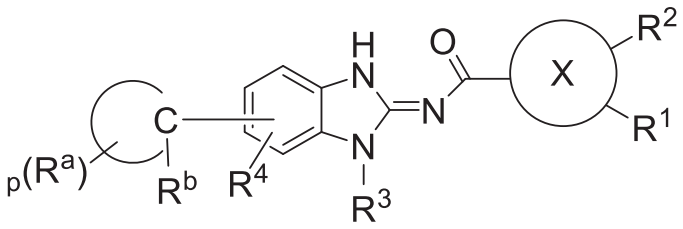
CLAIMS

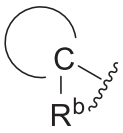
We claim:

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



I

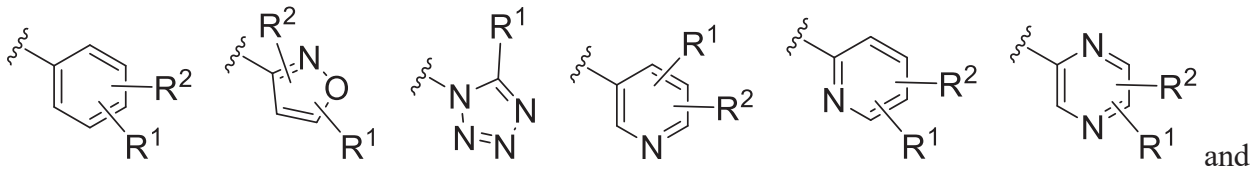
or a pharmaceutically acceptable salt thereof, wherein:

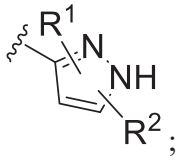
 is a 3-8 membered saturated or partially unsaturated carbocyclic ring, a 3-7 membered heterocylic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each R^a is independently –R, halogen, -haloalkyl, –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 $–N(R)_2$;

R^b is –R, halogen, -haloalkyl, –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 $–N(R)_2$; or R^b is absent;

Ring X is selected from:

 and

;

R^1 is –R, halogen, -haloalkyl, –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 $–N(R)_2$;

R^2 is –R, halogen, -haloalkyl, –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 $–N(R)_2$;

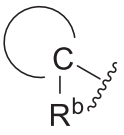
R^3 is $C_{1–6}$ aliphatic, $C_{3–10}$ aryl, or a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur; each of which is optionally substituted; or R^3 is -haloalkyl;

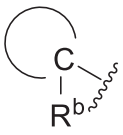
R^4 is –R, halogen, -haloalkyl, –OR, –SR, –CN, $–NO_2$, $-SO_2R$, -SOR, -C(O)R, $-CO_2R$, $-C(O)N(R)_2$, $-NRC(O)R$, $-NRC(O)N(R)_2$, $-NRSO_2R$, or $–N(R)_2$;

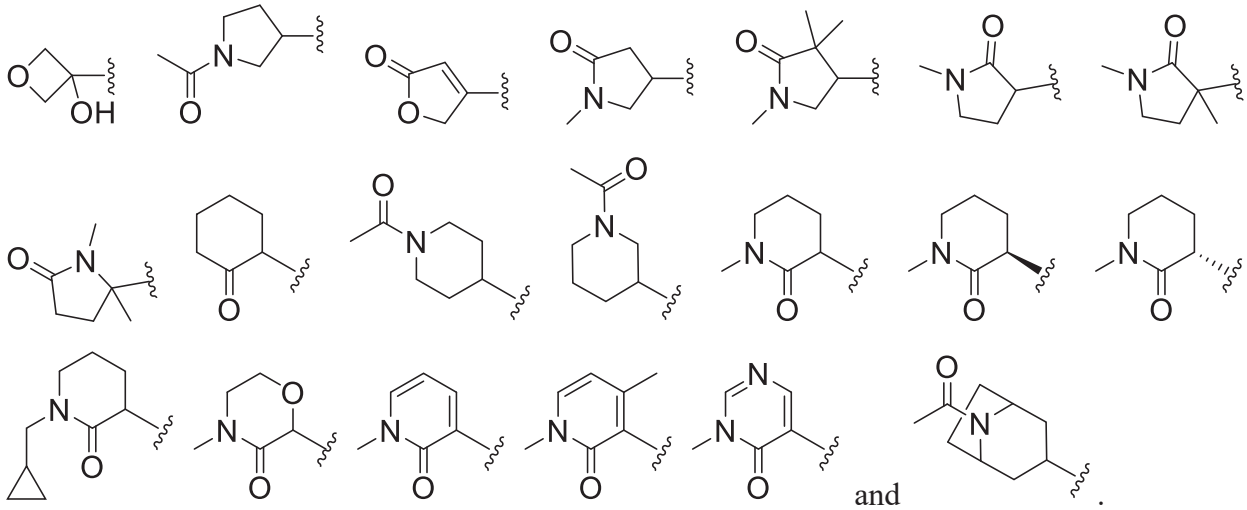
each R is independently hydrogen, $C_{1–6}$ aliphatic, $C_{3–10}$ aryl, a 3-8 membered saturated or partially unsaturated carbocyclic ring, a 3-7 membered heterocylic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 5-6 membered monocyclic heteroaryl ring having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

p is 0, 1, 2, 3, 4, or 5.

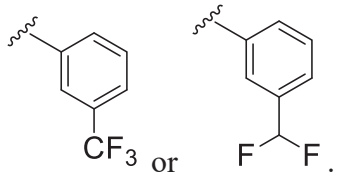
2. The compound of claim 1, wherein  is cyclohexanone, furanone, piperidinone, pyridinone, pyrimidinone, pyrrolidinone, or oxetanyl.

3. The compound of claim 1, wherein  is selected from:



and .

4. The compound of claim 1, wherein Ring X is:

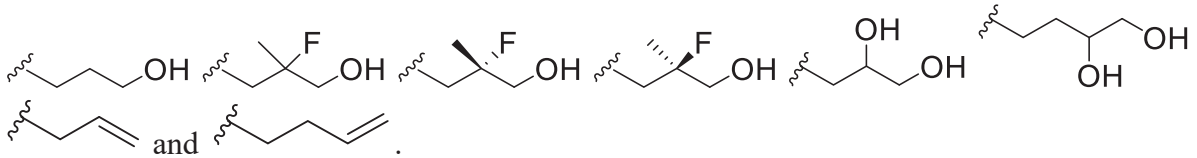


or .

5. The compound of claim 1, wherein R^3 is C_{1-6} aliphatic which is optionally substituted.

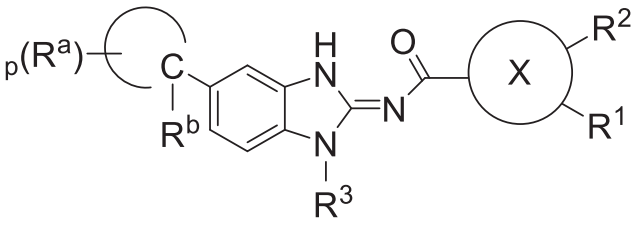
6. The compound of claim 5, wherein R^3 is methyl, ethyl, propyl, i-propyl, n-butyl, s-butyl, t-butyl, a straight chain or branched pentyl, or a straight chain or branched hexyl; each of which is optionally substituted.

7. The compound of claim 6, wherein R^3 is selected from:



and .

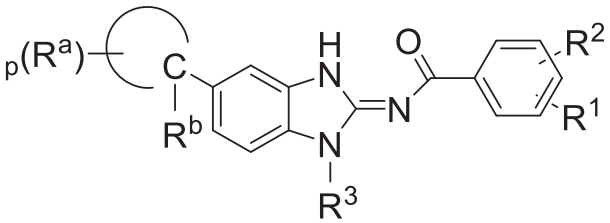
8. The compound of claim 1, of formula **I-a**,



I-a;

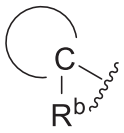
or a pharmaceutically acceptable salt thereof.

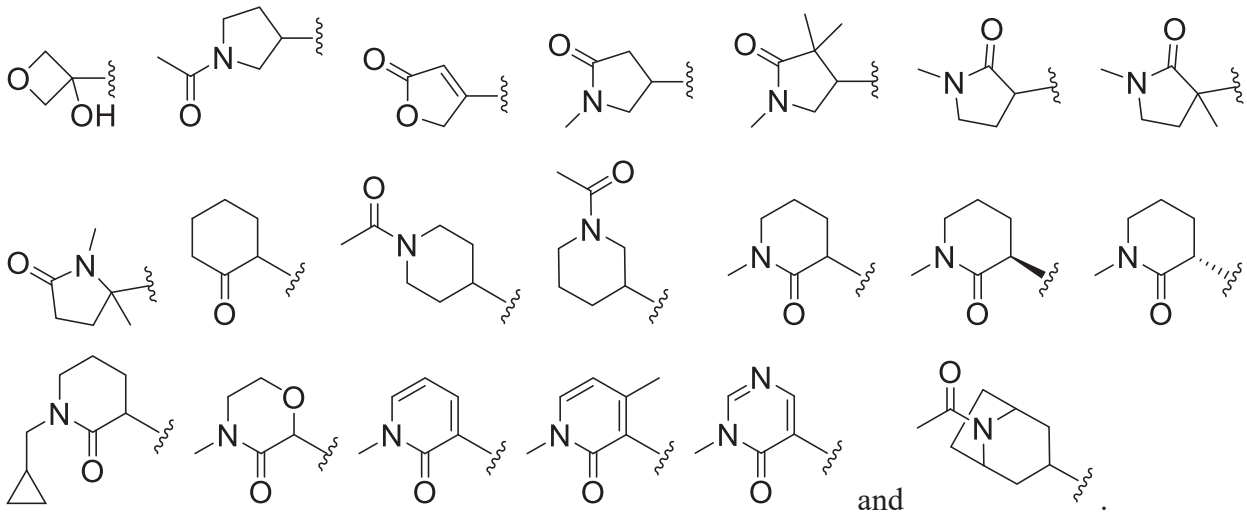
9. The compound of claim 1, of formula **I-b**,



I-b;

or a pharmaceutically acceptable salt thereof.

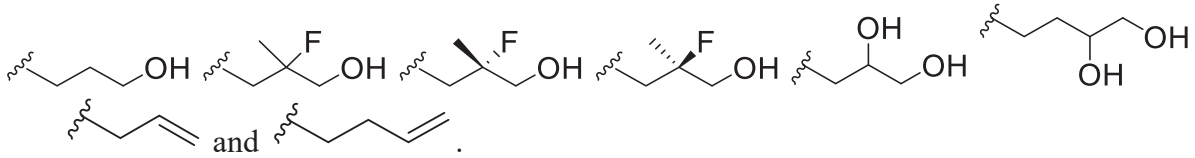
10. The compound of claim 9, wherein  is selected from:



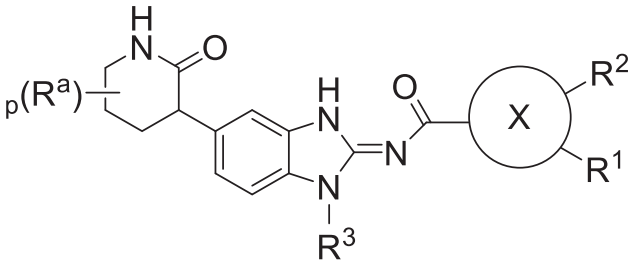
and .

11. The compound of claim 9, wherein R^1 is –haloalkyl.

12. The compound of claim 9, wherein R^3 is selected from:



13. The compound of claim 1, of formula **I-c**,

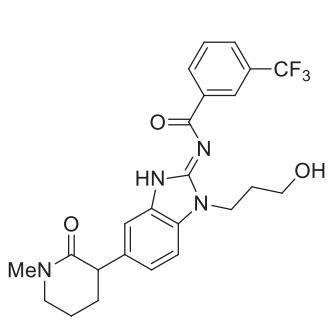


I-c;

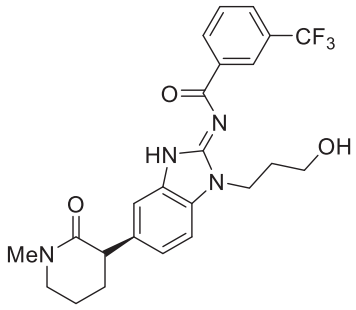
or a pharmaceutically acceptable salt thereof.

14. The compound of claim 1, selected from the following compounds from Table 1:

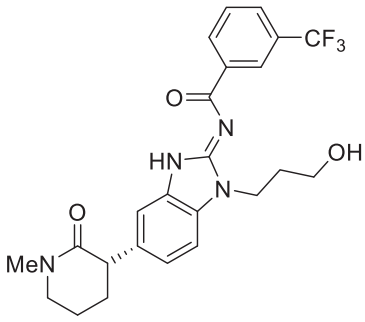
Table 1



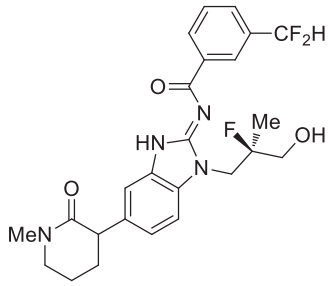
1



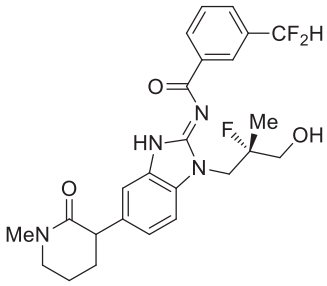
1a



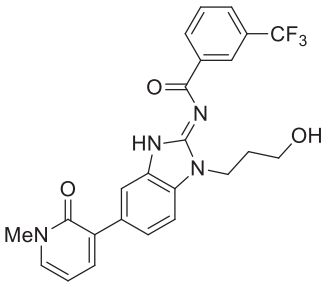
1b



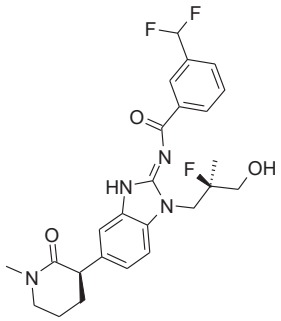
2a



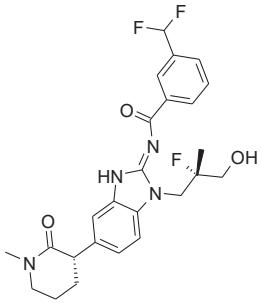
2b



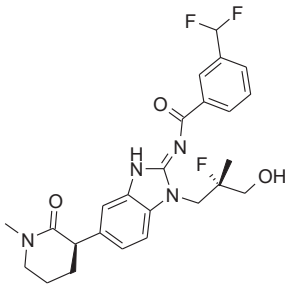
4



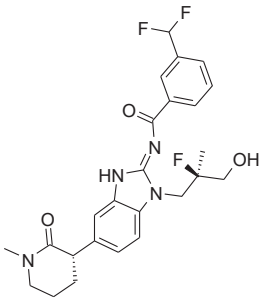
3a



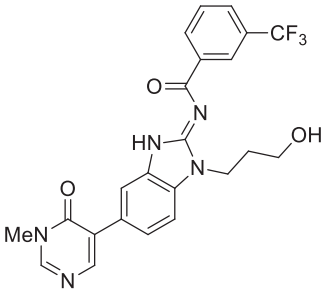
3b



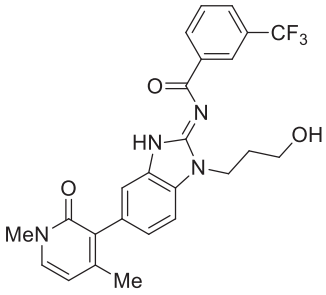
3c



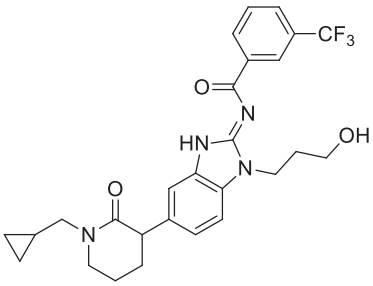
3d



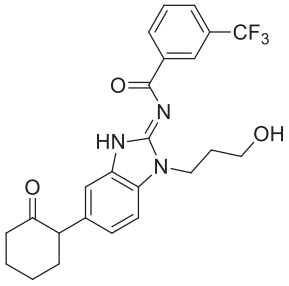
5



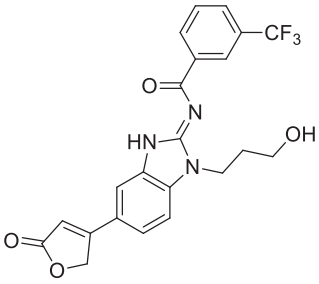
6



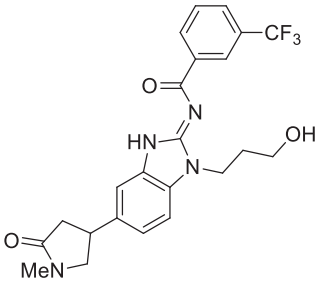
7



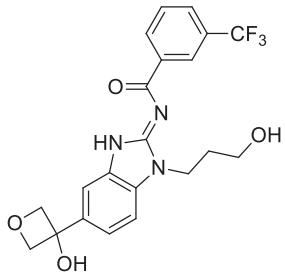
8



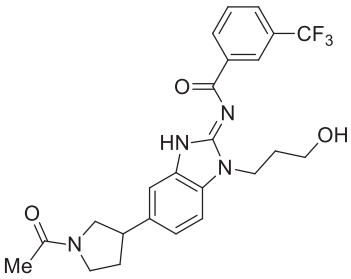
9



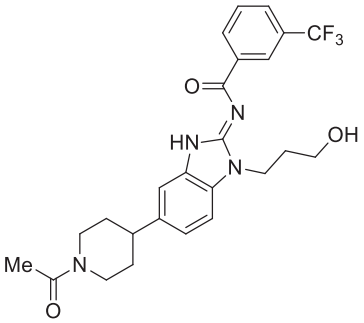
10



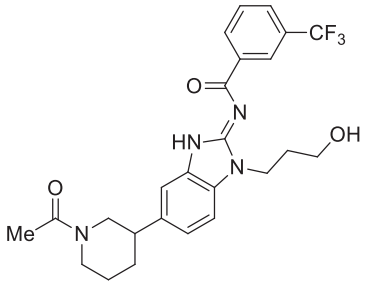
11



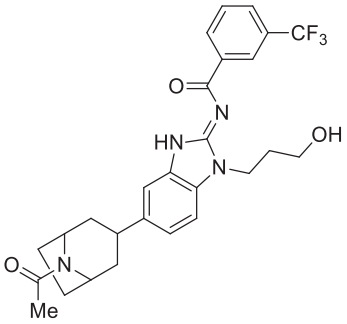
12



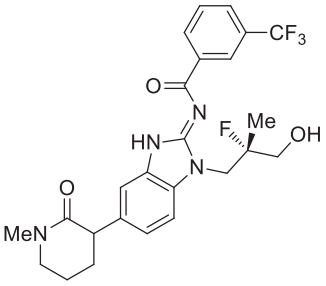
13



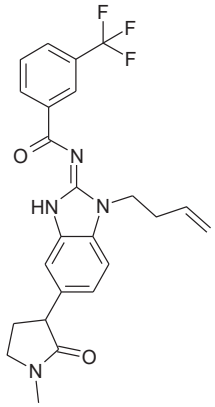
14



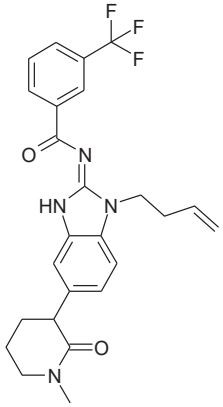
15



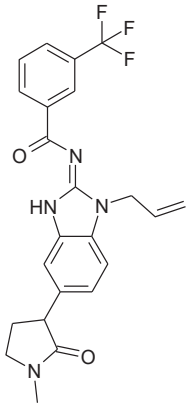
16



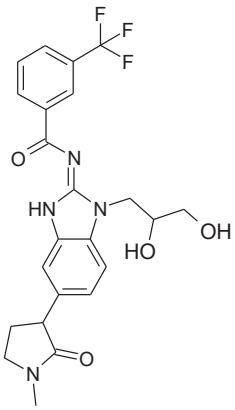
17



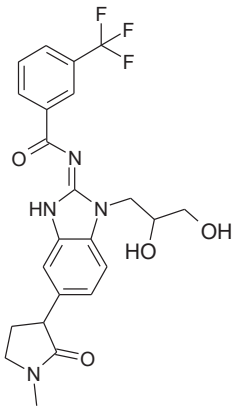
18



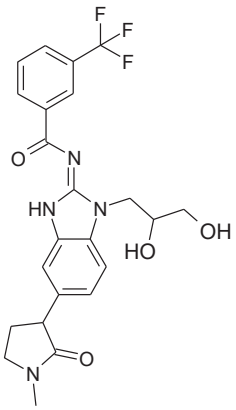
19



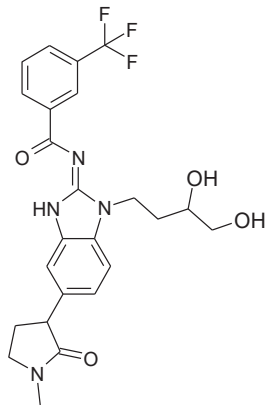
20



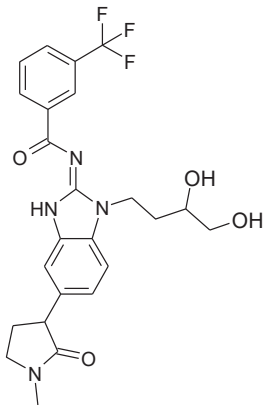
20a



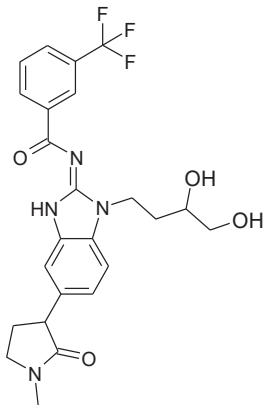
20b



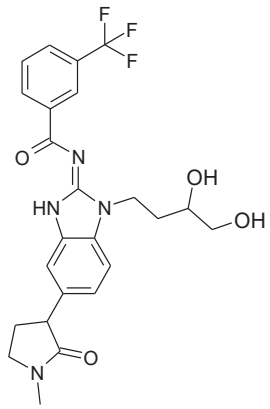
21



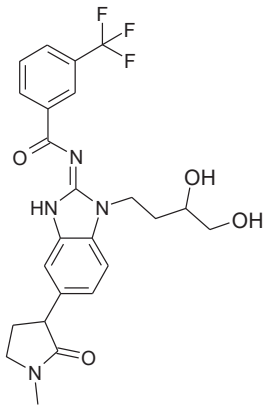
21a



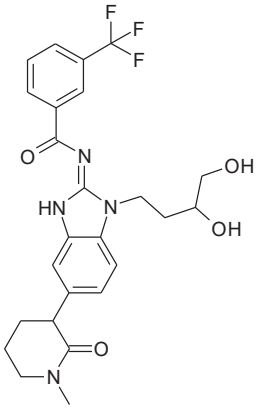
21b



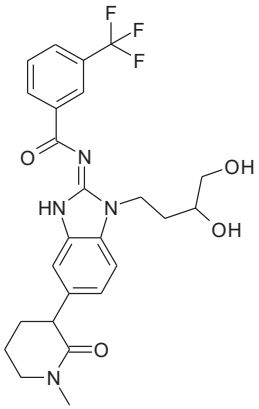
21c



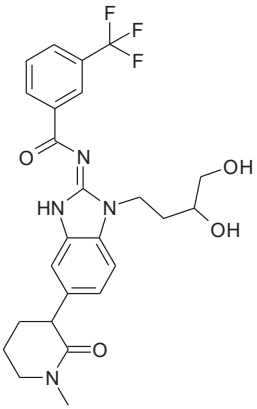
21d



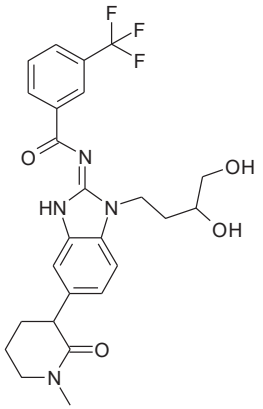
22



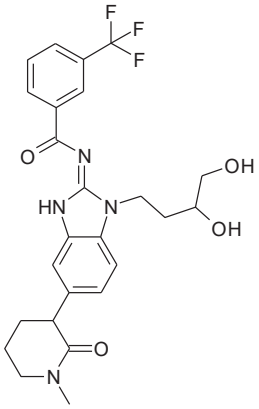
22a



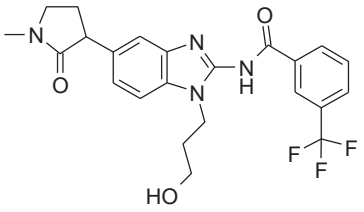
22b



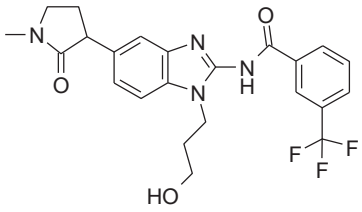
22c



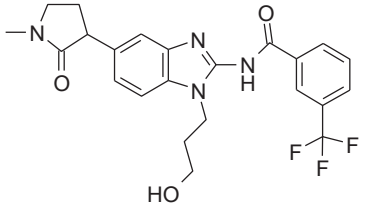
22d



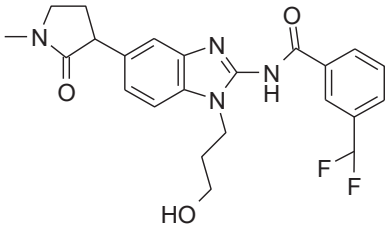
23



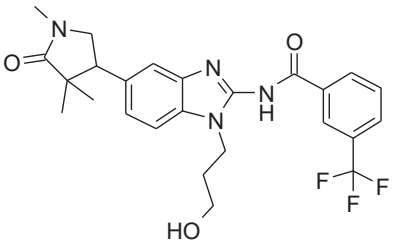
23a



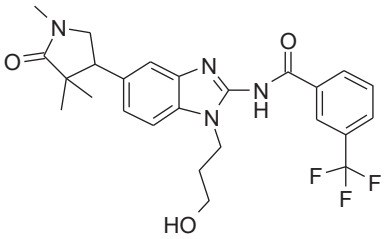
23b



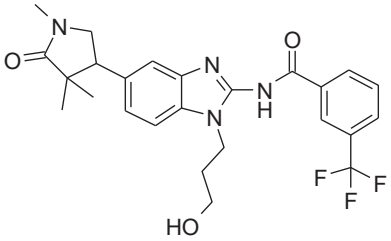
24



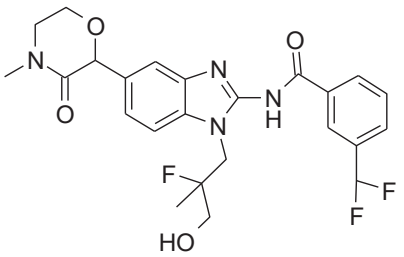
25



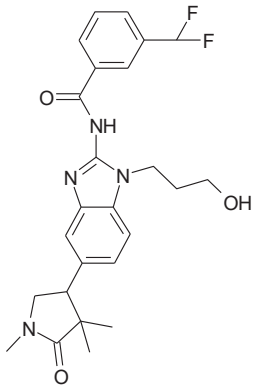
25a



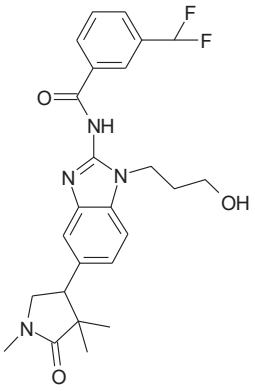
25b



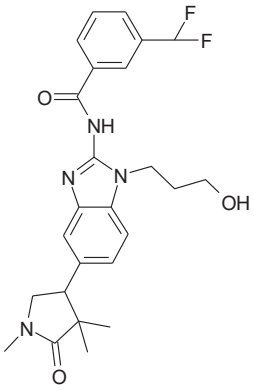
26



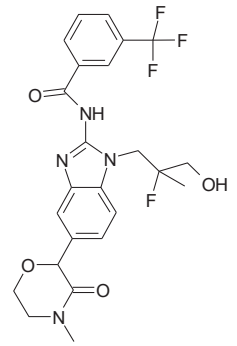
27



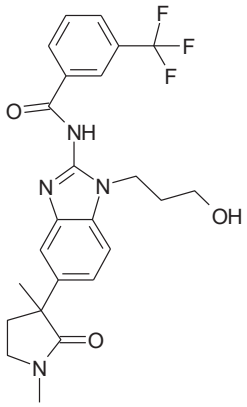
27a



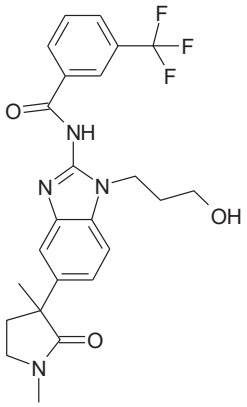
27b



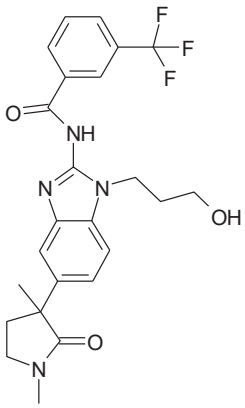
28



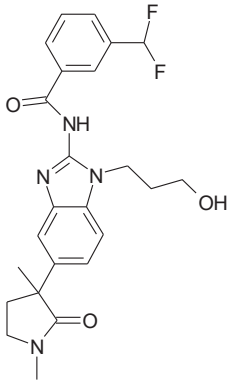
29



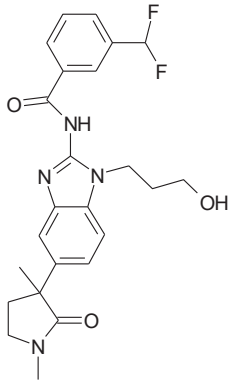
29a



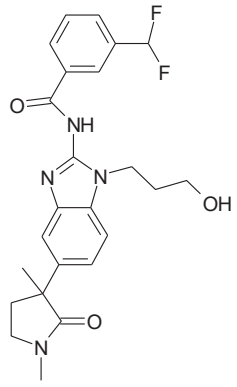
29b



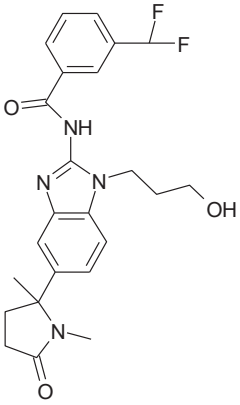
30



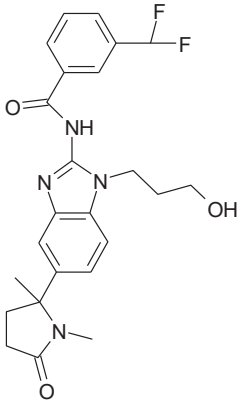
30a



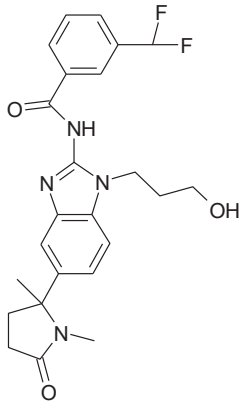
30b



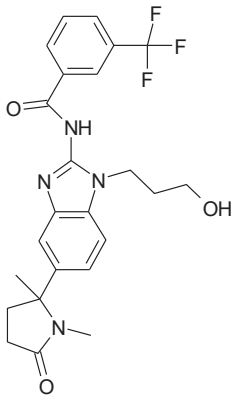
31



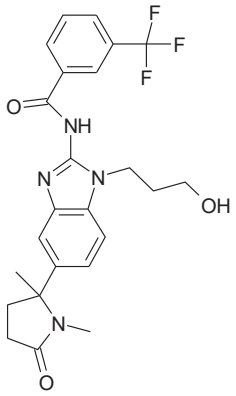
31a



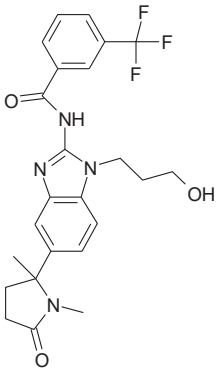
31b



32



32a and



32b.

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

16. A method for inhibiting IRAK, or a mutant thereof, activity in a patient or in a biological sample, comprising the step of administering to said patient or contacting said biological sample with a compound of claim 1 or a physiologically acceptable salt thereof.

17. A method for treating an IRAK-mediated disorder in a patient in need thereof, comprising the step of administering to said patient a compound of claim 1.

18. The method of claim 17, wherein the disorder is selected from Rheumatoid Arthritis, Psoriatic arthritis, Osteoarthritis, Systemic Lupus Erythematosus, Lupus nephritis, Ankylosing

Spondylitis, Osteoporosis, Systemic sclerosis, Multiple Sclerosis, Psoriasis, Type I diabetes, Type II diabetes, Inflammatory Bowel Disease (Cronh's Disease and Ulcerative Colitis), Hyperimmunoglobulinemia D and periodic fever syndrome, Cryopyrin-associated periodic syndromes, Schnitzler's syndrome, Systemic juvenile idiopathic arthritis, Adult's onset Still's disease, Gout, Pseudogout, SAPHO syndrome, Castleman's disease, Sepsis, Stroke, Atherosclerosis, Celiac disease, DIRA (Deficiency of IL-1 Receptor Antagonist), Alzheimer's disease, Parkinson's disease, and Cancer.

19. A method for treating cancer in a subject, comprising the step of administering to said subject a compound of claim 1 or a physiologically acceptable salt thereof.

20. The method of claim 18, wherein the disorder is selected from Rheumatoid Arthritis, Systemic Lupus Erythematosus, Lupus nephritis, and Multiple Sclerosis.