

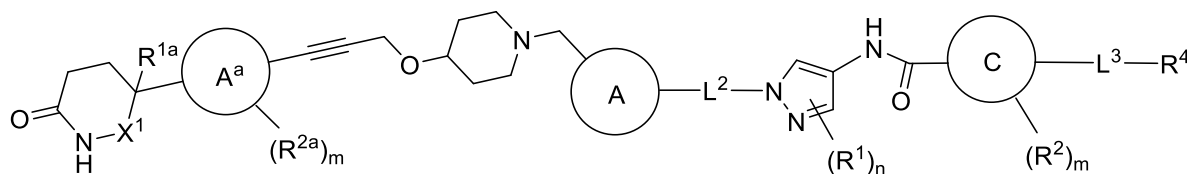
remain as obstacles to the development of effective anti-cancer agents. As such, small molecule therapeutic agents that leverage E3 ligase mediated protein degradation to target cancer-associated proteins such as interleukin-1 receptor-associated kinases (“IRAK”) hold promise as therapeutic agents. Accordingly, there remains a need to find compounds that are IRAK degraders useful as therapeutic agents.

## SUMMARY

**[0009]** The present application relates novel bifunctional compounds, which function to recruit IRAK kinases to E3 Ubiquitin Ligase for degradation, and methods of preparation and uses thereof. In particular, the present disclosure provides bifunctional compounds, which find utility as modulators of targeted ubiquitination of IRAK kinases, which are then degraded and/or otherwise inhibited by the bifunctional compounds as described herein. Also provided are monovalent compounds, which find utility as inducers of targeted ubiquitination of IRAK kinases, which are then degraded and/or otherwise inhibited by the monovalent compounds as described herein. An advantage of the compounds provided herein is that a broad range of pharmacological activities is possible, consistent with the degradation/inhibition of IRAK kinases. In addition, the description provides methods of using an effective amount of the compounds as described herein for the treatment or amelioration of a disease condition, such as cancer, e.g., multiple myeloma.

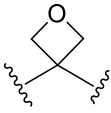
**[0010]** The present application further relates to targeted degradation of IRAK kinases through the use of bifunctional molecules, including bifunctional molecules that link a cereblon-binding moiety to a ligand that binds IRAK kinases.

**[0010a]** In an aspect of the present disclosure, there is provided a compound of formula **II-f-5**:



**II-f-5**

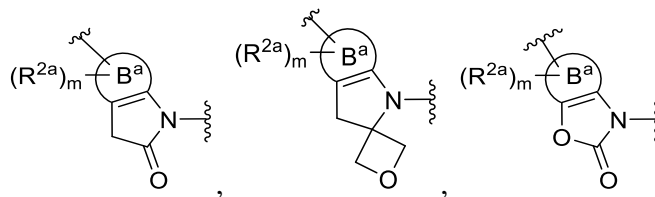
or a pharmaceutically acceptable salt thereof, wherein:

X<sup>1</sup> is a bivalent moiety selected from a covalent bond, -CH<sub>2</sub>-, -C(O)-, -C(S)-, and  ;

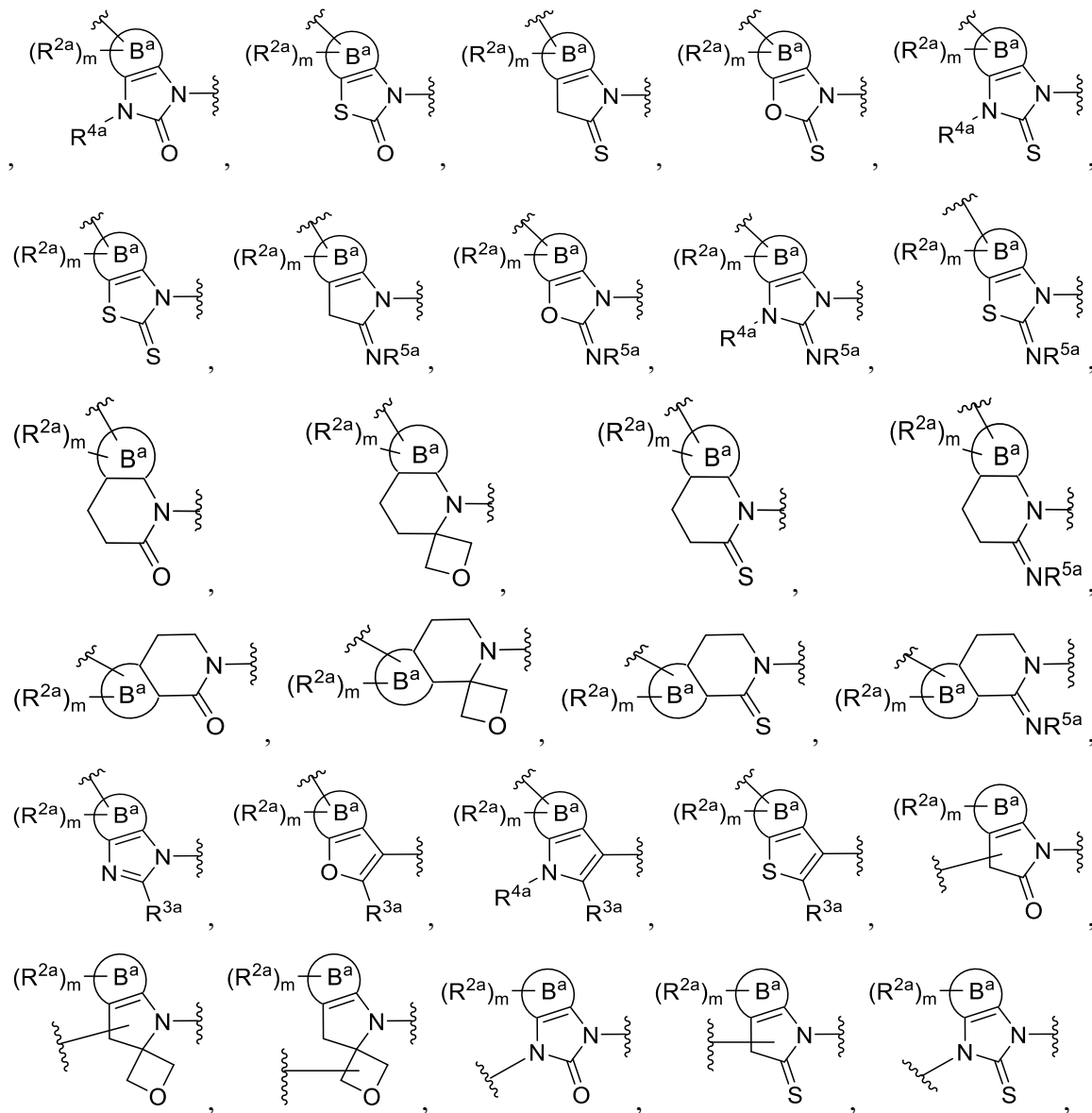
R<sup>1a</sup> is hydrogen, halogen, -CN, -OR, -SR, -S(O)R, -S(O)<sub>2</sub>R, -N(R)<sub>2</sub>, -Si(R)<sub>3</sub>, or an optionally substituted

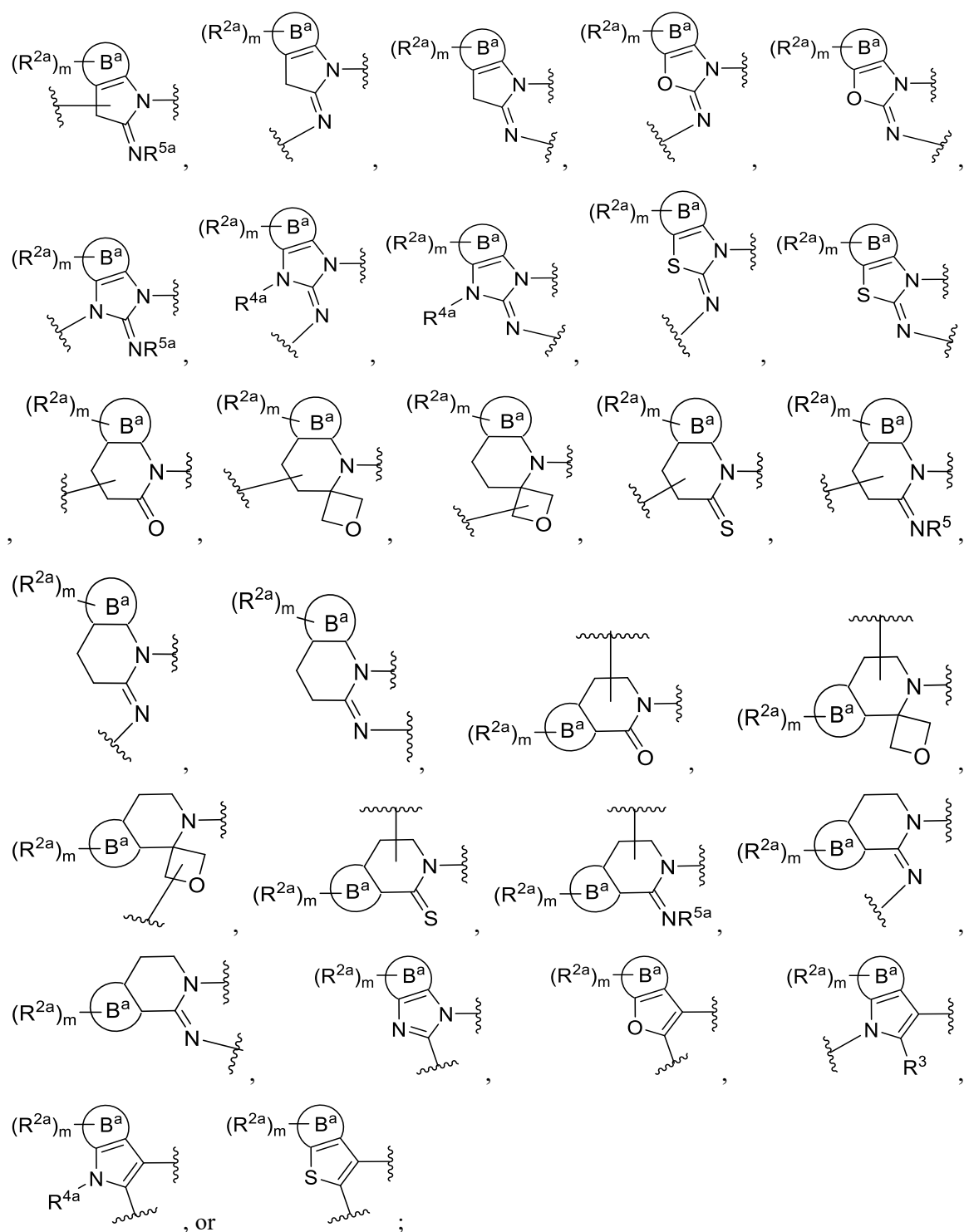
C<sub>1-4</sub> aliphatic;

each R<sup>2a</sup> is independently hydrogen, R<sup>6a</sup>, halogen, -CN, -NO<sub>2</sub>, -OR, -SR, -NR<sub>2</sub>, -S(O)<sub>2</sub>R, -S(O)<sub>2</sub>NR<sub>2</sub>, -S(O)R, -C(O)R, -C(O)OR, -C(O)NR<sub>2</sub>, -C(O)N(R)OR, -OC(O)R, -OC(O)NR<sub>2</sub>, -N(R)C(O)OR, -N(R)C(O)R, -N(R)C(O)NR<sub>2</sub>, or -N(R)S(O)<sub>2</sub>R;



Ring A<sup>a</sup> is a bicyclic or tricyclic ring selected from





Ring B<sup>a</sup> is a fused ring selected from 6-membered aryl containing 0-2 nitrogen atoms, 5 to 7-membered partially saturated carbocyclyl, 5 to 7-membered partially saturated heterocyclyl with 1-2 heteroatoms independently selected from nitrogen, oxygen or sulfur, or 5-membered heteroaryl with 1-3 heteroatoms independently selected from nitrogen, oxygen or sulfur;

R<sup>3a</sup> is selected from hydrogen, halogen, -OR, -N(R)<sub>2</sub>, or -SR;

each R<sup>4a</sup> is independently hydrogen, R<sup>6a</sup>, halogen, -CN, -NO<sub>2</sub>, -OR, -SR, -NR<sub>2</sub>, -S(O)<sub>2</sub>R, -S(O)<sub>2</sub>NR<sub>2</sub>, -S(O)R, -C(O)R, -C(O)OR, -C(O)NR<sub>2</sub>, -C(O)N(R)OR, -OC(O)R, -OC(O)NR<sub>2</sub>, -N(R)C(O)OR, -N(R)C(O)R, -N(R)C(O)NR<sub>2</sub>, or -N(R)S(O)<sub>2</sub>R;

R<sup>5a</sup> is hydrogen, C<sub>1-4</sub> aliphatic, or -CN;

each R<sup>6a</sup> is independently an optionally substituted group selected from C<sub>1-6</sub> aliphatic, phenyl, a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

Ring A is a 4-10 membered saturated monocyclic or bicyclic carbocyclic or heterocyclic ring having 0-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

Ring C is phenyl, or a 5-10 membered monocyclic or bicyclic heteroaryl ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

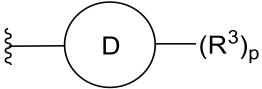
each of L<sup>2</sup> and L<sup>3</sup> is independently a covalent bond or a C<sub>1-3</sub> bivalent straight or branched saturated or unsaturated hydrocarbon chain wherein 1-3 methylene units of the chain are independently and optionally replaced with -O-, -C(O)-, -C(S)-, -C(R)<sub>2</sub>-, -CH(R)-, -C(F)<sub>2</sub>-, -N(R)-, -S-, -S(O)<sub>2</sub>- or -CR=CR-;

each R<sup>1</sup> is independently hydrogen, R<sup>5</sup>, halogen, -CN, -NO<sub>2</sub>, -OR, -SR, -NR<sub>2</sub>, -S(O)<sub>2</sub>R, -S(O)<sub>2</sub>NR<sub>2</sub>, -S(O)R, -S(O)(NR)R, -P(O)(OR)<sub>2</sub>, -P(O)(NR<sub>2</sub>)<sub>2</sub>, -CFR<sub>2</sub>, -CF<sub>2</sub>(R), -CF<sub>3</sub>, -CR<sub>2</sub>(OR), -CR<sub>2</sub>(NR<sub>2</sub>), -C(O)R, -C(O)OR, or -C(O)NR<sub>2</sub>;

each R is independently hydrogen or an optionally substituted group selected from C<sub>1-6</sub> aliphatic, phenyl, a 4-7 membered saturated or partially unsaturated heterocyclic having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or:

two R groups on the same atom are optionally taken together with their intervening atom to form an optionally substituted 4-11 membered saturated or partially unsaturated carbocyclic or heterocyclic monocyclic, bicyclic, bridged bicyclic, spirocyclic, or heteroaryl ring having 0-3 heteroatoms, in addition to the atom to which they are attached, independently selected from nitrogen, oxygen, and sulfur;

each R<sup>2</sup> is independently hydrogen, R<sup>5</sup>, halogen, -CN, -NO<sub>2</sub>, -OR, -SR, -NR<sub>2</sub>, -S(O)<sub>2</sub>R, -S(O)<sub>2</sub>NR<sub>2</sub>, -S(O)R, -S(O)(NR)R, -P(O)(OR)<sub>2</sub>, -P(O)(NR<sub>2</sub>)<sub>2</sub>, -CF<sub>2</sub>(R), -CF<sub>3</sub>, -CR<sub>2</sub>(OR), -CR<sub>2</sub>(NR<sub>2</sub>), -C(O)R, -C(O)OR, -C(O)NR<sub>2</sub>, -C(O)N(R)OR, -OC(O)R, -OC(O)NR<sub>2</sub>, -N(R)C(O)OR, -N(R)C(O)R, -N(R)C(O)NR<sub>2</sub>, or -N(R)S(O)<sub>2</sub>R;


  
 $R^4$  is selected from \_\_\_\_\_, hydrogen, or an optionally substituted group selected from  $C_{1-6}$  aliphatic or a 4-11 membered saturated or partially unsaturated monocyclic, bicyclic, bridged bicyclic or spirocyclic carbocyclic or heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

Ring D is phenyl, a 4-10 membered saturated or partially unsaturated monocyclic or bicyclic carbocyclic or heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

each  $R^3$  is independently hydrogen,  $R^5$ , halogen, -CN, -NO<sub>2</sub>, -OR, -SR, -NR<sub>2</sub>, -S(O)<sub>2</sub>R, -S(O)<sub>2</sub>NR<sub>2</sub>, -S(O)R, -S(O)(NR)R, -P(O)(OR)<sub>2</sub>, -P(O)(NR<sub>2</sub>)<sub>2</sub>, -CF<sub>2</sub>(R), -CF<sub>3</sub>, -CR<sub>2</sub>(OR), -CR<sub>2</sub>(NR<sub>2</sub>), -C(O)R, -C(O)OR, -C(O)NR<sub>2</sub>, -C(O)N(R)OR, -OC(O)R, -OC(O)NR<sub>2</sub>, -N(R)C(O)OR, -N(R)C(O)R, -N(R)C(O)NR<sub>2</sub>, or -N(R)S(O)<sub>2</sub>R;

each  $R^5$  is independently an optionally substituted group selected from  $C_{1-6}$  aliphatic, phenyl, a 3-7 membered saturated or partially unsaturated carbocyclic or heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

$n$  is 0, 1, or 2;

each  $m$  is independently 0, 1, 2, 3 or 4; and

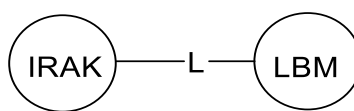
$p$  is 0, 1, 2, 3 or 4.

**[0010b]** In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising a compound disclosed herein and a pharmaceutically acceptable carrier, adjuvant, or vehicle.

**[0010c]** In a further aspect of the present disclosure, there is provided a use of a compound disclosed herein, or a pharmaceutical composition thereof, in the manufacture of a medicament for treating an autoimmune disease, an inflammatory disorder, or an immunodeficiency disorder in a patient.

**[0010d]** In another aspect of the present disclosure, there is provided a compound disclosed herein, or a pharmaceutical composition thereof, for use in therapy.

**[0011]** It has now been found that compounds of this present disclosure, and pharmaceutically acceptable compositions thereof, are effective as degraders of IRAK kinases. Such compounds have the general formula **I**:

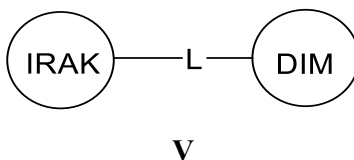


**I**

or a pharmaceutically acceptable salt thereof, wherein each variable is as defined and described herein.

**[0012]** It has also now been found that compounds of this present disclosure, and pharmaceutically acceptable compositions thereof, are effective as degraders of IRAK kinases. Such compounds

have the general formula **V**:



or a pharmaceutically acceptable salt thereof, wherein each variable is as defined and described herein.

**[0013]** Compounds of the present disclosure, and pharmaceutically acceptable compositions thereof, are useful for treating a variety of diseases, disorders or conditions, associated with regulation of signaling pathways implicating IRAK kinases. Such diseases, disorders, or conditions include those described herein.

**[0014]** Compounds provided by this present disclosure are also useful for the study of IRAK enzymes in biological and pathological phenomena; the study of intracellular signal transduction pathways occurring in bodily tissues; and the comparative evaluation of new IRAK inhibitors or IRAK degraders or other regulators of kinases, signaling pathways, and cytokine levels in vitro or in vivo.

#### **BRIEF DESCRIPTION OF THE FIGURES**

**[0015]** FIG. 1 is an image showing a western blot of degrader **I-30** in OCI-LY10 at 24 h.

**[0016]** FIG. 2 is an image of a dose response curve for IKAK4 (% control)(y-axis) versus degrader **I-30** concentration ( $\mu\text{M}$ ) (x-axis) for OCI-LY10 and TMD8 cell lines and in vitro degradation results ( $\text{DC}_{90}$ ,  $\mu\text{M}$ ).

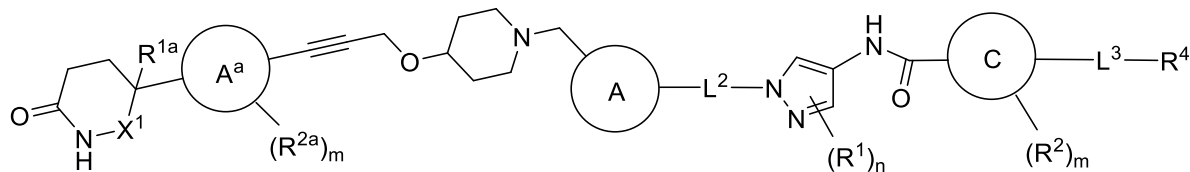
**[0017]** FIG. 3 is an image of a deep TMT proteomics scatterplot in OCI-LY10 at 8h showing Log2 FC 10 nM degrader **I-30** in DMSO (y-axis) and Log2 FC 10 nM degrader in DMSO Rep1 (x-axis).

**[0018]** FIG. 4 includes graphical images showing the decrease of IRAK4 at 24h with count (y-axis) versus IRAK (MFI) (x-axis) using several concentrations of degrader **I-30** (A); the time dependent induction of apoptosis with 50 nM degrader **I-30** showing IRAK4 (% control) (left y-axis) and cleaved CASP3 (% control) (right y-axis) versus time (h) (x-axis) (B); the inhibition of cell proliferation at 72 h showing count (y-axis) versus Ki67 (MFI) (x-axis) at several concentrations of degrader **I-30** (C); and the induction of apoptosis is mechanism specific showing cleaved CASP3 (% control) (y-axis) for degrader **I-30** and inactive (x-axis) at several concentrations respectively (D).

## CLAIMS

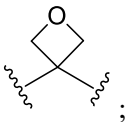
We claim:

1. A compound of formula **II-f-5**:

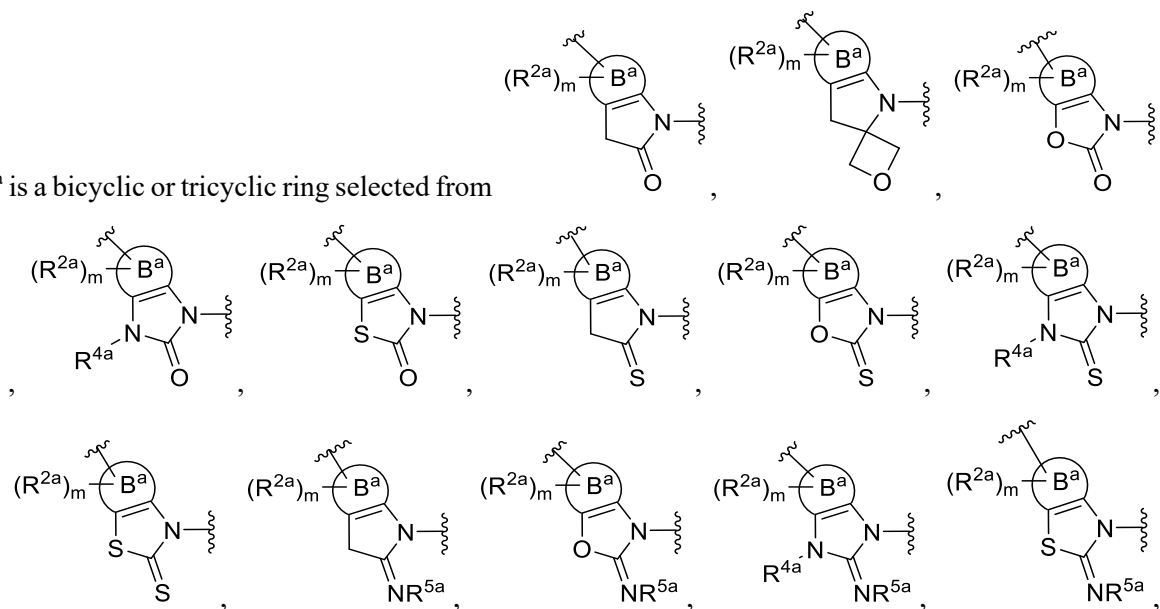


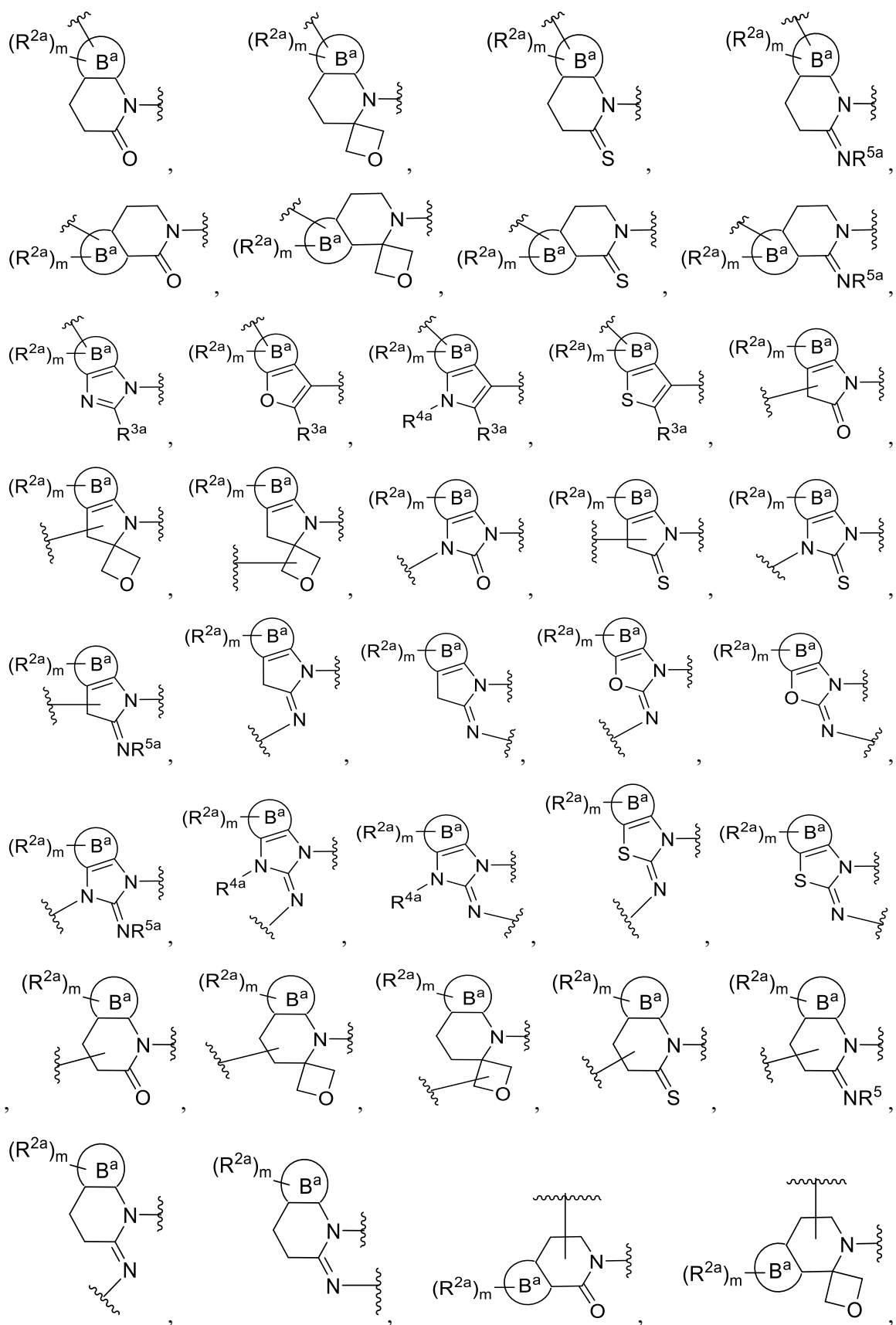
**II-f-5**

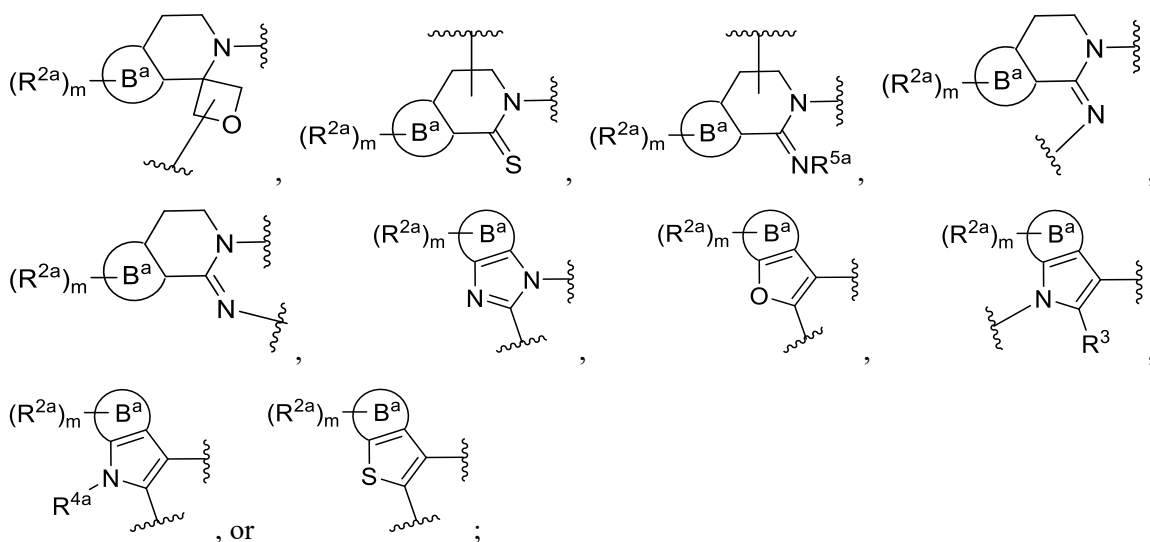
or a pharmaceutically acceptable salt thereof, wherein:

$X^1$  is a bivalent moiety selected from a covalent bond,  $-CH_2-$ ,  $-C(O)-$ ,  $-C(S)-$ , and  ;  
 $R^{1a}$  is hydrogen, halogen,  $-CN$ ,  $-OR$ ,  $-SR$ ,  $-S(O)R$ ,  $-S(O)_2R$ ,  $-N(R)_2$ ,  $-Si(R)_3$ , or an optionally substituted  $C_{1-4}$  aliphatic;  
each  $R^{2a}$  is independently hydrogen,  $R^{6a}$ , halogen,  $-CN$ ,  $-NO_2$ ,  $-OR$ ,  $-SR$ ,  $-NR_2$ ,  $-S(O)_2R$ ,  $-S(O)_2NR_2$ ,  $-S(O)R$ ,  $-C(O)R$ ,  $-C(O)OR$ ,  $-C(O)NR_2$ ,  $-C(O)N(R)OR$ ,  $-OC(O)R$ ,  $-OC(O)NR_2$ ,  $-N(R)C(O)OR$ ,  $-N(R)C(O)R$ ,  $-N(R)C(O)NR_2$ , or  $-N(R)S(O)_2R$ ;

Ring  $A^a$  is a bicyclic or tricyclic ring selected from







Ring  $B^a$  is a fused ring selected from 6-membered aryl containing 0-2 nitrogen atoms, 5 to 7-membered partially saturated carbocyclyl, 5 to 7-membered partially saturated heterocyclyl with 1-2 heteroatoms independently selected from nitrogen, oxygen or sulfur, or 5-membered heteroaryl with 1-3 heteroatoms independently selected from nitrogen, oxygen or sulfur;

$R^{3a}$  is selected from hydrogen, halogen,  $-OR$ ,  $-N(R)_2$ , or  $-SR$ ;

each  $R^{4a}$  is independently hydrogen,  $R^{6a}$ , halogen,  $-CN$ ,  $-NO_2$ ,  $-OR$ ,  $-SR$ ,  $-NR_2$ ,  $-S(O)_2R$ ,  $-S(O)_2NR_2$ ,  $-S(O)R$ ,  $-C(O)R$ ,  $-C(O)OR$ ,  $-C(O)NR_2$ ,  $-C(O)N(R)OR$ ,  $-OC(O)R$ ,  $-OC(O)NR_2$ ,  $-N(R)C(O)OR$ ,  $-N(R)C(O)R$ ,  $-N(R)C(O)NR_2$ , or  $-N(R)S(O)_2R$ ;

$R^{5a}$  is hydrogen,  $C_{1-4}$  aliphatic, or  $-CN$ ;

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

Ring A is a 4-10 membered saturated monocyclic or bicyclic carbocyclic or heterocyclic ring having 0-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

Ring C is phenyl, or a 5-10 membered monocyclic or bicyclic heteroaryl ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

each of  $L^2$  and  $L^3$  is independently a covalent bond or a  $C_{1-3}$  bivalent straight or branched saturated or unsaturated hydrocarbon chain wherein 1-3 methylene units of the chain are independently and optionally replaced with  $-O-$ ,  $-C(O)-$ ,  $-C(S)-$ ,  $-C(R)_2-$ ,  $-CH(R)-$ ,  $-C(F)_2-$ ,  $-N(R)-$ ,  $-S-$ ,  $-S(O)_2-$  or  $-CR=CR-$ ;

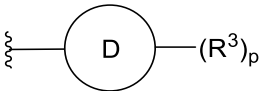
each  $R^1$  is independently hydrogen,  $R^5$ , halogen,  $-CN$ ,  $-NO_2$ ,  $-OR$ ,  $-$

SR, -NR<sub>2</sub>, -S(O)<sub>2</sub>R, -S(O)<sub>2</sub>NR<sub>2</sub>, -S(O)R, -S(O)(NR)R, -P(O)(OR)<sub>2</sub>, -P(O)(NR<sub>2</sub>)<sub>2</sub>, -CFR<sub>2</sub>, -CF<sub>2</sub>(R), -CF<sub>3</sub>, -CR<sub>2</sub>(OR), -CR<sub>2</sub>(NR<sub>2</sub>), -C(O)R, -C(O)OR, or -C(O)NR<sub>2</sub>;

each R is independently hydrogen or an optionally substituted group selected from C<sub>1-6</sub> aliphatic, phenyl, a 4-7 membered saturated or partially unsaturated heterocyclic having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or:

two R groups on the same atom are optionally taken together with their intervening atom to form an optionally substituted 4-11 membered saturated or partially unsaturated carbocyclic or heterocyclic monocyclic, bicyclic, bridged bicyclic, spirocyclic, or heteroaryl ring having 0-3 heteroatoms, in addition to the atom to which they are attached, independently selected from nitrogen, oxygen, and sulfur;

each R<sup>2</sup> is independently hydrogen, R<sup>5</sup>, halogen, -CN, -NO<sub>2</sub>, -OR, -SR, -NR<sub>2</sub>, -S(O)<sub>2</sub>R, -S(O)<sub>2</sub>NR<sub>2</sub>, -S(O)R, -S(O)(NR)R, -P(O)(OR)<sub>2</sub>, -P(O)(NR<sub>2</sub>)<sub>2</sub>, -CF<sub>2</sub>(R), -CF<sub>3</sub>, -CR<sub>2</sub>(OR), -CR<sub>2</sub>(NR<sub>2</sub>), -C(O)R, -C(O)OR, -C(O)NR<sub>2</sub>, -C(O)N(R)OR, -OC(O)R, -OC(O)NR<sub>2</sub>, -N(R)C(O)OR, -N(R)C(O)R, -N(R)C(O)NR<sub>2</sub>, or -N(R)S(O)<sub>2</sub>R;

R<sup>4</sup> is selected from , hydrogen, or an optionally substituted group selected from C<sub>1-6</sub> aliphatic or a 4-11 membered saturated or partially unsaturated monocyclic, bicyclic, bridged bicyclic or spirocyclic carbocyclic or heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

Ring D is phenyl, a 4-10 membered saturated or partially unsaturated monocyclic or bicyclic carbocyclic or heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

each R<sup>3</sup> is independently hydrogen, R<sup>5</sup>, halogen, -CN, -NO<sub>2</sub>, -OR, -SR, -NR<sub>2</sub>, -S(O)<sub>2</sub>R, -S(O)<sub>2</sub>NR<sub>2</sub>, -S(O)R, -S(O)(NR)R, -P(O)(OR)<sub>2</sub>, -P(O)(NR<sub>2</sub>)<sub>2</sub>, -CF<sub>2</sub>(R), -CF<sub>3</sub>, -CR<sub>2</sub>(OR), -CR<sub>2</sub>(NR<sub>2</sub>), -C(O)R, -C(O)OR, -C(O)NR<sub>2</sub>, -C(O)N(R)OR, -OC(O)R, -OC(O)NR<sub>2</sub>, -N(R)C(O)OR, -N(R)C(O)R, -N(R)C(O)NR<sub>2</sub>, or -N(R)S(O)<sub>2</sub>R;

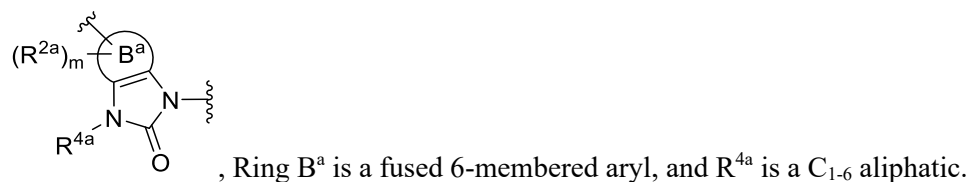
each R<sup>5</sup> is independently an optionally substituted group selected from C<sub>1-6</sub> aliphatic, phenyl, a 3-7 membered saturated or partially unsaturated carbocyclic or heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

n is 0, 1, or 2;

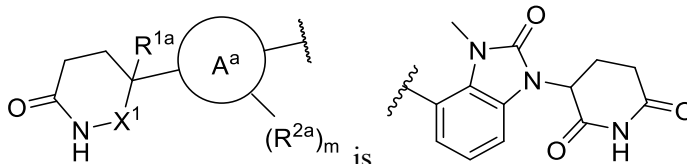
each m is independently 0, 1, 2, 3 or 4; and

p is 0, 1, 2, 3 or 4.

2. The compound of claim 1, wherein  $X^1$  is  $-C(O)-$ ,  $R^{1a}$  is hydrogen, m of  $(R^{2a})_m$  is 0, Ring  $A^a$  is



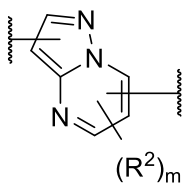
3. The compound of claim 1, wherein



4. The compound of claim 1, wherein Ring A is a 4-6 membered saturated monocyclic carbocyclic or heterocyclic ring having 0-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

5. The compound of claim 1, wherein Ring A is cyclohexyl.

6. The compound of claim 1, wherein Ring C is a 5-10 membered monocyclic or bicyclic heteroaryl ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, and sulfur.



7. The compound of claim 1, wherein Ring C is  $(R^2)_m$ .

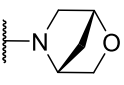
8. The compound of claim 1, wherein  $L^2$  and  $L^3$  are covalent bonds.

9. The compound of claim 1, wherein n is 1 and  $R^1$  is hydrogen,  $R^5$ , halogen,  $-CN$ ,  $-NO_2$ ,  $-OR$ ,  $-SR$ ,  $-NR_2$ ,  $-S(O)_2R$ ,  $-S(O)_2NR_2$ ,  $-S(O)R$ ,  $-CFR_2$ ,  $-CF_2(R)$ ,  $-CF_3$ ,  $-CR_2(OR)$ ,  $-CR_2(NR_2)$ ,  $-C(O)R$ ,  $-C(O)OR$ , or  $-C(O)NR_2$ .

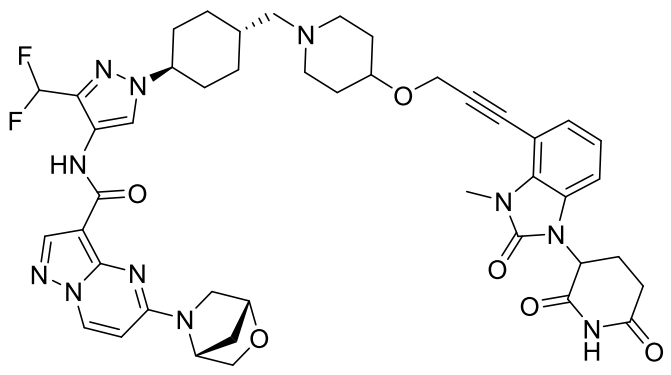
10. The compound of claim 1, wherein n is 1 and  $R^1$  is  $-CHF_2$ ,

11. The compound of claim 1, wherein  $R^4$  is an optionally substituted group selected from  $C_{1-6}$  aliphatic

or a 4-11 membered saturated or partially unsaturated monocyclic, bicyclic, bridged bicyclic, or spirocyclic carbocyclic or heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

12. The compound of claim 1, wherein R<sup>4</sup> is .

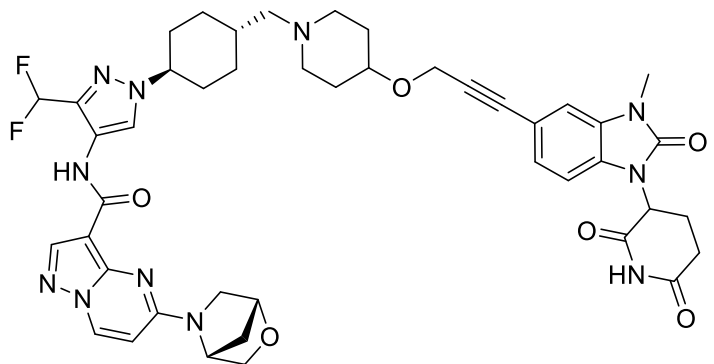
13. The compound of claim 1, wherein said compound is



**I-417**

or a pharmaceutically acceptable salt thereof.

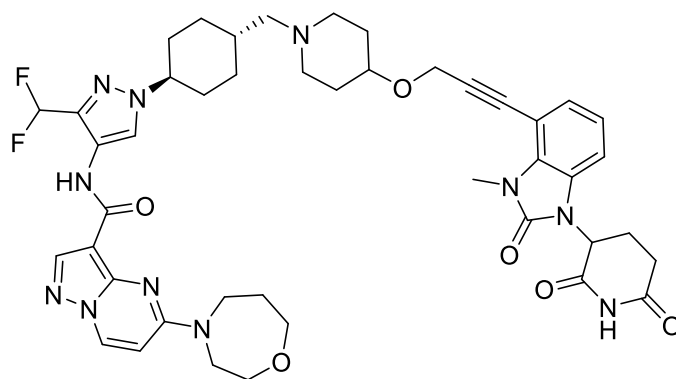
14. The compound of claim 1, wherein said compound is



**I-483**

or a pharmaceutically acceptable salt thereof.

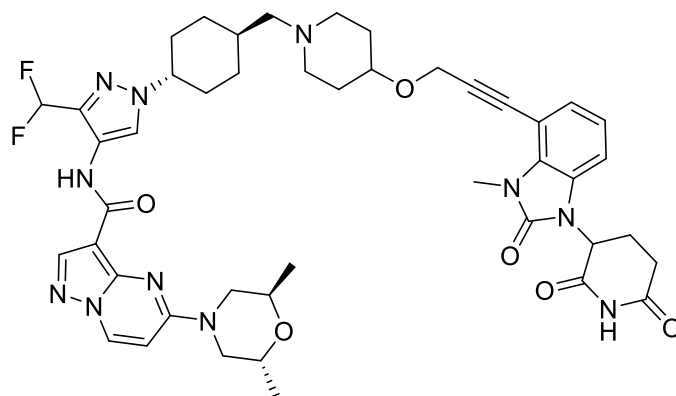
15. The compound of claim 1, wherein said compound is



**I-522**

or a pharmaceutically acceptable salt thereof.

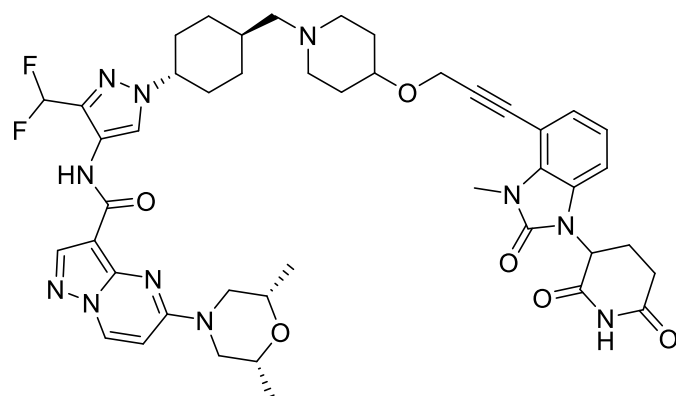
16. The compound of claim 1, wherein said compound is



**I-527**

or a pharmaceutically acceptable salt thereof.

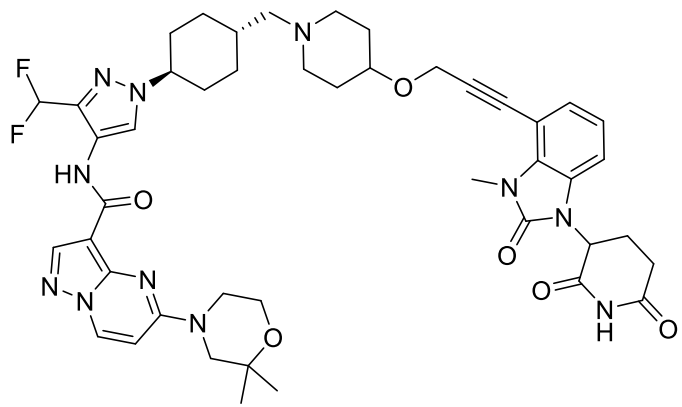
17. The compound of claim 1, wherein said compound is



**I-531**

or a pharmaceutically acceptable salt thereof.

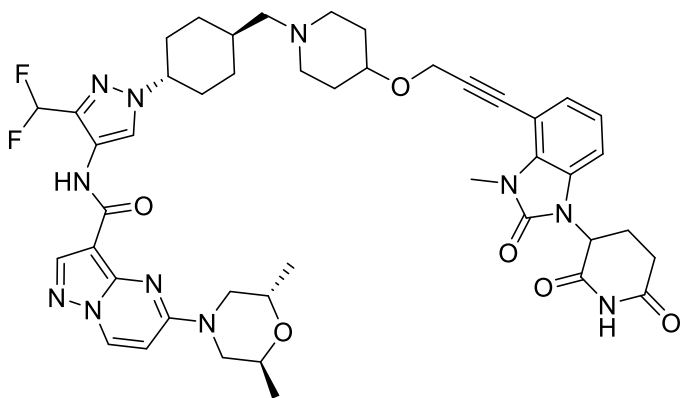
18. The compound of claim 1, wherein said compound is



**I-533**

or a pharmaceutically acceptable salt thereof.

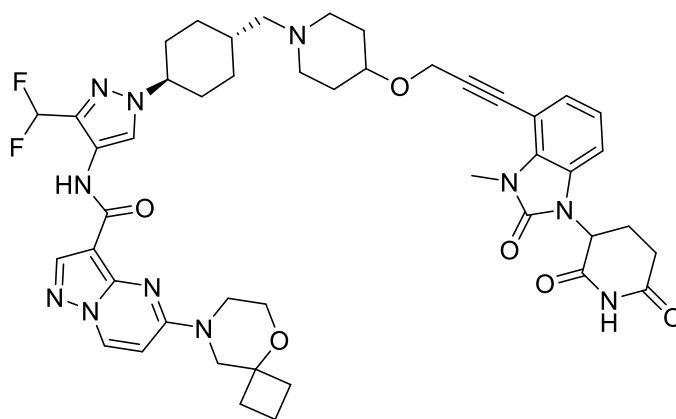
19. The compound of claim 1, wherein said compound is



**I-536**

or a pharmaceutically acceptable salt thereof.

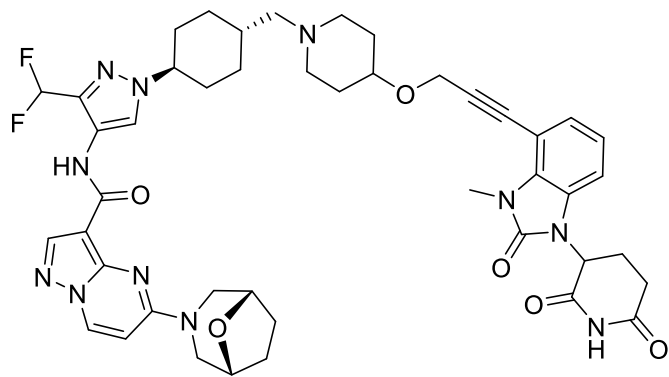
20. The compound of claim 1, wherein said compound is



**I-541**

or a pharmaceutically acceptable salt thereof.

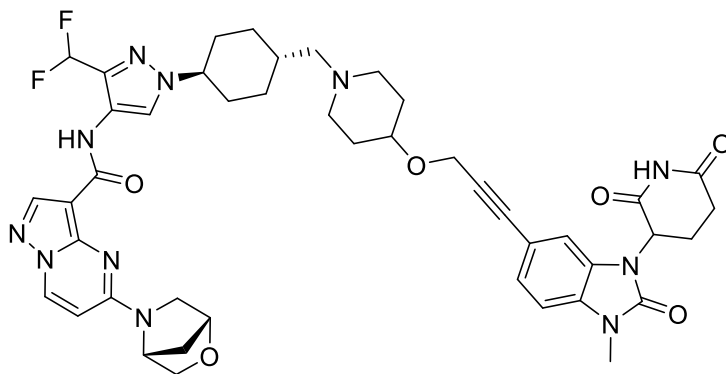
21. The compound of claim 1, wherein said compound is



**I-547**

or a pharmaceutically acceptable salt thereof.

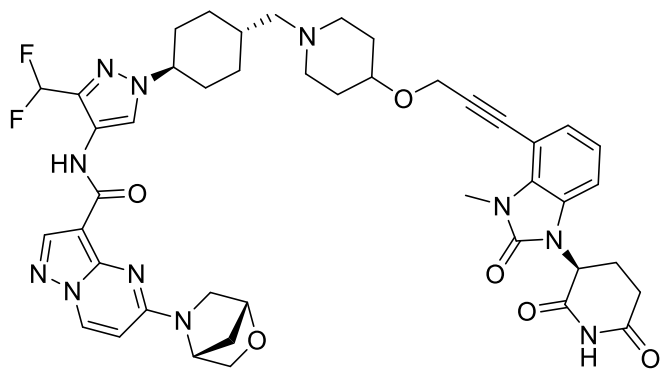
22. The compound of claim 1, wherein said compound is



**I-548**

or a pharmaceutically acceptable salt thereof.

23. The compound of claim 1, wherein said compound is



arthritis, polychondritis, scleroderma, Wegener granulomatosis, dermatomyositis, chronic active hepatitis, myasthenia gravis, Steven-Johnson syndrome, idiopathic sprue, ulcerative colitis, Crohn's disease, irritable bowel syndrome, celiac disease, periodontitis, hyaline membrane disease, kidney disease, glomerular disease, alcoholic liver disease, endocrine ophthalmopathy, Grave's disease, sarcoidosis, alveolitis, chronic hypersensitivity pneumonitis, multiple sclerosis, primary biliary cirrhosis, uveitis (anterior and posterior), Sjogren's syndrome, vernal keratoconjunctivitis, interstitial lung fibrosis, psoriatic arthritis, systemic juvenile idiopathic arthritis, nephritis, diverticulitis, interstitial cystitis, glomerulonephritis (with and without nephrotic syndrome, optionally including idiopathic nephrotic syndrome or minimal change nephropathy), chronic granulomatous disease, endometriosis, leptospirosis renal disease, glaucoma, retinal disease, aging, headache, pain, complex regional pain syndrome, cardiac hypertrophy, muscle wasting, catabolic disorders, obesity, fetal growth retardation, hypercholesterolemia, heart disease, chronic heart failure, mesothelioma, anhidrotic ectodermal dysplasia, Behcet's disease, incontinentia pigmenti, Paget's disease, pancreatitis, hereditary periodic fever syndrome, asthma (allergic, non-allergic, mild, moderate, severe, bronchitic, or exercise-induced), acute lung injury, acute respiratory distress syndrome, eosinophilia, hypersensitivities, anaphylaxis, nasal sinusitis, silica induced diseases, COPD (reduction of damage, airways inflammation, bronchial hyperreactivity, remodeling or disease progression), pulmonary disease, cystic fibrosis, acid-induced lung injury, pulmonary hypertension, polyneuropathy, cataracts, muscle inflammation in conjunction with systemic sclerosis, inclusion body myositis, myasthenia gravis, thyroiditis, Addison's disease, lichen planus, Type 1 diabetes, Type 2 diabetes, appendicitis, atopic dermatitis, allergy, blepharitis, bronchiolitis, bronchitis, bursitis, cervicitis, cholangitis, cholecystitis, chronic graft rejection, colitis, conjunctivitis, cystitis, dacryoadenitis, dermatitis, dermatomyositis, encephalitis, endocarditis, endometritis, enteritis, enterocolitis, epicondylitis, epididymitis, fasciitis, fibrositis, gastritis, gastroenteritis, Henoch-Schonlein purpura, hepatitis, hidradenitis suppurativa, immunoglobulin A nephropathy, interstitial lung disease, laryngitis, mastitis, meningitis, myelitis, myocarditis, myositis, nephritis, oophoritis, orchitis, osteitis, otitis, pancreatitis, parotitis, pericarditis, peritonitis, pharyngitis, pleuritis, phlebitis, pneumonia, polymyositis, proctitis, prostatitis, pyelonephritis, rhinitis, salpingitis, sinusitis, stomatitis, synovitis, tendonitis, tonsillitis, vaginitis, vasculitis, vulvitis, alopecia areata, erythema multiforme, dermatitis herpetiformis, scleroderma, vitiligo, hypersensitivity angiitis, urticaria, bullous pemphigoid, pemphigus vulgaris, pemphigus foliaceus, paraneoplastic pemphigus, epidermolysis bullosa acquisita, acute and chronic gout, chronic gouty arthritis, psoriasis, psoriatic arthritis, rheumatoid arthritis, juvenile rheumatoid arthritis, cryopyrin associated periodic syndrome, adult onset Still's disease, macrophage activation syndrome, primary and secondary hemophagocytic lymphohistiocytosis, familial Mediterranean fever, NLRP12

autoinflammatory syndrome, or osteoarthritis.

28. The use of claim 26, wherein the disease or disorder is ocular allergy, conjunctivitis, keratoconjunctivitis sicca, vernal conjunctivitis, allergic rhinitis, chronic rhinosinusitis with nasal polyps (CRSwNP), hemolytic anemia, aplastic anemia, pure red cell anemia, idiopathic thrombocytopenia, eosinophilia, hypereosinophilia, Löffler's syndrome, eosinophilic pneumonia, tropical eosinophilia, bronchopulmonary aspergillosis, polyarteritis nodosa, Churg-Strauss syndrome, eosinophilic granuloma, eosinophilic asthma, eosinophilic COPD, psoriasis, generalized pustular psoriasis, psoriasis vulgaris, contact dermatitis, atopic dermatitis, alopecia areata, erythema multiforma, dermatitis, herpetiformis, scleroderma, vitiligo, hypersensitivity angiitis, urticaria, bullous pemphigoid, lupus, erythematosus, systemic lupus erythematosus, pemphigus vulgaris, pemphigus foliaceus, paraneoplastic pemphigus, epidermolysis bullosa acquisita, acne vulgaris, hidradenitis suppurativa, Sweet Syndrome, pyoderma gangrenosum, allergic conditions of the skin, acute and chronic gout, chronic gouty arthritis, psoriasis, psoriatic arthritis, rheumatoid arthritis, juvenile rheumatoid arthritis, cryopyrin associated periodic syndrome, adult onset Still's disease, macrophage activation syndrome, primary and secondary hemophagocytic lymphohistiocytosis, familial Mediterranean fever, NLRP12 autoinflammatory syndrome.

29. A compound of claim 1, or a pharmaceutical composition thereof, for use in therapy.