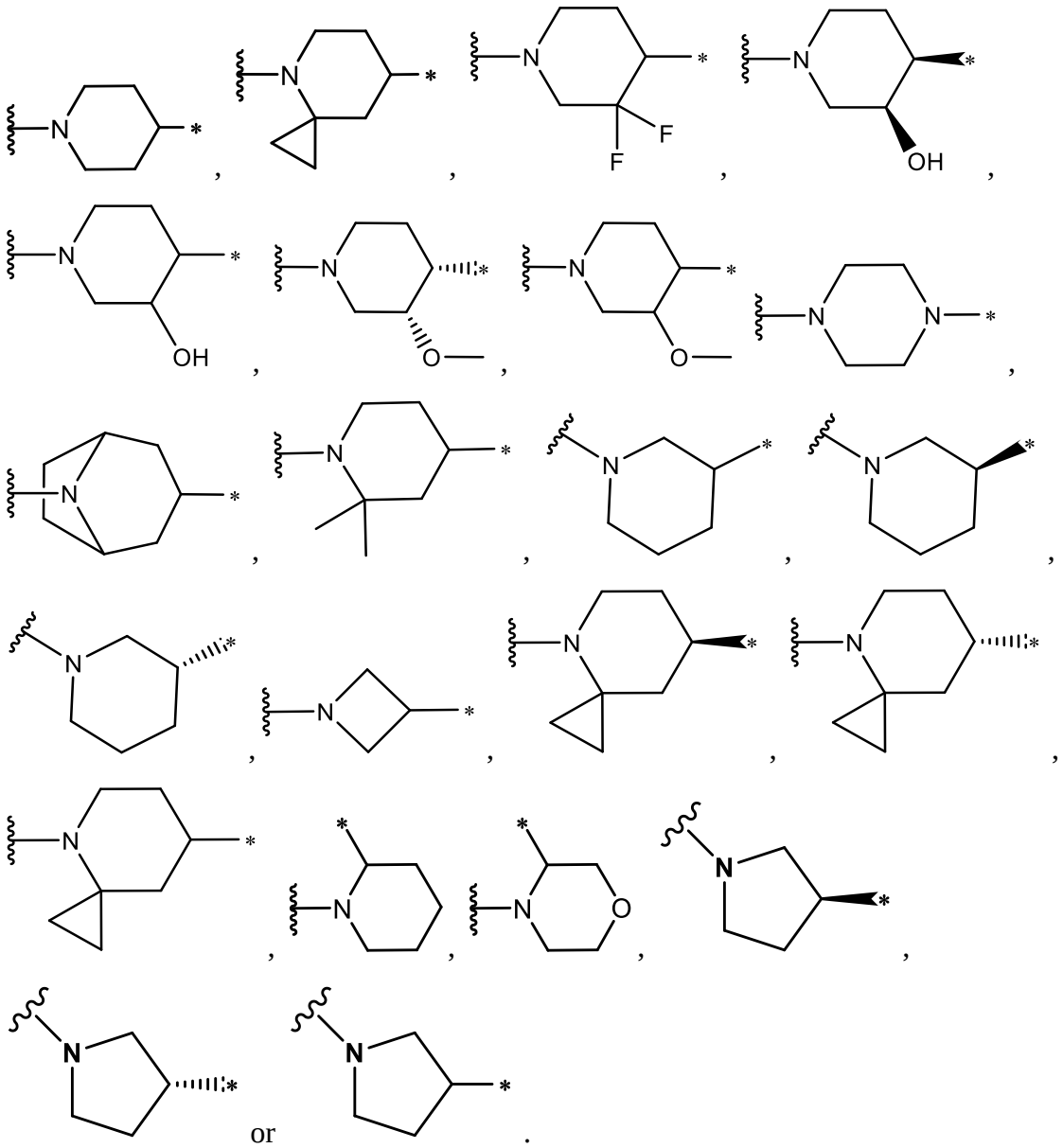
(iii) p is 1 and q is 3.

18. The compound of any one of claims 15-17, or a pharmaceutically acceptable salt thereof, wherein Het_1 is

(i) azetidine, piperidine, piperazine, pyrrolidine, azabicyclo[3.2.1]octane, or azaspiro[2.5]octane, each of which is optionally substituted with 1 to 3 substituents

independently selected from C_{1-3} alkyl, halogen, OH and C_{1-3} alkoxy, or two of the substituents together with the carbon atom from which they are attached form a C_{3-6} cycloalkyl, preferably wherein the substituent is independently selected from $–CH_3$, F, Cl, OH and $–OCH_3$;

(ii) represented by the following formula:

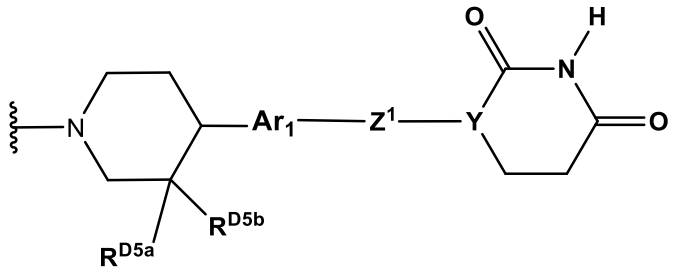


19. The compound of any one of claims 15-18, or a pharmaceutically acceptable salt thereof, wherein

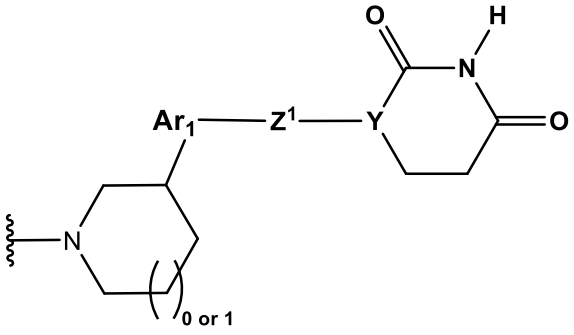
(i) R^{D1}, R^{D2}, R^{D3} are each independently H or $–CH_3$, preferably wherein R^{D1}, R^{D2}, R^{D3} are each H; and/or

(ii) R^{D6} is H or $–CH_3$, preferably wherein R^{D6} is H.

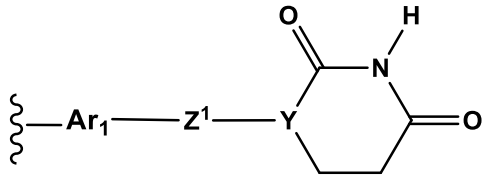
20. The compound of claim 15, or a pharmaceutically acceptable salt thereof, wherein DSM is a degradation signaling moiety represented by the following formula:



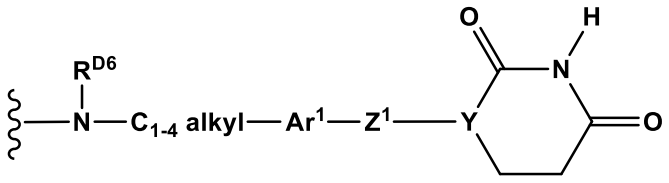
(D-IA1-1),



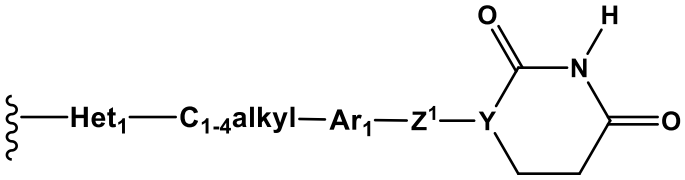
(D-IA3),



(D-IIA),



(D-IIIA), or



(D-IVA),

wherein:

Ar^1 is phenyl, pyrazol, pyrazolo-pyridinyl, pyridinyl, pyrimidinyl, pyridazinyl, benzoisoxazolyl, benzo[*cd*]indol-2(1*H*)-onyl, imidazo-pyridinyl or indazolyl, each or which is optionally substituted with 1 or 2 substituents independently selected from halogen and C_{1-3} alkyl;

Z^1 is a bond, NH or O;

R^{D5a} and R^{D5b} are each independently H, OH, F or $–OCH_3$;

R^{D6} is H or CH_3;

Het_1 is piperidine, piperazine, or pyrrolidine, and

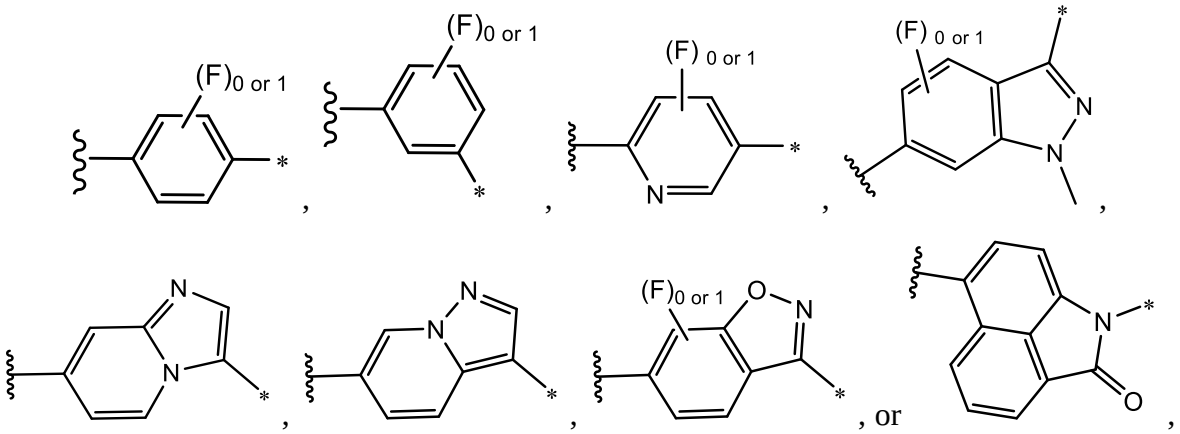
Y is CH, $C(CH_3)$ or –N-.

21. The compound of claim 20, or a pharmaceutically acceptable salt thereof, wherein

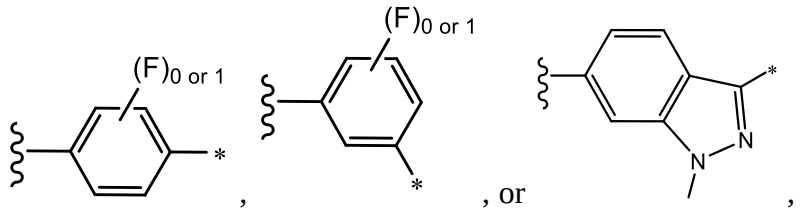
(a) Ar^1 is:

(i) phenyl, pyrazolo-pyridinyl, pyridinyl, benzoisoxazolyl, benzo[*cd*]indol-2(1*H*)-onyl, imidazo-pyridinyl or indazolyl, each of which is optionally substituted with one or two substituents independently selected from halogen and $C_{1\text{-}3}$alkyl,preferably wherein Ar^1 is phenyl or indazolyl; or

(ii) represented by the following formula:



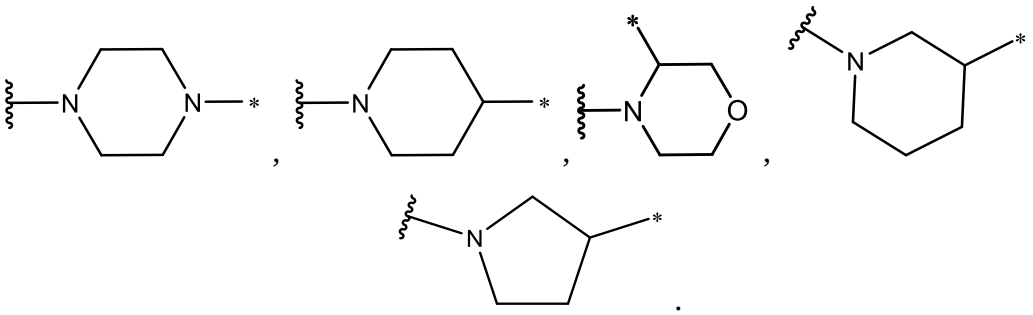
preferably wherein Ar^1 is represented by the following formula:



wherein * — represents a bond to Z^1;

and/or

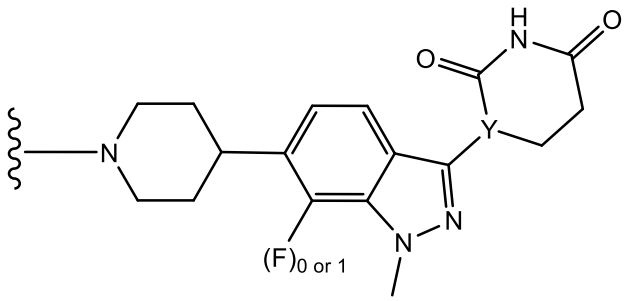
(b) Het_1 is represented by the following formula:



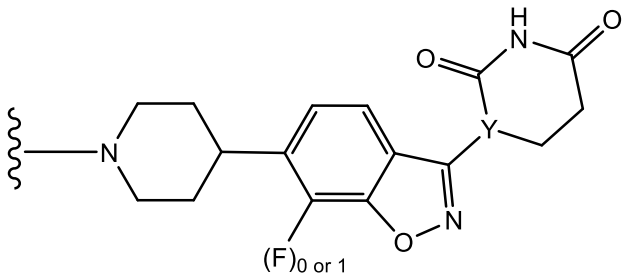
or

22. The compound of any one of claims 1-14, or a pharmaceutically acceptable salt thereof, wherein DSM is:

(i) represented by any one of the following:



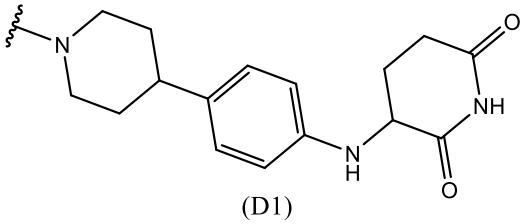
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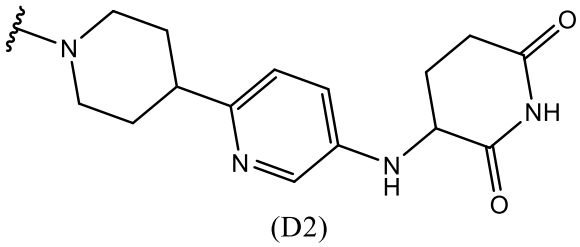
wherein Y is CH or N; or

(ii) represented by any one of the following attached to L:



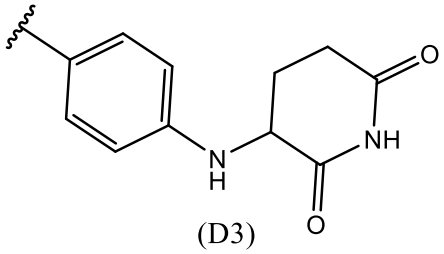
(D1)

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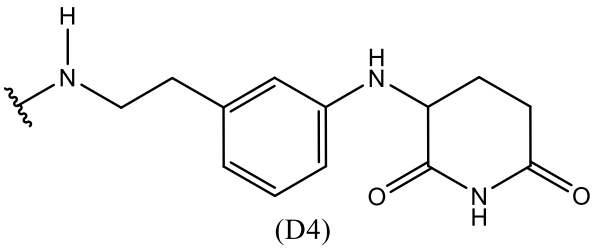
(D2)

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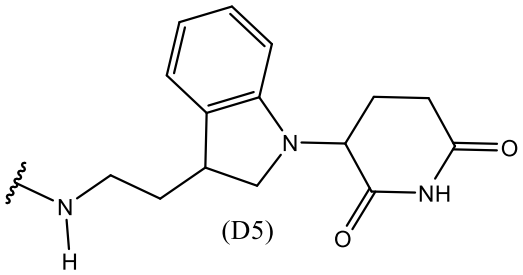
(D3)

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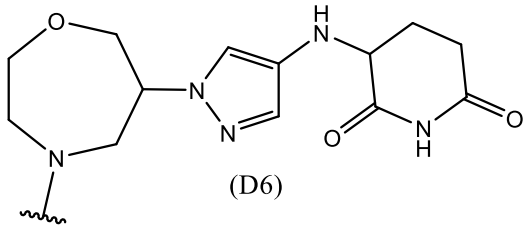
(D4)

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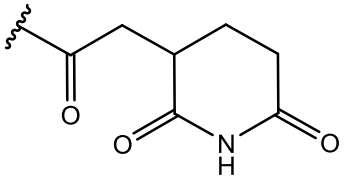
(D5)

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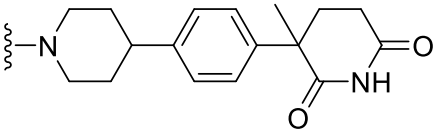
(D6)

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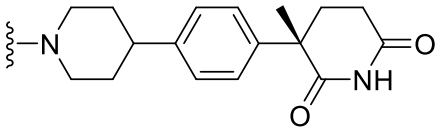
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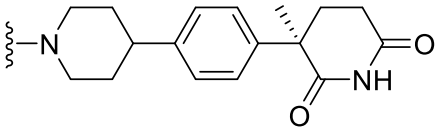
(D8)

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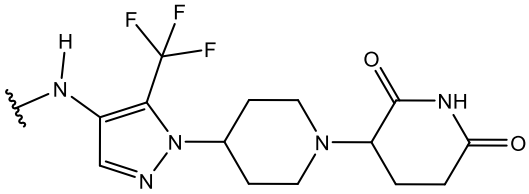
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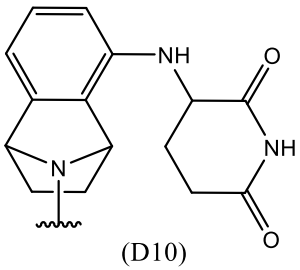
(D8b)

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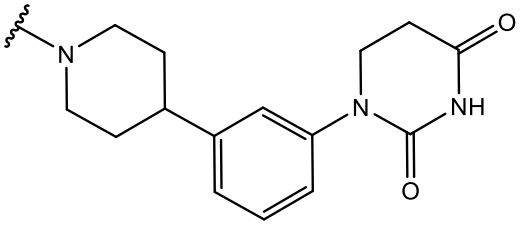
(D9)

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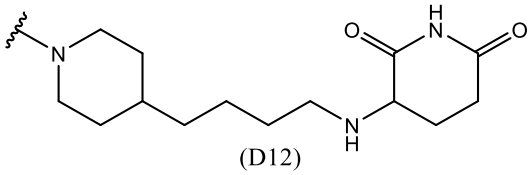
(D10)

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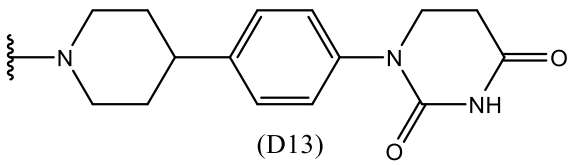
(D11)

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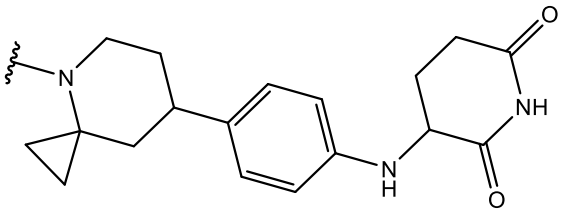


(D12)

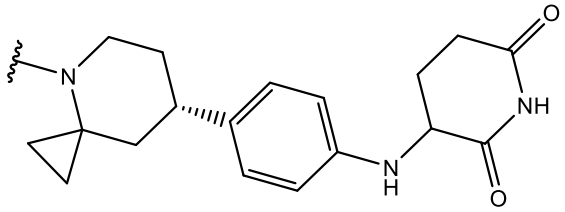
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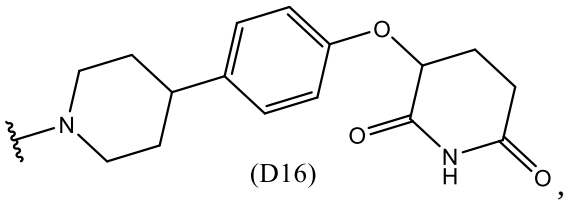
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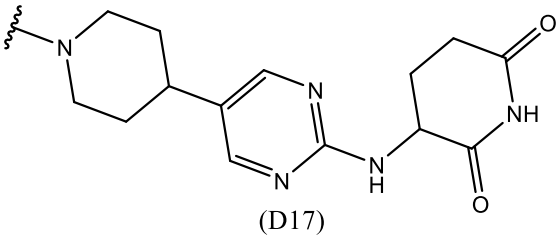
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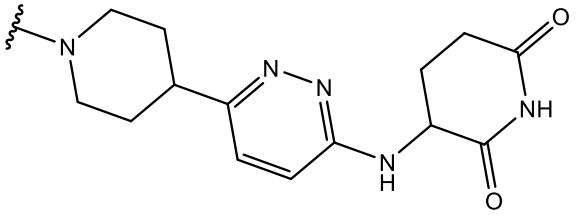
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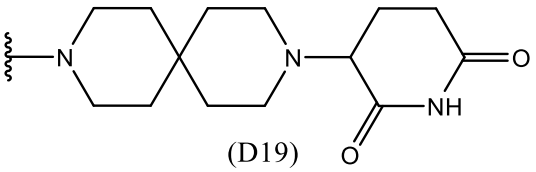
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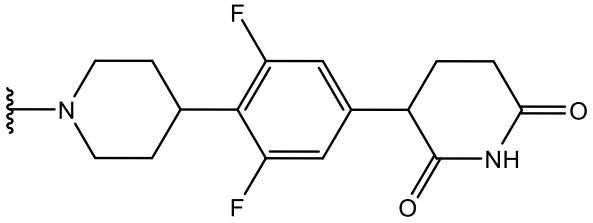
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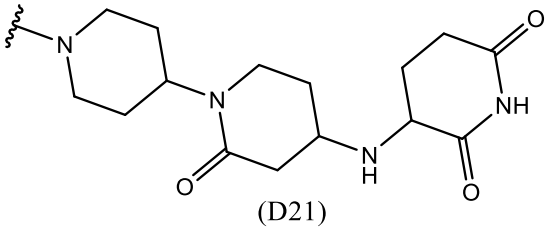
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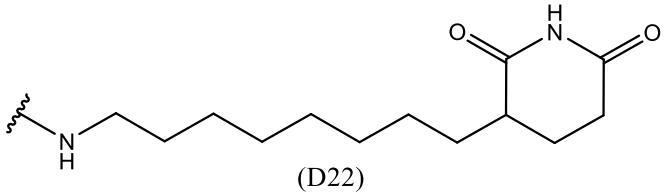
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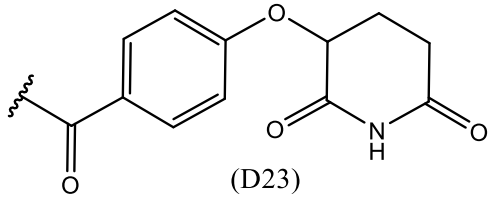
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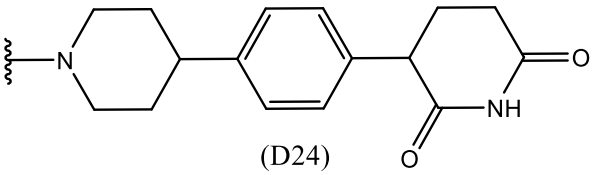
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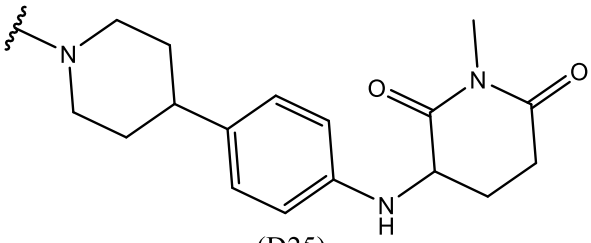
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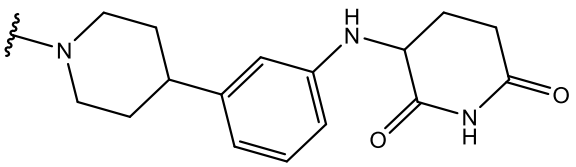


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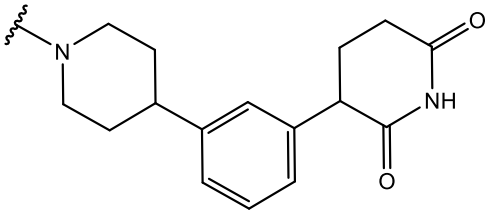


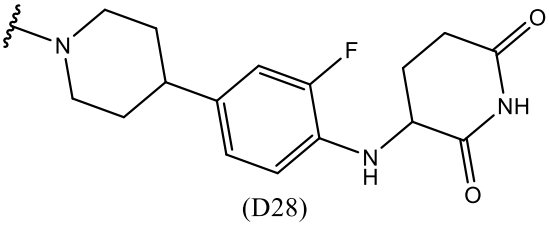
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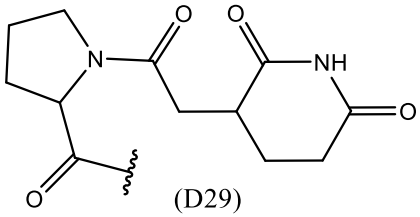
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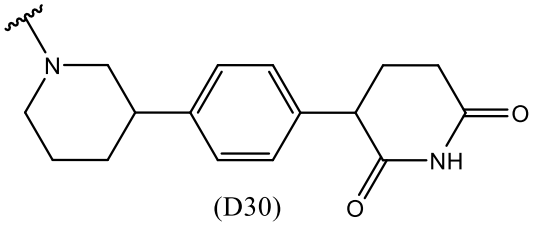
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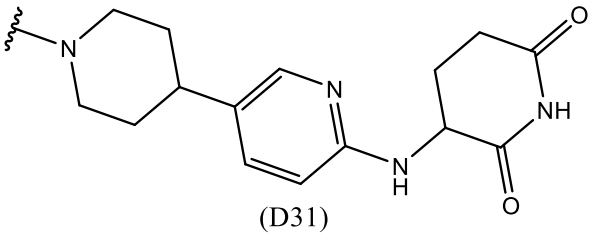
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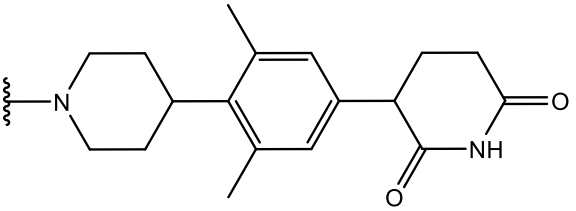
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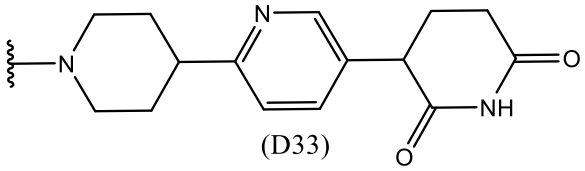
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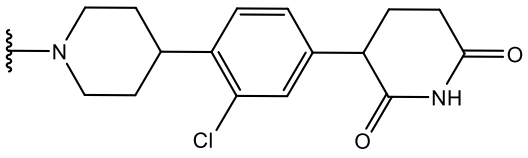
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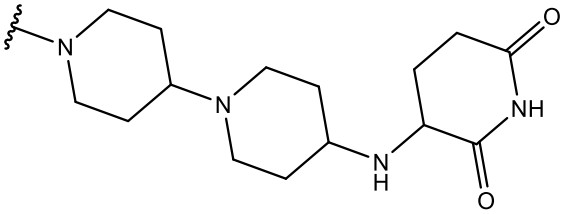
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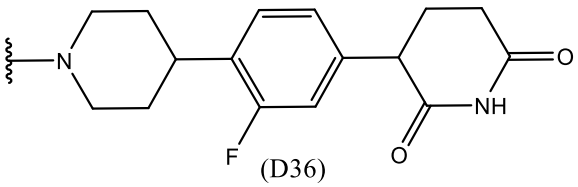
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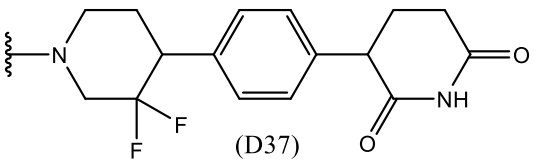
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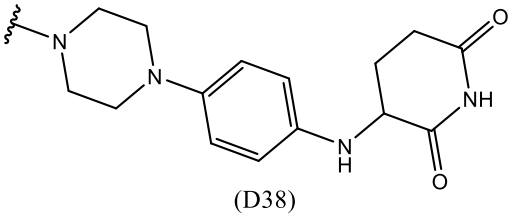
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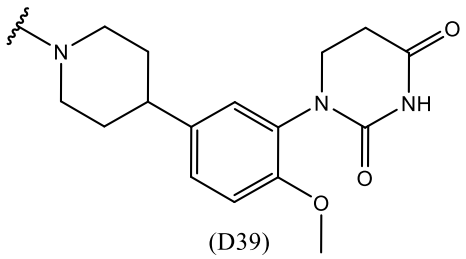
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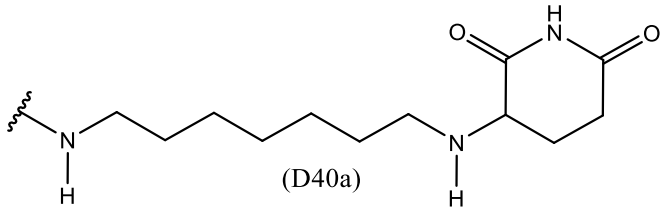


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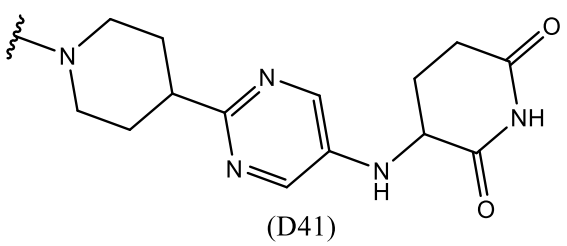
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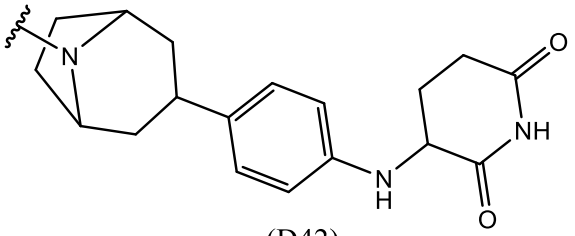
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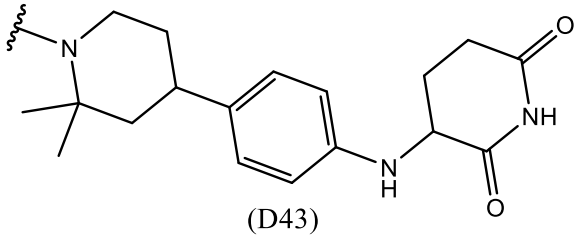
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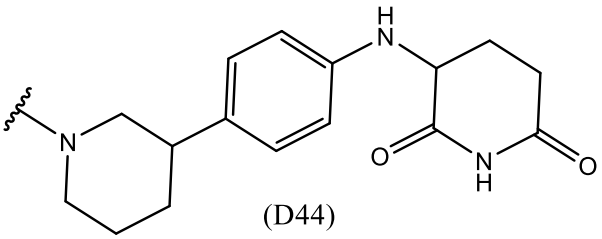
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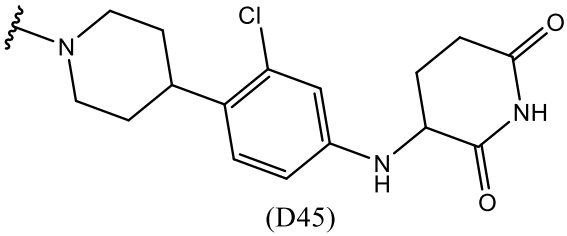
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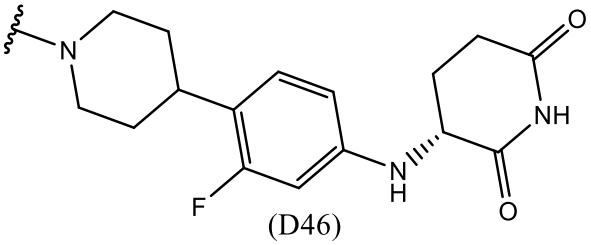
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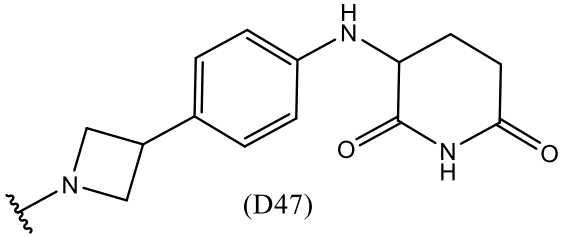
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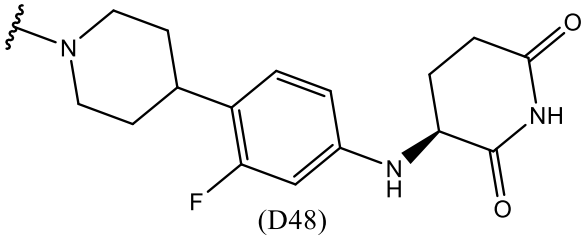
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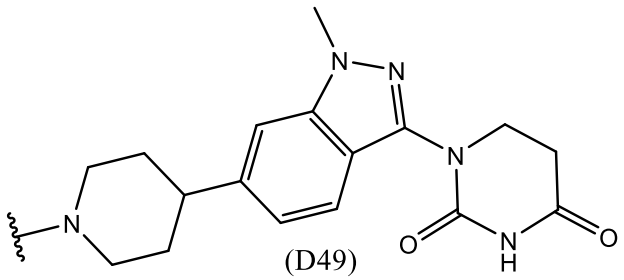
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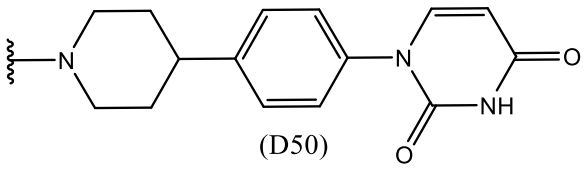
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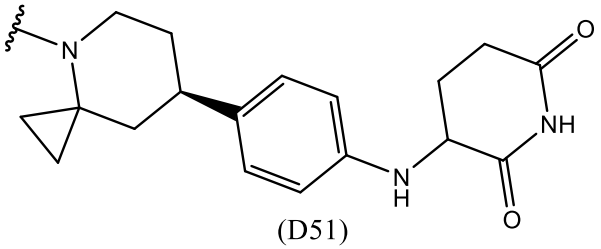
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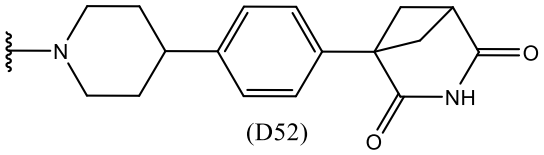
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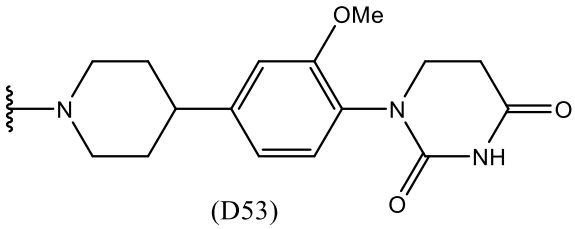
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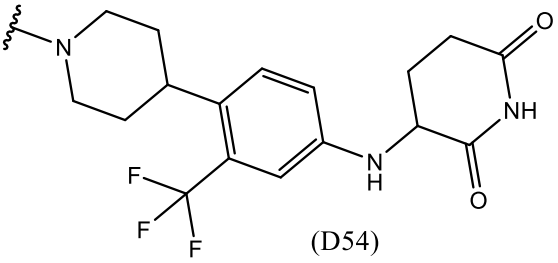
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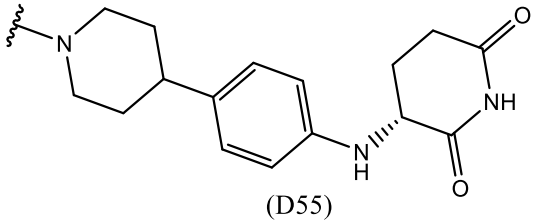
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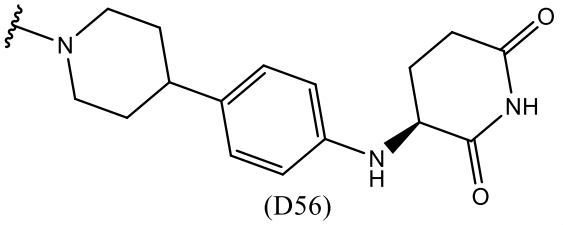
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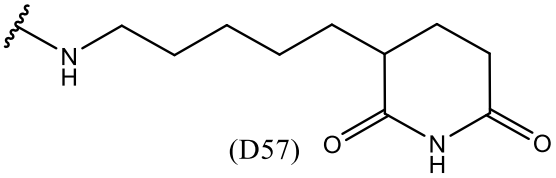
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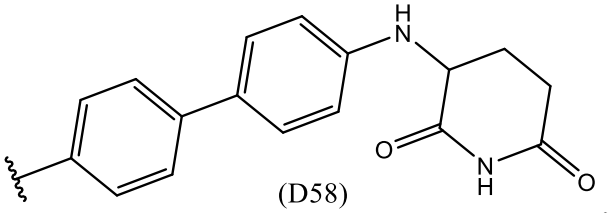
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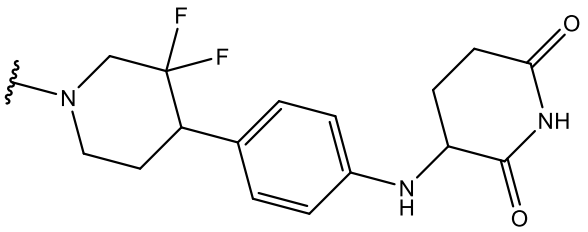
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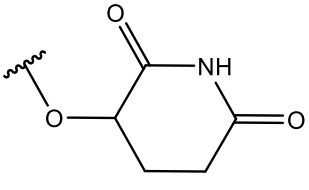
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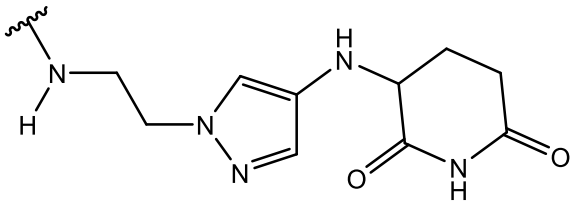
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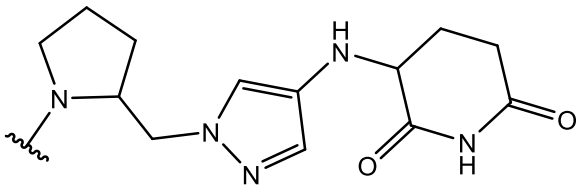
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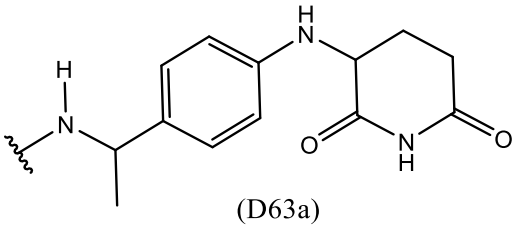
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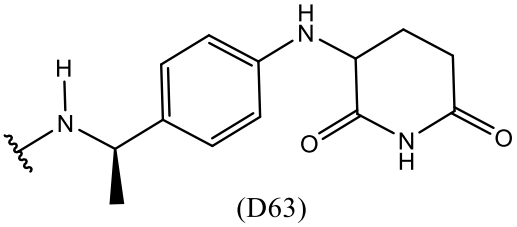
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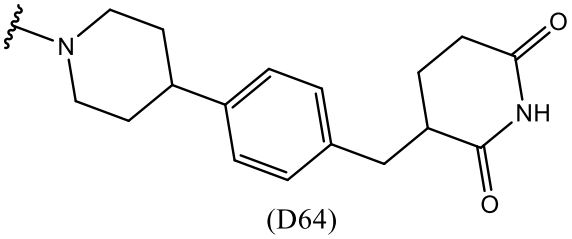
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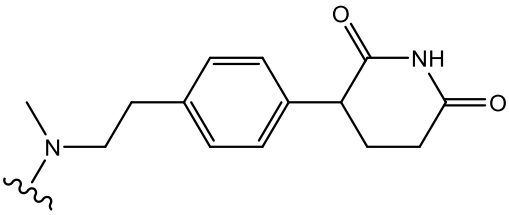
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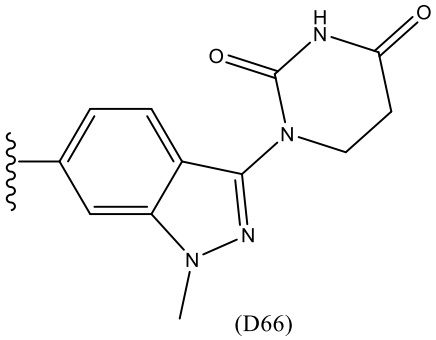
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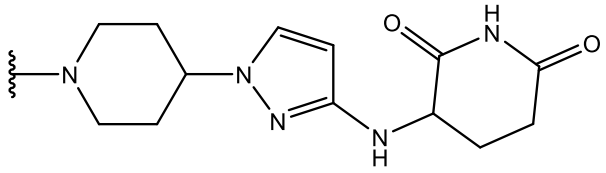
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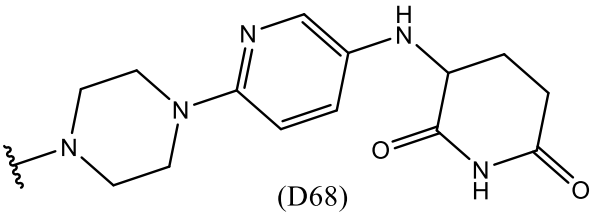
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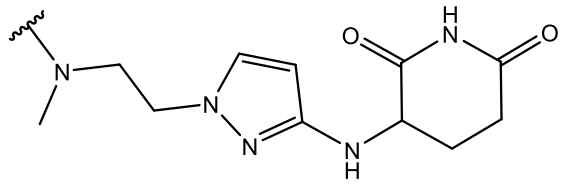
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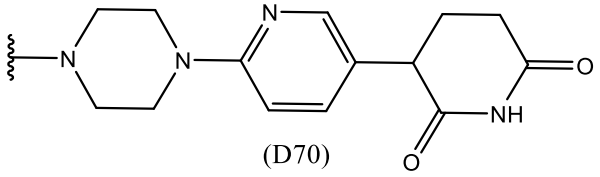
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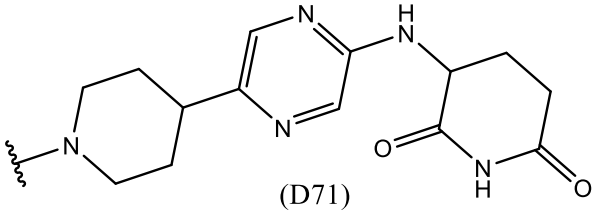
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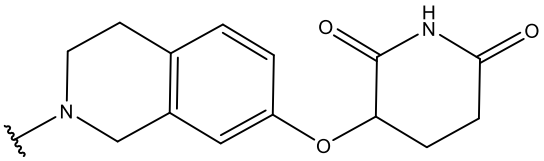
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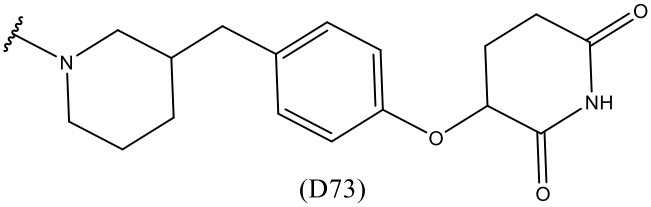
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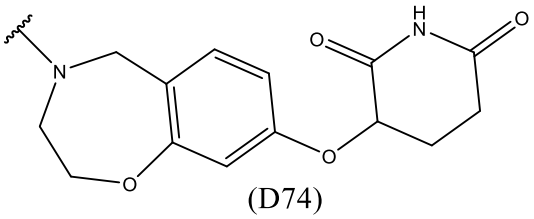
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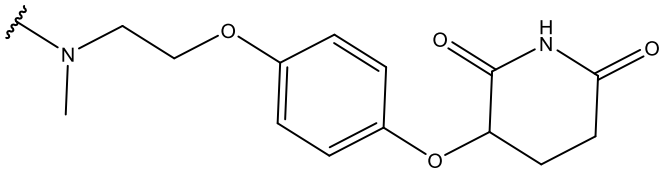
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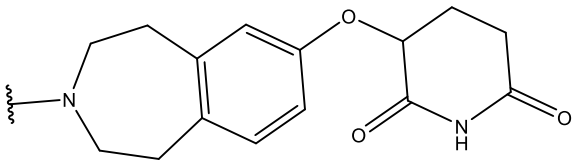
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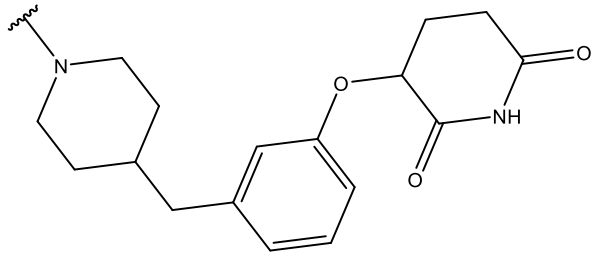
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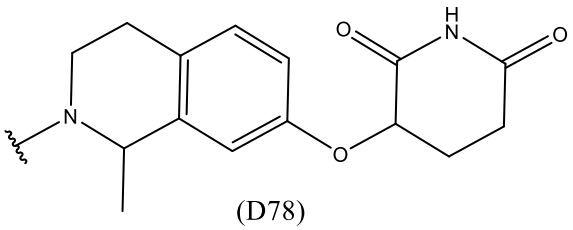
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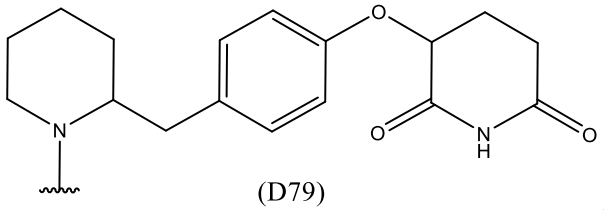
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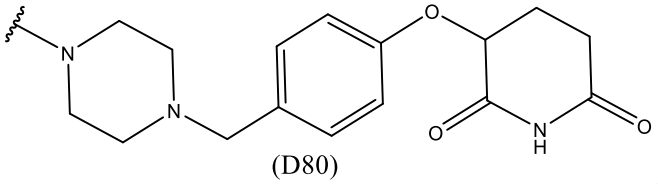
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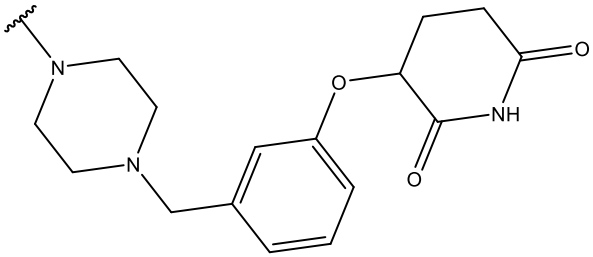
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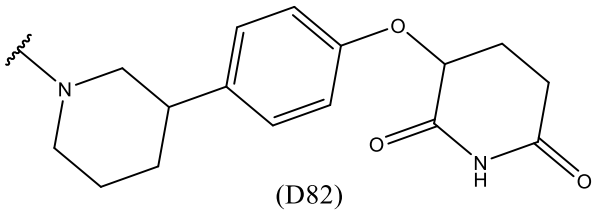
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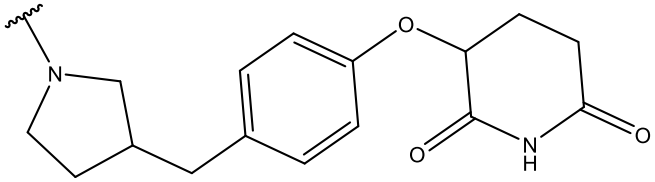
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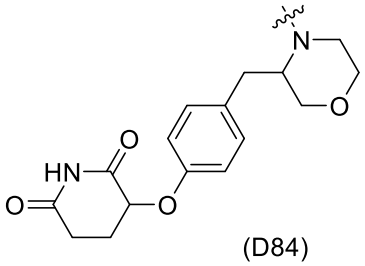
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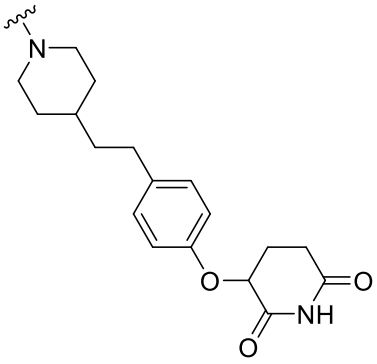
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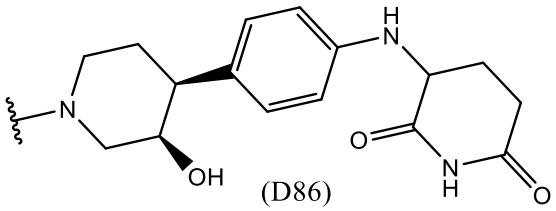
(D83) ,



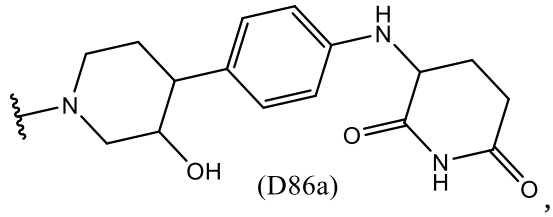
(D84) ,



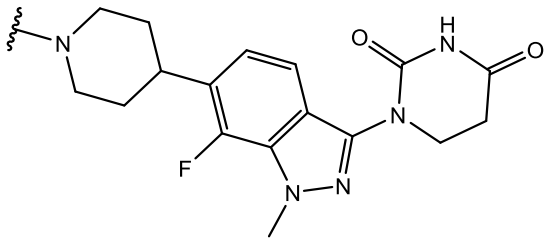
(D85) ,



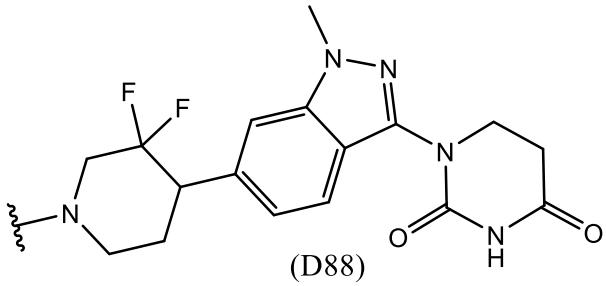
(D86) ,



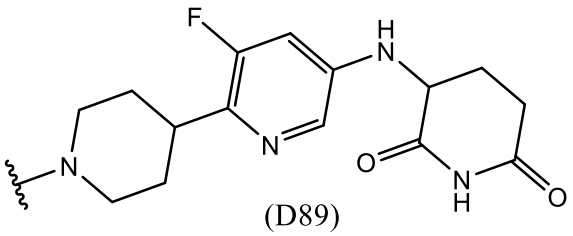
(D86a),



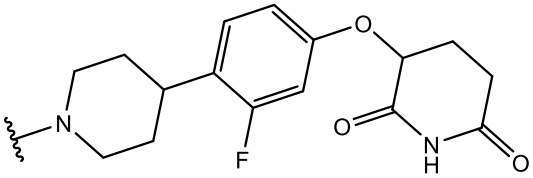
(D87),



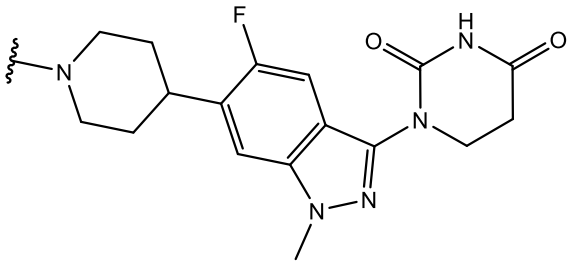
(D88),



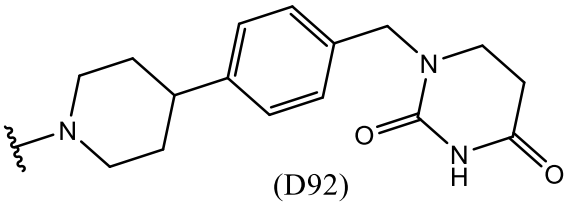
(D89),



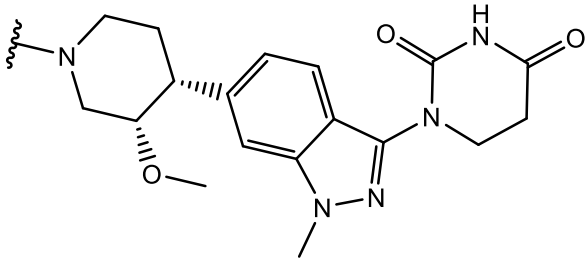
(D90),



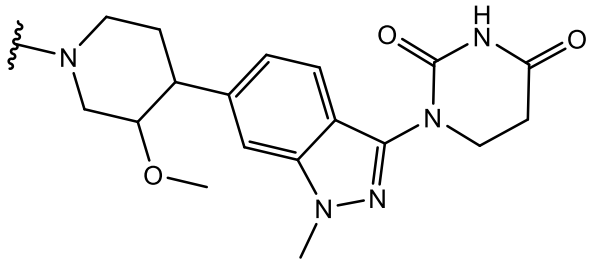
(D91),



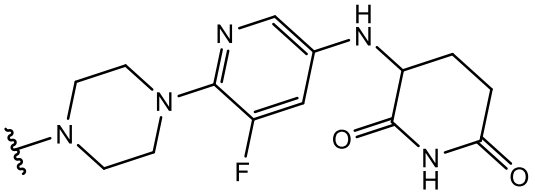
(D92),



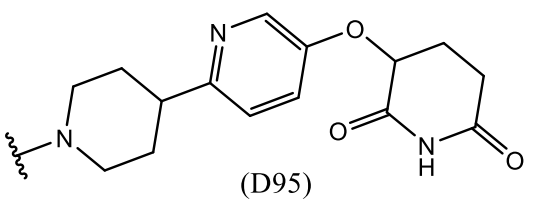
(D93),



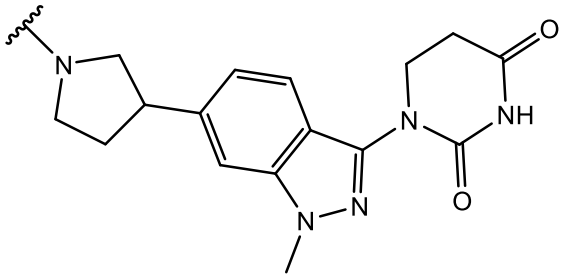
(D93a),



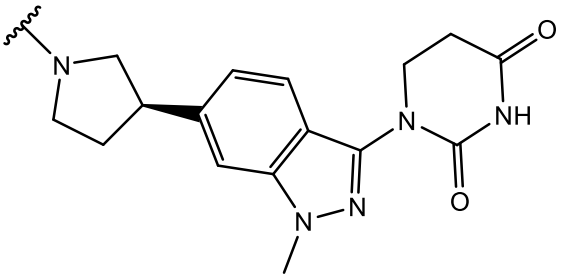
(D94),



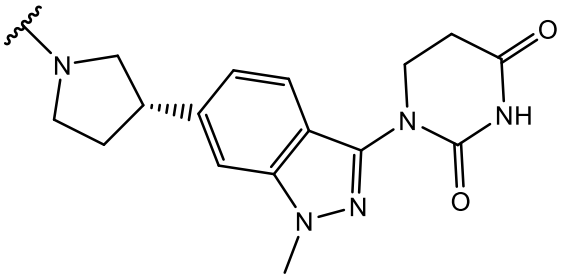
(D95),



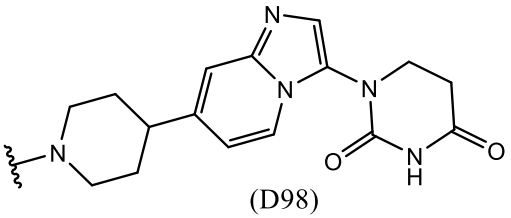
(D96a),



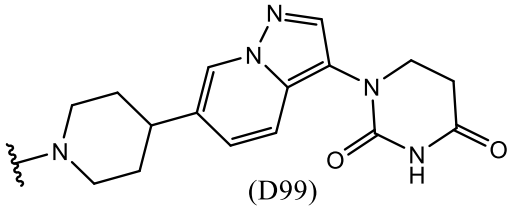
(D96),



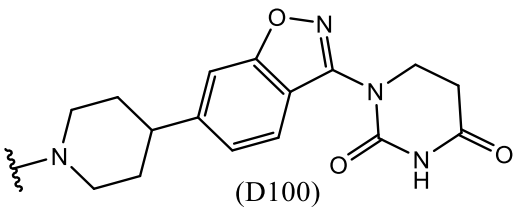
(D97),



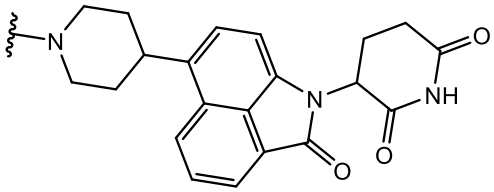
(D98),



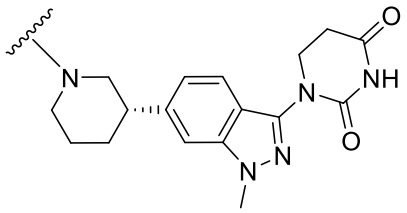
(D99);



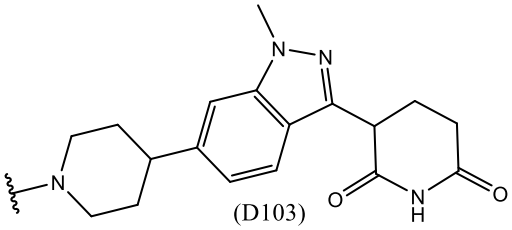
(D100),



(D101),

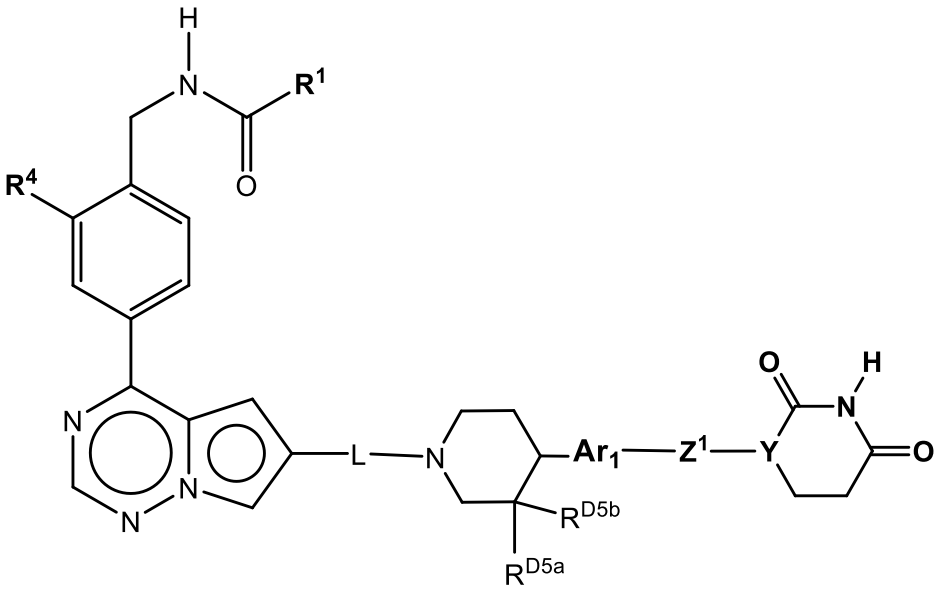


(D102) or

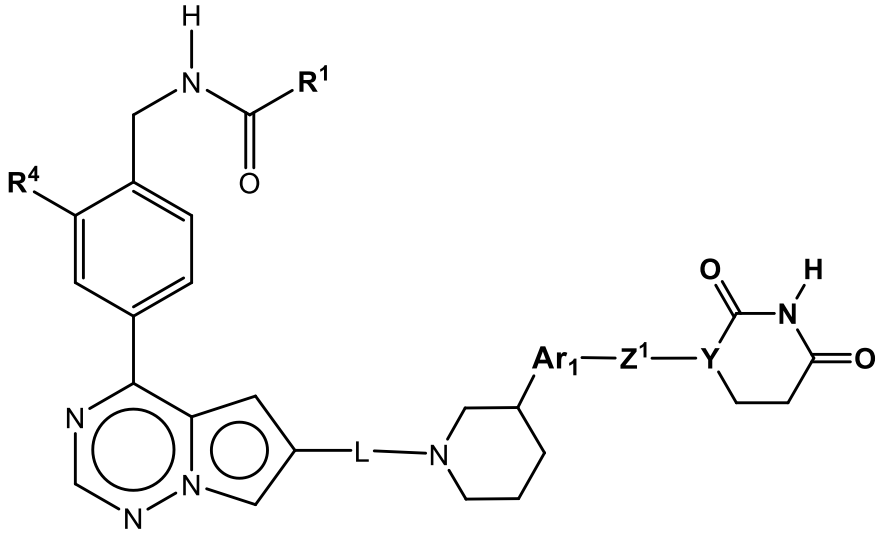


(D103).

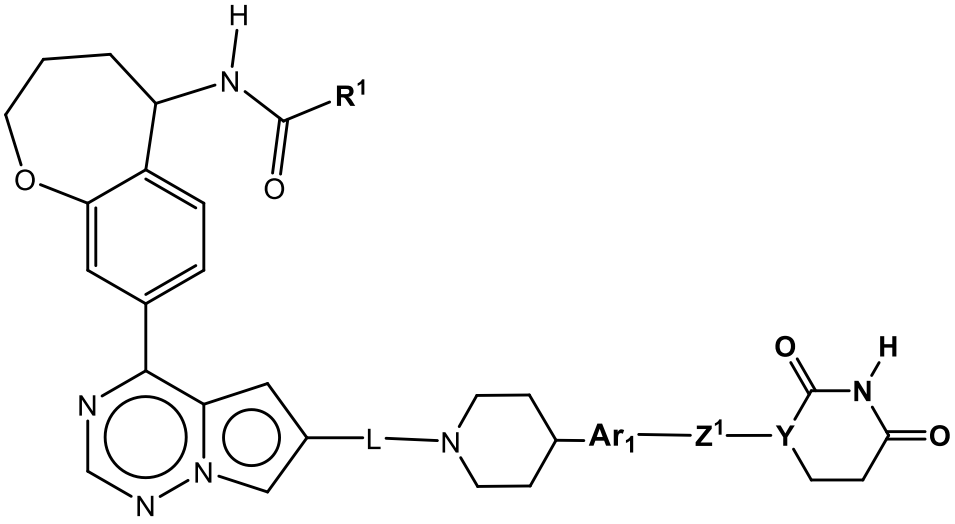
23. The compound of claim 1, wherein the compound is represented by the following formula:



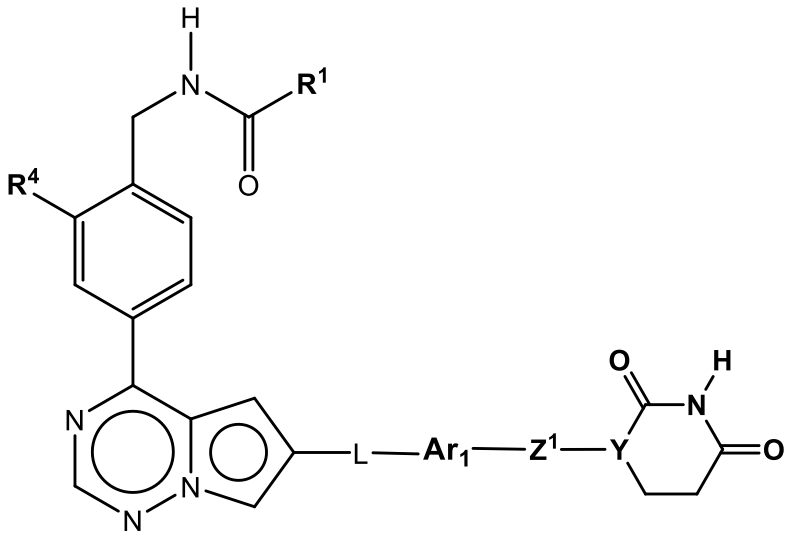
(A-Ia-1);



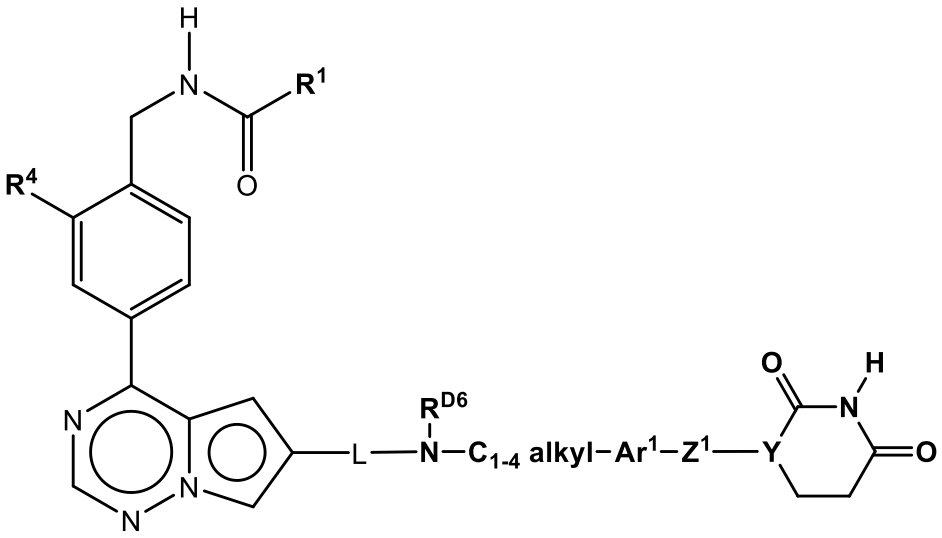
(A-Ib);



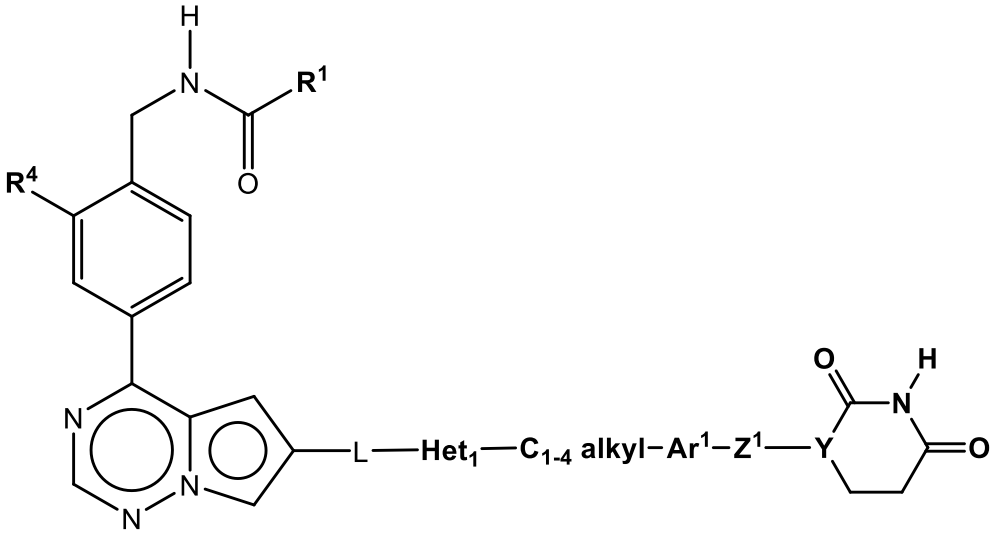
(A-Ic);



(A-II);



(A-III), or



(A-IV),

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is phenyl, 1,2,4-oxadiazolyl, pyrazolyl, triazolyl, or azetidinyl, each of which is optionally substituted with 1 to 3 R^{10};

R^{10} is C_{1-4} alkyl, C_{1-4} haloalkyl or C_{3-6} cycloalkyl optionally substituted with 1 to 3 halogen;

R^4 is selected from H, C_{1-4} alkyl, halogen and -OR^{4a};

R^{4a} is C_{1-4} alkyl;

Ar^1 is phenyl, pyrazol, pyrazolo-pyridinyl, pyridinyl, pyrimidinyl, pyridazinyl, benzoisoxazolyl, benzo[*cd*]indol-2(1*H*)-onyl, imidazo-pyridinyl or indazolyl, each or which is optionally substituted with 1 or 2 halogen;

Z^1 is a bond, CH_2, NH or O;

R^{D5a} and R^{D5b} are each independently H, OH, F or $–OCH_3$;

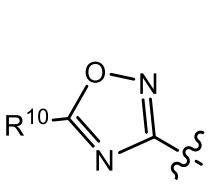
R^{D6} is H or CH_3;

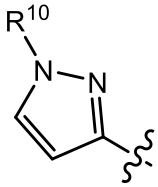
Het_1 is piperidine or piperazine; and

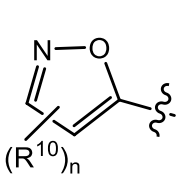
Y is CH, $C(CH_3)$ or –N-.

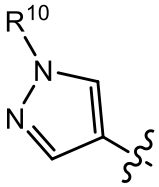
24. The compound of claim 23, or a pharmaceutically acceptable salt thereof, wherein:

(i) R^1 is represented by the following formula:

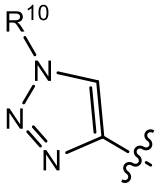

(C4)


(C23)


(C24)

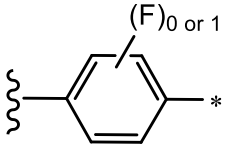

(C25)

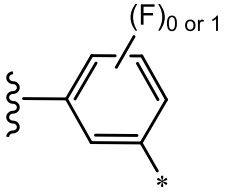
or

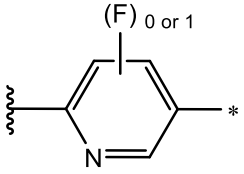

(C26)

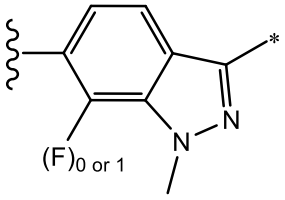
;

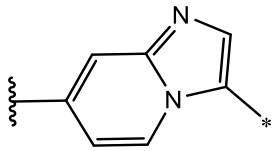
Ar^1 is

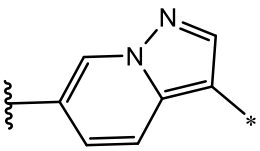


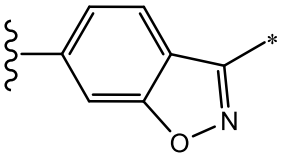




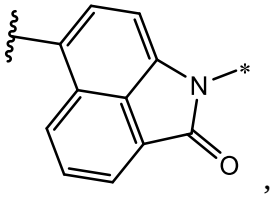






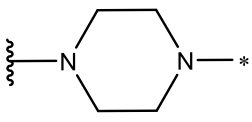


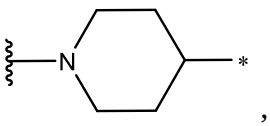
or

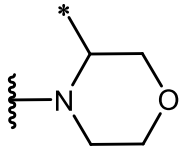


wherein * — represents a bond to Z^1; and

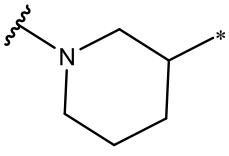
Het_1 is





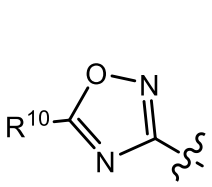


, or

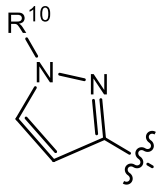


wherein * — represents a bond to C_{1-4} alkyl; or

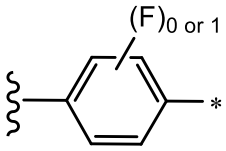
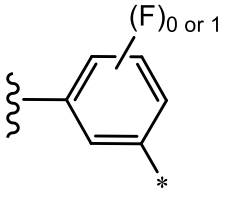
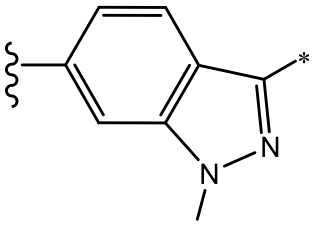
(ii) R^1 is represented by the following formula:


(C4)

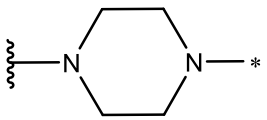
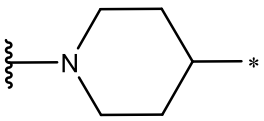
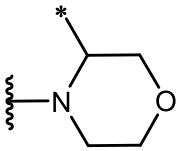
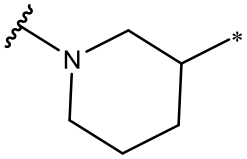
, or


(C23)

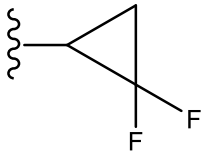
,

Ar^1 is , , or ,

wherein * — represents a bond to Z^1; and

Het_1 is , , , or 

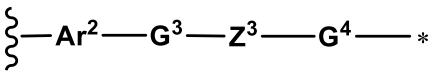
wherein * — represents a bond to $C_{1\text{-}4}$ alkyl, optionally, wherein:

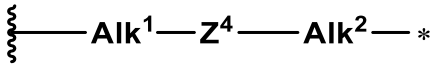
R^{10} is $-C(CH_3)_3$ or ;

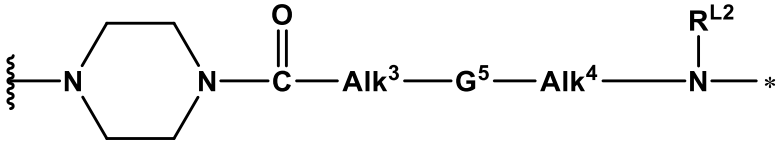
R^4 is F or $–CH_3$; and

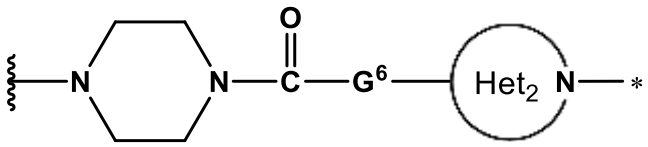
Y is CH or N.

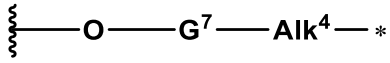
25. The compound of any one of claims 1-24, or a pharmaceutically acceptable salt thereof, wherein L is represented by the following formula:

(a)  (L-1),

(b)  (L-2),

(c)  (L-3),

(d)  (L-4), or

(e)  (L-5),

Ar^2 is phenyl, naphthyl, phenyl fused with 5- or 6-membered heterocycle, 5- or 6-membered monocyclic heteroaryl or 9- to 10-membered bicyclic heteroaryl, each of which is optionally substituted with 1 to 3 R^{L1};

G^3 is a bond, C_{1-6} alkyl, -O- or -O–C_{1-6}alkyl–O-;

Z^3 is a bond, -NR^{L2}-, -O-, -C(=O)-, C_{4-6} cycloalkyl, phenyl, 4- to 6-membered saturated monocyclic heterocyclyl, or 5- to 6-membered monocyclic heteroaryl, wherein the phenyl, 4- to 6-membered saturated monocyclic heterocyclyl, and 5- to 6-membered monocyclic heteroaryl are each optionally substituted with 1 to 3 R^{L1};

G^4 is a bond or C_{1-8} alkyl,

R^{L1}, for each occurrence, is independently H, halogen, C_{1-4} alkyl, C_{1-4} haloalkyl, or C_{1-4} alkoxy;

R^{L2} is H or C_{1-3} alkyl;

Alk^1 is a bond, C_{1-4} alkyl, C_{2-4} alkynyl or C_{3-6} cycloalkyl, wherein the C_{1-4} alkyl, C_{2-4} alkynyl and C_{3-6} cycloalkyl are each optionally substituted with 1 to 3 halogen;

Z^4 is a bond, -O- , -NR^{L2}, or 4- to 10-membered saturated monocyclic or bicyclic heterocyclyl;

Alk^2 is a bond or C_{1-8} alkyl optionally substituted with 1 to 3 halogen;

G^5 is bond, phenyl, naphthyl, a 5- or 6-membered heteoaryl, a 4- to 10-membered monocyclic or bicyclic saturated heterocyclyl, 3- to 10-membered monocyclic or bicylic saturated carbocyclyl, or –$(O\text{-}CH_2\text{-}CH_2)_t$-, wherein the phenyl, naphthyl, a 5- or 6-membered heteoaryl, a 4- to 10-membered monocyclic or bicyclic saturated heterocyclyl, 3- to 10-membered monocyclic and bicylic saturated carbocyclyl are each optionally substituted with 1 to 3 R^{L1};

t is an integer from 2 to 8;

Alk^3 is a bond or C_{1-6} alkyl optionally substituted with 1 to 3 halogen or C_{3-6} cycloalkyl;

Alk^4 is a bond or C_{1-6} alkyl optionally substituted with 1 to 3 halogen;

G^6 is a bond, C_{1-6} alkyl, or -C_{1-4} alkyl-NH-C(=O)-**, wherein -** represents a bond to Het_2;

Het_2 is 4- to 10-membered saturated monocyclic or bicyclic heterocyclycl;

G^7 is C_{3-7} cycloalkyl;


represents a bond to DSM; represents a bond to BTK

provided that for formula (L-2), one of Alk^1 and Alk^2 is not a bond; and for formula (L-3), at least one of Alk^3, G^5 and Alk^4 is not a bond, optionally,

(i) Ar^2 is phenyl, naphthyl, pyridinyl, pyrimidinyl, pyrazolyl, thiazolyl, thiophenyl, imidazolyl, oxazolyl, imidazolthiazolyl, imidazopyridinyl, indazolyl, thienopyridinyl, $2\lambda^2$-isoindolinyl, 2,3-dihydrobenzo[b][1,4]dioxinyl, or 3,4-dihydro-1H-$2\lambda^2$-isoquinolinyl, each or which is optionally substituted with 1 or 2 R^{L1};

Z^3 is a bond, -NR^{L2}-, -O-, -C(=O)-, cyclobutyl, piperazinyl, or pyrazolyl;

G^5 is phenyl, naphthyl, cyclopropyl, cyclobutyl, cyclohexyl, tetrahydrofuranyl, azetidinyl, oxazolyl, pyrazolyl, or pyridinyl, each of which is optionally substituted with 1 or 2 R^{L1};

Z^4 is a bond, -O- , -NR^{L2}, azaspiro[3.3]heptanyl, or piperazinyl; and

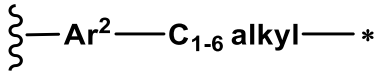
Het_2 is azaspiro[5.5]undecanyl, azaspiro[2.4]heptanyl, azaspiro[4.4]nonanyl, azaspiro[3.4]octanyl, 6-oxa-azaspiro[3.4]octanyl, hexahydro-2H-thieno[2,3-c]pyrrolyl 1,1-dioxide, pyrrolidinyl, morpholinyl, piperidinyl, or azepanyl; and/or

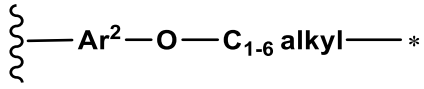
(ii) R^{L1}, for each occurrence, is independently F, Cl, CH_3 or OCH_3; and

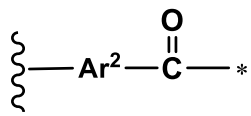
R^{L2} is H or CH_3.

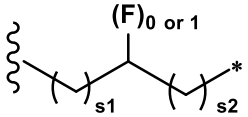
26. The compound of claim 25, or a pharmaceutically acceptable salt thereof, wherein:

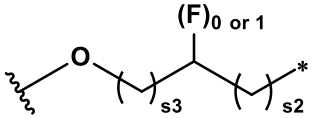
(i) L is represented by the following formula:

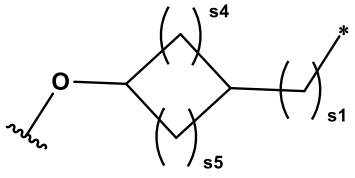


(L-1A),


(L-1B),


(L-1C),


(L-2A) ,


(L-2B) or


(L-3),

wherein:

Ar^2 is phenyl, phenyl fused with 5-membered heterocycle, 6-membered saturated monocyclic heterocyclyl or 6-membered heteroaryl, each of which is optionally substituted with 1 or 2 halogen, preferably wherein Ar^2 is piperazinyl, phenyl, pyridine, pyrimidine, or $2\lambda^2$-isoindoline, each of which is optionally substituted with 1 or 2 F;

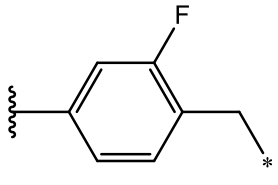
s1 is 0 or an integer from 1 to 4;

s2 is 0 or an integer from 1 to 4;

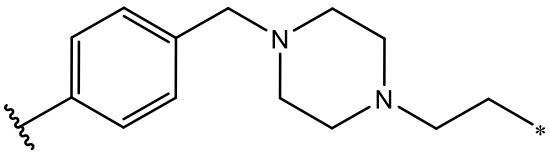
s3 is an integer from 1 to 3;

s4 and s5 are each independently 0 or an integer from 1 to 3, provided at least one of s4 and s5 is not 0; or

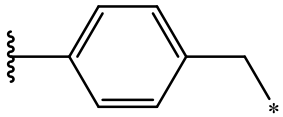
(ii) L represents any one of the following:



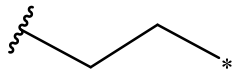
(L1) ,



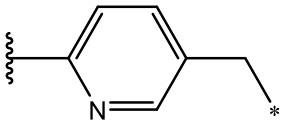
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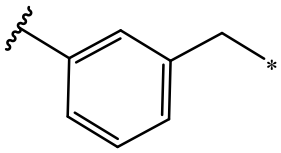
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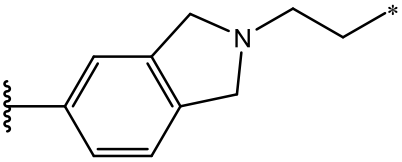
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(L5) ,



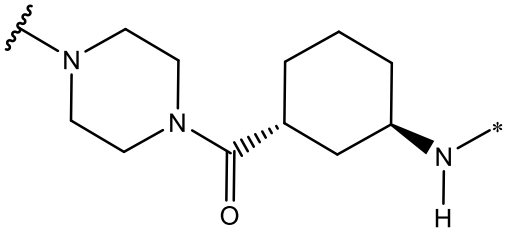
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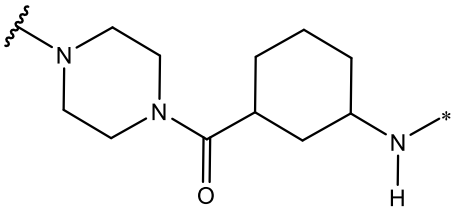
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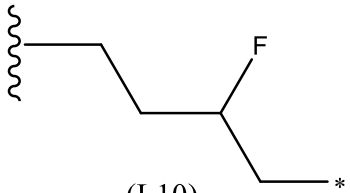
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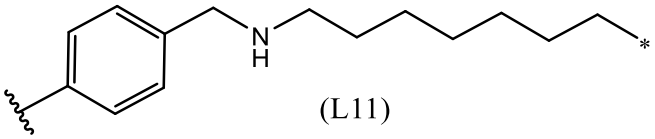
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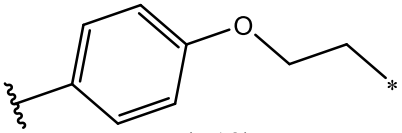
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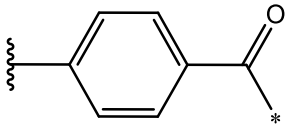
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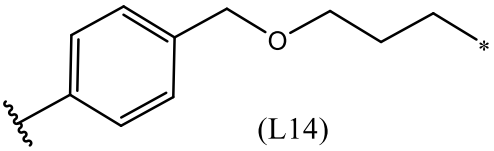
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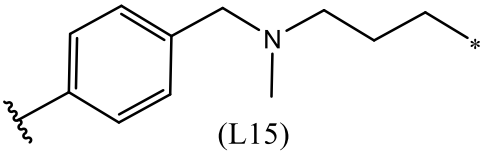
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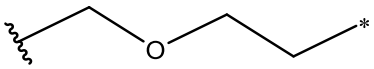
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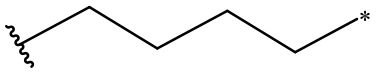
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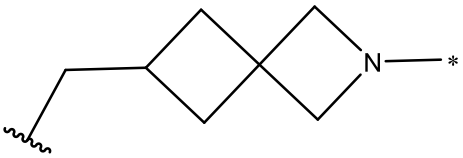
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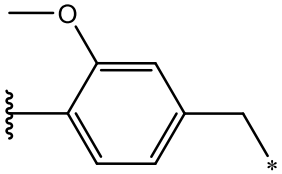
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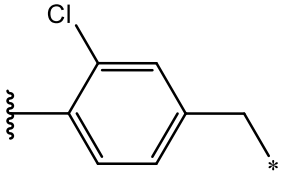
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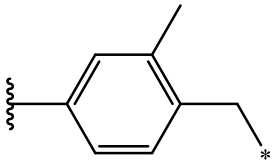
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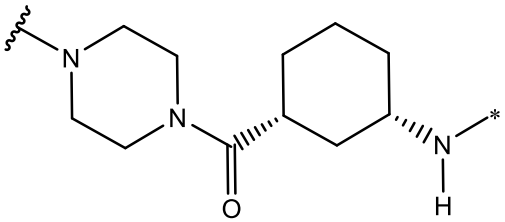
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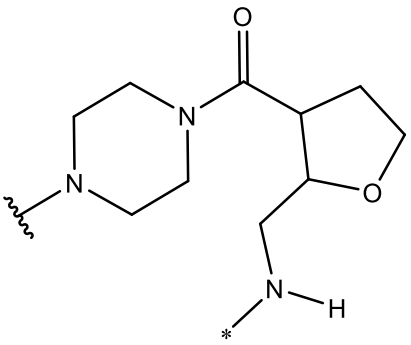
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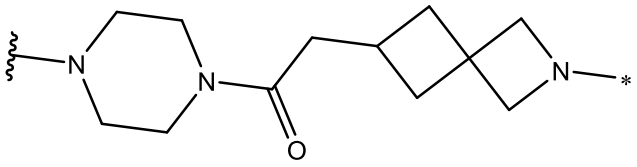
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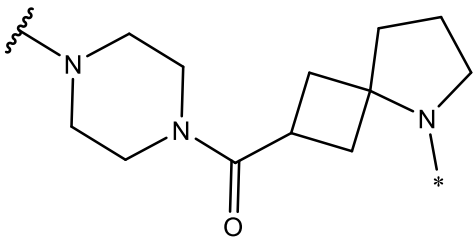
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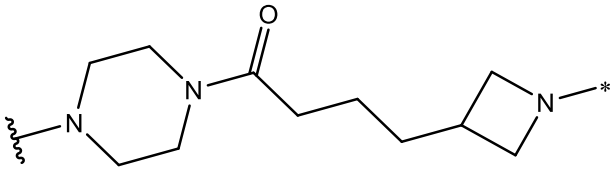
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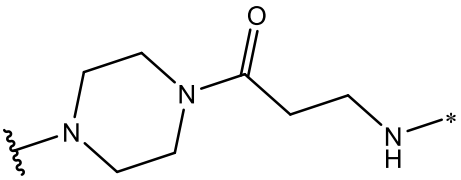
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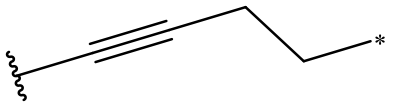
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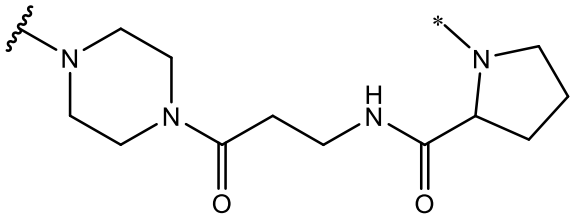
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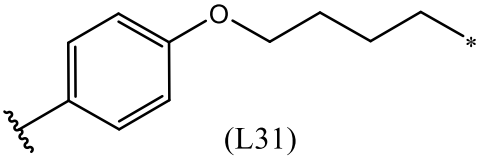
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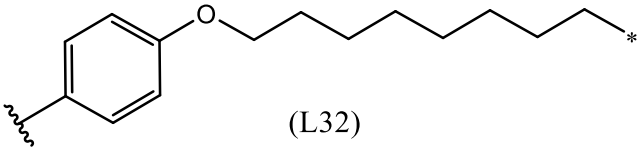
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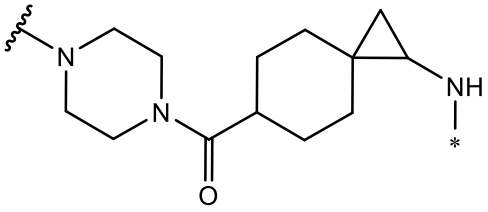
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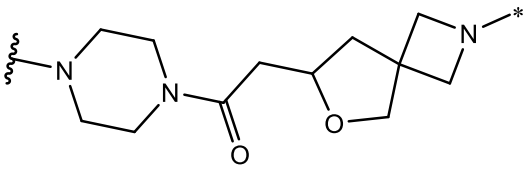


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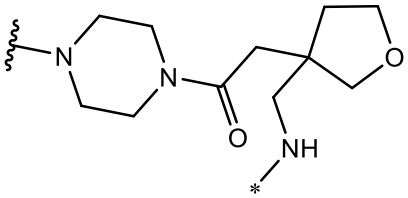


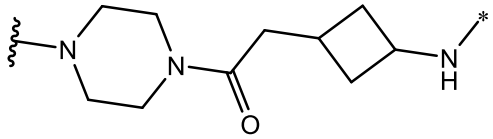
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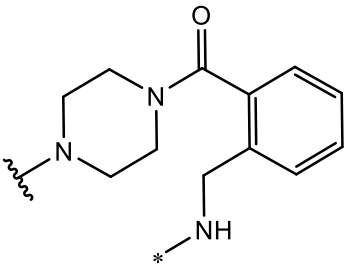
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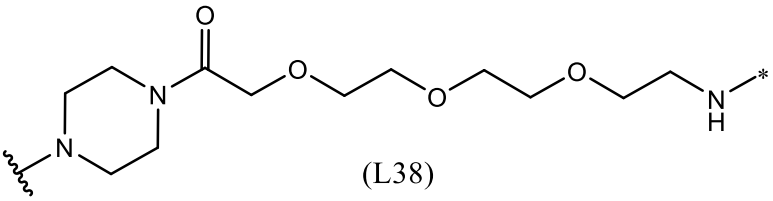
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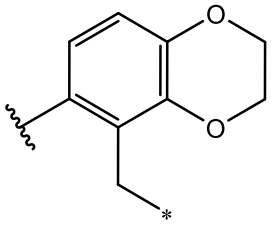
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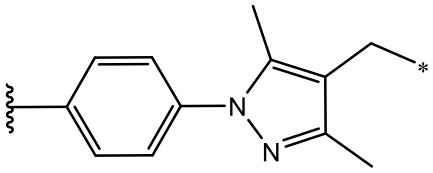
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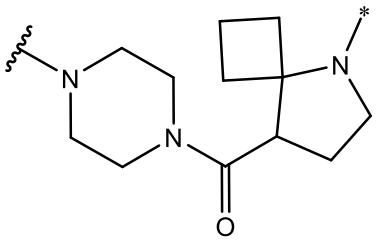


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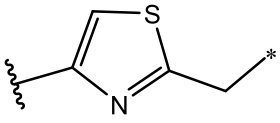
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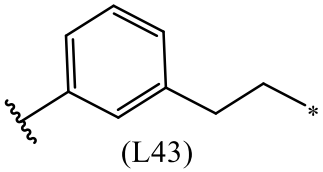


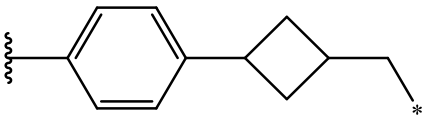
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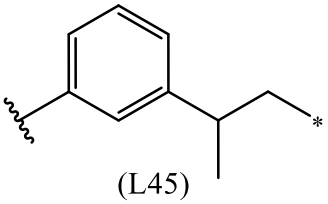
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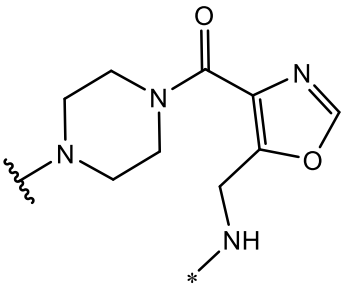


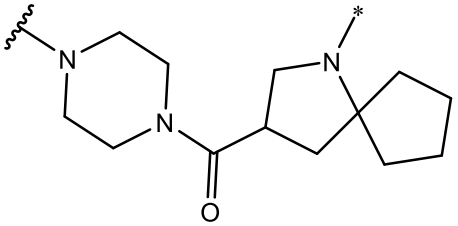
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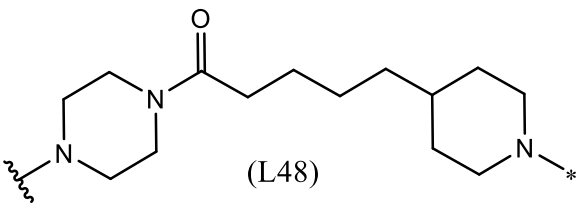
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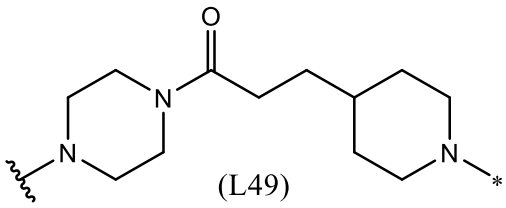
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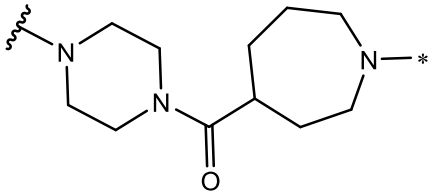
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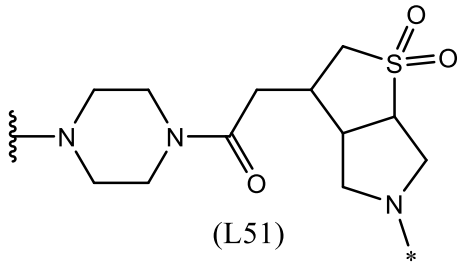
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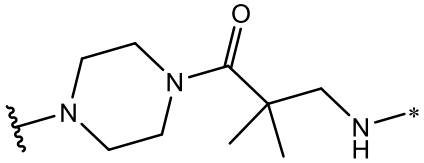
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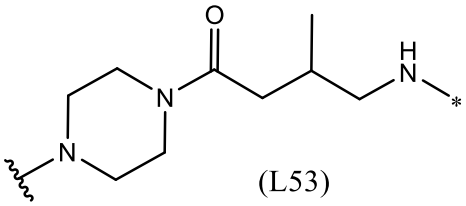
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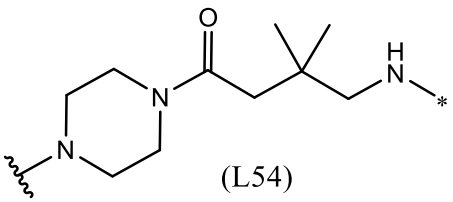
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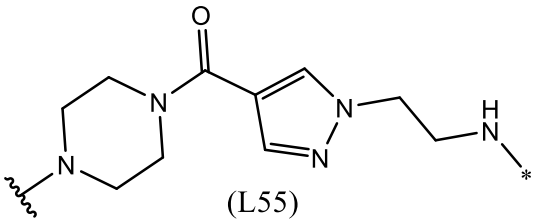
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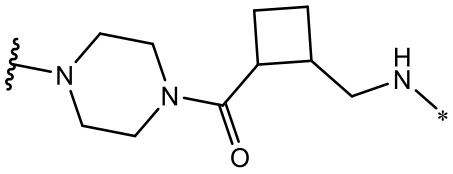
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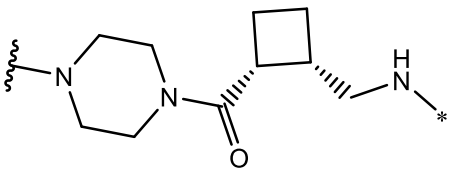
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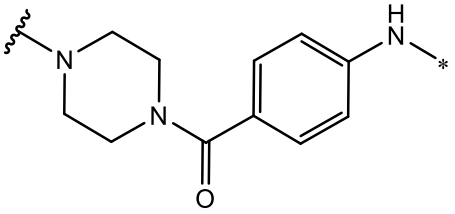
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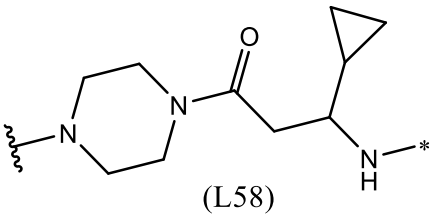
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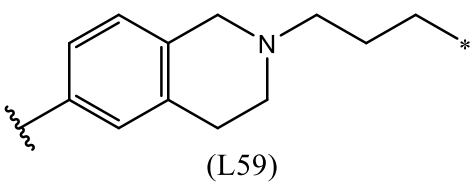
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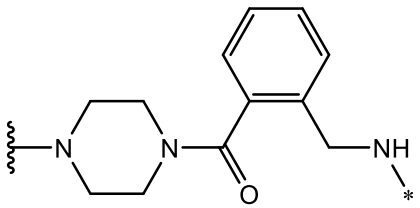
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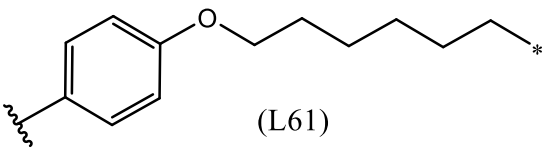
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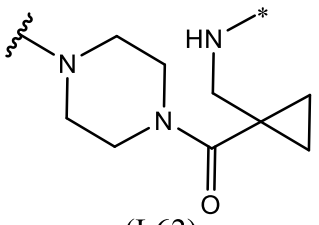


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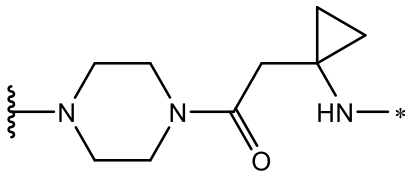
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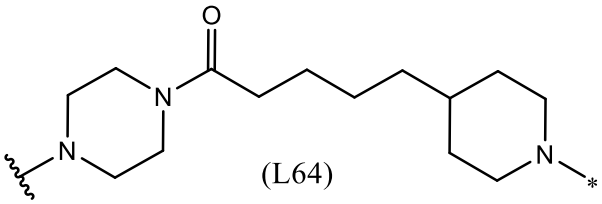
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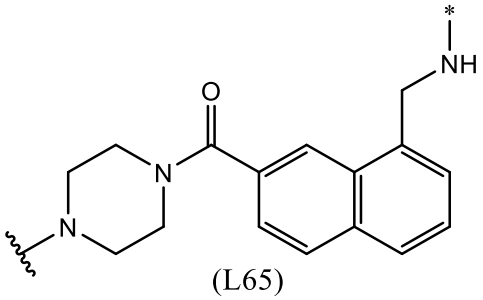
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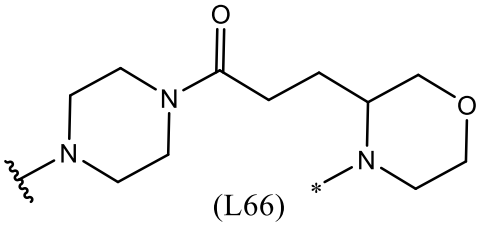
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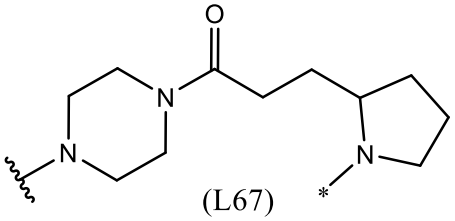
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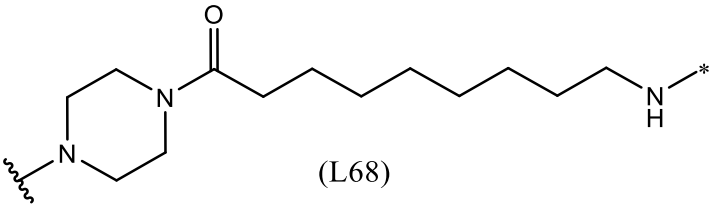
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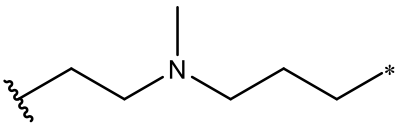
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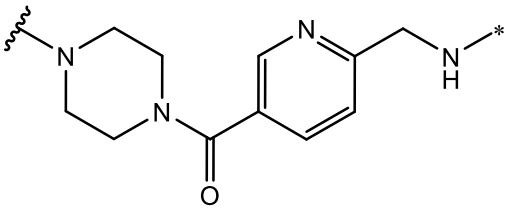
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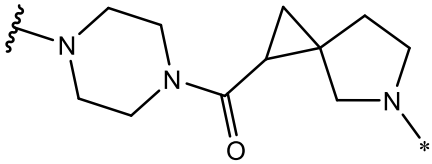
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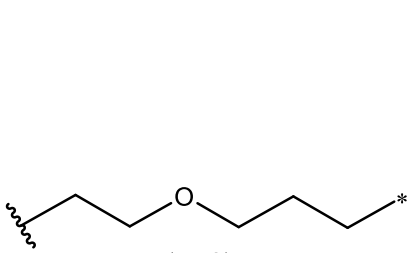
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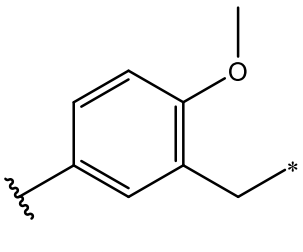


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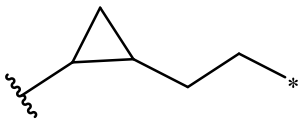
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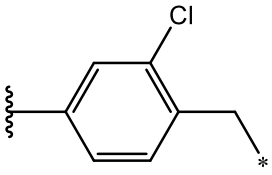
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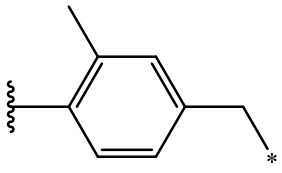
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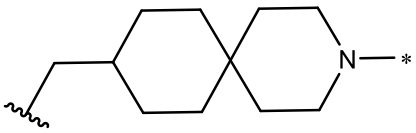
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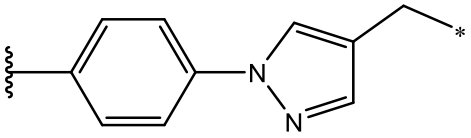
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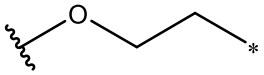
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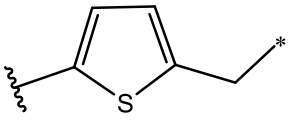
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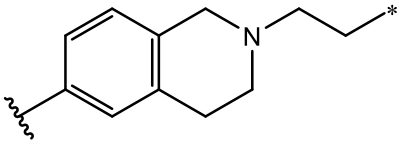
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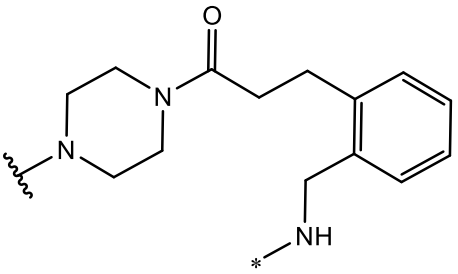
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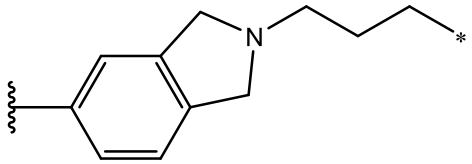
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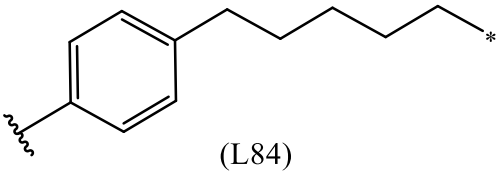
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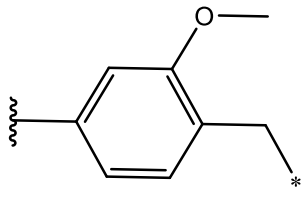
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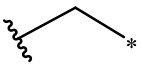
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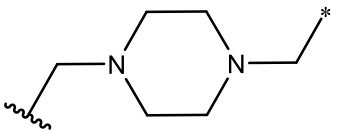
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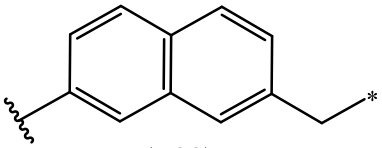
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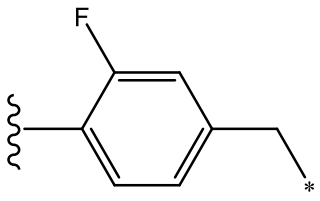


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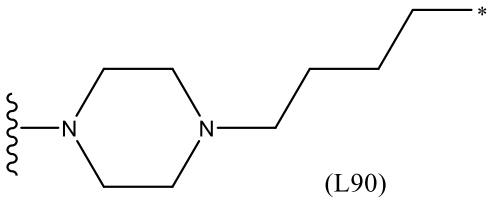
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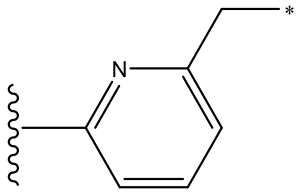
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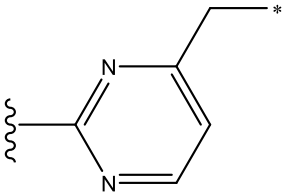
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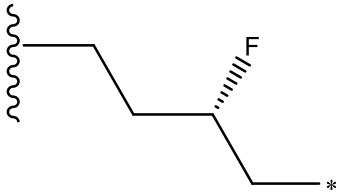
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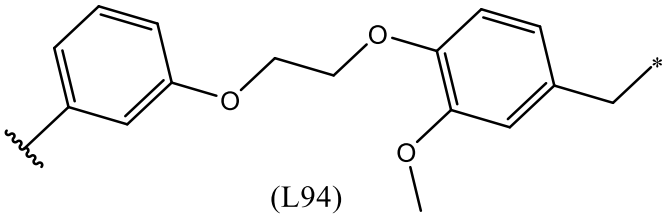
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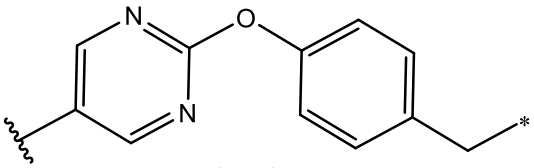
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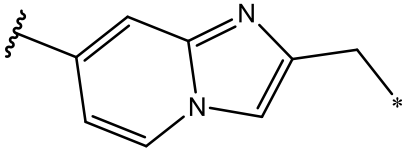
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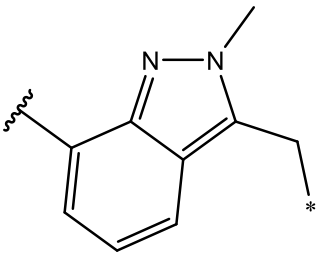
(L95)

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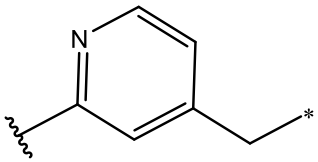
(L96)

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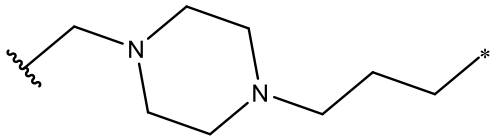


(L97)

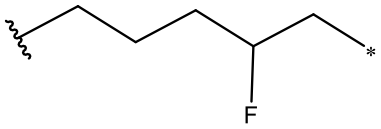
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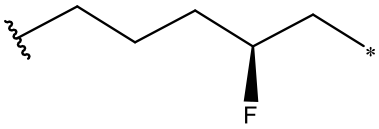
(L98) ,



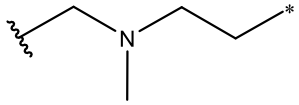
(L99) ,



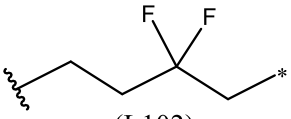
(L100a) ,



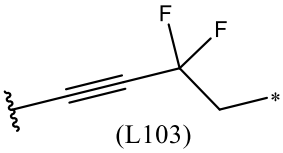
(L100) ,



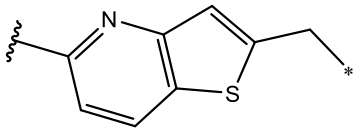
(L101) ,



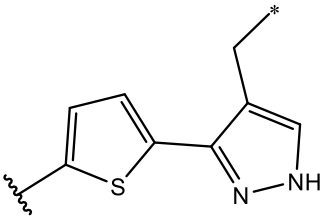
(L102) ,



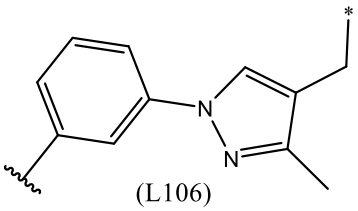
(L103) ,



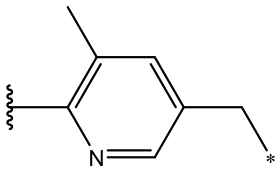
(L104) ,



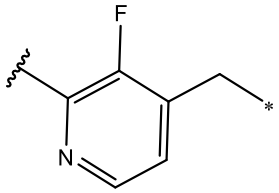
(L105) ,



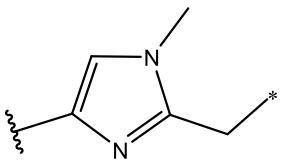
(L106) ,



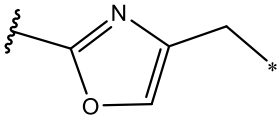
(L107) ,



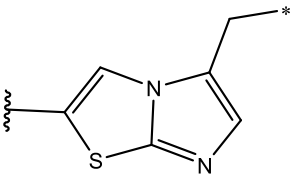
(L108) ,



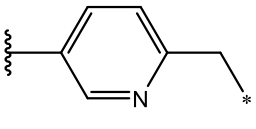
(L109) ,



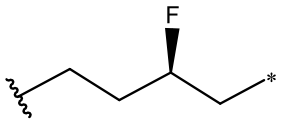
(L110) ,



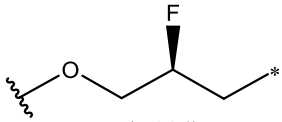
(L111) ,



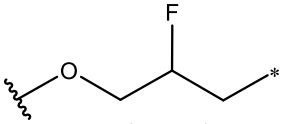
(L112) ,



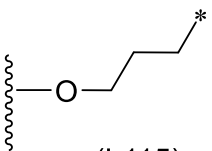
(L113) ,



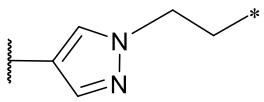
(L114) ,

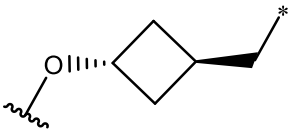


(L114a) ,

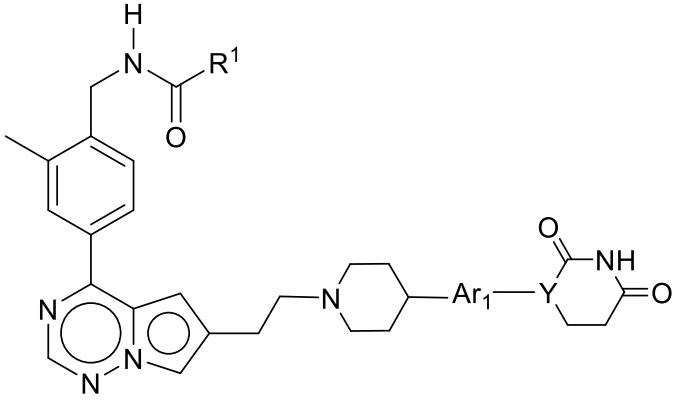


(L115) ,



(L116) or  (L117) .

27. The compound of claim 1, wherein the compound is represented by the following formula:



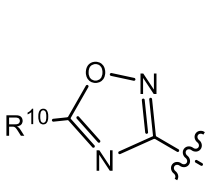
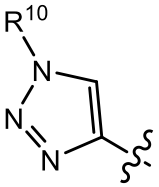
(A-V),

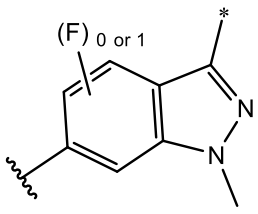
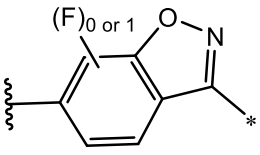
or a pharmaceutically acceptable salt thereof, wherein:

R^1 is 1,2,4-oxadiazolyl or triazolyl, each of which is substituted with R^{10}, wherein R^{10} is $C_{1\text{-}4}$alkyl;

Y is N or CH; and

Ar_1 is indozolyl or benzoisoxazolyl, each of which is optionally substituted with 1 or 2 substituents independently selected from halo and $C_{1\text{-}2}$alkyl, optionally, wherein:

R^1 is  (C4) or  (C26) ; and

Ar_1 is  , or  , wherein * represents a bond to Y, preferably, wherein R^{10} is $-C(CH_3)_3$.

28. A pharmaceutical composition comprising a compound of any one of claims 1-27 or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

29. Use of a compound of any one of claims 1-27, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition according to claim 28, in the manufacture of a medicament for treating a disorder responsive to degradation and/or inhibition of Bruton's tyrosine kinase in a subject, optionally

wherein the disorder is an autoimmune disorder, rheumatoid arthritis, systemic lupus erythematosus, atopic dermatitis, or cancer, preferably,

wherein the autoimmune disorder is multiple sclerosis and wherein the cancer is leukemia or lymphoma.

30. A compound of any one of claims 1-27, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition according to claim 28, for use in therapy.