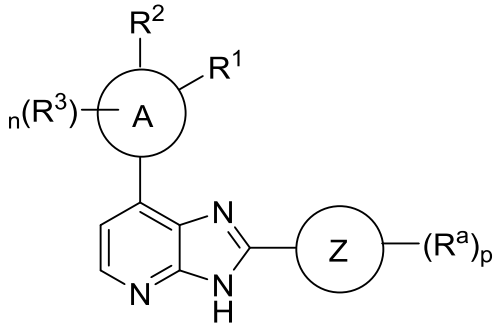
CLAIMS

We claim:

1. A compound of formula **I**,



I

or a tautomer, or a pharmaceutically acceptable salt thereof, wherein:

Ring A is a phenyl or pyridine;

R^1 is H, halo, $(C(R^5)(R^5))_mNR_2$, $N(R^4)C(O)R$, $N(R^4)C(O)NR_2$, $N(R^4)CO_2R$, $N(R^4)S(O)_2R$, $N(R^4)S(O)R$, $N(R^4)(R^4)$, 3-7 membered heterocyclic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, optionally substituted with one or more of C_1-C_6 alkyl, C_5-C_6 aryl, 5-6 membered heteroaryl, or halo, or R^1 is 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, optionally substituted with aryl; or R^1 is absent;

R^2 is H, $(C(R^5)(R^5))_mOR^4$, $(C(R^5)(R^5))_mN(R^4)COR$, $(C(R^5)(R^5))_mN(R^4)C(O)C(O)NR_2$, or $(C(R^5)(R^5))_mN(R^4)(R^4)$; or R^2 is absent;

or R^1 and R^2 together with the atoms to which they are connected, form a fused 3-7 membered ring which is optionally substituted with C_1-C_6 alkyl or C(O)R;

wherein R^1 and R^2 are both not H; and wherein R^1 and R^2 are both not absent;

each R^3 is independently halogen, C_{1-6} aliphatic, C_{5-10} aryl, a 3-8 membered saturated or partially unsaturated carbocyclic ring, a 3-7 membered heterocyclic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; each of which is optionally substituted;

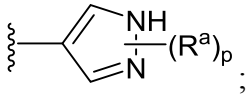
each R^4 is independently -R, $-SO_2R$, -SOR, -C(O)R, $-CO_2R$, or $-C(O)N(R)_2$;

each R^5 is independently -R, halogen, -OR, –SR, –CN, $–NO_2$, $-SO_2R$, -SOR, -C(O)R, $-CO_2R$, $-C(O)N(R)_2$, $-NRC(O)R$, $-NRC(O)N(R)_2$, $-NRSO_2R$, or $–N(R)_2$;

each R is independently hydrogen, $C_{1–6}$ aliphatic, $C_{5–10}$ aryl, a 3-8 membered saturated or partially unsaturated carbocyclic ring, a 3-7 membered heterocyclic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; each of which is optionally substituted; or

two R groups on the same atom are taken together with the atom to which they are attached to form a $C_{5–10}$ aryl, a 3-8 membered saturated or partially unsaturated carbocyclic ring, a 3-7 membered heterocyclic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 10-15 membered fused aryl ring; a 6-15 membered saturated or partially unsaturated fused carbocyclic ring; a 10-15 membered fused heteroaryl ring; or a 6-15 membered saturated or partially unsaturated fused heterocyclic ring; each of which is optionally substituted;

Ring Z is



;

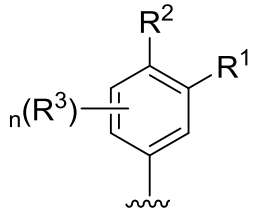
each R^a is independently -R, halogen, -OR, –SR, –CN, $–NO_2$, $-SO_2R$, -SOR, -C(O)R, $-CO_2R$, $-C(O)N(R)_2$, $-NRC(O)R$, $-NRC(O)N(R)_2$, $-NRSO_2R$, or $–N(R)_2$;

m is 1, 2, or 3;

n is 0, 1, or 2; and

p is 0, 1, 2, or 3.

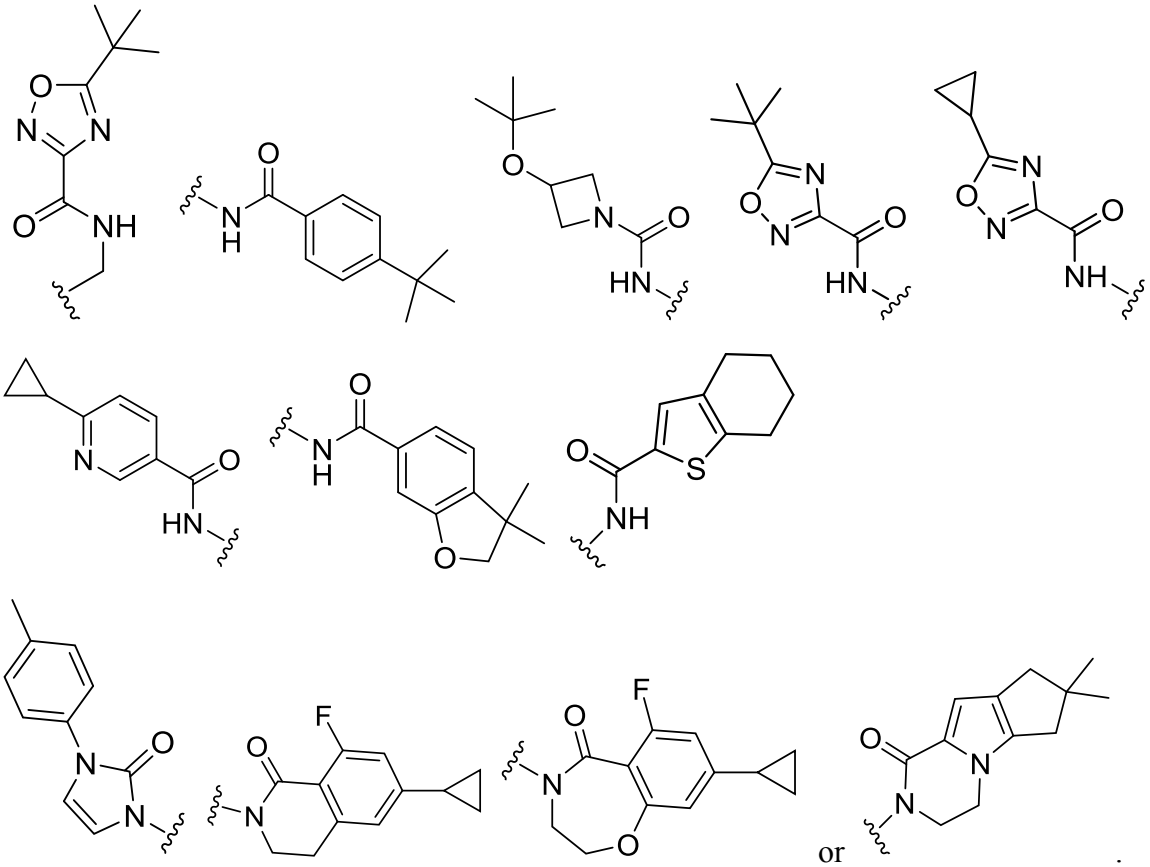
2. The compound of claim 1, wherein Ring A is



.

3. The compound of claim 1, wherein R^1 is H, F, $(C(R^5)(R^5))_mNR_2$, $N(R^4)C(O)R$, $N(R^4)C(O)NR_2$, $N(R^4)(R^4)$, optionally substituted 3-7 membered heterocyclic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

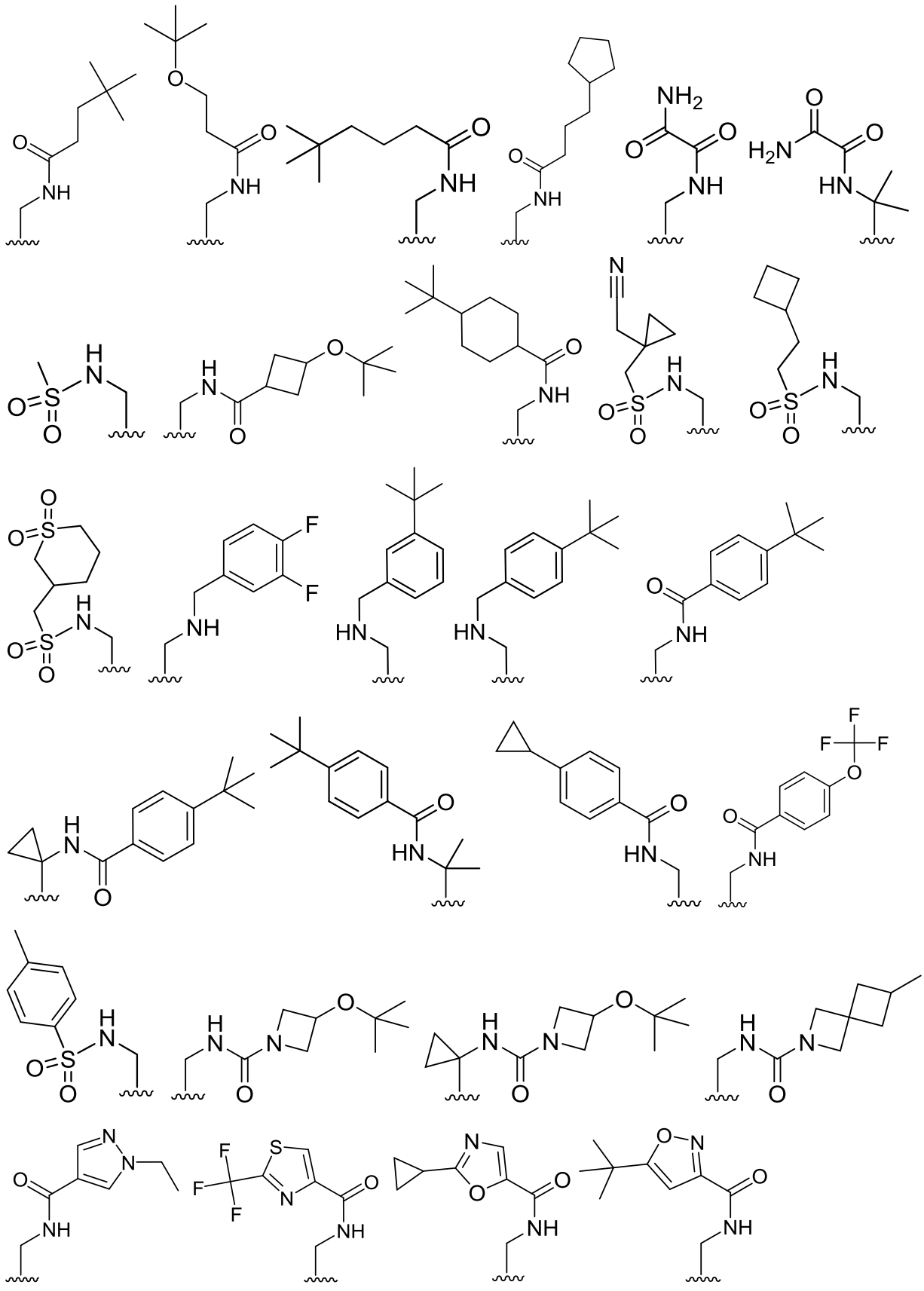
4. The compound of any preceding claim, wherein R^1 is

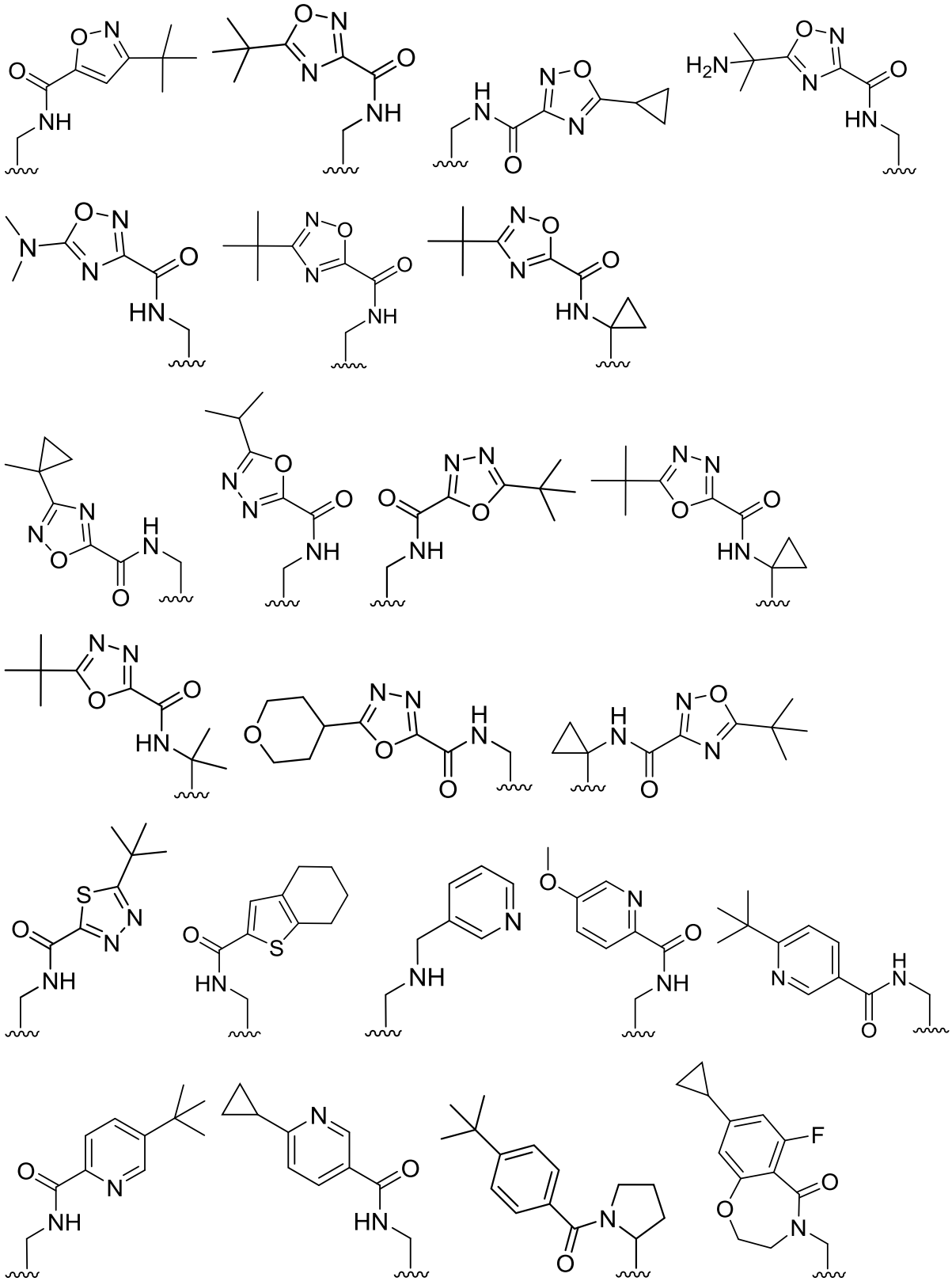


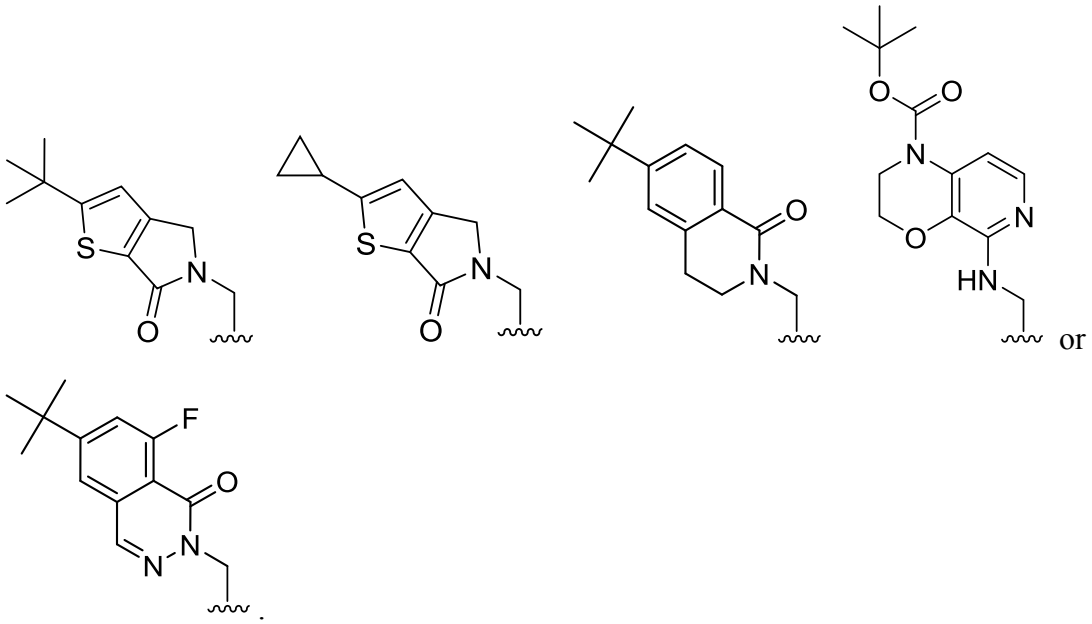
5. The compound of claim 1, wherein R^1 is absent.

6. The compound of claim 1, wherein R^2 is H or R^2 is $(C(R^5)(R^5))_mOR^4$, $(C(R^5)(R^5))_mN(R^4)COR$, $(C(R^5)(R^5))_mN(R^4)C(O)C(O)NR_2$, OR $(C(R^5)(R^5))_mN(R^4)(R^4)$.

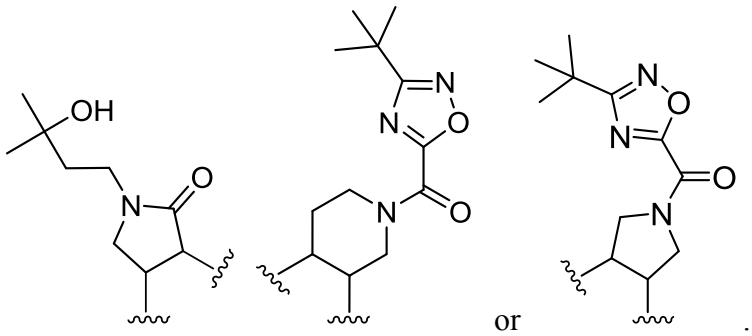
7. The compound of claim 1, wherein R^2 is $–CH_2OH$, $–CH_2NH_2$,







8. The compound of any preceding claim, wherein R^1 and R^2 together form



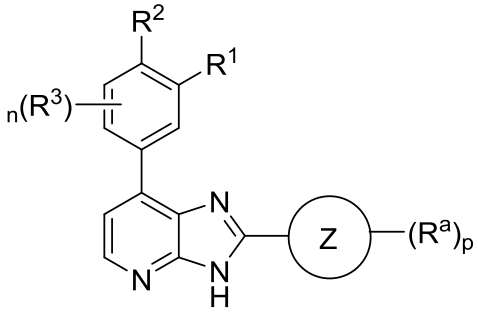
or .

9. The compound of claim 1, wherein each R^3 is independently F, Cl, Br, I, methyl, ethyl, ethyl, propyl, i-propyl, butyl, s-butyl, t-butyl, straight or branched pentyl, or straight or branched hexyl; each of which is optionally substituted.

10. The compound of claim 1, wherein each R^3 is independently is cyclopropyl, phenyl, furanyl, furazanyl, imidazolidinyl, imidazolinyl, imidazolyl, 1H-indazolyl, indolenyl, indolinyl, indolizinyl, indolyl, 3*H*-indolyl, isoindolinyl, isoindolenyl, isoindazolyl, isoindolinyl, isoindolyl, isoquinolinyl, isothiazolyl, isoxazolyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl;- 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidinyl, oxazolyl, oxazolidinyl, piperidine-one, pyrimidinyl,

purinyl, pyranyl, pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pyridooxazole, pyridoimidazole, pyridothiazole, pyridinyl, pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolinyl, 2*H*-pyrrolyl, pyrrolyl, tetrahydropyridine, tetrahydropyran, thiazolyl, thienyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thiophenyl, triazinyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, or 1,3,4-triazolyl; each of which is optionally substituted.

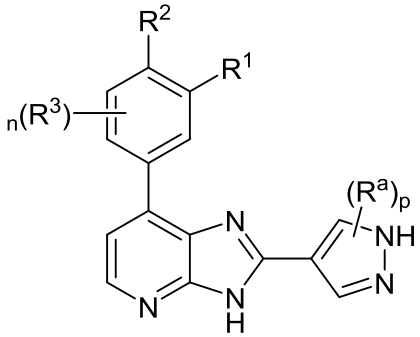
11. The compound of claim 1, of formula **II**,



II;

or a tautomer, or a pharmaceutically acceptable salt thereof.

12. The compound of claim 1, of formula **II-c**,

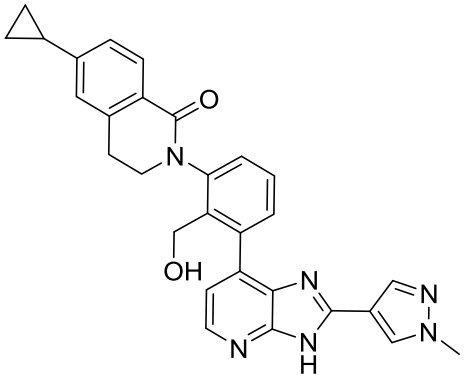


II-c;

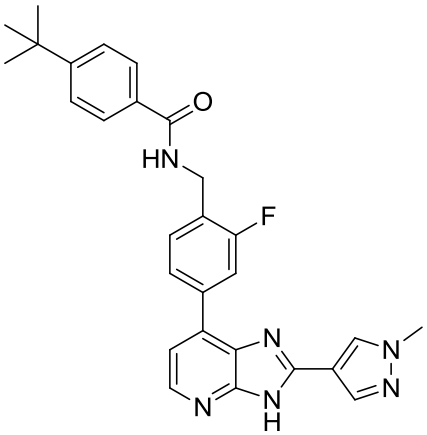
or a tautomer, or a pharmaceutically acceptable salt thereof.

13. The compound of claim 1, selected from Table 1:

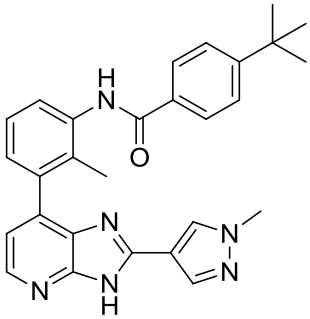
Table 1



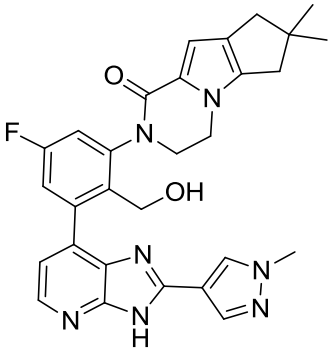
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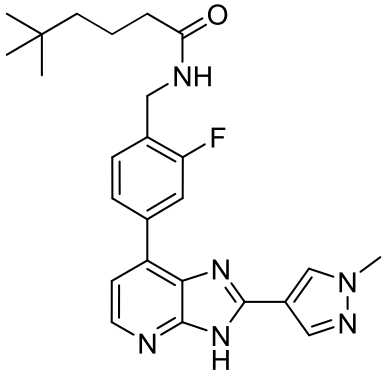
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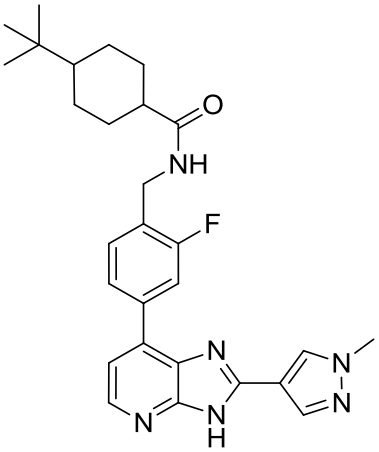
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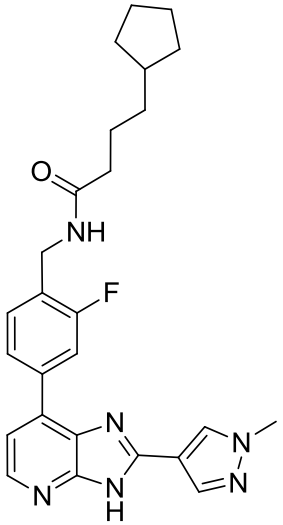
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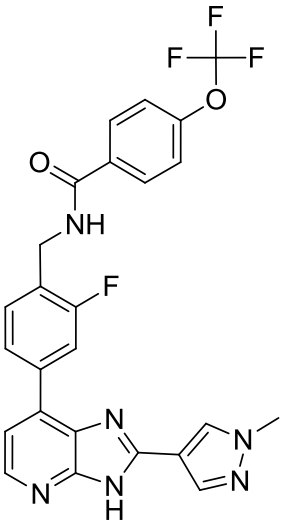
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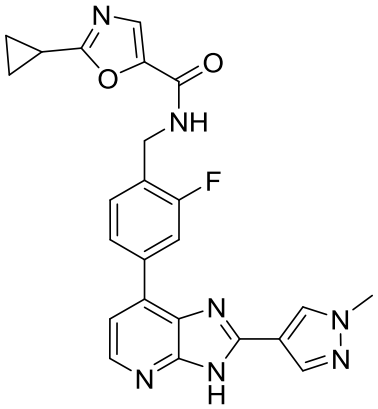
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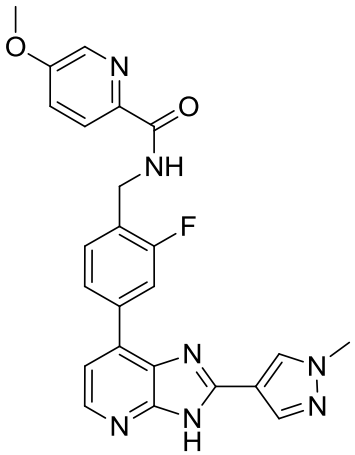
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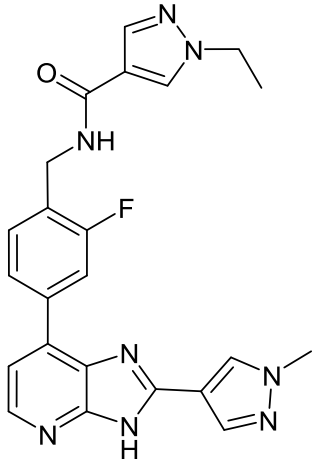
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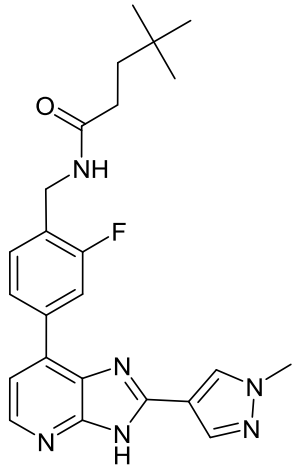
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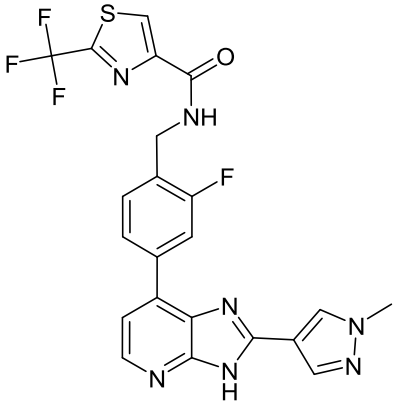
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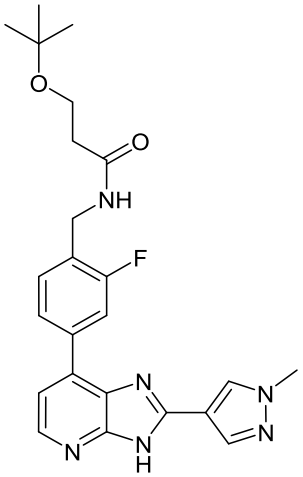
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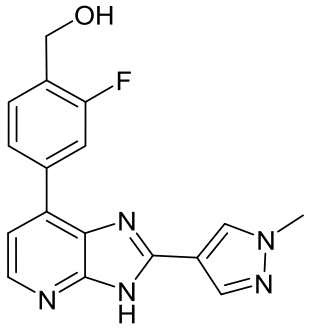
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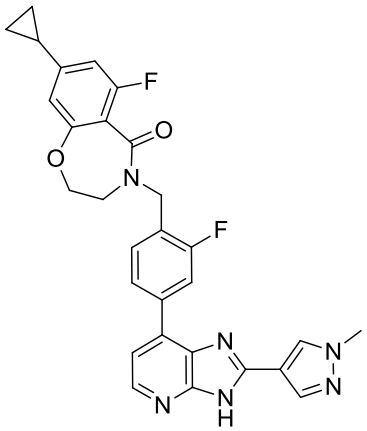
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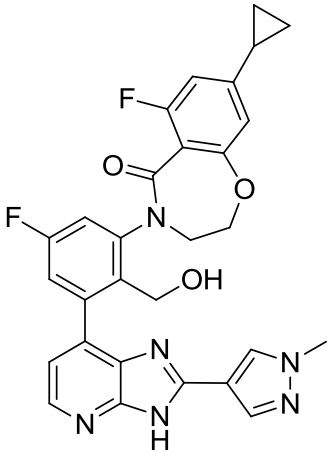
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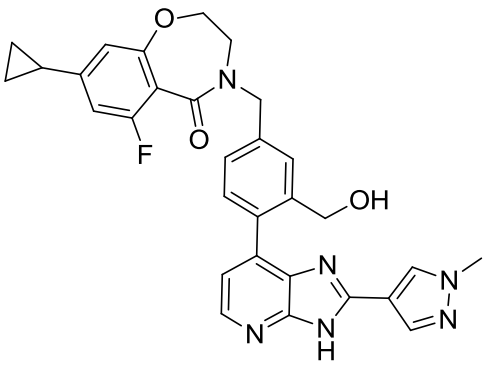
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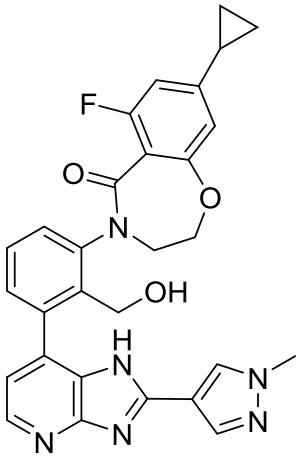
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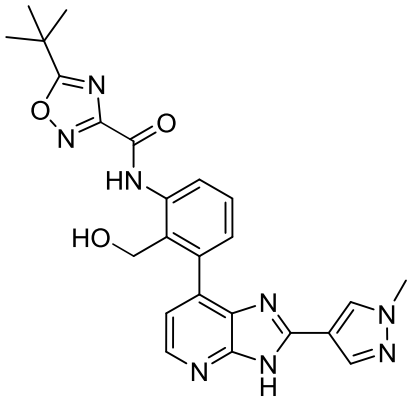
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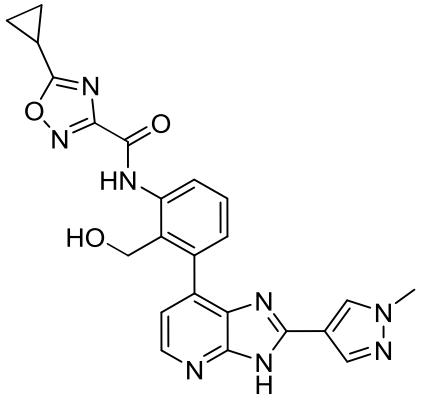
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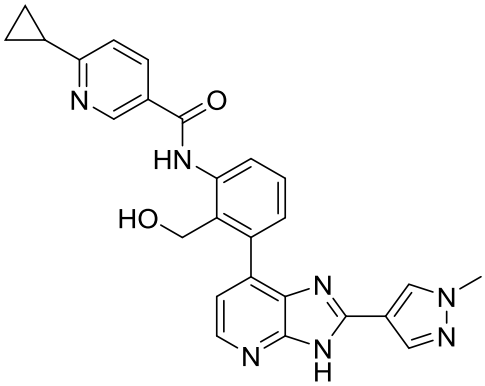
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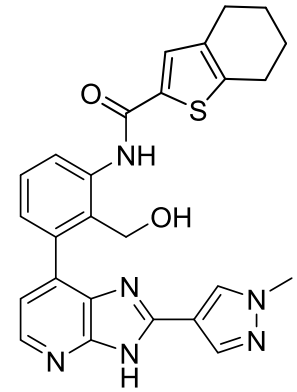
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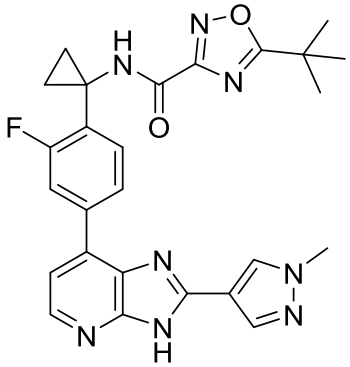
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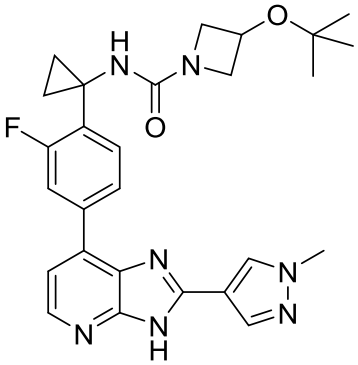
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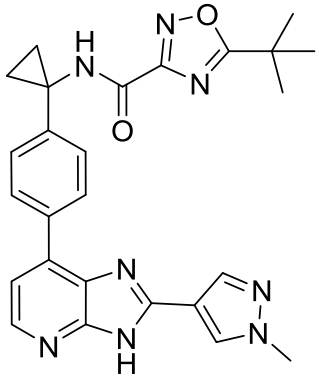
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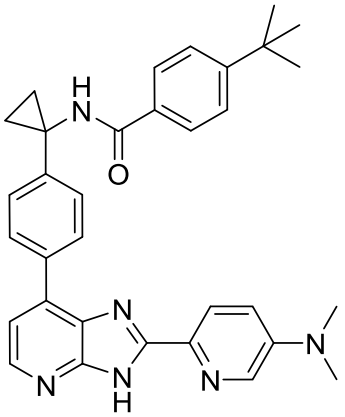
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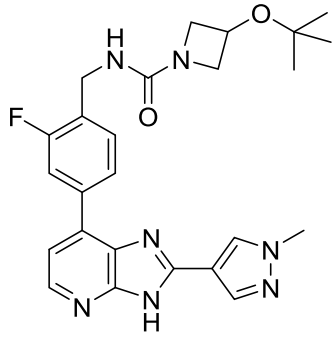
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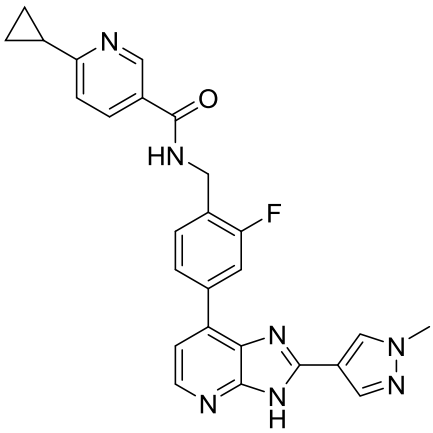
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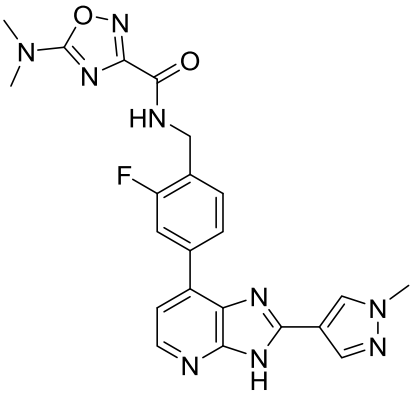
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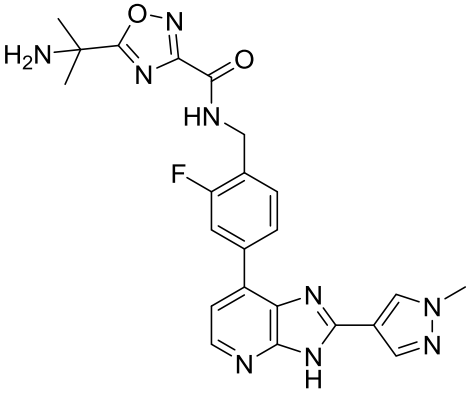
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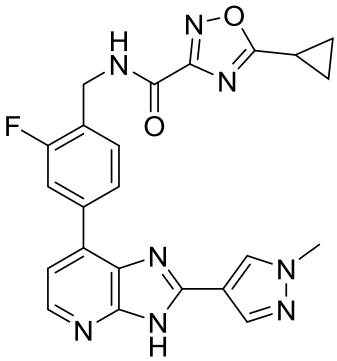
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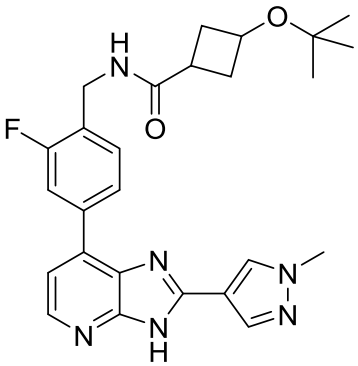
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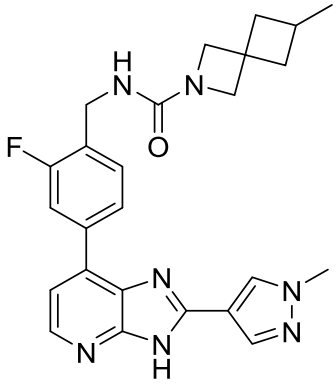
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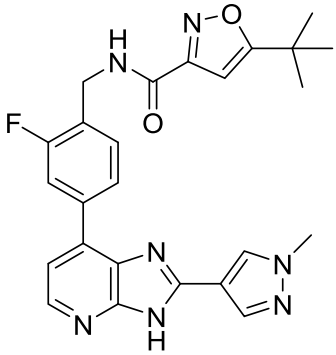
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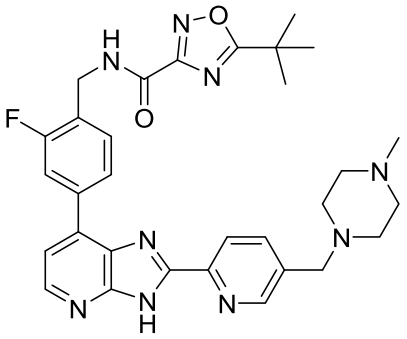


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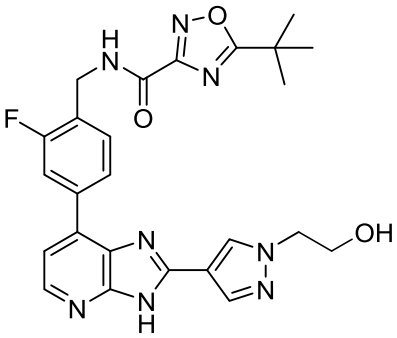


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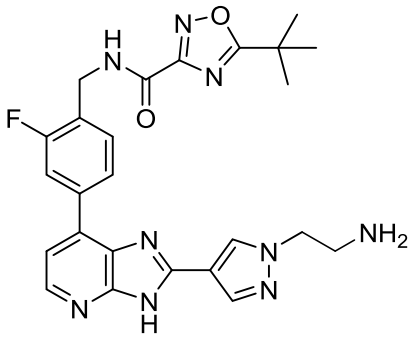


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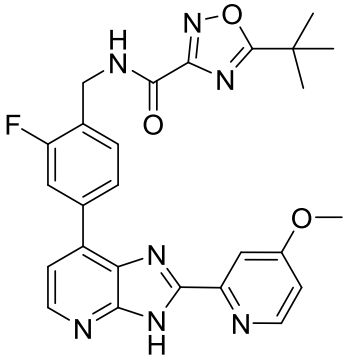


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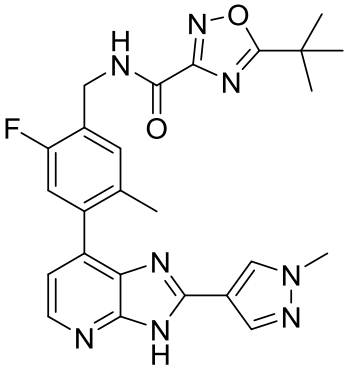
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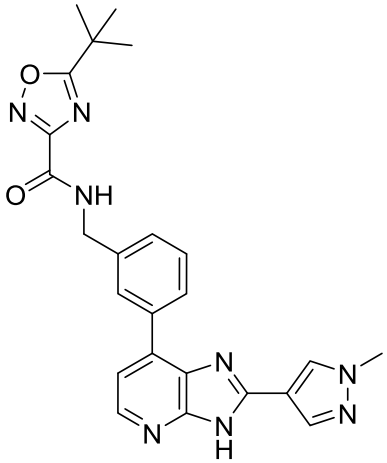
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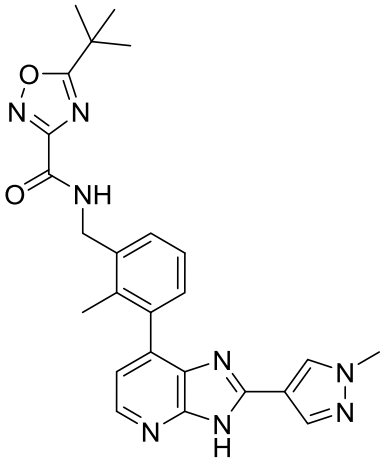


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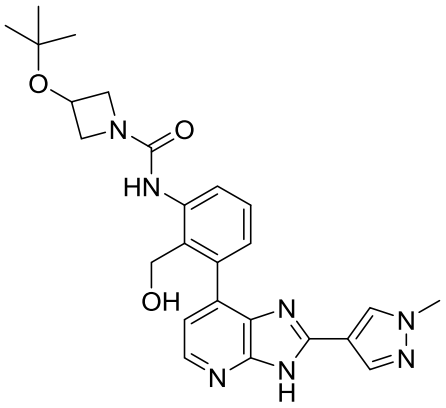


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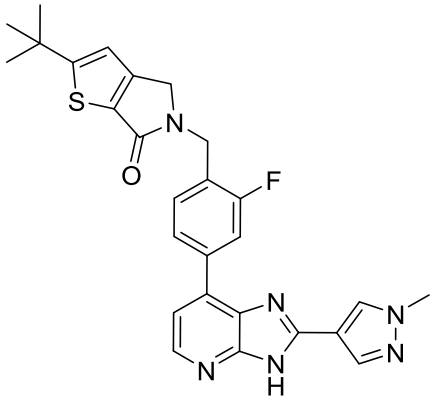




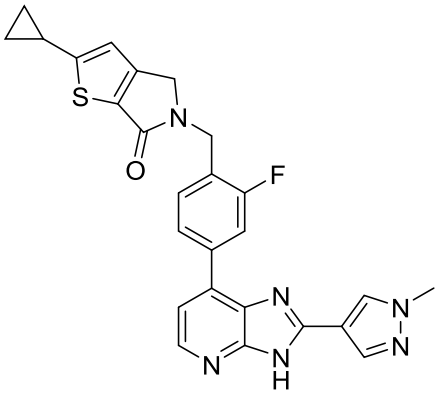
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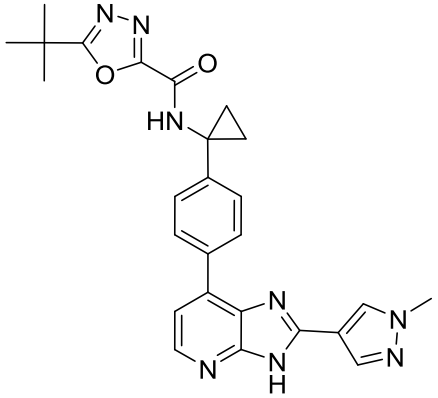
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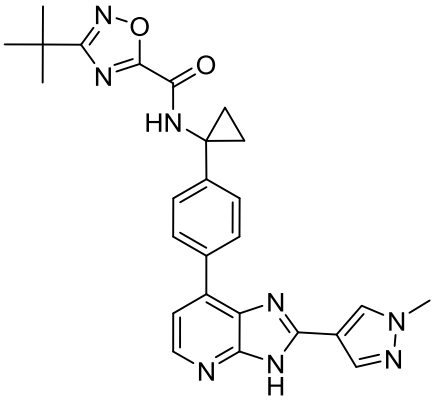


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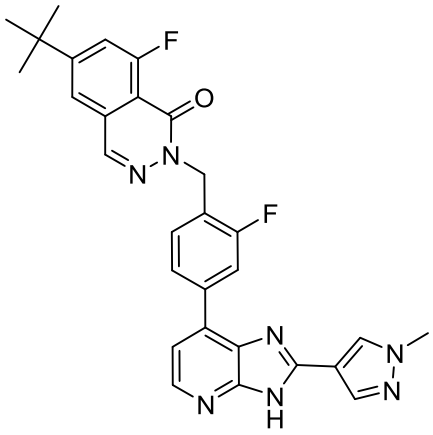


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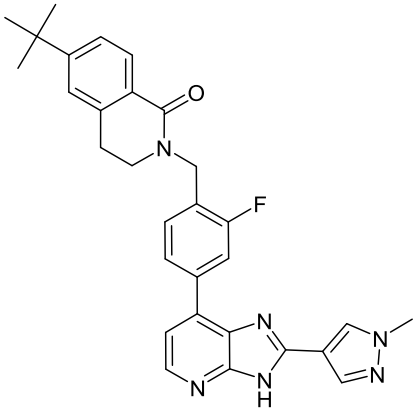
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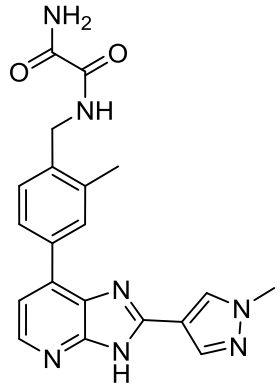
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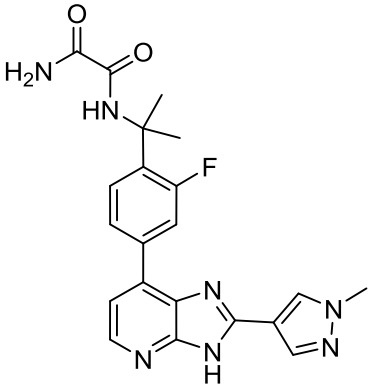
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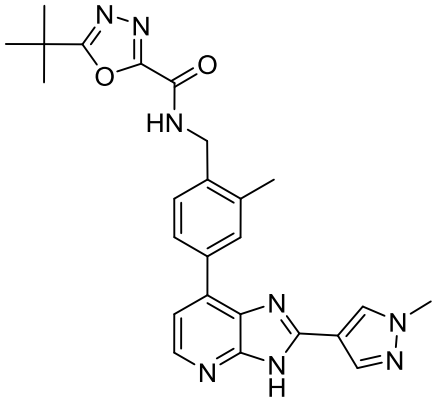
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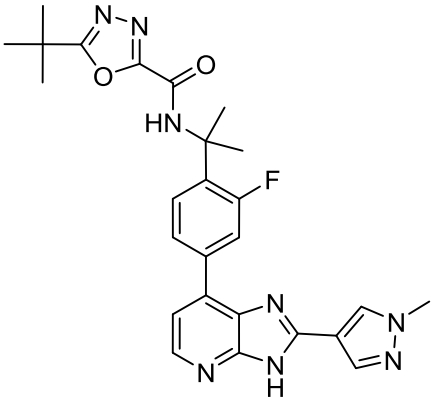
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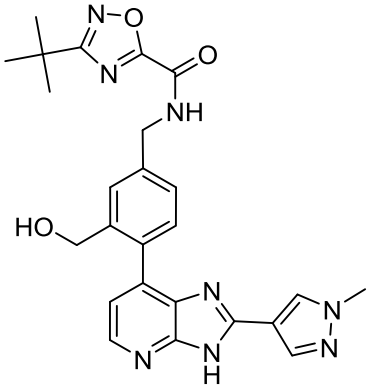
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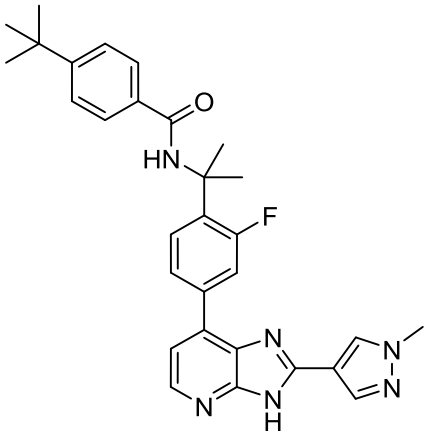
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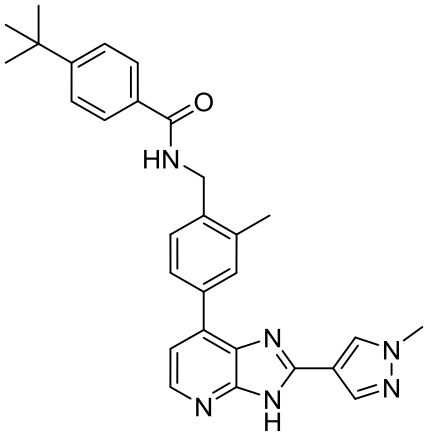
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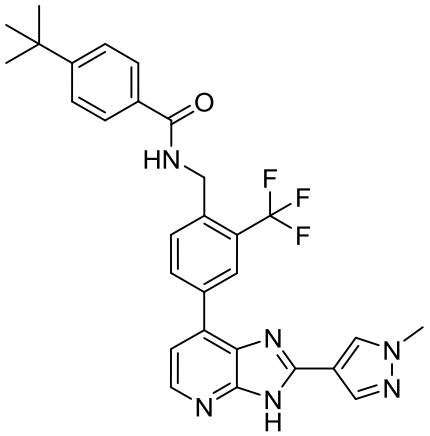
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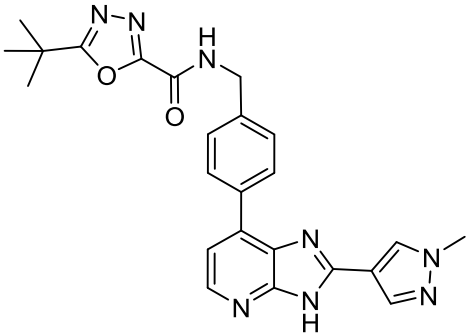
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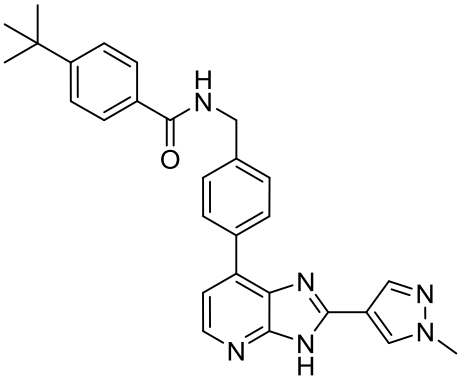
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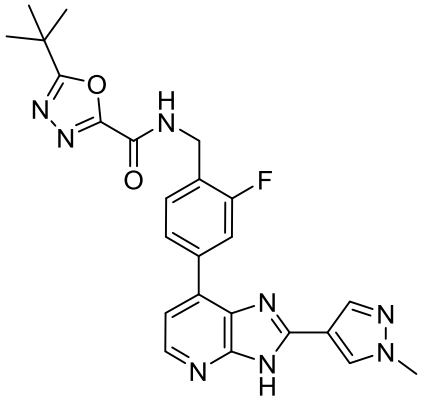
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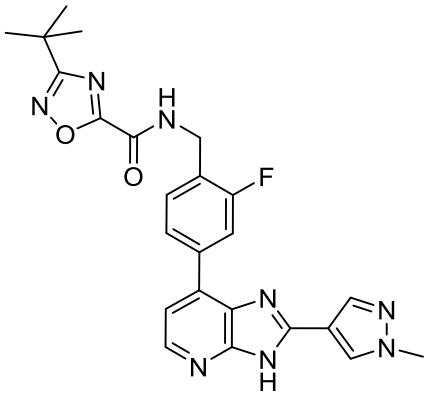
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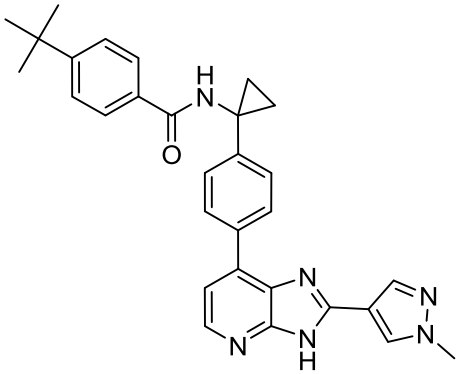
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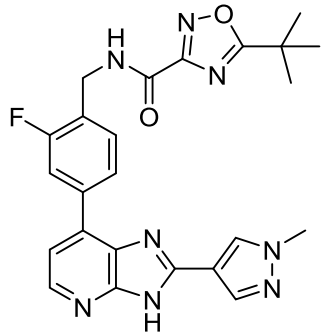
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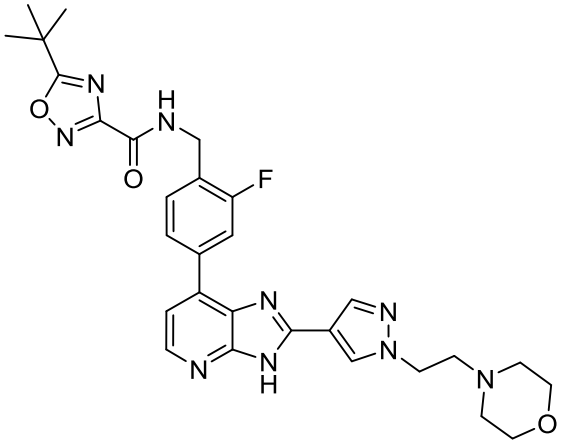
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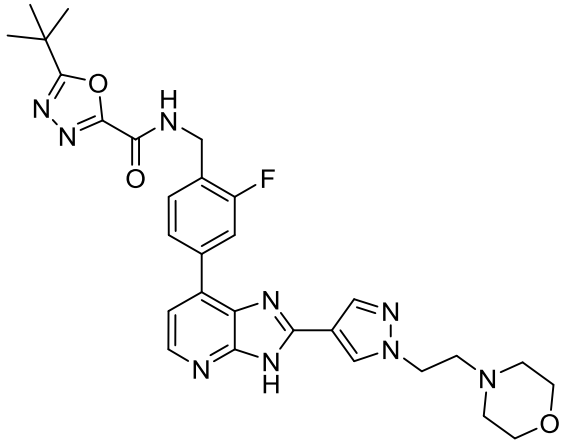
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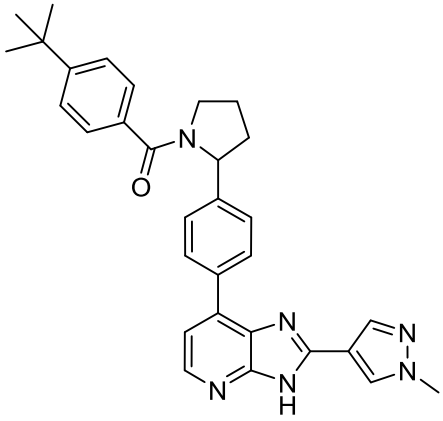
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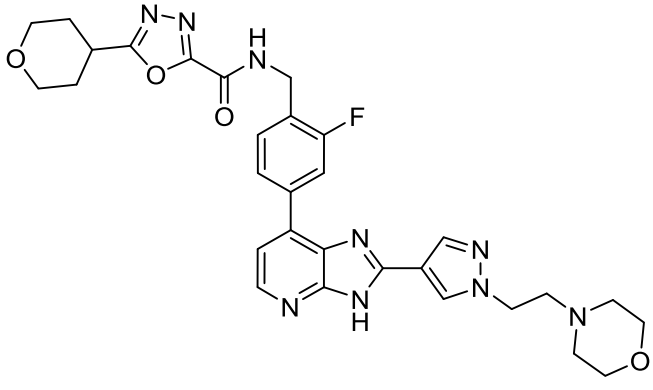


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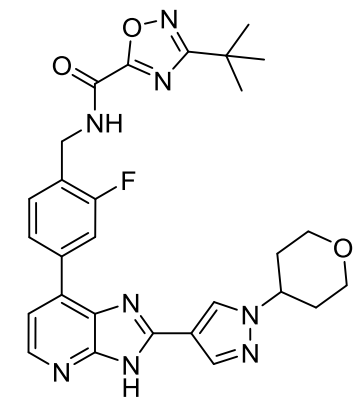


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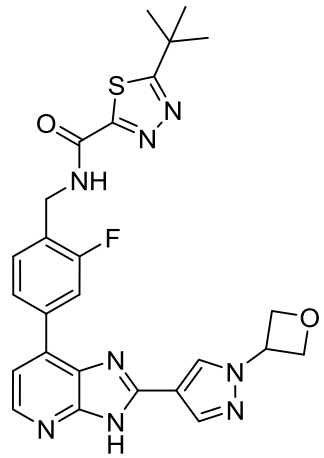


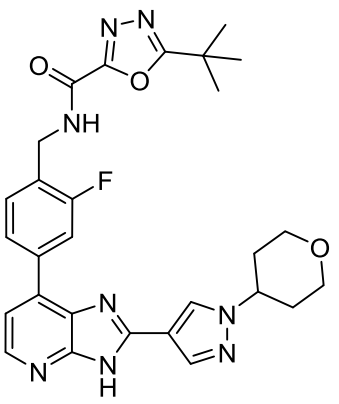


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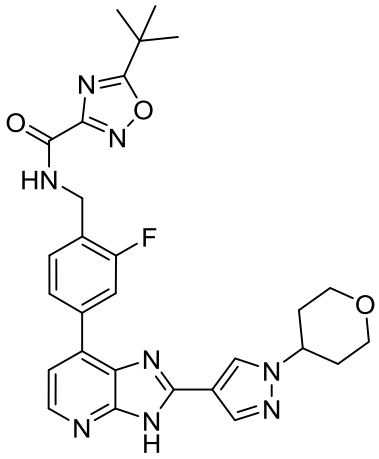


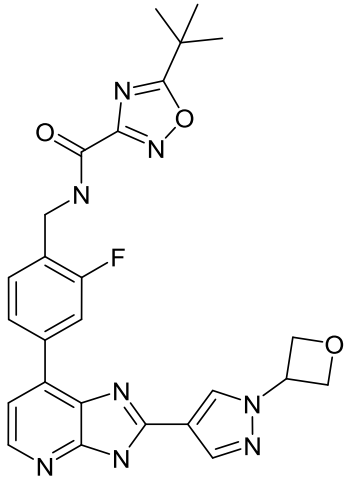
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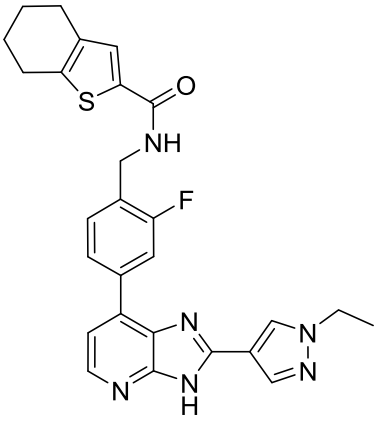




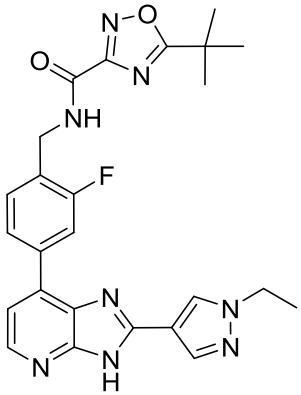
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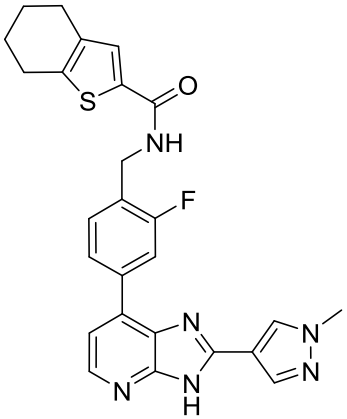


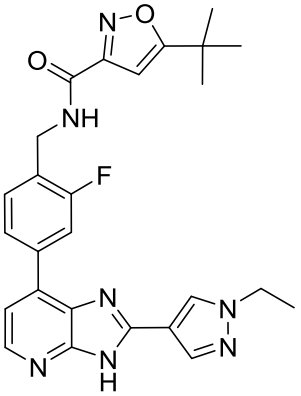




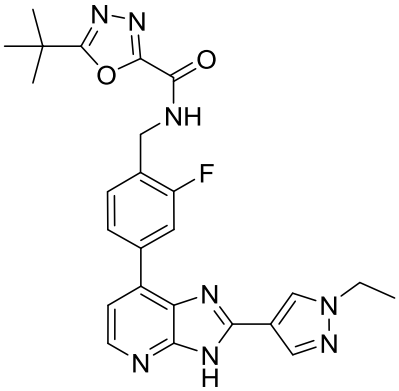
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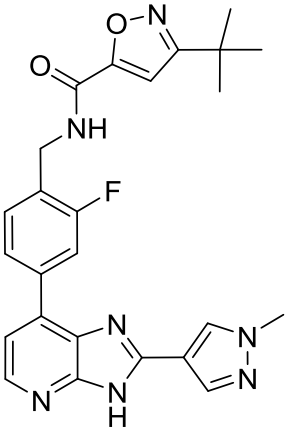




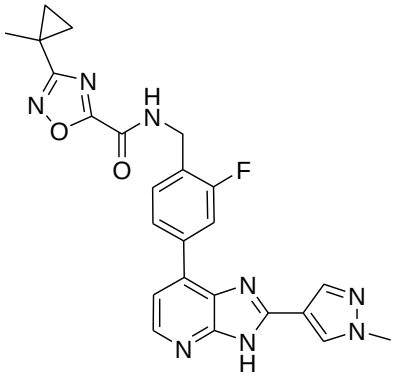
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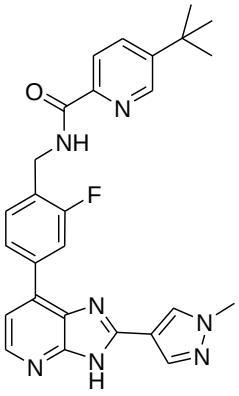
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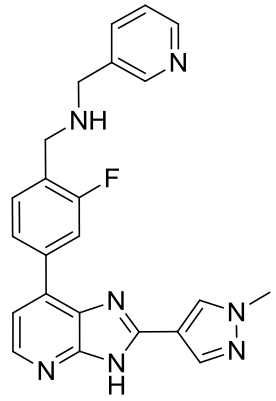


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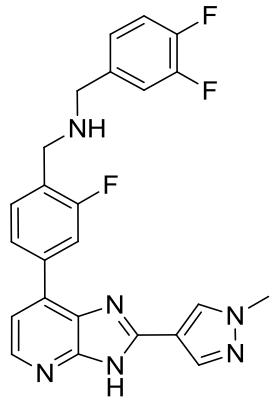


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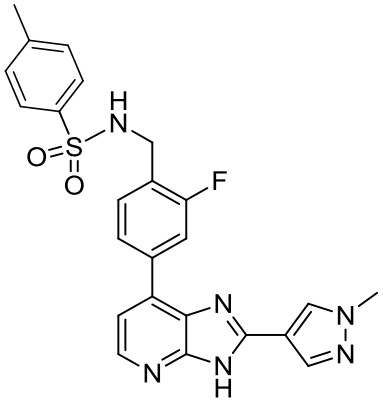
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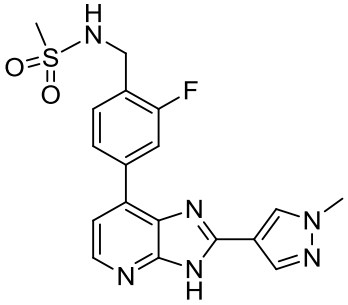
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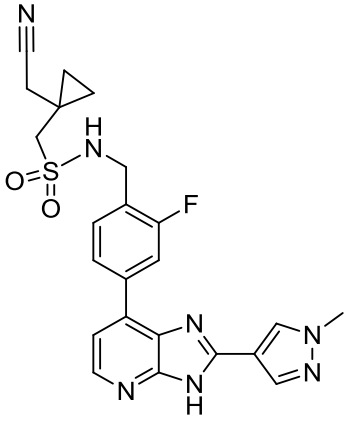
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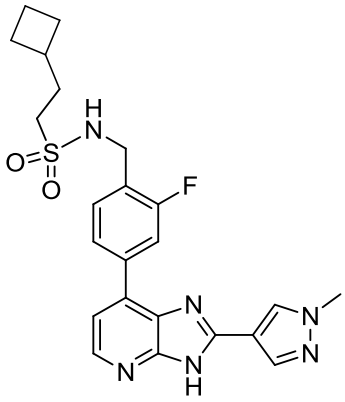
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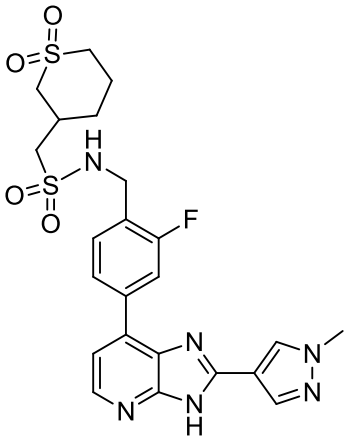
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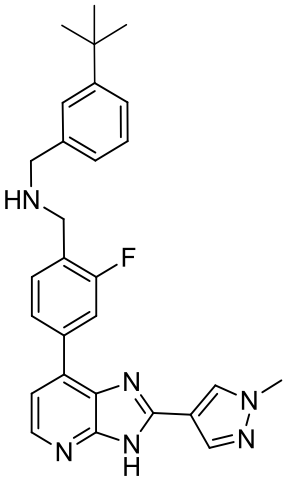
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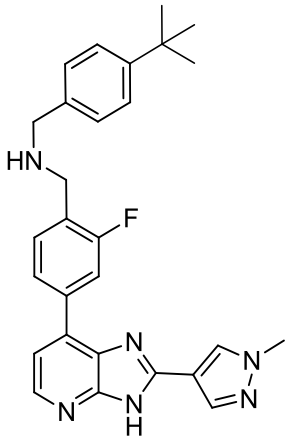
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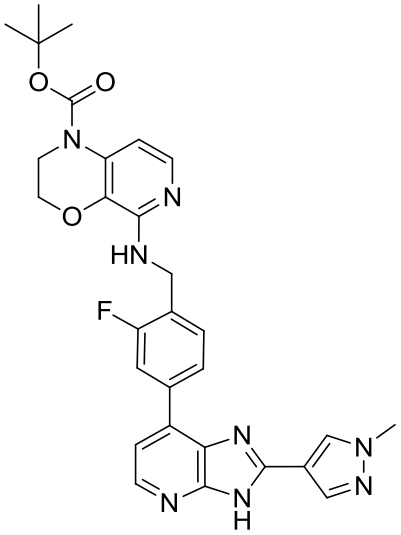
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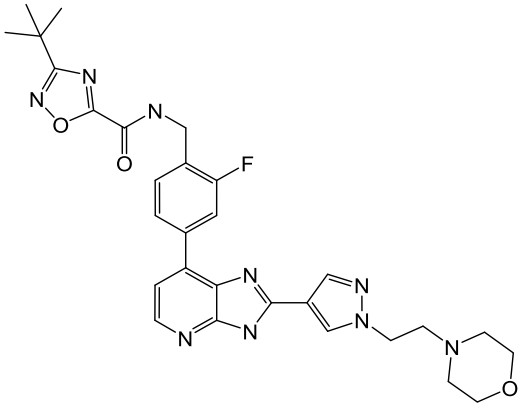
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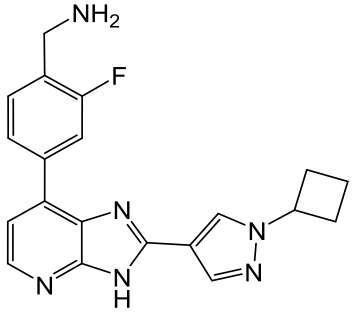
181



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187



188

14. A pharmaceutical composition comprising a compound of claim 1, and a pharmaceutically acceptable adjuvant, carrier, or vehicle.

15. Use of a compound or a physiologically acceptable salt thereof as set forth in any one of claims 1 to 4 for the preparation of a medicament for treating a BTK-mediated disorder in a patient in need thereof, wherein the disorder is at least one disease selected from the group consisting of inflammatory pelvic disease, urethritis, skin sunburn, sinusitis, pneumonitis, encephalitis, meningitis, myocarditis, nephritis, osteomyelitis, myositis, hepatitis, gastritis, enteritis, dermatitis, gingivitis, appendicitis, pancreatitis, cholocystitus, agammaglobulinemia, psoriasis, allergy, Crohn's disease, irritable bowel syndrome, ulcerative colitis, Sjogren's disease, tissue graft rejection, hyperacute rejection of transplanted organs, asthma, allergic rhinitis, chronic obstructive pulmonary disease, autoimmune polyglandular disease, autoimmune alopecia, pernicious anemia, glomerulonephritis, dermatomyositis, multiple sclerosis, scleroderma, vasculitis, autoimmune hemolytic and thrombocytopenic states, Goodpasture's syndrome, atherosclerosis, Addison's disease, Parkinson's disease, diabetes, septic shock, systemic lupus erythematosus, rheumatoid arthritis, psoriatic arthritis, juvenile arthritis, osteoarthritis, chronic idiopathic thrombocytopenic purpura, Waldenstrom macroglobulinemia, myasthenia gravis, Hashimoto's thyroiditis, atopic dermatitis, degenerative joint disease, vitiligo, autoimmune hypopituitarism, Guillain-Barre syndrome, Behcet's disease, scleraderma, mycosis fungoides, acute inflammatory responses, and Graves' disease.

16.. Use of a compound or a physiologically acceptable salt thereof as set forth in any one of claims 1 to 4 for the preparation of a medicament for treating lupus in a subject in need thereof.