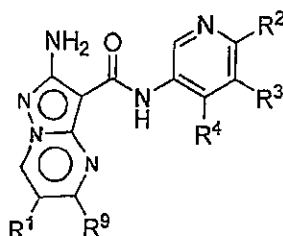


Claims

1. A compound having the formula I:



I

or a pharmaceutically acceptable salt thereof, wherein:

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

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

J^1 is independently selected from 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^1 is optionally substituted with 0-3 occurrences of J^{LM} ;

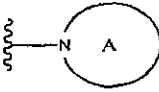
J^{LM} is independently selected from halo, $-CN$, or a $C_{1-4}aliphatic$ chain wherein up to two methylene units of the aliphatic chain are optionally replaced with $-O-$, $-NR-$, $-C(O)-$, or $-S(O)_n-$;

W is independently selected from 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 oxygen, nitrogen, or sulfur; wherein W is optionally substituted with 0-5 occurrences of J^W ;

J^W is independently selected from $-CN$, halo, $-CF_3$; a $C_{1-4}aliphatic$ 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 oxygen, nitrogen, or sulfur;

R^2 is independently selected from 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 independently selected from H; halo; C_{1-4} alkyl optionally substituted with 1-3 occurrences of halo; C_{3-4} cycloalkyl; 3-4 membered heterocyclyl; -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 selected from -CN; halo; =O; Q^2 ; or a C_{1-3} 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 oxygen, nitrogen, or 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 oxygen, nitrogen, or sulfur; or an 7-12 membered fully saturated, partially unsaturated, or aromatic bicyclic ring having 0-5 heteroatoms selected from oxygen, nitrogen, or sulfur;

J^R is independently selected from -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 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;

Q³ is 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 oxygen, nitrogen, or sulfur;

J^X is independently selected from -CN; =O; halo; or a C₁₋₄aliphatic 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 selected from halo, -CN; =O; -OH; 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-; or a 3-6 membered non-aromatic ring having 0-2 heteroatoms selected from oxygen, nitrogen, or 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 Q³, form a 6-10 membered saturated or partially unsaturated bridged ring system;

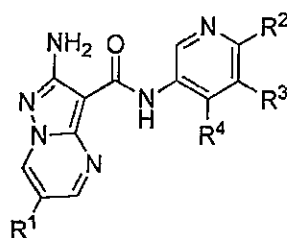
J^M is independently selected from halo or C₁₋₆aliphatic;

n is 0, 1 or 2; and

R is independently selected from H or C₁₋₄aliphatic.

2. The compound of any one of claims 1, wherein R⁹ is H.
3. The compound of any one of claims 1-2, wherein R⁹ is M.
4. The compound of claim 3, 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, 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, wherein M is C₁₋₄alkyl.
7. The compound of any one of claims 4-6, wherein J^{LM} is halo.
8. The compound of any one of claims 1-2, wherein R⁹ is -(L¹)_k-W.

9. The compound of claim 8, wherein k is 0.
10. The compound of claim 8, wherein k is 1.
11. The compound of claim 10, wherein L is a C₁₋₈aliphatic wherein up to three methylene units are optionally replaced with -O- or -NR-.
12. The compound of claim 11, wherein L is -O-, -O(C₁₋₄aliphatic)-, or -NR(C₁₋₃alkyl)-.
13. The compound of any one of claims 8-12, wherein W is a 3-7 membered fully saturated, partially unsaturated, or aromatic monocyclic ring having 0-2 heteroatoms selected from oxygen, nitrogen or sulfur.
14. The compound of claim 13, wherein W is a 3-7 membered heterocyclyl.
15. The compound of claim 14, wherein W is independently selected from pyrrolidinyl, piperidinyl, piperazinyl, oxetanyl, or azetidiny.
16. The compound of any one of claims 8-12, wherein W is a 7-12 membered fully saturated, partially unsaturated, or aromatic bicyclic ring having 0-5 heteroatoms selected from oxygen, nitrogen, or sulfur.
17. The compound of any one of claims 8-16, wherein J^W is selected from C₁₋₃alkyl or CF₃.
18. The compound of any one of claims 8-16, wherein two occurrences of J^W on the same atom, together with atom to which they are joined, form a 3-6 membered ring having 0-2 heteroatoms selected from oxygen, nitrogen, or sulfur.
19. The compound of claim 18, wherein the ring formed by the two occurrences of J^W on the same atom is oxetanyl.
20. A compound having the formula I-A:



I-A

or a pharmaceutically acceptable salt thereof, wherein:

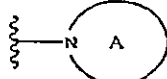
R^1 is independently selected from fluoro, chloro, or $-C(J^1)_2CN$;

J^1 is independently selected from 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 independently selected from 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 independently selected from 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 selected from $-CN$; 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 oxygen, nitrogen, or 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 oxygen, nitrogen, or sulfur; or an 7-12 membered fully saturated, partially unsaturated, or aromatic bicyclic ring having 0-5 heteroatoms selected from oxygen, nitrogen, or sulfur;

J^R is independently selected from $-CN$; 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 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 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 oxygen, nitrogen, or sulfur;

J^X is independently selected from $-CN$; $=O$; 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 selected from 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 oxygen, nitrogen, or 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

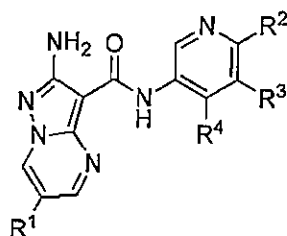
two occurrences of J^T , together with Q^3 , form a 6-10 membered saturated or partially unsaturated bridged ring system;

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

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

n is 0, 1 or 2; and

21. A compound having the formula I-A:



I-A

or a pharmaceutically acceptable salt thereof, wherein:

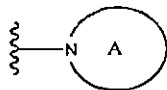
R^1 is independently selected from fluoro, chloro, or $-C(J^1)_2CN$;

J^1 is independently selected from 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 independently selected from 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 independently selected from 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 selected from $-CN$; 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 oxygen, nitrogen, or 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 oxygen, nitrogen, or sulfur; or an 7-12 membered fully saturated, partially unsaturated, or aromatic bicyclic ring having 0-5 heteroatoms selected from oxygen, nitrogen, or sulfur;

J^R is independently selected from $-\text{CN}$; halo; $=\text{O}$; Q^3 ; or a C_{1-6} aliphatic chain wherein up to three methylene units of the aliphatic chain are optionally replaced with $-\text{O}-$, $-\text{NR}-$, $-\text{C}(\text{O})-$, or $-\text{S}(\text{O})_n-$; 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 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 oxygen, nitrogen, or sulfur;

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

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

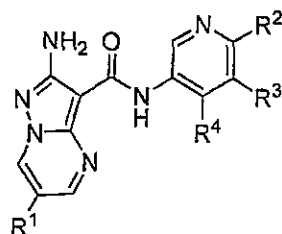
two occurrences of J^T , together with Q^3 , form a 6-10 membered saturated or partially unsaturated bridged ring system;

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

n is 0, 1 or 2; and

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

22. A compound having the formula I-A:



I-A

or a pharmaceutically acceptable salt thereof, wherein:

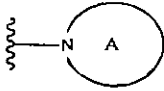
R^1 is independently selected from fluoro, chloro, or $-C(J^1)_2CN$;

J^1 is independently selected from 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 independently selected from H; chloro; NH_2 ; or a $C_{1-2}alkyl$ optionally substituted with fluoro;

R^3 is independently selected from 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 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 selected from 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 oxygen, nitrogen, or 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 oxygen, nitrogen, or sulfur; or an 8-12 membered fully saturated, partially unsaturated, or aromatic bicyclic ring having 0-5 heteroatoms selected from oxygen, nitrogen, or sulfur;

J^R is independently selected from halo; =O; O; a 3-7 membered fully saturated, partially unsaturated, or aromatic monocyclic ring having 0-3 heteroatoms selected from oxygen, nitrogen, or 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 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;

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

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

n is 1 or 2; and

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

23. The compounds of any one of claims 1-22, wherein R^1 is fluoro.

24. The compounds of any one of claims 1-22, wherein R^1 is $-CH_2CN$, $-C(CH_3)_2CN$ or $-CH(C_{1-2}alkyl)CN$.

25. The compound of any one of claims 1-22, wherein R^1 is chloro.

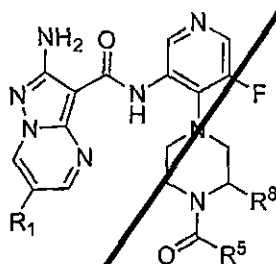
26. The compound of any one of claims 1-25, wherein R^2 is independently selected from $-CF_3$, $-NH(C_{1-2}alkyl)$, chloro, or H.

27. The compound of claim 26, wherein R^2 is H.
28. The compound of claim 26, wherein R^2 is -chloro.
29. The compound of any one of claims 1-28, wherein R^3 is independently selected from H, chloro, fluoro, CHF_2 , -CN, cyclopropyl, or C_{1-4} alkyl.
30. The compound of claim 29, wherein R^3 is independently selected from H, chloro, or fluoro.
31. The compound of claim 30, wherein R^3 is H.
32. The compound of claim 30, wherein R^3 is chloro.
33. The compound of claim 30, wherein R^3 is fluoro.
34. The compound of claim 1, wherein Ring A is a 3-7 membered fully saturated, partially unsaturated, or aromatic monocyclic ring having 1-3 heteroatoms selected from oxygen, nitrogen or sulfur.
35. The compound of claim 34, wherein Ring A is a 3-7 membered heterocycl.
36. The compound of claim 35, wherein Ring A is independently selected from 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, and azetidiny.
37. The compound of claim 36, wherein Ring A is independently selected from piperidinyl, piperazinyl, 1,4-diazepanyl, thiomorpholinyl, pyrrolidinyl, azepanyl, morpholinyl.
38. The compound of claim 37, wherein Ring A is independently selected from piperazinyl or piperidinyl.

- 39 The compound of claim 34, wherein Ring A is a 5 membered heteroaryl.
- 40 The compound of claim 39, wherein Ring A is independently selected from pyrrolyl, imidazolyl, pyrazolyl, 1,2,3-triazolyl, or 1,2,4-triazolyl.
- 41 The compound of claim 40, wherein Ring A is independently selected from pyrazolyl or imidazolyl.
- 42 The compound of claim 1, wherein Ring A is an 7-12 membered fully saturated, partially unsaturated, or aromatic bicyclic ring having 1-5 heteroatoms selected from oxygen, nitrogen, or sulfur.
- 43 The compound of claim 42, wherein Ring A is independently selected from 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.
- 44 The compound of any one of claims 1-41, 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)-.
- 45 The compound of claim 44, wherein J^Q is independently selected from -O-, -C(O)-, -S(O)₂-, C_{1-4} alkyl, -(C₀₋₄alkyl)NH₂, -(C₀₋₄alkyl)NH(C₁₋₄alkyl), -(C₀₋₄alkyl)N(C₁₋₄alkyl)₂, -(C₀₋₄alkyl)OH, -(C₀₋₄alkyl)O(C₁₋₄alkyl), -C(O)OH, -S(O)₂N(C₁₋₃alkyl)-, -C(O)(C₁₋₄alkyl)-, -(O)C(C₁₋₄alkyl)N(C₁₋₂alkyl)₂ or -C(O)O(C₁₋₄alkyl).
- 46 The compound of claim 45, wherein J^Q is C_{1-4} alkyl, -O-, or -C(O)-.
- 47 The compound of any one of claims 1-43, wherein J^Q is Q^2 .
- 48 The compound of claim 47, wherein Q^2 is a 3-7 membered heterocyclyl or carbocyclyl; the heterocyclyl having 1-3 heteroatoms selected from oxygen, nitrogen, or sulfur.

- 49 The compound of claim 48, wherein Q^2 is independently selected from selected from oxetanyl, tetrahydropyranyl, tetrahydrofuranyl, cyclopropyl, azetidiny, pyrrolidiny, piperaziny, cyclobutyl, thiomorpholiny, or morpholiny.
- 50 The compound of claim 49, wherein Q^2 is independently selected from oxetanyl, tetrahydropyranyl, or tetrahydrofuranyl.
- 51 The compound of claim 50, wherein Q^2 is oxetanyl.
- 52 The compound of claim 51, wherein Q^2 is a 7-12 membered fully saturated, partially unsaturated, or aromatic bicyclic ring having 0-5 heteroatoms selected from oxygen, nitrogen, or sulfur.
- 53 The compound of claim 52, wherein Q^2 is independently selected from 5,6,7,8-tetrahydroimidazo[1,5-a]pyraziny or 5,6,7,8-tetrahydroimidazo[1,2-a]pyraziny.
- 54 The compound of any one of claims 1-38, wherein two occurrences of J^Q , together with Ring A, form a bridged ring system.
- 55 The compound of any one of claims 1-43, wherein J^Q is =O.
- 56 The compound of any one of claims 44-54, wherein J^R is a 3-6 membered heterocyclyl having 1-3 heteroatoms selected from oxygen, nitrogen, or sulfur.
- 57 The compound of claim 56, wherein J^R is independently selected from oxetanyl, piperadiny, azetidiny, piperaziny, pyrrolidiny, or morpholiny.
- 58 The compound of claim 57, wherein J^R is a piperaziny.
- 59 The compound of any one of claims 44-54, wherein J^R is independently selected from halo, =O, -OH, C_{1-4} alkyl, $-(C_{0-4}alkyl)N(C_{1-4}alkyl)_2$, or $-(C_{0-4}alkyl)O(C_{1-4}alkyl)$.
- 60 The compound of any one of claims 47-54, 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.

- 61 The compound of claim 60, wherein J^R is independently selected from oxetanyl or azetidiny.
- 62 The compound of any one of claims 47-49, wherein two occurrences of J^R , together with Ring A, form a bridged ring system.
- 63 The compound of claim 58, wherein J^T is a 3-6 membered non-aromatic ring having 0-2 heteroatoms selected from oxygen, nitrogen, or sulfur.
- 64 The compound of claim 63, wherein J^T is oxetanyl.
- 65 The compound of claim 1 having formula I-A-1:



I-A-1

wherein:

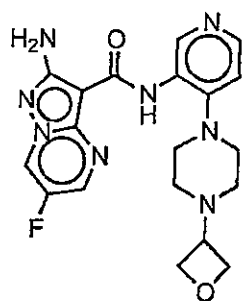
R^5 is selected from C_{1-4} aliphatic, a 3-6 membered cycloalkyl, or a 3-6 membered heterocyclyl having 1-2 heteroatoms selected from oxygen or sulfur;

R^8 is selected from H or C_{1-3} alkyl; or

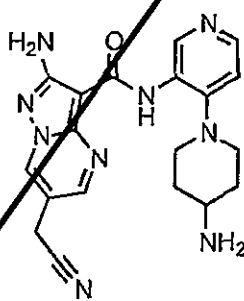
R^5 and R^8 , taken together with the atoms to which they are bound, form a 5-6 membered non-aromatic ring having 1-2 heteroatoms selected from oxygen, nitrogen or sulfur.

- 66 The compound of claim 65, wherein R^1 is fluoro.
- 67 The compound of claim 66, wherein R^5 is C_{1-4} aliphatic.
- 68 The compound of claim 67, wherein R^5 is independently selected from methyl or ethyl.
- 69 The compound of claim 65, wherein R^5 is a 3-6 membered cycloalkyl.

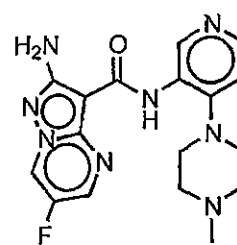
- 70 The compound of claim 69, wherein R^5 is cyclopropyl.
- 71 The compound of claim 65, wherein R^5 is a 3-6 membered heterocyclyl having 1-2 heteroatoms selected from oxygen or sulfur.
- 72 The compound of claim 71, wherein R^5 is tetrahydrofuranyl or oxytanyl.
- 73 The compound of claim 65, wherein R^5 and R^6 , taken together with the atoms to which they are bound, form a 5-6 membered non-aromatic ring having 1-2 heteroatoms selected from oxygen, nitrogen or sulfur.
- 74 The compound of claim 73, wherein the ring formed by R^5 and R^6 is a five-membered ring.
- 75 The compound of claim 73, wherein the ring formed by R^5 and R^6 is a six-membered ring.
- 76 The compound of any one of claims 34-75 independently selected from:



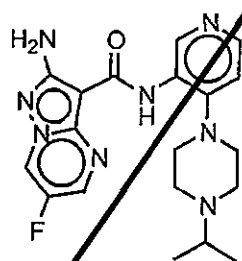
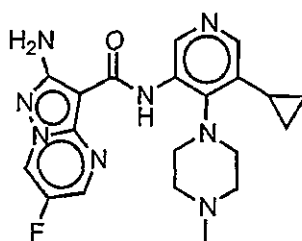
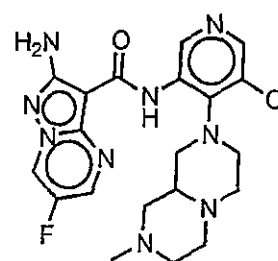
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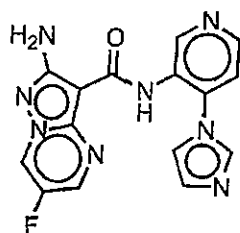
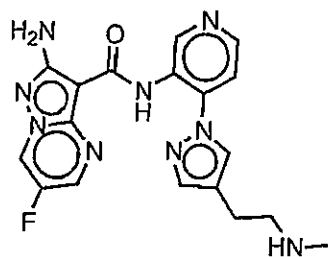
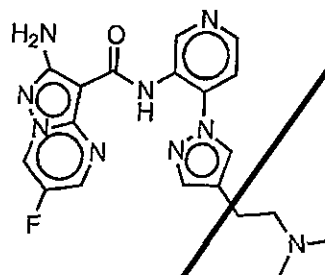
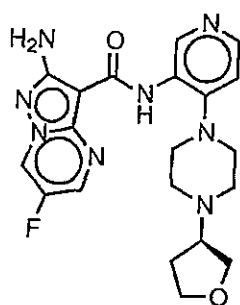
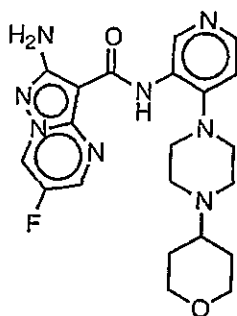
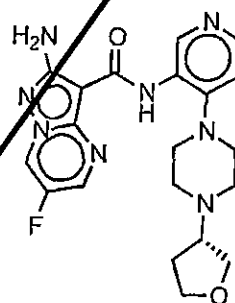
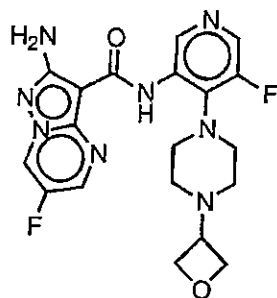
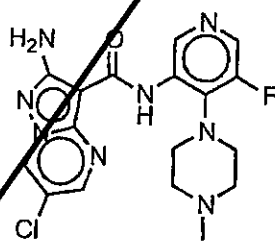
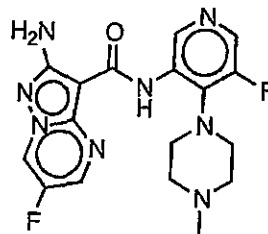


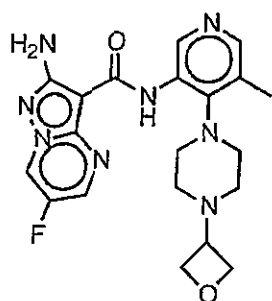
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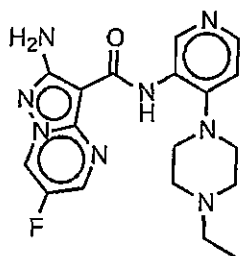
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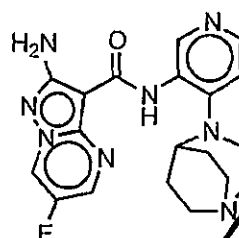
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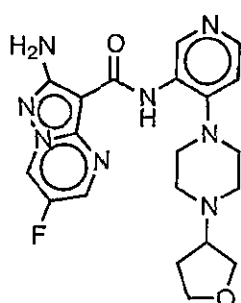
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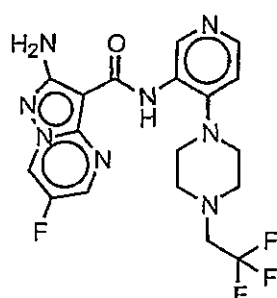
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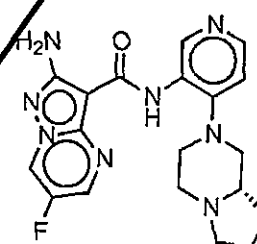
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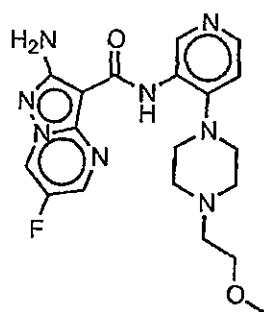
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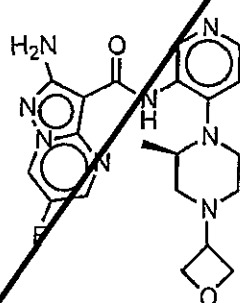
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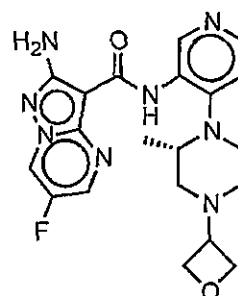
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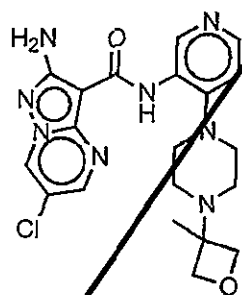
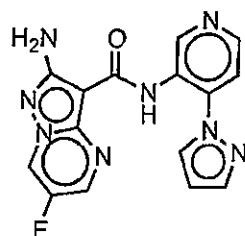
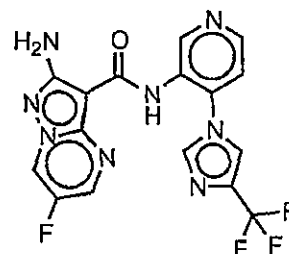
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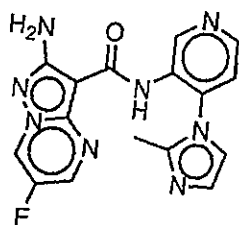
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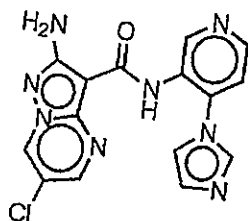
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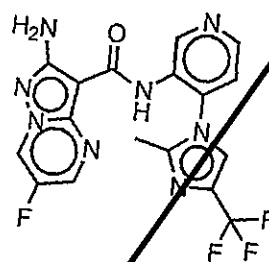
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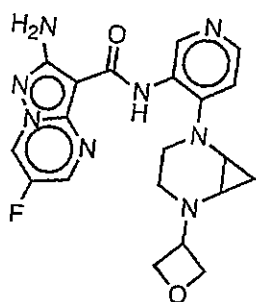
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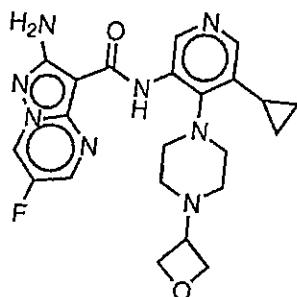
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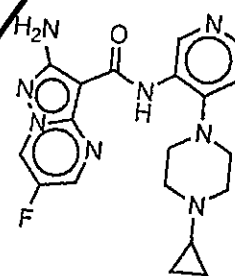
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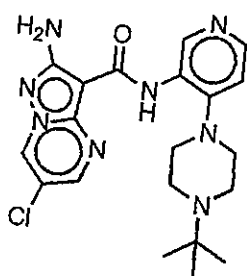
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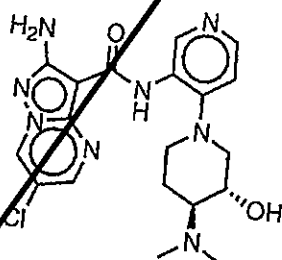
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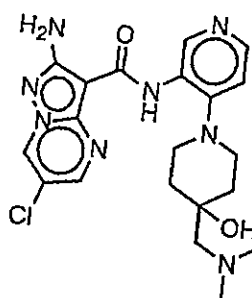
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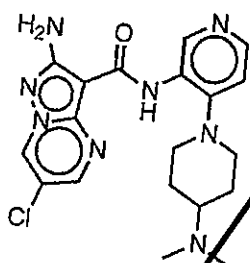
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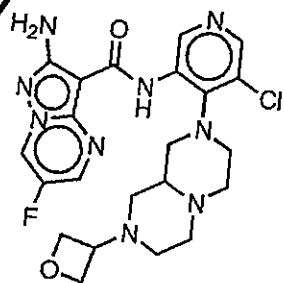
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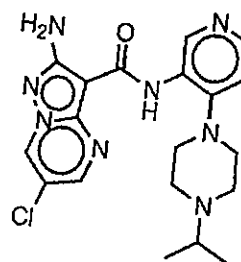
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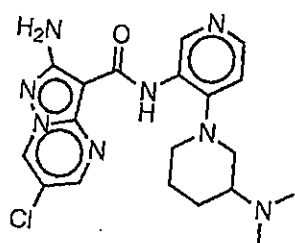
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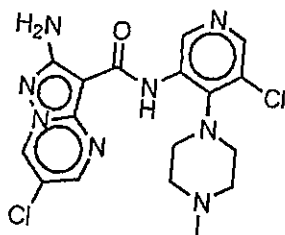
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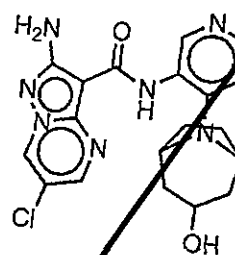
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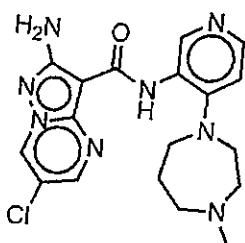
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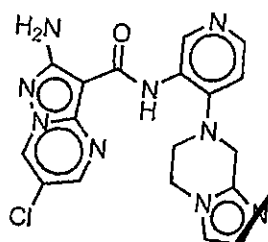
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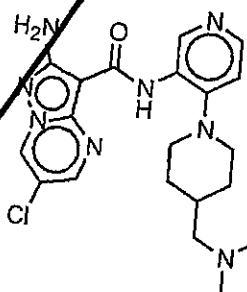
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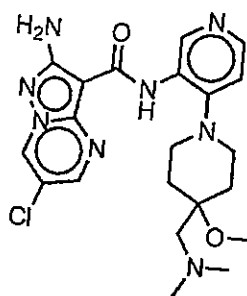
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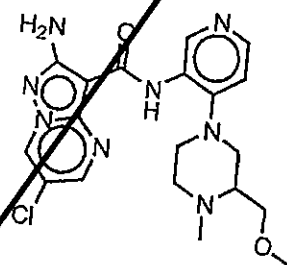
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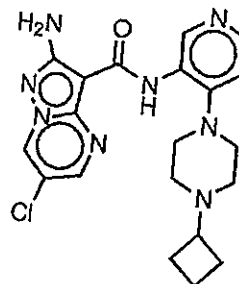
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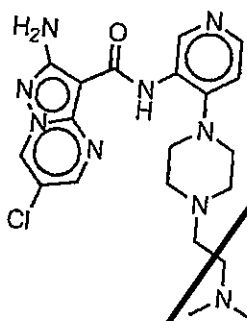
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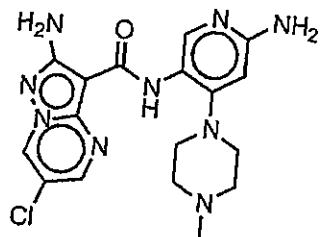
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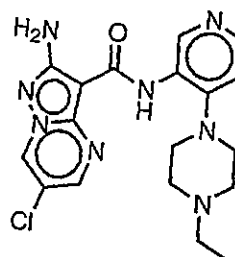
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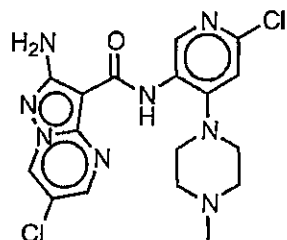
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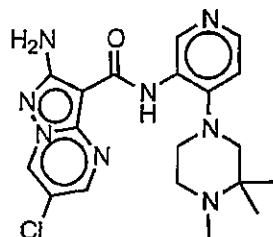
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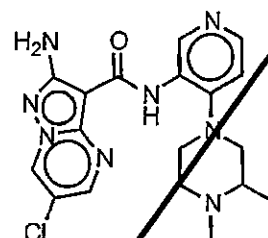
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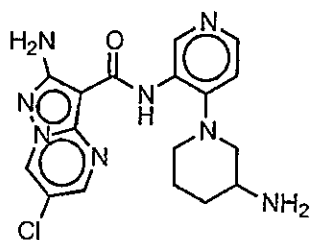
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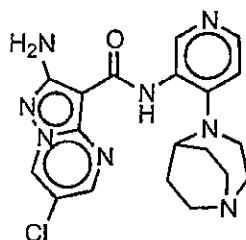
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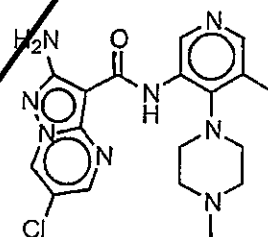
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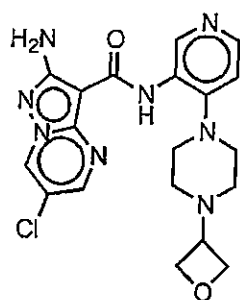
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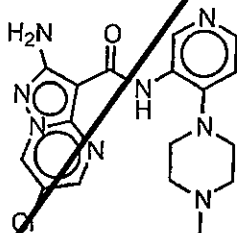
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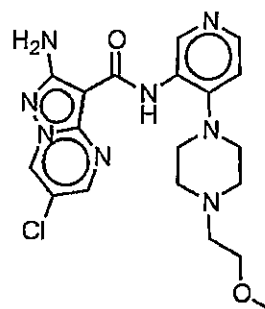
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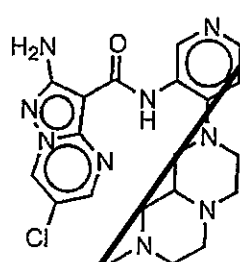
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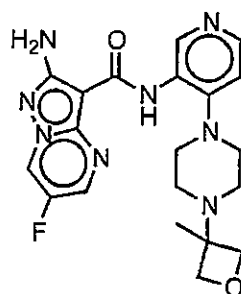
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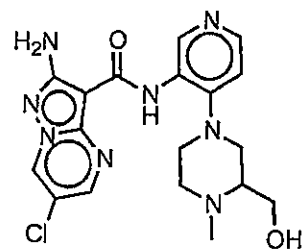
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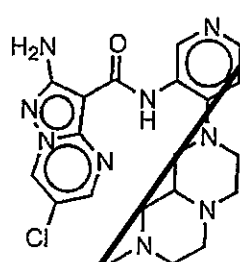
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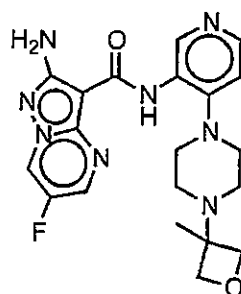
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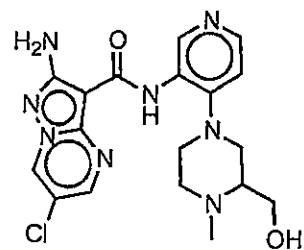
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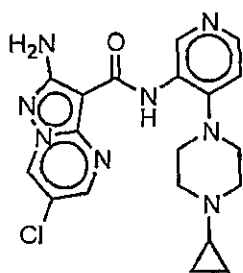


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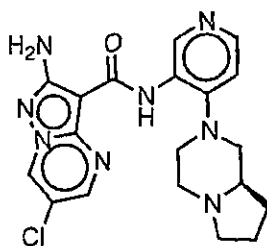


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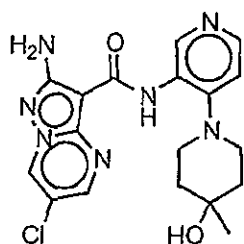




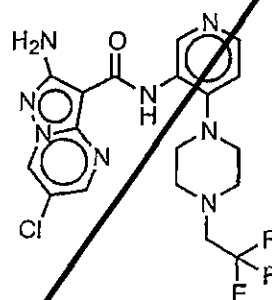
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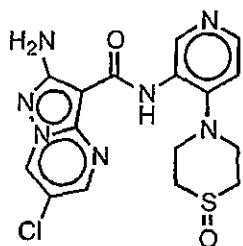
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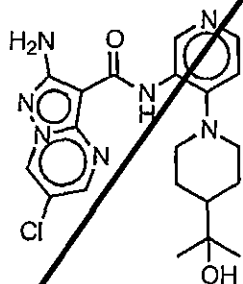
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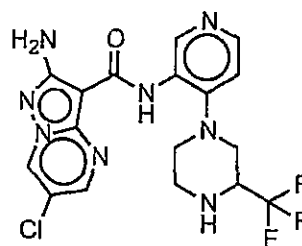
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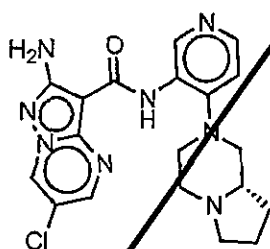
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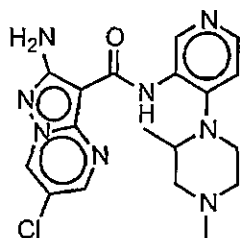
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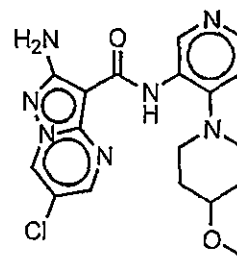
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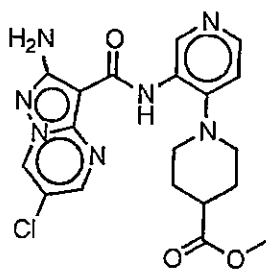
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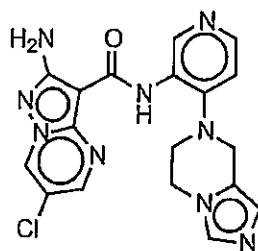
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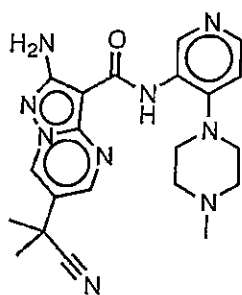
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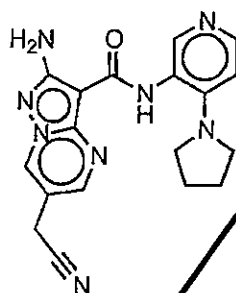
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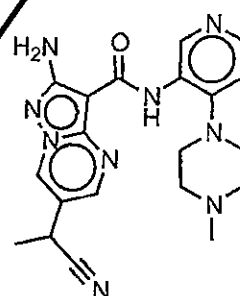
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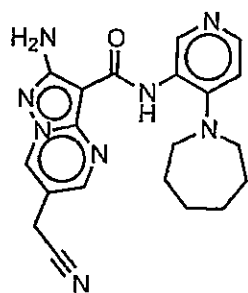
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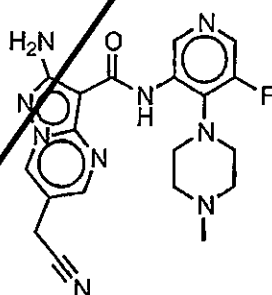
I-N-77



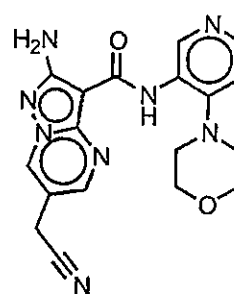
I-N-78



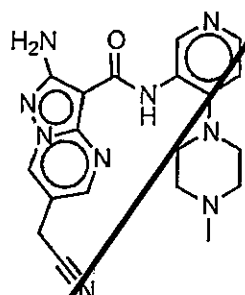
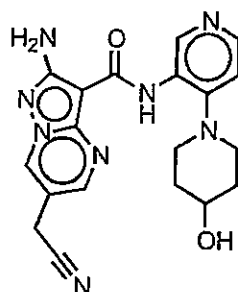
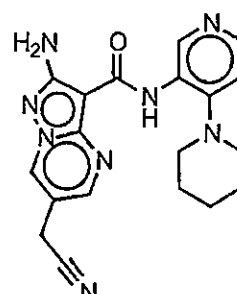
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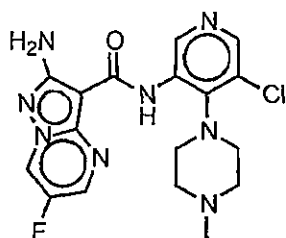
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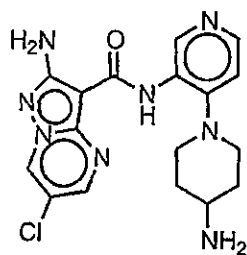
I-N-81



I-N-82

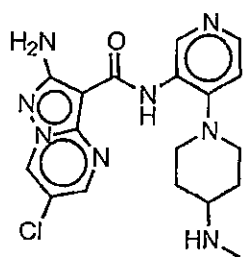


I-N-83

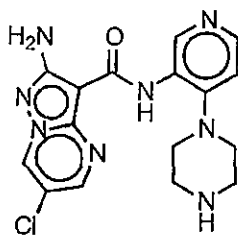
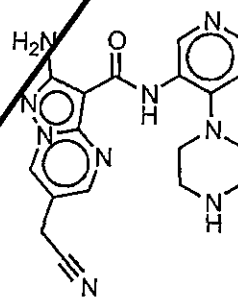


I-N-84

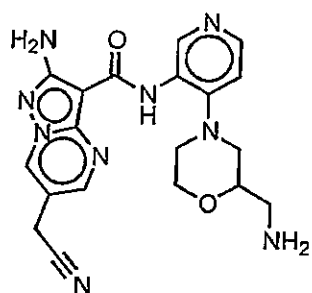
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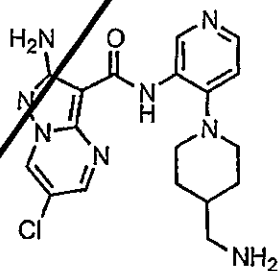
I-N-86



I-N-87



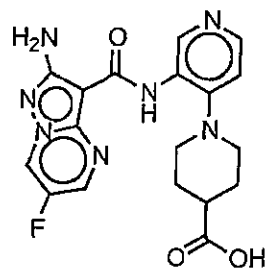
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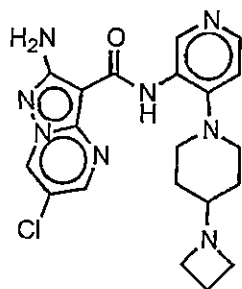
I-N-89

I-N-90

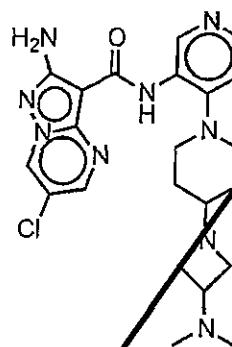
I-N-91



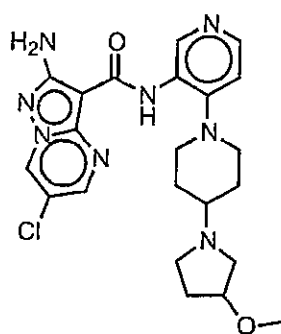
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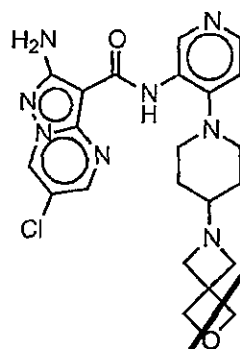
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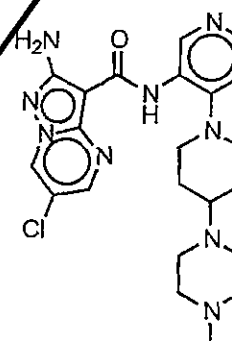
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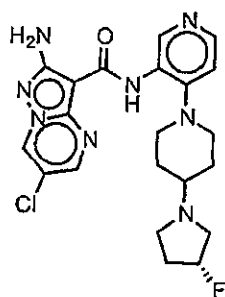
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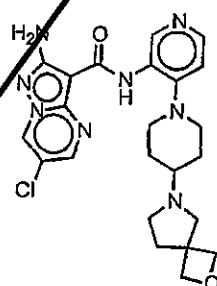
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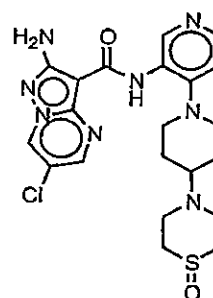
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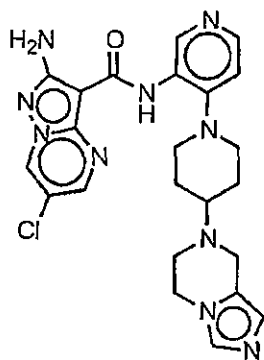
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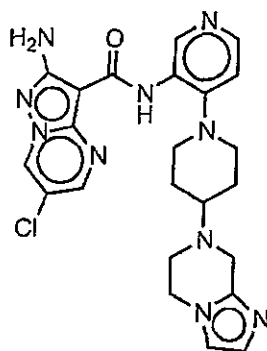
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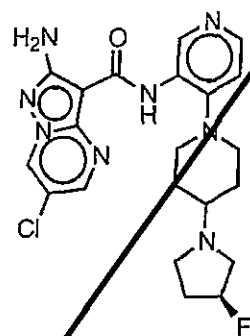
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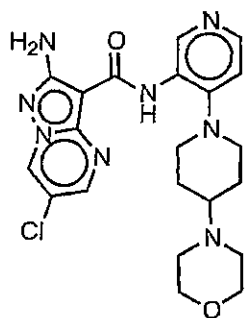
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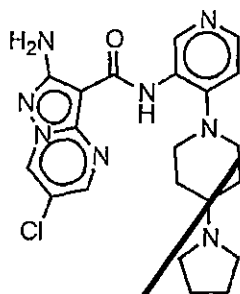
I-N-102



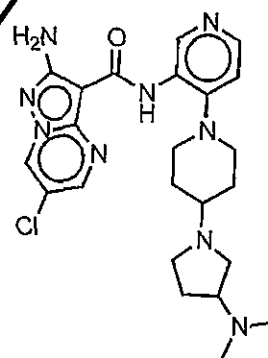
I-N-103



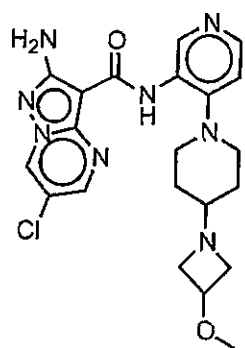
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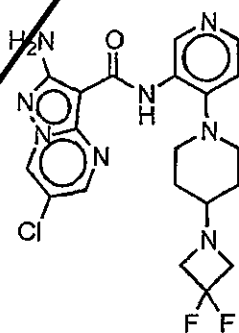
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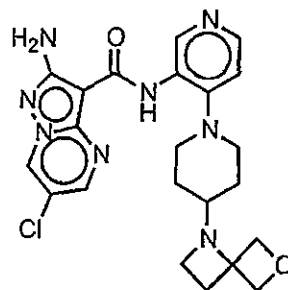
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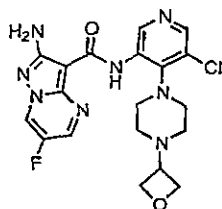
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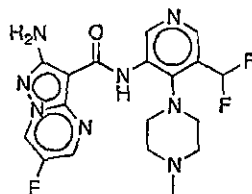
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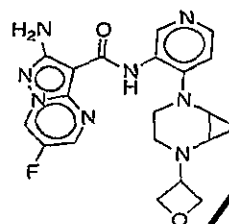
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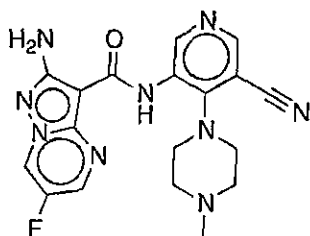
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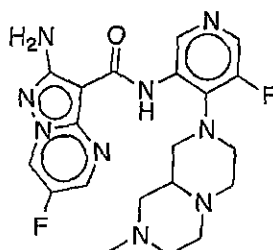
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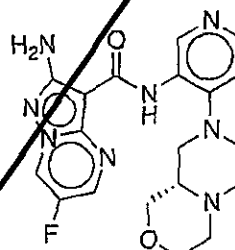
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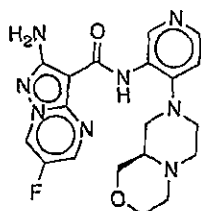
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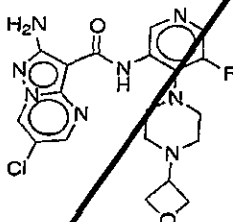
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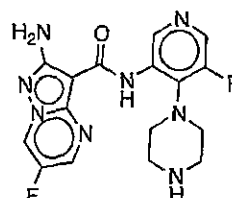
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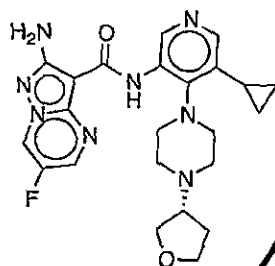
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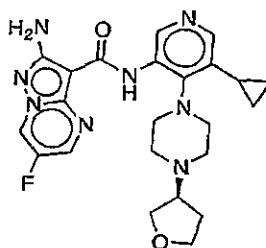
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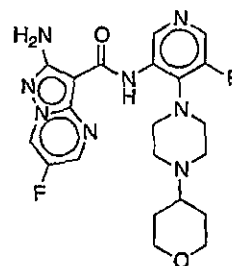
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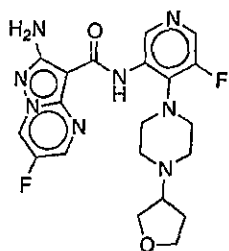
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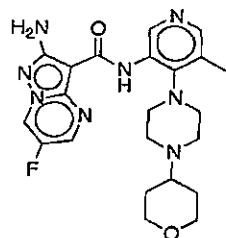
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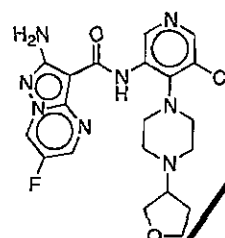
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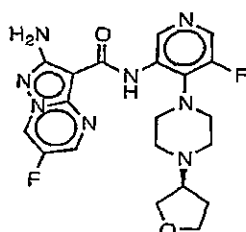
I-N-122



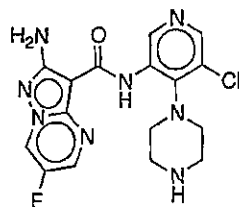
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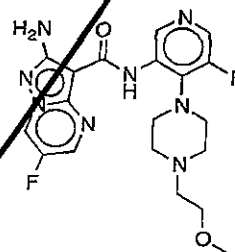
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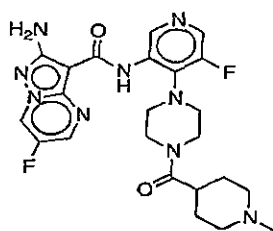
I-N-125



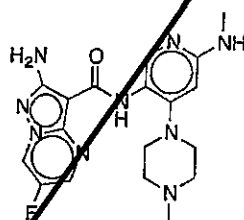
I-N-126



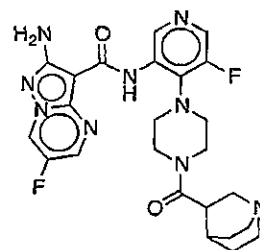
I-N-127



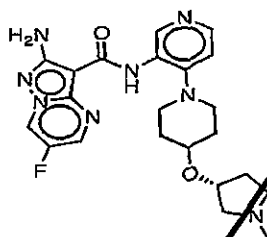
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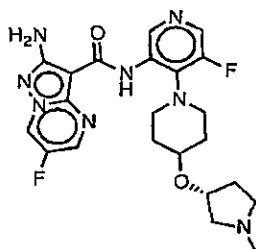
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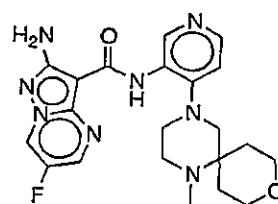
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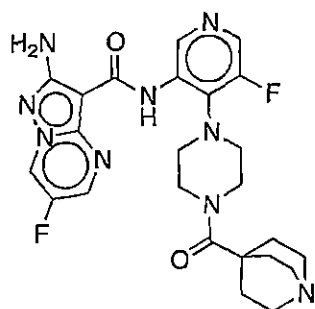
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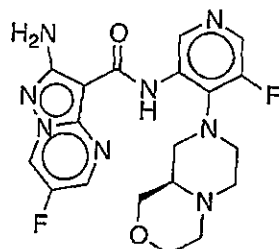
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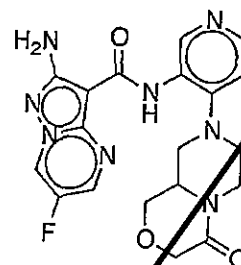
I-N-133



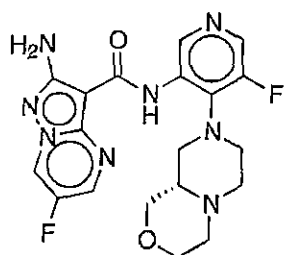
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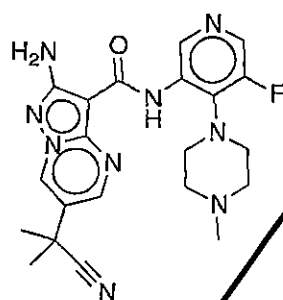
I-N-135



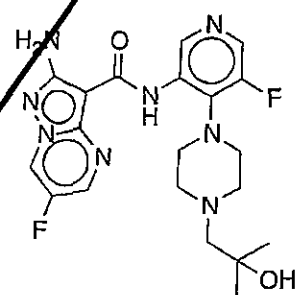
I-N-136



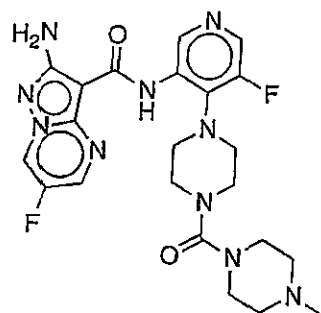
I-N-137



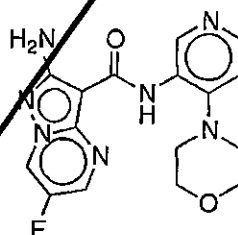
I-N-138



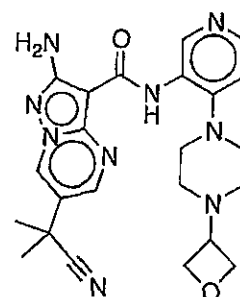
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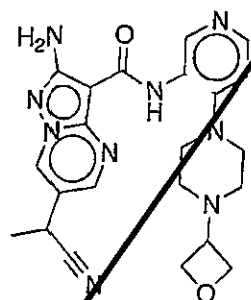
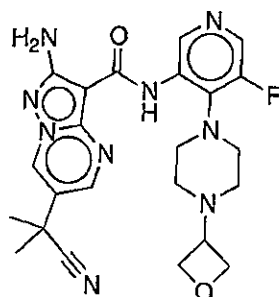
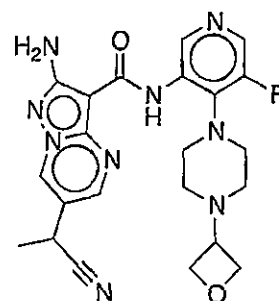
I-N-140

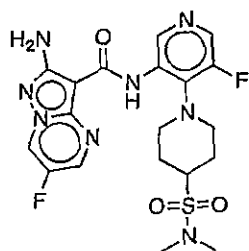
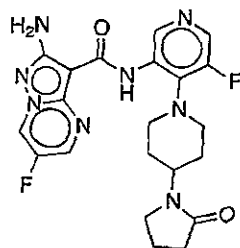
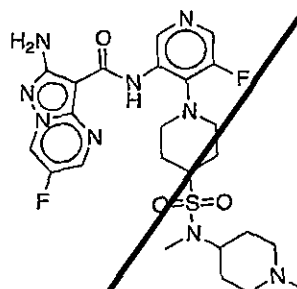
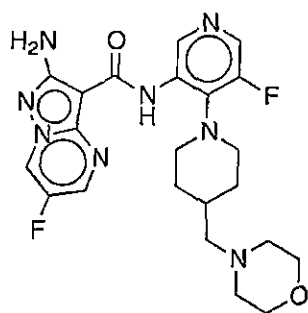
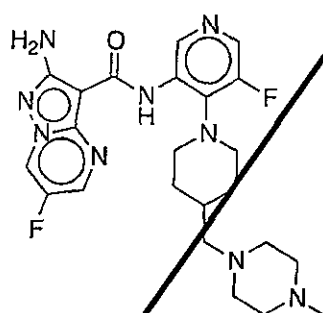
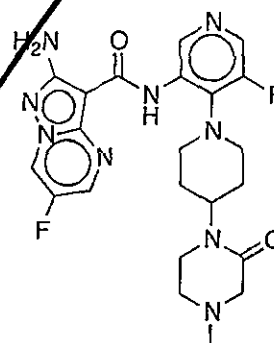
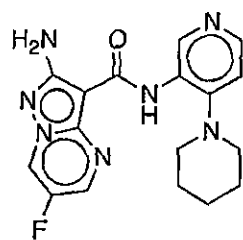
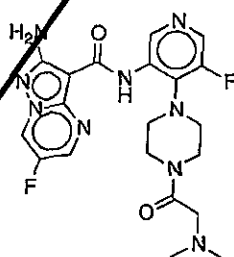
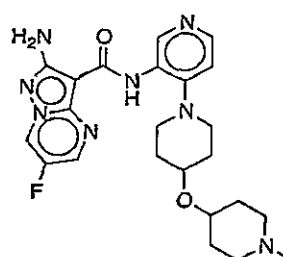


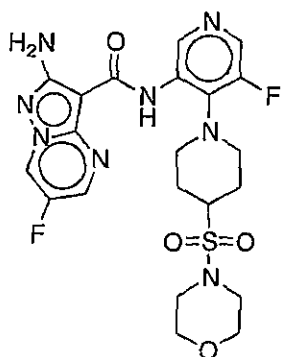
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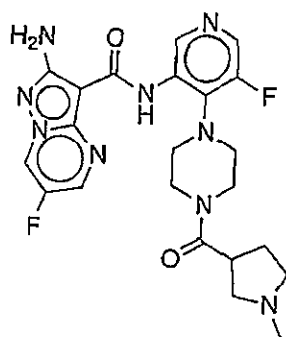
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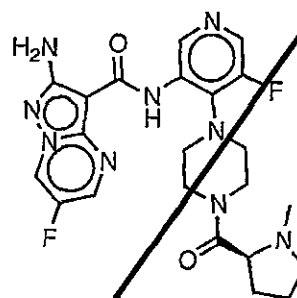
I-N-143**I-N-144****I-N-145****I-N-146****I-N-147****I-N-148****I-N-149****I-N-150****I-N-151****I-N-152****I-N-153****I-N-154**



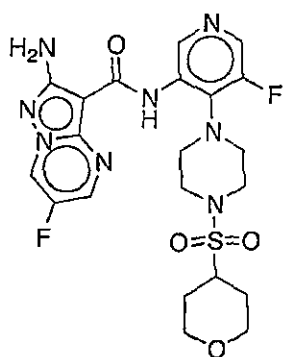
I-N-155



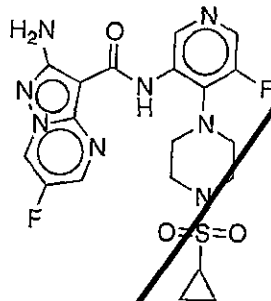
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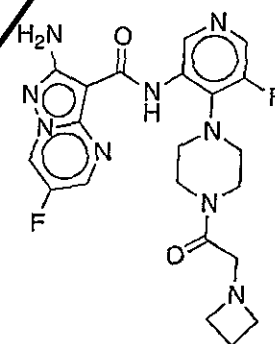
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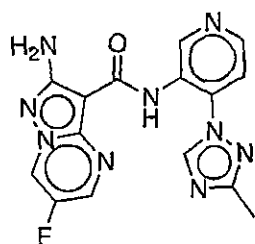
I-N-158



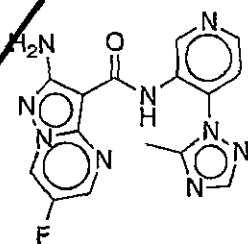
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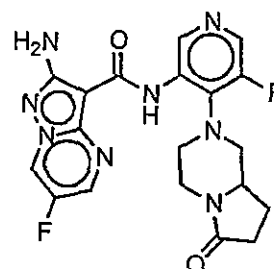
I-N-160



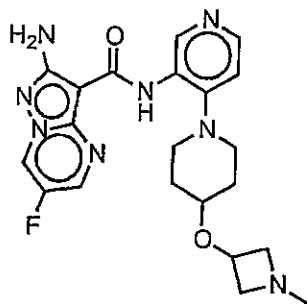
I-N-161



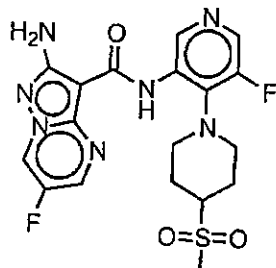
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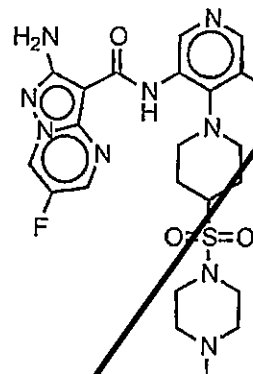
I-N-163



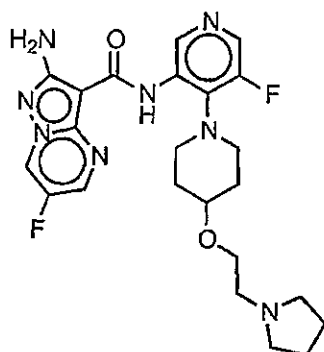
I-N-164



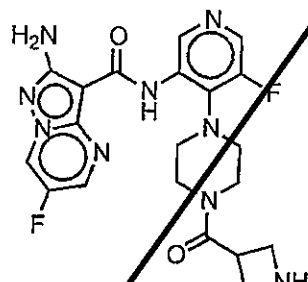
I-N-165



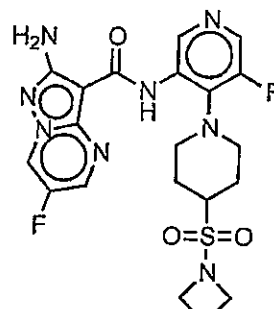
I-N-166



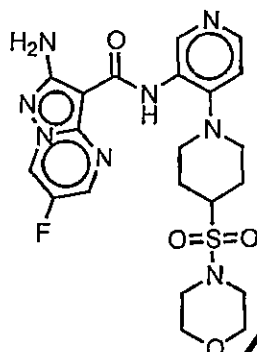
I-N-167



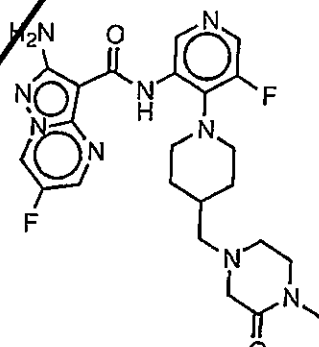
I-N-168



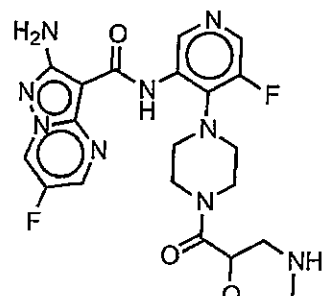
I-N-169



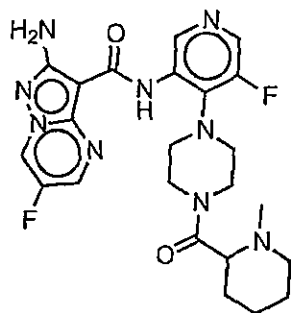
I-N-170



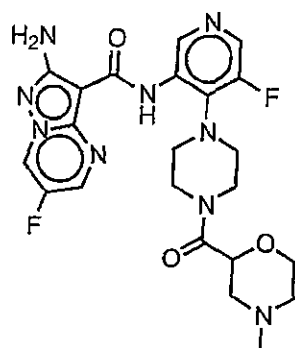
I-N-171



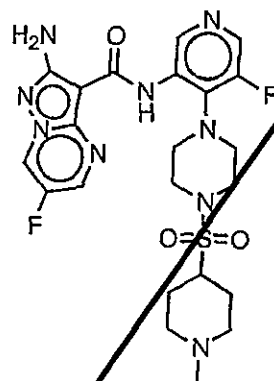
I-N-172



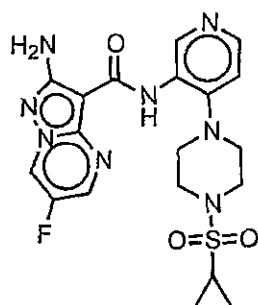
I-N-173



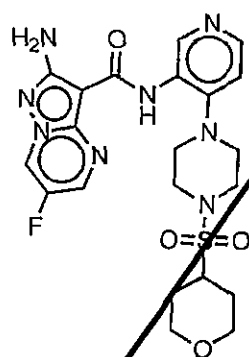
I-N-174



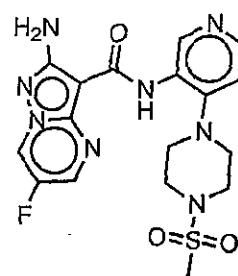
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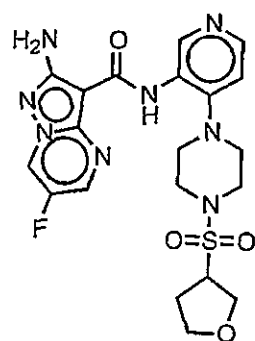
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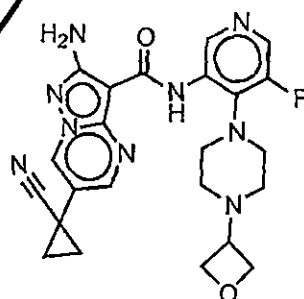
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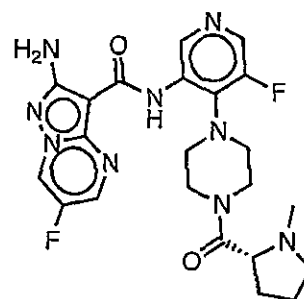
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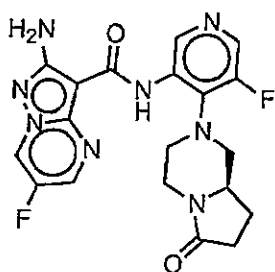
I-N-179



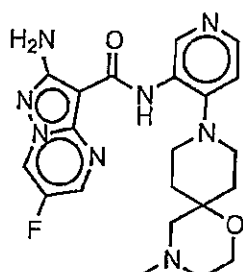
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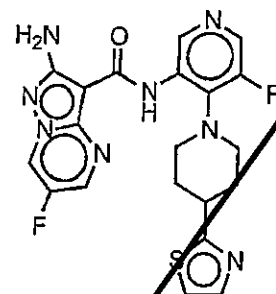
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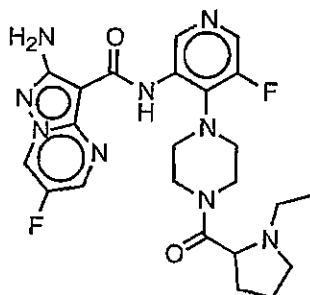
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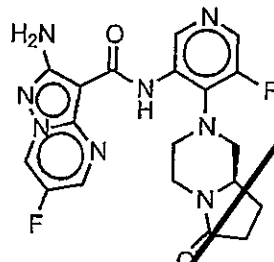
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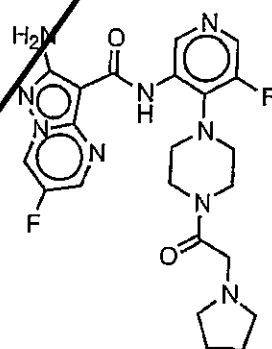
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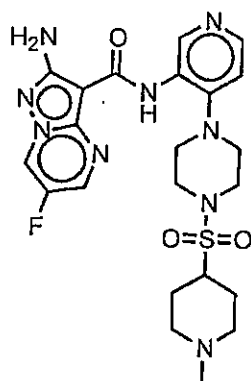
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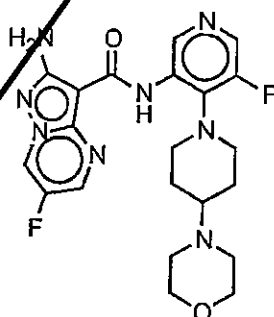
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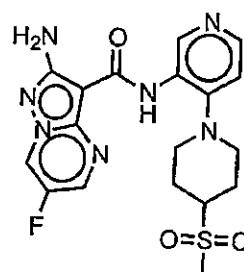
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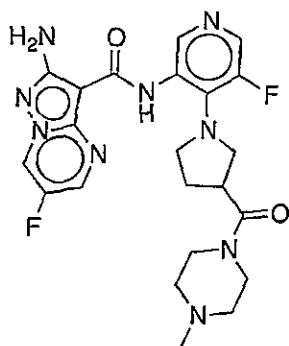
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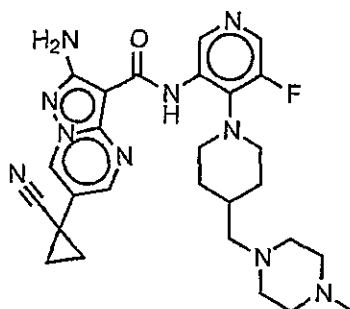
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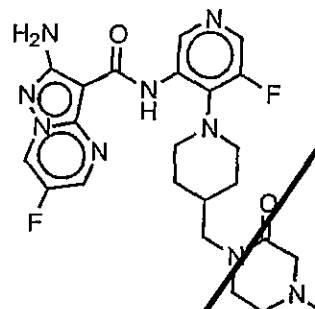
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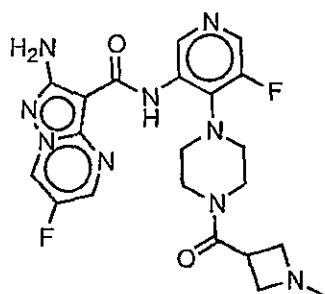
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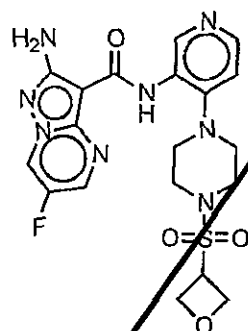
I-N-192



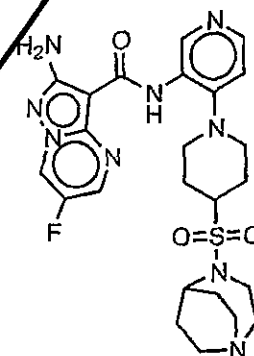
I-N-193



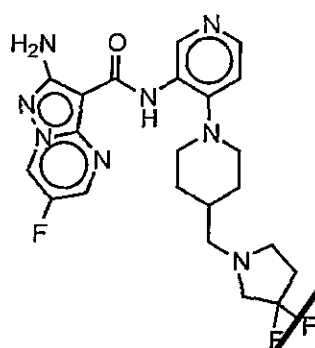
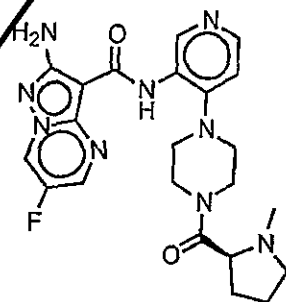
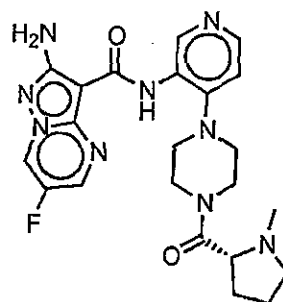
I-N-194

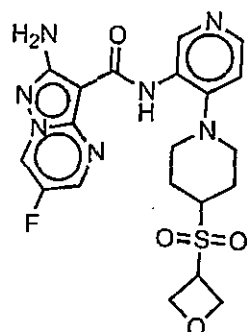
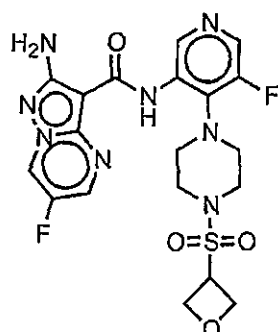
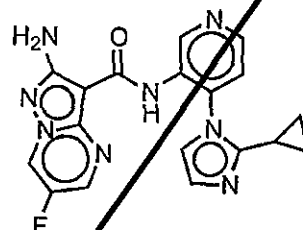
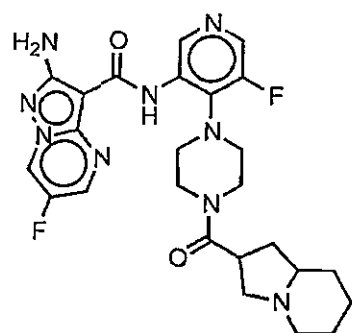
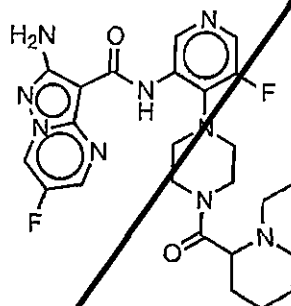
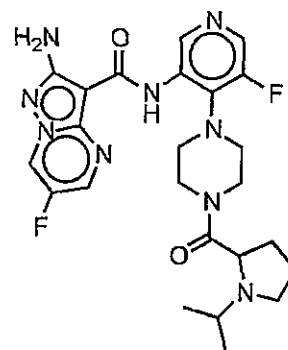
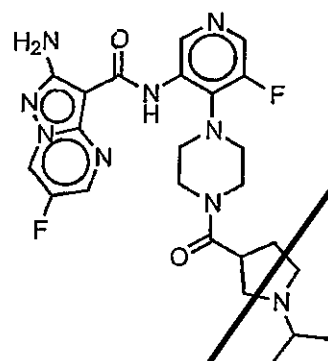
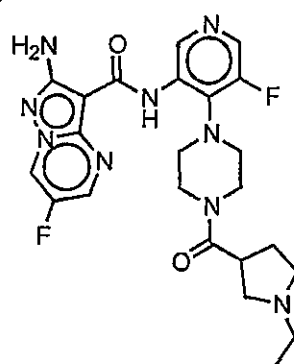
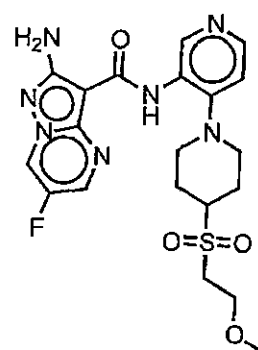


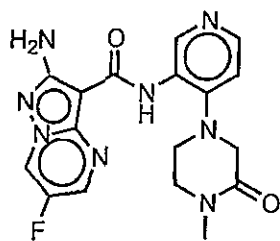
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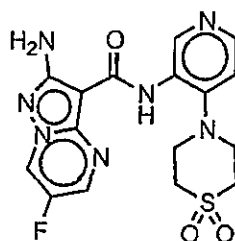
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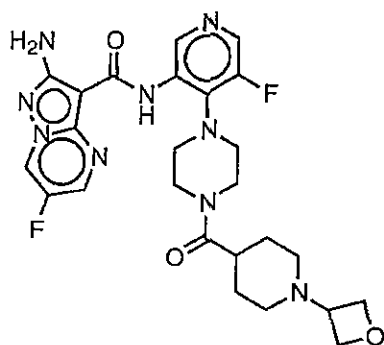
I-N-197**I-N-198****I-N-199****I-N-200****I-N-201****I-N-202****I-N-203****I-N-204****I-N-205****I-N-206****I-N-207****I-N-208**



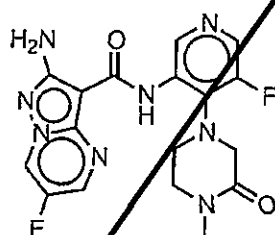
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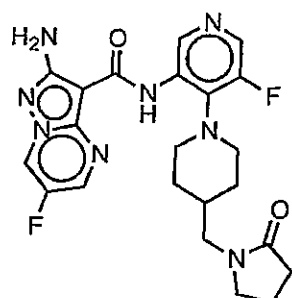
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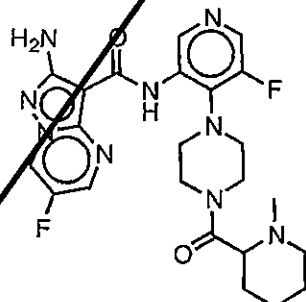
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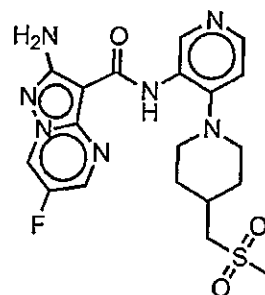
I-N-212



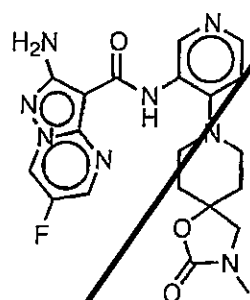
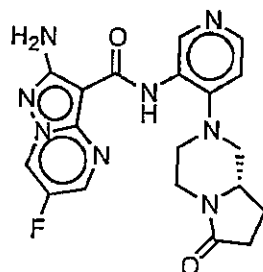
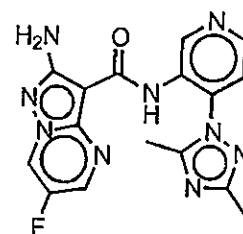
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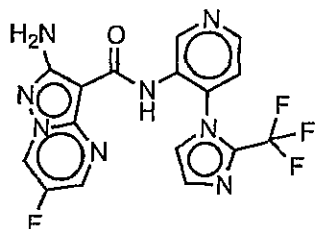
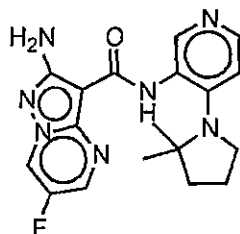
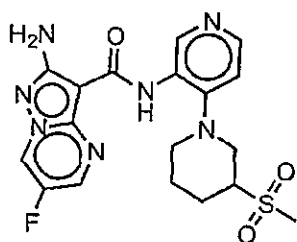
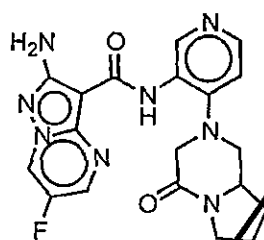
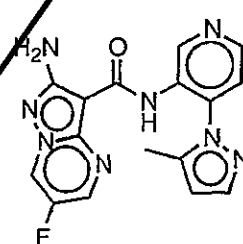
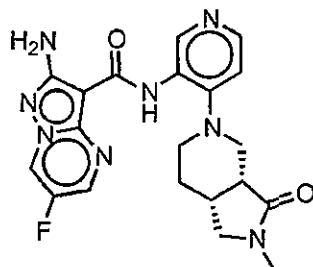
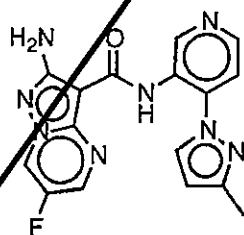
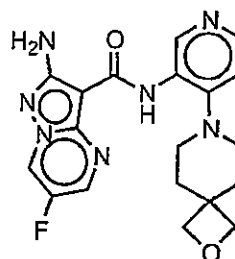
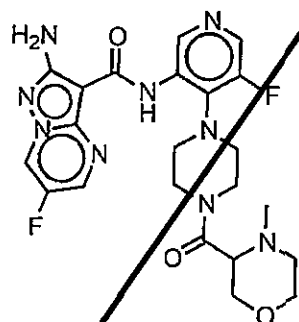
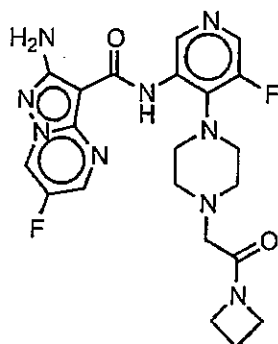
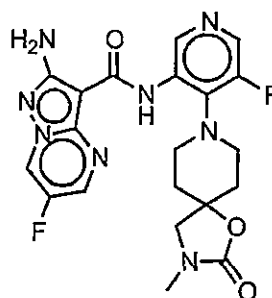


I-N-214

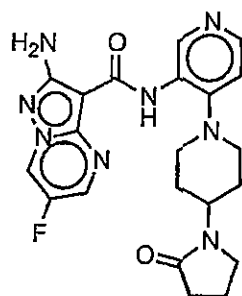


I-N-215

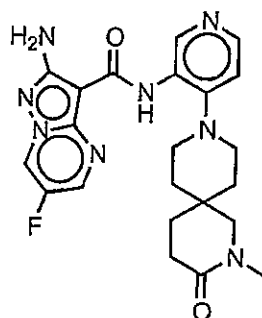


I-N-216**I-N-217****I-N-218****I-N-219****I-N-220****I-N-221****I-N-222****I-N-223****I-N-224****I-N-225****I-N-226**

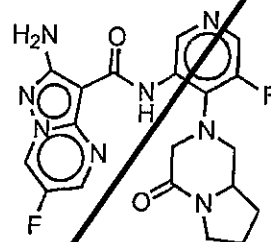
I-N-227



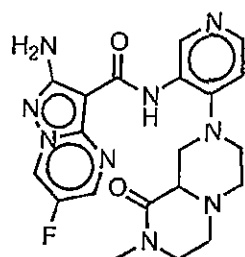
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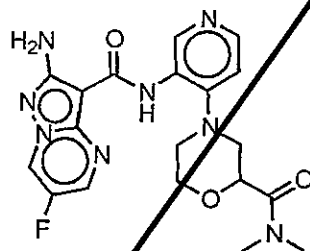
I-N-229



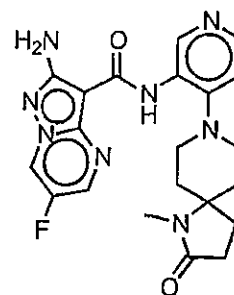
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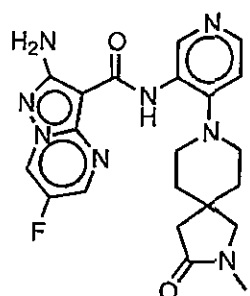
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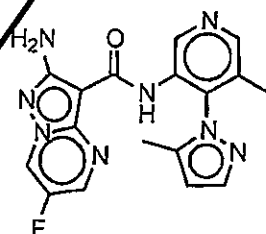
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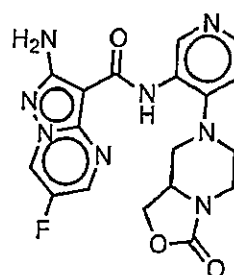
I-N-233



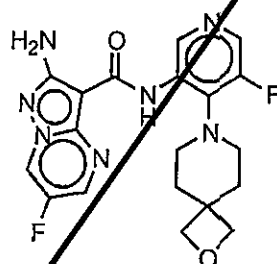
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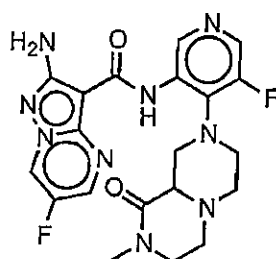
I-N-235



I-N-236

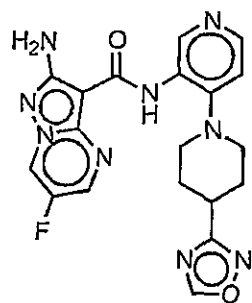


I-N-237

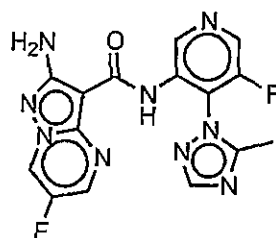


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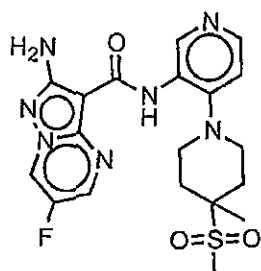
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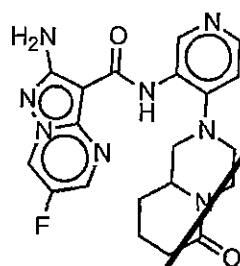
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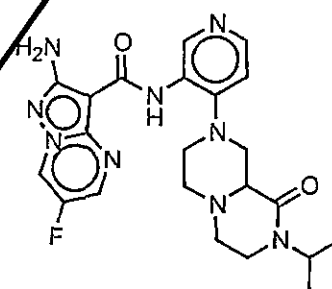
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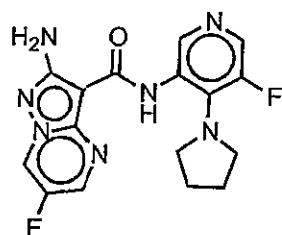
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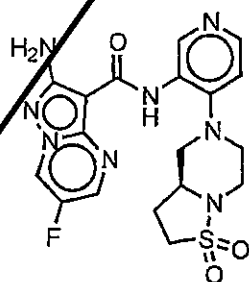
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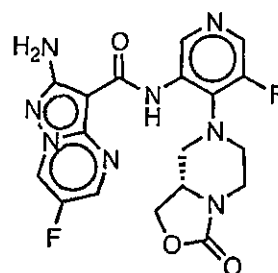
I-N-244



I-N-245

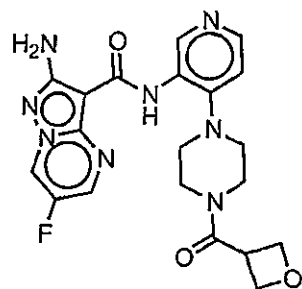


I-N-246

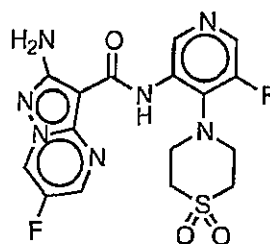


I-N-247

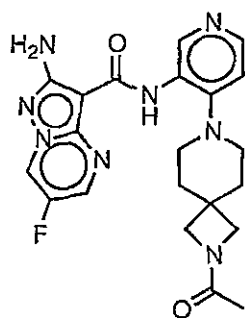
I-N-248



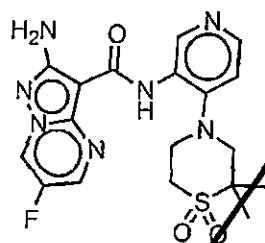
I-N-249



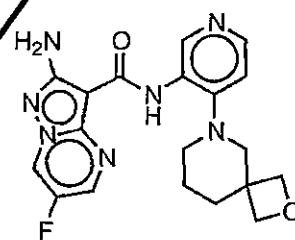
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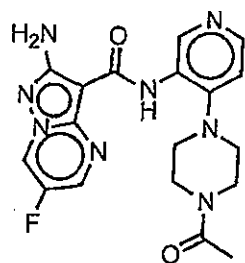
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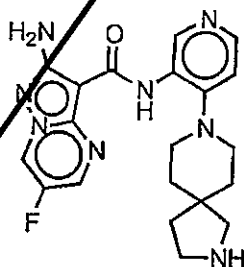
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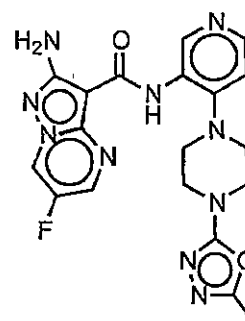
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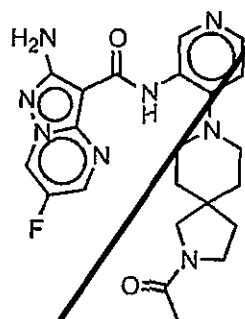
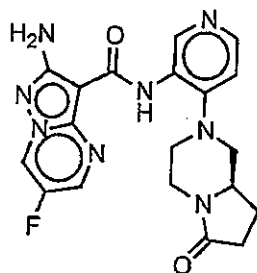
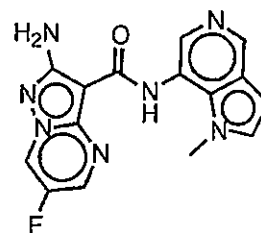
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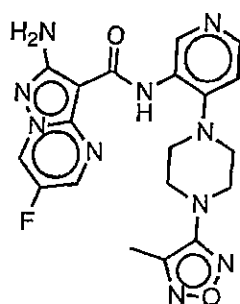
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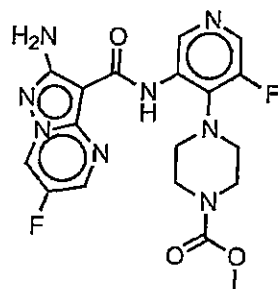
I-N-256



I-N-257

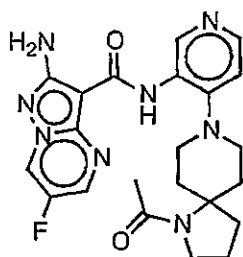


I-N-258

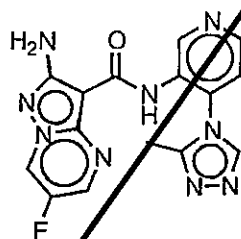


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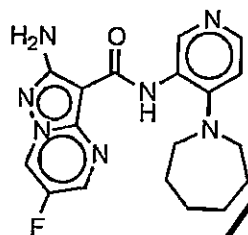
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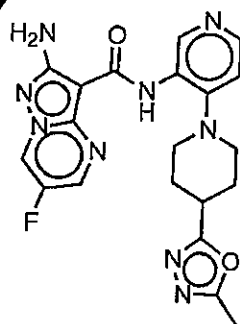
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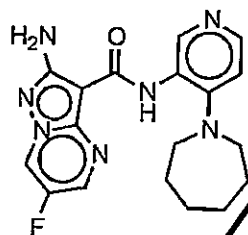
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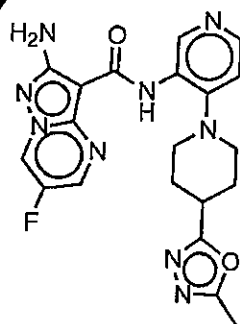
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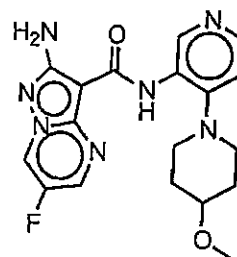
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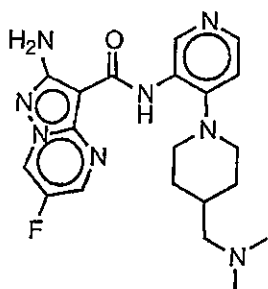


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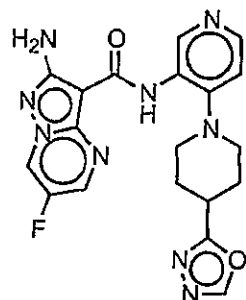


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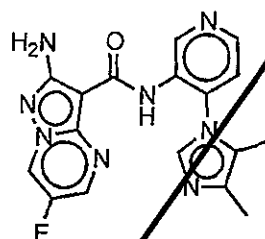




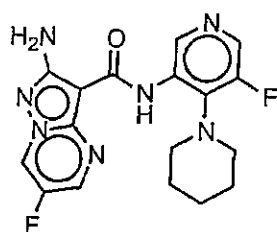
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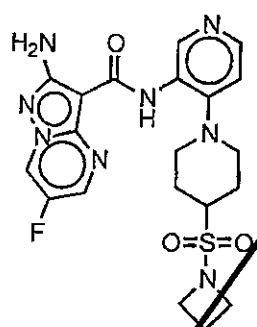
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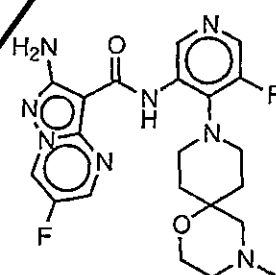
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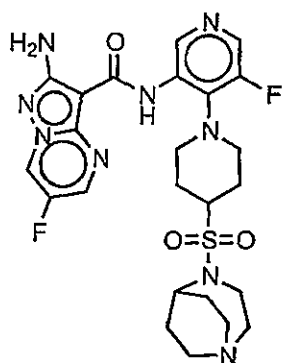
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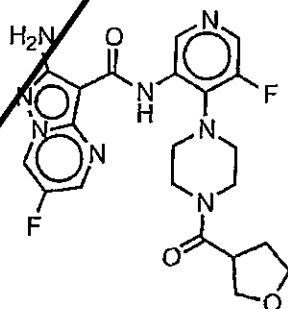
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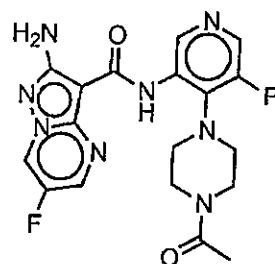
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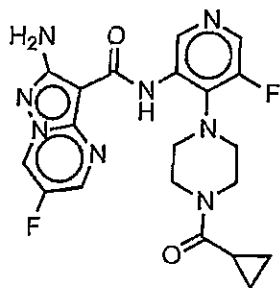
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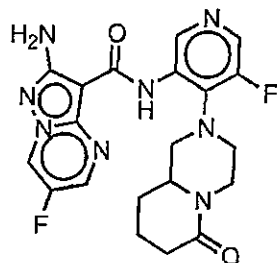
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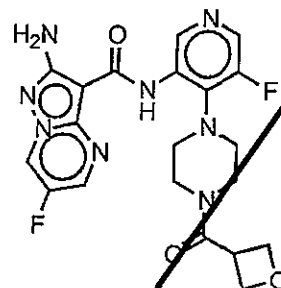
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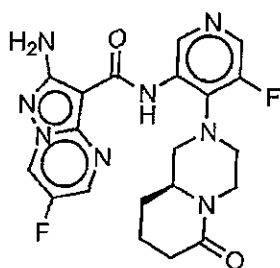
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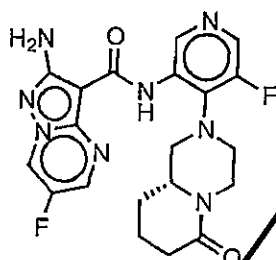
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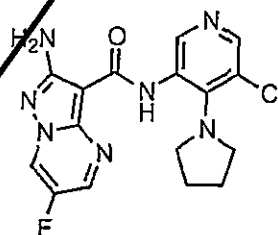
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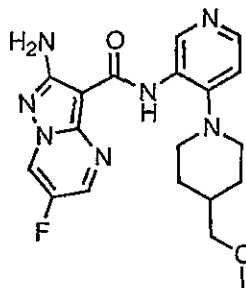
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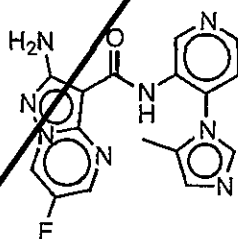
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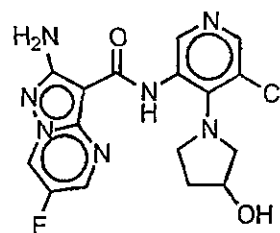
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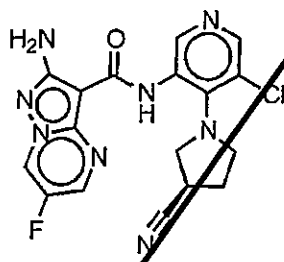
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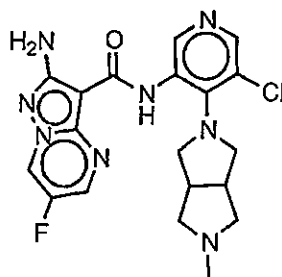
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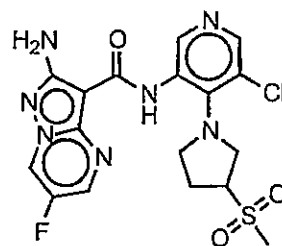
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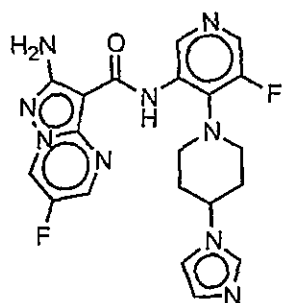
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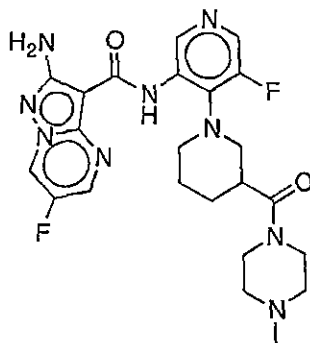
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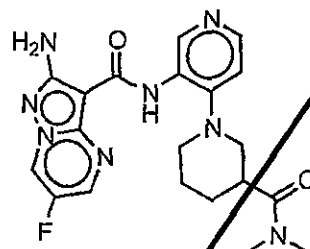
I-N-287



I-N-288

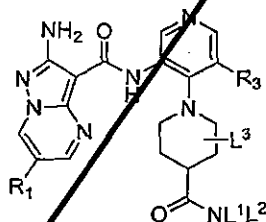


I-N-289



I-N-290.

77. A compound having the formula I-B:



I-B

or a pharmaceutically acceptable salt thereof, wherein:

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

J^1 is independently selected from 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 independently selected from 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 oxygen, nitrogen, or 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 oxygen, nitrogen, or 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 independently selected from 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 selected from halo; -N(R°)₂; a 3-6 membered carbocyclyl; a 3-6 membered heterocyclyl having 1-2 heteroatoms selected from oxygen nitrogen, or 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;

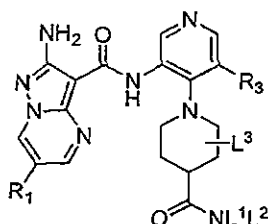
J^K is a 3-7 membered aromatic or non-aromatic ring having 0-2 heteroatoms selected from oxygen, nitrogen, or sulfur;

L^3 is independently selected from 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.

78. A compound having the formula I-B:



I-B

or a pharmaceutically acceptable salt thereof, wherein:

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

J^1 is independently selected from 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 independently selected from 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 oxygen, nitrogen, or 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 oxygen, nitrogen, or 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 H; $C_{1-3}aliphatic$; or CN ;

Ring D is independently selected from 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 selected from halo; -CN; -N(R^o)₂; →O; a 3-6 membered carbocycyl; a 3-6 membered heterocycyl having 1-2 heteroatoms selected from oxygen nitrogen, or sulfur; or a C₁₋₄ 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;

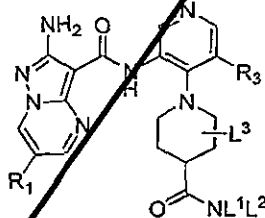
two occurrences of J^G , together with Ring D, form a 6-10 membered saturated or partially unsaturated bridged ring system;

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

n is 0, 1, or 2; and

R and R^o are H or C₁₋₄alkyl.

79. A compound having the formula I-B:



I-B

or a pharmaceutically acceptable salt thereof, wherein:

R¹ is independently selected from fluoro, chloro, or -C(J¹)₂CN;

J¹ is independently selected from 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 independently selected from 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;

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 oxygen, nitrogen, or 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 oxygen, nitrogen, or 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 independently selected from 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 selected from halo; -CN; -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 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;

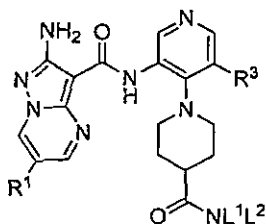
two occurrences of J^G , together with Ring D, form a 6-10 membered saturated or partially unsaturated bridged ring system;

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

n is 0, 1, or 2; and

R and R ^{o} are H or C_{1-4} alkyl.

80. A compound of formula I-B:



I-B

or a pharmaceutically acceptable salt thereof, wherein:

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

J^1 is independently selected from 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 independently selected from 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 oxygen, nitrogen, or 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 oxygen, nitrogen, or 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 independently selected from 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 selected from halo; $-N(R^o)_2$; a 3-6 membered carbocycl; a 3-6 membered heterocyclyl having 1-2 heteroatoms selected from oxygen nitrogen, or 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;

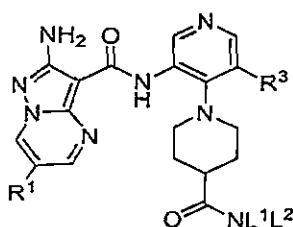
two occurrences of J^G , together with Ring D, form a 6-10 membered saturated or partially unsaturated bridged ring system;

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

n is 0, 1, or 2; and

R and R° are H or C_{1-4} alkyl.

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



I-B

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is independently selected from fluoro, chloro, or $-C(F)_2CN$;

J^1 is independently selected from 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 independently selected from 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 independently selected from a 3-7 membered heterocyclyl ring having 1-2 heteroatoms selected from oxygen, nitrogen or sulfur; or an 8-12 membered fully saturated or partially unsaturated bicyclic ring having 0-5 heteroatoms selected from oxygen, nitrogen, or sulfur;

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

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

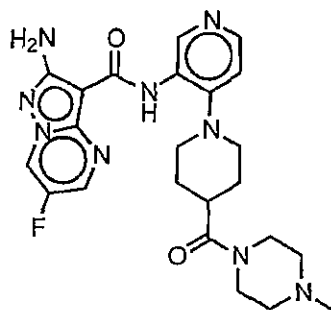
R° is H or C_{1-4} alkyl.

82. The compound of any one of claims 77-80, wherein R^1 is fluoro.
83. The compound of any one of claims 77-80, wherein R^1 is $-\text{CH}_2\text{CN}$.
84. The compound of any one of claims 77-80, wherein R^1 is chloro.
85. The compound of any one of claims 77-83, wherein R^3 is independently selected from H, chloro, fluoro, cyclopropyl, or C_{1-4} alkyl.
86. The compound of claim 85, wherein R^3 is independently selected from H, chloro, or fluoro.
87. The compound of claim 85, wherein R^3 is H.
88. The compound of claim 85, wherein R^3 is chloro.
89. The compound of claim 85, wherein R^3 is fluoro.
90. The compound of any one of claims 86-89, wherein L^1 and L^2 are H; $-(\text{C}_{1-3}\text{alkyl})\text{O}(\text{C}_{1-2}\text{alkyl})$; $-(\text{C}_{1-3}\text{alkyl})\text{N}(\text{C}_{1-2}\text{alkyl})_2$; C_{1-4} alkyl; azetidiny; piperidiny; oxytanyl; or pyrrolidiny.
91. The compound of any one of claims 82-89, wherein L^1 and L^2 , together with the nitrogen to which they are attached, form Ring D.
92. The compound of claim 91, wherein Ring D is a 3-7 membered heterocyclyl ring having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur.
93. The compound of claim 92, wherein Ring D is independently selected from piperazinyl, piperidiny, morpholinyl, tetrahydropyranyl, azetidiny, pyrrolidiny, or 1,4-diazepanyl.
94. The compound of claim 93, wherein Ring D is piperazinyl, piperidiny, 1,4-diazepanyl, pyrrolidiny or azetidiny.

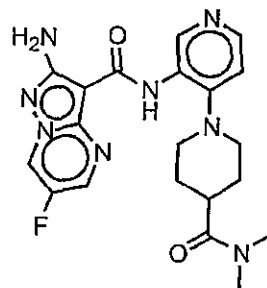
95. The compound of claim 94, wherein Ring D is piperazinyl or piperidinyl.
96. The compound of claim 92, wherein Ring D is an 8-12 membered fully saturated or partially unsaturated bicyclic ring having 0-5 heteroatoms selected from oxygen, nitrogen, or sulfur.
97. The compound of claim 96, wherein Ring D is octahydropyrrolo[1,2-a]pyrazine or octahydropyrrolo[3,4-c]pyrrole.
98. The compound of any one of claims 92-97, wherein J^G is halo, C_{1-4} alkyl, $-O(C_{1-3}$ alkyl), C_{3-6} cycloalkyl, a 3-6 membered heterocyclyl, $-NH(C_{1-3}$ alkyl), $-OH$, or $-N(C_{1-4}$ alkyl)₂.
99. The compound of claim 98, wherein J^G is methyl, $-N(C_{1-4}$ alkyl)₂, ethyl, $-O(C_{1-3}$ alkyl), cyclopropyl, oxetanyl, cyclobutyl, pyrrolidinyl, piperidinyl, or azetidiny.
100. The compound of claim 99, wherein J^G is methyl, $-O(C_{1-3}$ alkyl), oxetanyl, pyrrolidinyl, piperidinyl, or azetidiny.
101. The compound of claim 100, wherein J^G is methyl.
102. The compound of any one of claims 93-96, wherein two occurrences of J^G , together with Ring D, form a 6-10 membered saturated or partially unsaturated bridged ring system.
103. The compound of claim 102, 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.
104. The compounds of any one of claims 92-95, 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 oxygen, nitrogen, or sulfur.

105. The compound of claim 104, wherein the ring formed by the two occurrences of J^G on the same atom is selected from oxetanyl or cyclopropyl.

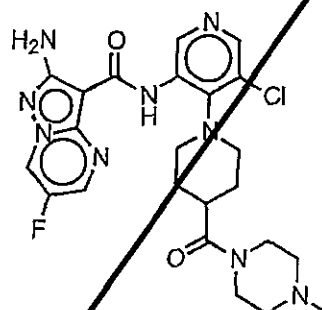
106. A compound of any one of claims 77-105 independently selected from:



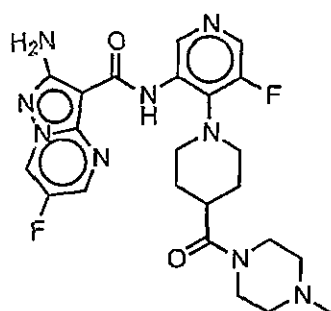
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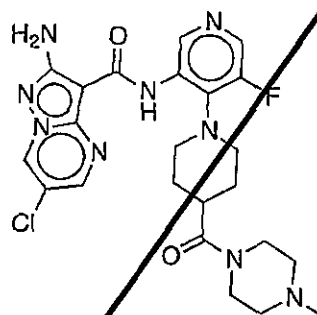
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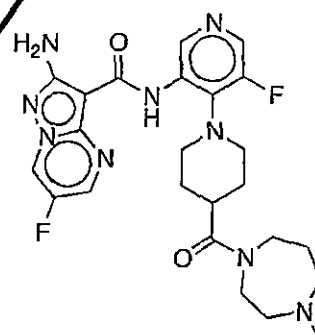
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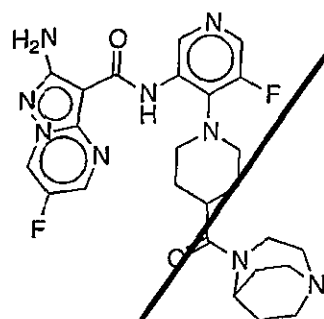
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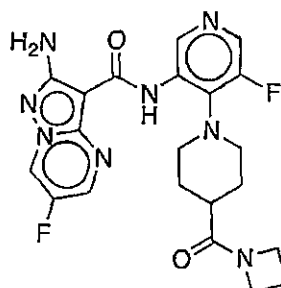
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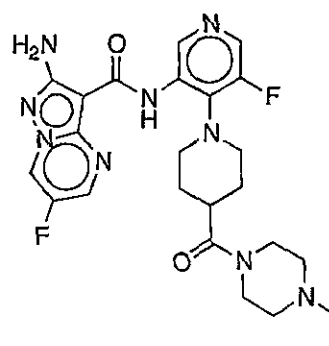
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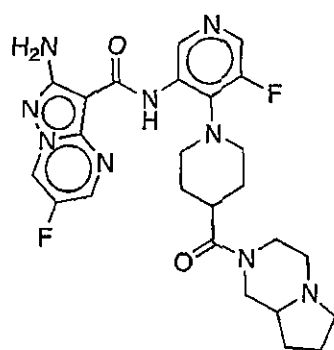
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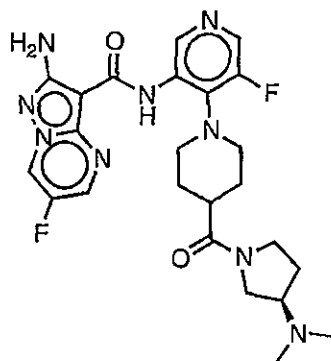
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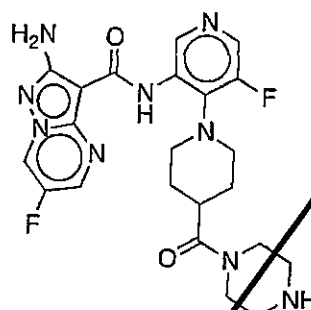
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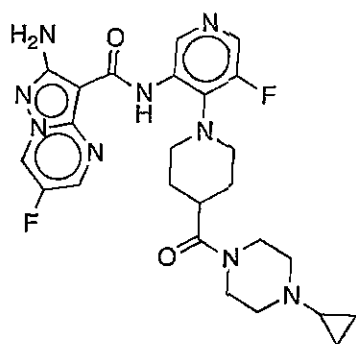
I-G-10



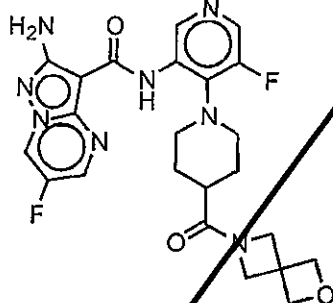
I-G-11



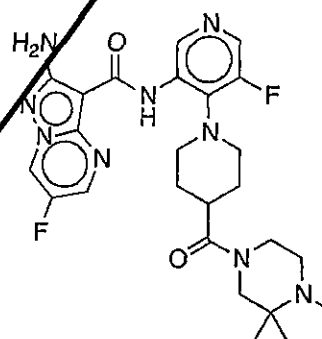
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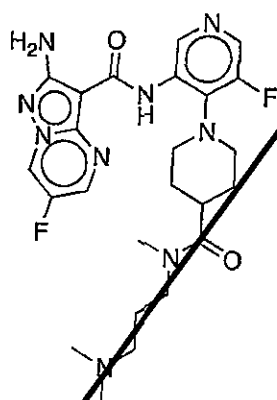
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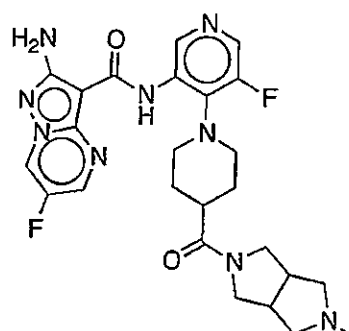
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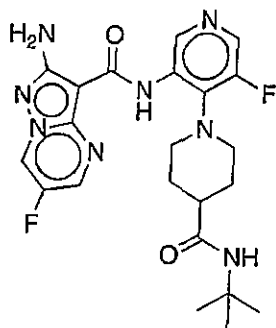
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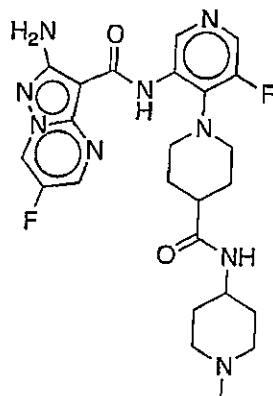
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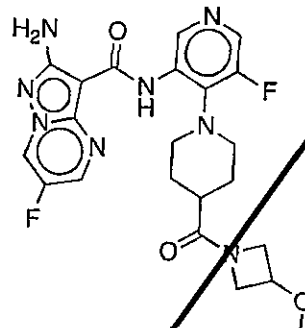
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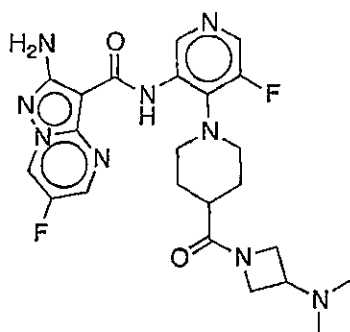
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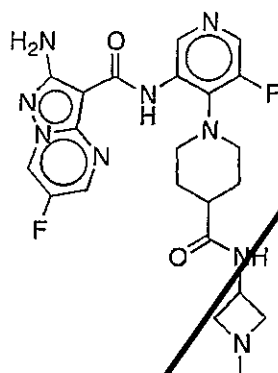
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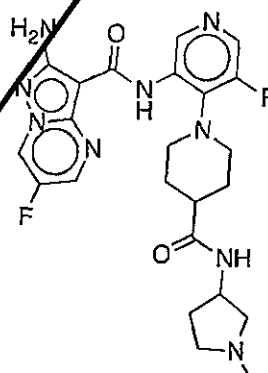
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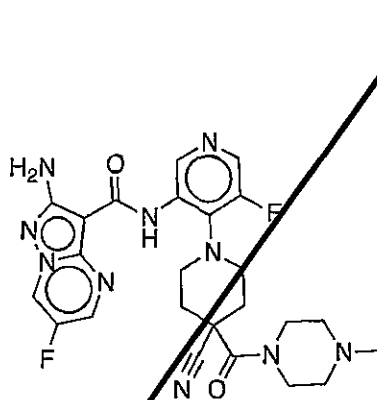
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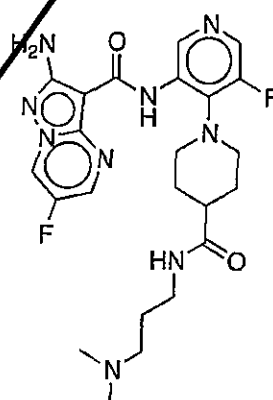
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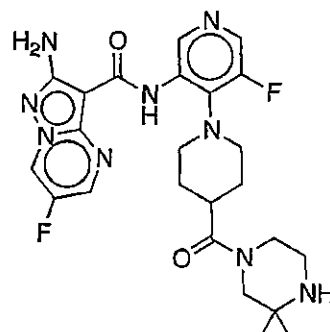
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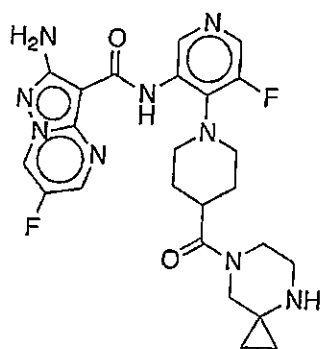
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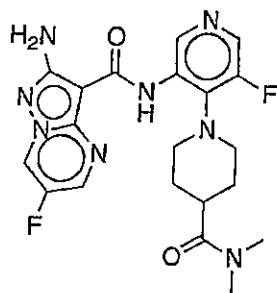
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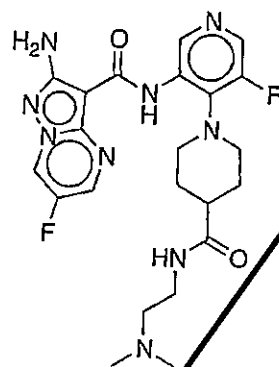
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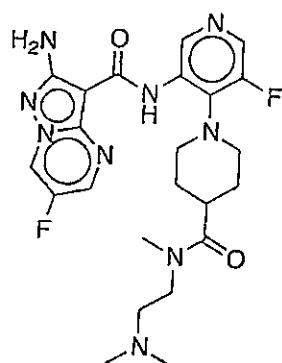
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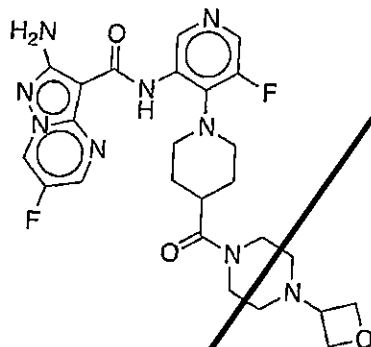
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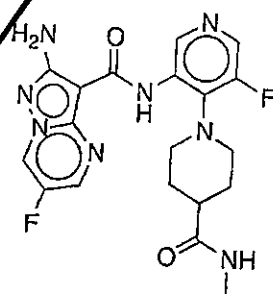
I-G-30



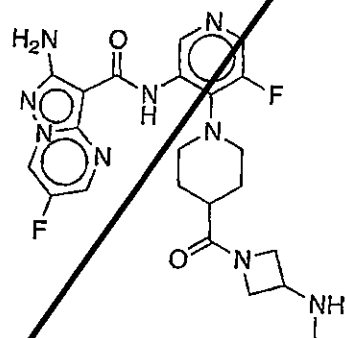
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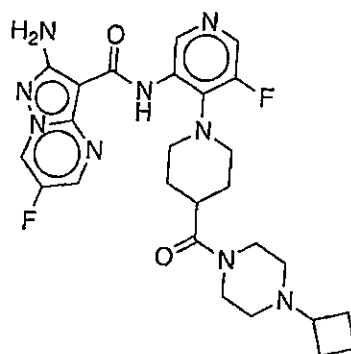
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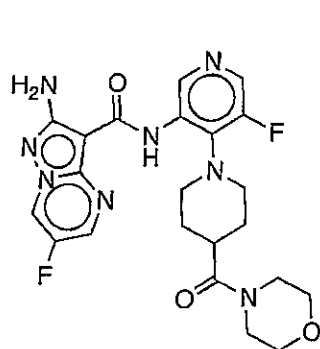
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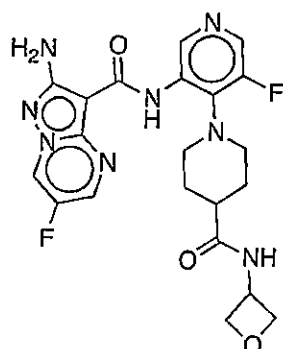
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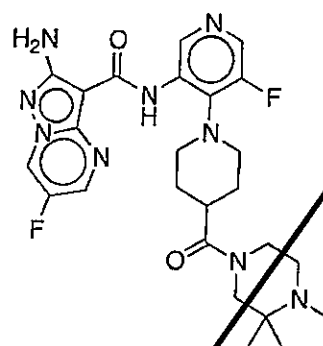
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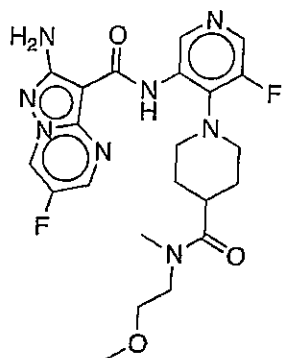
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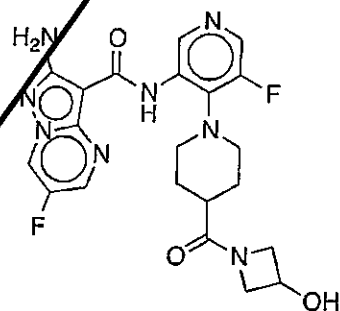
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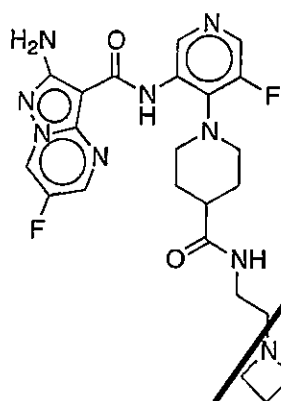
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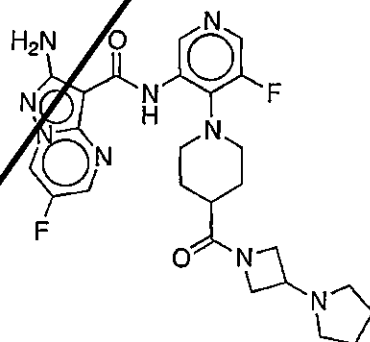
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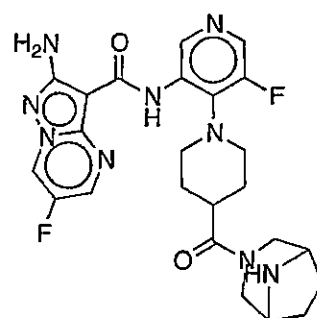
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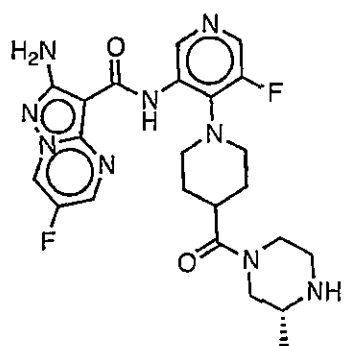
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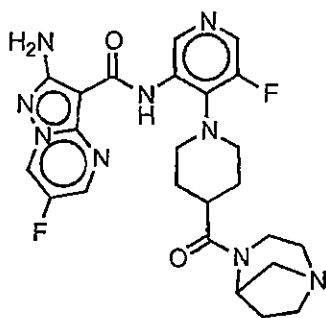
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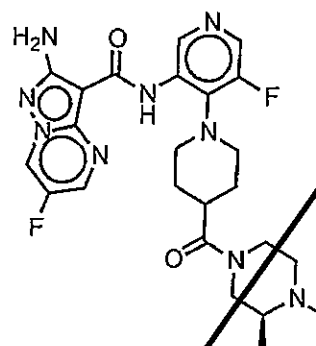
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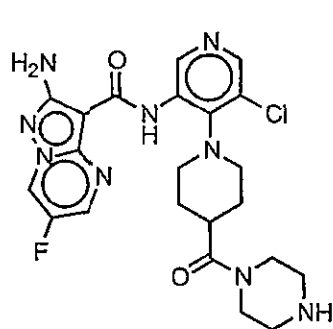
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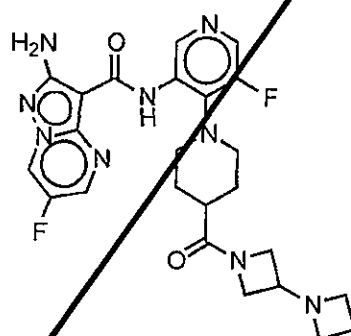
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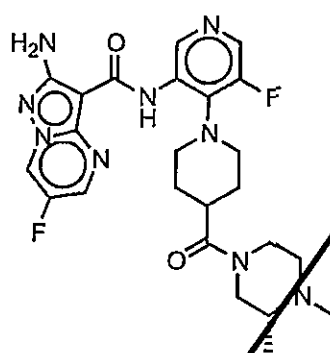
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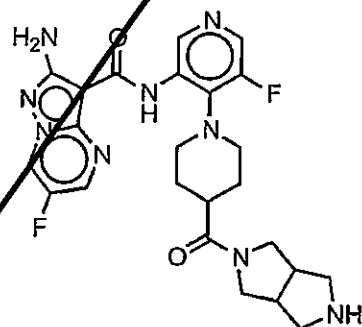
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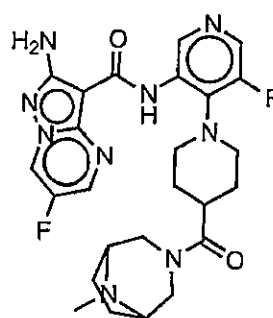
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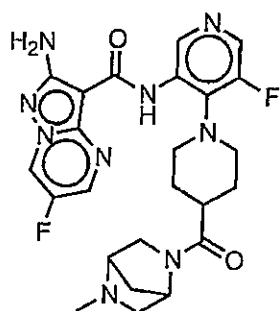
I-G-50



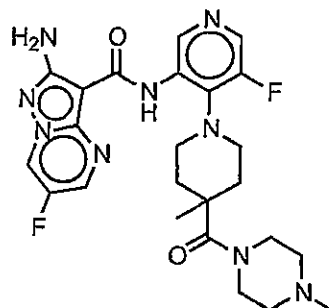
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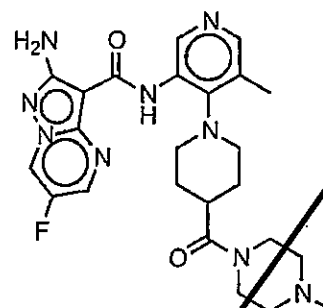
I-G-52



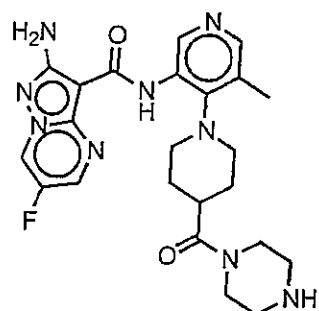
I-G-53



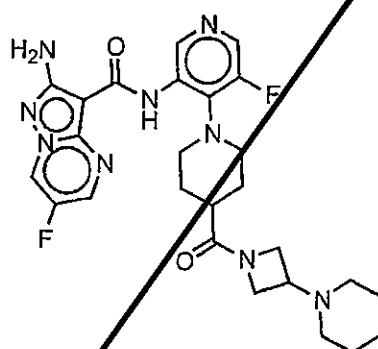
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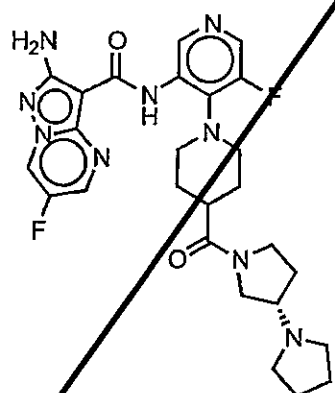
I-G-55



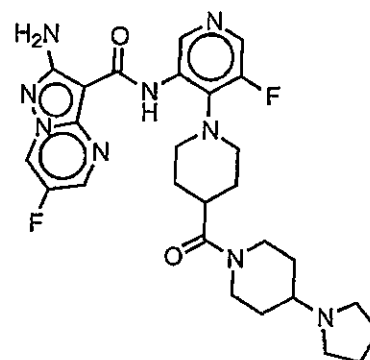
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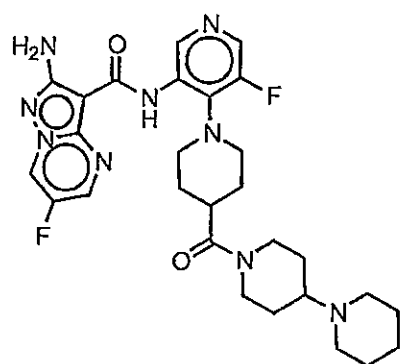
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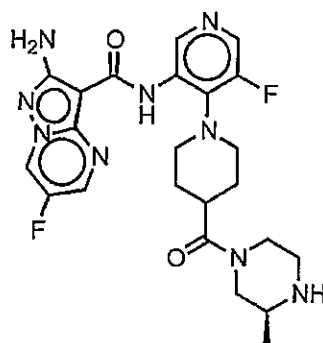
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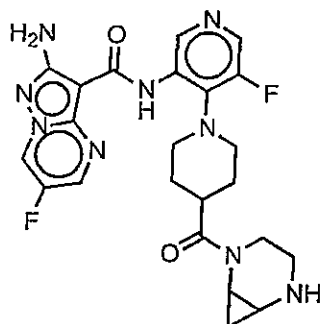
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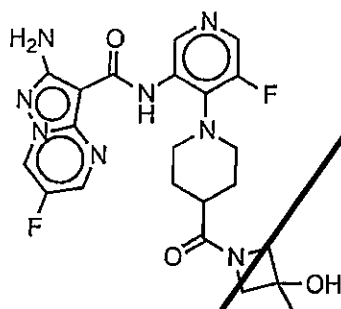
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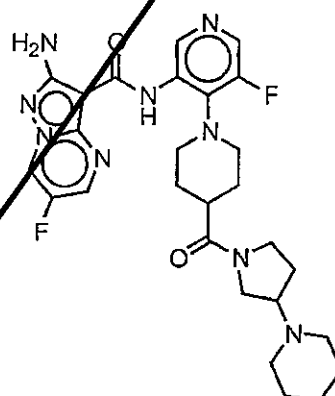
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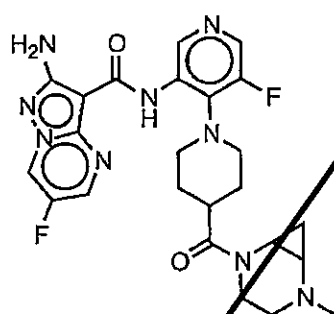
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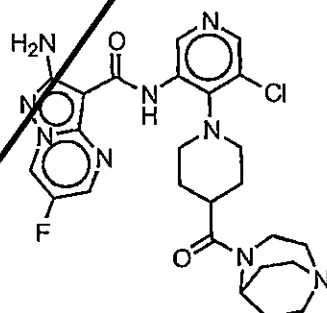
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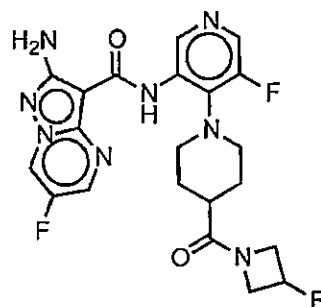
I-G-64



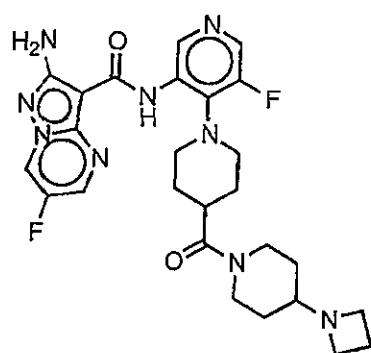
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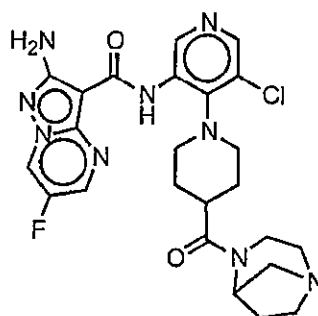
I-G-66



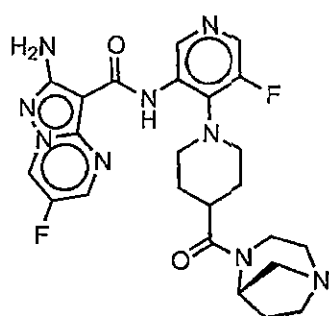
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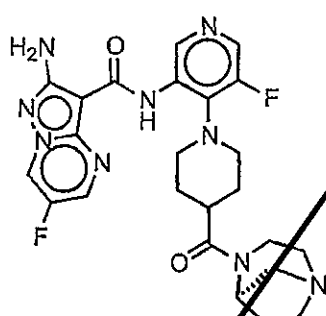
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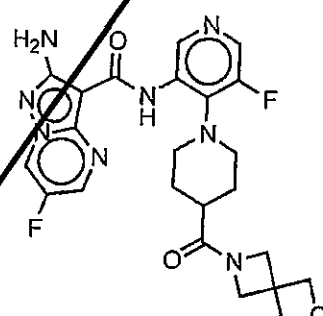
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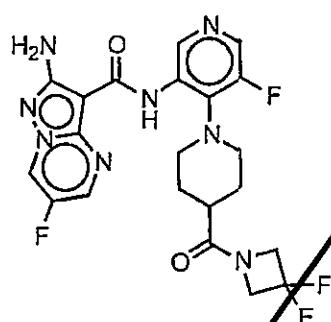
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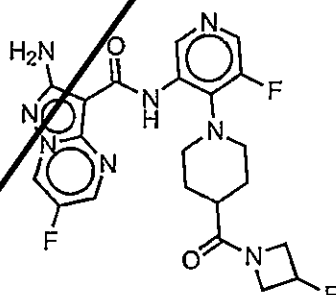
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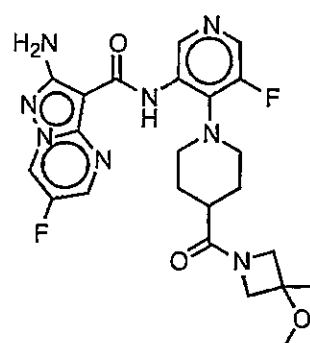
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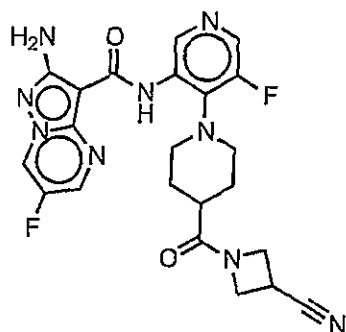
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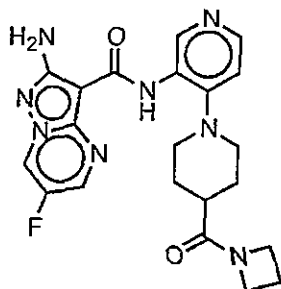
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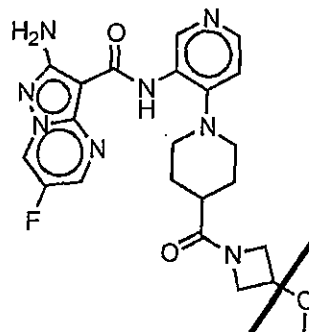
I-G-75



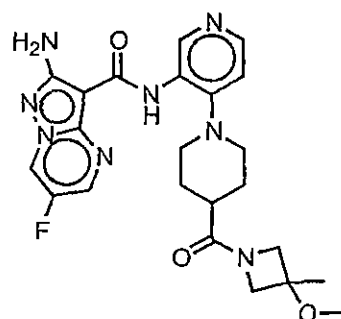
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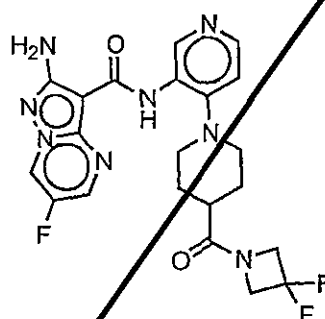
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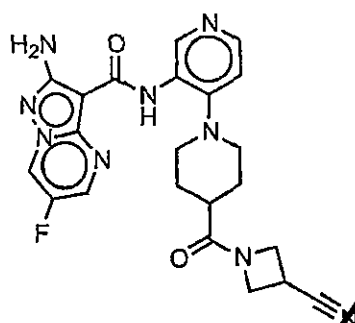
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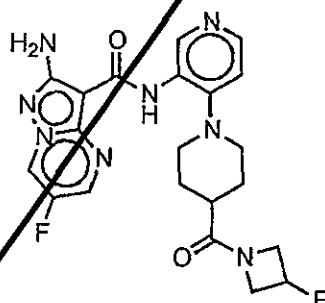
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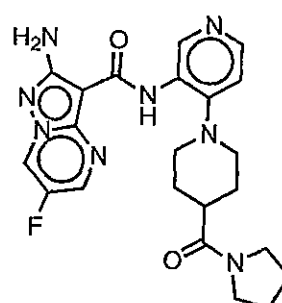
I-G-80



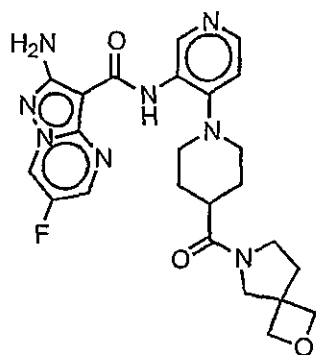
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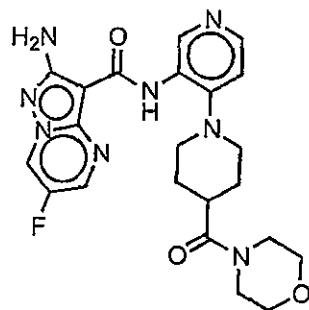
I-G-82



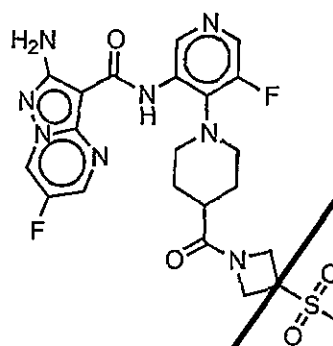
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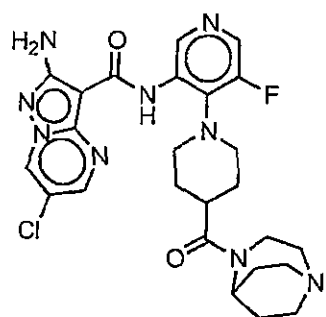
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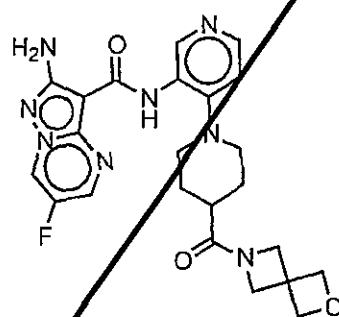
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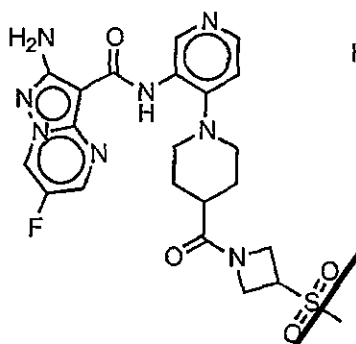
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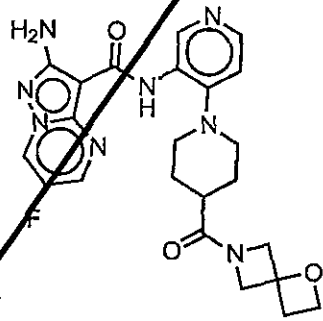
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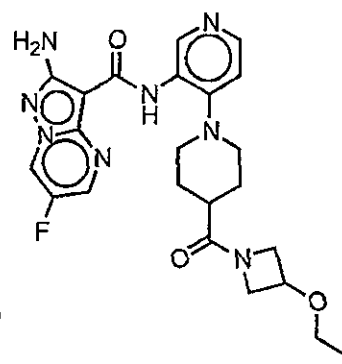
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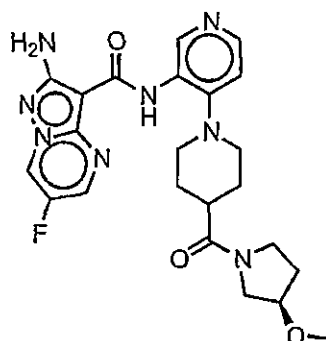
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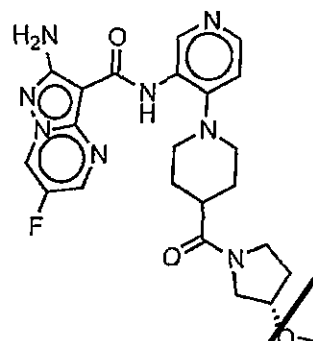
I-G-90



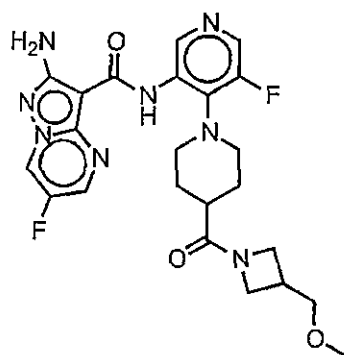
I-G-91



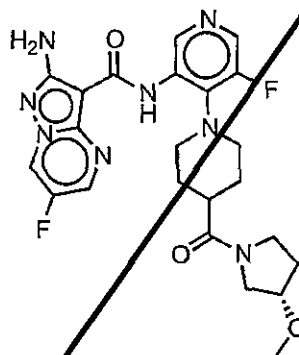
I-G-93



I-G-94



I-G-98



I-G-99.

107. A pharmaceutical composition comprising a compound of any one of claims 1-33, 34-76, or 77-106 and a pharmaceutically acceptable carrier.
108. A compound of any one of claims 1-33, 34-76, or 77-107 or a pharmaceutically acceptable derivative thereof for use in the treatment of cancer in a patient .
109. The use of claim 108, wherein an additional therapeutic agent is administered together with said compound as a single dosage form or separately from said compound as part of a multiple dosage form, wherein said additional therapeutic agent is independently selected from a DNA-damaging agent; and wherein said additional therapeutic agent is appropriate for the disease being treated; .
110. The use of claim 109, wherein said DNA-damaging agent is selected chemotherapy or radiation treatment.

111. The use of claim 109, wherein said DNA-damaging agent is independently selected from ionizing radiation, radiomimetic neocarzinostatin, a platinating agent, a Topo I inhibitor, a Topo II inhibitor, an antimetabolite, an alkylating agent, an alkyl sulphonates, or an antibiotic.
112. The use of claim 111, wherein said DNA-damaging agent is independently selected from ionizing radiation, a platinating agent, a Topo I inhibitor, a Topo II inhibitor, an antimetabolite, an alkylating agent, or an alkyl sulphonates.
113. The use of claim 111, wherein said DNA-damaging agent is independently selected from ionizing radiation, a platinating agent, a Topo I inhibitor, a Topo II inhibitor, or an antibiotic.
114. The use of claim 112, wherein said platinating agent is independently selected from Cisplatin, Oxaliplatin, Carboplatin, Nedaplatin, Lobaplatin, Triplatin Tetranitrate, Picoplatin, Satraplatin, ProLindac and Aroplatin; said Topo I inhibitor is selected from Camptothecin, Topotecan, Irinotecan/SN38, Rubitecan and Belotecan; said Topo II inhibitor is selected from Etoposide, Daunorubicin, Doxorubicin, Aclarubicin, Epirubicin, Idarubicin, Amrubicin, Pirarubicin, Valrubicin, Zorubicin and Teniposide; said antimetabolite is selected from Aminopterin, Methotrexate, Pemetrexed, Raltitrexed, Pentostatin, Cladribine, Clofarabine, Fludarabine, Thioguanine, Mercaptopurine, Fluorouracil, Capecitabine, Tegafur, Carmofur, Floxuridine, Cytarabine, Gemcitabine, Azacitidine and Hydroxyurea; said alkylating agent is selected from Mechlorethamine, Cyclophosphamide, 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 and Plicamycin.

115. The use of claim 114, wherein said platinating agent is independently selected from Cisplatin, Oxaliplatin, Carboplatin, Nedaplatin, or Satraplatin; said Topo I inhibitor is selected from Camptothecin, Topotecan, irinotecan/SN38, rubitecan; said Topo II inhibitor is selected from Etoposide; said antimetabolite is selected from methotrexate, pemetrexed, Thioguanine, Fludarabine, Cladribine, Cytarabine, gemcitabine, 6-Mercaptopurine, or 5-Fluorouracil; said alkylating agent is selected from nitrogen mustards, nitrosoureas, triazenes, alkyl sulfonates, Procarbazine, or aziridines; and said antibiotic is selected from Hydroxyurea, Anthracyclines, Anthracenediones, or Streptomyces family.
116. The use of claim 114, wherein said DNA-damaging agent is independently selected from a platinating agent or ionizing radiation.
117. The use of claim 112, wherein the antimetabolite is gemcitabine.
118. The use of claim 112, wherein the DNA-damaging agent is ionizing radiation.
119. The use of claim 112, wherein the DNA-damaging agent is a platinating agent independently selected from Cisplatin or Carboplatin.
120. The use of claim 112, wherein the DNA-damaging agent is a Topo II inhibitor selected from Etoposide.
121. The use of claim 110, wherein the DNA-damaging agent is an alkylating agent selected from Temozolomide.
122. The use of claim 112, wherein the DNA-damaging agent is independently selected from one or more of the following: Cisplatin, Carboplatin, gemcitabine, Etoposide, Temozolomide, or ionizing radiation.
123. The use of claim 122, wherein the additional therapeutic agents are selected from one or more of the following: gemcitabine, cisplatin or carboplatin, and etoposide.

124. The use of any one of claims 108-123, wherein said cancer is a solid tumor selected from the following cancers: Oral: buccal cavity, lip, tongue, mouth, pharynx; Cardiac: sarcoma (angiosarcoma, fibrosarcoma, rhabdomyosarcoma, liposarcoma), myxoma, rhabdomyoma, fibroma, lipoma and teratoma; Lung: bronchogenic carcinoma (squamous cell or epidermoid, undifferentiated small cell, undifferentiated large cell, adenocarcinoma), alveolar (bronchiolar) carcinoma, bronchial adenoma, sarcoma, lymphoma, chondromatous hamartoma, mesothelioma; Gastrointestinal: esophagus (squamous cell carcinoma, larynx, adenocarcinoma, leiomyosarcoma, lymphoma), stomach (carcinoma, lymphoma, leiomyosarcoma), pancreas (ductal adenocarcinoma, insulinoma, glucagonoma, gastrinoma, carcinoid tumors, vipoma), small bowel or small intestines (adenocarcinoma, lymphoma, carcinoid tumors, Kaposi's sarcoma, leiomyoma, hemangioma, lipoma, neurofibroma, fibroma), large bowel or large intestines (adenocarcinoma, tubular adenoma, villous adenoma, hamartoma, leiomyoma), colon, colon-rectum, colorectal; rectum; Genitourinary tract: kidney (adenocarcinoma, Wilm's tumor [nephroblastoma], lymphoma), bladder and urethra (squamous cell carcinoma, transitional cell carcinoma, adenocarcinoma), prostate (adenocarcinoma, sarcoma), testis (seminoma, teratoma, embryonal carcinoma, teratocarcinoma, choriocarcinoma, sarcoma, interstitial cell carcinoma, fibroma, fibroadenoma, adenomatoid tumors, lipoma); Liver: hepatoma (hepatocellular carcinoma), cholangiocarcinoma, hepatoblastoma, angiosarcoma, hepatocellular adenoma, hemangioma, biliary passages; Bone: osteogenic sarcoma (osteosarcoma), fibrosarcoma, malignant fibrous histiocytoma, chondrosarcoma, Ewing's sarcoma, malignant lymphoma (reticulum cell sarcoma), multiple myeloma, malignant giant cell tumor chordoma, osteochondroma (osteochondrogenous exostoses), benign chondroma, chondroblastoma, chondromyxofibroma, osteoid osteoma and giant cell tumors; Nervous system: skull (osteoma, hemangioma, granuloma, xanthoma, osteitis deformans), meninges (meningioma, meningiosarcoma, gliomatosis), brain (astrocytoma, medulloblastoma, glioma, ependymoma, germinoma [pinealoma], glioblastoma multiform, oligodendroglioma, schwannoma, retinoblastoma, congenital tumors),

spinal cord neurofibroma, meningioma, glioma, sarcoma); Gynecological/Female: uterus (endometrial carcinoma), cervix (cervical carcinoma, pre-tumor cervical dysplasia), ovaries (ovarian carcinoma [serous cystadenocarcinoma, mucinous cystadenocarcinoma, unclassified carcinoma], granulosa-thecal cell tumors, Sertoli-Leydig cell tumors, dysgerminoma, malignant teratoma), vulva (squamous cell carcinoma, intraepithelial carcinoma, adenocarcinoma, fibrosarcoma, melanoma), vagina (clear cell carcinoma, squamous cell carcinoma, botryoid sarcoma (embryonal rhabdomyosarcoma), fallopian tubes (carcinoma), breast; Skin: malignant melanoma, basal cell carcinoma, squamous cell carcinoma, Kaposi's sarcoma, keratoacanthoma, moles dysplastic nevi, lipoma, angioma, dermatofibroma, keloids, psoriasis, Thyroid gland: papillary thyroid carcinoma, follicular thyroid carcinoma; medullary thyroid carcinoma, multiple endocrine neoplasia type 2A, multiple endocrine neoplasia type 2B, familial medullary thyroid cancer, pheochromocytoma, paraganglioma; and Adrenal glands: neuroblastoma.

125. The use of claim 124, wherein said cancer is selected from a cancer of the lung or the pancreas.
126. The use of claim 125, wherein said cancer is lung cancer.
127. The use of claim 126, wherein the lung cancer is non-small cell lung cancer or small cell lung cancer.
128. The use of claim 127, wherein the lung cancer is small cell lung cancer and the additional therapeutic agents are cisplatin and etoposide.
129. The use of claim 127, wherein the lung cancer is non-small cell lung cancer and the additional therapeutic agents are gemcitabine and cisplatin.
130. The use of claim 129, wherein the non-small cell lung cancer is squamous non-small cell lung cancer.

131. The use of any one of claims 108-123, wherein said cancer is selected from lung cancer, head and neck cancer, pancreatic cancer, gastric cancer, or brain cancer.
132. The use of any one of claims 108-123, wherein said cancer is selected from 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.
133. The use of claim 132, wherein the cancer is breast cancer and the additional therapeutic agent is cisplatin.
134. The use of claim 133, wherein the cancer is triple negative breast cancer.
135. The use of claim 116, wherein the additional therapeutic agent is Gemcitabine and the cancer is pancreatic cancer.
136. A compound of any one of claims 1-33, 34-76, or 77-106 in combination with an additional therapeutic agent selected from Gemcitabine, radiation therapy, or both Gemcitabine and radiation therapy together for use in the treatment of pancreatic cancer.
137. A compound of any one of claims 1-33, 34-76, or 77-106 for use in increasing the sensitivity of pancreatic cancer cells to a cancer therapy selected from chemotherapy or radiation therapy.
138. The use of claim 137, wherein the chemotherapy is gemcitabine.
139. The use of claim 137, wherein the cancer therapy is gemcitabine.
140. The use of claim 137, wherein the cancer therapy is radiation.
141. The use of claim 129, wherein the cancer therapy is gemcitabine and radiation.

142. A compound of any one of claims 1-33, 34-76, or 77-107 in combination with gemcitabine (100 nM) and/or radiation (6 Gy) for use in the inhibition of phosphorylation of Chk1 (Ser 345) in a pancreatic cancer cell.
143. A compound of any one of claims 1-33, 34-79, or 77-106 in combination with chemoradiation for use in the sensitization of pancreatic cancer cells to chemoradiation.
144. The use of claim 114, wherein the chemoradiation is gemcitabine and radiation.
145. A compound of any one of claims 1-33, 34-76, or 77-106 in combination with radiation therapy for use in the radiosensitization of hypoxic pancreatic cancer cells.
146. A compound of any one of claims 1-33, 34-76, or 77-106 in combination with chemotherapy for use in the sensitization of hypoxic pancreatic cancer cells.
147. The use of any one of claims 143-146 wherein said cancer cell is a PSN-1, MiaPaCa-2 or PancM cancer cell.
148. A compound of any one of claims 1-33, 34-76, or 77-106 in combination with radiation therapy and/or gemcitabine for use in the disruption of damage-induced cell cycle checkpoints.
149. A compound of any one of claims 1-33, 34-76, or 77-104 in combination with radiation therapy and/or gemcitabine for use in the inhibition of repair of DNA damage by homologous recombination in a pancreatic cancer cell.
150. The use of any one of claims 143-149 wherein the compound is administered to a patient.
151. The use of any one of claims 144-149 wherein the compound is administered to a pancreatic cancer cell.

152. The use of claim 151, wherein the pancreatic cancer cells are derived from a pancreatic cell line selected from PSN-1, MiaPaCa-2 or Panc-1.
153. A compound of any one of claim 1-33, 34-76, or 77-106 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.
154. A compound of any one of claims 1-33, 34-76, or 77-106 for the promotion of cell death in cancer cells.
155. A compound of any one of claims 1-33, 34-76, or 77-106 for use in the prevention of cell repair from DNA damage.
156. A compound of any one of claims 1-33, 34-76, or 77-106 for use in the inhibition of ATR in a biological sample.
157. The use of claim 156, wherein said biological sample is a cell.
158. A compound of any one of claims 1-33, 34-76, or 77-106 for use in the sensitization of cells to DNA damaging agents.
159. The use of any one of claims 109-158, wherein said cell is a cancer cell having defects in the ATM signaling cascade.
160. The use of claim 159, wherein said defect is altered expression or activity of one or more of the following: ATM, p53, CHK2, MRE11, RAD50, NBS1, 53BP1, MDC1, H2AX, MCPH1/BRIT1, CTIP, or SMC1.
161. The use of claim 159, wherein said defect is altered expression or activity of one or more of the following: ATM, p53, CHK2, MRE11, RAD50, NBS1, 53BP1, MDC1 or H2AX.

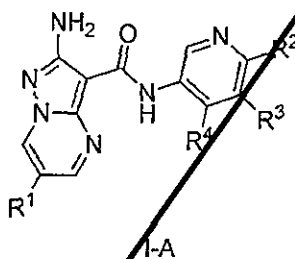
162. The use of any one of claims 108-158, wherein said cell is a cancer cell expressing DNA damaging oncogenes.
163. The use of claim 162, wherein said cancer cell has altered expression or activity of one or more of the following: K-Ras, N-Ras, H-Ras, Raf, Myc, Mos, E2F, Cdc25A, CDC4, CDK2, Cyclin E, Cyclin A and Rb.
164. The use of any one of claims 108-158, wherein said cancer, cancer cell, or cell has a defect in a base excision repair protein.
165. The use of claim 164, wherein the base excision repair protein is UNG, SMUG1, MBD4, TDG, OGG1, MYH, NTH1, MPG, NEIL1, NEIL2, NEIL3 (DNA glycosylases); APE1, APEX2 (AP endonucleases); LIG1, LIG3 (DNA ligases I and III); XRCC1 (LIG3 accessory); PNK, PNKP (polynucleotide kinase and phosphatase); PARP1, PARP2 (Poly(ADP-Ribose) Polymerases); PolB, PolG (polymerases); FEN1 (endonuclease) or Aprataxin.
166. The use of claim 165, wherein the base excision repair protein is PARP1, PARP2, or PolB.
167. The use of claim 166, wherein the base excision repair protein is PARP1 or PARP2.
168. The use of any one of claims 109-167, wherein the compound is used with an additional therapeutic agent wherein said agent inhibits or modulates a base excision repair protein.
169. The use of claim 168, wherein the base excision repair protein is selected from UNG, SMUG1, MBD4, TDG, OGG1, MYH, NTH1, MPG, NEIL1, NEIL2, NEIL3 (DNA glycosylases); APE1, APEX2 (AP endonucleases); LIG1, LIG3 (DNA ligases I and III); XRCC1 (LIG3 accessory); PNK, PNKP (polynucleotide kinase and phosphatase); PARP1, PARP2 (Poly(ADP-Ribose) Polymerases); PolB, PolG (polymerases); FEN1 (endonuclease) or Aprataxin.

170. The use of claim 169, wherein the base excision repair protein is selected from PARP1, PARP2, or PolB.

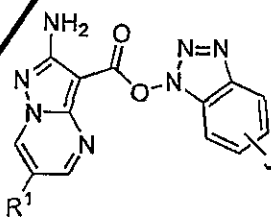
171. The use of claim 170, wherein the base excision repair protein is selected from PARP1 or PARP2.

172. The use of claim 171, wherein said agent is selected from 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.

173. A process for preparing a compound of formula I-A:

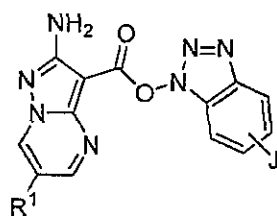


comprising reacting a compound of formula 6:



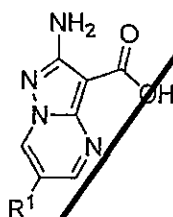
under suitable conditions to form an amide bond, wherein J, R¹, R², R³, and R⁴ are as defined in claims 1-33, 34-76, or 77-106.

174. The process of claim 173, further comprising the step of preparing a compound of formula 6:



6

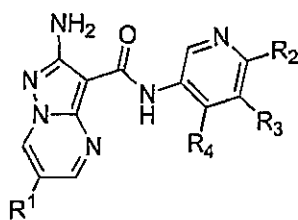
by reacting a compound of formula 5:



5

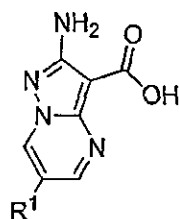
under suitable conditions to form an activated ester.

175. A process for preparing a compound of formula I-A:



I-A

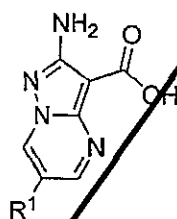
comprising reacting a compound of formula 5:



5

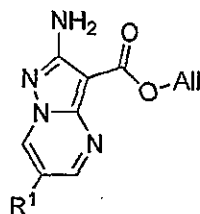
under suitable conditions to form an amide bond, wherein R^1 , R^2 , R^3 , and R^4 are as defined in claims 1-33, 34-76, or 77-106.

176. The process of any one of claims 173-175, further comprising the step of preparing a compound of formula 5:



5

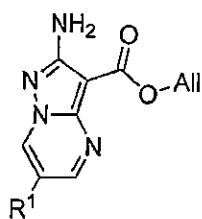
by reacting a compound of formula 4:



4

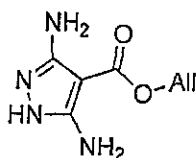
under suitable deprotection conditions.

177. The process of claim 176, further comprising the step of preparing a compound of formula 4:



4

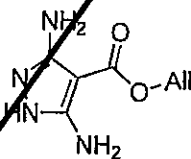
by reacting a compound of formula 3:



3

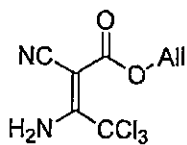
under suitable condensation conditions to form a pyrimidine ring.

178. The process of claim 177, further comprising the step of preparing the compound of formula 3:



3

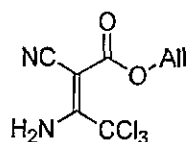
by reacting a compound of formula 2:



2

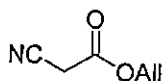
under suitable condensation conditions to form a pyrazole ring.

179. The process of claim 178, further comprising the step of preparing a compound of formula 2:



2

by reacting a compound of formula 1:



1

under suitable anion condensation conditions.

180. The process of any one of claims 173 wherein R¹ is independently selected from halo or -CH₂CN.

181. The process of claim 180, wherein R¹ is independently selected from fluoro or chloro.

182. The process of claim 173, wherein suitable conditions for forming an amide bond comprise reacting the compound of formula 6 with a substituted 3-aminopyridine in an aprotic solvent in the presence of heat.

183. The process of claim 182, wherein the aprotic solvent is selected from NMP, pyridine, or DMF.

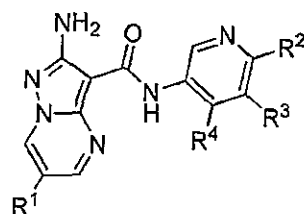
184. The process of claim 182, wherein the aprotic solvent is optionally substituted pyridine.

185. The process of any one of claims 182-184, wherein the reaction is carried out at a temperature of at least 80°C.

186. The process of claim 185, wherein the reaction is carried out at a temperature of at least 100°C.
187. The process of any one of claims 174, wherein suitable conditions for forming the activated ester comprises reacting the compound of formula 5 with an amide coupling agent in the presence of an organic base.
188. The process of claim 187, wherein the organic base is an aliphatic amine.
189. The process of claim 188, wherein the organic base is independently selected from DIPEA or triethylamine.
190. The process of any one of claims 187-189, wherein the amide coupling agent is independently selected from EDCI, TBTU, TCTU, HATU, T3P, or COMU.
191. The process of claim 190, wherein the amide coupling agent is independently selected from TBTU or TCTU.
192. The process of claim 191, wherein the amide coupling agent is TCTU.
193. The process of claim 176, wherein suitable hydrolytic conditions comprise reacting the compound of formula 4 with a silane in the presence of a metal catalyst.
194. The process of claim 193, wherein the silane is phenylsilane.
195. The process of claim 194, wherein the metal catalyst is a palladium catalyst.
196. The process of claim 195, wherein the metal catalyst is $\text{Pd}(\text{PPh}_3)_4$.
197. The process of claim 176, wherein suitable hydrolytic conditions comprise reacting the compound of formula 4 with an aqueous alkali.
198. The process of claim 197, wherein the aqueous alkali is independently selected from LiOH, NaOH, or KOH.

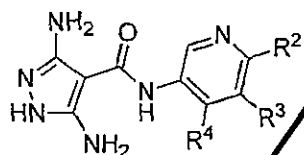
199. The process of claim 177, wherein suitable condensation conditions for forming a pyrimidine ring comprise reacting the compound of formula 3 with a 1,3-dielectrophilic species in the presence of a solvent.
200. The process of claim 199, wherein the 1,3-dielectrophilic species is 1,3-dialdehyde or 3-(dialkylamino)-prop-2-enal.
201. The process of any one of claims 199 or 200, wherein the solvent is selected from DMF or DMSO.
202. The process of claim 199, wherein the 1,3-dielectrophilic species is generated *in situ* from a protected 1,3-dielectrophilic species.
203. The process of claim 202, wherein the 1,3-dielectrophilic species is generated from a ketal in the presence of a sulfonic acid.
204. The process of claim 203, wherein the sulfonic acid is PTSA.
205. The process of claim 178, 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.
206. The process of claim 205, wherein the aprotic solvent is DMF.
207. The process of claim 205, wherein the basic conditions comprise reacting the compound of formula 2 in the presence of potassium acetate or sodium acetate.
208. The process of claim 179, 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.
209. The process of claim 208, wherein the base is potassium acetate.
210. The process of claim 208, wherein the solvent is an alcohol.
211. The process of claim 210, wherein the solvent is isopropylalcohol.

212. A process for preparing a compound of formula I-A:



I-A

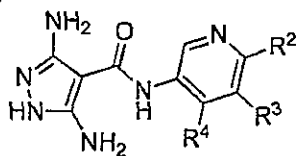
comprising reacting a compound of formula 9:



9

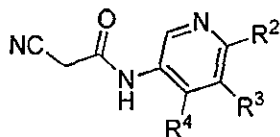
under suitable condensation conditions to form a pyrimidine ring, wherein R¹, R², R³ and R⁴ are as defined in claims 1-33, 34-76, or 77-104.

213. The process of claim 212, further comprising the step of preparing a compound of formula 9:



9

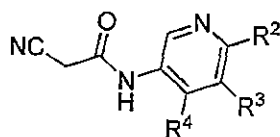
by reacting a compound of formula 8:



8

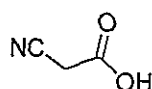
under suitable condensation conditions to form a pyrazole ring.

214. The process of claim 213, further comprising the step of preparing a compound of formula 8:



8

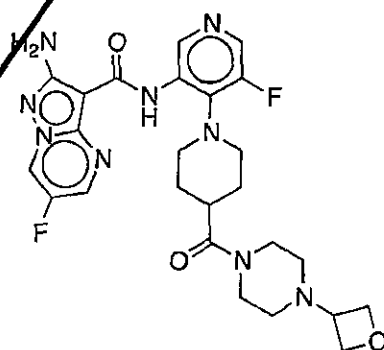
by reacting a compound of formula 7:



7

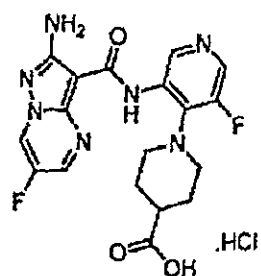
under suitable conditions to form an amide bond.

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



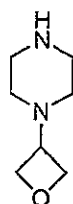
I-G-32

comprising the step of reacting the compound of formula 30:



30

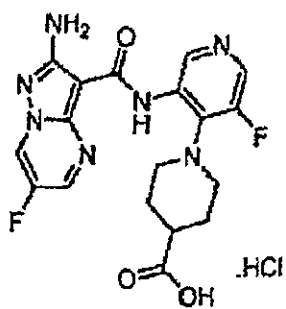
with a compound of formula 25:



25

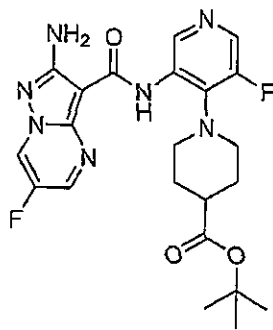
under suitable conditions to form an amide bond.

216. The process of claim 215, further comprising the step of preparing the compound of formula 30:



30

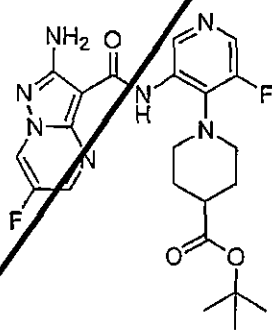
by reacting the compound of formula 28:



28

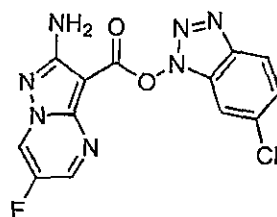
under suitable deprotection conditions to form the carboxylic acid.

217. The process of claim 216, further comprising the step of preparing a compound of formula 28:



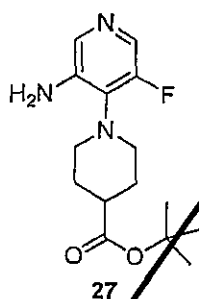
28

by reacting the compound of formula 6a*:



6a*

with a compound of formula 27:



27

under suitable conditions to form an amide bond.

218. The compound of claim 215, wherein suitable conditions for forming the amide bond comprise reacting the compound of formula 29 with the compound of formula 25 in the presence of an amide coupling partner, an aprotic solvent, and a base.

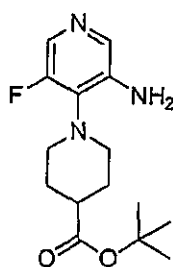
219. The compound of claim 218, wherein the aprotic solvent is independently selected from NMP, DMF, or tetrahydrofuran.

220. The process of claim 219, wherein the aprotic solvent is tetrahydrofuran.

221. The process of claim 219, wherein the base is an aliphatic amine.

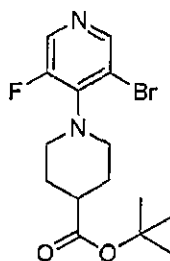
222. The process of claim 221, wherein the base is DIPEA.

223. The process of any one of claims 218-222, wherein the amide coupling partner is independently selected from TBTU or TCTU.
224. The process of claim 223, wherein the amide coupling partner is TCTU.
225. The process of claim 216, wherein suitable deprotection conditions comprise reacting the compound of formula 28 with an acid in the presence of a solvent.
226. The process of claim 225, wherein the acid is HCl.
227. The process of claim 226, wherein the solvent is 1,4-dioxane.
228. The process of claim 217, 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.
229. The process of claim 228, wherein the aprotic solvent is independently selected from NMP, pyridine, or DMF.
230. The process of claim 229, wherein the aprotic solvent is pyridine.
231. The process of any one of claims 228, wherein the reaction is carried out at a temperature of at least 80°C.
232. A process of preparing a compound of formula 27:



27

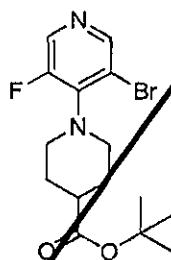
comprising the step of reacting a compound of formula 26:



26

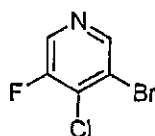
under suitable conditions to form an amine.

233. The process of claim 232, further comprising the step of preparing a compound of formula 26:



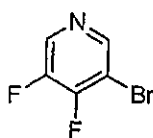
26

by 1) reacting a compound of formula 18:



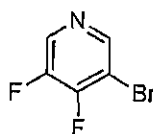
18

under suitable halogen exchange conditions to generate the compound of formula 32



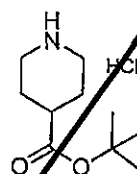
32, and

2) reacting the compound of formula 32:



32

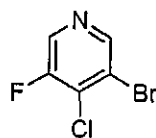
with a compound of formula 22:



22

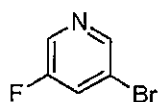
under suitable displacement conditions.

234. The process of claim 230, further comprising the step of preparing a compound of formula 18:



18

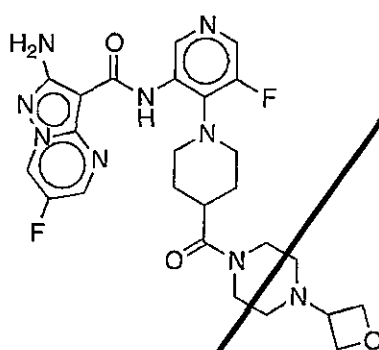
by reacting the compound of formula 31:



31

under suitable halogenation conditions.

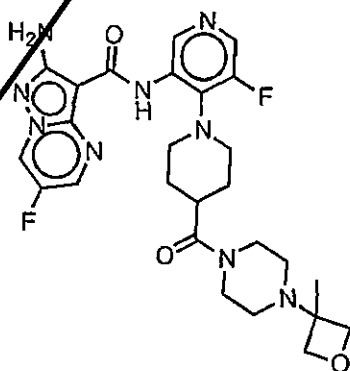
235. A compound having the structure I-G-32:



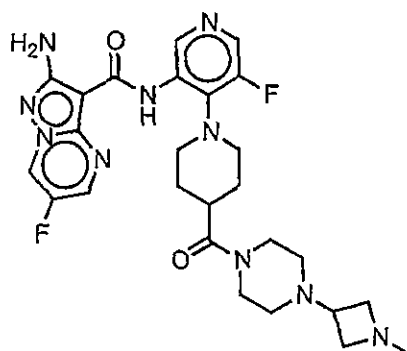
I-G-32

or a pharmaceutically acceptable salt thereof.

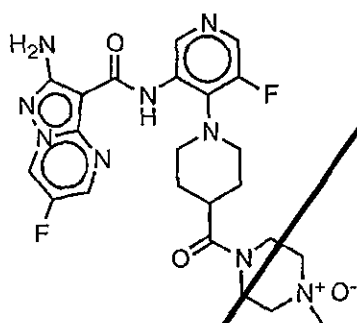
236. A compound selected from:



I-G-92

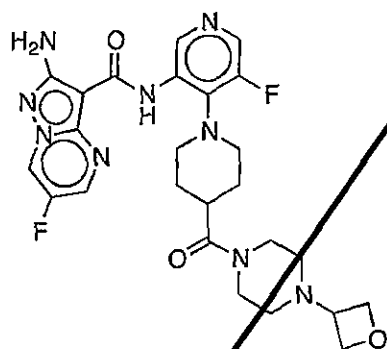


I-G-95



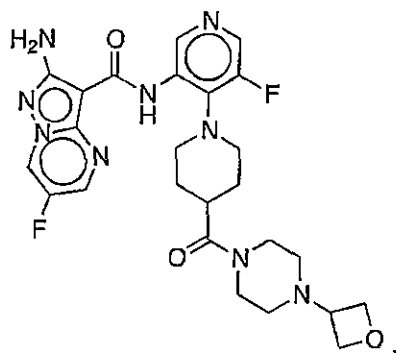
I-G-96

237. A pharmaceutical composition comprising the compound of claim 235 having the structure:



or a pharmaceutically acceptable salt thereof;
and a pharmaceutically acceptable carrier.

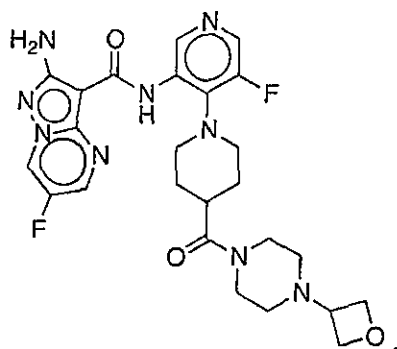
238. A compound of claim 235, wherein the compound is a pharmaceutically



acceptable salt of

239. A pharmaceutical composition comprising the compound of claim 238 and a pharmaceutically acceptable carrier.

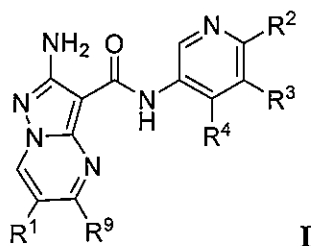
240. The compound of claim 235, wherein the compound has the structure:



241. A pharmaceutical composition comprising the compound of claim 240 and a pharmaceutically acceptable carrier.

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;

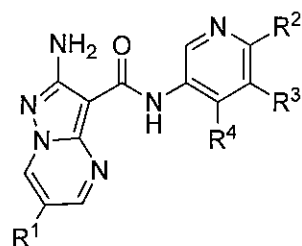
J^M is independently halo or C_{1-6} aliphatic;

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 azetidiny.
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:

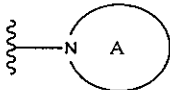
R^1 is fluoro, chloro, or $-C(J^1)_2CN$;

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

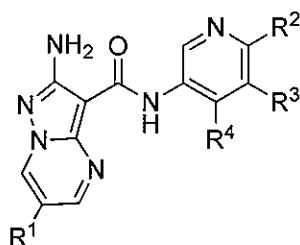
two occurrences of J^T , together with Q^3 , form a 6-10 membered saturated or partially unsaturated bridged ring system;

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:

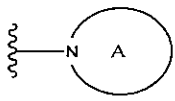
R^1 is fluoro, chloro, or $-C(J^1)_2CN$;

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;

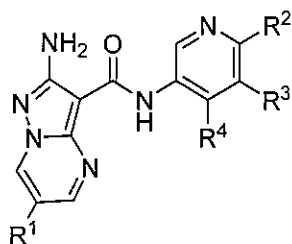
two occurrences of J^T , together with Q^3 , form a 6-10 membered saturated or partially unsaturated bridged ring system;

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:

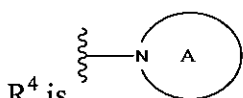
R^1 is fluoro, chloro, or $-C(J^1)_2CN$;

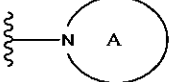
J^1 is independently H or C_{1-2} alkyl; or

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.

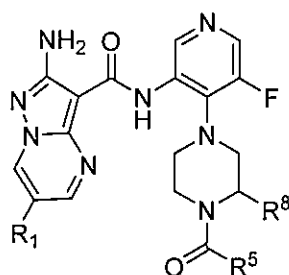
21. The compounds of any one of claims 1-20, or a pharmaceutically acceptable salt thereof, wherein R¹ is fluoro.
22. The compounds of any one of claims 1-20, wherein R¹ is -CH₂CN, -C(CH₃)₂CN or -CH(C₁₋₂alkyl)CN.
23. The compound of any one of claims 1-20, or a pharmaceutically acceptable salt thereof, 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 heterocyclyl.
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, piperadiny, 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.

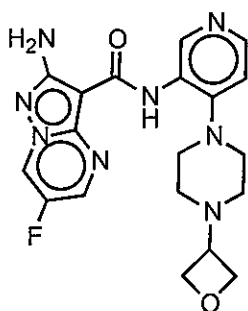
70. The compound of claim 69, or a pharmaceutically acceptable salt thereof, wherein R⁵ is tetrahydrofuranyl or oxetanyl.

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.

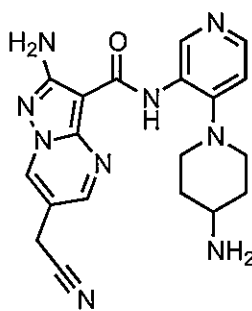
72. The compound of claim 71, or a pharmaceutically acceptable salt thereof, wherein the ring formed by R⁵ and R⁸ is a five-membered ring.

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.

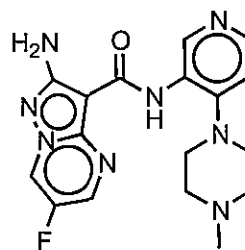
74. A compound, wherein the compound is:



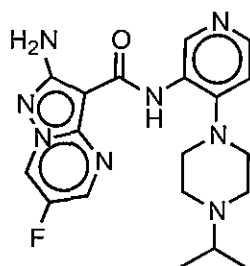
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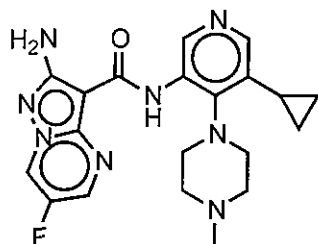
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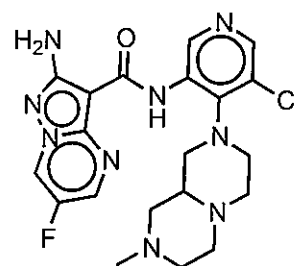
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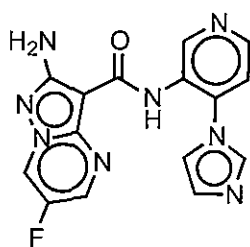
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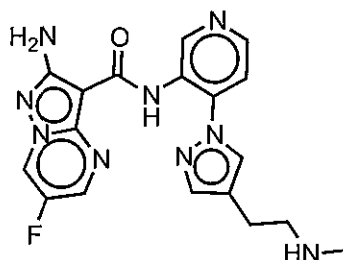
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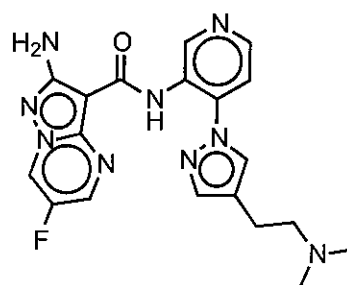
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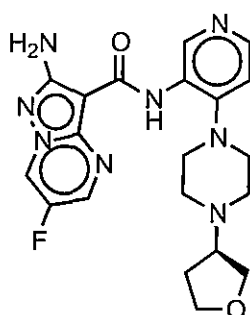
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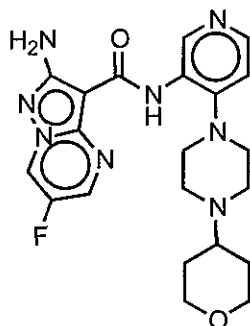
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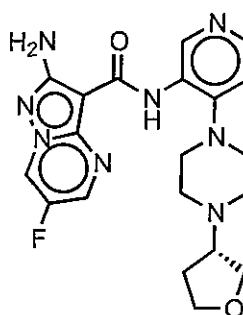
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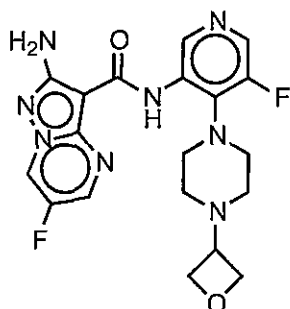
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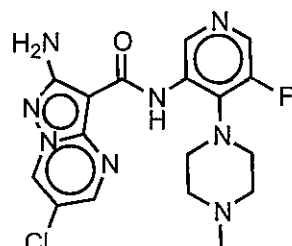
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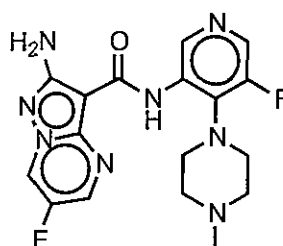
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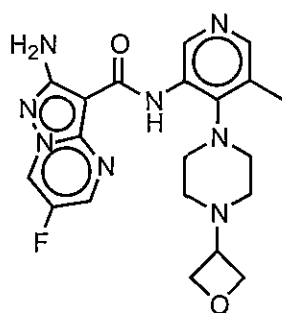
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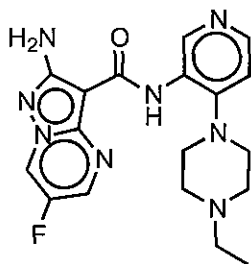
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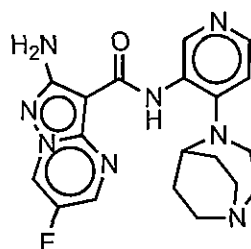
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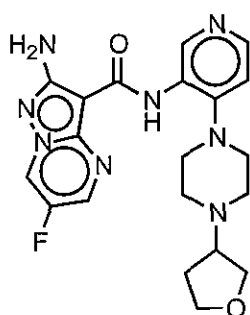
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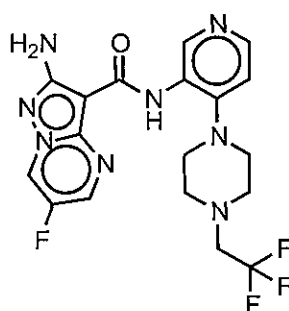
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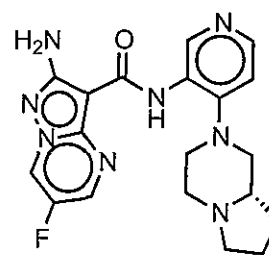
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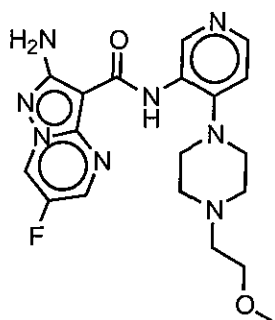
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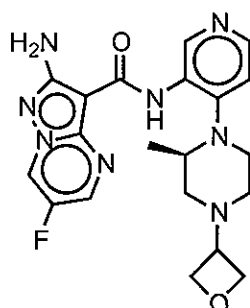
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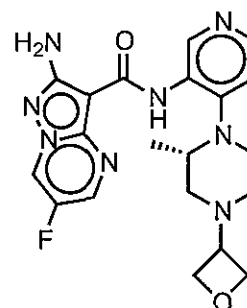
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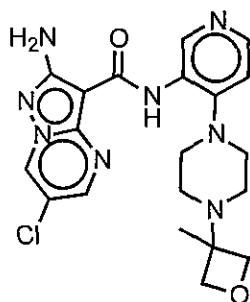
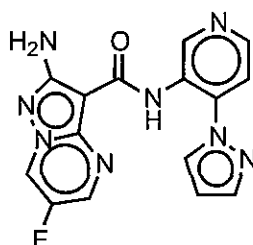
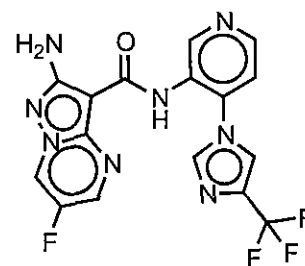
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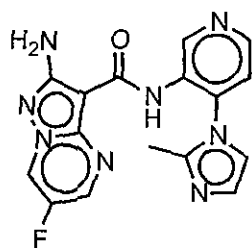
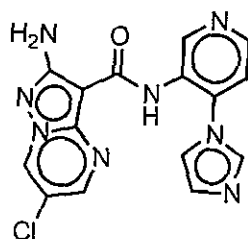
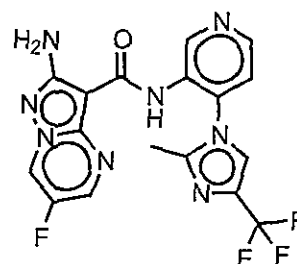
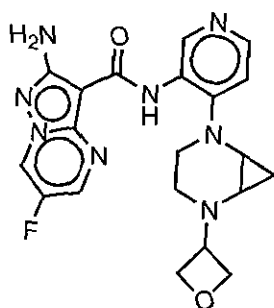
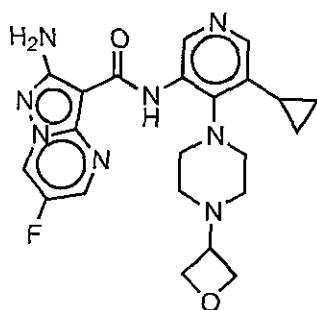
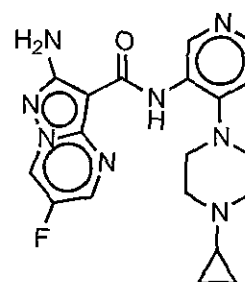
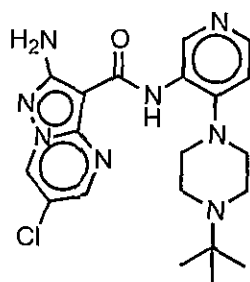
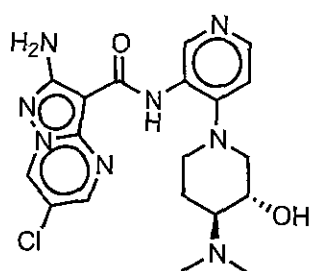
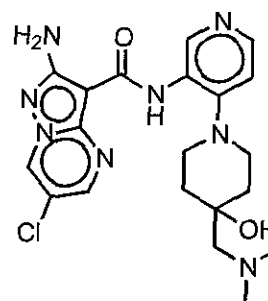
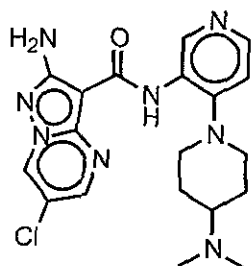
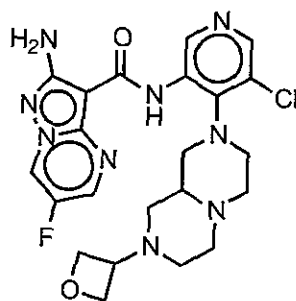
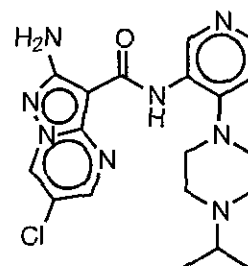


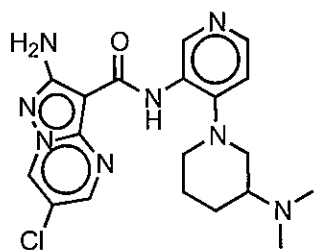
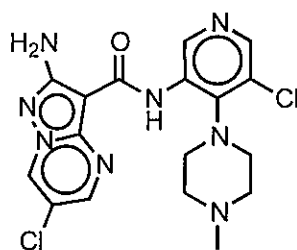
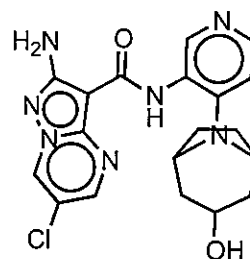
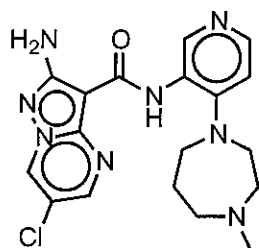
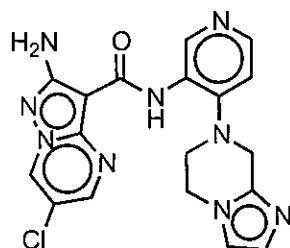
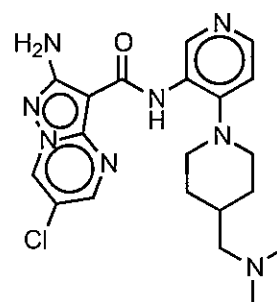
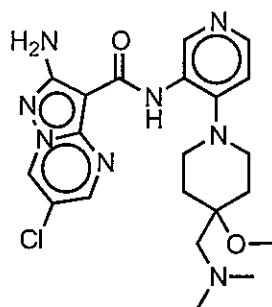
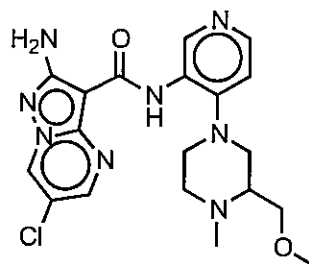
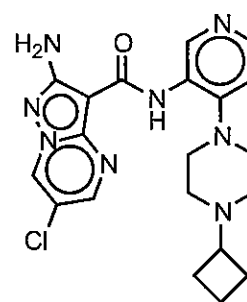
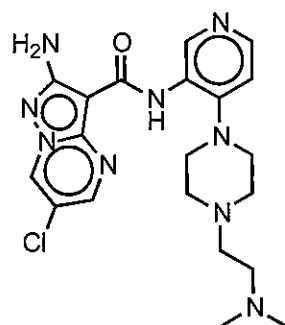
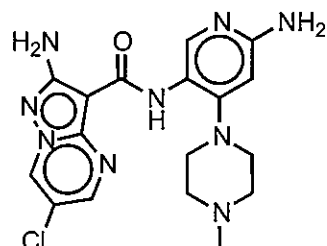
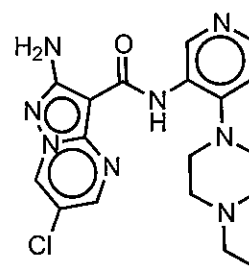
I-N-23

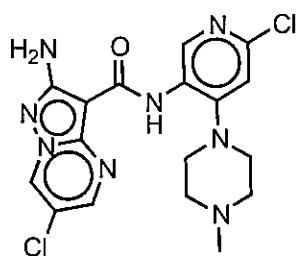
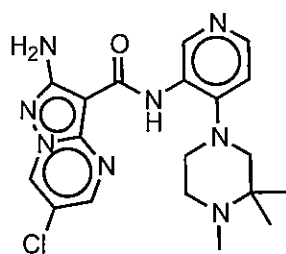
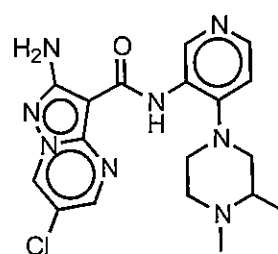
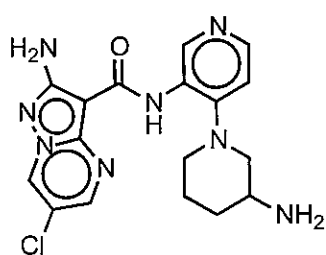
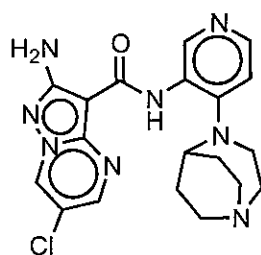
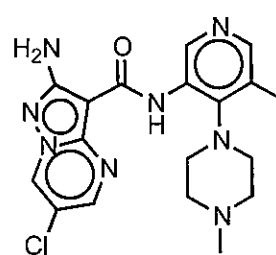
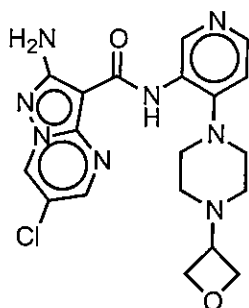
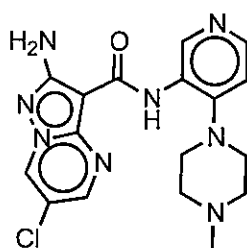
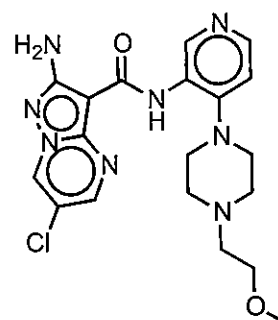
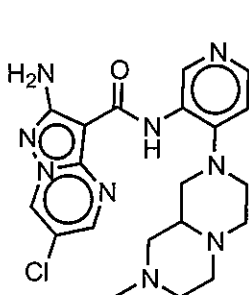
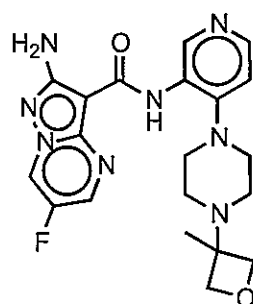
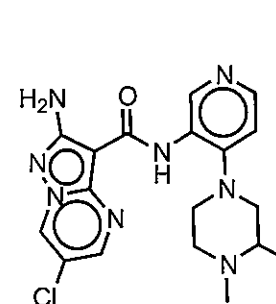


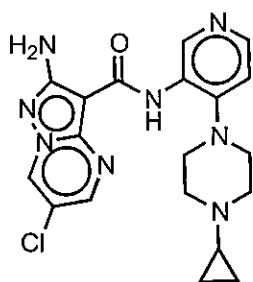
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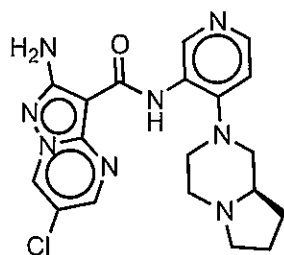
I-N-25**I-N-26****I-N-27****I-N-28****I-N-29****I-N-30****I-N-31****I-N-32****I-N-33****I-N-34****I-N-35****I-N-36**

I-N-37**I-N-38****I-N-39****I-N-40****I-N-41****I-N-42****I-N-43****I-N-44****I-N-45****I-N-46****I-N-47****I-N-48**

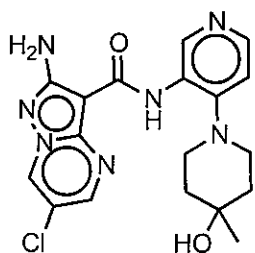
I-N-49**I-N-50****I-N-51****I-N-52****I-N-53****I-N-54****I-N-55****I-N-56****I-N-57****I-N-58****I-N-59****I-N-60****I-N-61****I-N-62****I-N-63**



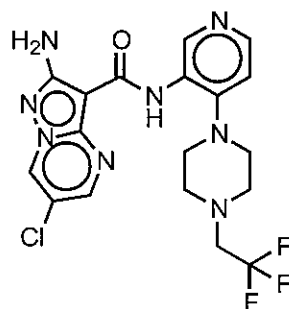
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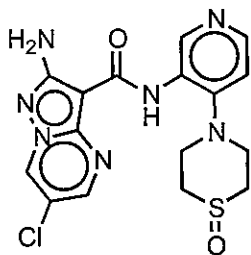
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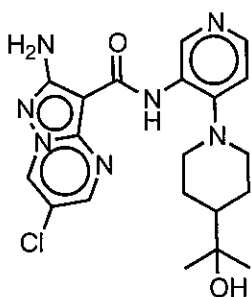
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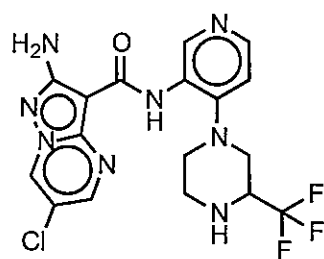
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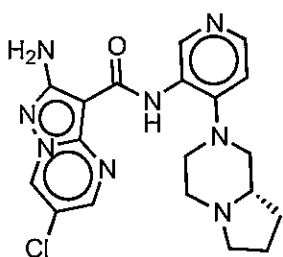
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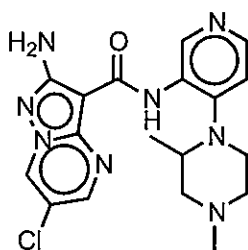
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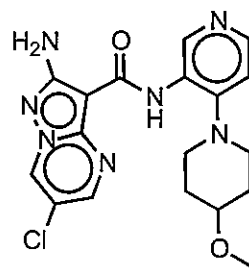
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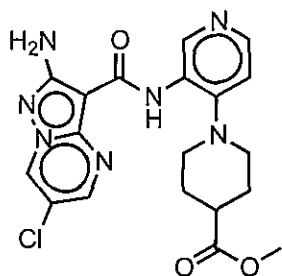
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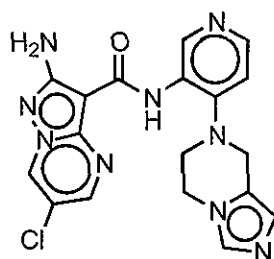
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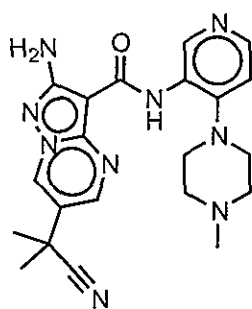
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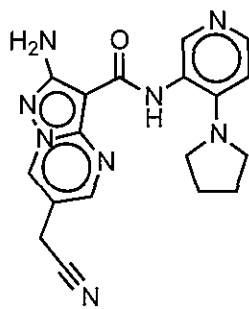
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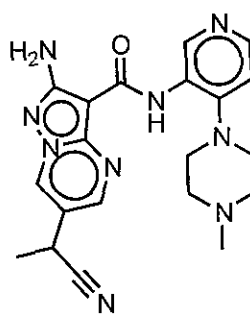
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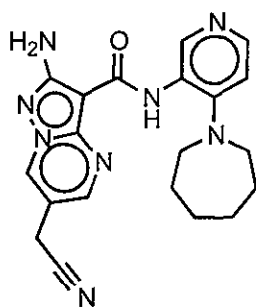
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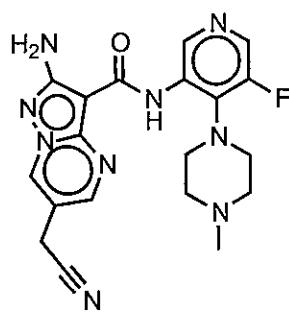
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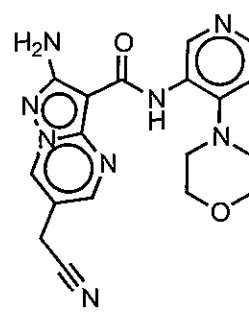
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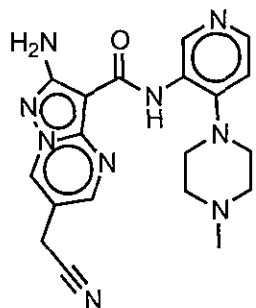
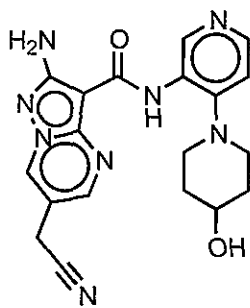
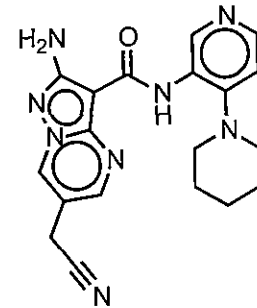
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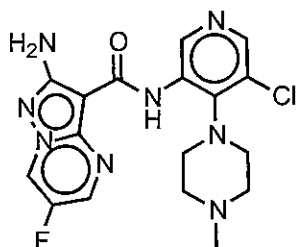
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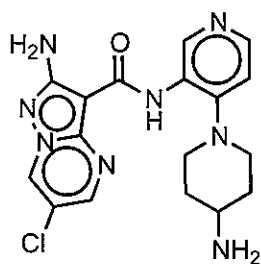
I-N-81



I-N-82

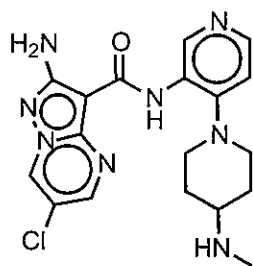


I-N-83

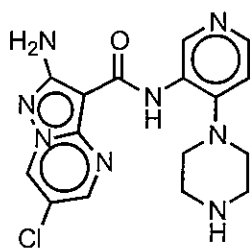
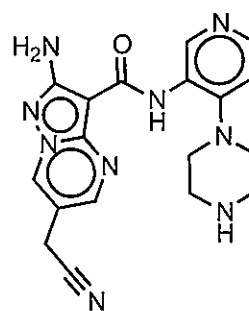


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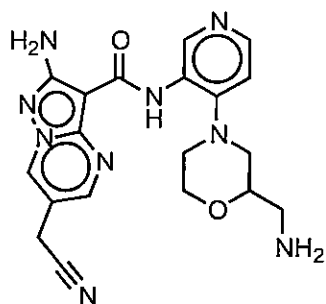
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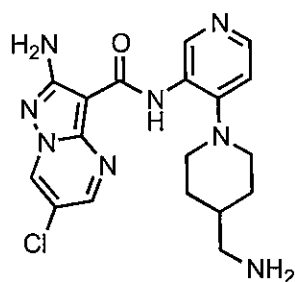
I-N-86



I-N-87



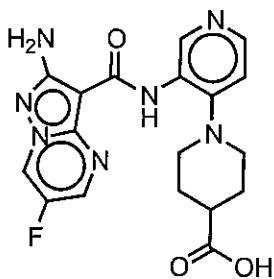
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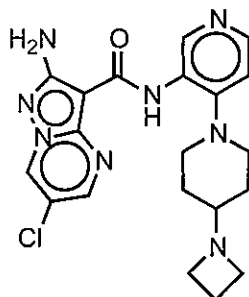
I-N-89

I-N-90

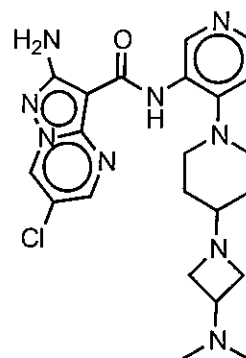
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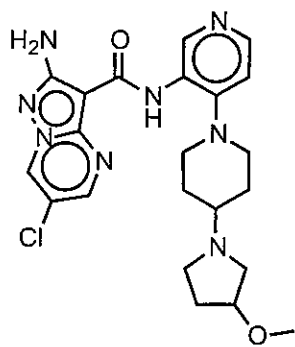
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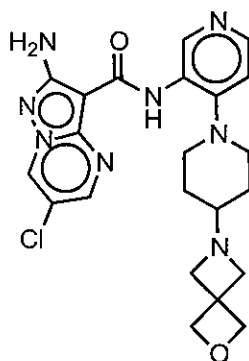
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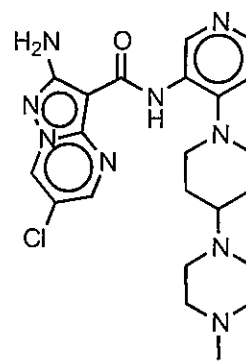
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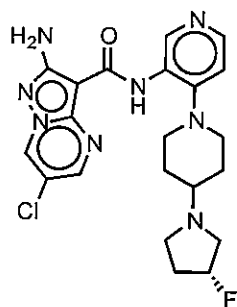
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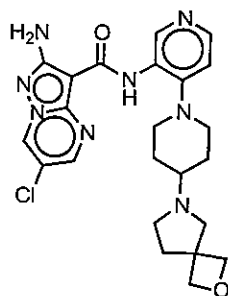
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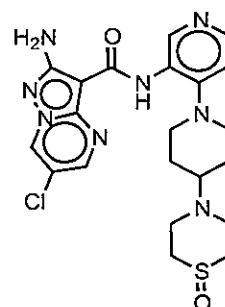
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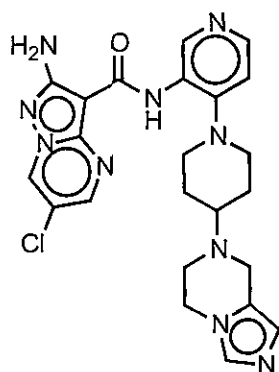
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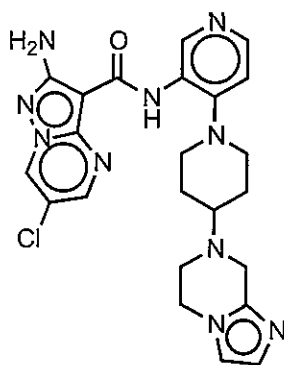
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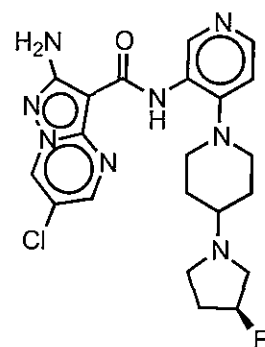
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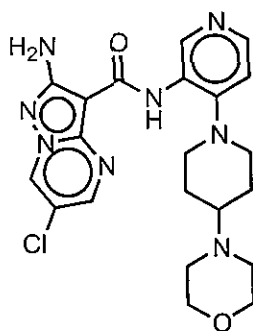
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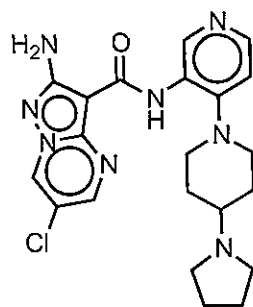
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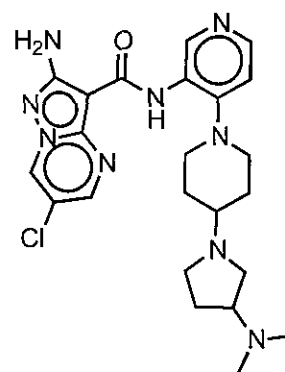
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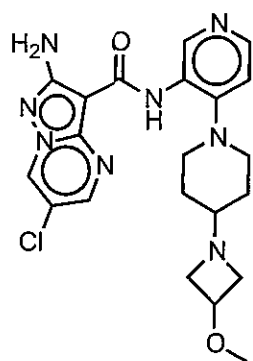
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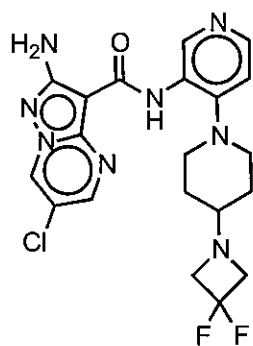
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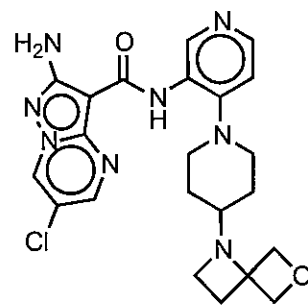
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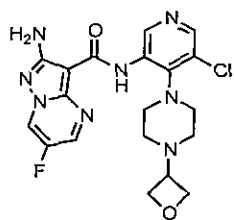
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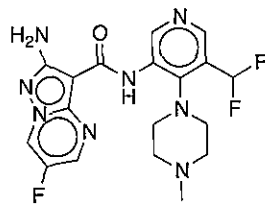
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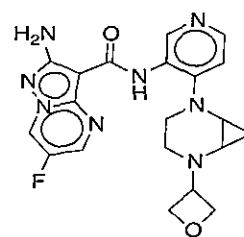
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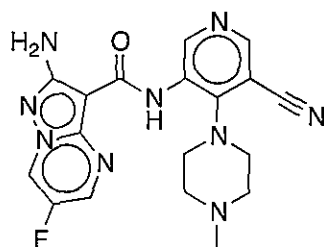
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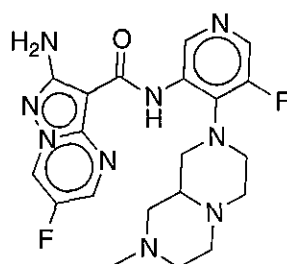
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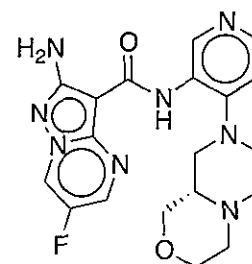
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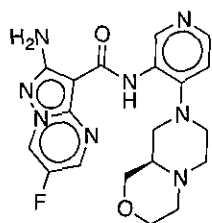
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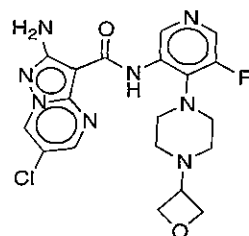
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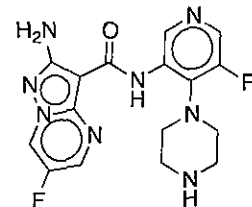
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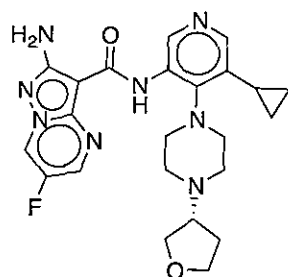
I-N-116



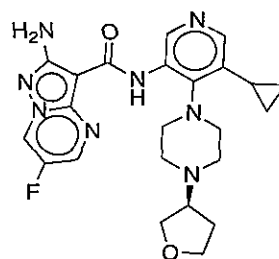
I-N-117



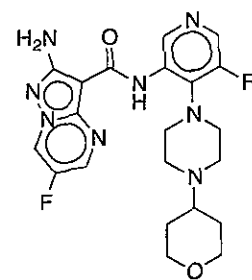
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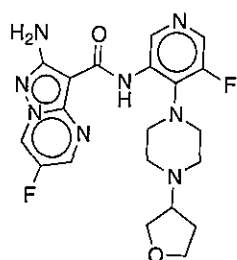
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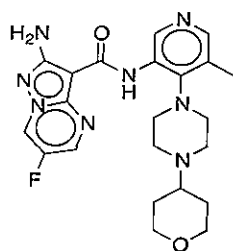
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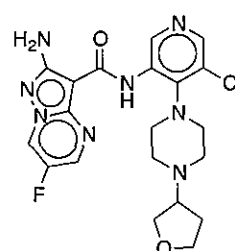
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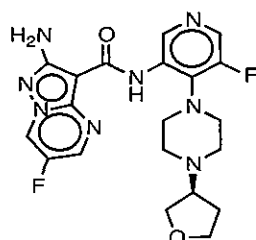
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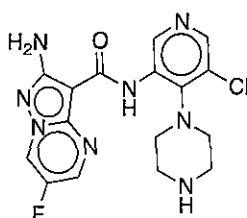
I-N-123



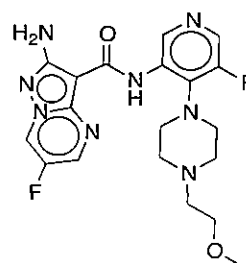
I-N-124



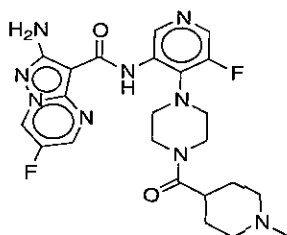
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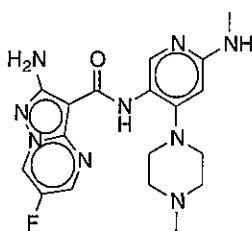
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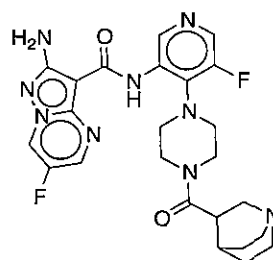
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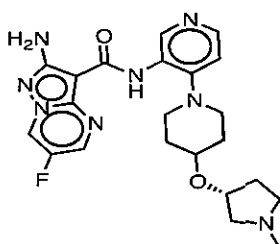
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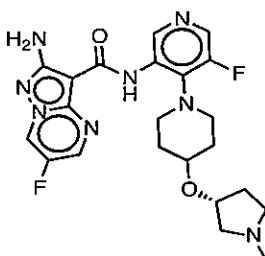
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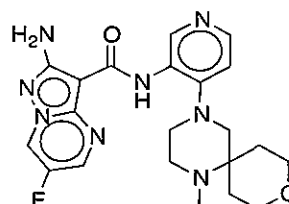
I-N-130



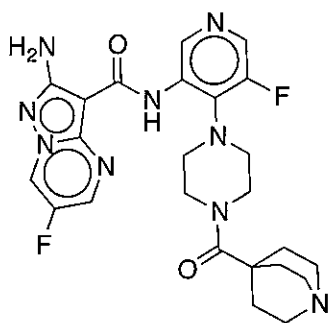
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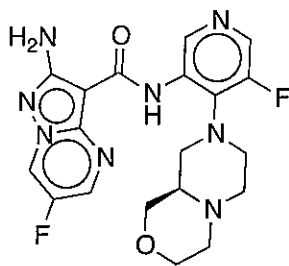
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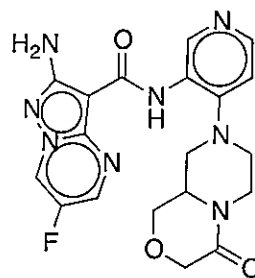
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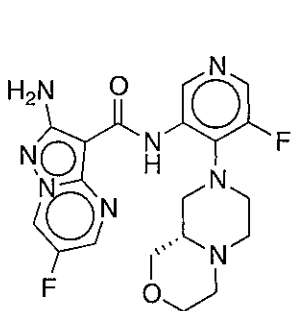
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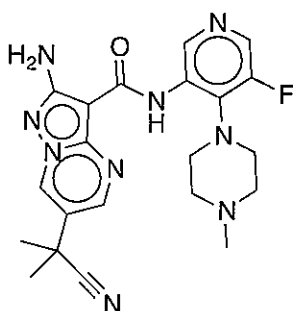
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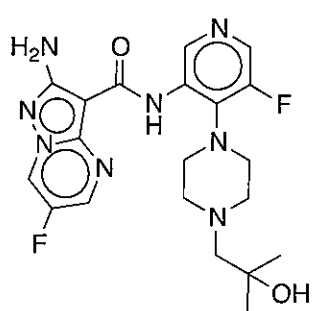
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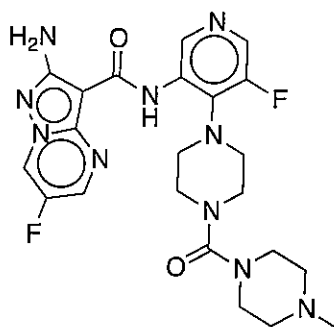
I-N-137



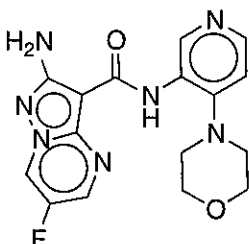
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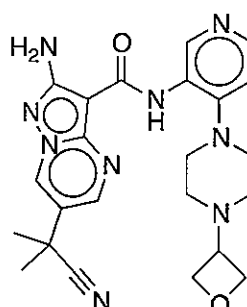
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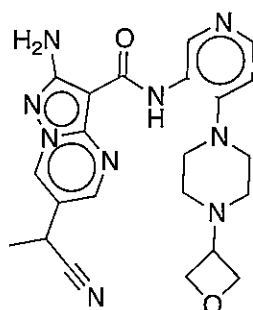
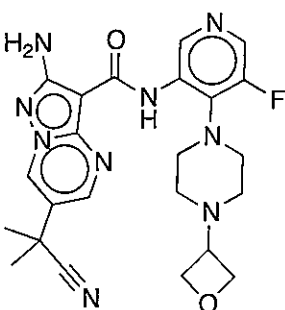
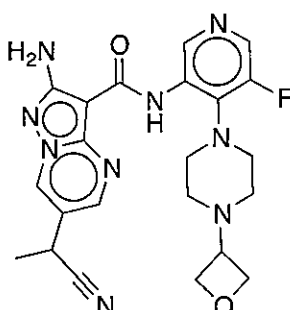
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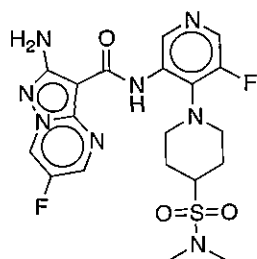
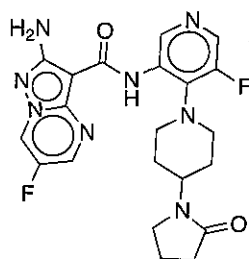
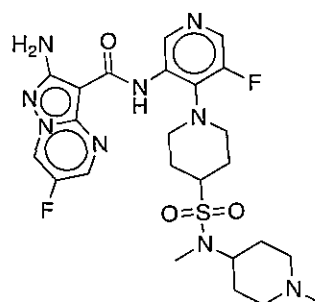
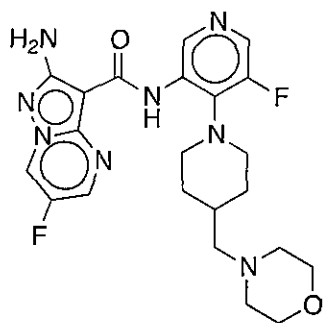
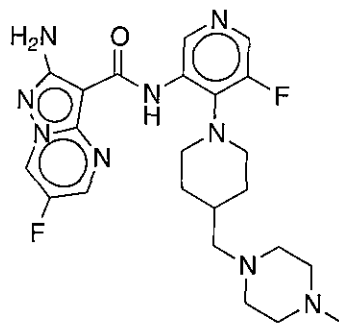
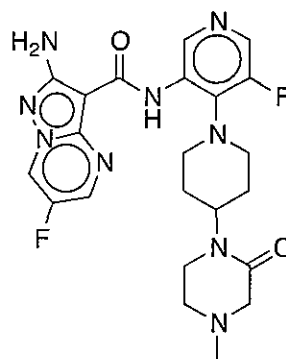
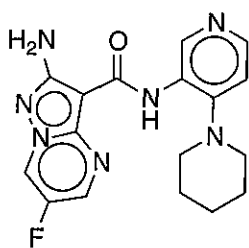
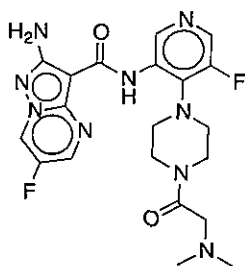
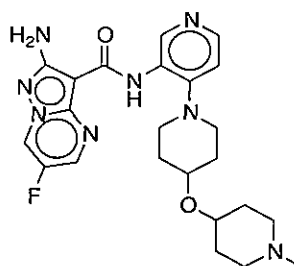


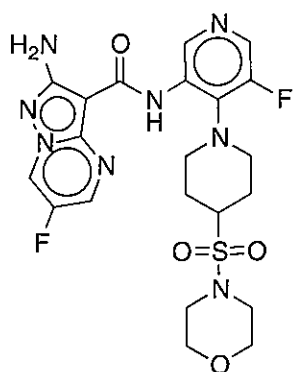
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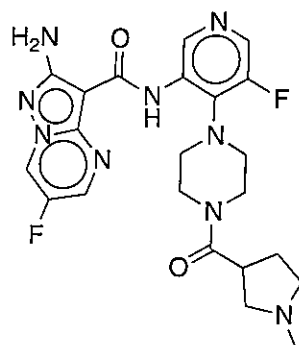
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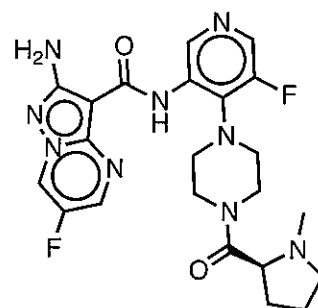
I-N-143**I-N-144****I-N-145****I-N-146****I-N-147****I-N-148****I-N-149****I-N-150****I-N-151****I-N-152****I-N-153****I-N-154**



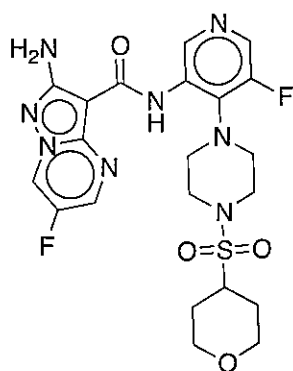
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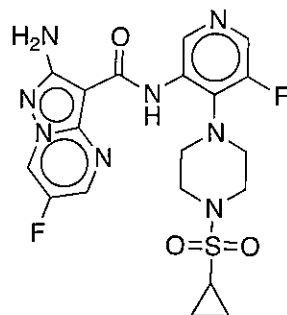
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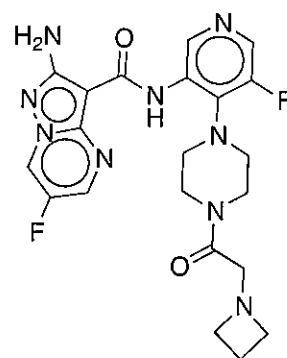
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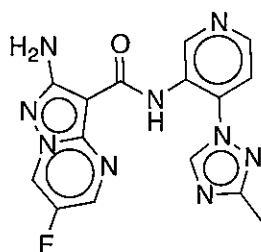
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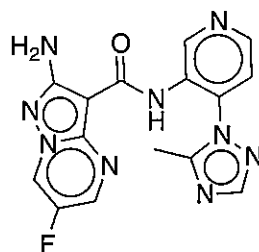
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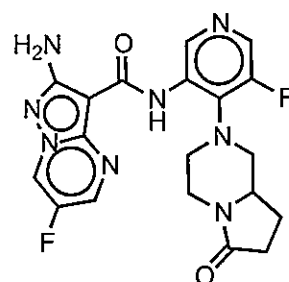
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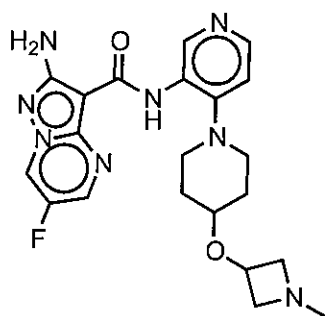
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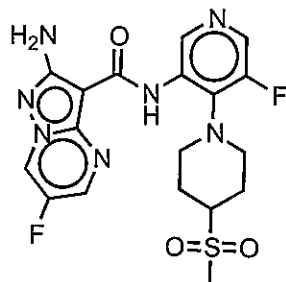
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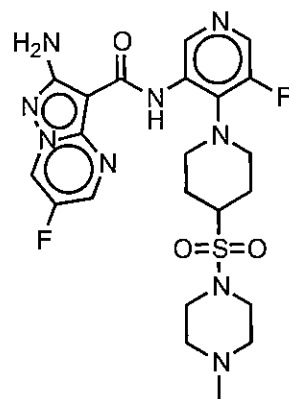
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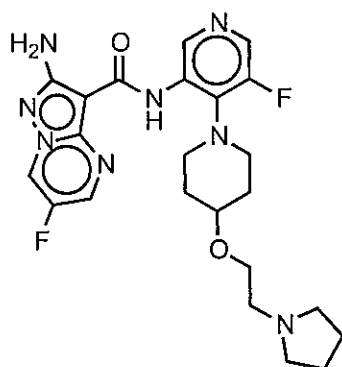
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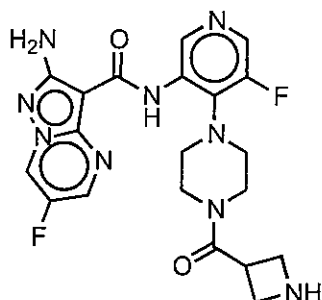
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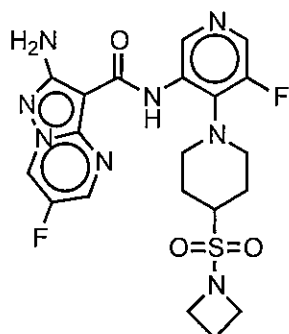
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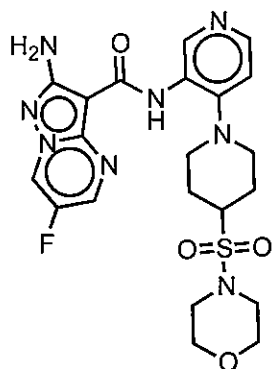
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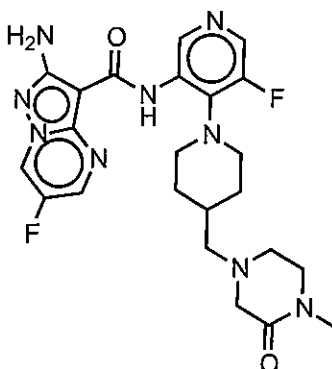
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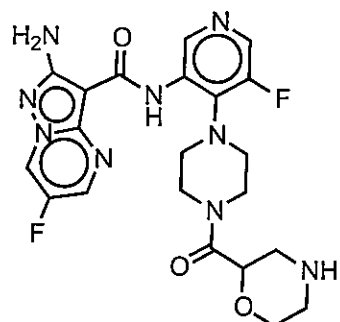
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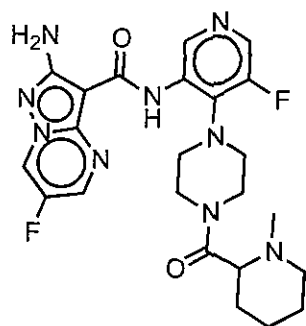
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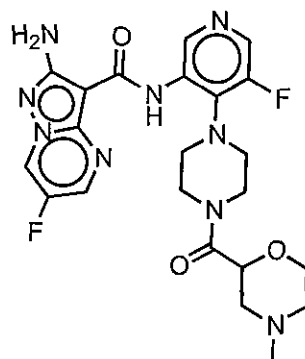
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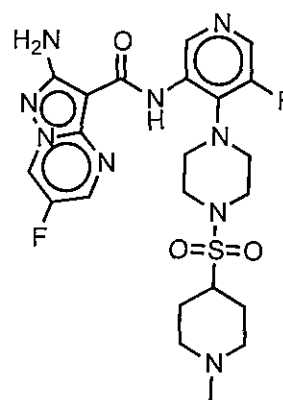
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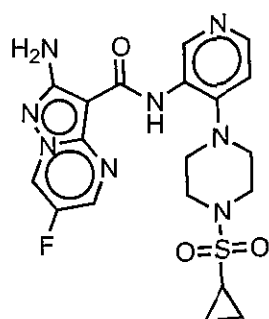
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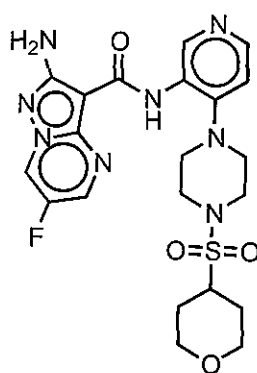
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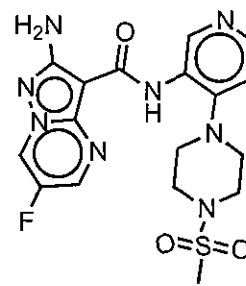
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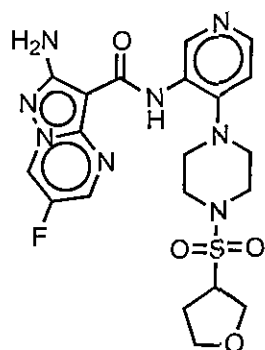
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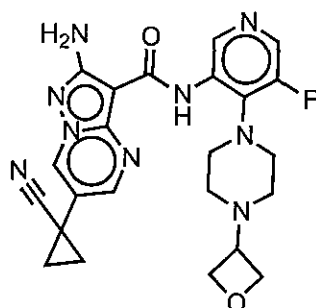
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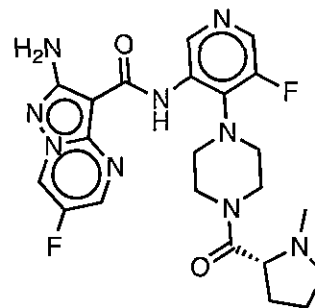
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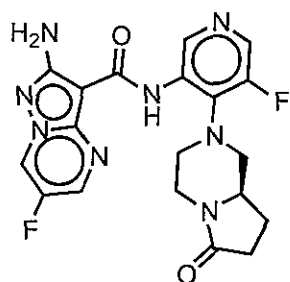
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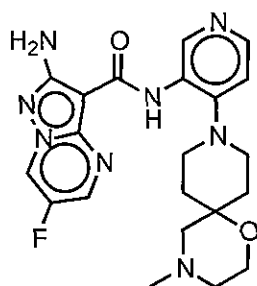
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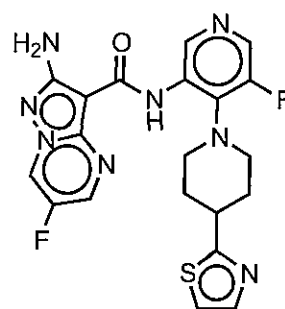
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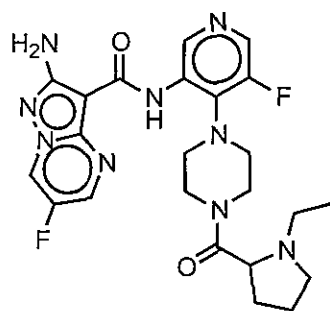
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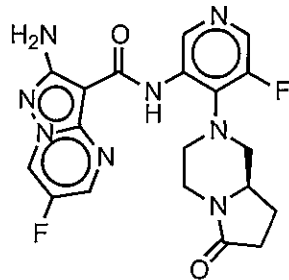
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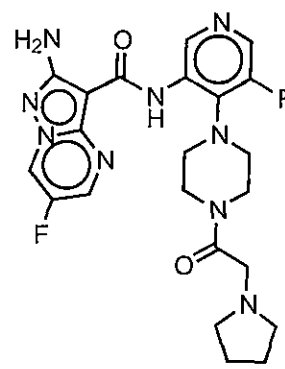
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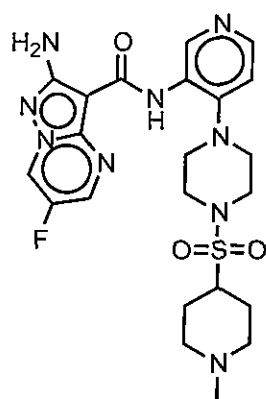
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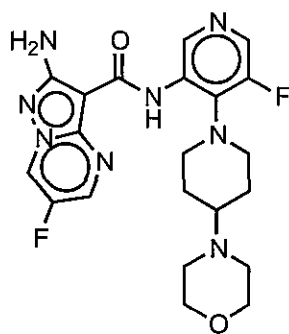
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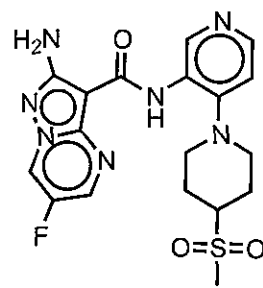
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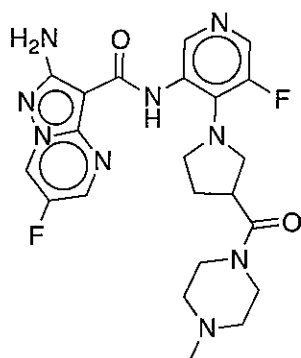
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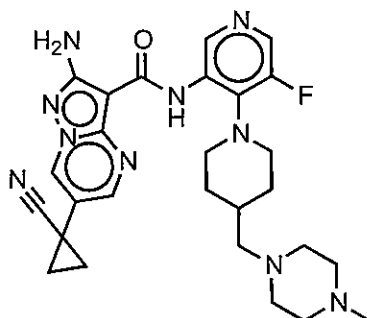
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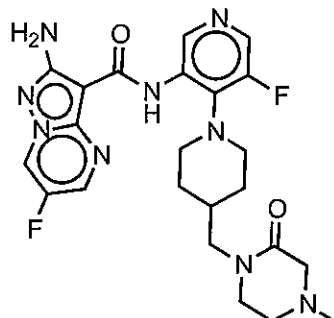
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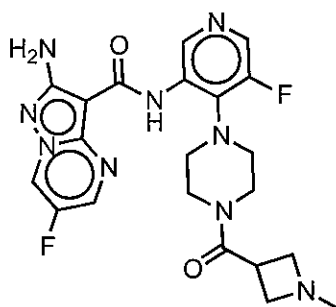
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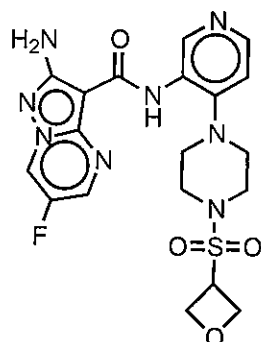
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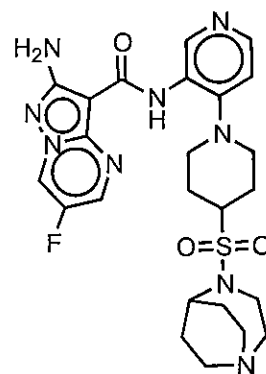
I-N-193



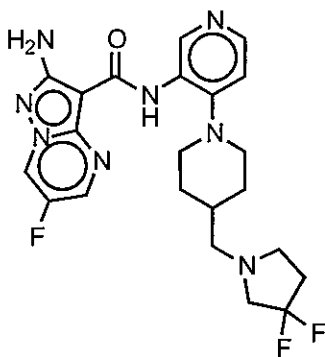
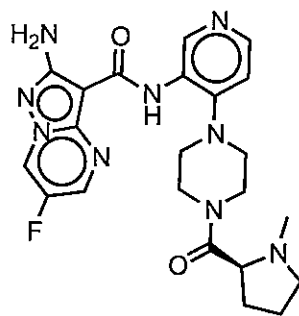
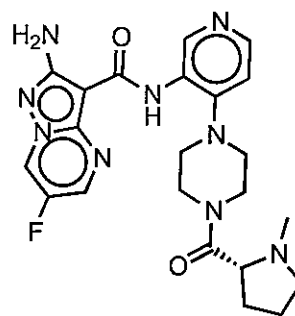
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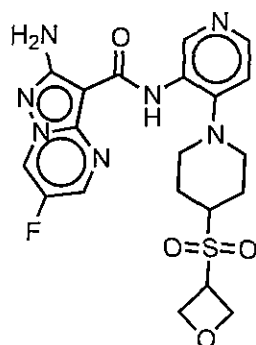
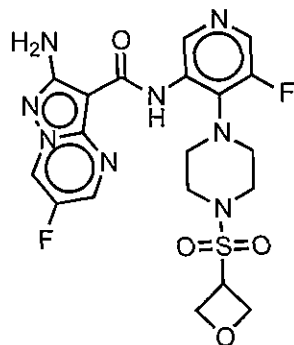
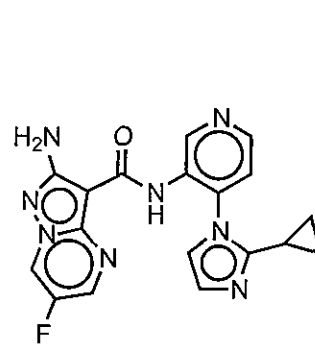
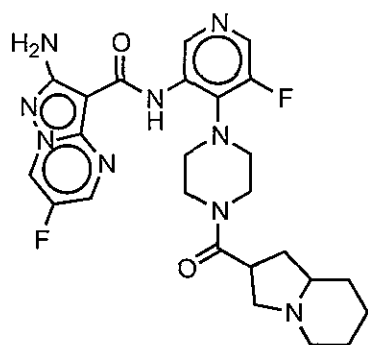
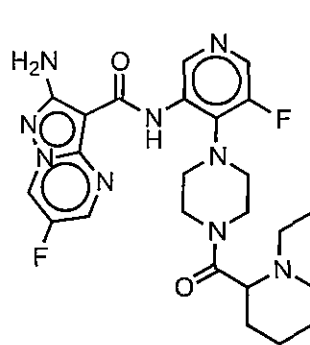
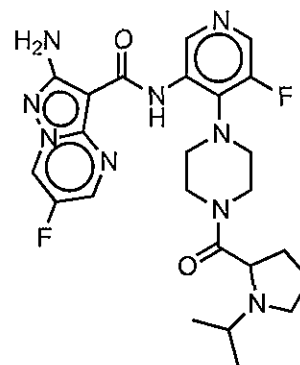
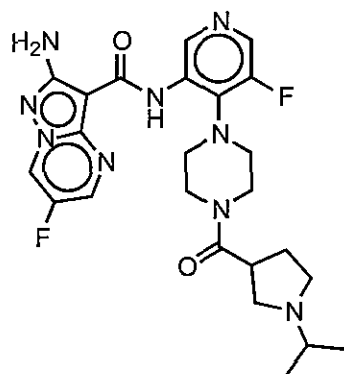
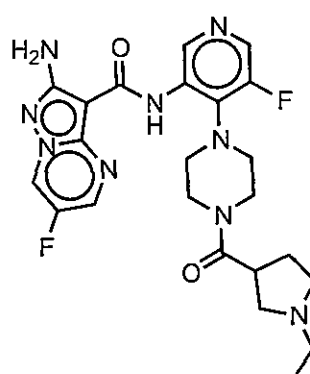
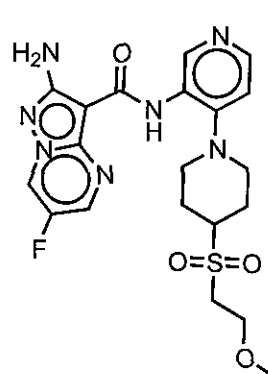


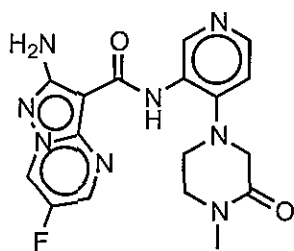
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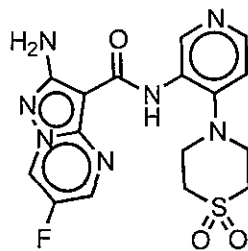
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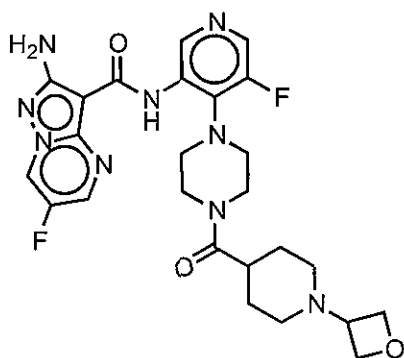
I-N-197**I-N-198****I-N-199****I-N-200****I-N-201****I-N-202****I-N-203****I-N-204****I-N-205****I-N-206****I-N-207****I-N-208**



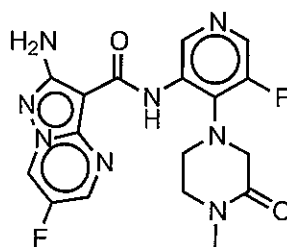
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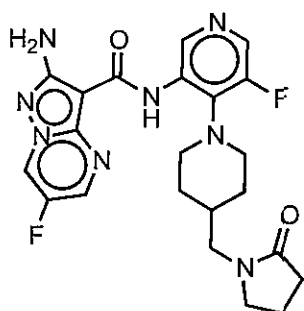
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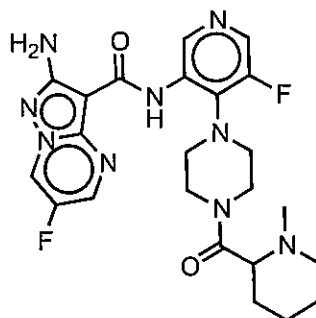
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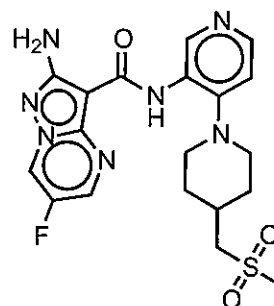
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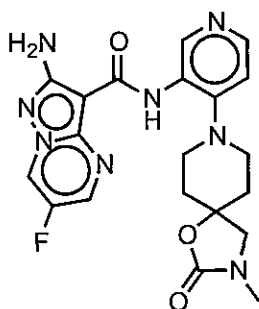
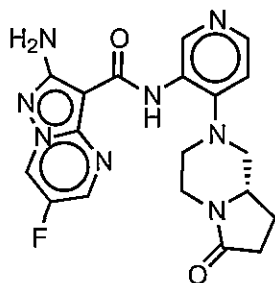
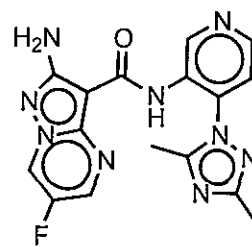
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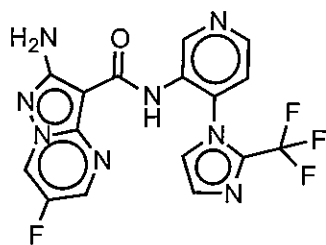
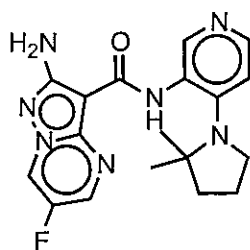
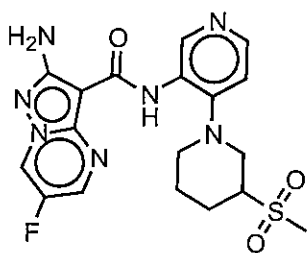
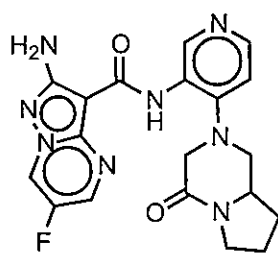
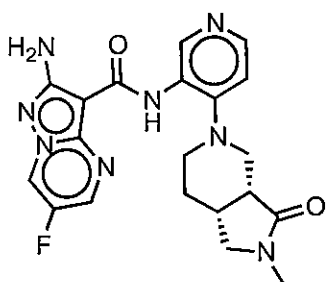
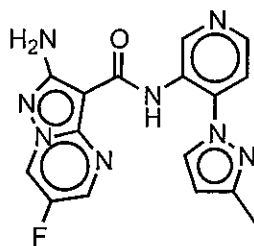
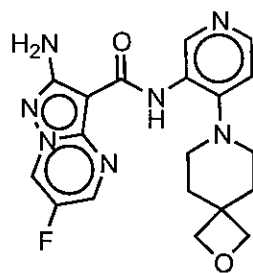
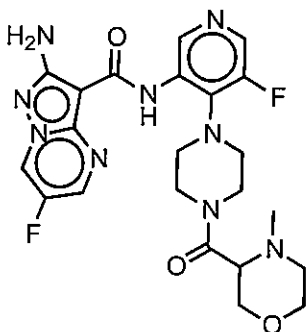
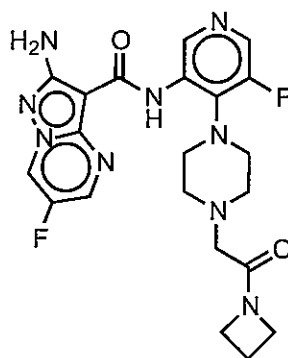
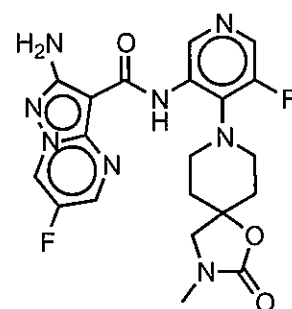


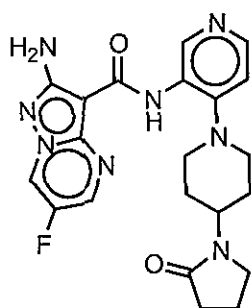
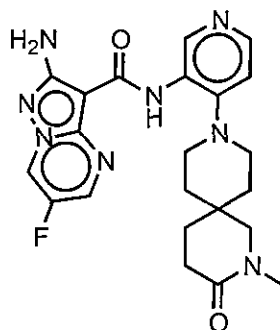
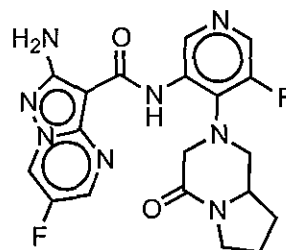
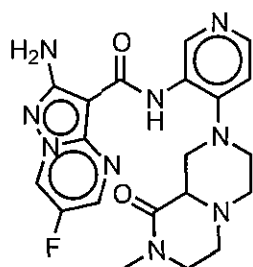
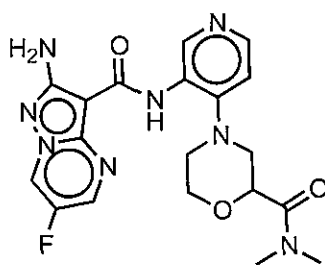
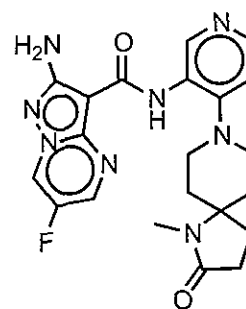
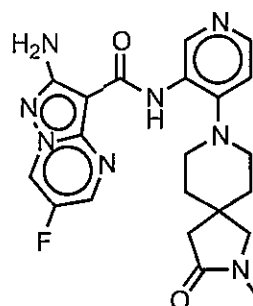
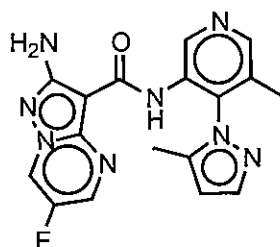
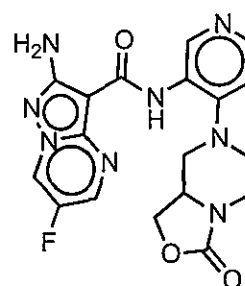
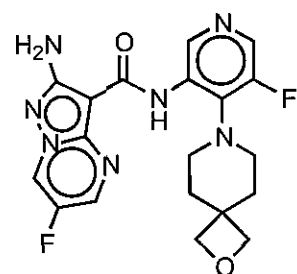
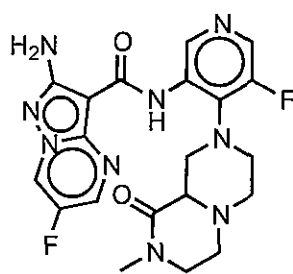
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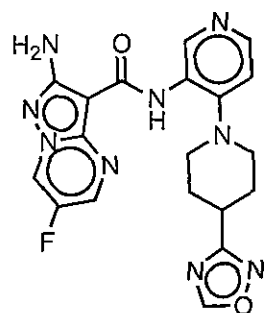
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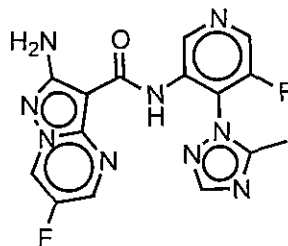
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I-N-227**I-N-228****I-N-229****I-N-230****I-N-231****I-N-232****I-N-233****I-N-234****I-N-235****I-N-236****I-N-237****I-N-238**

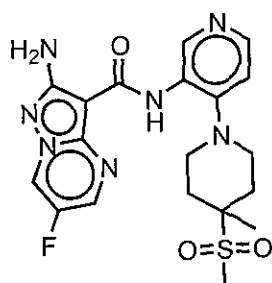
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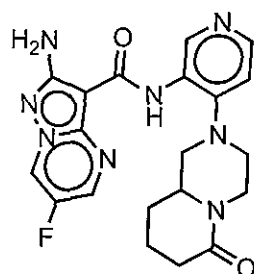
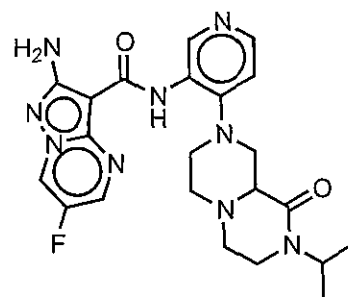
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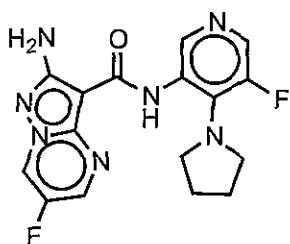
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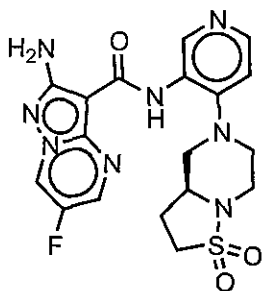
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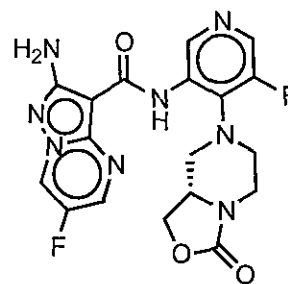
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I-N-244



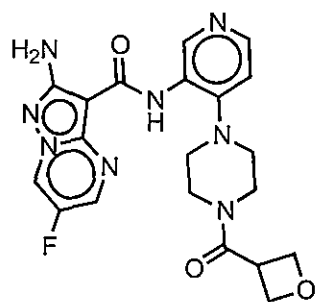
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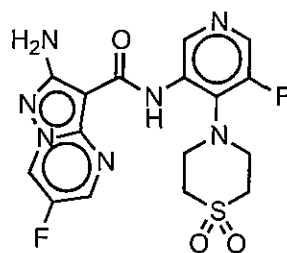
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I-N-247

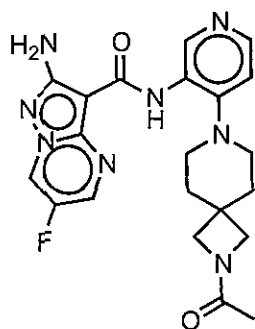
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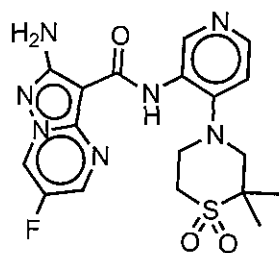
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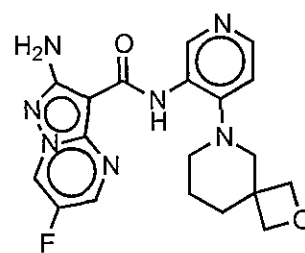
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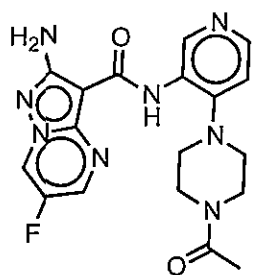
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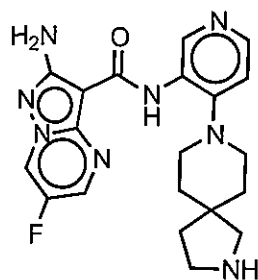
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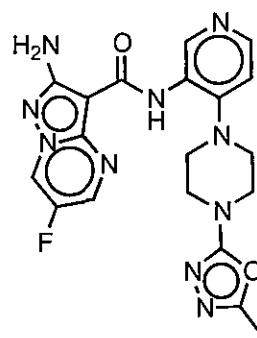
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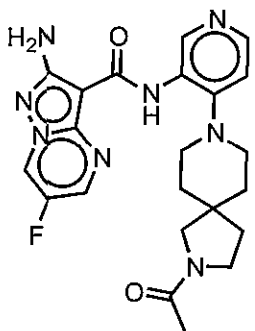
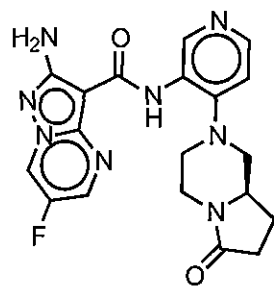
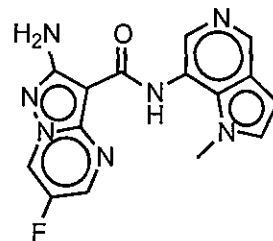
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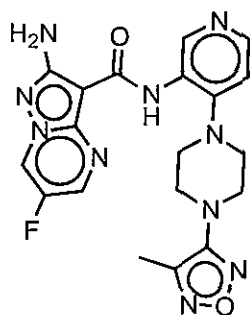
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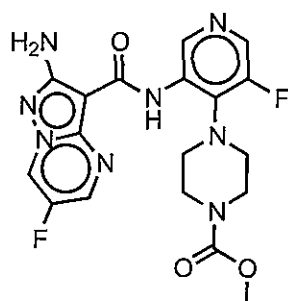
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I-N-257

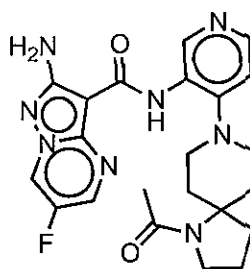


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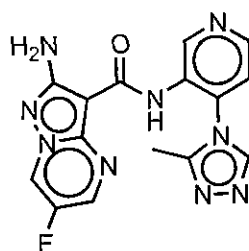


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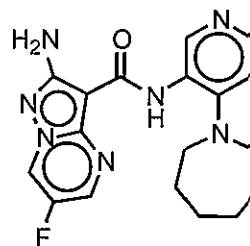
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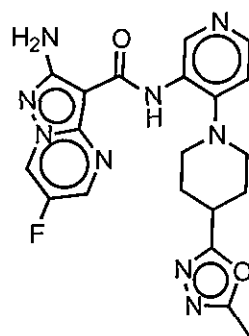
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I-N-262



I-N-263



I-N-264

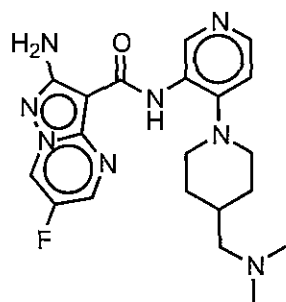


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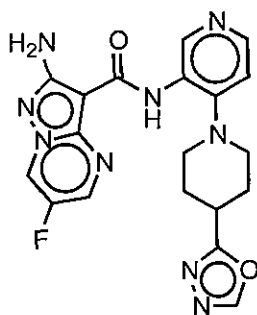


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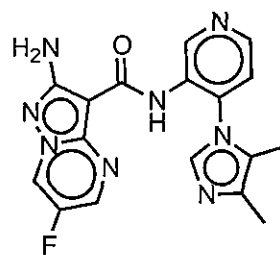




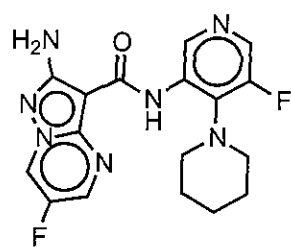
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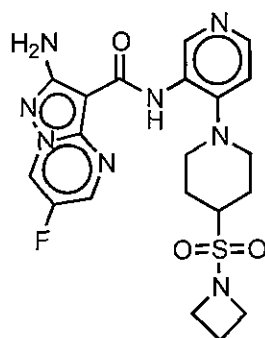
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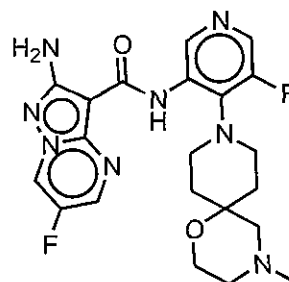
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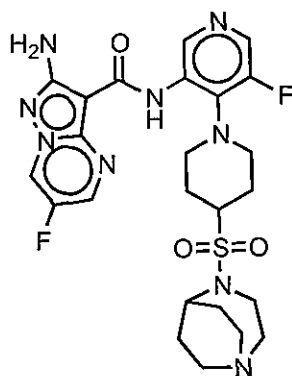
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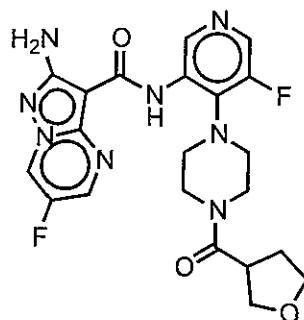
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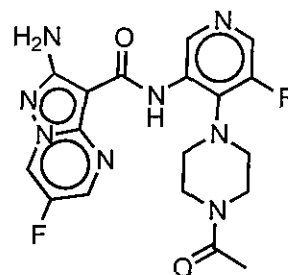
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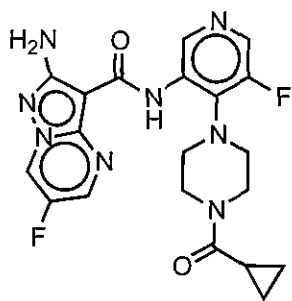
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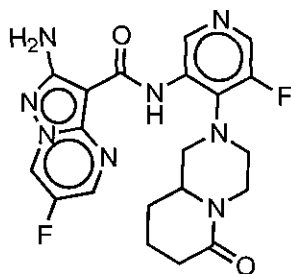
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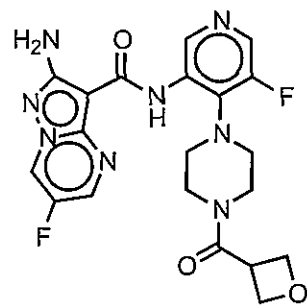
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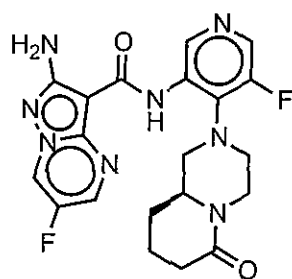
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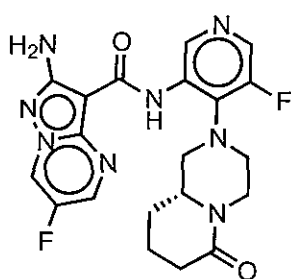
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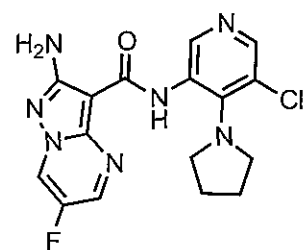
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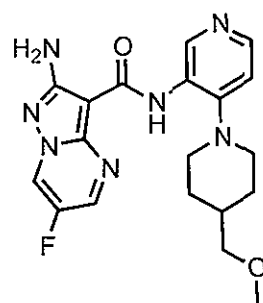
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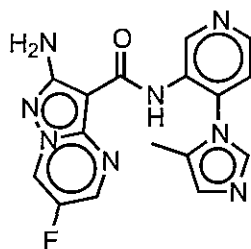
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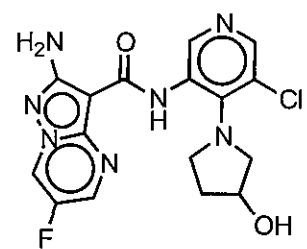
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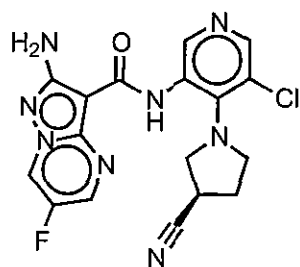
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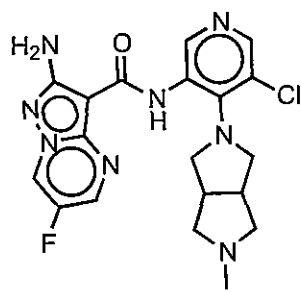
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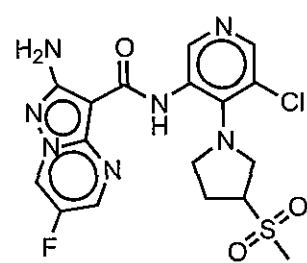
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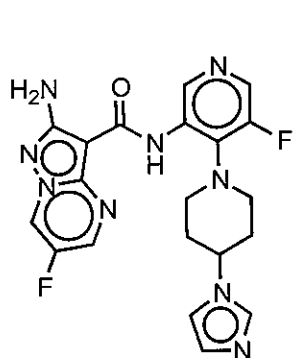
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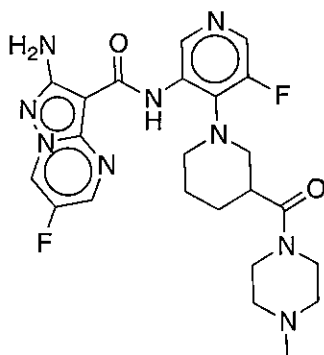
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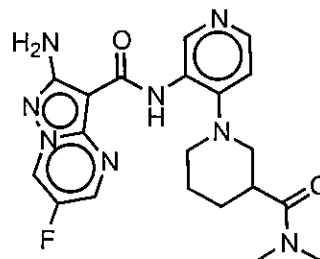
I-N-287



I-N-288



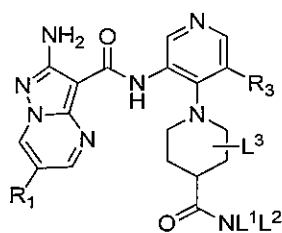
I-N-289



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;

R^3 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 the group consisting of oxygen nitrogen, and 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 the group consisting of oxygen nitrogen, and 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 ;

Ring D is a 3-7 membered heterocyclcyl 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 carbocyclcyl; a 3-6 membered heterocyclcyl having 1-2 heteroatoms selected from oxygen nitrogen, or 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 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;

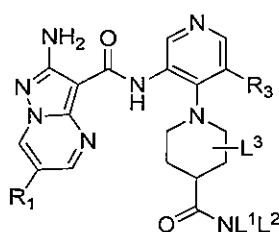
J^K is independently a 3-7 membered aromatic or non-aromatic ring having 0-2 heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur;

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 o 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;

R^3 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;

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 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 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;

L³ is independently H; C₁₋₃aliphatic; or CN;

Ring D is a 3-7 membered heterocyclcyl 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^o)₂; →O; a 3-6 membered carbocyclcyl; a 3-6 membered heterocyclcyl having 1-2 heteroatoms selected from the group consisting of oxygen nitrogen, and 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 oxygen, nitrogen, or sulfur;

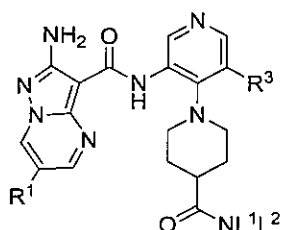
two occurrences of J^G, together with Ring D, form a 6-10 membered saturated or partially unsaturated bridged ring system;

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;

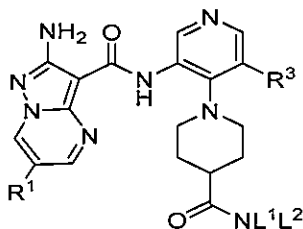
two occurrences of J^G , together with Ring D, form a 6-10 membered saturated or partially unsaturated bridged ring system;

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:

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; or -CN;

L¹ is an optionally substituted C₁₋₆aliphatic;

L² is an optionally substituted C₁₋₆aliphatic; 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 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 C₁₋₄alkyl, -N(R^o)₂, or a 3-5 membered carbocycl; or

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

R^o is H or C₁₋₄alkyl.

79. The compound of any one of claims 75, 76, and 77, wherein R¹ is fluoro.

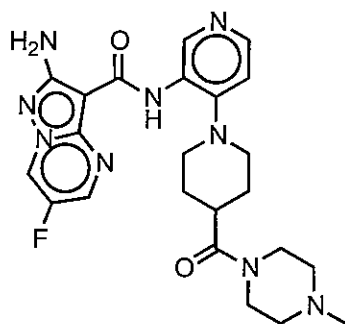
80. The compound of any one of claims 75, 76, and 77, wherein R¹ is -CH₂CN.

81. The compound of any one of claims 75, 76, and 77, wherein R¹ is chloro.

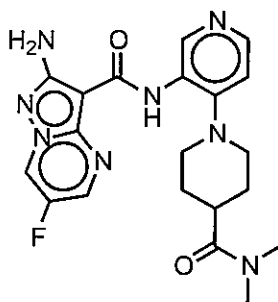
82. The compound of any one of claims 75, 76, 77, 79, and 80, wherein R^3 is H, chloro, fluoro, cyclopropyl, or C_{1-4} alkyl.
83. The compound of claim 82, wherein R^3 is H, chloro, or fluoro.
84. The compound of claim 82, wherein R^3 is H.
85. The compound of claim 82, wherein R^3 is chloro.
86. The 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 heterocyclyl 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, C_{1-4} alkyl, $-O(C_{1-3}$ alkyl), C_{3-6} cycloalkyl, a 3-6 membered heterocyclyl, $-NH(C_{1-3}$ alkyl), $-OH$, or $-N(C_{1-4}$ alkyl)₂.
96. The compound of claim 95, wherein J^G is methyl, $-N(C_{1-4}$ alkyl)₂, ethyl, $-O(C_{1-3}$ alkyl), cyclopropyl, oxetanyl, cyclobutyl, pyrrolidinyl, piperidinyl, or azetidiny.
97. The compound of claim 96, wherein J^G is methyl, $-O(C_{1-3}$ alkyl), 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.

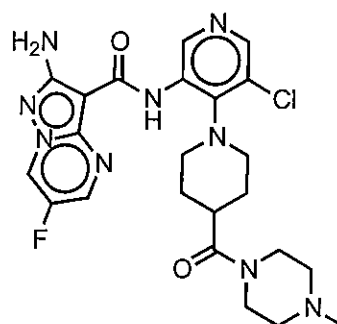
103. A compound, wherein the compound is::



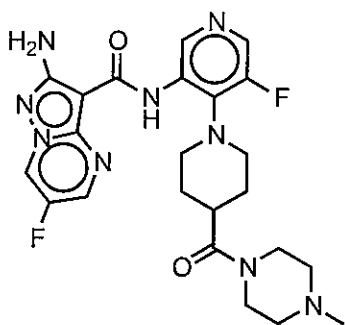
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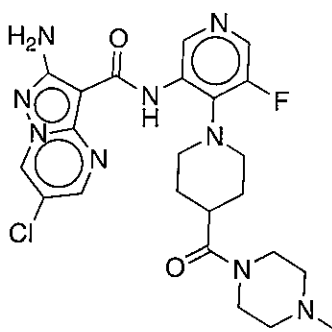
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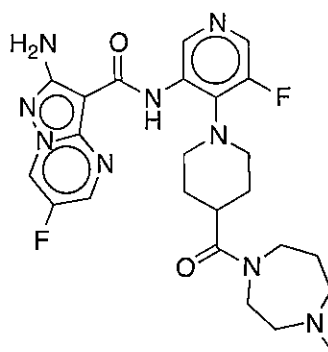
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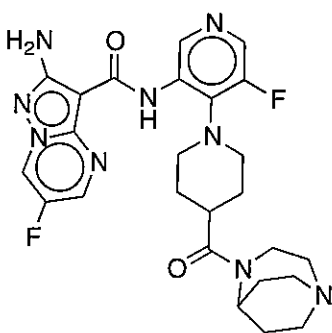
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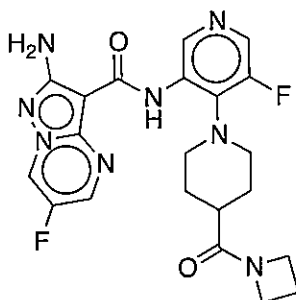
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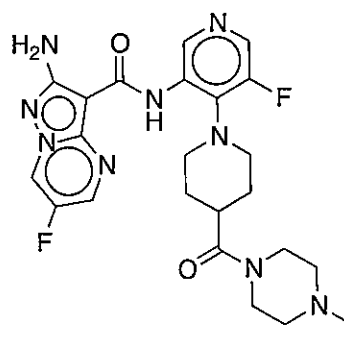
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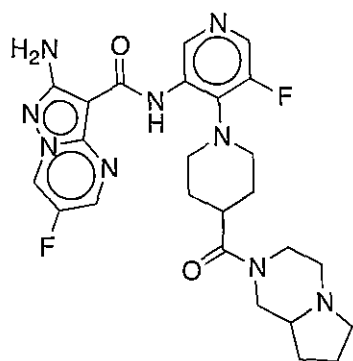
I-G-7



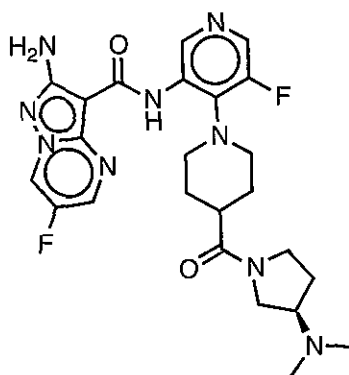
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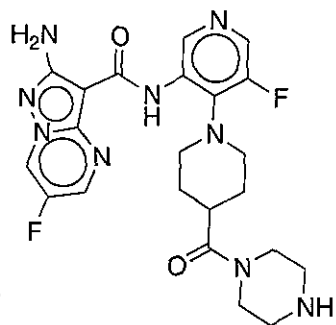
I-G-9



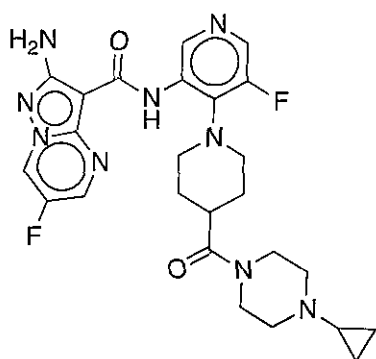
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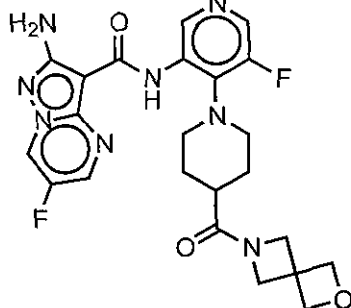
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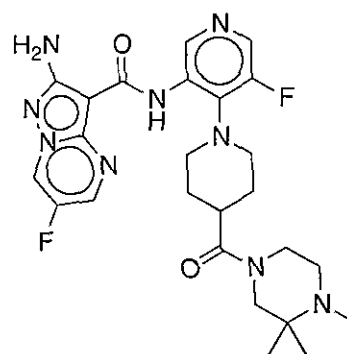
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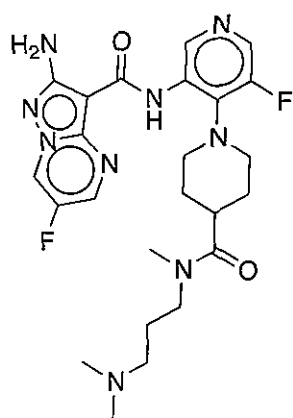
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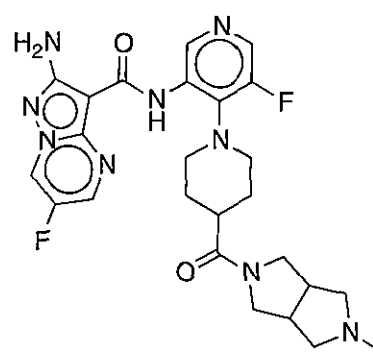
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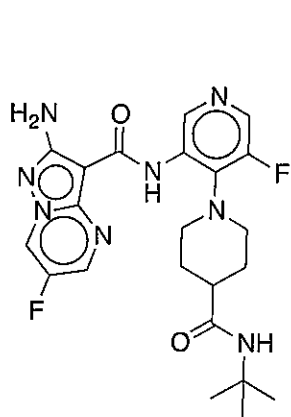
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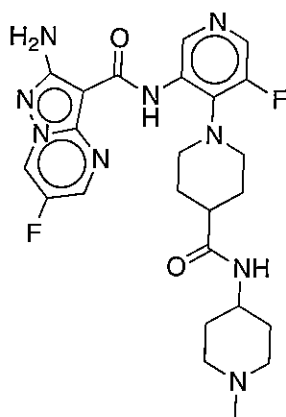
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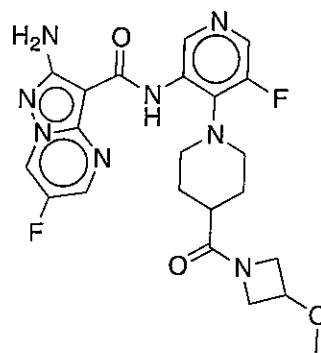
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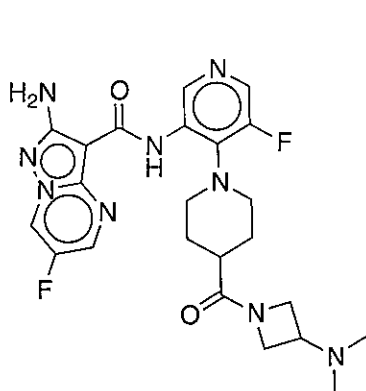
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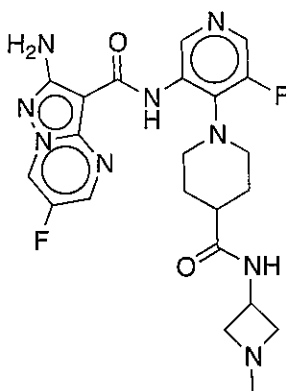
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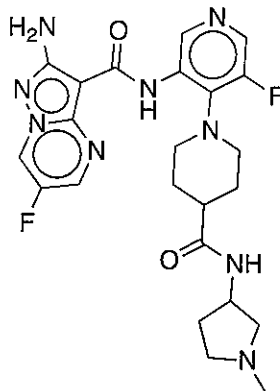
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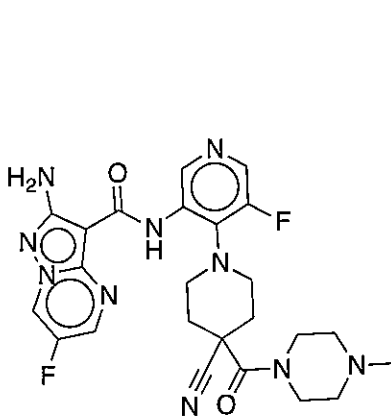
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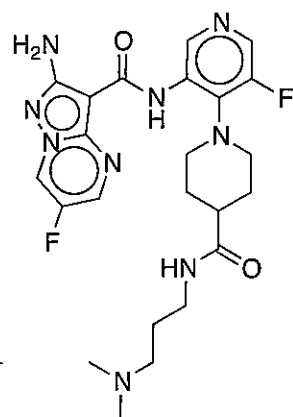
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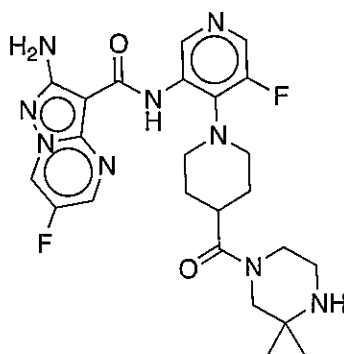
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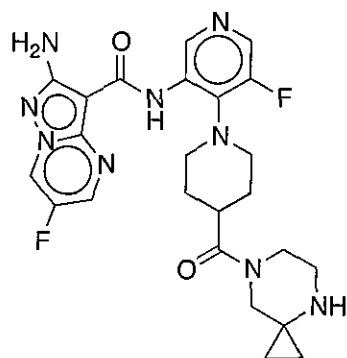
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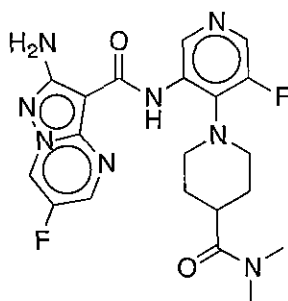
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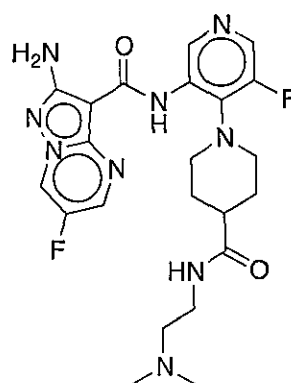
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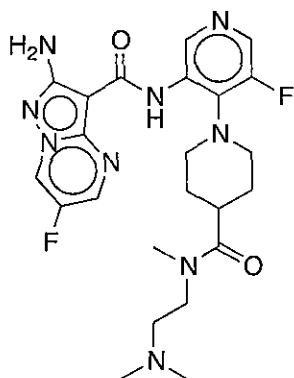
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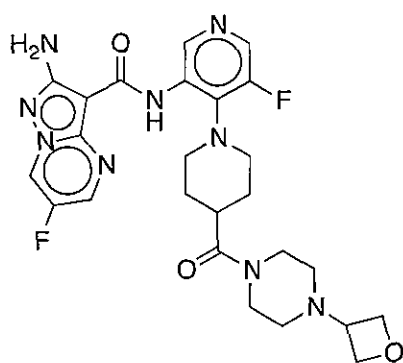
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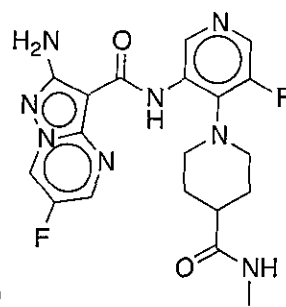
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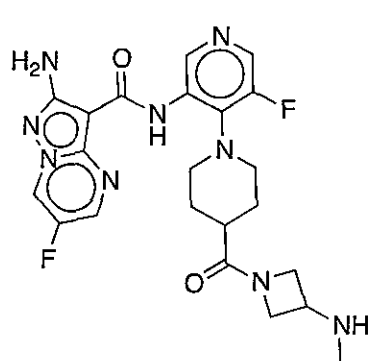
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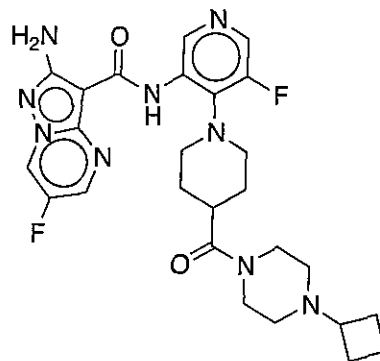
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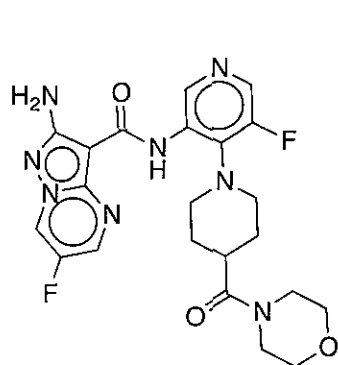
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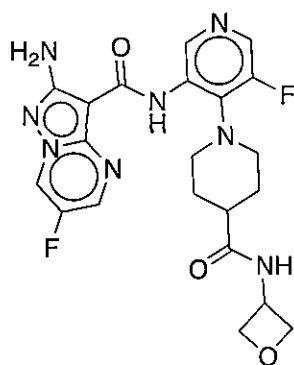
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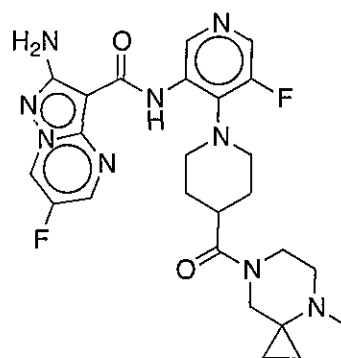
I-G-35



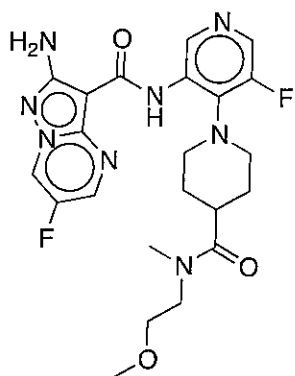
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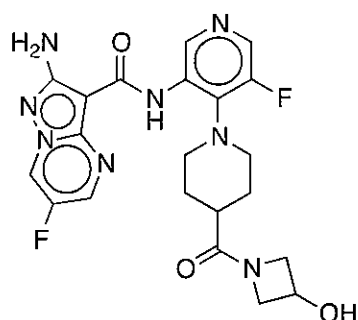
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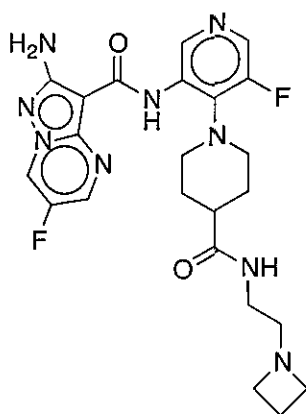
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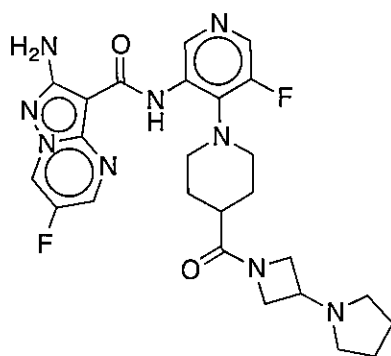
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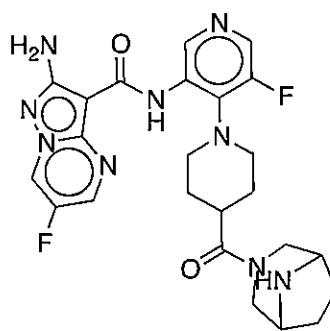
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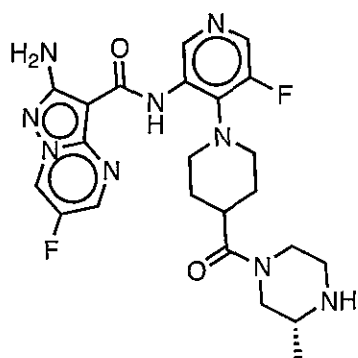
I-G-42



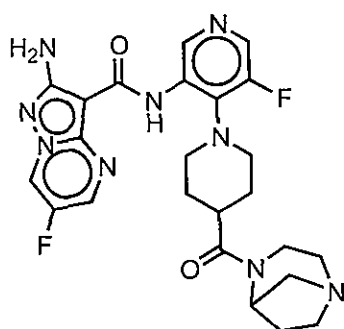
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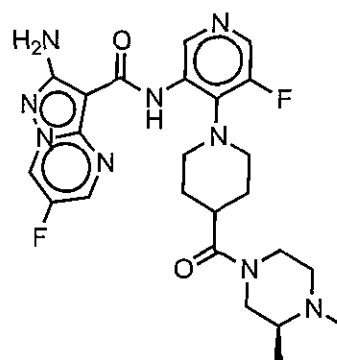
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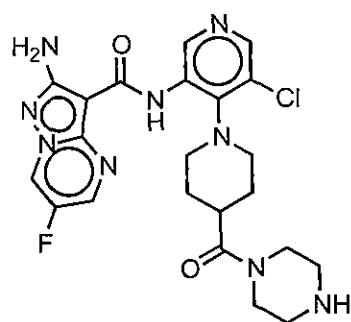
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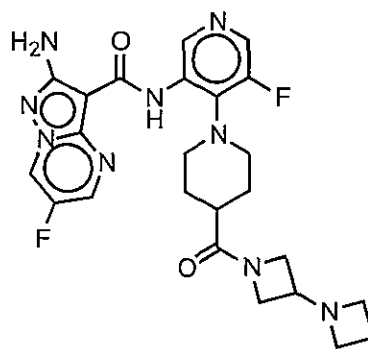
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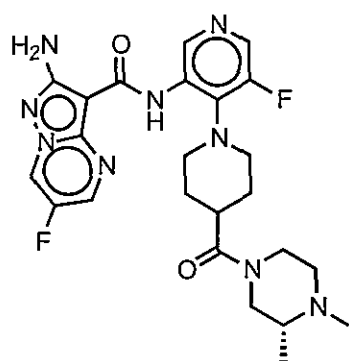
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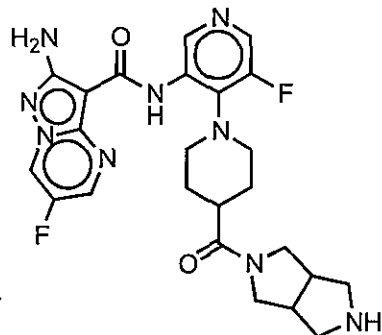
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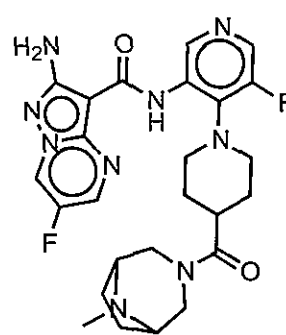
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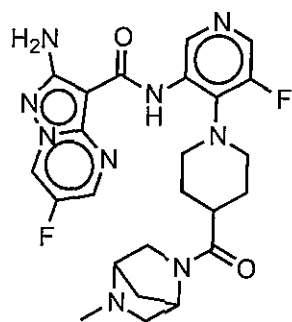
I-G-50



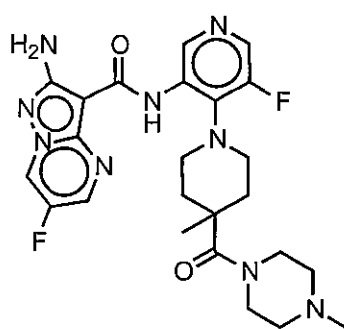
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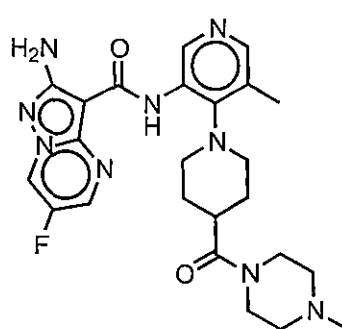
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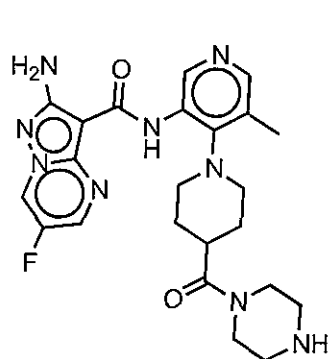
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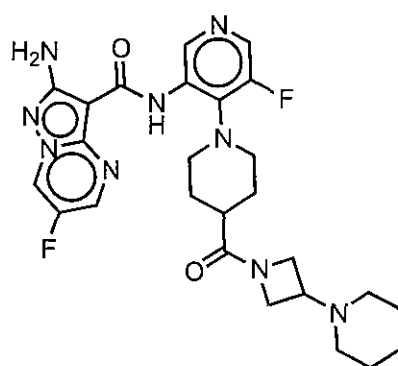
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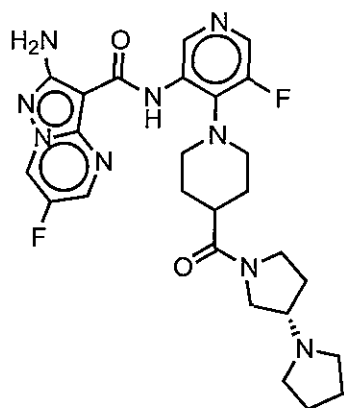
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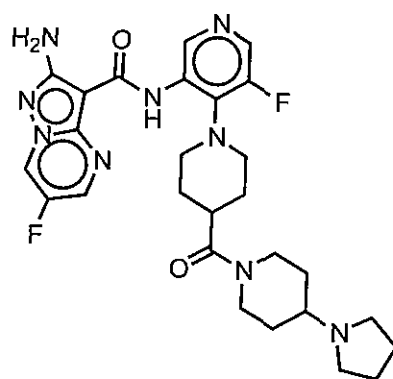
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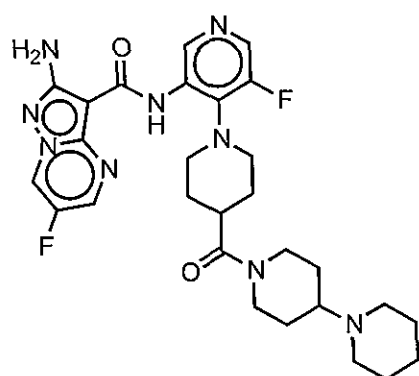
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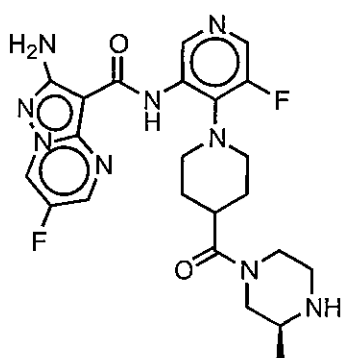
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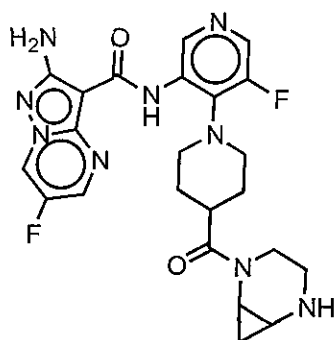
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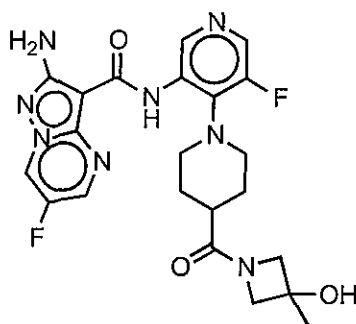
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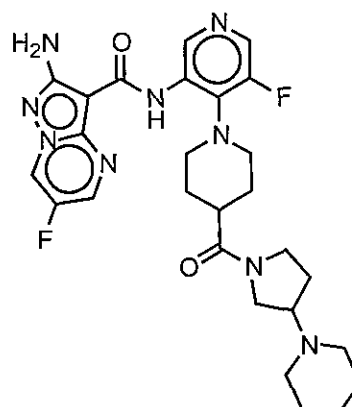
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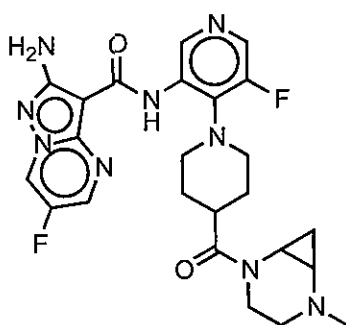
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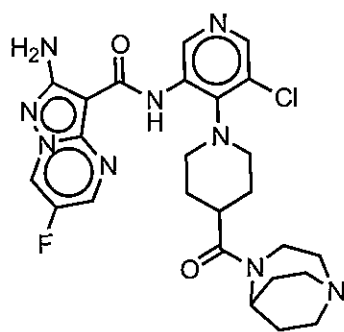
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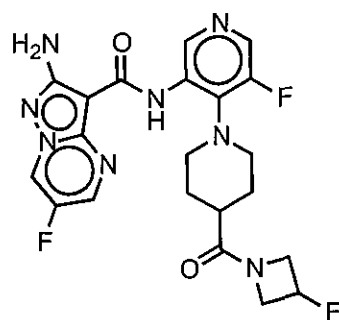
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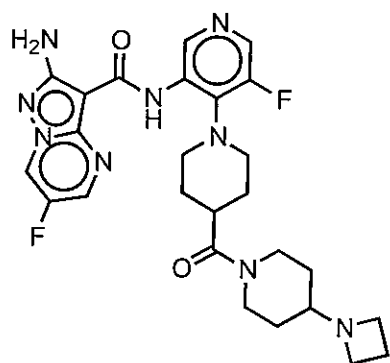
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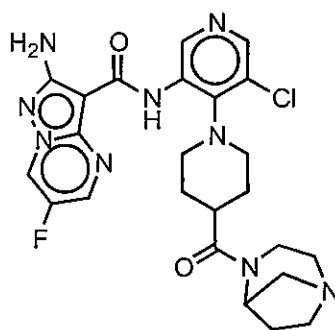
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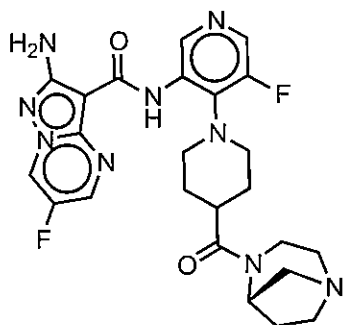
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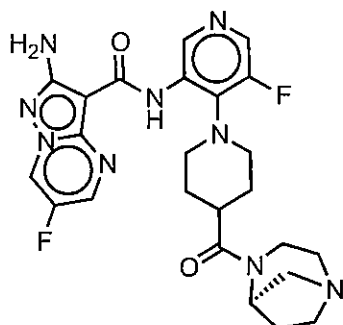
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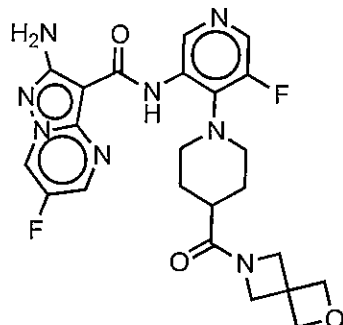
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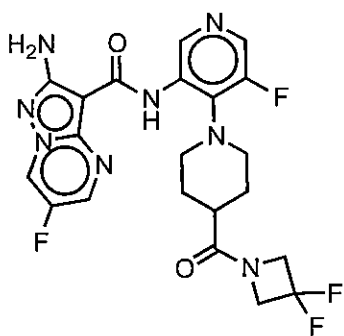
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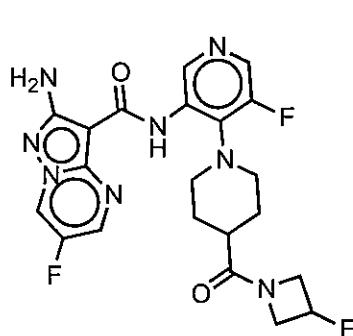
I-G-71



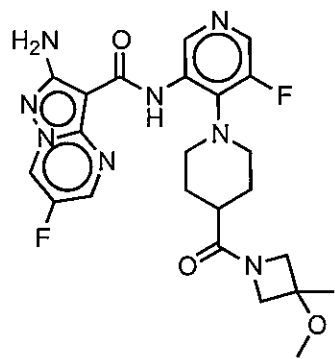
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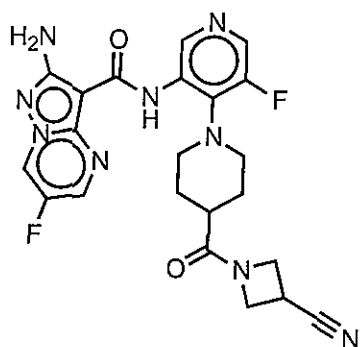
I-G-73



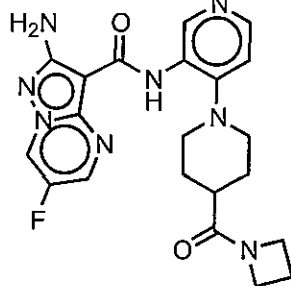
I-G-74



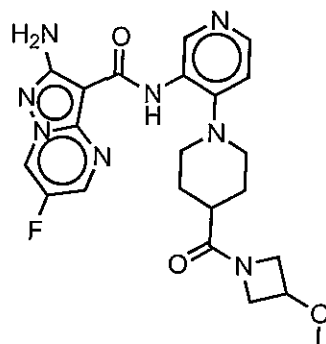
I-G-75



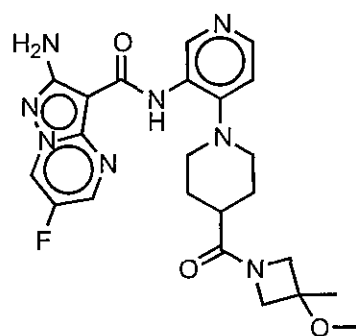
I-G-76



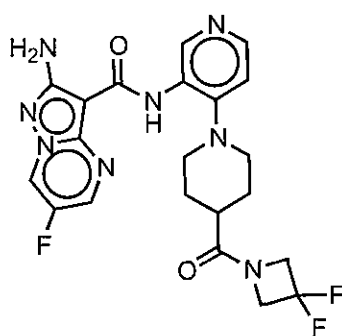
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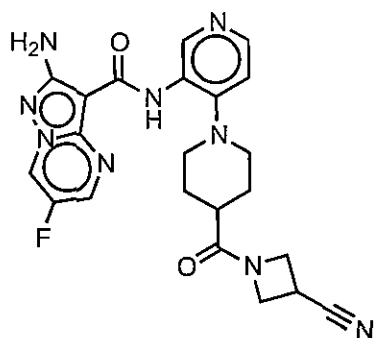
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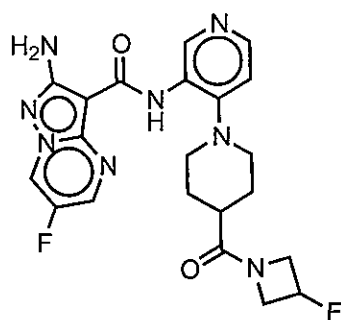
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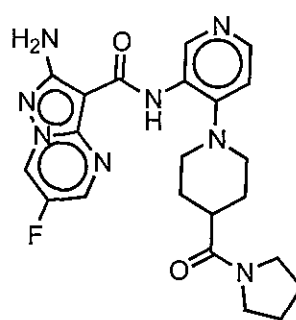
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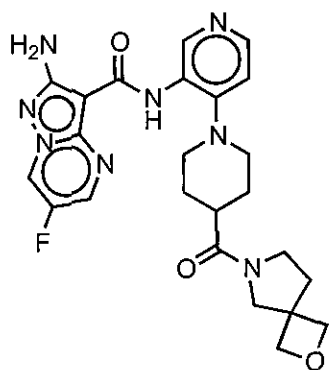
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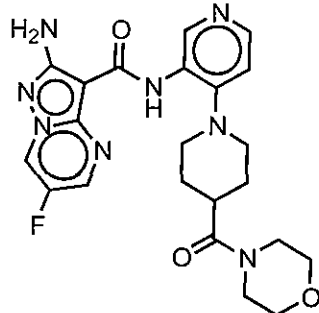
I-G-82



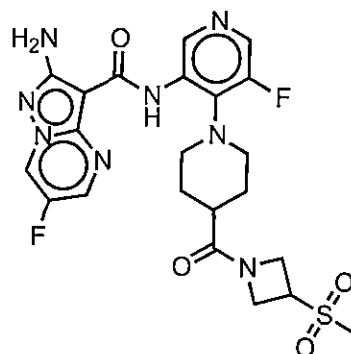
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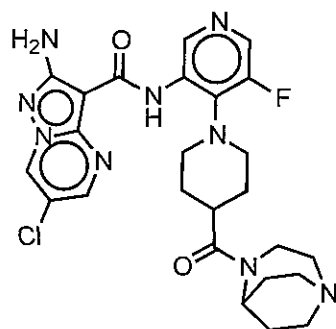
I-G-84



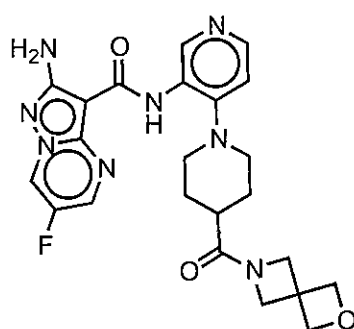
I-G-85



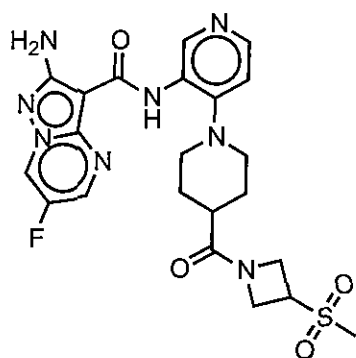
I-G-86



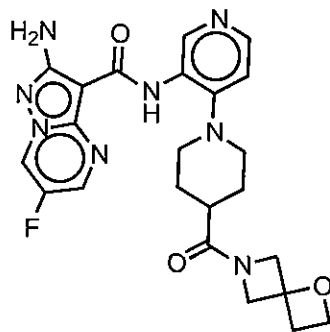
I-G-87



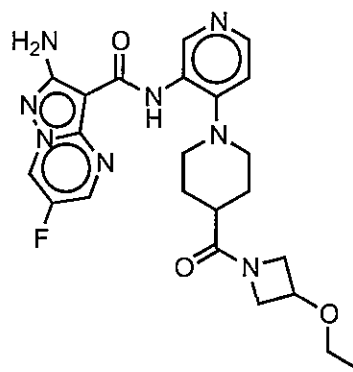
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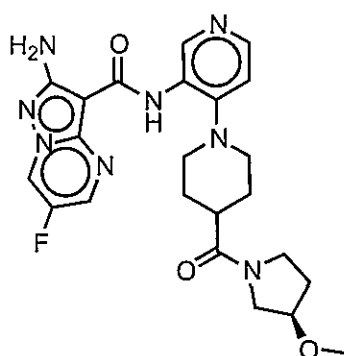
I-G-89



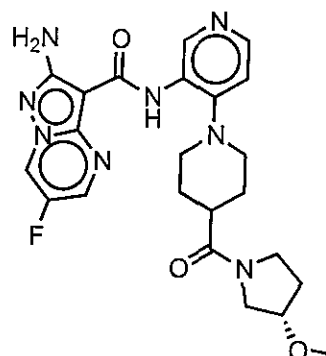
I-G-90



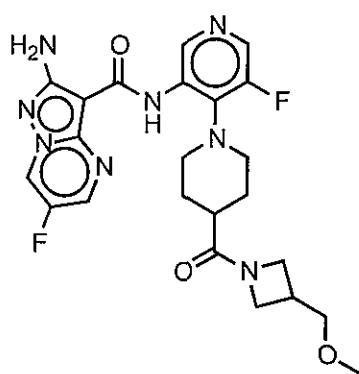
I-G-91



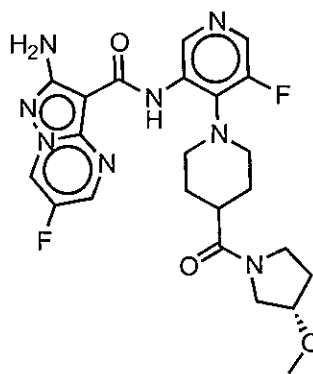
I-G-93



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, 215, 218, and 220, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.
105. A compound of any one of claims 1-103, 215, 218, and 220, 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 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 224, 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 223, or a pharmaceutically acceptable salt thereof, wherein the DNA-damaging agent is Etoposide.
118. The compound for use according to claim 225, 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, 215,218 and 220, 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, 215,218 and 220, or 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, 215,218 and 220, 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.

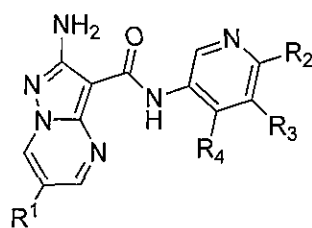
139. A compound of any one of claims 1-103, 215,218 and 220, or a pharmaceutically acceptable salt thereof, in combination with chemoradiation for use in the sensitization of pancreatic cancer cells to chemoradiation.
140. The compound for use according to claim 139, or a pharmaceutically acceptable salt thereof, wherein the chemoradiation is gemcitabine and radiation.
141. A compound of any one of claims 1-103, 215,218 and 220, 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, 215,218 and 220, 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, 215,218 and 220, or a pharmaceutically acceptable salt thereof, in combination with radiation therapy and/or gemcitabine for use in the disruption of damage-induced cell cycle checkpoints in a patient.
145. A compound of any one of claims 1-103, 215,218 and 220, or a pharmaceutically acceptable salt thereof, in combination with radiation therapy and/or gemcitabine for use in the inhibition of repair of DNA damage by homologous recombination in a pancreatic cancer cell in a patient.
146. A compound of any one of claims 1-103, 215,218 and 220, 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.

147. A compound of any one of claims 1-103, 215,218 and 220, or a pharmaceutically acceptable salt thereof, for the promotion of cell death in cancer cells.
148. A compound of any one of claims 1-103, 215,218 and 220, or a pharmaceutically acceptable salt thereof, for use in the prevention of cell repair from DNA damage in a patient.
149. A compound of any one of claims 1-103, 215,218 and 220, or a pharmaceutically acceptable salt thereof, for use in the inhibition of ATR in a biological sample *in vitro*.
150. The compound for use according to claim 149, or a pharmaceutically acceptable salt thereof, wherein said biological sample is a cell.
151. A compound of any one of claims 1-103, 215,218 and 220, or a pharmaceutically acceptable salt thereof, for use in the sensitization of cells to DNA damaging agents in a patient.
152. The compound for use according to any one of claims 105-151, 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,.
153. The compound for use according to claim 152, or a pharmaceutically acceptable salt thereof, wherein said defect is altered expression or activity of one or more of the following: ATM, p53, CHK2, MRE11, RAD50, NBS1, 53BP1, MDC1, H2AX, MCPH1/BRIT1, CTIP, and SMC1.

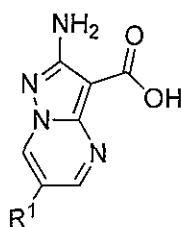
154. The compound for use according to claim 152, or a pharmaceutically acceptable salt thereof, wherein said defect is altered expression or activity of one or more of the following: ATM, p53, CHK2, MRE11, RAD50, NBS1, 53BP1, MDC1, and H2AX.
155. The compound for use according to any one of claims 105-151, or a pharmaceutically acceptable salt thereof, wherein said cancer expresses DNA damaging oncogenes, said cancer cell expresses DNA damaging oncogenes, or said cell is a cancer cell expressing DNA damaging oncogenes.
156. The compound for use according to claim 155, or a pharmaceutically acceptable salt thereof, wherein said cancer or cancer cell has altered expression or activity of one or more of the following: K-Ras, N-Ras, H-Ras, Raf, Myc, Mos, E2F, Cdc25A, CDC4, CDK2, Cyclin E, Cyclin A and Rb.
157. The compound for use according to any one of claims 105-151, or a pharmaceutically acceptable salt thereof, wherein said cancer, cancer cell, or cell has a defect in a base excision repair protein.
158. The compound for use according to claim 157, or a pharmaceutically acceptable salt thereof, wherein the base excision repair protein is selected from the group consisting of DNA glycosylases, AP endonucleases, DNA ligases I and III, LIG3 accessory, polynucleotide kinases, and polynucleotide phosphatase, Poly(ADP-Ribose) Polymerases, polymerases, endonuclease, and Aprataxin.
159. The compound for use according to claim 158 or 243, or a pharmaceutically acceptable salt thereof, wherein the base excision repair protein is PARP1, PARP2, or PolB.
160. The compound for use according to claim 159, or a pharmaceutically acceptable salt thereof, wherein the base excision repair protein is PARP1 or PARP2.

161. The compound for use according to any one of claims 105-160, 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.
162. The compound for use according to claim 161, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt thereof, wherein the base excision repair protein is selected from the group consisting of DNA glycosylases, AP endonucleases, DNA ligases I and III, LIG3 accessory, polynucleotide kinases, and polynucleotide phosphatase, Poly(ADP-Ribose) Polymerases, polymerases, endonuclease, and Aprataxin.
163. The compound for use according to claim 162, or a pharmaceutically acceptable salt thereof, wherein the base excision repair protein is PARP1, PARP2, or PolB.
164. The compound for use according to claim 163, or a pharmaceutically acceptable salt thereof, wherein the base excision repair protein is PARP1 or PARP2.
165. The compound for use according to any one of claims 161-164, 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.
166. A process for preparing a compound of formula **I-A**:



I-A

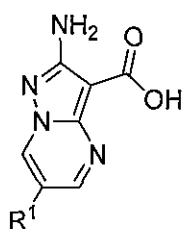
or a pharmaceutically acceptable salt thereof, comprising reacting a compound of formula 5:



5

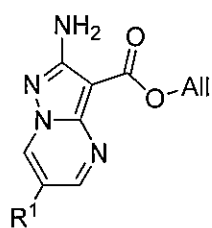
or a pharmaceutically acceptable salt thereof, under suitable conditions to form an amide bond, wherein R^1 , R^2 , R^3 , and R^4 are as defined in claims 1-106.

167. The process of claim 166, further comprising the step of preparing a compound of formula 5:



5

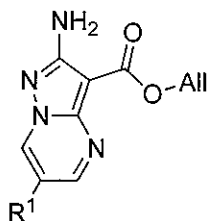
or a pharmaceutically acceptable salt thereof, by reacting a compound of formula 4:



4

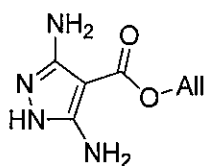
or a pharmaceutically acceptable salt thereof, under suitable deprotection conditions, wherein All is allyl.

168. The process of claim 167, further comprising the step of preparing a compound of formula 4:



4

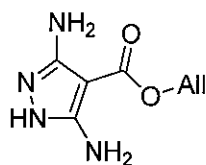
or a pharmaceutically acceptable salt thereof, by reacting a compound of formula 3:



3

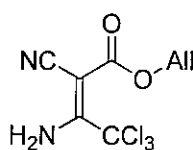
or a pharmaceutically acceptable salt thereof, under suitable condensation conditions to form a pyrimidine ring, wherein All is allyl.

169. The process of claim 168, further comprising the step of preparing the compound of formula 3:



3

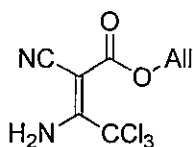
or a pharmaceutically acceptable salt thereof, by reacting a compound of formula 2:



2

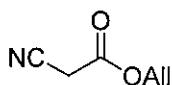
or a pharmaceutically acceptable salt thereof, under suitable condensation conditions to form a pyrazole ring, wherein All is allyl.

170. The process of claim 169, 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:

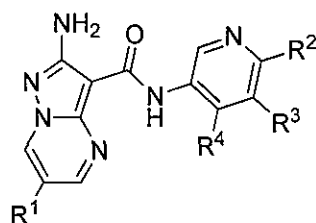


1

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

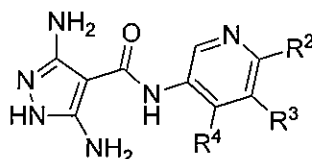
171. The process of claim 166, wherein R¹ is from halo or -CH₂CN.
172. The process of claim 171, wherein R¹ is fluoro or chloro.
173. The process of claim 167, wherein suitable deprotection conditions comprise reacting the compound of formula 4 with a silane in the presence of a metal catalyst.
174. The process of claim 173, wherein the silane is phenylsilane.
175. The process of claim 174, wherein the metal catalyst is a palladium catalyst.
176. The process of claim 175, wherein the metal catalyst is Pd(PPh₃)₄.
177. The process of claim 167, wherein suitable deprotection conditions comprise reacting the compound of formula 4 with an aqueous alkali.
178. The process of claim 177, wherein the aqueous alkali is LiOH, NaOH, or KOH.
179. The process of claim 168, 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.
180. The process of claim 179, wherein the 1,3-dielectrophilic species is 1,3-dialdehyde or 3-(dialkylamino)-prop-2-enal.
181. The process of any one of claims 179 or 180, wherein the solvent is DMF or DMSO.
182. The process of claim 179, wherein the 1,3-dielectrophilic species is generated *in situ* from a protected 1,3-dielectrophilic species.

183. The process of claim 182, wherein the 1,3-dielectrophilic species is generated from a ketal in the presence of a sulfonic acid.
184. The process of claim 183, wherein the sulfonic acid is PTSA.
185. The process of claim 169, 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.
186. The process of claim 185, wherein the aprotic solvent is DMF.
187. The process of claim 185, wherein the basic conditions comprise reacting the compound of formula **2** in the presence of potassium acetate or sodium acetate.
188. The process of claim 170, 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.
189. The process of claim 188, wherein the base is potassium acetate.
190. The process of claim 188, wherein the solvent is an alcohol.
191. The process of claim 190, wherein the solvent is isopropylalcohol.
192. A process for preparing a compound of formula **I-A**:



I-A

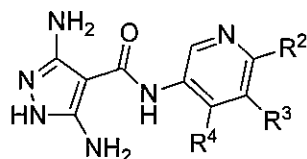
or a pharmaceutically acceptable salt thereof, comprising reacting a compound of formula 9:



9

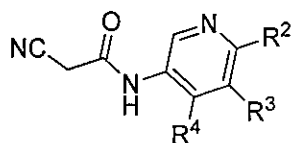
or a pharmaceutically acceptable salt thereof, under suitable condensation conditions to form a pyrimidine ring, wherein R¹, R², R³ and R⁴ are as defined in claims 1-106.

193. The process of claim 192, further comprising the step of preparing a compound of formula 9:



9

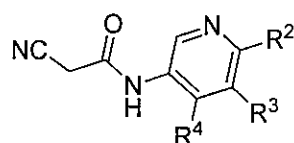
or a pharmaceutically acceptable salt thereof, by reacting a compound of formula 8:



8

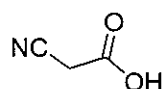
or a pharmaceutically acceptable salt thereof, under suitable condensation conditions to form a pyrazole ring.

194. The process of claim 193, further comprising the step of preparing a compound of formula 8:



8

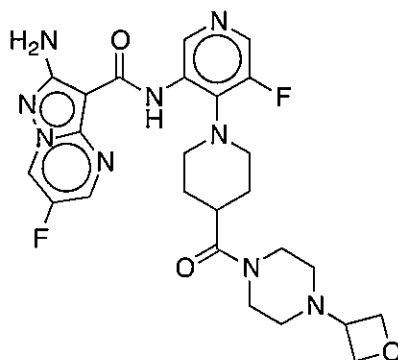
or a pharmaceutically acceptable salt thereof, by reacting a compound of formula 7:



7

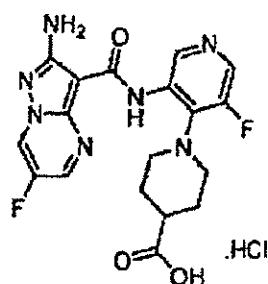
or a pharmaceutically acceptable salt thereof, under suitable conditions to form an amide bond.

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



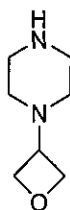
I-G-32

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



30

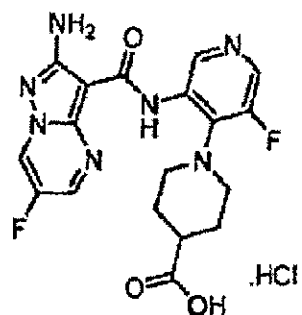
with a compound of formula **25**:



25

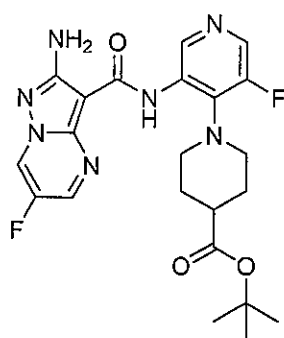
or a pharmaceutically acceptable salt thereof, under suitable conditions to form an amide bond.

196. The process of claim 195, further comprising the step of preparing the compound of formula **30**:



30

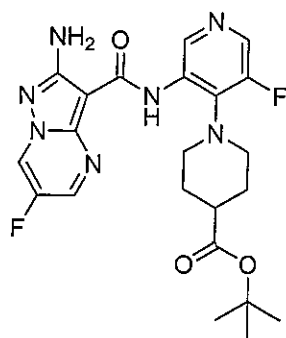
by reacting the compound of formula **28**:



28

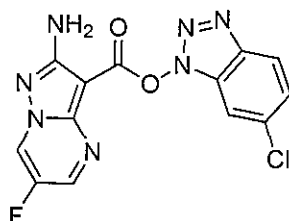
or a pharmaceutically acceptable salt thereof, under suitable deprotection conditions to form the carboxylic acid.

197. The process of claim 196, further comprising the step of preparing a compound of formula **28**:



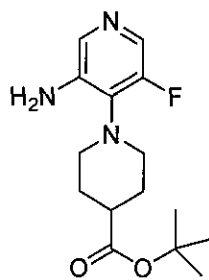
28

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**:



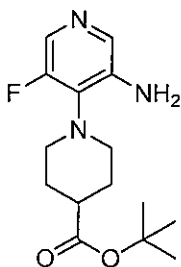
27

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

198. The process of claim 195, 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.
199. The process of claim 198, wherein the aprotic solvent is NMP, DMF, or tetrahydrofuran.
200. The process of claim 199, wherein the aprotic solvent is tetrahydrofuran.
201. The process of claim 199, wherein the base is an aliphatic amine.
202. The process of claim 201, wherein the base is DIPEA.
203. The process of any one of claims 198-202, wherein the amide coupling partner is TBTU or TCTU.
204. The process of claim 203, wherein the amide coupling partner is TCTU.
205. The process of claim 196, wherein suitable deprotection conditions comprise reacting the compound of formula **28** with an acid in the presence of a solvent.
206. The process of claim 205, wherein the acid is HCl.
207. The process of claim 206, wherein the solvent is 1,4-dioxane.
208. The process of claim 197, 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.
209. The process of claim 208, wherein the aprotic solvent is NMP, pyridine, or DMF.
210. The process of claim 209, wherein the aprotic solvent is pyridine.

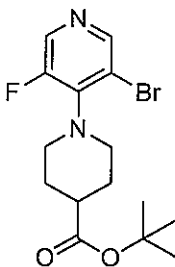
211. The process of any one of claims 208, wherein the reaction is carried out at a temperature of at least 80°C.

212. A process of preparing a compound of formula **27**:



27

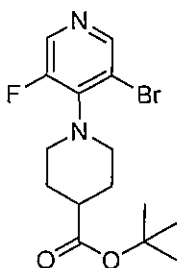
or a pharmaceutically acceptable salt thereof, comprising the step of reacting a compound of formula **26**:



26

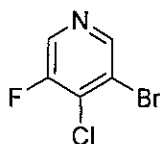
or a pharmaceutically acceptable salt thereof, under suitable conditions to form an amine.

213. The process of claim 212, further comprising the step of preparing a compound of formula **26**:



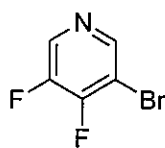
26

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



18

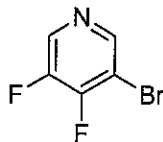
or a pharmaceutically acceptable salt thereof, under suitable halogen exchange conditions to generate the compound of formula **32**



32

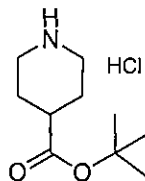
or a pharmaceutically acceptable salt thereof, and

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



32

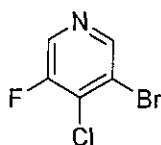
or a pharmaceutically acceptable salt thereof, with a compound of formula **22**:



22

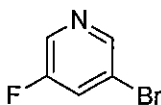
or a pharmaceutically acceptable salt thereof, under suitable displacement conditions.

214. The process of claim 210, further comprising the step of preparing a compound of formula **18**:



18

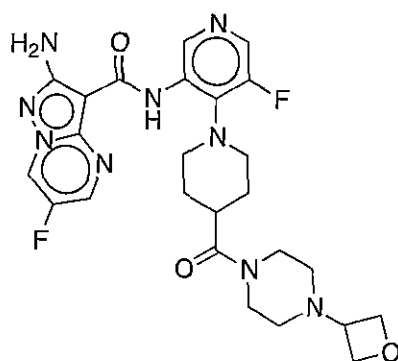
or a pharmaceutically acceptable salt thereof, by reacting the compound of formula **31**:



31

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

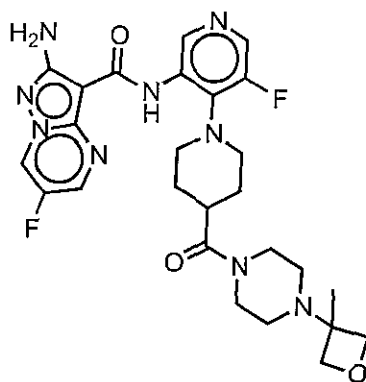
215. A compound **I-G-32**:



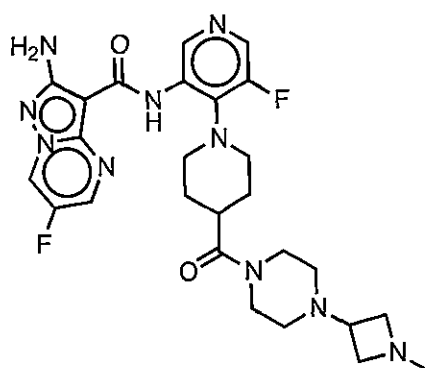
I-G-32

or a pharmaceutically acceptable salt thereof.

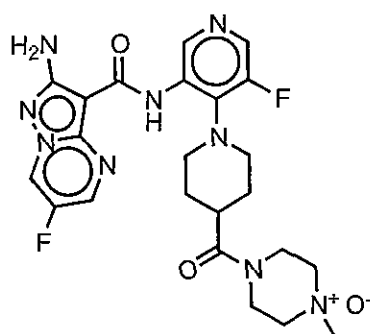
216. A compound, wherein the compound is:



I-G-92



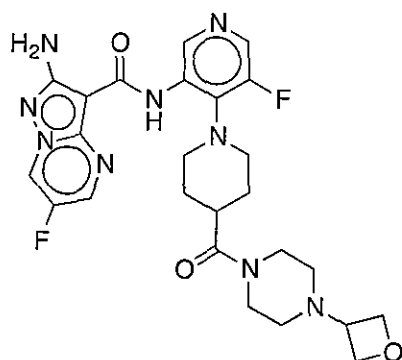
I-G-95,



I-G-96,

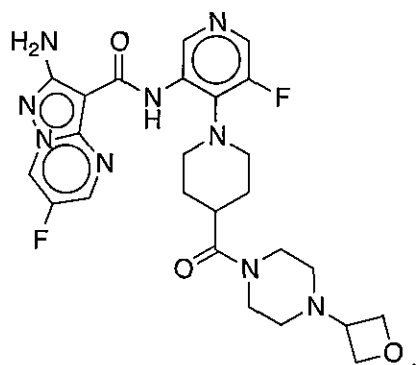
or a pharmaceutically acceptable salt thereof.

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



or a pharmaceutically acceptable salt thereof;
and a pharmaceutically acceptable carrier.

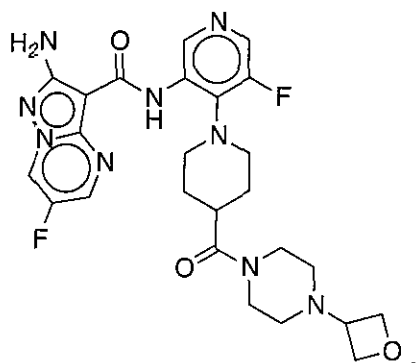
218. The compound of claim 215, wherein the compound is a pharmaceutically acceptable



salt of

219. A pharmaceutical composition comprising the compound of claim 218 and a pharmaceutically acceptable carrier.

220. The compound of claim 215, wherein the compound is compound I-G-32:



221. A pharmaceutical composition comprising the compound of claim 220, and a pharmaceutically acceptable carrier.

222. 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. *[[Support: PCT claim 166]]*

223. The compound for use according to claim 109, or a pharmaceutically acceptable salt thereof, wherein said Topo II inhibitor is etoposide, Daunorubicin, Doxorubicin, Aclarubicin, Epirubicin, idarubicin, amrubicin, pirarubicin, Valrubicin, Zorubicin, or Teniposide. *[[Support: PCT claim 166]]*

224. 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. *[[Support: PCT claim 166]]*

225. The compound for use according to claim 109, or a pharmaceutically acceptable salt thereof, wherein said alkylating agent is Mechlorethamine, Cyclophosphamide,

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. *[[Support: PCT claim 166]]*

226. The compound for use according to claim 222, or a pharmaceutically acceptable salt thereof, wherein said Topo I inhibitor is Camptothecin, Topotecan, Irinotecan/SN38, or Rubitecan. *[[Support: PCT claim 167]]*

227. The compound for use according to claim 223, or a pharmaceutically acceptable salt thereof, wherein said Topo II inhibitor is etoposide. *[[Support: PCT claim 167]]*

228. The compound for use according to claim 224, or a pharmaceutically acceptable salt thereof, wherein said antimetabolite is methotrexate, pemetrexed, Thioguanine, Fludarabine, Cladribine, Cytarabine, gemcitabine, 6-Mercaptopurine, or 5-Fluorouracil. *[[Support: PCT claim 167]]*

229. The compound for use according to claim 225, or a pharmaceutically acceptable salt thereof, wherein said alkylating agent is selected from the group consisting of nitrogen mustards, nitrosoureas, triazenes, alkyl sulfonates, Procarbazine, and aziridines. *[[Support: PCT claim 167]]*

230. 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. *[[Support: PCT claim 167]]*

231. 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.

[[Support: PCT claim 176]]

232.The compound for use according to claim 121, or a pharmaceutically acceptable salt thereof, wherein said cancer is a cardiac cancer selected from the group consisting of sarcomas, myxomas, rhabdomyomas, fibromas, lipomas, and teratomas. *[[Support: PCT claim 176]]*

233.The compound for use according to claim 121, or a pharmaceutically acceptable salt thereof, 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. *[[Support: PCT claim 176]]*

234.The compound for use according to claim 121, or a pharmaceutically acceptable salt thereof, 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. *[[Support: PCT claim 176]]*

235.The compound for use according to claim 121, or a pharmaceutically acceptable salt thereof, 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. *[[Support: PCT claim 176]]*

236.The compound for use according to claim 121, or a pharmaceutically acceptable salt thereof, said cancer is a liver cancer selected from the group consisting of hepatomas, cholangiocarcinomas, hepatoblastomas, angiosarcomas, hepatocellular adenomas, hemangiomas, and biliary passage cancers. *[[Support: PCT claim 176]]*

237. The compound for use according to claim 121, or a pharmaceutically acceptable salt thereof, 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. *[[Support: PCT claim 176]]*
238. The compound for use according to claim 121, or a pharmaceutically acceptable salt thereof, wherein said cancer is a nervous system cancer selected from the group consisting of skull cancers, meninges cancers, brain cancers, spinal cord cancers, neurofibromas, meningiomas, gliomas, and sarcomas. *[[Support: PCT claim 176]]*
239. The compound for use according to claim 121, or a pharmaceutically acceptable salt thereof, 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. *[[Support: PCT claim 176]]*
240. The compound for use according to claim 121, or a pharmaceutically acceptable salt thereof, 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. *[[Support: PCT claim 176]]*
241. The compound for use according to claim 121, or a pharmaceutically acceptable salt thereof, 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. *[[Support: PCT claim 176]]*

242.The compound for use according to claim 121, or a pharmaceutically acceptable salt thereof, wherein said adrenal glands cancer is a neuroblastoma. *[[Support: PCT claim 176]]*

243.The compound for use according to claim 157, 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.

244.The compound for use according to claim 162, 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.