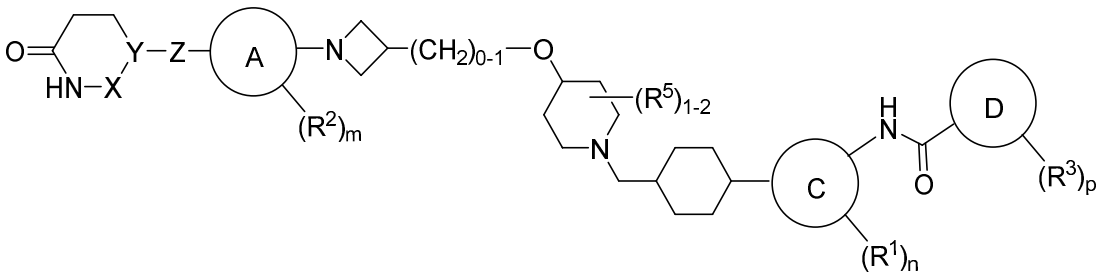
to E3 ubiquitin ligase and subsequent ubiquitination. These drug-like molecules offer the possibility of temporal control over protein expression. Such compounds are capable of inducing the inactivation of a protein of interest upon addition to cells or administration to an animal or human, and could be useful as biochemical reagents and lead to a new paradigm for the treatment of diseases by removing pathogenic or oncogenic proteins (Crews C, Chemistry & Biology, 2010, 17(6):551-555; Schnnekloth JS Jr., Chembiochem, 2005, 6(l):40-46).

[0006] An ongoing need exists in the art for effective treatments for disease, especially inflammatory diseases. However, non-specific effects, and the inability to target and modulate certain classes of proteins altogether, such as regulatory proteins, remain as obstacles to the development of effective therapeutic agents. As such, small molecule therapeutic agents that leverage E3 ligase mediated protein degradation to target 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

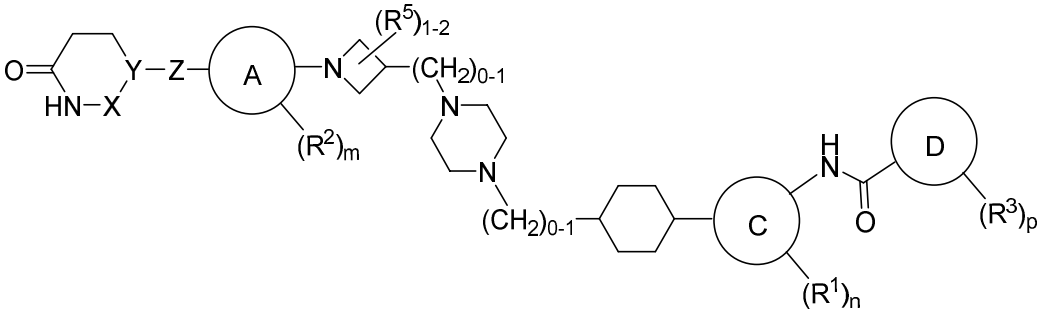
[0007] The present application relates novel bifunctional compounds, which function to recruit IRAK kinases to E3 ubiquitin ligase for degradation, and methods of preparation and uses thereof. In particular, the present disclosure provides bifunctional compounds, which find utility as modulators of targeted ubiquitination of IRAK kinases, which are then degraded and/or otherwise inhibited by the bifunctional compounds as described herein. 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 or an inflammatory disorder.

[0008] It has now been found that compounds of this present disclosure, and pharmaceutically acceptable compositions thereof, are effective for the modulation of targeted ubiquitination. Such compounds have the formula **I-a** to **I-i**:

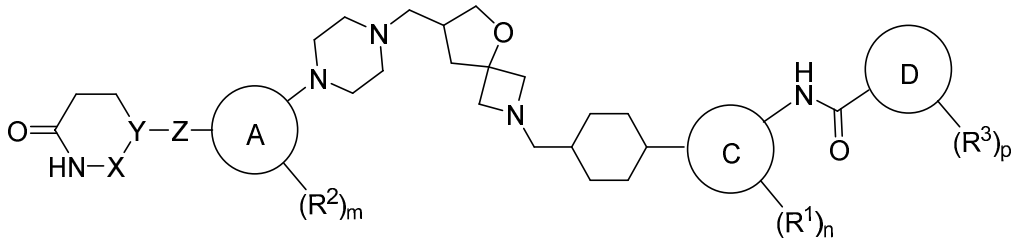


I-a

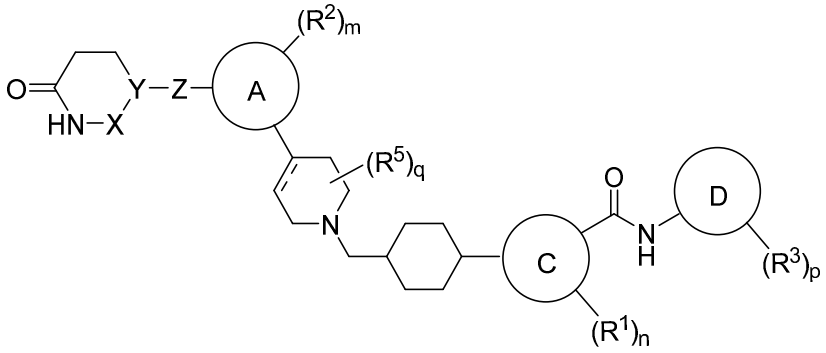
I-f



I-g



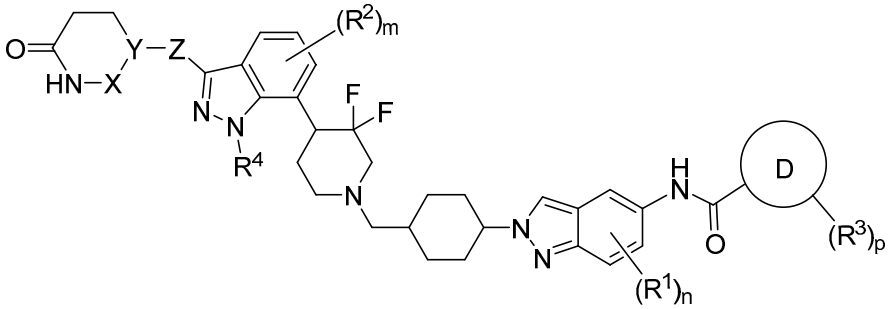
I-h



I-i

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

[0008a] In a first aspect of the present disclosure, there is provided a compound of formula:



I-f-11

or a pharmaceutically acceptable salt thereof, wherein:

X is a bivalent moiety selected from $-CH_2-$ or $-C(O)-$;

Y is a nitrogen or CH;

Z is covalent bond, $-CR_2-$, -CONR-, -NR-, or -O-;

R^4 is hydrogen, C_{1-5} alkyl, or C_{3-6} cycloalkyl;

each of R^1, R^2, and R^3 is independently hydrogen, R^A, halogen, -CN, $-NO_2$, oxo, -OR, -SR, $-NR_2$, $-SiR_3$, $-S(O)_2R$, $-S(O)_2NR_2$, -S(O)R, -C(O)R, -C(O)OR, $-C(O)NR_2$, -C(O)N(R)OR, $-CR_2N(R)C(O)R$, $-CR_2N(R)C(O)NR_2$, $-CFR_2$, $-CF_2R$, $-CF_3$, $-CR_2(OR)$, $-CR_2(NR_2)$, $-OC(O)R$, $-OC(O)NR_2$, $-OP(O)R_2$, $-OP(O)(OR)_2$, $-OP(O)(OR)NR_2$, $-OP(O)(NR_2)_2$, $-N(R)C(O)OR$, $-N(R)C(O)R$, $-N(R)C(O)NR_2$, $-N(R)S(O)_2R$, $-N(R)P(O)R_2$, $-N(R)P(O)(OR)_2$, $-N(R)P(O)(OR)NR_2$, $-N(R)P(O)(NR_2)_2$, or $-N(R)S(O)_2R$;

each R is independently hydrogen, or 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, or:

two R groups on the same carbon or nitrogen are optionally taken together with their intervening atoms to form a 4-11 membered saturated or partially unsaturated monocyclic, bicyclic, bridged bicyclic, or spirocyclic carbocyclic or heterocyclic ring having 1-3 heteroatoms, in addition to the carbon or nitrogen from which the two R groups are attached, independently selected from nitrogen, oxygen, and sulfur;

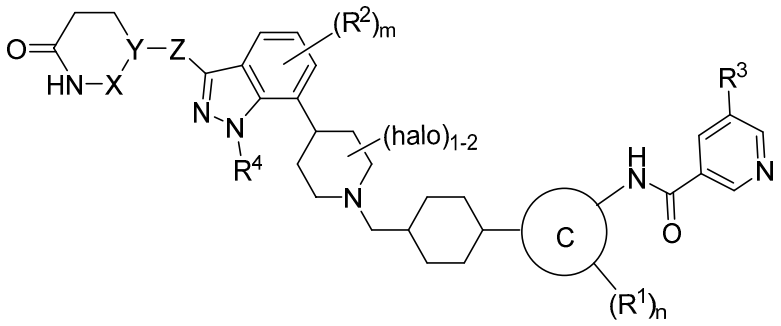
each R^A is independently an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 4-7 membered saturated or partially unsaturated carbocyclic or heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having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

Ring D is selected from phenyl or a 5-9 membered heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; and

each of m and n are independently 0, 1, 2, or 3; and

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

[0008b] In another aspect of the present disclosure, there is provided a compound of formula:



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or a pharmaceutically acceptable salt thereof, wherein:

X is a bivalent moiety selected from -CH_2-or -C(O)-;

Y is a nitrogen or CH;

Z is covalent bond, -CR_2-, -CONR-, -NR-, or -O-;

R^4 is hydrogen, C_{1-5} alkyl, or C_{3-6} cycloalkyl;

each of R^1, R^2, and R^3 is independently hydrogen, R^A, halogen, -CN, -NO_2, -OR, -SR, -NR_2, -SiR_3, -$S(O)_2R$, -$S(O)_2NR_2$, -S(O)R, -C(O)R, -C(O)OR, -$C(O)NR_2$, -C(O)N(R)OR, -$C(R)_2N(R)C(O)R$, -$C(R)_2N(R)C(O)NR_2$, -CFR_2, -CF_2R, -CF_3, -$CR_2(OR)$, -$CR_2(NR_2)$, -OC(O)R, -$OC(O)NR_2$, -$OP(O)R_2$, -$OP(O)(OR)_2$, -$OP(O)(OR)NR_2$, -$OP(O)(NR_2)_2$, -N(R)C(O)OR, -N(R)C(O)R, -$N(R)C(O)NR_2$, -$N(R)S(O)_2R$, -$N(R)P(O)R_2$, -$N(R)P(O)(OR)_2$, -$N(R)P(O)(OR)NR_2$, -$N(R)P(O)(NR_2)_2$, or -$N(R)S(O)_2R$;

each R is independently hydrogen, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 3-7 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 carbon or nitrogen are optionally taken together with their intervening atoms to form a 4-11 membered saturated or partially unsaturated monocyclic, bicyclic, bridged bicyclic, or spirocyclic carbocyclic or heterocyclic ring having 1-3 heteroatoms, in addition to the carbon or nitrogen from which the two R groups are attached, independently selected from nitrogen, oxygen, and sulfur;

each R^A is independently an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 4-7 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;

Ring C is selected from phenyl or a 5-9 membered heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; and

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

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

[0009] 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.

[0010] Compounds provided by this 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.

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

[0010b] In yet another aspect of the present disclosure, there is provided a use of a compound as disclosed herein, or a pharmaceutical composition thereof, in the manufacture of a medicament for degrading IRAK4 protein kinase in a patient or biological sample.

[0010c] In a further aspect of the present disclosure, there is provided a use of a compound as disclosed herein, or a pharmaceutical composition thereof, in the manufacture of a medicament for treating an IRAK4-mediated disorder, disease, or condition in a patient.

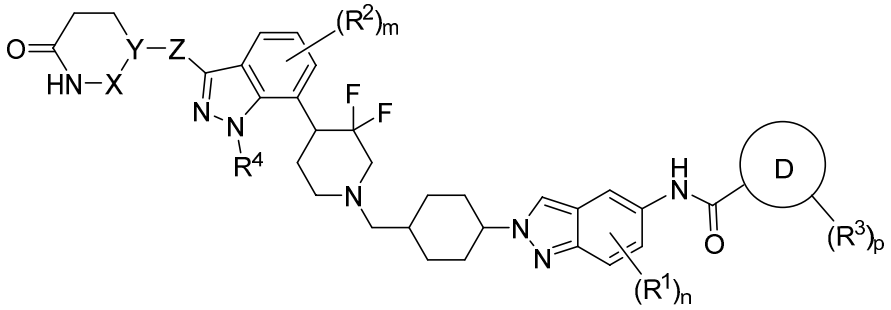
[0010d] In another aspect of the present disclosure, there is provided a use of a compound as disclosed herein, or a pharmaceutical composition thereof, in the manufacture of a medicament for treating an autoimmune disease, an inflammatory disorder, or an immunodeficiency disorder in a patient.

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

DETAILED DESCRIPTION OF CERTAIN EMBODIMENTS

CLAIMS

1. A compound of formula:



I-f-11

or a pharmaceutically acceptable salt thereof, wherein:

X is a bivalent moiety selected from -CH_2-or -C(O)-;

Y is a nitrogen or CH;

Z is covalent bond, -CR_2-, -CONR-, -NR-, or -O-;

R^4 is hydrogen, C_{1-5} alkyl, or C_{3-6} cycloalkyl;

each of R^1, R^2, and R^3 is independently hydrogen, R^A, halogen, -CN, -NO_2, oxo, -OR, -SR, -NR_2, -SiR_3, -$S(O)_2R$, -$S(O)_2NR_2$, -S(O)R, -C(O)R, -C(O)OR, -$C(O)NR_2$, -C(O)N(R)OR, -$CR_2N(R)C(O)R$, -$CR_2N(R)C(O)NR_2$, -CFR_2, -CF_2R, -CF_3, -$CR_2(OR)$, -$CR_2(NR_2)$, -OC(O)R, -$OC(O)NR_2$, -$OP(O)R_2$, -$OP(O)(OR)_2$, -$OP(O)(OR)NR_2$, -$OP(O)(NR_2)_2$, -N(R)C(O)OR, -N(R)C(O)R, -$N(R)C(O)NR_2$, -$N(R)S(O)_2R$, -$N(R)P(O)R_2$, -$N(R)P(O)(OR)_2$, -$N(R)P(O)(OR)NR_2$, -$N(R)P(O)(NR_2)_2$, or -$N(R)S(O)_2R$;

each R is independently hydrogen, or 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, or:

two R groups on the same carbon or nitrogen are optionally taken together with their intervening atoms to form a 4-11 membered saturated or partially unsaturated monocyclic, bicyclic, bridged bicyclic, or spirocyclic carbocyclic or heterocyclic ring having 1-3 heteroatoms, in addition to the carbon or nitrogen from which the two R groups are attached, independently selected from nitrogen, oxygen, and sulfur;

each R^A is independently an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 4-7 membered saturated or partially unsaturated carbocyclic or heterocyclic ring having 1-2

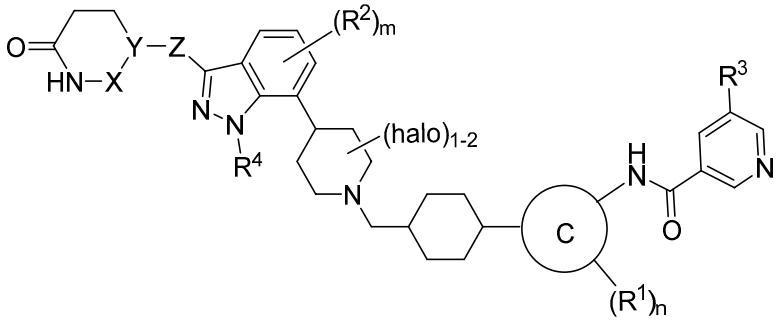
heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

Ring D is selected from phenyl or a 5-9 membered heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; and

each of m and n are independently 0, 1, 2, or 3; and

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

2. A compound of formula:



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or a pharmaceutically acceptable salt thereof, wherein:

X is a bivalent moiety selected from -CH_2-or -C(O)-;

Y is a nitrogen or CH;

Z is covalent bond, -CR_2-, -CONR-, -NR-, or -O-;

R^4 is hydrogen, C_{1-5} alkyl, or C_{3-6} cycloalkyl;

each of R^1, R^2, and R^3 is independently hydrogen, R^A, halogen, -CN, -NO_2, -OR, -SR, -NR_2, -SiR_3, -$S(O)_2R$, -$S(O)_2NR_2$, -S(O)R, -C(O)R, -C(O)OR, -$C(O)NR_2$, -C(O)N(R)OR, -$C(R)_2N(R)C(O)R$, -$C(R)_2N(R)C(O)NR_2$, -CFR_2, -CF_2R, -CF_3, -$CR_2(OR)$, -$CR_2(NR_2)$, -OC(O)R, -$OC(O)NR_2$, -$OP(O)R_2$, -$OP(O)(OR)_2$, -$OP(O)(OR)NR_2$, -$OP(O)(NR_2)_2$, -N(R)C(O)OR, -N(R)C(O)R, -$N(R)C(O)NR_2$, -$N(R)S(O)_2R$, -$N(R)P(O)R_2$, -$N(R)P(O)(OR)_2$, -$N(R)P(O)(OR)NR_2$, -$N(R)P(O)(NR_2)_2$, or -$N(R)S(O)_2R$;

each R is independently hydrogen, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 3-7 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 carbon or nitrogen are optionally taken together with their intervening atoms to form a 4-11 membered saturated or partially unsaturated monocyclic, bicyclic,

bridged bicyclic, or spirocyclic carbocyclic or heterocyclic ring having 1-3 heteroatoms, in addition to the carbon or nitrogen from which the two R groups are attached, independently selected from nitrogen, oxygen, and sulfur;

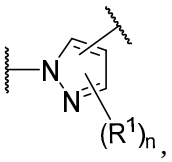
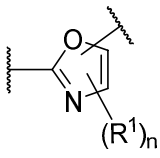
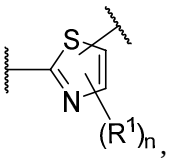
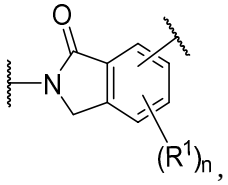
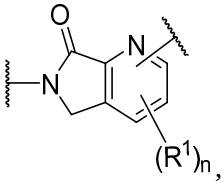
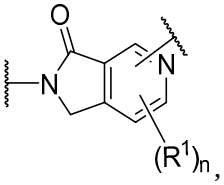
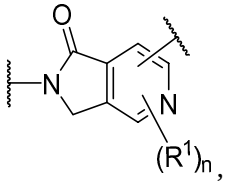
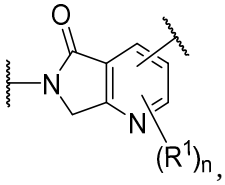
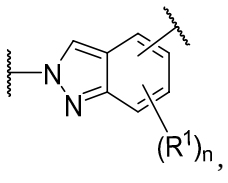
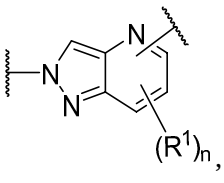
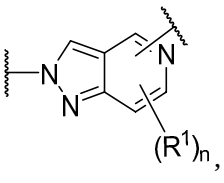
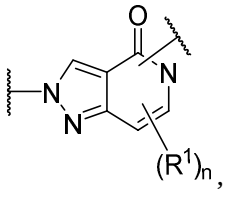
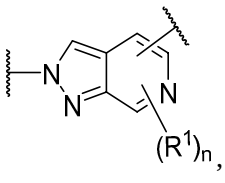
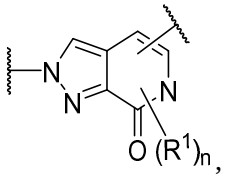
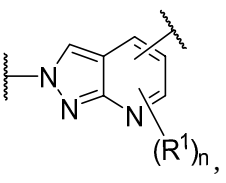
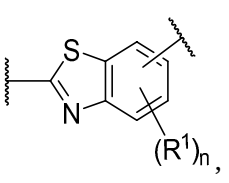
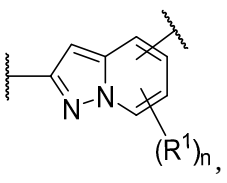
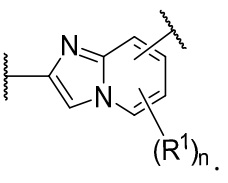
each R^A is independently an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 4-7 membered saturated or partially unsaturated carbocyclic or heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having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

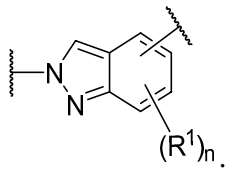
Ring C is selected from phenyl or a 5-9 membered heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; and

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

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

3. The compound of claim 2, wherein Ring C is a 5-9 membered heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

4. The compound of claim 3, wherein Ring C is , , , , , , , , , , , , , , , , , or .

5. The compound of claim 4, wherein Ring C is .

6. The compound of claim 1, wherein Ring D is phenyl, pyridyl, pyrazinyl, pyrazolo[1,5-a]pyrimidinyl, or pyrrolo[1,2-a]pyrimidine.

7. The compound of claim 6, wherein Ring D is pyridyl or pyrazinyl.

8. The compound of any one of claims 1-7, wherein n is 1 and R^1 is hydrogen, R^A, halogen, -CN, -OR, -SR, $-NR_2$, $-S(O)_2R$, $-S(O)_2NR_2$, -S(O)R, $-CFR_2$, $-CF_2R$, $-CF_3$, $-CR_2(OR)$, $-CR_2(NR_2)$, -C(O)R, -C(O)OR, $-C(O)NR_2$, $-C(S)NR_2$, -C(O)N(R)OR, -OC(O)R, or $-OC(O)NR_2$.

9. The compound of any one of claims 1-8, wherein n is 1 and R^1 is -OR or $-CR_2(OR)$.

10. The compound of any one of claims 1-9, wherein m is 1 and R^2 is hydrogen, R^A, halogen, -CN, -OR, -SR, $-NR_2$, $-S(O)_2R$, $-S(O)_2NR_2$, -S(O)R, $-CFR_2$, $-CF_2R$, $-CF_3$, $-CR_2(OR)$, $-CR_2(NR_2)$, -C(O)R, -C(O)OR, $-C(O)NR_2$, $-C(S)NR_2$, -C(O)N(R)OR, -OC(O)R, or $-OC(O)NR_2$.

11. The compound of any one of claims 1-10, wherein m is 1 and R^2 is hydrogen.

12. The compound of any one of claims 1-11, wherein R^3 is hydrogen, R^A, halogen, -CN, -OR, -SR, $-NR_2$, $-S(O)_2R$, $-S(O)_2NR_2$, -S(O)R, $-CFR_2$, $-CF_2R$, $-CF_3$, $-CR_2(OR)$, $-CR_2(NR_2)$, -C(O)R, -C(O)OR, $-C(O)NR_2$, $-C(S)NR_2$, -C(O)N(R)OR, -OC(O)R, or $-OC(O)NR_2$.

13. The compound of any one of claims 1-12, wherein R^3 is -CN or $-CF_3$.

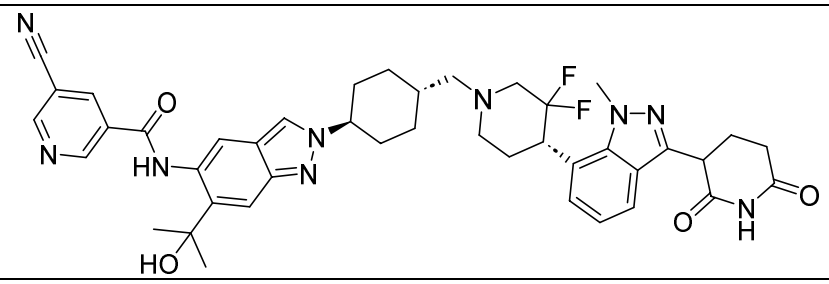
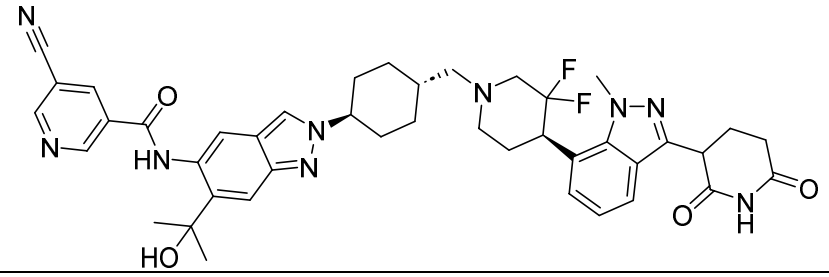
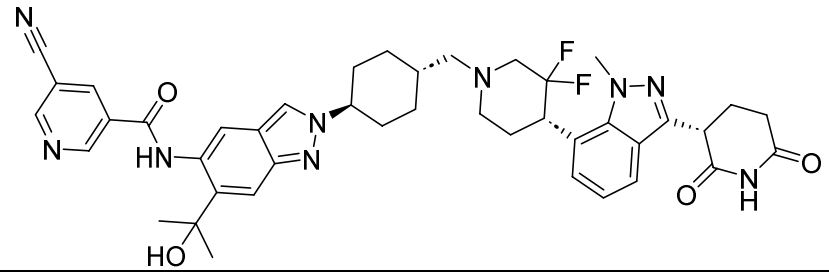
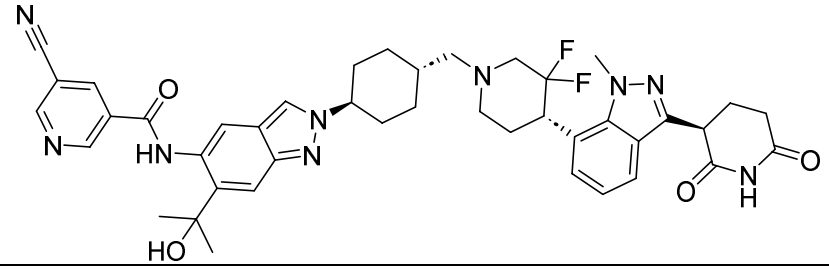
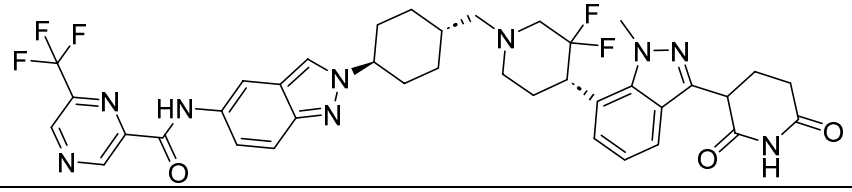
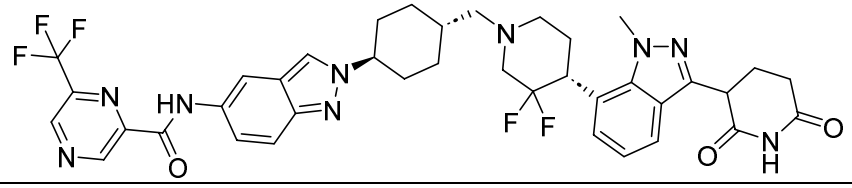
14. The compound of any one of claims 1-13, wherein R^4 is C_{1-5} alkyl.

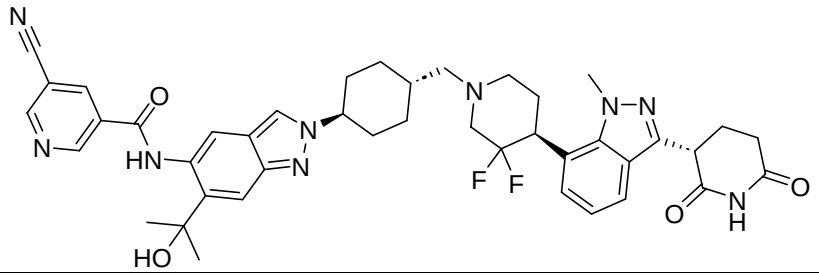
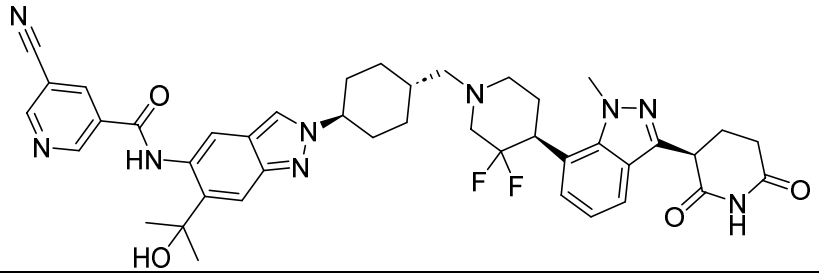
15. The compound of any one of claims 1-14, wherein X is -C(O)-.

16. The compound of any one of claims 1-15, wherein Y is CH.

17. The compound of any one of claims 1-16, wherein Z is a covalent bond.

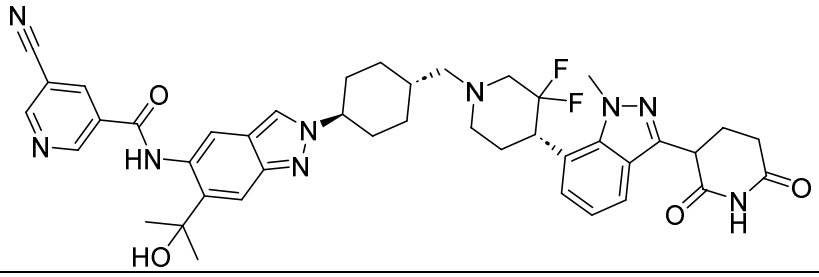
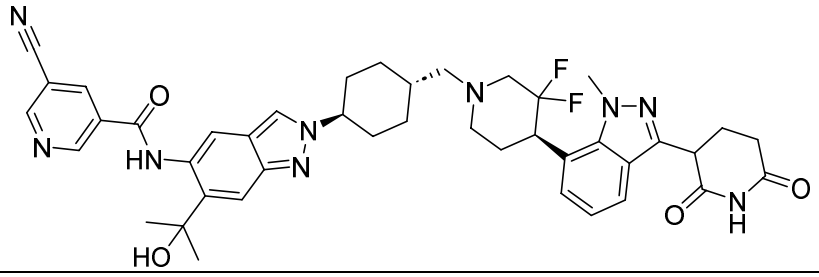
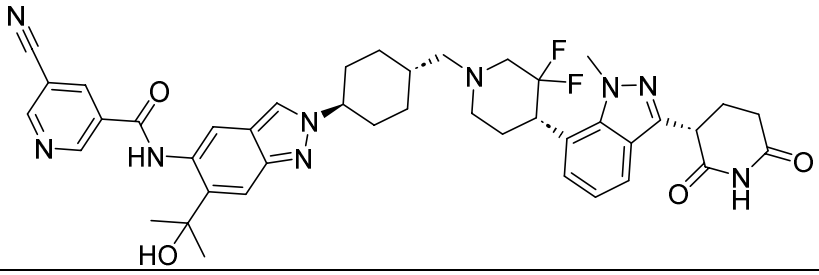
18. The compound of claim 1, wherein said compound is:

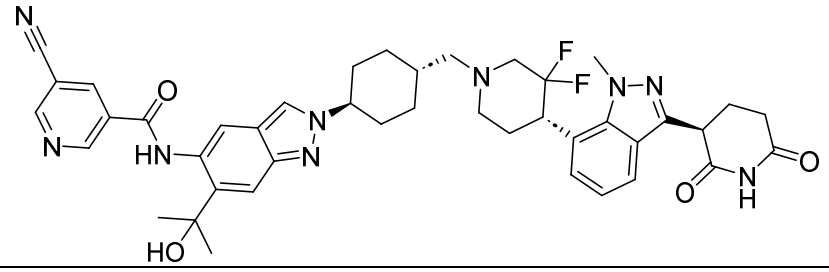
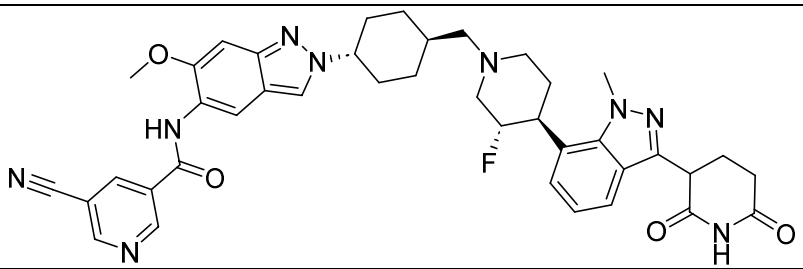
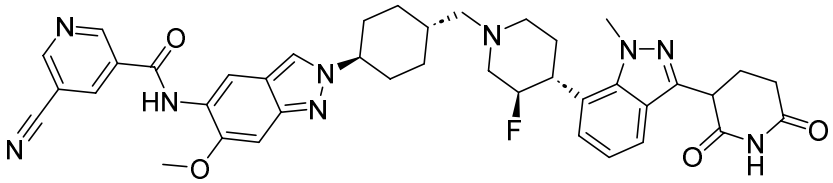
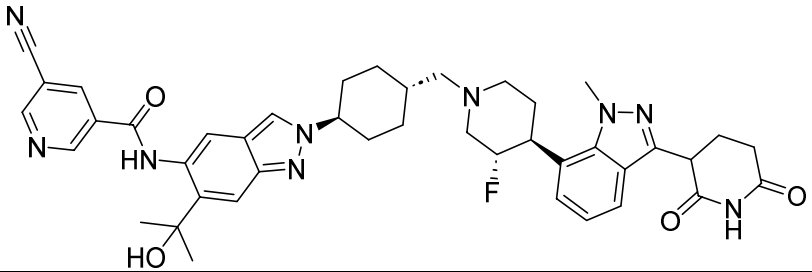
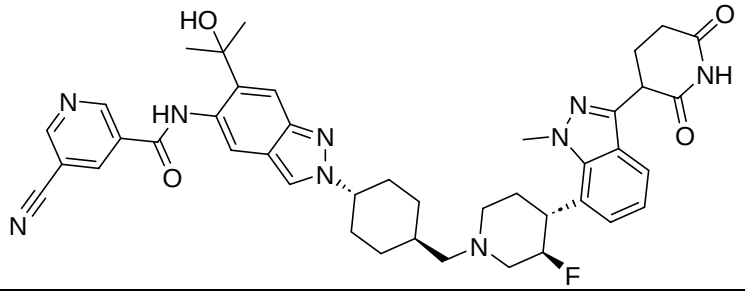
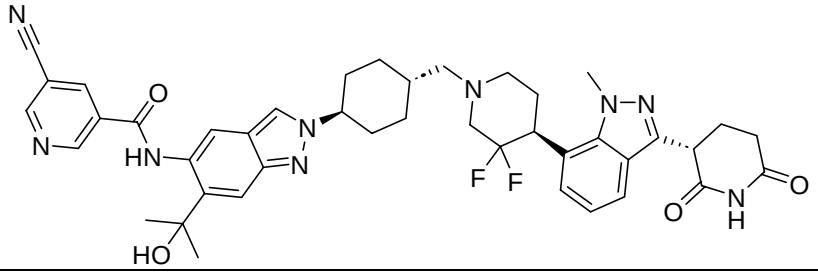
I-222	
I-223	
I-230	
I-231	
I-379	
I-380	

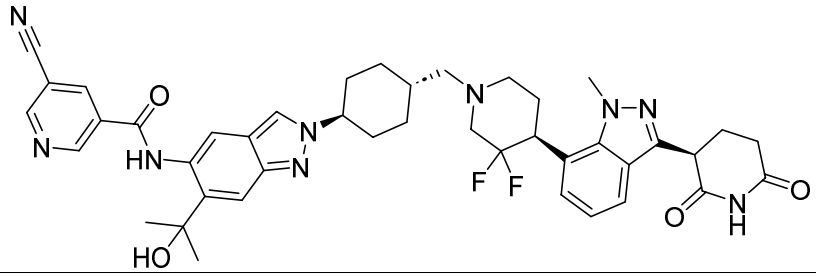
I-416	
I-417	

or a pharmaceutically acceptable salt thereof.

19. The compound of claim 2, wherein said compound is:

I-222	
I-223	
I-230	

I-231	
I-263	
I-264	
I-362	
I-363	
I-416	

I-417	

or a pharmaceutically acceptable salt thereof.

20. A pharmaceutical composition comprising a compound of any one of claims 1-19, and a pharmaceutically acceptable carrier, adjuvant, or vehicle.

21. Use of a compound of any one of claims 1-19, or a pharmaceutical composition thereof, in the manufacture of a medicament for degrading IRAK4 protein kinase in a patient or biological sample.

22. Use of a compound of any one of claims 1-19, or a pharmaceutical composition thereof, in the manufacture of a medicament for treating an IRAK4-mediated disorder, disease, or condition in a patient.

23. Use of a compound of any one of claims 1-19, 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.

24. The use of claim 23, wherein the disease or disorder is systemic lupus erythematosus, rheumatoid 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, Sjogren's syndrome, vernal keratoconjunctivitis, interstitial lung fibrosis, psoriatic arthritis, systemic juvenile idiopathic arthritis, nephritis, diverticulitis, interstitial cystitis, glomerulonephritis, 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, acute lung injury, acute respiratory distress syndrome, eosinophilia, hypersensitivities, anaphylaxis, nasal sinusitis, silica induced diseases, COPD, 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 multiforma, 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.

25. The use of claim 23, 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, Loffler'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, or NLRP12 autoinflammatory syndrome.

26. A compound of any one of claims 1-19, or a pharmaceutical composition thereof, for use in therapy.