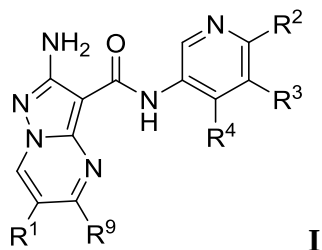


CLAIMS

1. A compound of formula I:



or a pharmaceutically acceptable salt thereof, wherein:

R^1 is $-C(J^1)_2CN$, halo, $-(L)_k-W$, or M;

R^9 is H, $-C(J^1)_2CN$, halo, $-(L)_k-W$, or M;

J^1 is independently H or $C_{1-2}alkyl$; or

two occurrences of J^1 , together with the carbon atom to which they are attached, form a 3-4 membered optionally substituted carbocyclic ring;

k is 0 or 1;

M and L are a $C_{1-8}aliphatic$, wherein up to three methylene units are optionally replaced with $-O-$, $-NR-$, $-C(O)-$, or $-S(O)_n-$, each M and L is optionally substituted with 0-3 occurrences of J^{LM} ;

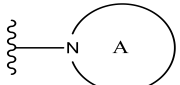
J^{LM} is independently halo, $-CN$, or a $C_{1-4}aliphatic$ chain, wherein up to two methylene units of the aliphatic chain are optionally replaced with $-O-$, $-NR-$, $-C(O)-$, or $-S(O)_n-$;

W is independently a 3-7 membered fully saturated, partially unsaturated, or aromatic monocyclic ring having 0-3 heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur; or an 7-12 membered fully saturated, partially unsaturated, or aromatic bicyclic ring having 0-5 heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur; wherein W is optionally substituted with 0-5 occurrences of J^W ;

J^W is independently -CN, halo, -CF₃; a C₁₋₄aliphatic wherein up to two methylene units are optionally replaced with -O-, -NR-, -C(O)-, or -S(O)_n-; or a 3-6 membered non-aromatic ring having 0-2 heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur;

R^2 is H; halo; -CN; NH₂; a C₁₋₂alkyl optionally substituted with 0-3 occurrences of fluoro; or a C₁₋₃aliphatic chain, wherein up to two methylene units of the aliphatic chain are optionally replaced with -O-, -NR-, -C(O)-, or -S(O)_n-;

R^3 is H; halo; C₁₋₄alkyl optionally substituted with 1-3 occurrences of halo; C₃₋₄cycloalkyl; 3-4 membered heterocyclyl; -CN; or a C₁₋₃aliphatic chain, wherein up to two methylene units of the aliphatic chain are optionally replaced with -O-, -NR-, -C(O)-, or -S(O)_n-;

R^4 is , wherein Ring A is a 3-7 membered fully saturated, partially unsaturated, or aromatic monocyclic ring having 1-3 heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur; or an 7-12 membered fully saturated, partially unsaturated, or aromatic bicyclic ring having 1-5 heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur; each R^4 is optionally substituted with 0-5 occurrences of J^Q ;

J^Q is independently -CN; halo; =O; Q²; or a C₁₋₈aliphatic chain, wherein up to three methylene units of the aliphatic chain are optionally replaced with -O-, -NR-, -C(O)-, or -S(O)_n-; each occurrence of J^Q is optionally substituted by 0-3 occurrences of J^R ; or

two occurrences of J^Q on the same atom, taken together with the atom to which they are joined, form a 3-6 membered ring having 0-2 heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur; wherein the ring formed by two occurrences of J^Q is optionally substituted with 0-3 occurrences of J^X ;

two occurrences of J^Q , together with Ring A, form a 6-10 membered saturated or partially unsaturated bridged ring system;

Q² is independently a 3-7 membered fully saturated, partially unsaturated, or aromatic monocyclic ring having 0-3 heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur; or an 7-12 membered fully saturated, partially unsaturated, or aromatic bicyclic ring having 0-5 heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur;

J^R is independently -CN; halo; =O; $\rightarrow$ O; Q^3 ; or a C_{1-6} aliphatic chain, wherein up to three methylene units of the aliphatic chain are optionally replaced with -O-, -NR-, -C(O)-, or -S(O)_n-; each J^R is optionally substituted with 0-3 occurrences of J^T ; or

two occurrences of J^R on the same atom, together with the atom to which they are joined, form a 3-6 membered ring having 0-2 heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur; wherein the ring formed by two occurrences of J^R is optionally substituted with 0-3 occurrences of J^X ; or

two occurrences of J^R , together with Q^2 , form a 6-10 membered saturated or partially unsaturated bridged ring system;

Q^3 is a 3-7 membered fully saturated, partially unsaturated, or aromatic monocyclic ring having 0-3 heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur; or an 7-12 membered fully saturated, partially unsaturated, or aromatic bicyclic ring having 0-5 heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur;

J^X is independently -CN; =O; halo; or a C_{1-4} aliphatic chain, wherein up to two methylene units of the aliphatic chain are optionally replaced with -O-, -NR-, -C(O)-, or -S(O)_n-;

J^T is independently halo, -CN; =O; -OH; a C_{1-6} aliphatic chain, wherein up to two methylene units of the aliphatic chain are optionally replaced with -O-, -NR-, -C(O)-, or -S(O)_n-; or a 3-6 membered non-aromatic ring having 0-2 heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur; each occurrence of J^T is optionally substituted with 0-3 occurrences of J^M ; or

two occurrences of J^T on the same atom, together with the atom to which they are joined, form a 3-6 membered ring having 0-2 heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur; or

two occurrences of J^T , together with Q^3 , form a 6-10 membered saturated or partially unsaturated bridged ring system;

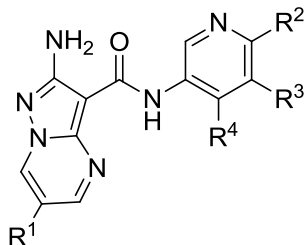
J^M is independently halo or C_{1-6} aliphatic;

n is 0, 1 or 2; and

R is independently H or C₁₋₄aliphatic.

2. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R⁹ is H.
3. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R⁹ is M.
4. The compound of claim 3, or a pharmaceutically acceptable salt thereof, wherein M is a C₁₋₈aliphatic, wherein up to three methylene units are optionally replaced with -O- or -NR-.
5. The compound of claim 4, wherein, or a pharmaceutically acceptable salt thereof, M is C₁₋₄alkyl, -(C₁₋₄alkyl)O(C₁₋₃aliphatic), -(C₁₋₃alkyl)OH, -O(C₁₋₄alkyl)N(C₁₋₂alkyl)₂, -NH(C₁₋₄alkyl), or -(C₁₋₄alkyl)NH(C₁₋₄alkyl).
6. The compound of claim 5, or a pharmaceutically acceptable salt thereof, wherein M is C₁₋₄alkyl.
7. The compound of any one of claims 4-6, or a pharmaceutically acceptable salt thereof, wherein J^{LM} is halo.
8. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R⁹ is -(L)_k-W.
9. The compound of claim 8, or a pharmaceutically acceptable salt thereof, wherein k is 0.
10. The compound of claim 8, or a pharmaceutically acceptable salt thereof, wherein k is 1.
11. The compound of claim 10, wherein L is a C₁₋₈aliphatic, or a pharmaceutically acceptable salt thereof, wherein up to three methylene units are optionally replaced with -O- or -NR-.

12. The compound of claim 11, or a pharmaceutically acceptable salt thereof, wherein L is -O-, -O(C₁₋₄aliphatic)-, or -NR(C₁₋₃alkyl)-.
13. The compound of any one of claims 8-12, or a pharmaceutically acceptable salt thereof, wherein W is a 3-7 membered fully saturated, partially unsaturated, or aromatic monocyclic ring having 0-3 heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur.
14. The compound of claim 13, or a pharmaceutically acceptable salt thereof, wherein W is a 3-7 membered heterocyclyl.
15. The compound of claim 14, or a pharmaceutically acceptable salt thereof, wherein W is pyrrolidinyl, piperidinyl, piperazinyl, oxetanyl, or azetidinyl.
16. The compound of any one of claims 8-12, or a pharmaceutically acceptable salt thereof, wherein W is a 7-12 membered fully saturated, partially unsaturated, or aromatic bicyclic ring having 0-5 heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur.
17. The compound of any one of claims 8-16, or a pharmaceutically acceptable salt thereof, wherein J^W is selected from C₁₋₃alkyl or CF₃.
18. A compound of formula **I-A**:



I-A

or a pharmaceutically acceptable salt thereof, wherein:

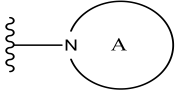
R^1 is fluoro, chloro, or $-C(J^1)_2CN$;

J^1 is independently H or C_{1-2} alkyl; or

two occurrences of J^1 , together with the carbon atom to which they are attached, form a 3-4 membered optionally substituted carbocyclic ring;

R^2 is H; halo; $-CN$; NH_2 ; a C_{1-2} alkyl optionally substituted with 0-3 occurrences of fluoro; or a C_{1-3} aliphatic chain, wherein up to two methylene units of the aliphatic chain are optionally replaced with $-O-$, $-NR-$, $-C(O)-$, or $-S(O)_n$;

R^3 is H; halo; C_{1-4} alkyl optionally substituted with 1-3 occurrences of halo; C_{3-4} cycloalkyl; $-CN$; or a C_{1-3} aliphatic chain, wherein up to two methylene units of the aliphatic chain are optionally replaced with $-O-$, $-NR-$, $-C(O)-$, or $-S(O)_n$;

R^4 is , wherein Ring A is independently selected from a 3-7 membered fully saturated, partially unsaturated, or aromatic monocyclic ring having 1-3 heteroatoms selected from oxygen, nitrogen or sulfur; or a 7-12 membered fully saturated, partially unsaturated, or aromatic bicyclic ring having 1-5 heteroatoms selected from oxygen, nitrogen, or sulfur; each R^4 is optionally substituted with 0-5 occurrences of J^Q ;

J^Q is independently $-CN$; halo; $=O$; Q^2 ; or a C_{1-8} aliphatic chain, wherein up to three methylene units of the aliphatic chain are optionally replaced with $-O-$, $-NR-$, $-C(O)-$, or $-S(O)_n$; each occurrence of J^Q is optionally substituted by 0-3 occurrences of J^R ; or

two occurrences of J^Q on the same atom, taken together with the atom to which they are joined, form a 3-6 membered ring having 0-2 heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur; wherein the ring formed by two occurrences of J^Q is optionally substituted with 0-3 occurrences of J^X ; or

two occurrences of J^Q , together with Ring A, form a 6-10 membered saturated or partially unsaturated bridged ring system;

Q^2 is independently a 3-7 membered fully saturated, partially unsaturated, or aromatic monocyclic ring having 0-3 heteroatoms selected from oxygen, nitrogen, or sulfur; or an 7-12 membered fully saturated, partially unsaturated, or aromatic bicyclic ring having 0-5 heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur;

J^R is independently $-CN$; halo; $=O$; $\rightarrow O$; Q^3 ; or a C_{1-6} aliphatic chain, wherein up to three methylene units of the aliphatic chain are optionally replaced with $-O-$, $-NR-$, $-C(O)-$, or $-S(O)_n-$; each J^R is optionally substituted with 0-3 occurrences of J^T ; or

two occurrences of J^R on the same atom, together with the atom to which they are joined, form a 3-6 membered ring having 0-2 heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur; wherein the ring formed by two occurrences of J^R is optionally substituted with 0-3 occurrences of J^X ; or

two occurrences of J^R , together with Q^2 , form a 6-10 membered saturated or partially unsaturated bridged ring system;

Q^3 is a 3-7 membered fully saturated, partially unsaturated, or aromatic monocyclic ring having 0-3 heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur; or an 7-12 membered fully saturated, partially unsaturated, or aromatic bicyclic ring having 0-5 heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur;

J^X is independently $-CN$; $=O$; halo; or a C_{1-4} aliphatic chain, wherein up to two methylene units of the aliphatic chain are optionally replaced with $-O-$, $-NR-$, $-C(O)-$, or $-S(O)_n-$;

J^T is independently halo, $-CN$; $=O$; a C_{1-6} aliphatic chain, wherein up to two methylene units of the aliphatic chain are optionally replaced with $-O-$, $-NR-$, $-C(O)-$, or $-S(O)_n-$; or a 3-6 membered

non-aromatic ring having 0-2 heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur; each occurrence of J^T is optionally substituted with 0-3 occurrences of J^M ; or

two occurrences of J^T on the same atom, together with the atom to which they are joined, form a 3-6 membered ring having 0-2 heteroatoms selected from oxygen, nitrogen, or sulfur; or

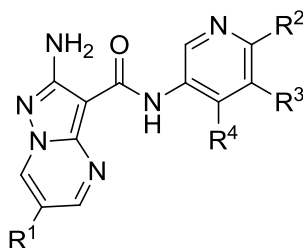
two occurrences of J^T , together with Q^3 , form a 6-10 membered saturated or partially unsaturated bridged ring system;

J^M is independently halo or C_{1-6} aliphatic;

R is independently H or C_{1-4} aliphatic; and

n is 0, 1 or 2.

19. A compound having the formula **I-A**:



I-A

or a pharmaceutically acceptable salt thereof, wherein:

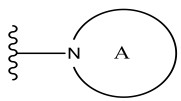
R^1 is fluoro, chloro, or $-C(J^1)_2CN$;

J^1 is independently H or C_{1-2} alkyl; or

two occurrences of J^1 , together with the carbon atom to which they are attached, form a 3-4 membered optionally substituted carbocyclic ring;

R^2 is H; halo; $-CN$; NH_2 ; a C_{1-2} alkyl optionally substituted with 0-3 occurrences of fluoro; or a C_{1-3} aliphatic chain, wherein up to two methylene units of the aliphatic chain are optionally replaced with $-O-$, $-NR-$, $-C(O)-$, or $-S(O)_n$;

R^3 is H; halo; C_{1-4} alkyl optionally substituted with 1-3 occurrences of halo; C_{3-4} cycloalkyl; -CN; or a C_{1-3} aliphatic chain, wherein up to two methylene units of the aliphatic chain are optionally replaced with -O-, -NR-, -C(O)-, or -S(O)_n;

R^4 is , wherein Ring A is a 3-7 membered fully saturated, partially unsaturated, or aromatic monocyclic ring having 1-3 heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur; or a 7-12 membered fully saturated, partially unsaturated, or aromatic bicyclic ring having 1-5 heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur; each R^4 is optionally substituted with 0-5 occurrences of J^Q ;

J^Q is independently -CN; halo; =O; Q^2 ; or a C_{1-8} aliphatic chain, wherein up to three methylene units of the aliphatic chain are optionally replaced with -O-, -NR-, -C(O)-, or -S(O)_n-; each occurrence of J^Q is optionally substituted by 0-3 occurrences of J^R ; or

two occurrences of J^Q on the same atom, taken together with the atom to which they are joined, form a 3-6 membered ring having 0-2 heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur; wherein the ring formed by two occurrences of J^Q is optionally substituted with 0-3 occurrences of J^X ; or

two occurrences of J^Q , together with Ring A, form a 6-10 membered saturated or partially unsaturated bridged ring system;

Q^2 is independently a 3-7 membered fully saturated, partially unsaturated, or aromatic monocyclic ring having 0-3 heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur; or an 7-12 membered fully saturated, partially unsaturated, or aromatic bicyclic ring having 0-5 heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur;

J^R is independently -CN; halo; =O; Q^3 ; or a C_{1-6} aliphatic chain, wherein up to three methylene units of the aliphatic chain are optionally replaced with -O-, -NR-, -C(O)-, or -S(O)_n-; each J^R is optionally substituted with 0-3 occurrences of J^T ; or

two occurrences of J^R on the same atom, together with the atom to which they are joined, form a 3-6 membered ring having 0-2 heteroatoms selected from oxygen, nitrogen, or sulfur; wherein the ring formed by two occurrences of J^R is optionally substituted with 0-3 occurrences of J^X ; or two occurrences of J^R , together with Q^2 , form a 6-10 membered saturated or partially unsaturated bridged ring system;

Q^3 is independently a 3-7 membered fully saturated, partially unsaturated, or aromatic monocyclic ring having 0-3 heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur; or an 7-12 membered fully saturated, partially unsaturated, or aromatic bicyclic ring having 0-5 heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur;

J^X is independently -CN; halo; or a C_{1-4} aliphatic, chain wherein up to two methylene units of the aliphatic chain are optionally replaced with -O-, -NR-, -C(O)-, or -S(O)_n-;

J^T is independently -CN; =O; -OH; a C_{1-6} aliphatic chain, wherein up to two methylene units of the aliphatic chain are optionally replaced with -O-, -NR-, -C(O)-, or -S(O)_n-; or a 3-6 membered non-aromatic ring having 0-2 heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur; each occurrence of J^T is optionally substituted with 0-3 occurrences of J^M ; or

two occurrences of J^T on the same atom, together with the atom to which they are joined, form a 3-6 membered ring having 0-2 heteroatoms selected from oxygen, nitrogen, or sulfur;

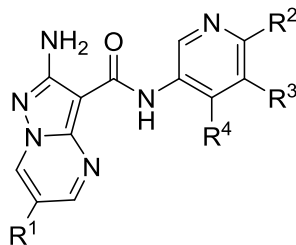
two occurrences of J^T , together with Q^3 , form a 6-10 membered saturated or partially unsaturated bridged ring system;

J^M is independently halo or C_{1-6} aliphatic;

n is 0, 1 or 2; and

R is independently H or C_{1-4} aliphatic.

20. A compound having the formula **I-A**:



I-A

or a pharmaceutically acceptable salt thereof, wherein:

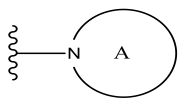
R^1 is fluoro, chloro, or $-C(J^1)_2CN$;

J^1 is independently H or C_{1-2} alkyl; or

two occurrences of J^1 , together with the carbon atom to which they are attached, form an optionally substituted 3-4 membered carbocyclic ring;

R^2 is H; chloro; NH_2 ; or a C_{1-2} alkyl optionally substituted with fluoro;

R^3 is H; chloro; fluoro; C_{1-4} alkyl optionally substituted with 1-3 occurrences of halo; C_{3-4} cycloalkyl; or $-CN$;

R^4 is , wherein Ring A is a 3-7 membered fully saturated, partially unsaturated, or aromatic monocyclic ring having 1-3 heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur; or a 7-12 membered fully saturated, partially unsaturated, or aromatic bicyclic ring having 1-5 heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur; each R^4 is optionally substituted with 0-5 occurrences of J^Q ;

J^Q is independently halo; $=O$; Q^2 ; or a C_{1-8} aliphatic chain, wherein up to two methylene units of the aliphatic chain are optionally replaced with $-O-$, $-NR-$, $-S-$, $-C(O)-$, or $-S(O)_n-$; each occurrence of J^Q is optionally substituted by 0-3 occurrences of J^R ; or

two occurrences of J^Q on the same atom, taken together with the atom to which they are joined, form a 3-6 membered ring having 0-2 heteroatoms selected from the group consisting of oxygen,

nitrogen, and sulfur; wherein the ring formed by two occurrences of J^Q is optionally substituted with 0-3 occurrences of J^X ; or

two occurrences of J^Q , together with Ring A, form a 6-10 membered saturated or partially unsaturated bridged ring system;

Q^2 is independently selected from a 3-7 membered fully saturated, partially unsaturated, or aromatic monocyclic ring having 0-3 heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur; or an 8-12 membered fully saturated, partially unsaturated, or aromatic bicyclic ring having 0-5 heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur;

J^R is independently halo; =O; O; a 3-7 membered fully saturated, partially unsaturated, or aromatic monocyclic ring having 0-3 heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur; or a C_{1-4} aliphatic chain, wherein up to two methylene units of the aliphatic chain are optionally replaced with -O-, -NR-, -S-, -C(O)-, or -S(O)_n-; each J^R is optionally substituted with 0-3 occurrences of J^T ; or

two occurrences of J^R on the same atom, together with the atom to which they are joined, form a 3-6 membered ring having 0-2 heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur; wherein the ring formed by two occurrences of J^R is optionally substituted with 0-3 occurrences of J^X ; or

two occurrences of J^R , together with Q^2 , form a 6-10 membered saturated or partially unsaturated bridged ring system;

J^X is independently halo or a C_{1-4} aliphatic chain, wherein up to two methylene units of the aliphatic chain are optionally replaced with -O-, -NR-, -S-, -C(O)-, or -S(O)_n-; or

J^T is independently a C_{1-6} aliphatic or a 3-6 membered non-aromatic ring having 0-2 heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur; each occurrence of J^T is optionally substituted with 0-3 occurrences of J^M ;

J^M is independently halo or C_{1-6} aliphatic;

n is 1 or 2; and

R is independently H or C₁₋₄aliphatic.

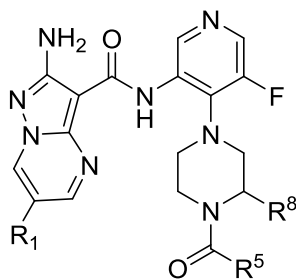
21. The compounds of any one of claims 1-20, or a pharmaceutically acceptable salt thereof, wherein R¹ is fluoro.
22. The compounds of any one of claims 1-20, wherein R¹ is -CH₂CN, -C(CH₃)₂CN or -CH(C₁₋₂alkyl)CN.
23. The compound of any one of claims 1-20, or a pharmaceutically acceptable salt thereof, wherein R¹ is chloro.
24. The compound of any one of claims 1-19 or 21-23, or a pharmaceutically acceptable salt thereof, wherein R² is -CF₃, -NH(C₁₋₂alkyl), chloro, or H.
25. The compound of claim 24, or a pharmaceutically acceptable salt thereof, wherein R² is H.
26. The compound of claim 24, or a pharmaceutically acceptable salt thereof, wherein R² is -chloro.
27. The compound of any one of claims 1-26, or a pharmaceutically acceptable salt thereof, wherein R³ is H, chloro, fluoro, CHF₂, -CN, cyclopropyl, or C₁₋₄alkyl.
28. The compound of claim 27, or a pharmaceutically acceptable salt thereof, wherein R³ is H, chloro, or fluoro.
29. The compound of claim 28, or a pharmaceutically acceptable salt thereof, wherein R³ is H.
30. The compound of claim 28, or a pharmaceutically acceptable salt thereof, wherein R³ is chloro.

31. The compound of claim 28, or a pharmaceutically acceptable salt thereof, wherein R³ is fluoro.
32. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein Ring A is a 3-7 membered fully saturated, partially unsaturated, or aromatic monocyclic ring having 1-3 heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur.
33. The compound of claim 32, or a pharmaceutically acceptable salt thereof, wherein Ring A is a 3-7 membered heterocycl.
34. The compound of claim 33, or a pharmaceutically acceptable salt thereof, wherein Ring A is pyrrolidinyl, piperidinyl, azepanyl, pyrazolidinyl, isoxazolidinyl, oxazolidinyl, thiazolidinyl, imidazolidinyl, piperazinyl, morpholinyl, thiomorpholinyl, 1,3-oxazinanyl, 1,3-thiazinanyl, dihydropyridinyl, dihydroimidazolyl, 1,3-tetrahydropyrimidinyl, dihydropyrimidinyl, 1,4-diazepanyl, 1,4-oxazepanyl, 1,4-thiazepanyl, or azetidiny.
35. The compound of claim 34, or a pharmaceutically acceptable salt thereof, wherein Ring A is piperidinyl, piperazinyl, 1,4-diazepanyl, thiomorpholinyl, pyrrolidinyl, azepanyl, morpholinyl.
36. The compound of claim 35, or a pharmaceutically acceptable salt thereof, wherein Ring A is independently selected from piperazinyl or piperidinyl.
37. The compound of claim 32, or a pharmaceutically acceptable salt thereof, wherein Ring A is a 5 membered heteroaryl.
38. The compound of claim 37, or a pharmaceutically acceptable salt thereof, wherein Ring A is pyrrolyl, imidazolyl, pyrazolyl, 1,2,3-triazolyl, or 1,2,4-triazolyl.

39. The compound of claim 38, or a pharmaceutically acceptable salt thereof, wherein Ring A is pyrazolyl or imidazolyl.
40. The compound of claim 32, or a pharmaceutically acceptable salt thereof, wherein Ring A is an 7-12 membered fully saturated, partially unsaturated, or aromatic bicyclic ring having 1-5 heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur.
41. The compound of claim 40, or a pharmaceutically acceptable salt thereof, wherein Ring A is octahydropyrrolo[1,2-a]pyrazinyl, 5,6,7,8-tetrahydroimidazo[1,2-a]pyridinyl, octahydro-1H-pyrazino[1,2-a]pyrazinyl, 5,6,7,8-tetrahydroimidazo[1,5-a]pyrazinyl, 2,5-diazabicyclo[4.1.0]heptane, or octahydropyrazino[2,1-c][1,4]oxazinyl.
42. The compound of any one of claims 32-39, or a pharmaceutically acceptable salt thereof, wherein J^Q is C_{1-8} aliphatic chain, wherein up to two methylene units of the aliphatic chain are optionally replaced with -O-, -NR-, or -C(O)-.
43. The compound of any one of claims 32-39, or a pharmaceutically acceptable salt thereof, wherein J^Q is independently -O-, -C(O)-, -S(O)₂-, C_{1-4} alkyl, -(C_{0-4} alkyl)NH₂, -(C_{0-4} alkyl)NH(C_{1-4} alkyl), -(C_{0-4} alkyl)N(C_{1-4} alkyl)₂, -(C_{0-4} alkyl)OH, -(C_{0-4} alkyl)O(C_{1-4} alkyl), -C(O)OH, -S(O)₂N(C_{1-3} alkyl)-, -C(O)(C_{1-4} alkyl)-, -(O)C(C_{1-4} alkyl)N(C_{1-2} alkyl)₂, or -C(O)O(C_{1-4} alkyl).
44. The compound of claim 43, or a pharmaceutically acceptable salt thereof, wherein J^Q is C_{1-4} alkyl, -O-, or -C(O)-.
45. The compound of any one of claims 32-41, or a pharmaceutically acceptable salt thereof, wherein J^Q is Q^2 .
46. The compound of claim 45, or a pharmaceutically acceptable salt thereof, wherein Q^2 is a 3-7 membered heterocyclyl or carbocyclyl; the heterocyclyl having 1-3 heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur.

47. The compound of claim 46, or a pharmaceutically acceptable salt thereof, wherein Q^2 is independently oxetanyl, tetrahydropyranyl, tetrahydrofuranyl, cyclopropyl, azetidiny, pyrrolidinyl, piperazinyl, cyclobutyl, thiomorpholinyl, or morpholinyl.
48. The compound of claim 47, or a pharmaceutically acceptable salt thereof, wherein Q^2 is independently selected from oxetanyl, tetrahydropyranyl, or tetrahydrofuranyl.
49. The compound of claim 48, or a pharmaceutically acceptable salt thereof, wherein Q^2 is oxetanyl.
50. The compound of claim 45, or a pharmaceutically acceptable salt thereof, wherein Q^2 is a 7-12 membered fully saturated, partially unsaturated, or aromatic bicyclic ring having 0-5 heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur.
51. The compound of claim 50, or a pharmaceutically acceptable salt thereof, wherein Q^2 is independently 5,6,7,8-tetrahydroimidazo[1,5-a]pyrazinyl or 5,6,7,8-tetrahydroimidazo[1,2-a]pyrazinyl.
52. The compound of any one of claims 32-36, or a pharmaceutically acceptable salt thereof, wherein two occurrences of J^Q , together with Ring A, form a bridged ring system.
53. The compound of any one of claims 32-41, or a pharmaceutically acceptable salt thereof, wherein J^Q is =O.
54. The compound of any one of claims 42-52, or a pharmaceutically acceptable salt thereof, wherein J^R is a 3-6 membered heterocyclyl having 1-3 heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur.
55. The compound of claim 54, or a pharmaceutically acceptable salt thereof, wherein J^R is independently oxetanyl, piperadinyl, azetidiny, piperazinyl, pyrrolidinyl, or morpholinyl.

56. The compound of claim 55, or a pharmaceutically acceptable salt thereof, wherein J^R is a piperazinyl.
57. The compound of any one of claims 42-52, or a pharmaceutically acceptable salt thereof, wherein J^R is independently halo, =O, -OH, C_{1-4} alkyl, $-(C_{0-4}alkyl)N(C_{1-4}alkyl)_2$, or $-(C_{0-4}alkyl)O(C_{1-4}alkyl)$.
58. The compound of any one of claims 45-52, or a pharmaceutically acceptable salt thereof, wherein two occurrences of J^R on the same atom, together with the atom to which they are joined, form a 3-6 membered aromatic or non-aromatic ring having 0-2 heteroatoms selected from oxygen, nitrogen, or sulfur.
59. The compound of claim 58, or a pharmaceutically acceptable salt thereof, wherein J^R is independently oxetanyl or azetidiny.
60. The compound of any one of claims 45-47, or a pharmaceutically acceptable salt thereof, wherein two occurrences of J^R , together with Q^2 , form a bridged ring system.
61. The compound of claim 56, or a pharmaceutically acceptable salt thereof, wherein J^T is a 3-6 membered non-aromatic ring having 0-2 heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur.
62. The compound of claim 61, or a pharmaceutically acceptable salt thereof, wherein J^T is oxetanyl.
63. The compound of claim 1 having formula **I-A-1**:



I-A-1 ;

or a pharmaceutically acceptable salt thereof, wherein:

R⁵ is C₁₋₄aliphatic, a 3-6 membered cycloalkyl, or a 3-6 membered heterocyclyl having 1-2 heteroatoms selected from the group consisting of oxygen and sulfur;

R⁸ is H or C₁₋₃ alkyl; or

R⁵ and R⁸, taken together with the atoms to which they are bound, form a 5-6 membered non-aromatic ring having 1-2 heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur.

64. The compound of claim 63, or a pharmaceutically acceptable salt thereof, wherein R¹ is fluoro.

65. The compound of claim 64, or a pharmaceutically acceptable salt thereof, wherein R⁵ is C₁₋₄aliphatic.

66. The compound of claim 65, or a pharmaceutically acceptable salt thereof, wherein R⁵ is methyl or ethyl.

67. The compound of claim 63, or a pharmaceutically acceptable salt thereof, wherein R⁵ is a 3-6 membered cycloalkyl.

68. The compound of claim 67, or a pharmaceutically acceptable salt thereof, wherein R⁵ is cyclopropyl.

69. The compound of claim 63, or a pharmaceutically acceptable salt thereof, wherein R⁵ is a 3-6 membered heterocyclyl having 1-2 heteroatoms selected from oxygen or sulfur.

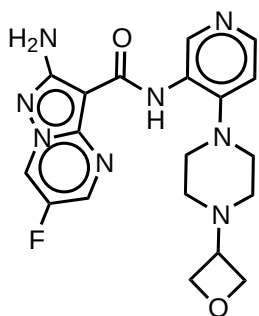
70. The compound of claim 69, or a pharmaceutically acceptable salt thereof, wherein R⁵ is tetrahydrofuranyl or oxetanyl.

71. The compound of claim 63, or a pharmaceutically acceptable salt thereof, wherein R⁵ and R⁸, taken together with the atoms to which they are bound, form a 5-6 membered non-aromatic ring having 1-2 heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur.

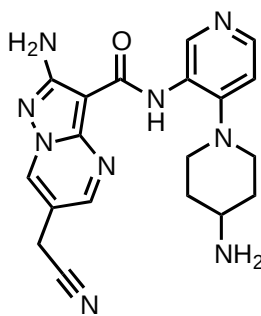
72. The compound of claim 71, or a pharmaceutically acceptable salt thereof, wherein the ring formed by R⁵ and R⁸ is a five-membered ring.

73. The compound of claim 71, or a pharmaceutically acceptable salt thereof, wherein the ring formed by R⁵ and R⁸ is a six-membered ring.

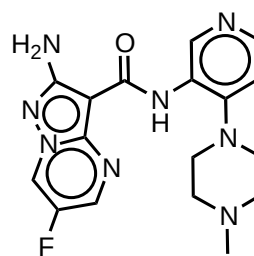
74. A compound, wherein the compound is:



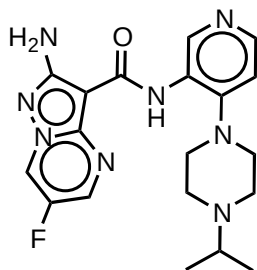
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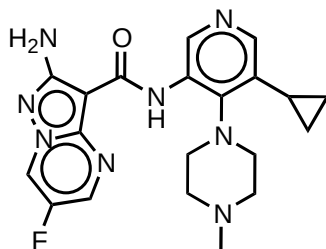
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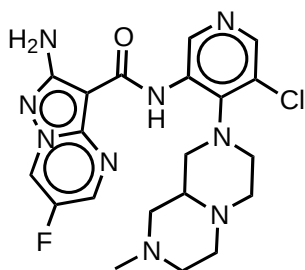
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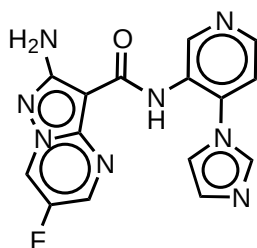
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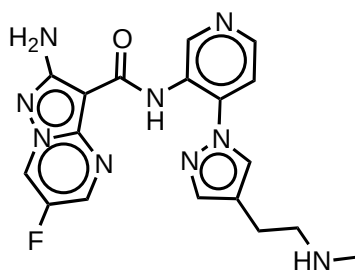
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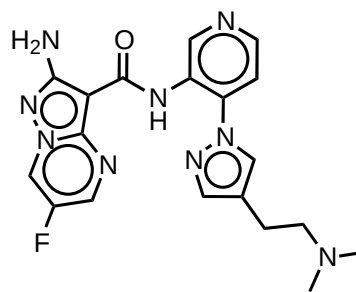
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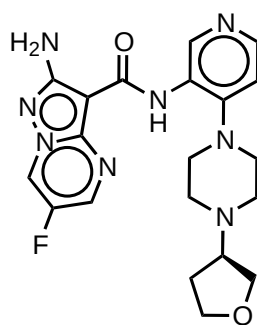
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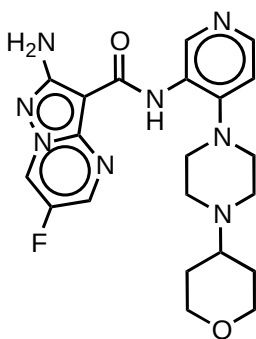
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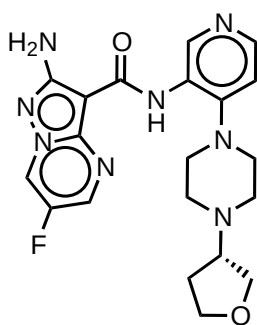
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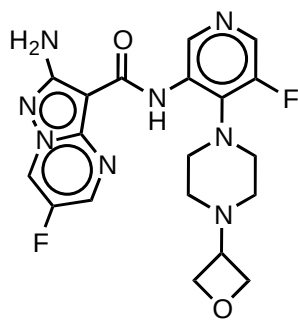
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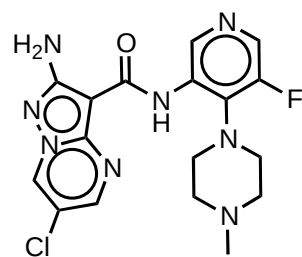
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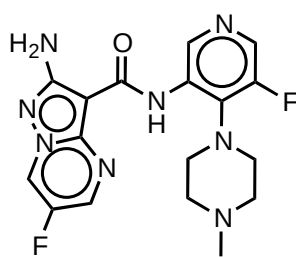
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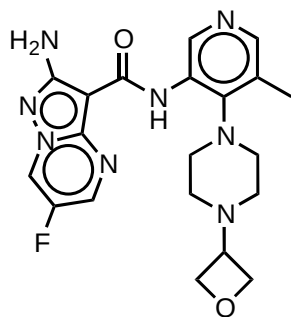
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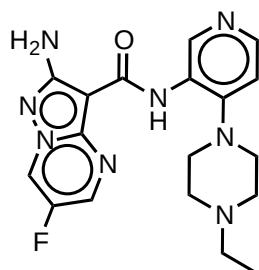
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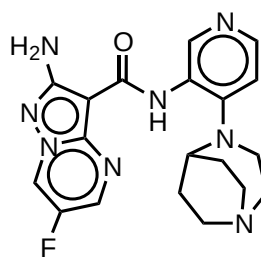
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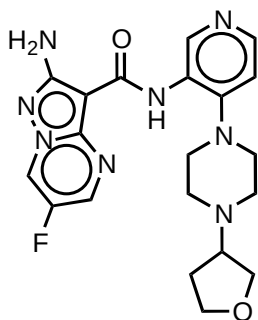
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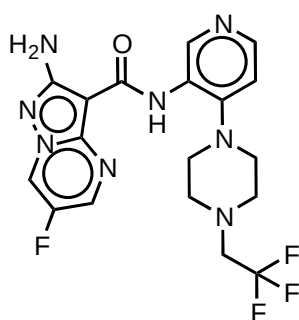
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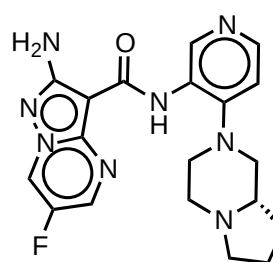
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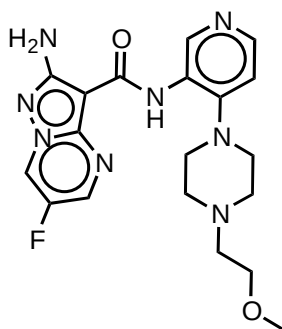
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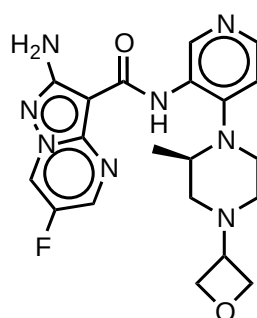
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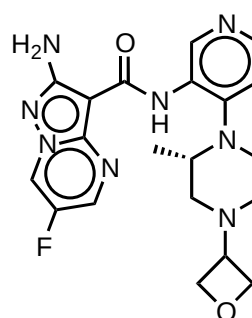
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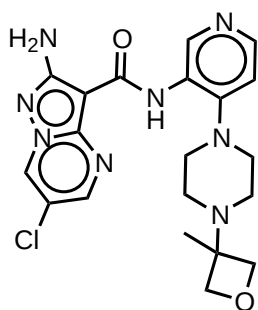
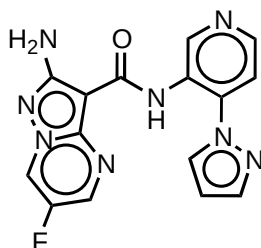
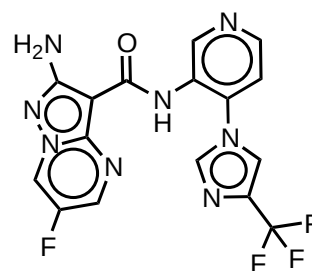
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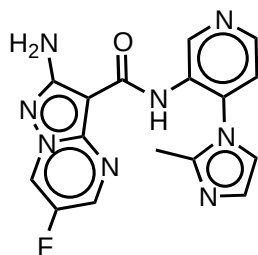
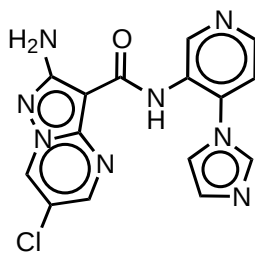
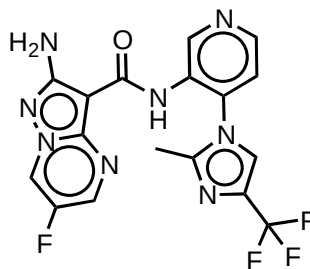
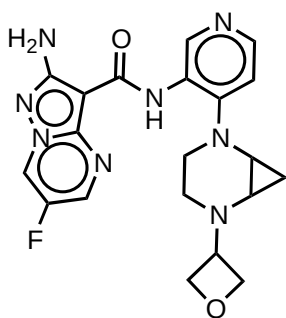
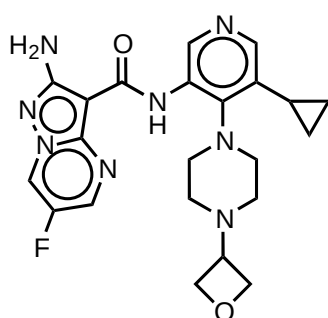
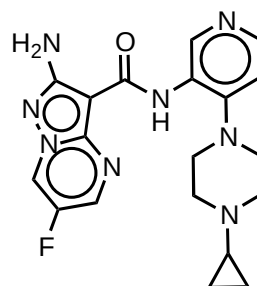
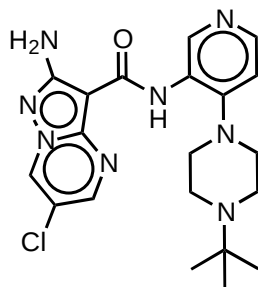
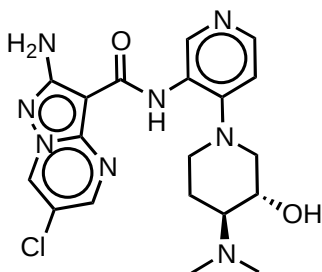
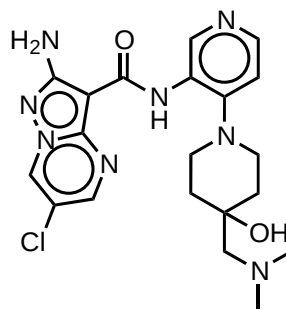
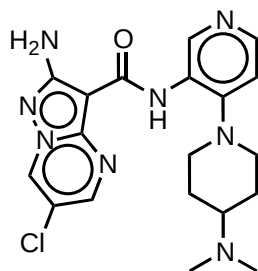
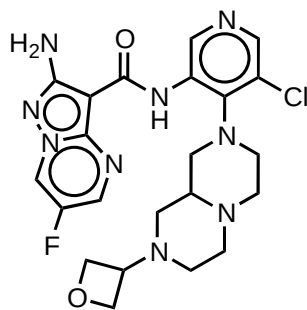
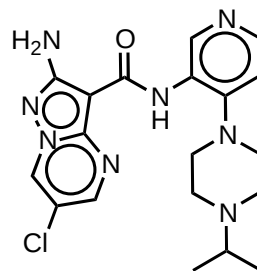


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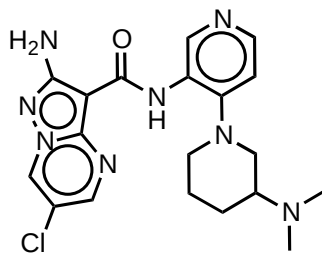


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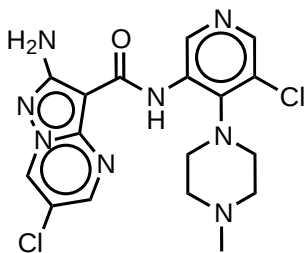


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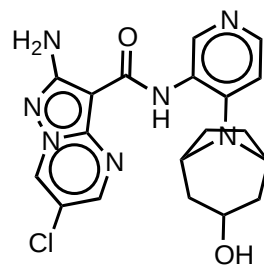
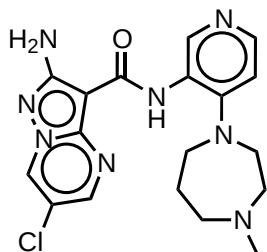
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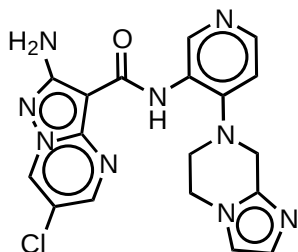
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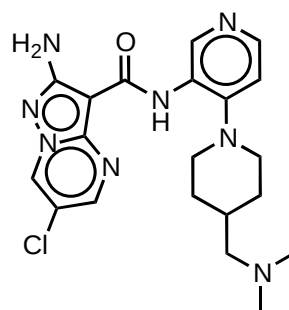
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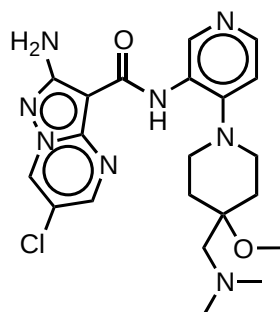
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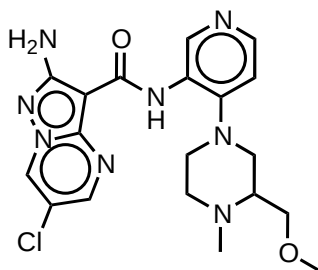
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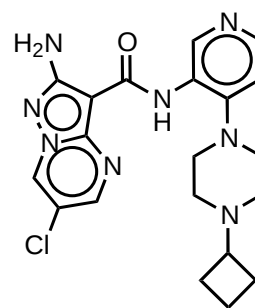
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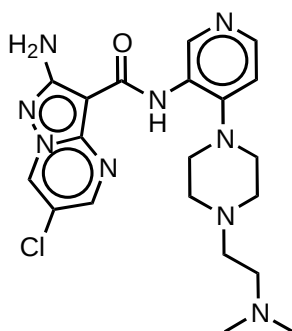
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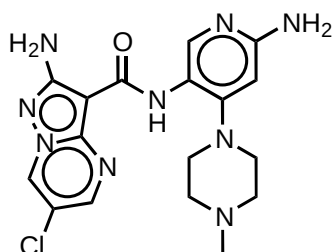
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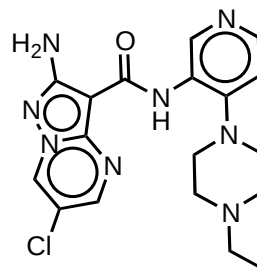
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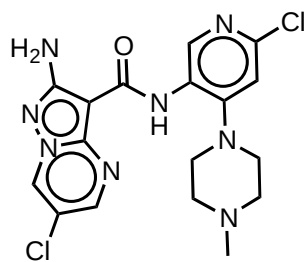
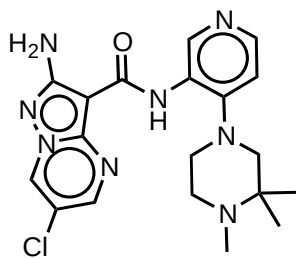
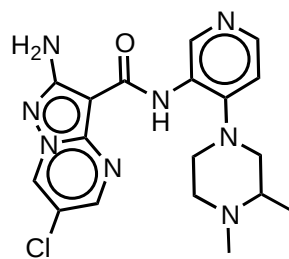
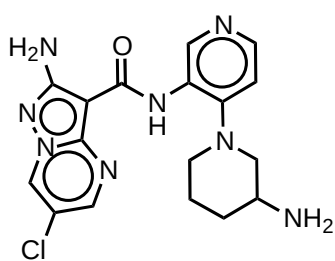
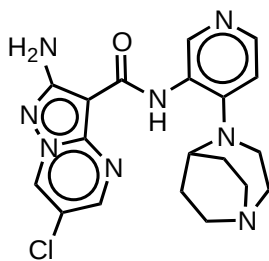
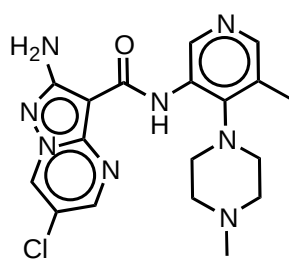
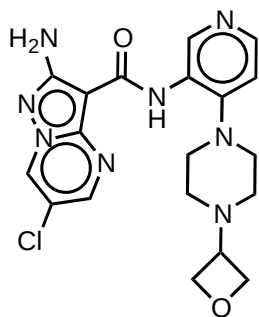
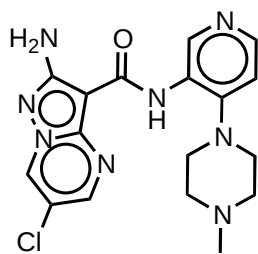
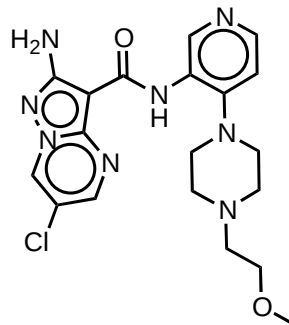
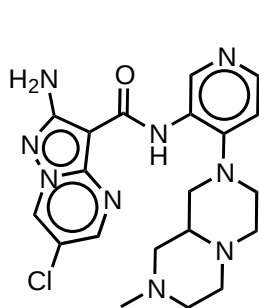
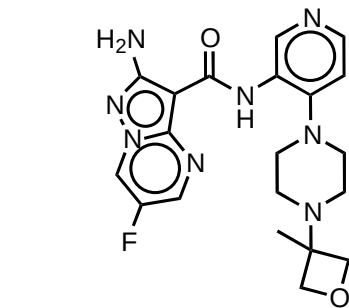
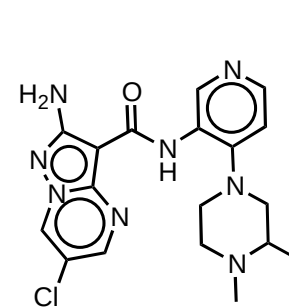


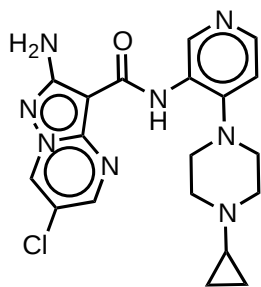
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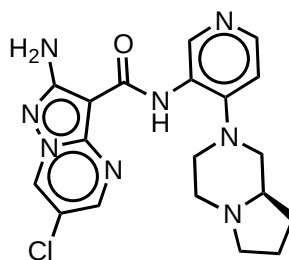
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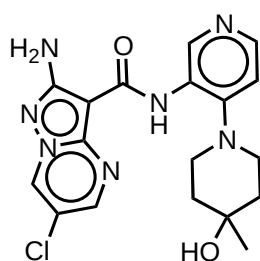
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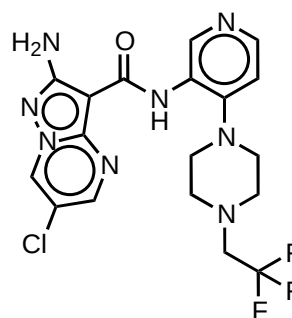
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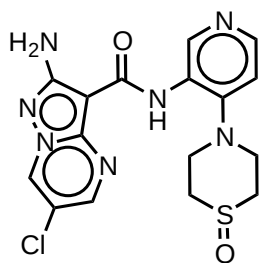
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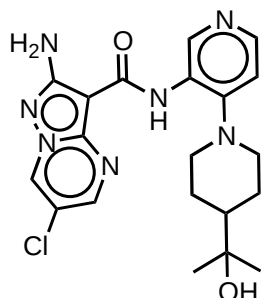
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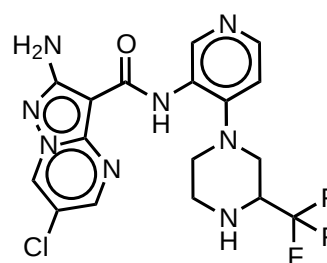
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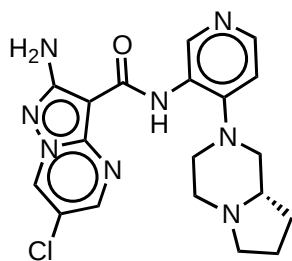
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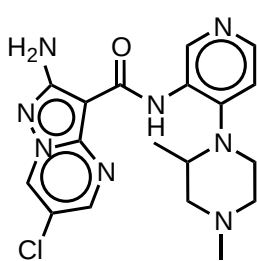
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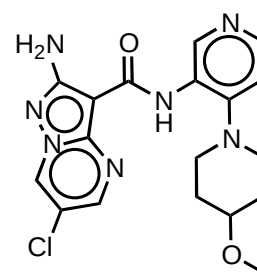
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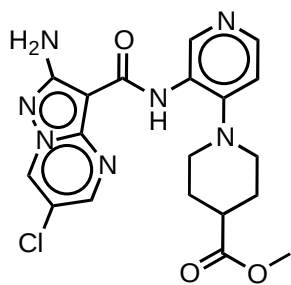
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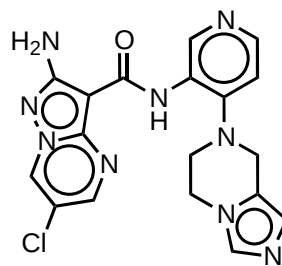
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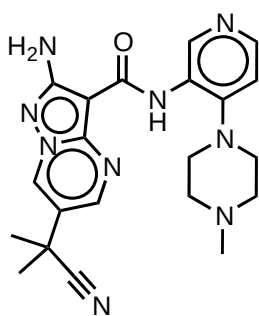
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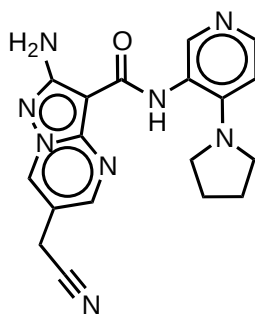
I-N-74



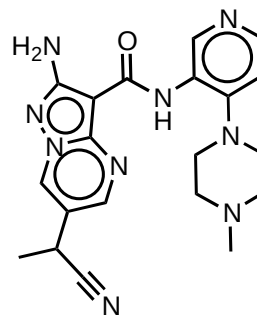
I-N-75



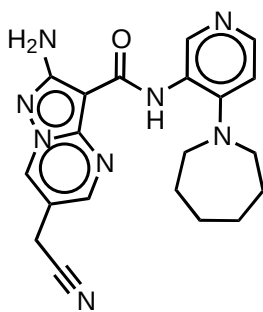
I-N-76



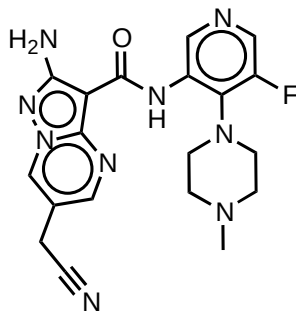
I-N-77



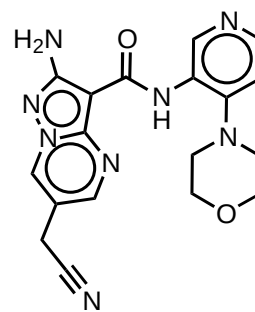
I-N-78



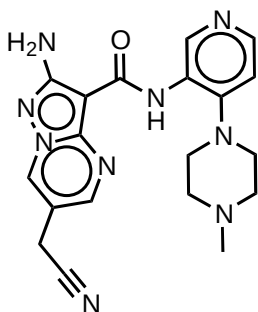
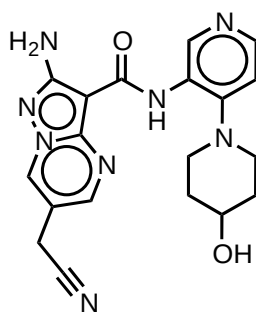
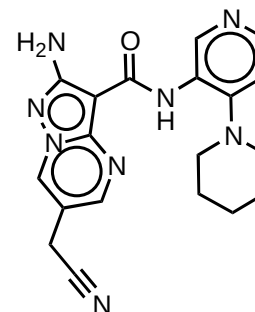
I-N-79

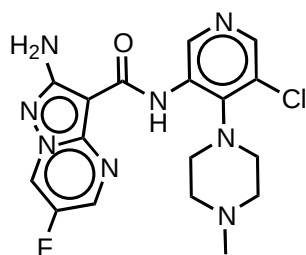
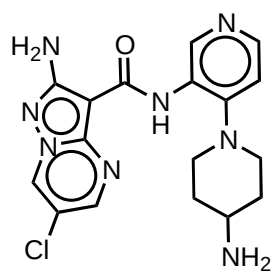
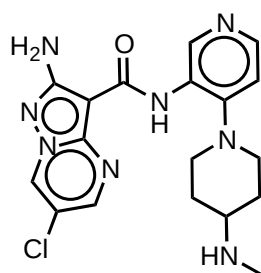
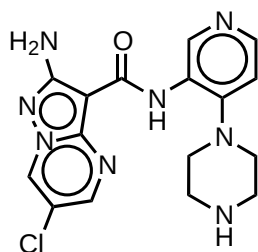
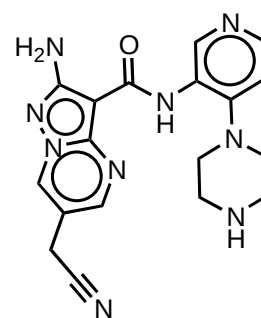
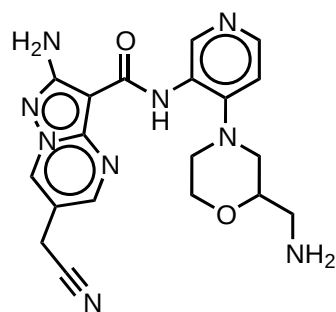
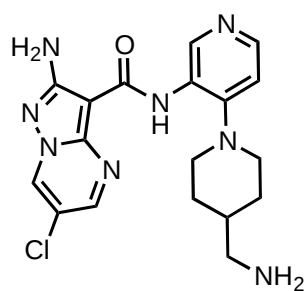


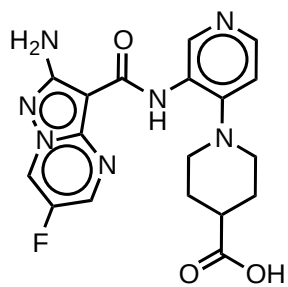
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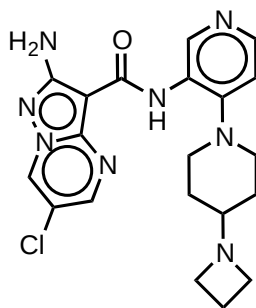
I-N-81



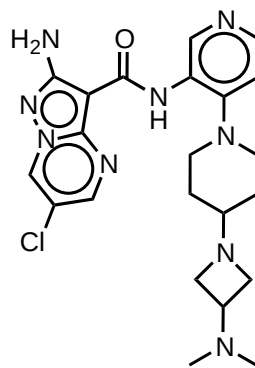
I-N-82**I-N-83****I-N-84****I-N-85****I-N-86****I-N-87****I-N-88****I-N-89****I-N-90****I-N-91**



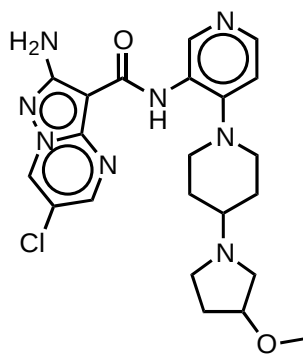
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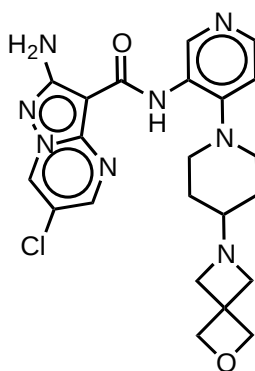
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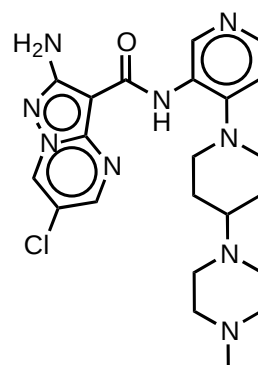
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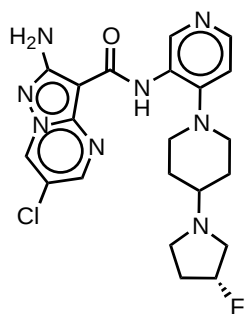
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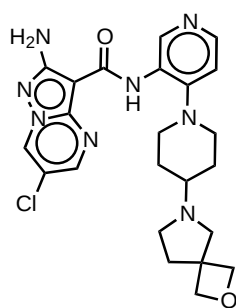
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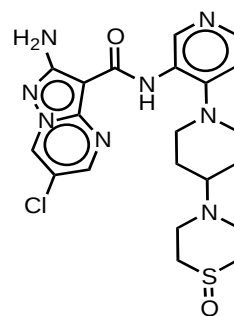
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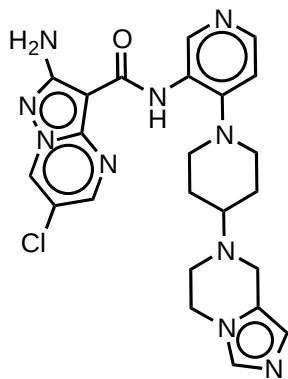
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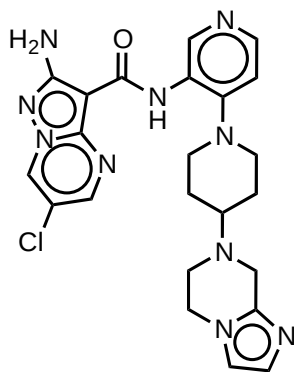
I-N-99



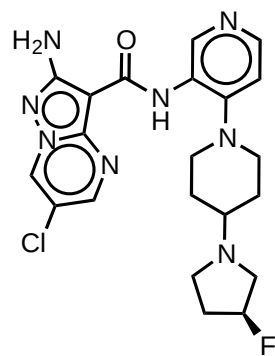
I-N-100



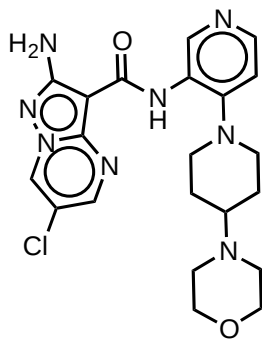
I-N-101



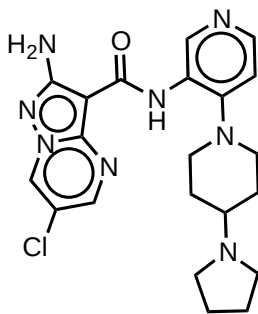
I-N-102



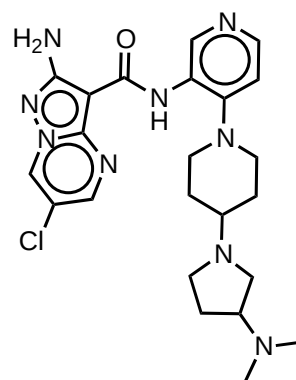
I-N-103



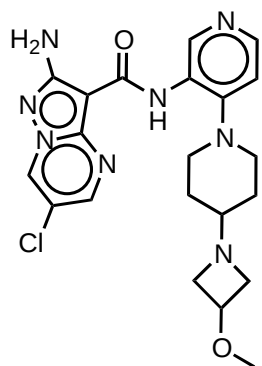
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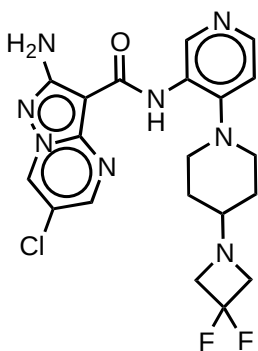
I-N-105



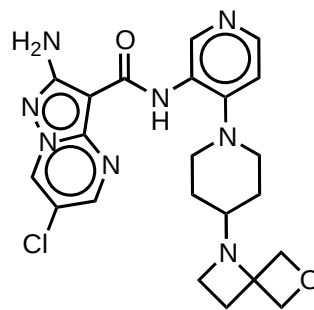
I-N-106



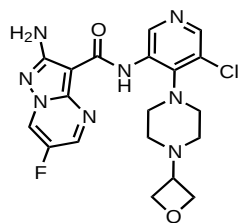
I-N-107



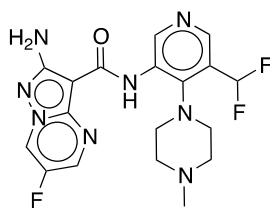
I-N-108



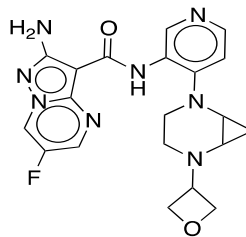
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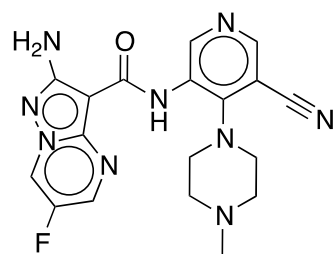
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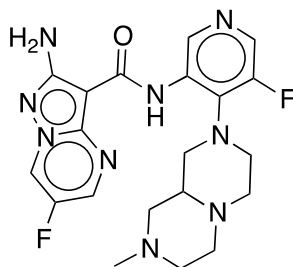
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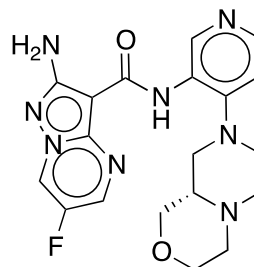
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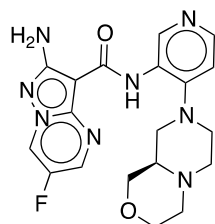
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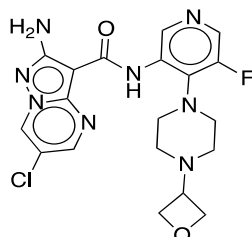
I-N-114



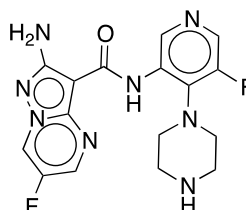
I-N-115



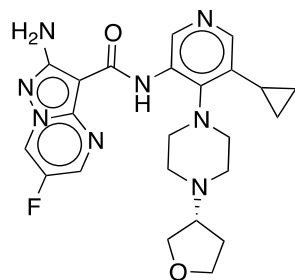
I-N-116



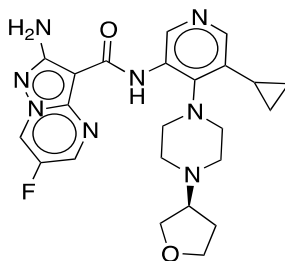
I-N-117



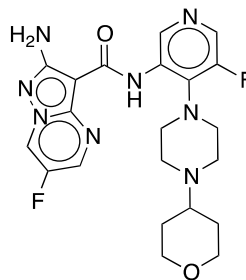
I-N-118



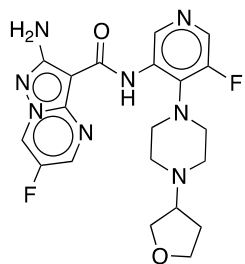
I-N-119



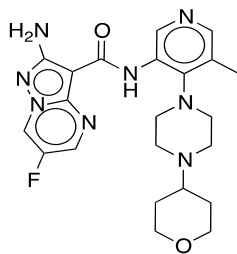
I-N-120



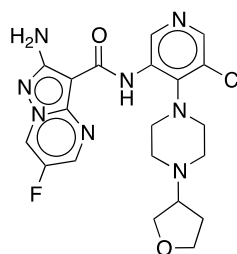
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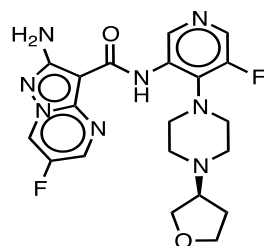
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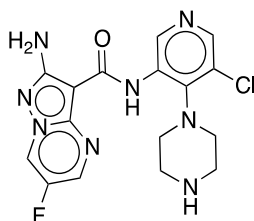
I-N-123



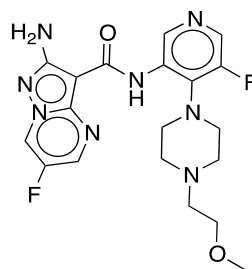
I-N-124



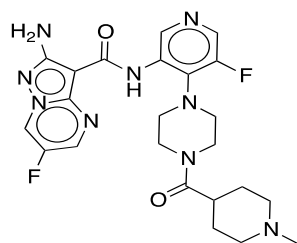
I-N-125



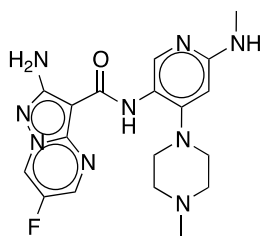
I-N-126



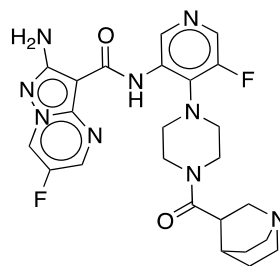
I-N-127



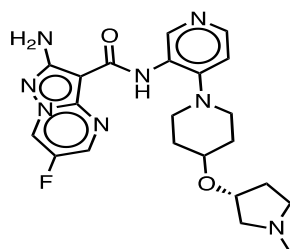
I-N-128



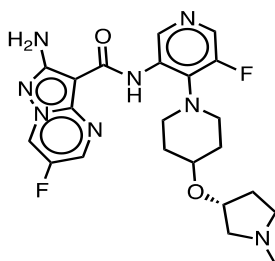
I-N-129



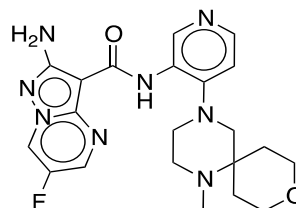
I-N-130



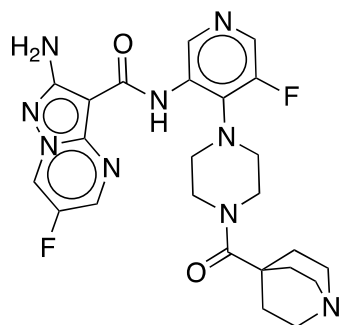
I-N-131



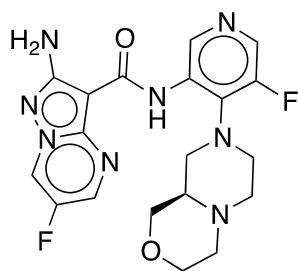
I-N-132



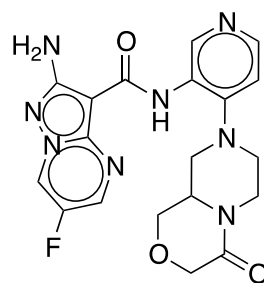
I-N-133



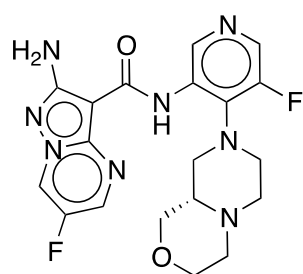
I-N-134



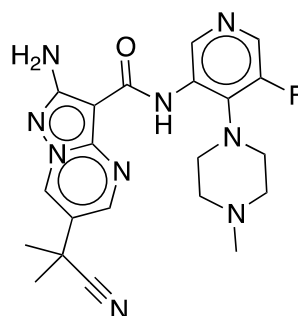
I-N-135



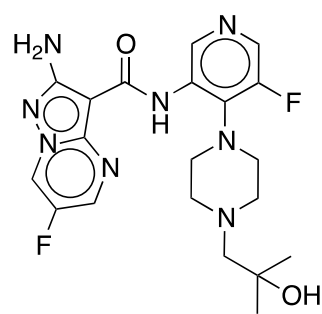
I-N-136



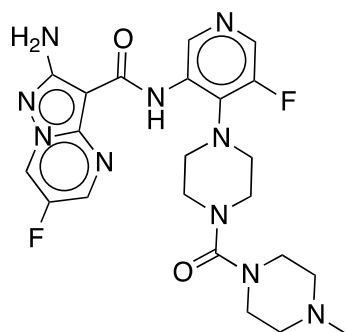
I-N-137



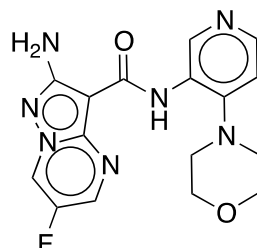
I-N-138



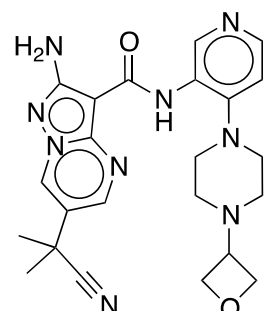
I-N-139



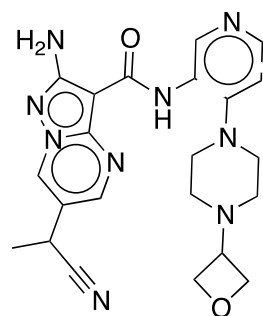
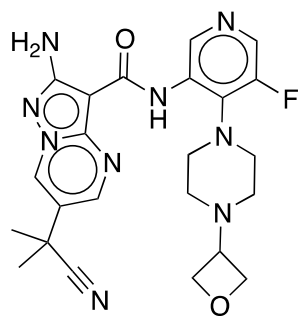
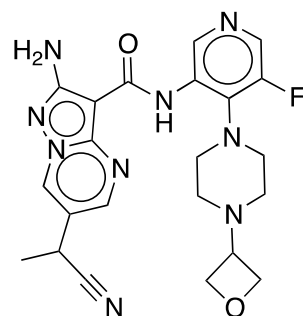
I-N-140

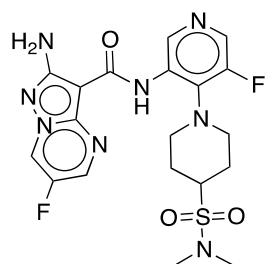
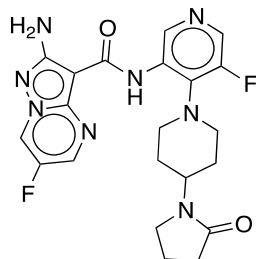
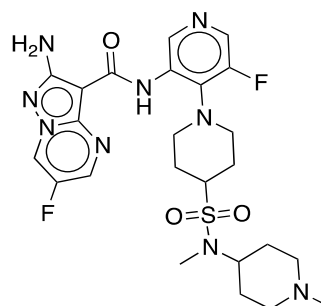
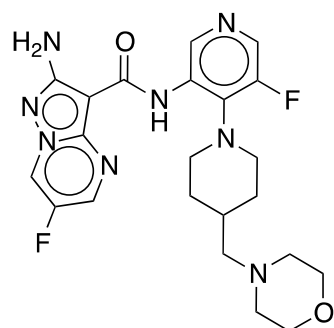
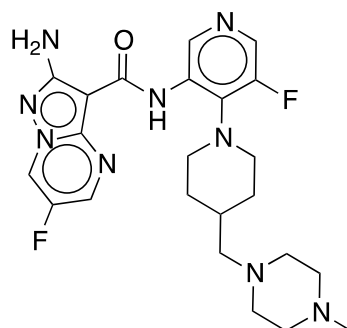
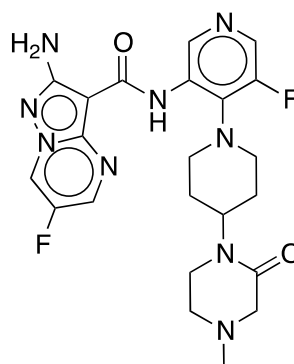
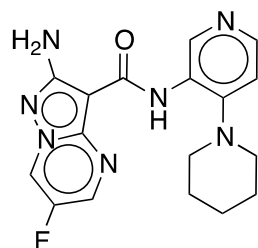
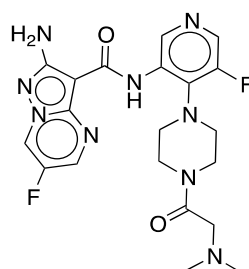
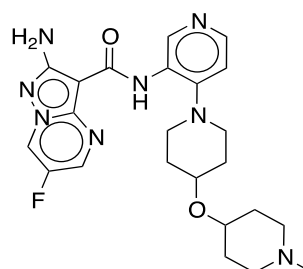


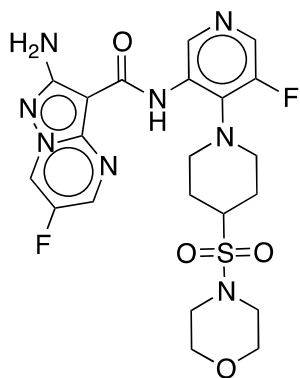
I-N-141



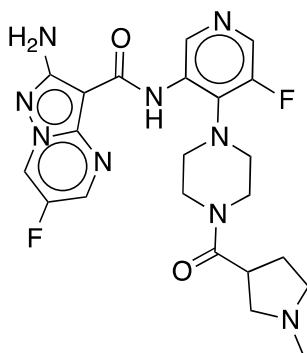
I-N-142



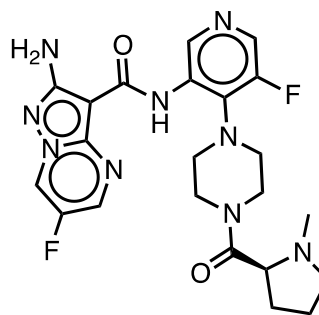
I-N-143**I-N-144****I-N-145****I-N-146****I-N-147****I-N-148****I-N-149****I-N-150****I-N-151****I-N-152****I-N-153****I-N-154**



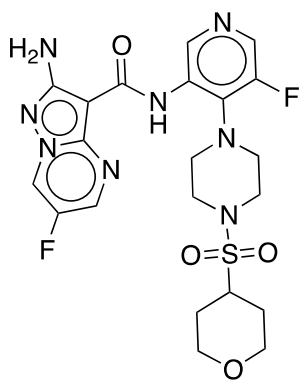
I-N-155



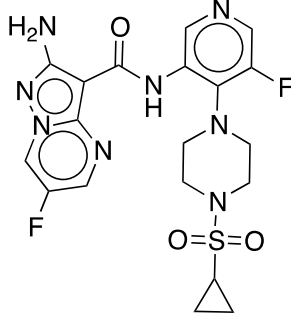
I-N-156



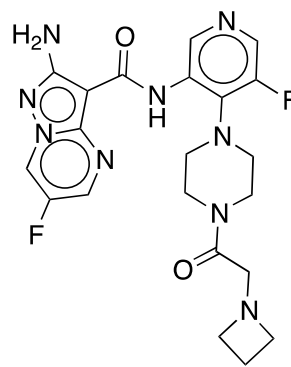
I-N-157



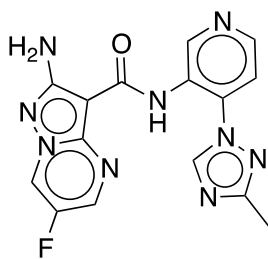
I-N-158



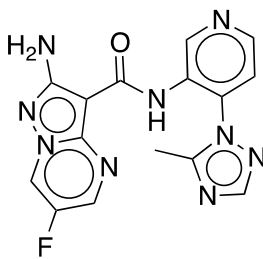
I-N-159



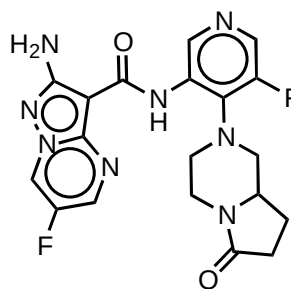
I-N-160



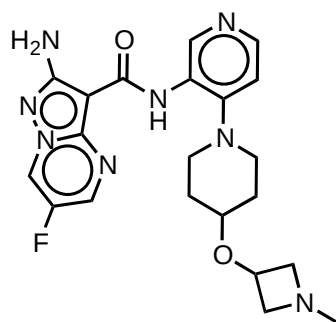
I-N-161



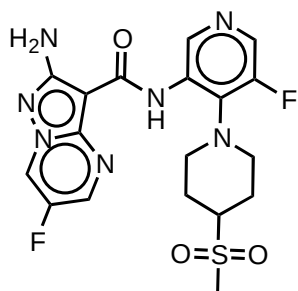
I-N-162



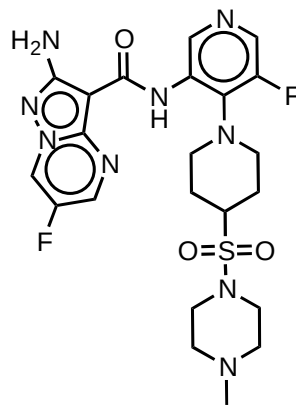
I-N-163



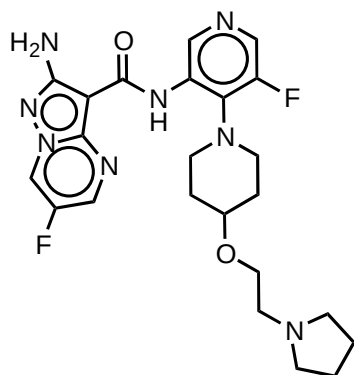
I-N-164



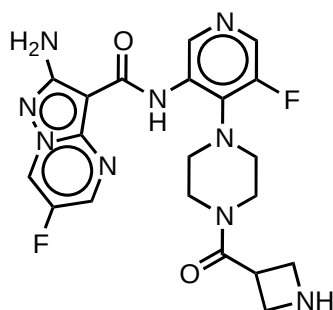
I-N-165



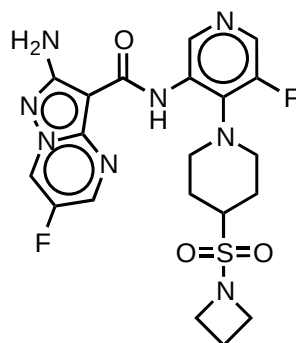
I-N-166



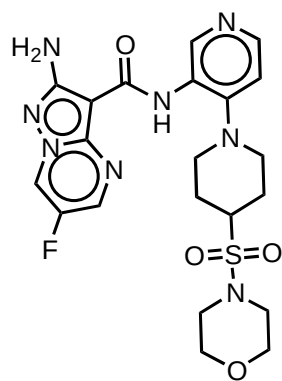
I-N-167



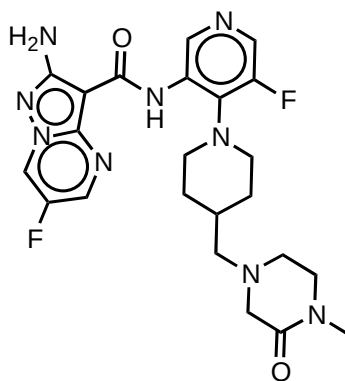
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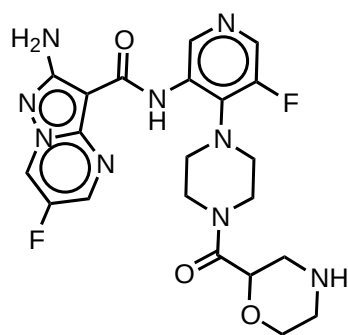
I-N-169



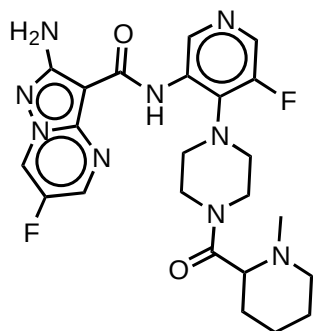
I-N-170



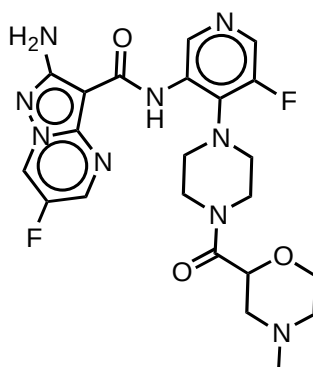
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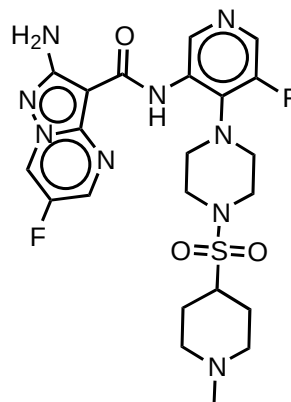
I-N-172



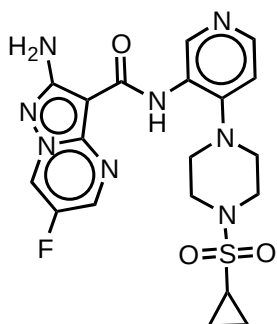
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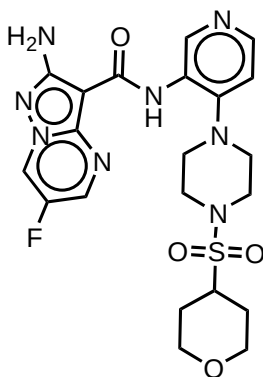
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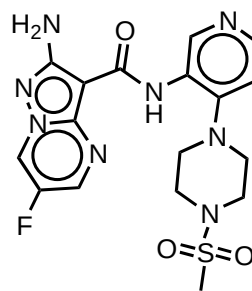
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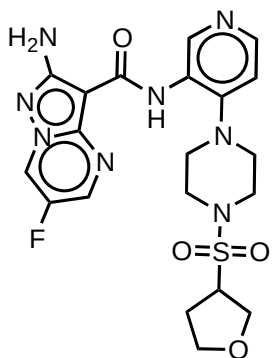
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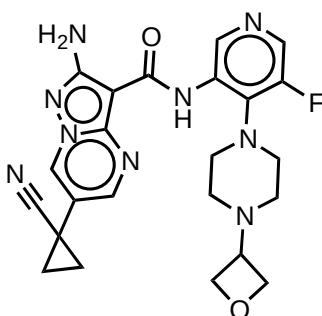
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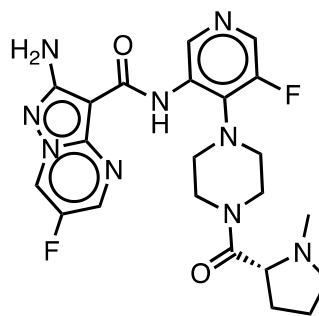
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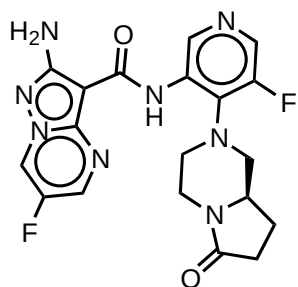
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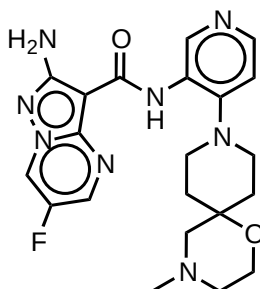
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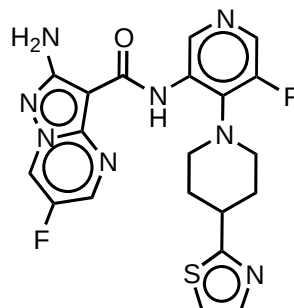
I-N-181



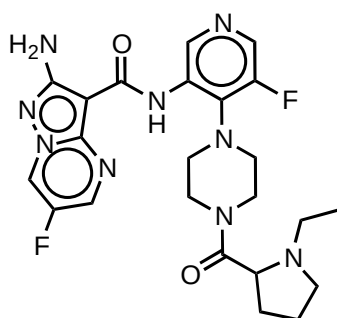
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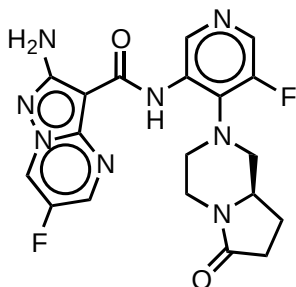
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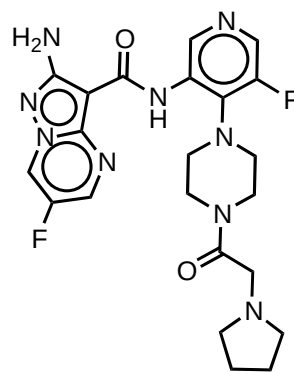
I-N-184



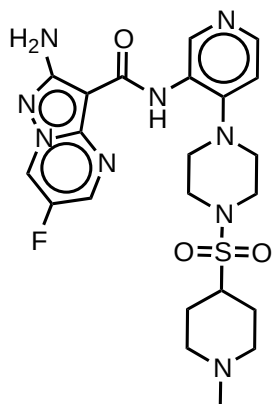
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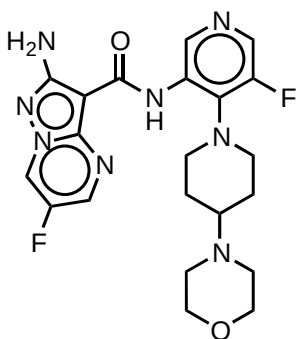
I-N-186



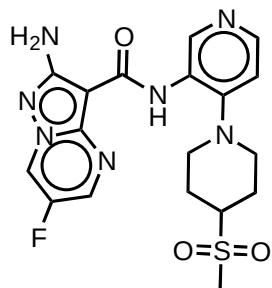
I-N-187



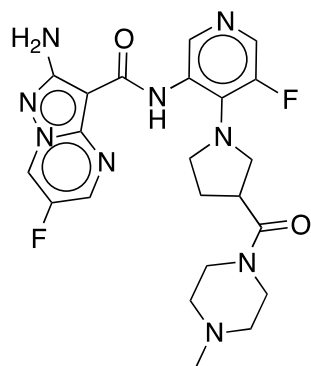
I-N-188



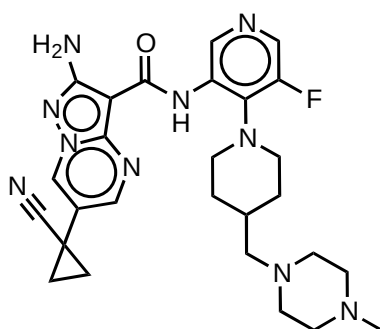
I-N-189



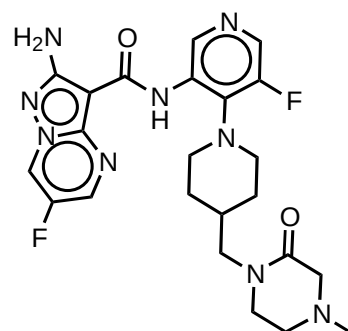
I-N-190



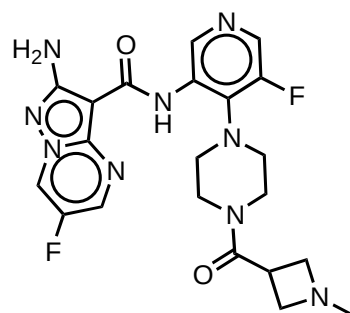
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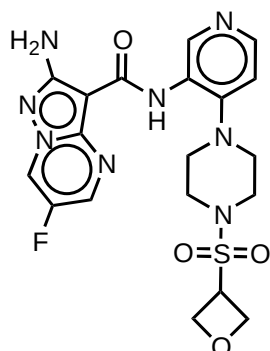
I-N-192



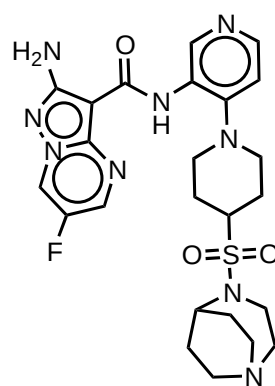
I-N-193



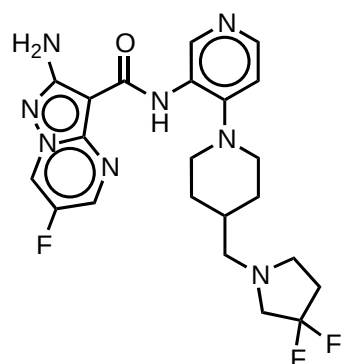
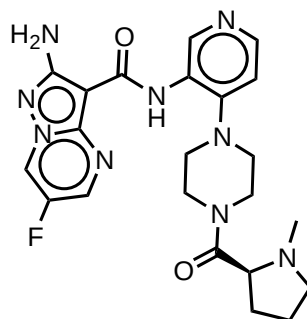
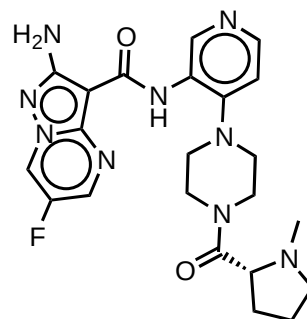
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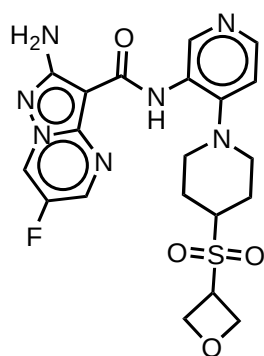
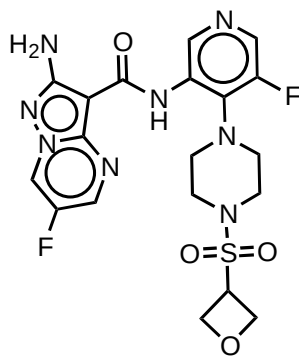
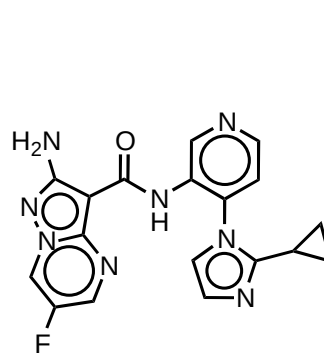
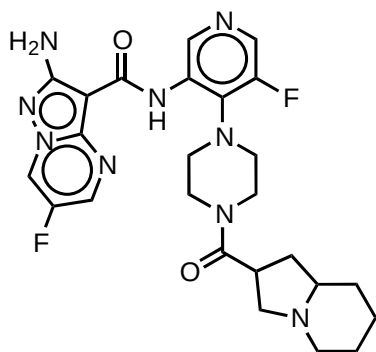
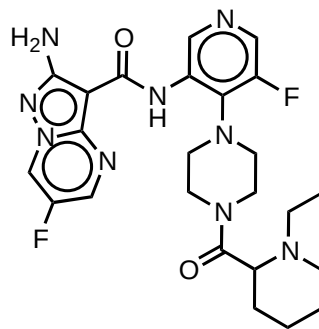
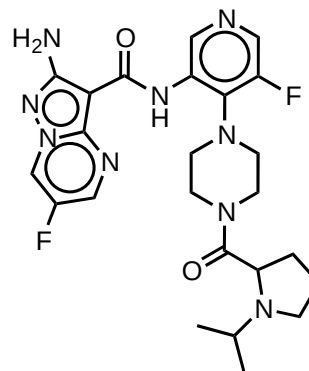
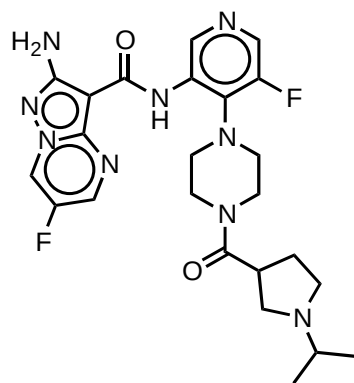
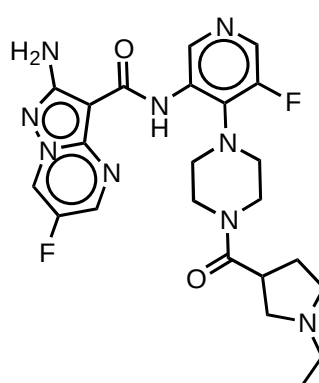
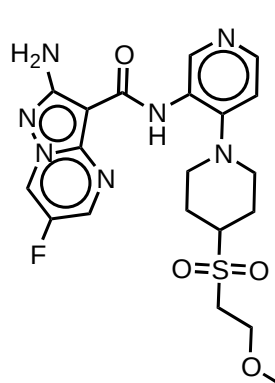


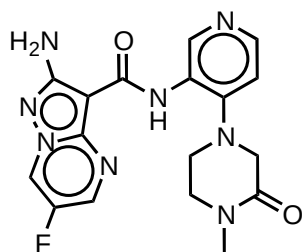
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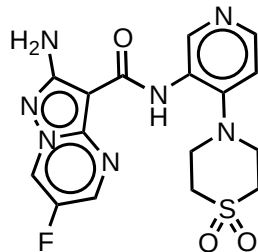
I-N-196



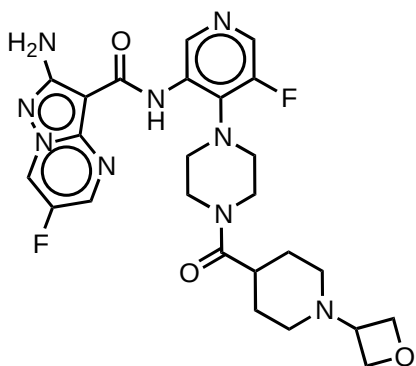
I-N-197**I-N-198****I-N-199****I-N-200****I-N-201****I-N-202****I-N-203****I-N-204****I-N-205****I-N-206****I-N-207****I-N-208**



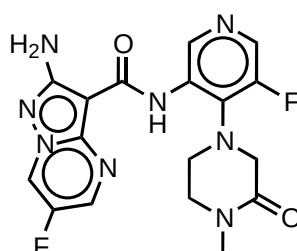
I-N-209



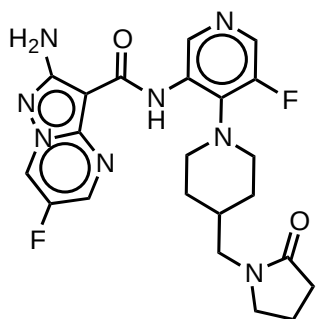
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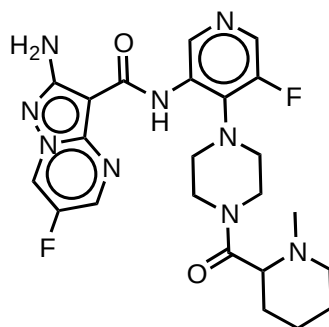
I-N-211



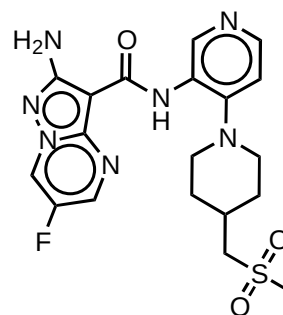
I-N-212



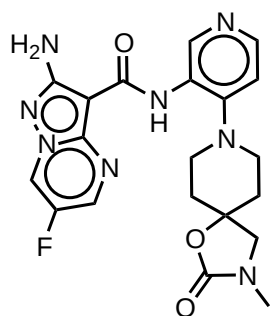
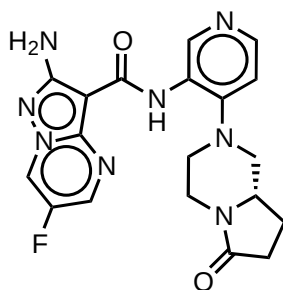
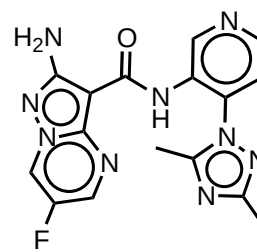
I-N-213

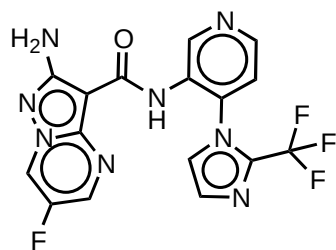
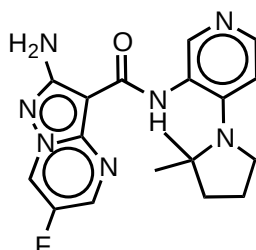
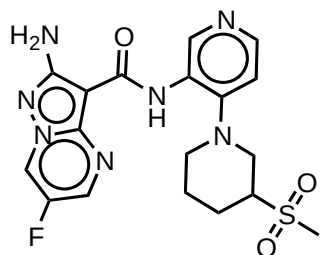
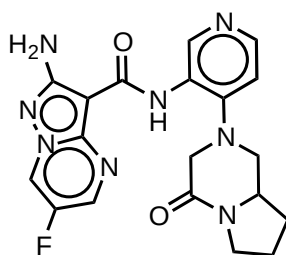
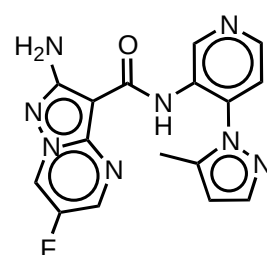
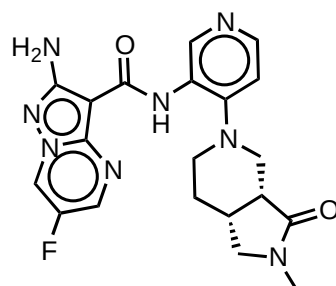
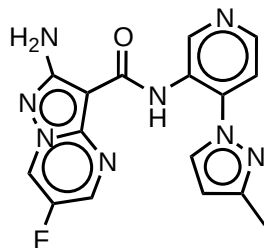
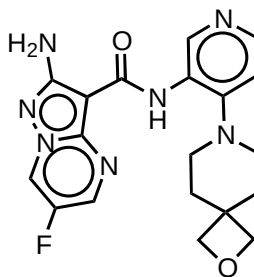
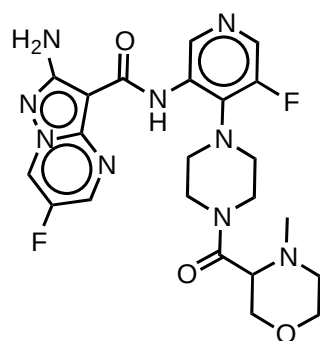
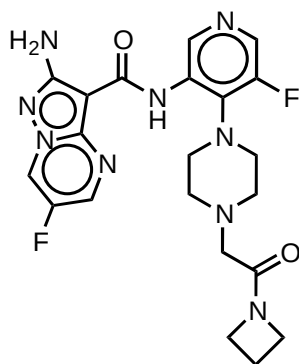
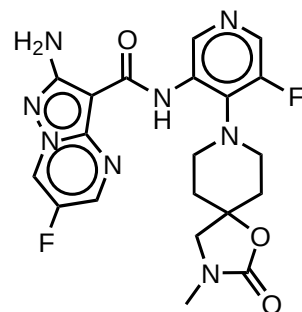


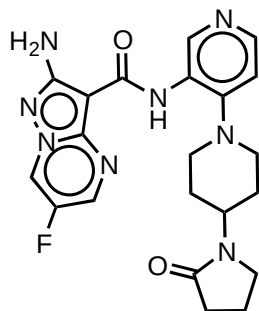
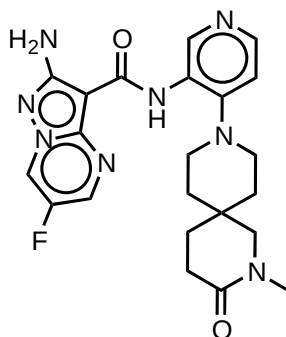
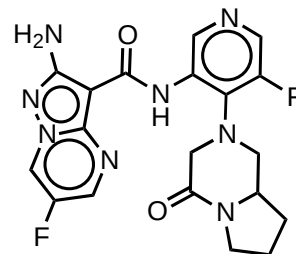
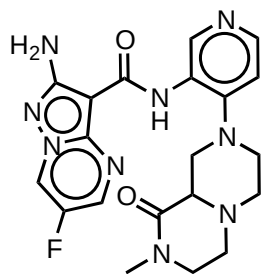
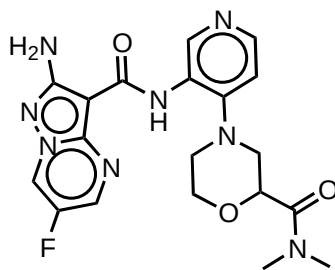
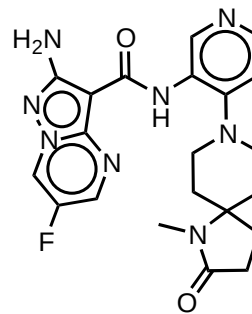
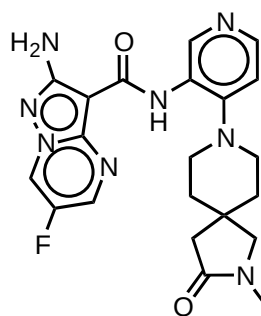
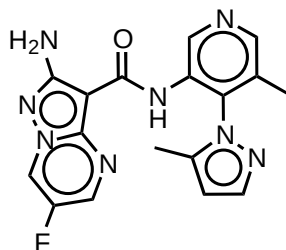
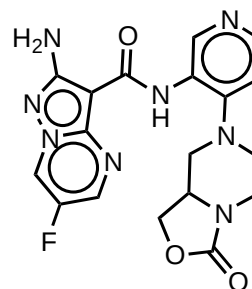
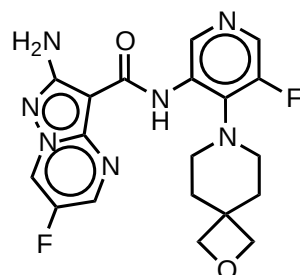
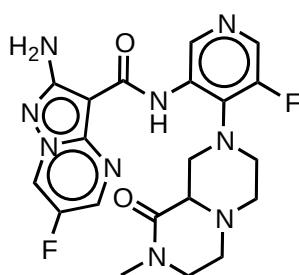
I-N-214



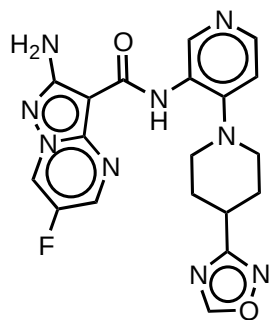
I-N-215



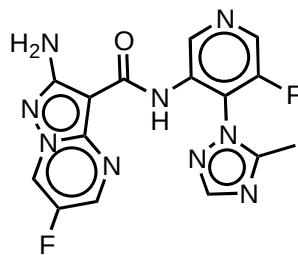
I-N-216**I-N-217****I-N-218****I-N-219****I-N-220****I-N-221****I-N-222****I-N-223****I-N-224****I-N-225****I-N-226**

I-N-227**I-N-228****I-N-229****I-N-230****I-N-231****I-N-232****I-N-233****I-N-234****I-N-235****I-N-236****I-N-237****I-N-238**

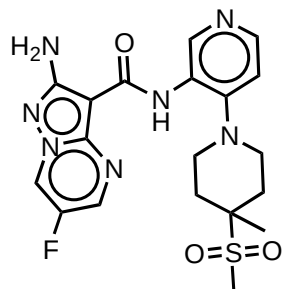
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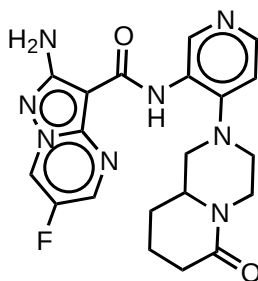
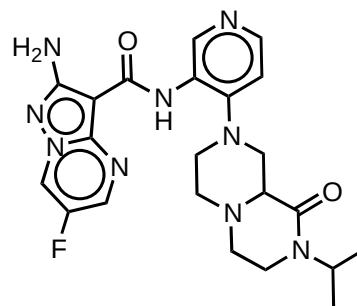
I-N-240



I-N-241



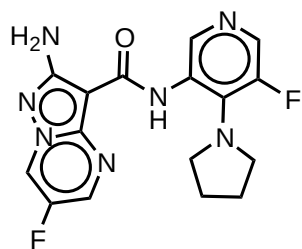
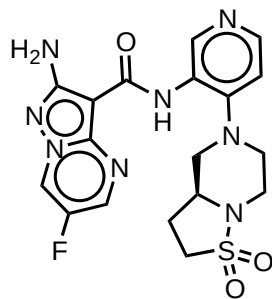
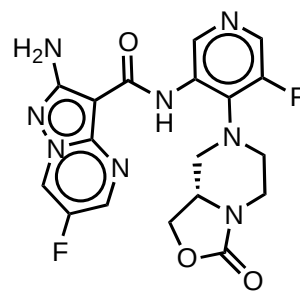
I-N-242



I-N-243

I-N-244

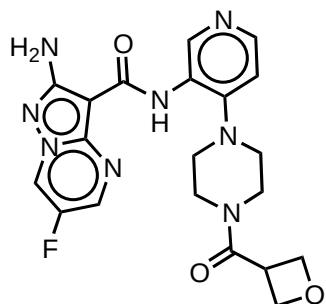
I-N-245



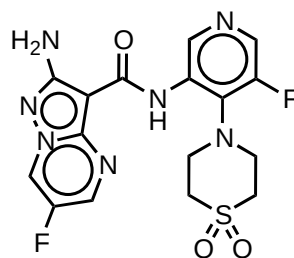
I-N-246

I-N-247

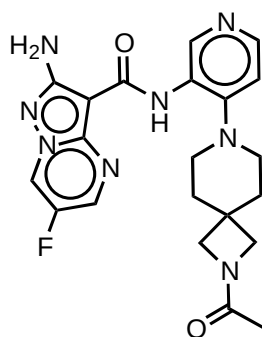
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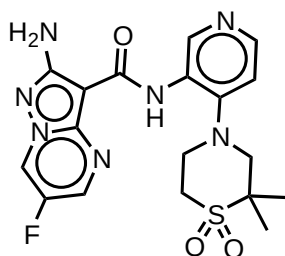
I-N-249



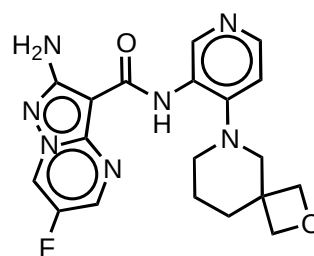
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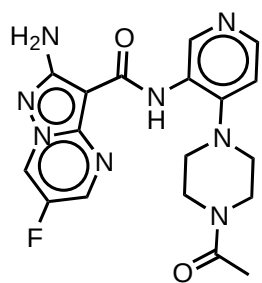
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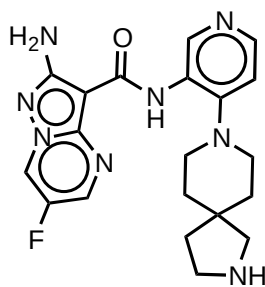
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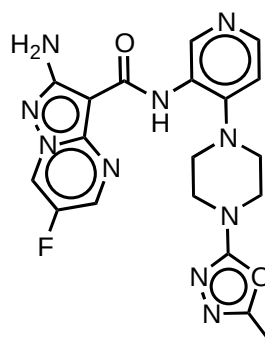
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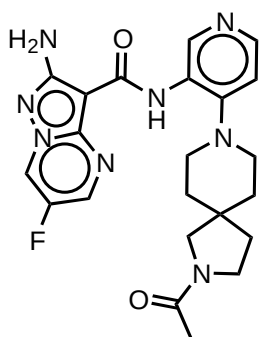
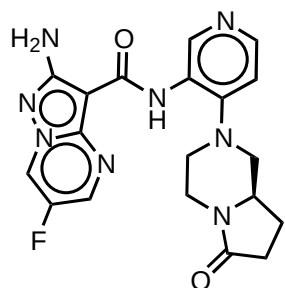
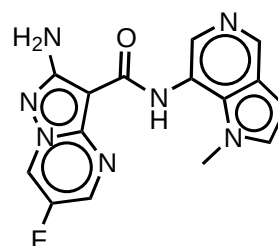
I-N-254



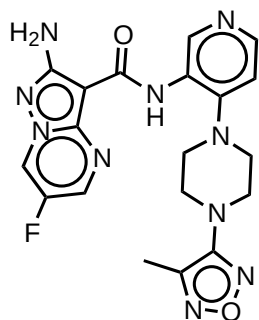
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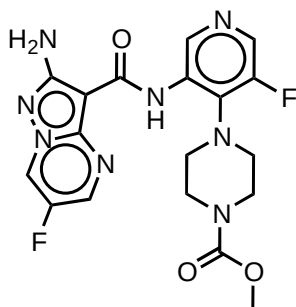
I-N-256



I-N-257

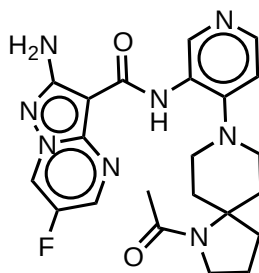


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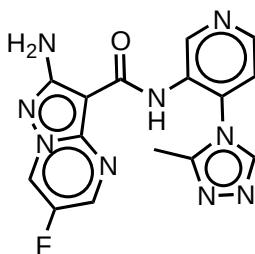


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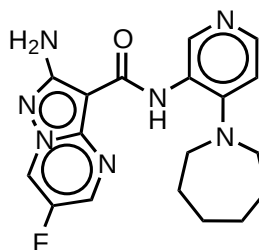
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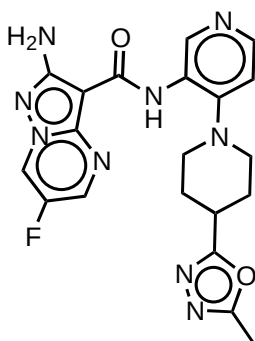
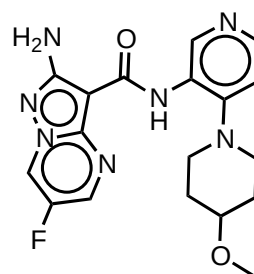
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I-N-262



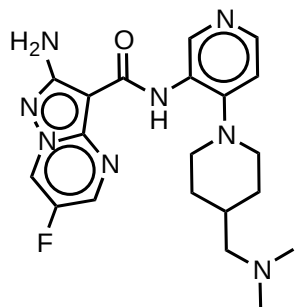
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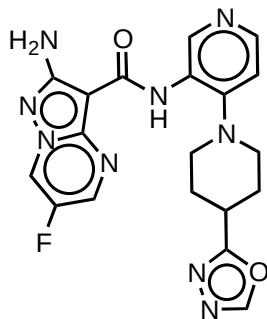
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I-N-265

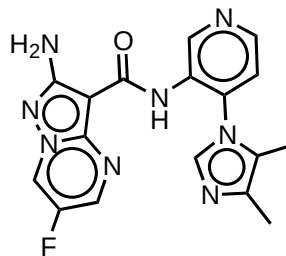
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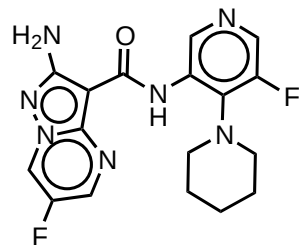
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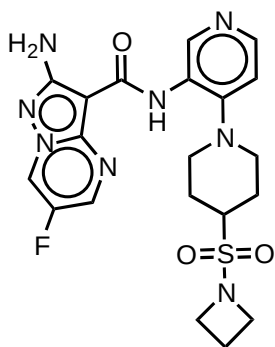
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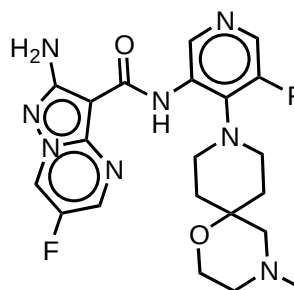
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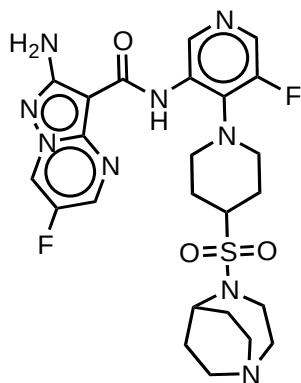
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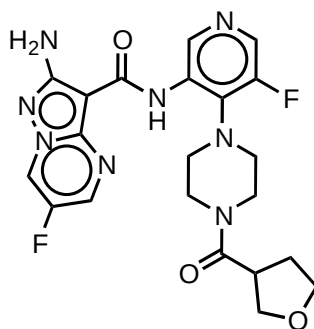
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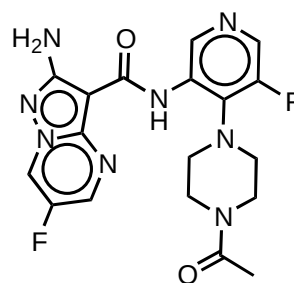
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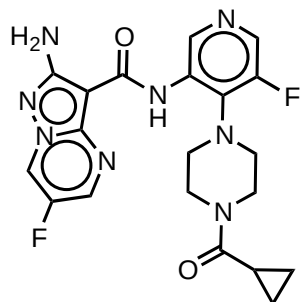
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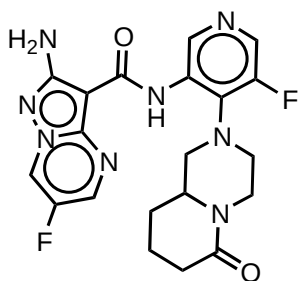
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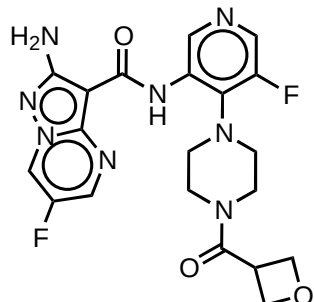
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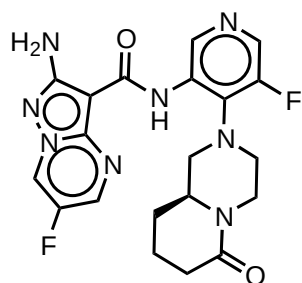
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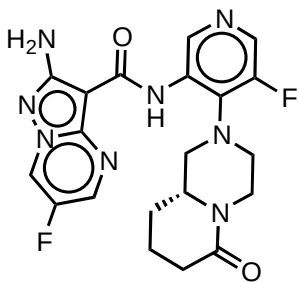
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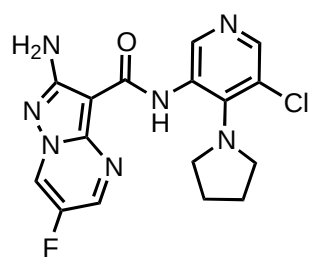
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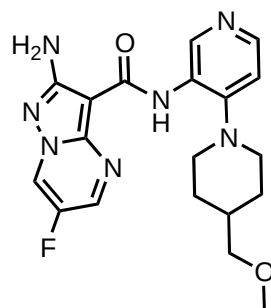
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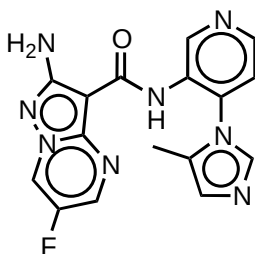
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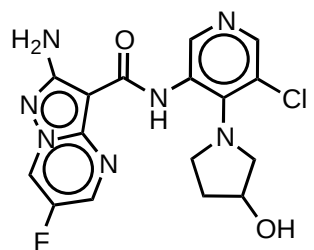
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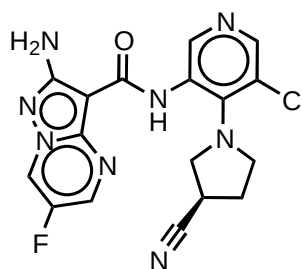
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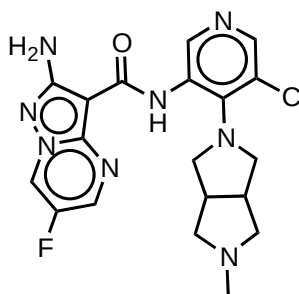
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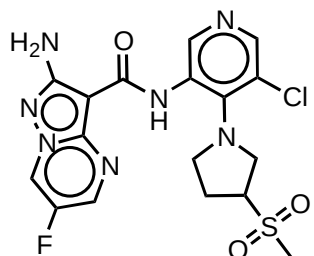
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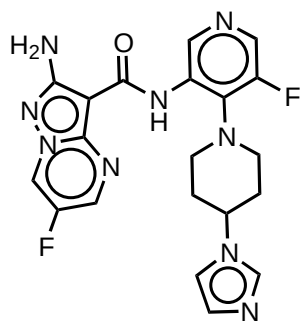
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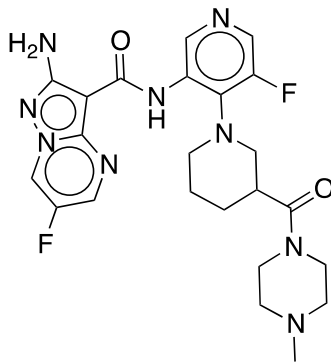
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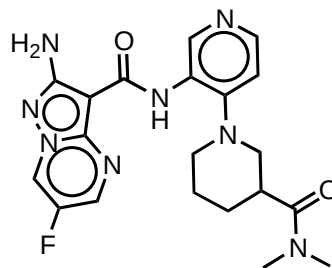
I-N-287



I-N-288



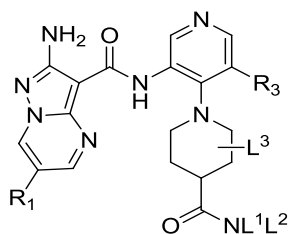
I-N-289



I-N-290

or a pharmaceutically acceptable salt thereof.

75. A compound of formula **I-B**:



I-B

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is fluoro, chloro, or $-C(J^1)_2CN$;

J^1 is independently H or $C_{1-2}alkyl$; or

two occurrences of J^1 , together with the carbon atom to which they are attached, form an optionally substituted 3-4 membered carbocyclic ring;

R³ is H; chloro; fluoro; C₁₋₄alkyl optionally substituted with 1-3 occurrences of halo; C₃₋₄cycloalkyl; -CN; or a C₁₋₃aliphatic chain wherein up to two methylene units of the aliphatic chain are optionally replaced with -O-, -NR-, -C(O)-, or -S(O)_n;

L¹ is H; a 3-7 membered aromatic or non-aromatic ring having 0-2 heteroatoms selected from the group consisting of oxygen nitrogen, and sulfur; or a C₁₋₆aliphatic chain, wherein up to two methylene units of the aliphatic chain are optionally replaced with -O-, -NR-, -C(O)-, or -S(O)_n; each L¹ is optionally substituted with C₁₋₄aliphatic; -CN; halo; -OH; or a 3-6 membered non-aromatic ring having 0-2 heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur;

L² is H; a 3-7 membered aromatic or non-aromatic ring having 0-2 heteroatoms selected from the group consisting of oxygen nitrogen, and sulfur; or a C₁₋₆aliphatic chain wherein up to two methylene units of the aliphatic chain are optionally replaced with -O-, -NR-, -C(O)-, or -S(O)_n; each L² is optionally substituted with C₁₋₄aliphatic; -CN; halo; -OH; or a 3-6 membered non-aromatic ring having 0-2 heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur; or

L¹ and L², together with the nitrogen to which they are attached, form a Ring D; Ring D is optionally substituted with 0-5 occurrences of J^G;

Ring D is a 3-7 membered heterocyclyl ring having 1-2 heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur; or an 7-12 membered fully saturated or partially unsaturated bicyclic ring having 1-5 heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur;

J^G is independently halo; -N(R^o)₂; a 3-6 membered carbocyclyl; a 3-6 membered heterocyclyl having 1-2 heteroatoms selected from oxygen nitrogen, or sulfur; or a C₁₋₄alkyl chain wherein up to two methylene units of the alkyl chain are optionally replaced with -O-, -NR-, -C(O)-, or -S(O)_n; each J^G is optionally substituted with 0-2 occurrences of J^K;

two occurrences of J^G on the same atom, together with the atom to which they are joined, form a 3-6 membered ring having 0-2 heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur;

two occurrences of J^G , together with Ring D, form a 6-10 membered saturated or partially unsaturated bridged ring system;

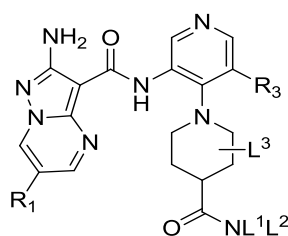
J^K is independently a 3-7 membered aromatic or non-aromatic ring having 0-2 heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur;

L^3 is independently H; chloro; fluoro; C_{1-4} alkyl optionally substituted with 1-3 occurrences of halo; -CN; or a C_{1-3} aliphatic chain, wherein up to two methylene units of the aliphatic chain are optionally replaced with -O-, -NR-, -C(O)-, or -S(O)_n;

n is 0, 1, or 2; and

R and R° are H or C_{1-4} alkyl.

76. A compound of formula **I-B**:



I-B

or a pharmaceutically acceptable salt thereof, wherein:

R¹ is fluoro, chloro, or -C(J¹)₂CN;

J¹ is independently H or C_{1-2} alkyl; or

two occurrences of J¹, together with the carbon atom to which they are attached, form an optionally substituted 3-4 membered carbocyclic ring;

R³ is H; chloro; fluoro; C_{1-4} alkyl optionally substituted with 1-3 occurrences of halo; C_{3-4} cycloalkyl; -CN; or a C_{1-3} aliphatic chain wherein up to two methylene units of the aliphatic chain are optionally replaced with -O-, -NR-, -C(O)-, or -S(O)_n;

L^1 is H; a 3-7 membered aromatic or non-aromatic ring having 0-2 heteroatoms selected from oxygen nitrogen or sulfur; or a C_{1-6} aliphatic chain wherein up to two methylene units of the aliphatic chain are optionally replaced with -O-, -NR-, -C(O)-, or $-S(O)_n$; each L^1 is optionally substituted with C_{1-4} aliphatic; -CN; halo; -OH; or a 3-6 membered non-aromatic ring having 0-2 heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur;

L^2 is H; a 3-7 membered aromatic or non-aromatic ring having 0-2 heteroatoms selected from oxygen nitrogen or sulfur; or a C_{1-6} aliphatic chain wherein up to two methylene units of the aliphatic chain are optionally replaced with -O-, -NR-, -C(O)-, or $-S(O)_n$; each L^2 is optionally substituted with C_{1-4} aliphatic; -CN; halo; -OH; or a 3-6 membered non-aromatic ring having 0-2 heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur; or

L^1 and L^2 , together with the nitrogen to which they are attached, form a Ring D; Ring D is optionally substituted with 0-5 occurrences of J^G ;

L^3 is independently H; C_{1-3} aliphatic; or CN;

Ring D is a 3-7 membered heterocyclyl ring having 1-2 heteroatoms selected from oxygen, nitrogen or sulfur; or an 7-12 membered fully saturated or partially unsaturated bicyclic ring having 1-5 heteroatoms selected from oxygen, nitrogen, or sulfur;

J^G is independently halo; -CN; $-N(R^\circ)_2$; $\rightarrow O$; a 3-6 membered carbocyclyl; a 3-6 membered heterocyclyl having 1-2 heteroatoms selected from the group consisting of oxygen nitrogen, and sulfur; or a C_{1-4} alkyl chain, wherein up to two methylene units of the alkyl chain are optionally replaced with -O-, -NR-, -C(O)-, or $-S(O)_n$; each J^G is optionally substituted with 0-2 occurrences of J^K ;

two occurrences of J^G on the same atom, together with the atom to which they are joined, form a 3-6 membered ring having 0-2 heteroatoms selected from oxygen, nitrogen, or sulfur;

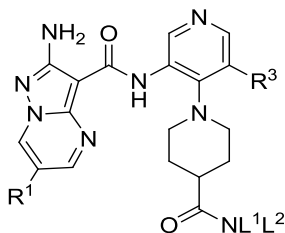
two occurrences of J^G , together with Ring D, form a 6-10 membered saturated or partially unsaturated bridged ring system;

J^K is independently a 3-7 membered aromatic or non-aromatic ring having 0-2 heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur;

n is 0, 1, or 2; and

R and R° are H or C₁₋₄alkyl.

77. A compound of represented by the following structural formula:



or a pharmaceutically acceptable salt thereof, wherein:

R¹ is fluoro, chloro, or -C(J¹)₂CN;

J¹ is independently H or C₁₋₂alkyl; or

two occurrences of J¹, together with the carbon atom to which they are attached, form an optionally substituted 3-4 membered carbocyclic ring;

R³ is H; chloro; fluoro; C₁₋₄alkyl optionally substituted with 1-3 occurrences of halo; C₃₋₄cycloalkyl; -CN; or a C₁₋₃aliphatic chain wherein up to two methylene units of the aliphatic chain are optionally replaced with -O-, -NR-, -C(O)-, or -S(O)_n;

L¹ is H; a 3-7 membered aromatic or non-aromatic ring having 0-2 heteroatoms selected from oxygen nitrogen or sulfur; or a C₁₋₆aliphatic chain, wherein up to two methylene units of the aliphatic chain are optionally replaced with -O-, -NR-, -C(O)-, or -S(O)_n; each L¹ is optionally substituted with C₁₋₄aliphatic; -CN; halo; -OH; or a 3-6 membered non-aromatic ring having 0-2 heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur;

L² is H; a 3-7 membered aromatic or non-aromatic ring having 0-2 heteroatoms selected from the group consisting of oxygen nitrogen, and sulfur; or a C₁₋₆aliphatic chain wherein up to two methylene units of the aliphatic chain are optionally replaced with -O-, -NR-, -C(O)-, or -S(O)_n; each L² is optionally substituted with C₁₋₄aliphatic; -CN; halo; -OH; or a 3-6 membered non-

aromatic ring having 0-2 heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur; or

L^1 and L^2 , together with the nitrogen to which they are attached, form a Ring D; Ring D is optionally substituted with 0-5 occurrences of J^G ;

Ring D is a 3-7 membered heterocyclyl ring having 1-2 heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur; or an 7-12 membered fully saturated or partially unsaturated bicyclic ring having 1-5 heteroatoms selected from the group consisting of oxygen, nitrogen, or sulfur;

J^G is independently halo; $-N(R^\circ)_2$; a 3-6 membered carbocyclyl; a 3-6 membered heterocyclyl having 1-2 heteroatoms selected from the group consisting of oxygen nitrogen, and sulfur; or a C_{1-4} alkyl chain, wherein up to two methylene units of the alkyl chain are optionally replaced with $-O-$, $-NR-$, $-C(O)-$, or $-S(O)_n$; each J^G is optionally substituted with 0-2 occurrences of J^K ;

two occurrences of J^G on the same atom, together with the atom to which they are joined, form a 3-6 membered ring having 0-2 heteroatoms selected from oxygen, nitrogen, or sulfur;

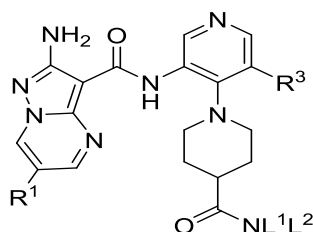
two occurrences of J^G , together with Ring D, form a 6-10 membered saturated or partially unsaturated bridged ring system;

J^K is independently a 3-7 membered aromatic or non-aromatic ring having 0-2 heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur;

n is 0, 1, or 2; and

R and R° are H or C_{1-4} alkyl.

78. A compound represented by the following structural formula:



or a pharmaceutically acceptable salt thereof, wherein:

R^1 is fluoro, chloro, or $-C(J^1)_2CN$;

J^1 is independently H or C_{1-2} alkyl; or

two occurrences of J^1 , together with the carbon atom to which they are attached, form an optionally substituted 3-4 membered carbocyclic ring;

R^3 is H; chloro; fluoro; C_{1-4} alkyl optionally substituted with 1-3 occurrences of halo; C_{3-4} cycloalkyl; or $-CN$;

L^1 is an optionally substituted C_{1-6} aliphatic;

L^2 is an optionally substituted C_{1-6} aliphatic; or

L^1 and L^2 , together with the nitrogen to which they are attached, form a Ring D; Ring D is optionally substituted with 0-5 occurrences of J^G ;

Ring D is a 3-7 membered heterocyclyl ring having 1-2 heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur; or an 8-12 membered fully saturated or partially unsaturated bicyclic ring having 0-5 heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur;

J^G is independently C_{1-4} alkyl, $-N(R^\circ)_2$, or a 3-5 membered carbocyclyl; or

two occurrences of J^G , together with Ring D, form a 6-10 membered saturated or partially unsaturated bridged ring system; and

R° is H or C_{1-4} alkyl.

79. The compound of any one of claims 75, 76, and 77, wherein R^1 is fluoro.

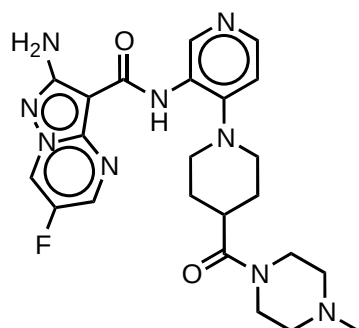
80. The compound of any one of claims 75, 76, and 77, wherein R^1 is $-CH_2CN$.

81. The compound of any one of claims 75, 76, and 77, wherein R^1 is chloro.

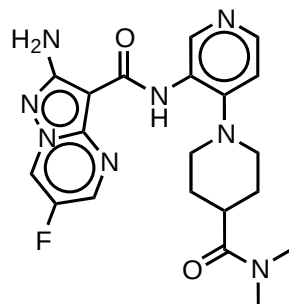
82. The compound of any one of claims 75, 76, 77, 79, and 80, wherein R^3 is H, chloro, fluoro, cyclopropyl, or C_{1-4} alkyl.
83. The compound of claim 82, wherein R^3 is H, chloro, or fluoro.
84. The compound of claim 82, wherein R^3 is H.
85. The compound of claim 82, wherein R^3 is chloro.
86. The compound of claim 82, wherein R^3 is fluoro.
87. The compound of any one of claims 83-86, wherein L^1 and L^2 are H; $-(C_{1-3}\text{alkyl})O(C_{1-2}\text{alkyl})$; $-(C_{1-3}\text{alkyl})N(C_{1-2}\text{alkyl})_2$; $C_{1-4}\text{alkyl}$; azetidiny; piperidinyl; oxetanyl; or pyrrolidinyl.
88. The compound of any one of claims 79-86, wherein L^1 and L^2 , together with the nitrogen to which they are attached, form Ring D.
89. The compound of claim 88, wherein Ring D is a 3-7 membered heterocyclcyl ring having 1-2 heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur.
90. The compound of claim 89, wherein Ring D is piperazinyl, piperidinyl, morpholinyl, tetrahydropyranyl, azetidiny, pyrrolidinyl, or 1,4-diazepanyl.
91. The compound of claim 90, wherein Ring D is piperazinyl, piperidinyl, 1,4-diazepanyl, pyrrolidinyl or azetidiny.
92. The compound of claim 91, wherein Ring D is piperazinyl or piperidinyl.

93. The compound of claim 88, wherein Ring D is an 8-12 membered fully saturated or partially unsaturated bicyclic ring having 0-5 heteroatoms selected from oxygen, nitrogen, or sulfur.
94. The compound of claim 93, wherein Ring D is octahydropyrrolo[1,2-a]pyrazine or octahydropyrrolo[3,4-c]pyrrole.
95. The compound of any one of claims 89-94, wherein J^G is halo, C₁₋₄alkyl, -O(C₁₋₃alkyl), C₃₋₆cycloalkyl, a 3-6 membered heterocyclyl, -NH(C₁₋₃alkyl), -OH, or -N(C₁₋₄alkyl)₂.
96. The compound of claim 95, wherein J^G is methyl, -N(C₁₋₄alkyl)₂, ethyl, -O(C₁₋₃alkyl), cyclopropyl, oxetanyl, cyclobutyl, pyrrolidinyl, piperidinyl, or azetidiny.
97. The compound of claim 96, wherein J^G is methyl, -O(C₁₋₃alkyl), oxetanyl, pyrrolidinyl, piperidinyl, or azetidiny.
98. The compound of claim 97, wherein J^G is methyl.
99. The compound of any one of claims 90-93, wherein two occurrences of J^G, together with Ring D, form a 6-10 membered saturated or partially unsaturated bridged ring system.
100. The compound of claim 99, wherein the bridged ring system is 1,4-diazabicyclo[3.2.2]nonane, 1,4-diazabicyclo[3.2.1]octane, or 2,5-diazabicyclo[2.2.1]heptane.
101. The compounds of any one of claims 89-92, wherein two occurrences of J^G on the same atom, together with the atom to which they are joined, form a 3-6 membered ring having 0-2 heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur.
102. The compound of claim 101, wherein the ring formed by the two occurrences of J^G on the same atom is selected from oxetanyl or cyclopropyl.

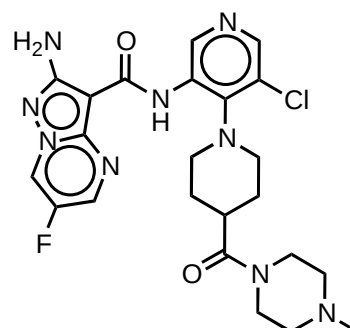
103. A compound, wherein the compound is::



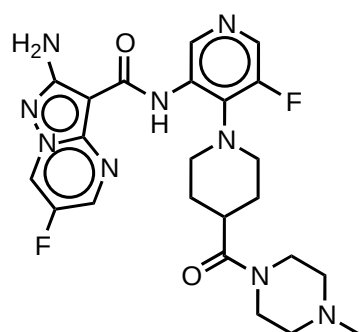
I-G-1



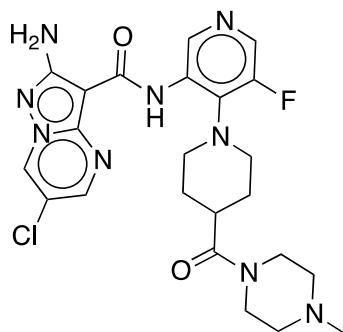
I-G-2



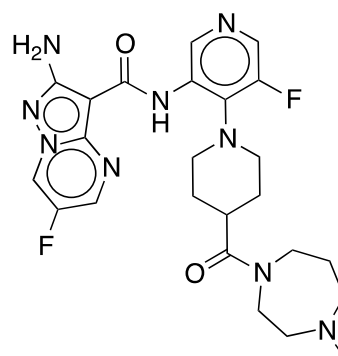
I-G-3



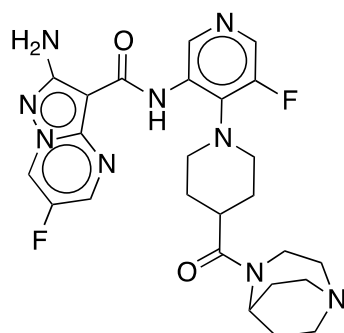
I-G-4



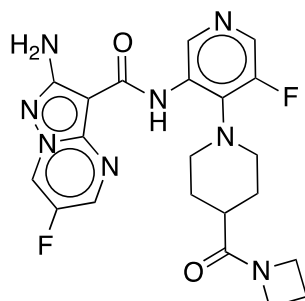
I-G-5



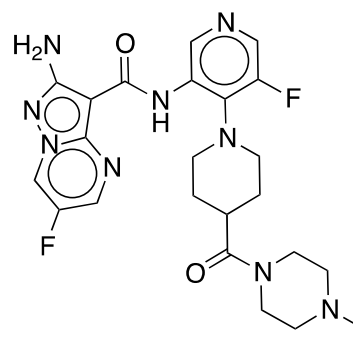
I-G-6



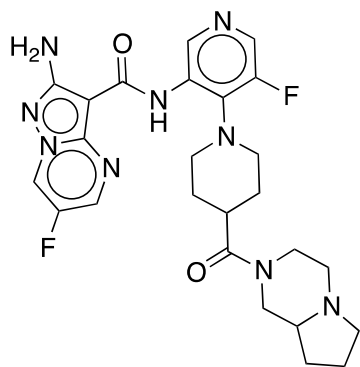
I-G-7



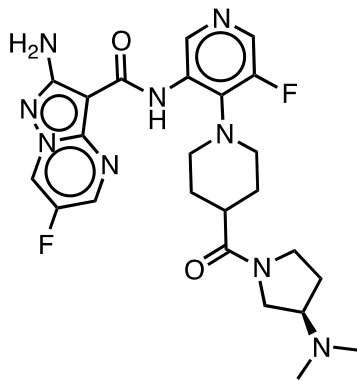
I-G-8



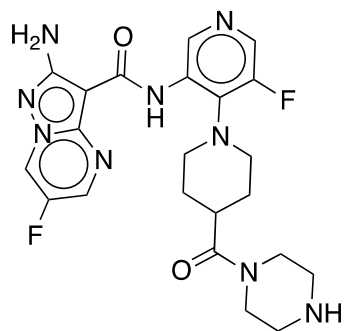
I-G-9



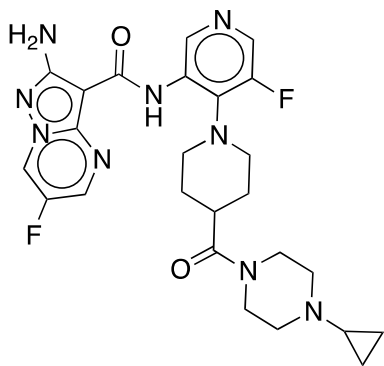
I-G-10



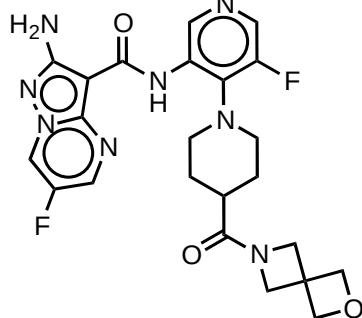
I-G-11



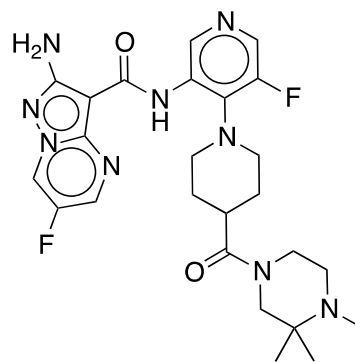
I-G-12



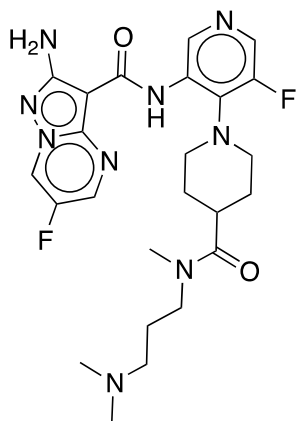
I-G-13



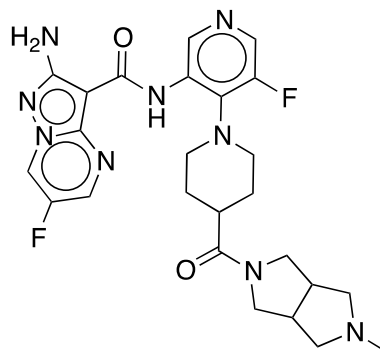
I-G-14



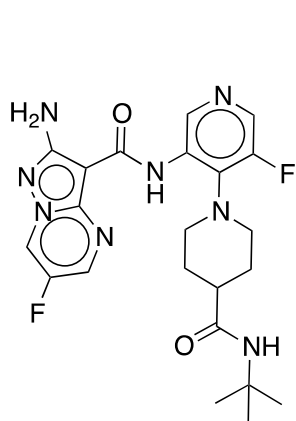
I-G-15



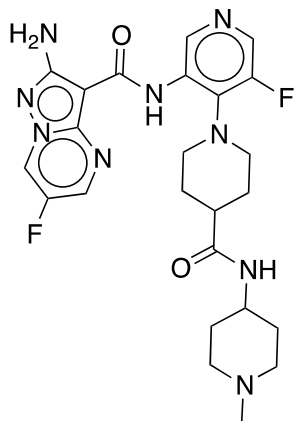
I-G-16



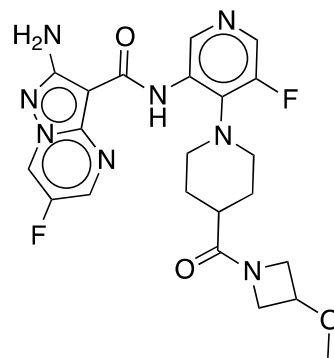
I-G-18



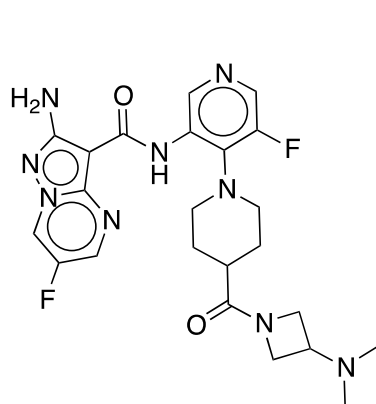
I-G-19



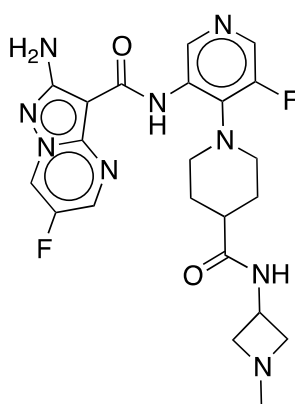
I-G-20



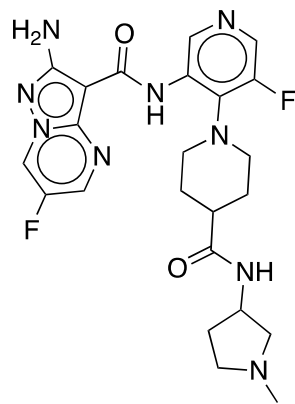
I-G-21



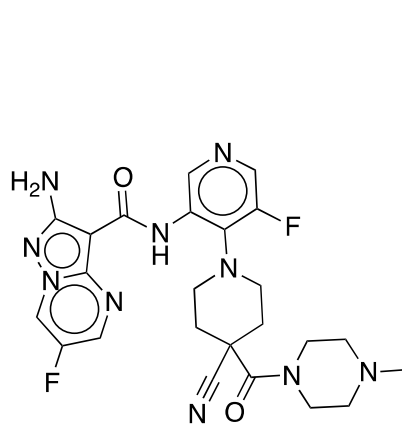
I-G-22



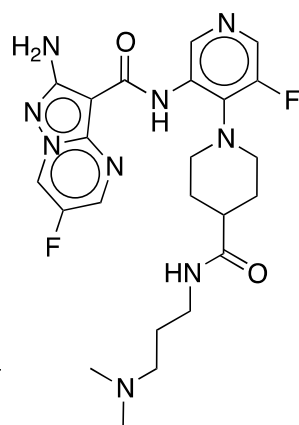
I-G-23



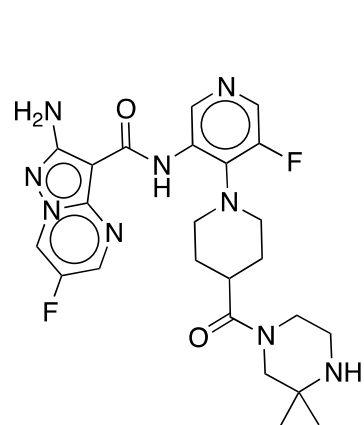
I-G-24



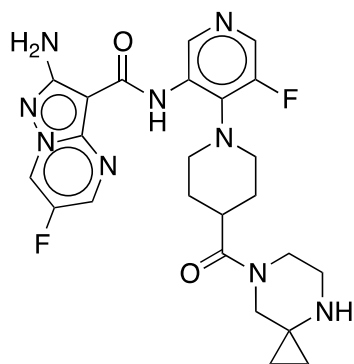
I-G-25



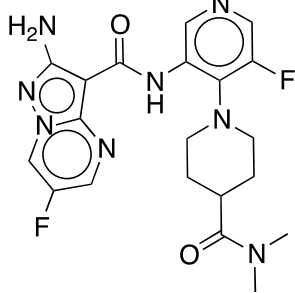
I-G-26



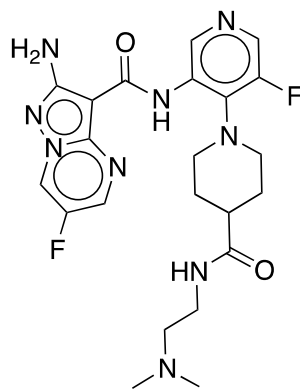
I-G-27



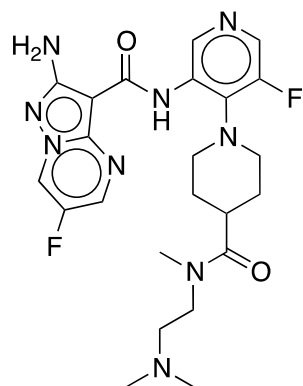
I-G-28



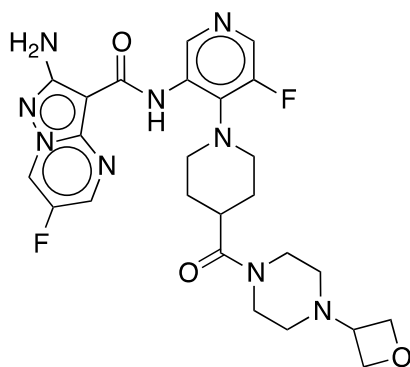
I-G-29



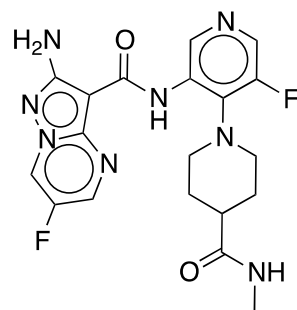
I-G-30



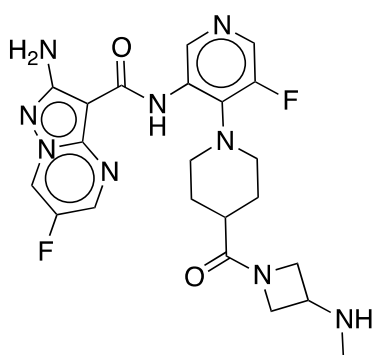
I-G-31



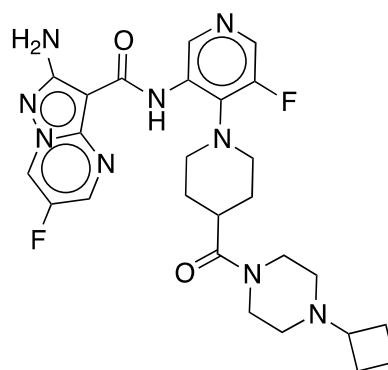
I-G-32



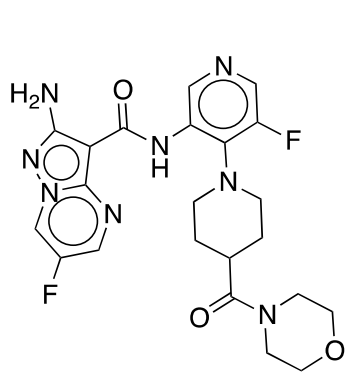
I-G-33



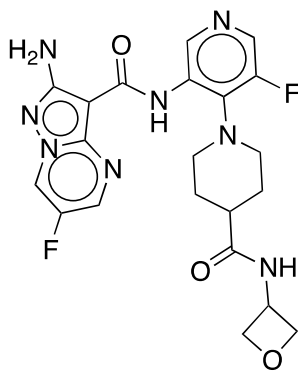
I-G-34



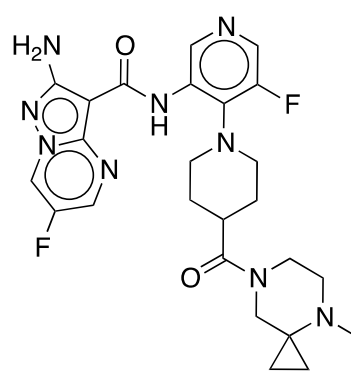
I-G-35



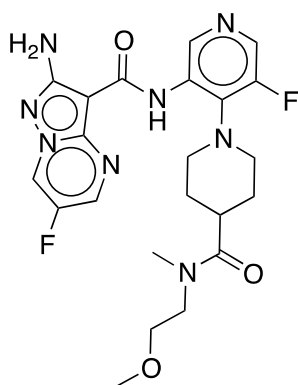
I-G-36



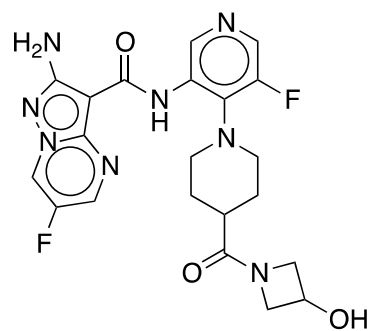
I-G-37



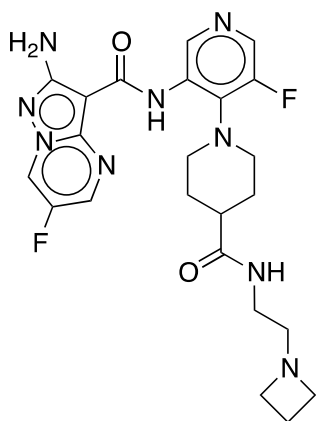
I-G-38



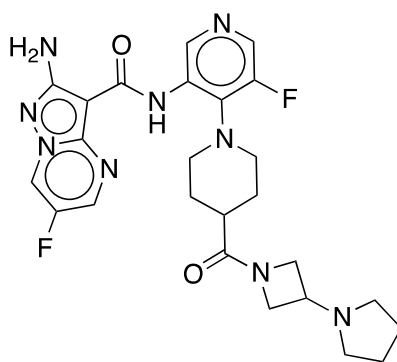
I-G-40



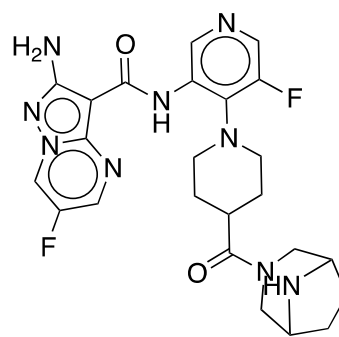
I-G-41



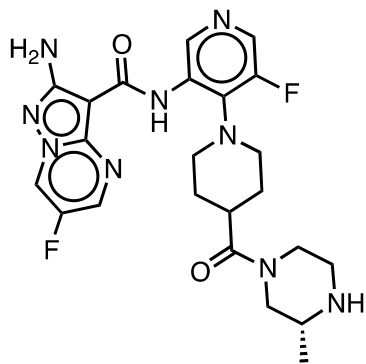
I-G-42



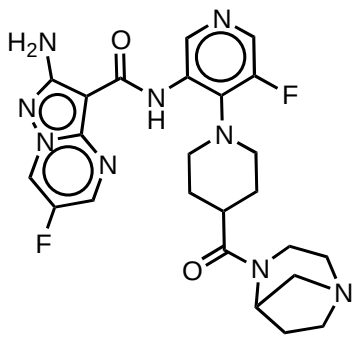
I-G-43



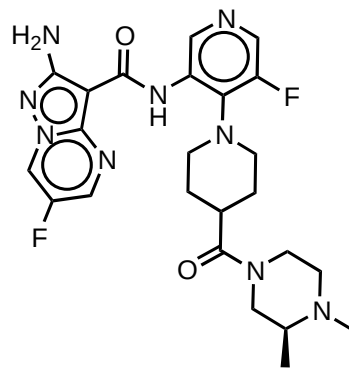
I-G-44



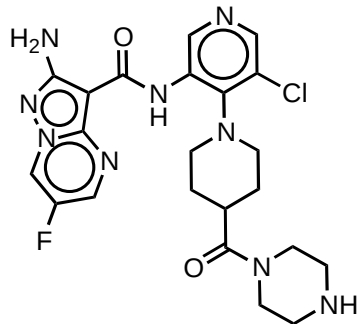
I-G-45



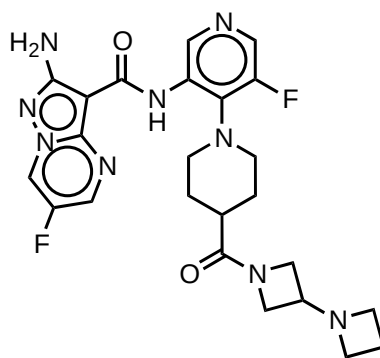
I-G-46



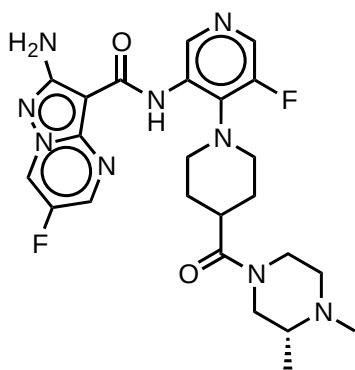
I-G-47



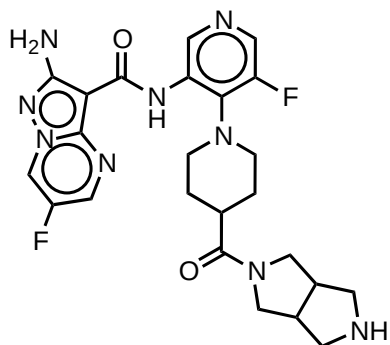
I-G-48



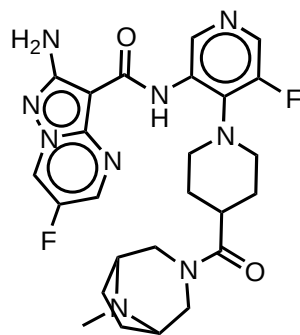
I-G-49



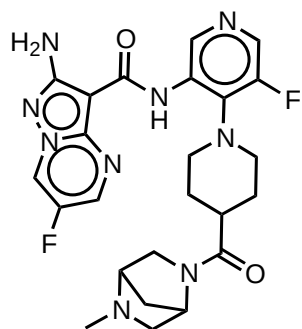
I-G-50



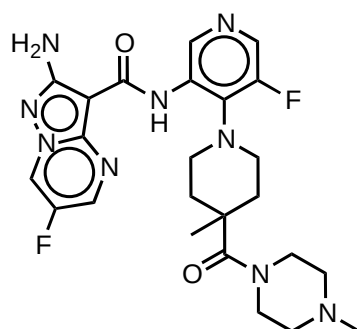
I-G-51



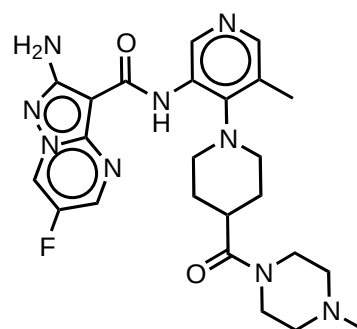
I-G-52



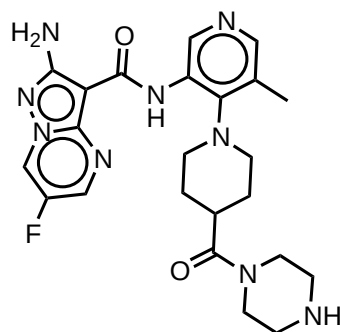
I-G-53



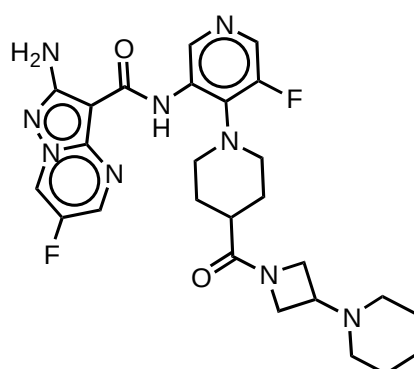
I-G-54



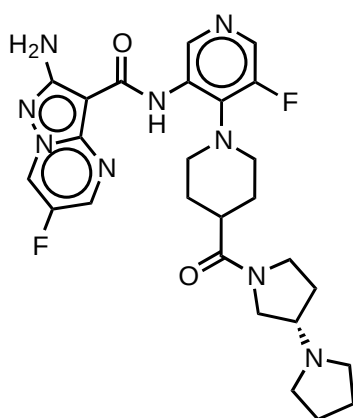
I-G-55



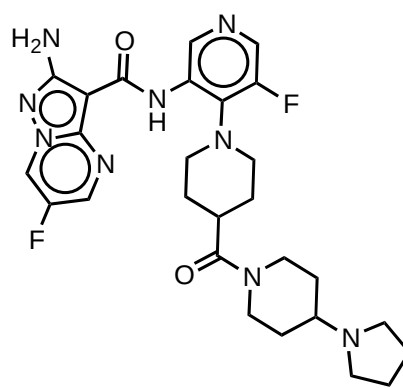
I-G-56



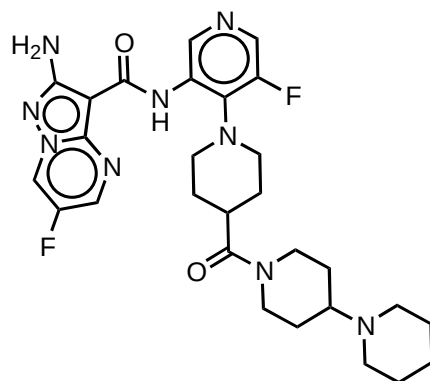
I-G-57



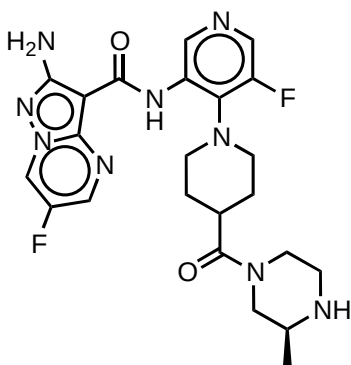
I-G-58



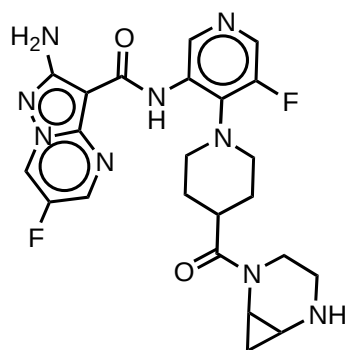
I-G-59



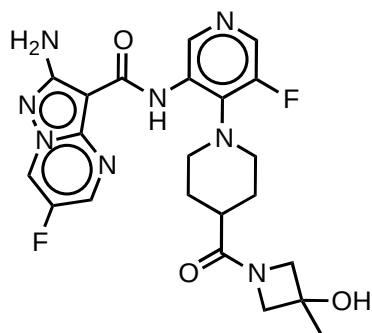
I-G-60



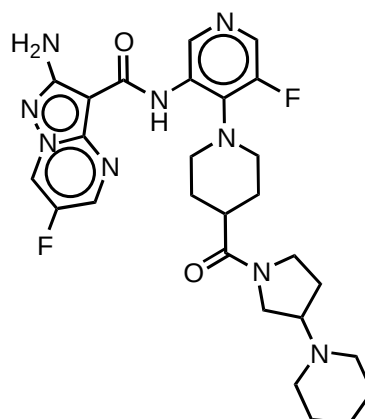
I-G-61



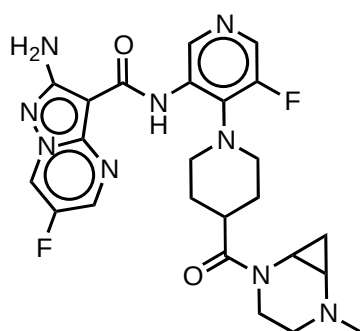
I-G-62



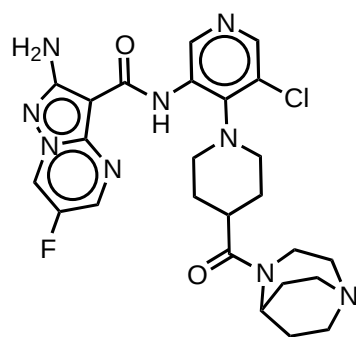
I-G-63



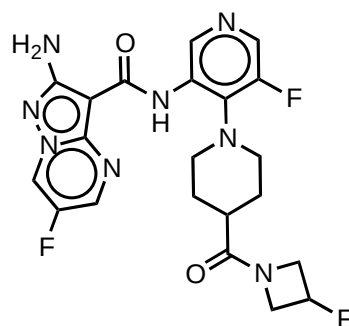
I-G-64



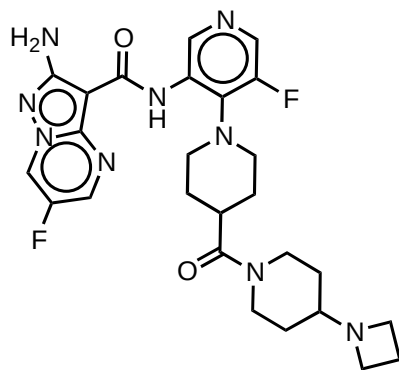
I-G-65



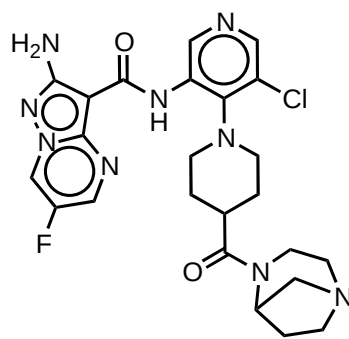
I-G-66



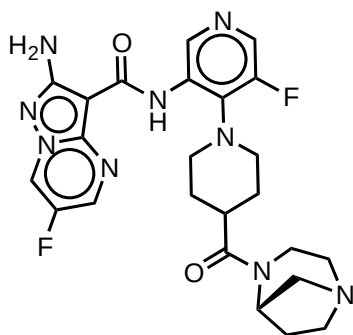
I-G-67



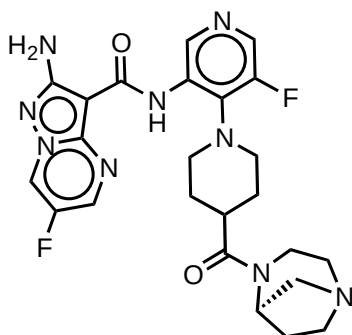
I-G-68



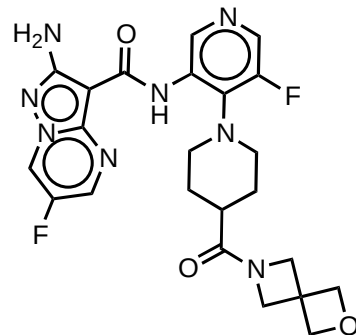
I-G-69



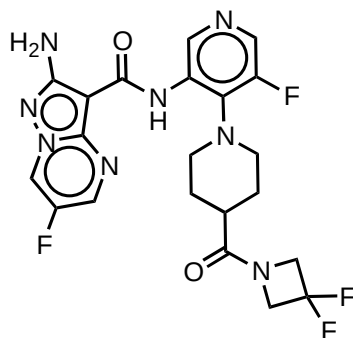
I-G-70



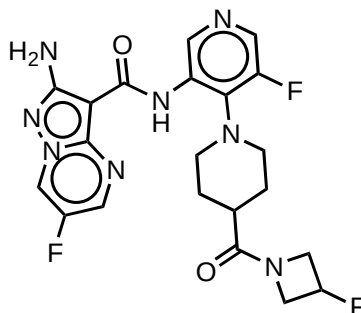
I-G-71



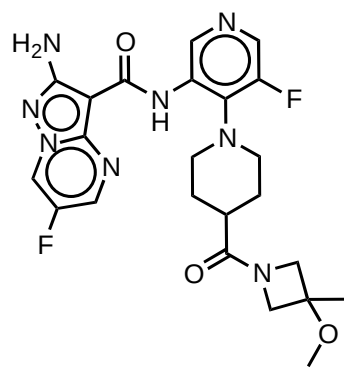
I-G-72



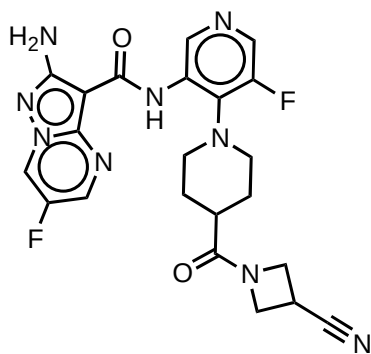
I-G-73



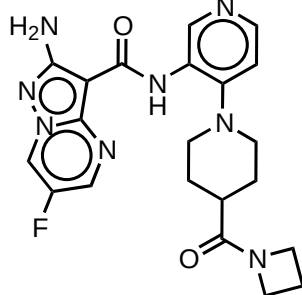
I-G-74



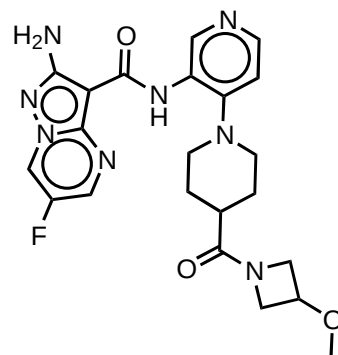
I-G-75



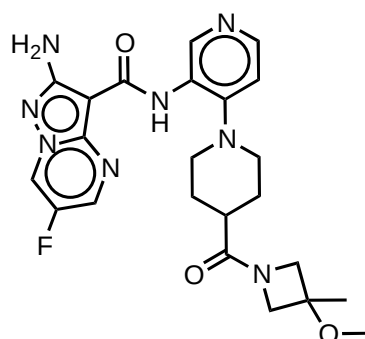
I-G-76



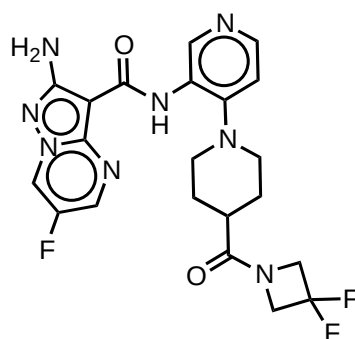
I-G-77



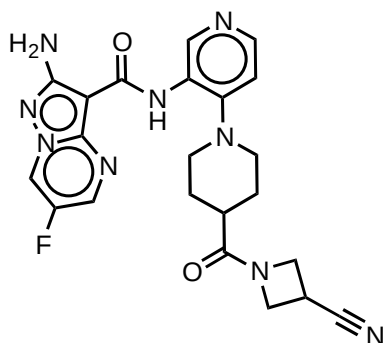
I-G-78



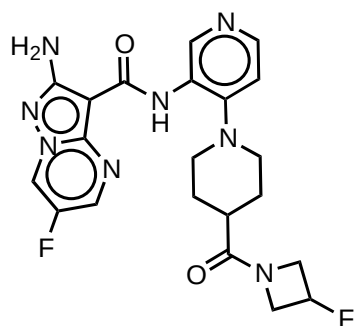
I-G-79



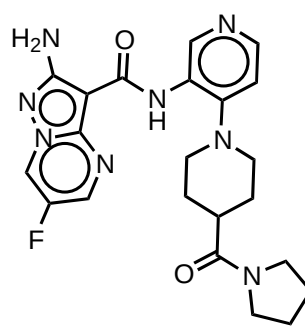
I-G-80



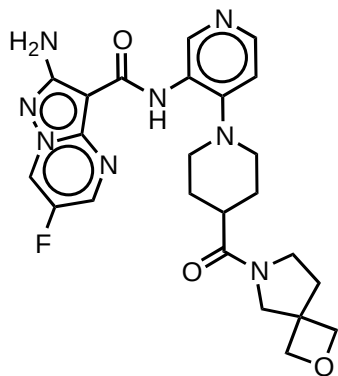
I-G-81



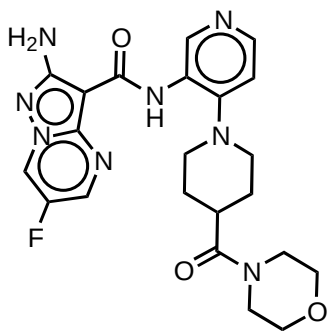
I-G-82



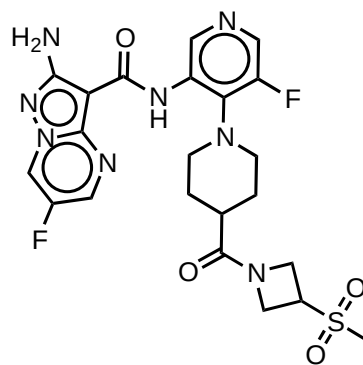
I-G-83



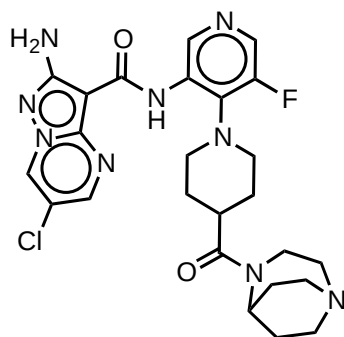
I-G-84



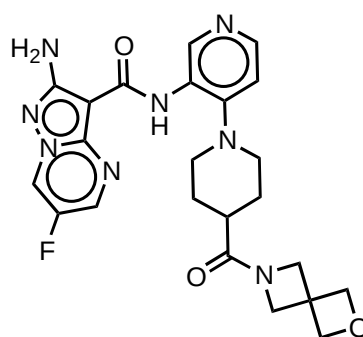
I-G-85



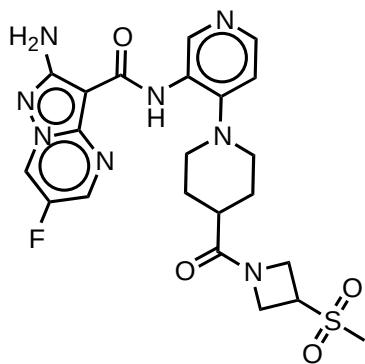
I-G-86



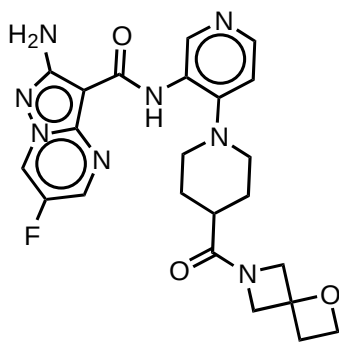
I-G-87



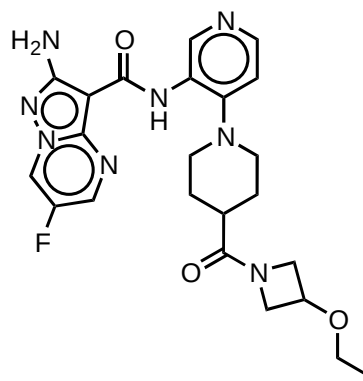
I-G-88



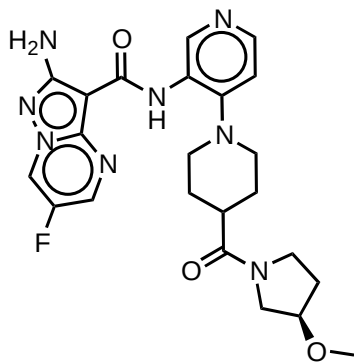
I-G-89



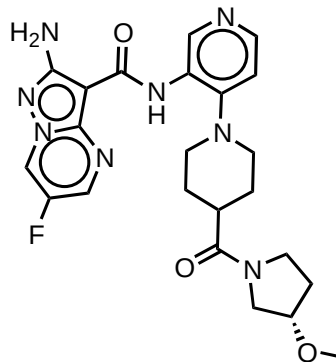
I-G-90



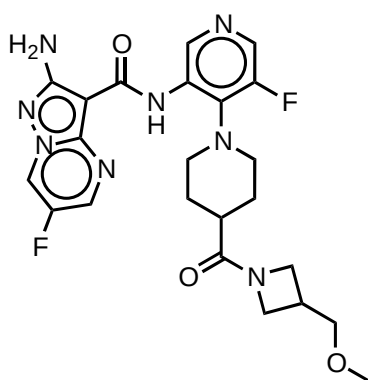
I-G-91



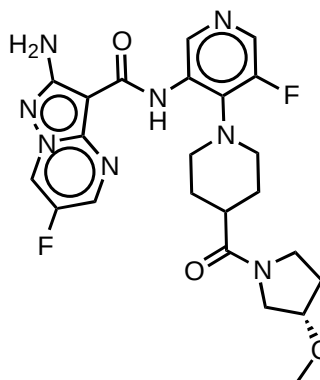
I-G-93



I-G-94



I-G-98



I-G-99

or a pharmaceutically acceptable salt thereof.

104. A pharmaceutical composition comprising a compound of any one of claims 1-103, 199, 202, and 204, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.
105. A compound of any one of claims 1-103, 199, 202, and 204, or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer in a patient.
106. The compound for use according to claim 105, or a pharmaceutically acceptable salt thereof, in combination with a DNA-damaging agent, wherein the DNA-damaging agent is used together with said compound as a single dosage form or separately from said

compound as part of a multiple dosage form; and wherein said DNA-damaging agent is appropriate for the disease being treated.

107. The compound for use according to claim 106, or a pharmaceutically acceptable salt thereof, wherein said DNA-damaging agent is chemotherapy or radiation treatment.
108. The compound for use according to claim 106, or a pharmaceutically acceptable salt thereof, wherein said DNA-damaging agent is ionizing radiation, radiomimetic neocarzinostatin, a platinating agent, a Topo I inhibitor, a Topo II inhibitor, an antimetabolite, an alkylating agent, an alkyl sulphonate, or an antibiotic.
109. The compound for use according to claim 108, or a pharmaceutically acceptable salt thereof, wherein said DNA-damaging agent is ionizing radiation, a platinating agent, a Topo I inhibitor, a Topo II inhibitor, an antimetabolite, an alkylating agent, or an alkyl sulphonate.
110. The compound for use according to claim 108, or a pharmaceutically acceptable salt thereof, wherein said DNA-damaging agent is ionizing radiation, a platinating agent, a Topo I inhibitor, a Topo II inhibitor, or an antibiotic.
111. The compound for use according to claim 109, or a pharmaceutically acceptable salt thereof, wherein said platinating agent is Cisplatin, Oxaliplatin, Carboplatin, Nedaplatin, Lobaplatin, Triplatin Tetranitrate, Picoplatin, Satraplatin, ProLindac, or Aroplatin.
112. The compound for use according to claim 111, or a pharmaceutically acceptable salt thereof, wherein said platinating agent is Cisplatin, Oxaliplatin, Carboplatin, Nedaplatin, or Satraplatin.
113. The compound for use according to claim 110, or a pharmaceutically acceptable salt thereof, wherein said DNA-damaging agent is a platinating agent or ionizing radiation.

114. The compound for use according to claim 208, or a pharmaceutically acceptable salt thereof, wherein the antimetabolite is gemcitabine.
115. The compound for use according to claim 109, or a pharmaceutically acceptable salt thereof, wherein the DNA-damaging agent is ionizing radiation.
116. The compound for use according to claim 109, or a pharmaceutically acceptable salt thereof, wherein the DNA-damaging agent is a platinating agent selected from the group consisting of cisplatin and carboplatin.
117. The compound for use according to claim 207, or a pharmaceutically acceptable salt thereof, wherein the DNA-damaging agent is Etoposide.
118. The compound for use according to claim 207, or a pharmaceutically acceptable salt thereof, wherein the DNA-damaging agent is Temozolomide.
119. The compound for use according to claim 109, or a pharmaceutically acceptable salt thereof, wherein the DNA-damaging agent is one or more of the following: cisplatin, carboplatin, gemcitabine, etoposide, temozolomide, and ionizing radiation.
120. The compound for use according to claim 119, or a pharmaceutically acceptable salt thereof, wherein the DNA-damaging agent is one or more of the following: gemcitabine, cisplatin or carboplatin, and etoposide.
121. The compound for use according to any one of claims 105-120, or a pharmaceutically acceptable salt thereof, wherein said cancer is a solid tumor selected from the group consisting of oral cancers, cardiac cancers, lung cancers, gastrointestinal cancers, genitourinary tract cancers, liver cancers, bone cancers, nervous system cancers, gynecological/female cancers, skin cancers, thyroid gland cancers, and adrenal glands cancers.

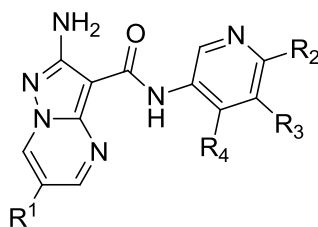
122. The compound for use according to claim 121, or a pharmaceutically acceptable salt thereof, wherein said cancer is a lung cancer or pancreatic cancer.
123. The compound for use according to claim 122, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt thereof, wherein said cancer is lung cancer.
124. The compound for use according to claim 123, or a pharmaceutically acceptable salt thereof, wherein the lung cancer is non-small cell lung cancer or small cell lung cancer.
125. The compound for use according to claim 124, or a pharmaceutically acceptable salt thereof, wherein the lung cancer is small cell lung cancer and the DNA damaging agent is cisplatin and etoposide.
126. The compound for use according to claim 124, or a pharmaceutically acceptable salt thereof, wherein the lung cancer is non-small cell lung cancer and the DNA damaging agent is gemcitabine and cisplatin.
127. The compound for use according to claim 126, or a pharmaceutically acceptable salt thereof, wherein the non-small cell lung cancer is squamous non-small cell lung cancer.
128. The compound for use according to any one of claims 105-120, or a pharmaceutically acceptable salt thereof, wherein said cancer is lung cancer, head and neck cancer, pancreatic cancer, gastric cancer, or brain cancer.
129. The compound for use according to any one of claims 105-120, or a pharmaceutically acceptable salt thereof, wherein said cancer is non-small cell lung cancer, small cell lung cancer, pancreatic cancer, biliary tract cancer, head and neck cancer, bladder cancer, colorectal cancer, glioblastoma, esophageal cancer, breast cancer, hepatocellular carcinoma, or ovarian cancer.

130. The compound for use according to claim 129, or a pharmaceutically acceptable salt thereof, wherein the cancer is breast cancer, and the DNA damaging agent is cisplatin.
131. The compound for use according to claim 130, or a pharmaceutically acceptable salt thereof, wherein the cancer is triple negative breast cancer.
132. A compound of any one of claims 1-103, 199, 202, and 204, or a pharmaceutically acceptable salt thereof, in combination with a DNA damaging agent selected from the group consisting of Gemcitabine, radiation therapy, and both Gemcitabine and radiation therapy together for use in the treatment of pancreatic cancer.
133. A compound of any one of claims 1-103, 199, 202, and 204, a pharmaceutically acceptable salt thereof, for use in increasing the sensitivity of pancreatic cancer cells to a cancer therapy selected from the group consisting of chemotherapy, radiation therapy, and combinations thereof .
134. The compound for use according to claim 133, or a pharmaceutically acceptable salt thereof, wherein the chemotherapy is gemcitabine.
135. The compound for use according to claim 133, or a pharmaceutically acceptable salt thereof, wherein the cancer therapy is gemcitabine.
136. The compound for use according to claim 133, or a pharmaceutically acceptable salt thereof, wherein the cancer therapy is radiation.
137. The compound for use according to claim 126, or a pharmaceutically acceptable salt thereof, wherein the cancer therapy is gemcitabine and radiation.
138. A compound of any one of claims 1-103, 199, 202, and 204, or a pharmaceutically acceptable salt thereof, in combination with gemcitabine and/or radiation for use in the inhibition of phosphorylation of Chk1 (Ser 345) in a pancreatic cancer cell in a patient.

139. A compound of any one of claims 1-103, 199, 202, and 204, or a pharmaceutically acceptable salt thereof, in combination with chemoradiation for use in the sensitization of pancreatic cancer cells to chemoradiation.
140. The compound for use according to claim 139, or a pharmaceutically acceptable salt thereof, wherein the chemoradiation is gemcitabine and radiation.
141. A compound of any one of claims 1-103, 199, 202, and 204, or a pharmaceutically acceptable salt thereof, in combination with radiation therapy for use in the radiosensitization of hypoxic pancreatic cancer cells in a patient.
142. A compound of any one of claims 1-103, 199, 202, and 204, or a pharmaceutically acceptable salt thereof, in combination with chemotherapy for use in the sensitization of hypoxic pancreatic cancer cells in a patient.
143. The compound for use according to any one of claims 139-142 or a pharmaceutically acceptable salt thereof, wherein said cancer cell is a PSN-1, MiaPaCa-2 or PancM cancer cell.
144. A compound of any one of claims 1-103, 199, 202, and 204, or a pharmaceutically acceptable salt thereof, in combination with one or more of the following additional therapeutic agents: cisplatin or carboplatin, etoposide, and ionizing radiation for use in the treatment of non-small cell lung cancer.
145. A compound of any one of claims 1-103, 199, 202, and 204, or a pharmaceutically acceptable salt thereof, for use in the sensitization of cells to DNA damaging agents in a patient.
146. The compound for use in the treatment of cancer in a patient according to any one of claims 105-145, or a pharmaceutically acceptable salt thereof, wherein said cancer has

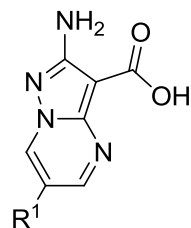
defects in the ATM signaling cascade, said cancer cells has defects in the ATM signaling cascade, or said cell is a cancer cell having defects in the ATM signaling cascade,.

147. The compound for use in the treatment of cancer in a patient according to any one of claims 105-146, or a pharmaceutically acceptable salt thereof, wherein the compound is used with an additional therapeutic agent, wherein said additional therapeutic agent inhibits or modulates a base excision repair protein.
148. The compound for use according to claim 147, or a pharmaceutically acceptable salt thereof, wherein the base excision repair protein is PARP1, PARP2, or PolB.
149. The compound for use according to claim 147 or 148, or a pharmaceutically acceptable salt thereof, wherein said additional therapeutic agent is Olaparib (also known as AZD2281 or KU-0059436), Iniparib (also known as BSI-201 or SAR240550), Veliparib (also known as ABT-888), Rucaparib (also known as PF-01367338), CEP-9722, INO-1001, MK-4827, E7016, BMN673, or AZD2461.
150. A process for preparing a compound of formula **I-A**:



I-A

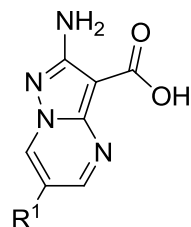
or a pharmaceutically acceptable salt thereof, comprising reacting a compound of formula 5:



5

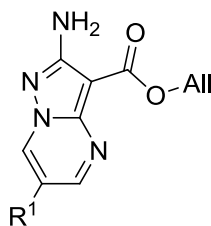
or a pharmaceutically acceptable salt thereof, under suitable conditions to form an amide bond, wherein R¹, R², R³, and R⁴ are as defined in claims 1-106.

151. The process of claim 150, further comprising the step of preparing a compound of formula 5:



5

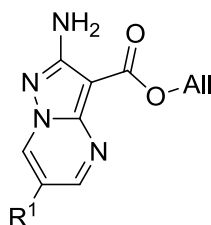
or a pharmaceutically acceptable salt thereof, by reacting a compound of formula 4:



4

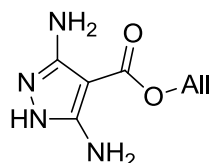
or a pharmaceutically acceptable salt thereof, under suitable deprotection conditions, wherein All is allyl.

152. The process of claim 151, further comprising the step of preparing a compound of formula 4:



4

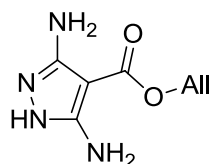
or a pharmaceutically acceptable salt thereof, by reacting a compound of formula 3:



3

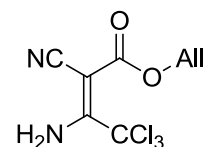
or a pharmaceutically acceptable salt thereof, under suitable condensation conditions to form a pyrimidine ring, wherein All is allyl.

153. The process of claim 152, further comprising the step of preparing the compound of formula 3:



3

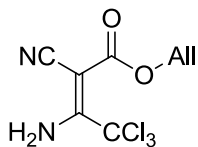
or a pharmaceutically acceptable salt thereof, by reacting a compound of formula 2:



2

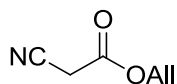
or a pharmaceutically acceptable salt thereof, under suitable condensation conditions to form a pyrazole ring, wherein All is allyl.

154. The process of claim 153, further comprising the step of preparing a compound of formula **2**:



2

or a pharmaceutically acceptable salt thereof, by reacting a compound of formula **1**:



1

or a pharmaceutically acceptable salt thereof, under suitable anion condensation conditions, wherein All is allyl.

155. The process of claim 150, wherein R^1 is from halo or $-\text{CH}_2\text{CN}$.

156. The process of claim 155, wherein R^1 is fluoro or chloro.

157. The process of claim 151, wherein suitable deprotection conditions comprise reacting the compound of formula **4** with a silane in the presence of a metal catalyst.

158. The process of claim 157, wherein the silane is phenylsilane.

159. The process of claim 158, wherein the metal catalyst is a palladium catalyst.

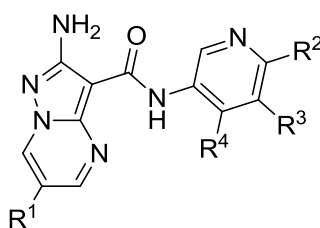
160. The process of claim 159, wherein the metal catalyst is $\text{Pd}(\text{PPh}_3)_4$.

161. The process of claim 151, wherein suitable deprotection conditions comprise reacting the compound of formula **4** with an aqueous alkali.

162. The process of claim 161, wherein the aqueous alkali is LiOH , NaOH , or KOH .

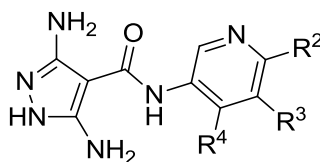
163. The process of claim 152, wherein suitable condensation conditions for forming a pyrimidine ring comprise reacting the compound of formula **3** with a 1,3-dielectrophilic species in the presence of a solvent.
164. The process of claim 163, wherein the 1,3-dielectrophilic species is 1,3-dialdehyde or 3-(dialkylamino)-prop-2-enal.
165. The process of any one of claims 163 or 164, wherein the solvent is DMF or DMSO.
166. The process of claim 163, wherein the 1,3-dielectrophilic species is generated *in situ* from a protected 1,3-dielectrophilic species.
167. The process of claim 166, wherein the 1,3-dielectrophilic species is generated from a ketal in the presence of a sulfonic acid.
168. The process of claim 167, wherein the sulfonic acid is PTSA.
169. The process of claim 153, wherein suitable condensation conditions for forming a pyrazole ring comprise reacting the compound of formula **2** with a hydrazine or hydrazine hydrate in the presence of an aprotic solvent under basic conditions.
170. The process of claim 169, wherein the aprotic solvent is DMF.
171. The process of claim 169, wherein the basic conditions comprise reacting the compound of formula **2** in the presence of potassium acetate or sodium acetate.
172. The process of claim 154, wherein suitable anion condensation conditions comprise 1) reacting the compound of formula **1** with a base, in the presence of a solvent, to generate the anion of the compound of formula **1**; and 2) reacting the anion of the compound of formula **1** with trichloroacetonitrile.

173. The process of claim 172, wherein the base is potassium acetate.
174. The process of claim 172, wherein the solvent is an alcohol.
175. The process of claim 174, wherein the solvent is isopropylalcohol.
176. A process for preparing a compound of formula **I-A**:



I-A

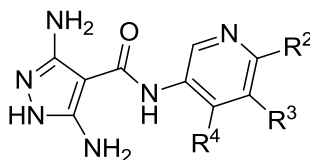
or a pharmaceutically acceptable salt thereof, comprising reacting a compound of formula **9**:



9

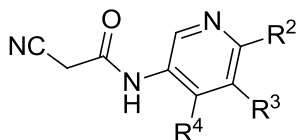
or a pharmaceutically acceptable salt thereof, under suitable condensation conditions to form a pyrimidine ring, wherein R¹, R², R³ and R⁴ are as defined in claims 1-106.

177. The process of claim 176, further comprising the step of preparing a compound of formula **9**:



9

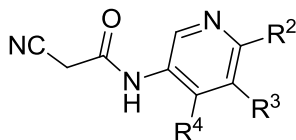
or a pharmaceutically acceptable salt thereof, by reacting a compound of formula **8**:



8

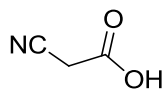
or a pharmaceutically acceptable salt thereof, under suitable condensation conditions to form a pyrazole ring.

178. The process of claim 177, further comprising the step of preparing a compound of formula **8**:



8

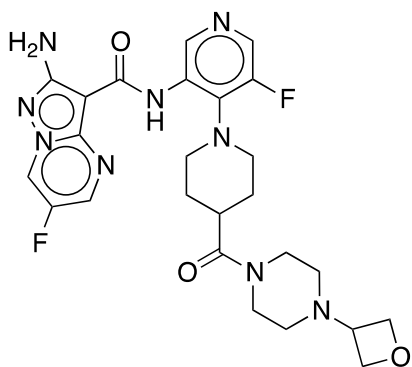
or a pharmaceutically acceptable salt thereof, by reacting a compound of formula **7**:



7

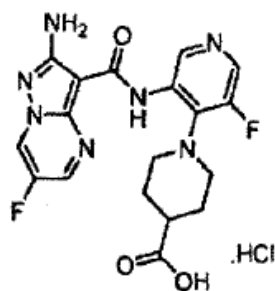
or a pharmaceutically acceptable salt thereof, under suitable conditions to form an amide bond.

179. A process of preparing a compound of formula **I-G-32**:



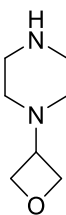
I-G-32

or a pharmaceutically acceptable salt thereof, comprising the step of reacting the compound of formula **30**:



30

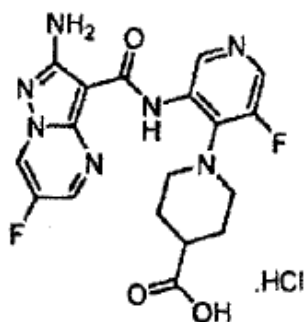
with a compound of formula **25**:



25

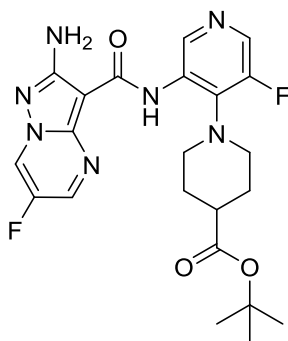
or a pharmaceutically acceptable salt thereof, under suitable conditions to form an amide bond.

180. The process of claim 179, further comprising the step of preparing the compound of formula **30**:



30

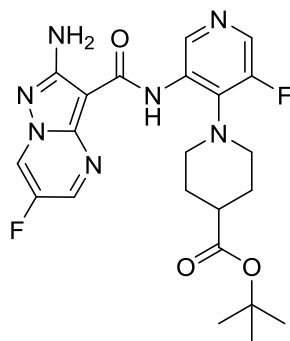
by reacting the compound of formula **28**:



28

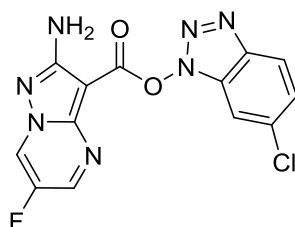
or a pharmaceutically acceptable salt thereof, under suitable deprotection conditions to form the carboxylic acid.

181. The process of claim 180, further comprising the step of preparing a compound of formula **28**:



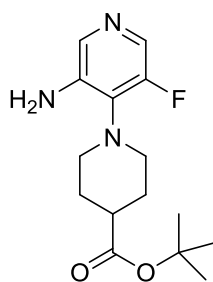
28

or a pharmaceutically acceptable salt thereof, by reacting the compound of formula **6a***:



6a*

or a pharmaceutically acceptable salt thereof, with a compound of formula **27**:



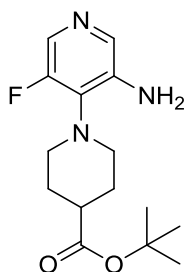
27

or a pharmaceutically acceptable salt thereof, under suitable conditions to form an amide bond.

182. The process of claim 179, wherein suitable conditions for forming the amide bond comprise reacting the compound of formula **30** with the compound of formula **25** in the presence of an amide coupling partner, an aprotic solvent, and a base.
183. The process of claim 182, wherein the aprotic solvent is NMP, DMF, or tetrahydrofuran.
184. The process of claim 183, wherein the aprotic solvent is tetrahydrofuran.
185. The process of claim 183, wherein the base is an aliphatic amine.
186. The process of claim 185, wherein the base is DIPEA.
187. The process of any one of claims 182-186, wherein the amide coupling partner is TBTU or TCTU.
188. The process of claim 187, wherein the amide coupling partner is TCTU.
189. The process of claim 180, wherein suitable deprotection conditions comprise reacting the compound of formula **28** with an acid in the presence of a solvent.
190. The process of claim 189 wherein the acid is HCl.
191. The process of claim 190, wherein the solvent is 1,4-dioxane.
192. The process of claim 181, wherein the suitable conditions for forming the amide bond comprise reacting the compound of formula **6a*** with the compound of formula **27** in an aprotic solvent under heat.
193. The process of claim 192, wherein the aprotic solvent is NMP, pyridine, or DMF.
194. The process of claim 193, wherein the aprotic solvent is pyridine.

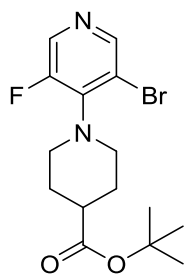
195. The process of any one of claims 192, wherein the reaction is carried out at a temperature of at least 80°C.

196. The process of claim 181, further comprising the step of preparing a compound of formula **27**:



27

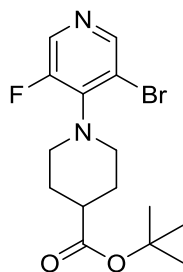
or a pharmaceutically acceptable salt thereof, comprising the step of reacting a compound of formula **26**:



26

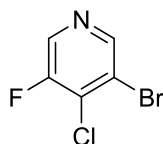
or a pharmaceutically acceptable salt thereof, under suitable conditions to form an amine.

197. The process of claim 196, further comprising the step of preparing a compound of formula **26**:



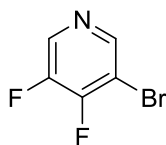
26

or a pharmaceutically acceptable salt thereof, by 1) reacting a compound of formula **18**:



18

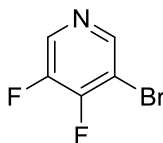
or a pharmaceutically acceptable salt thereof, under suitable halogen exchange conditions to generate the compound of formula **32**



32

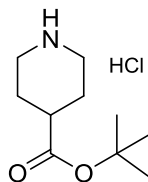
or a pharmaceutically acceptable salt thereof, and

2) reacting the compound of formula **32**:



32

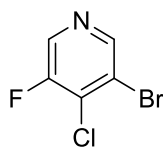
or a pharmaceutically acceptable salt thereof, with a compound of formula **22**:



22

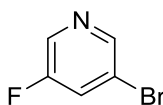
or a pharmaceutically acceptable salt thereof, under suitable displacement conditions.

198. The process of claim 194, further comprising the step of preparing a compound of formula **18**:



18

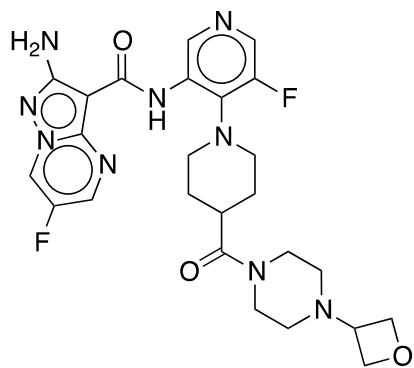
or a pharmaceutically acceptable salt thereof, by reacting the compound of formula **31**:



31

or a pharmaceutically acceptable salt thereof, under suitable halogenation conditions.

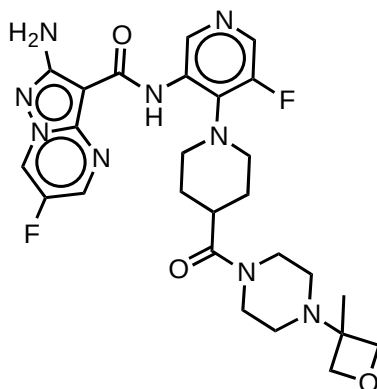
199. A compound **I-G-32**:



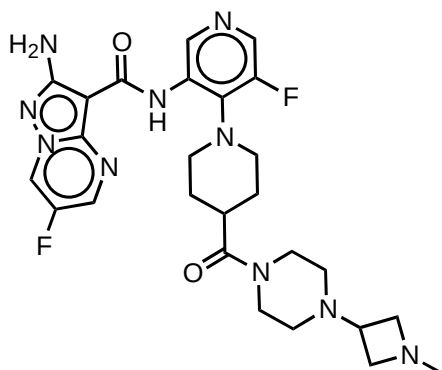
I-G-32

or a pharmaceutically acceptable salt thereof.

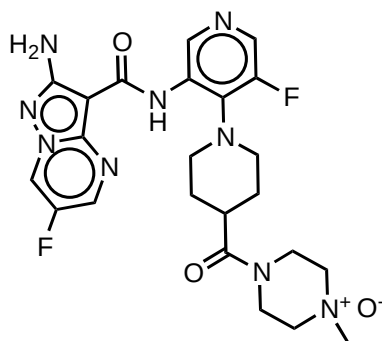
200. A compound, wherein the compound is:



I-G-92



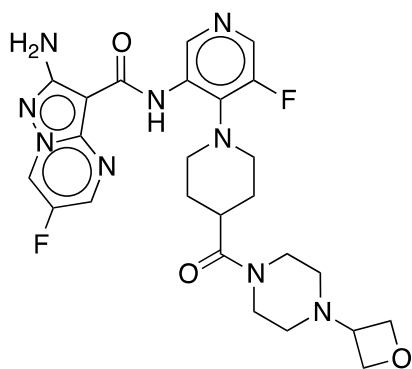
I-G-95,



I-G-96,

or a pharmaceutically acceptable salt thereof.

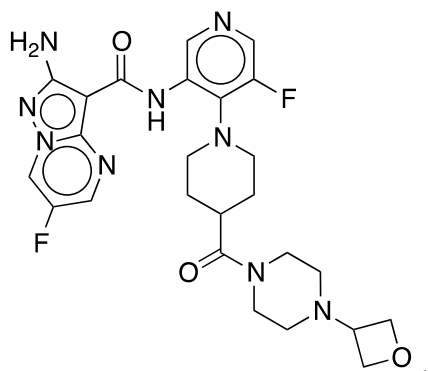
201. A pharmaceutical composition comprising a compound I-G-32:



or a pharmaceutically acceptable salt thereof;

and a pharmaceutically acceptable carrier.

202. The compound of claim 199, wherein the compound is a pharmaceutically acceptable



salt of

203. A pharmaceutical composition comprising the compound of claim 202 and a pharmaceutically acceptable carrier.

Nc1nc2c(cnc2c1F)C(=O)Nc3ccnc(F)c3N4CCCCC4C(=O)N5CCCN(C5)C6OC6

206. The compound for use according to claim 109, or a pharmaceutically acceptable salt thereof, wherein said Topo I inhibitor is camptothecin, topotecan, irinotecan/SN38, rubitecan, or belotecan.

208. The compound for use according to claim 109, or a pharmaceutically acceptable salt thereof, wherein said antimetabolite is Aminopterin, Methotrexate, Pemetrexed, Raltitrexed, Pentostatin, Cladribine, Clofarabine, Fludarabine, Thioguanine, Mercaptopurine, Fluorouracil, Capecitabine, Tegafur, Carmofur, Floxuridine, Cytarabine, Gemcitabine, Azacitidine, or Hydroxyurea.

501

Ifosfamide, Trofosfamide, Chlorambucil, Melphalan, Prednimustine, Bendamustine, Uramustine, Estramustine, Carmustine, Lomustine, Semustine, Fotemustine, Nimustine, Ranimustine, Streptozocin, Busulfan, Mannosulfan, Treosulfan, Carboquone, ThioTEPA, Triaziquone, Triethylenemelamine, Procarbazine, Dacarbazine, Temozolomide, Altretamine, Mitobronitol, Actinomycin, Bleomycin, Mitomycin, or Plicamycin.

210. The compound for use according to claim 110, or a pharmaceutically acceptable salt thereof, wherein said antibiotic is selected from the group consisting of Hydroxyurea, Anthracyclines, Anthracenediones, and antibiotics from the *Streptomyces* family.

211. The compound for use according to claim 121, or a pharmaceutically acceptable salt thereof, wherein said cancer is an oral cancer selected from the group consisting of buccal cavity cancers, lip cancers, tongue cancers, mouth cancers, and pharynx cancers,

or wherein said cancer is a cardiac cancer selected from the group consisting of sarcomas, myxomas, rhabdomyomas, fibromas, lipomas, and teratomas, or wherein said cancer is a lung cancer selected from the group consisting of bronchogenic carcinomas, alveolar carcinomas, bronchial adenomas, sarcomas, lymphomas, chondromatous hamartomas, and mesotheliomas,

or wherein said cancer is a gastrointestinal cancer selected from the group consisting of esophageal cancers, stomach cancers, pancreatic cancers, small bowel or small intestinal cancers, large bowel or large intestinal cancers, colon cancers, colon-rectum cancers, colorectal cancers, and rectal cancers,

or wherein said cancer is a genitourinary tract cancer selected from the group consisting of kidney cancers, bladder and urethra cancers, prostate cancers, and testicular cancers,

or wherein said cancer is a liver cancer selected from the group consisting of hepatomas, cholangiocarcinomas, hepatoblastomas, angiosarcomas, hepatocellular adenomas, hemangiomas, and biliary passage cancers,

or wherein said cancer is bone cancer selected from the group consisting of osteogenic sarcomas, fibrosarcomas, malignant fibrous histiocytomas, chondrosarcomas, Ewing's sarcomas, malignant lymphomas of bone, multiple myelomas, malignant giant cell tumor chordomas,

osteochondromas, benign chondromas, chondroblastomas, chondromyxofibromas, osteoid osteomas, and giant cell tumors,

or wherein said cancer is a nervous system cancer selected from the group consisting of consisting of skull cancers, meninges cancers, brain cancers, spinal cord cancers, neurofibromas, meningiomas, gliomas, and sarcomas,

or wherein said cancer is a gynecological cancer selected from the group consisting of uterus cancers, cervix cancers, vulva cancers, vagina cancers, fallopian tube cancers, and breast cancers,

or wherein said cancer is a skin cancer selected from the group consisting of malignant melanomas, basal cell carcinomas, squamous cell carcinomas, Kaposi's sarcomas, keratoacanthomas, moles dysplastic nevis, lipomas, and angiomas,

or wherein said cancer is a thyroid gland cancer selected from the group consisting of papillary thyroid carcinomas, follicular thyroid carcinomas, medullary thyroid carcinomas, multiple endocrine neoplasias type 2A, multiple endocrine neoplasias type 2B, familial medullary thyroid cancers, pheochromocytomas, and paragangliomas.

212. The compound for use according to claim 121, or a pharmaceutically acceptable salt thereof, wherein said adrenal glands cancer is a neuroblastoma.

213. The compound for use according to claim 147, or a pharmaceutically acceptable salt thereof, wherein the base excision repair protein is selected from the group consisting of UNG, SMUG1, MBD4, TDG, OGG1, MYH, NTH1, MPG, NEIL1, NEIL2, NEIL3, APE1, APEX2, LIG1, LIG3, XRCC1, PNK, PNKP, PARP1, PARP2, PolB, PolG, FEN1, and Aprataxin.