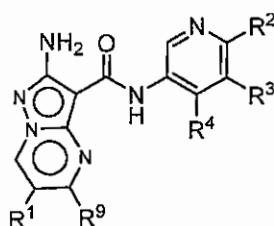


CLAIMS

We claim:

1. A compound having the formula I:



I

or a pharmaceutically acceptable salt or prodrug 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 independently selected from Q^1 or a C_{1-10} aliphatic chain wherein up to four methylene units of the aliphatic chain are optionally replaced with -O-, -NR-, -C(O)-, or -S(O) $_n$; each R^4 is optionally substituted with 0-5 occurrences of J^Q ; or

R^3 and R^4 , taken together with the atoms to which they are bound, form a 5-6 membered aromatic or non-aromatic ring having 0-2 heteroatoms selected from oxygen, nitrogen or sulfur; the ring formed by R^3 and R^4 is optionally substituted with 0-3 occurrences of J^Z ;

Q^1 is independently selected from a 3-7 membered fully saturated, partially unsaturated, or aromatic monocyclic ring, the 3-7 membered 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^Z is independently selected from C_{1-6} aliphatic =O, halo, or $\rightarrow O$;

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 Q^1 , 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; $\rightarrow$ O; =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 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;

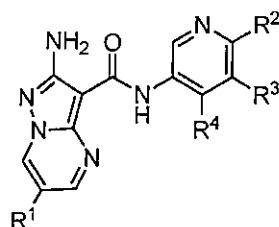
J^M is independently selected from halo or C_{1-6} aliphatic;

n is 0, 1 or 2; and

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

2. The compound of any one of claims 1, wherein R^9 is H.
3. The compound of any one of claims 1-2, wherein R^9 is M.
4. The compound of claim 3, wherein M is a C_{1-8} aliphatic wherein up to three methylene units are optionally replaced with -O- or -NR-.
5. The compound of claim 4, wherein, M is C_{1-4} alkyl, -(C_{1-4} alkyl)O(C_{1-3} aliphatic), -(C_{1-3} alkyl)OH, -O(C_{1-4} alkyl)N(C_{1-2} alkyl)₂, -NH(C_{1-4} alkyl), or -(C_{1-4} alkyl)NH(C_{1-4} alkyl).

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 C₁₋₃aliphatic 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 0-3 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 or prodrug 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 independently selected from Q^1 or a $C_{1-10}aliphatic$ chain wherein up to four methylene units of the aliphatic chain are optionally replaced with $-O-$, $-NR-$, $-C(O)-$, or $-S(O)_n$; each R^4 is optionally substituted with 0-5 occurrences of J^Q ; or

R^3 and R^4 , taken together with the atoms to which they are bound, form a 5-6 membered aromatic or non-aromatic ring having 0-2 heteroatoms selected from oxygen, nitrogen or sulfur; the ring formed by R^3 and R^4 is optionally substituted with 0-3 occurrences of J^Z ;

Q^1 is independently selected from a 3-7 membered fully saturated, partially unsaturated, or aromatic monocyclic ring, the 3-7 membered 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^Z is independently selected from $C_{1-6}aliphatic$, $=O$, halo, or $\rightarrow O$;

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 Q^1 , 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; $=\text{O}$; $\rightarrow\text{O}$; 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 $-\text{CN}$; $=\text{O}$; 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 halo, $-\text{CN}$; $=\text{O}$; 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; or

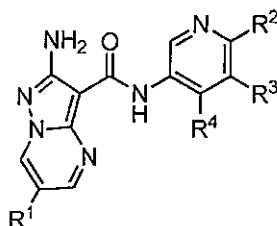
two occurrences of J^T , together with Q^3 , form a 6-10 membered saturated or partially unsaturated bridged ring system;

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

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

n is 0, 1 or 2; and

21. A compound having the formula I-A:



I-A

or a pharmaceutically acceptable salt or prodrug thereof, wherein:

R¹ is independently selected from fluoro, chloro, or -C(F)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 a 3-4 membered optionally substituted carbocyclic ring;

R² is independently selected from 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;

R³ is independently selected from H; halo; 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;

R⁴ is independently selected from Q¹ or a C₁₋₁₀aliphatic chain wherein up to four methylene units of the aliphatic chain are optionally replaced with -O-, -NR-, -C(O)-, or -S(O)_n-; each R⁴ is optionally substituted with 0-5 occurrences of J^Q; or

R³ and R⁴, taken together with the atoms to which they are bound, form a 5-6 membered non-aromatic ring having 0-2 heteroatoms selected from oxygen, nitrogen or sulfur; the ring formed by R³ and R⁴ is optionally substituted with 0-3 occurrences of J^Z;

Q¹ is independently selected from a 3-7 membered fully saturated, partially unsaturated, or aromatic monocyclic ring, the 3-7 membered 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^Z is independently selected from C₁₋₆aliphatic, =O, halo, or ->O;

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 Q^1 , 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; 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 -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 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;

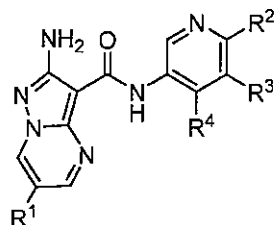
two occurrences of J^T , together with Q^3 , form a 6-10 membered saturated or partially unsaturated bridged ring system;

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 or prodrug 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 independently selected from Q^1 or a C_{1-16} aliphatic chain wherein up to three methylene units of the aliphatic chain are optionally replaced with $-O-$, $-NR-$, or $-S-$; each R^4 is optionally substituted with 0-5 occurrences of J^Q ; or

R^3 and R^4 , taken together with the atoms to which they are bound, form a 5-6 membered non-aromatic ring having 0-2 heteroatoms selected from oxygen, nitrogen or sulfur; the ring formed by R^3 and R^4 is optionally substituted with 0-3 occurrences of J^Z ;

Q^1 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^Z is independently selected from C_{1-6} aliphatic, $=O$, halo, or $\rightarrow O$;

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 Q^1 , 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; $\rightarrow O$; 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;

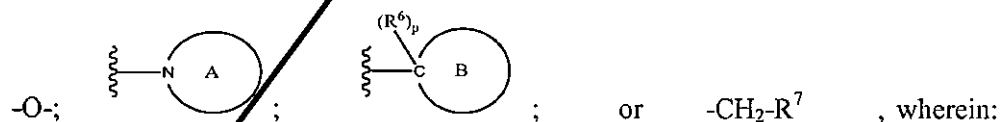
n is 1 or 2; and

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 $-\text{CH}_2\text{CN}$, $-\text{C}(\text{CH}_3)_2\text{CN}$ or $-\text{CH}(\text{C}_{1-2}\text{alkyl})\text{CN}$.

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 $-\text{CF}_3$, $-\text{NH}(\text{C}_{1-2}\text{alkyl})$, 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 , $-\text{CN}$, cyclopropyl, or $\text{C}_{1-4}\text{alkyl}$.
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 any one of claims 1-33, wherein R^4 is independently selected from:



$-\text{O}-$ is substituted with one J^Q ;

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;

Ring B 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;

R⁶ is H;

R⁷ is independently selected from H or a C₁₋₈ aliphatic chain wherein up to three methylene units of the aliphatic chain are optionally replaced with -O-, -NR-, -S-, -C(O)-, or -S(O)_p, and

p is 0 or 1.

35. The compound of claim 34, wherein R⁴ is -O-.

36. The compound of claim 35, wherein J^Q is independently selected from -(C₁₋₄alkyl), -(C₁₋₄alkyl)N(C₁₋₄alkyl)₂, -(C₁₋₃alkyl)O(C₁₋₂alkyl)N(C₁₋₃alkyl)₂, (C₁₋₄alkyl)OH, -(C₁₋₄alkyl)NH₂, or -(C₁₋₄alkyl)O(C₁₋₄alkyl).

37. The compound of claim 35, wherein J^Q is Q².

38. The compound of claim 37, wherein Q² is a 3-7 membered fully saturated, partially unsaturated, or aromatic monocyclic ring having 0-3 heteroatoms selected from oxygen, sulfur, or nitrogen.

39. The compound of claim 38, wherein Q² is independently selected from a 5-6 membered aryl, a 5-6 membered heteroaryl, a 4-6 membered cycloaliphatic, or a 3-7 membered heterocyclyl.

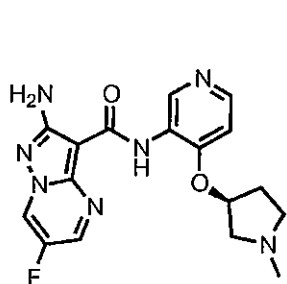
40. The compound of claim 39, wherein Q² is independently selected from a 4-7 membered cycloaliphatic or a 3-7 membered heterocyclyl.

41. The compound of claim 40, wherein Q² is a 3-7 membered heterocyclyl.

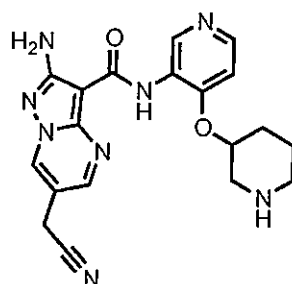
42. The compound of claim 41, wherein Q² is independently selected from pyrrolidinyl, piperidinyl, azepanyl, pyrazolidinyl, isoxazolidinyl, oxazolidinyl, thiazolidinyl, imidazolidinyl, piperazinyl, morpholinyl, thiomorpholinyl, 1,3-oxazinanyl, 1,3-thiazinanyl, dihydropyridinyl, dihydroimidazolyl, 1,3-tetrahydropyrimidinyl, dihydropyrimidinyl, 1,4-diazepanyl, 1,4-oxazepanyl, 1,4-thiazepanyl, tetrahydrothiopyranyl, tetrahydrofuranyl, tetrahydropyranyl, azetidiny, and oxetanyl.

43. The compound of claim 42, wherein Q^2 is independently selected from tetrahydrothiopyranyl, pyrrolidinyl, piperidinyl, piperazinyl, tetrahydrofuranyl, tetrahydropyranyl, or azetidiny.
44. The compound of claim 43, wherein Q^2 is piperidinyl.
45. The compound of claim 39, wherein Q^2 is a 5-6 membered heteroaryl.
46. The compound of claim 45, wherein Q^2 is independently selected from imidazolyl, pyrrolyl, pyridinyl, pyrazinyl, pyrimidinyl, pyrazolyl, 1,2,3-triazolyl, or 1,2,4-triazolyl.
47. The compound of claim 46, wherein Q^2 is pyridinyl.
48. The compound of claim 39, wherein Q^2 is a 4-6 membered cycloaliphatic.
49. The compound of claim 48, wherein Q^2 is independently selected from cyclobutyl or cyclohexyl.
50. The compound of claim 39, wherein Q^2 is phenyl.
51. The compound of claim 37, wherein Q^2 is an 7-12 membered fully saturated, partially unsaturated, or aromatic bicyclic ring having 0-5 heteroatoms selected from oxygen, nitrogen, or sulfur.
52. The compound of claim 51, wherein Q^2 is 6,7-dihydro-5H-pyrrolo[1,2-a]imidazole.
53. The compound of any one of claims 36-52, wherein J^R is C_{1-6} 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-.
54. The compound of claim 53, wherein J^R is independently selected from C_{1-4} alkyl, -N(C_{1-4} alkyl)₂, -C(O)OH, -C(O)O(C_{1-4} alkyl), -C(O)N(C_{1-4} alkyl)₂, -(C_{1-4} alkyl)O(C_{1-4} alkyl), or -C(O)-.
55. The compound of claim 54, wherein J^R is C_{1-4} alkyl.
56. The compound of any one of claims 36-52, wherein J^R is Q^3 .

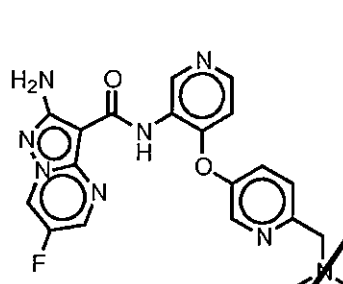
57. The compound of claim 56, wherein Q^3 is a 3-6 membered fully saturated, partially unsaturated, or aromatic monocyclic ring having 0-3 heteroatoms selected from oxygen, sulfur, or nitrogen.
58. The compound of claim 57, wherein Q^3 is a 3-6 membered heterocyclyl having 1-3 heteroatoms selected from oxygen, nitrogen, or sulfur.
59. The compound of claim 58, wherein Q^3 is independently independently selected from oxetanyl, piperidinyl, azetidiny, piperazinyl, pyrrolidinyl, morpholinyl.
60. The compound of claim 59, wherein Q^3 is oxetanyl.
61. The compound of claim 57, wherein Q^3 is cyclopropyl.
62. The compound of any one of claims 39-43, wherein J^R is =O or halo.
63. The compound of claim 39-43, wherein two occurrences of J^R on the same atom, taken together with the atom to which they are joined, form a 3-6 membered non-aromatic ring having 0-2 heteroatoms selected from oxygen, nitrogen, or sulfur.
64. The compound of claim 63, wherein the ring formed by the two occurrences of J^R on the same atom, taken together with the atom to which they are joined, is selected from oxetanyl, cyclobutyl, or azetidiny.
65. The compound of any one of claims 56-61, wherein J^T is a 4-6 membered heterocyclyl ring having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur.
66. The compound of claim 65, wherein J^T is piperazinyl.
67. The compound of any one of claims 34-66 independently selected from:



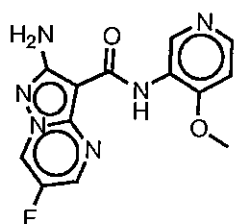
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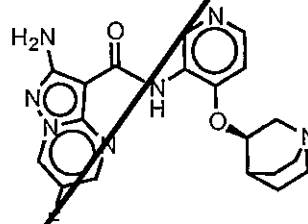
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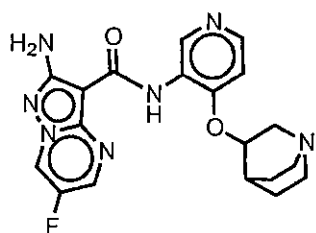
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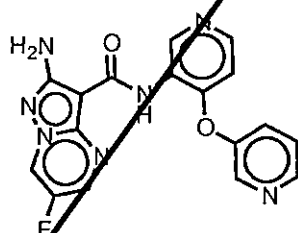
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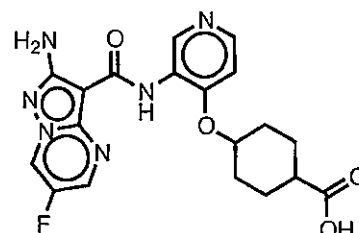
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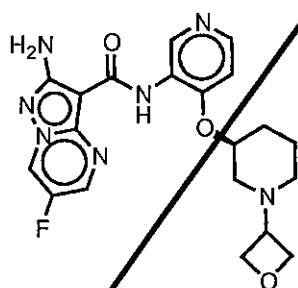
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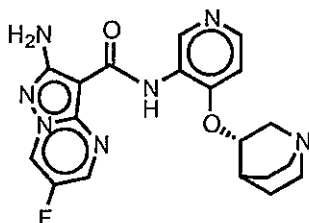
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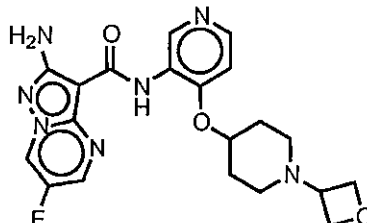
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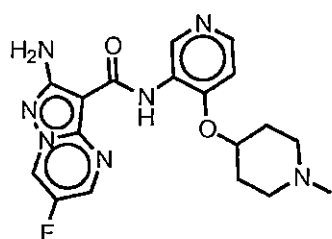
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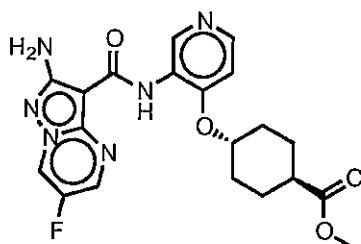
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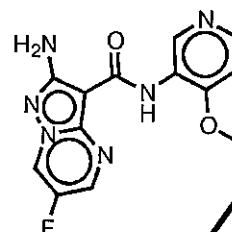
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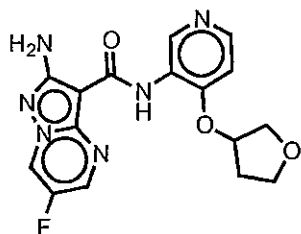
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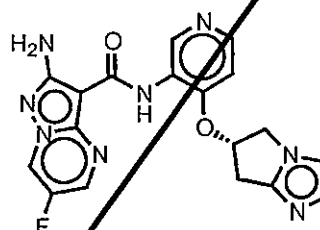
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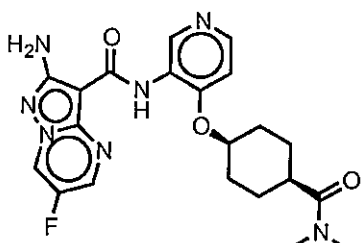
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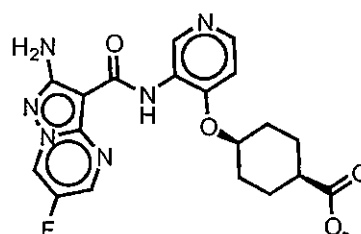
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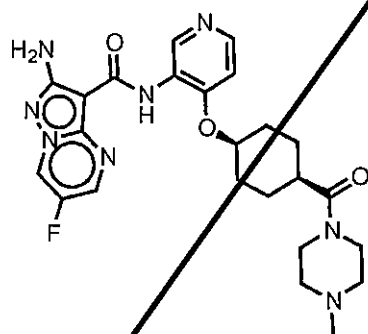
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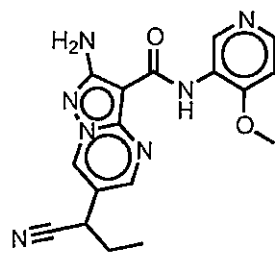
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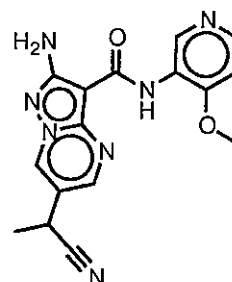
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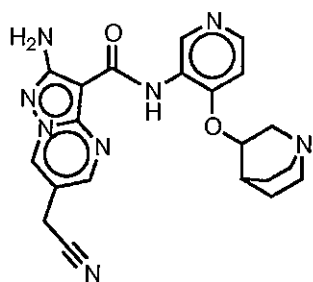
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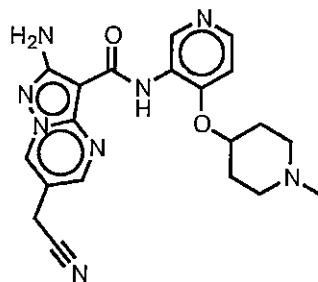
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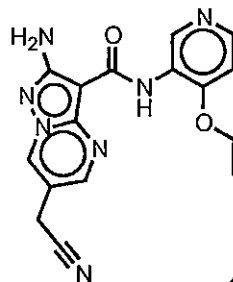
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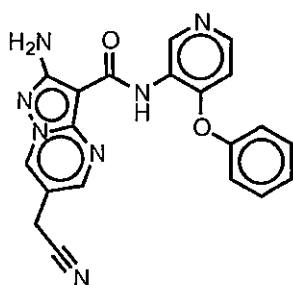
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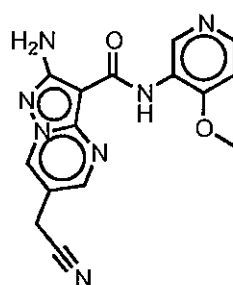
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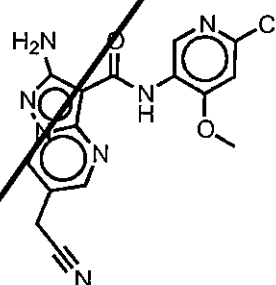
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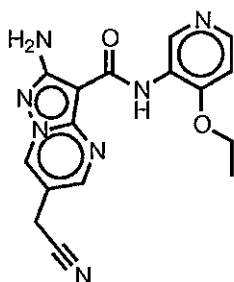
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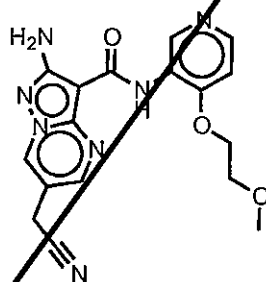
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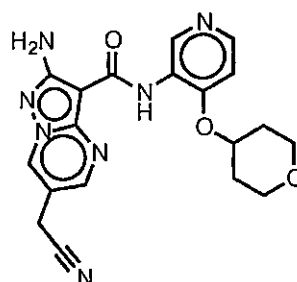
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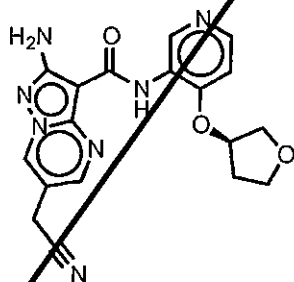
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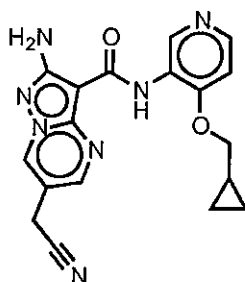
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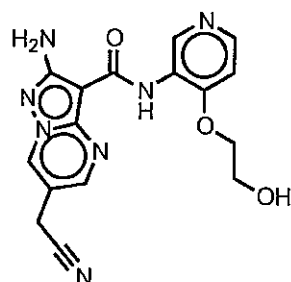
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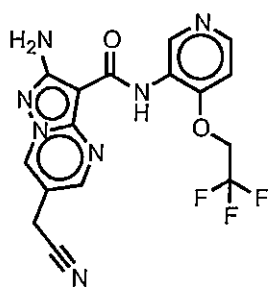
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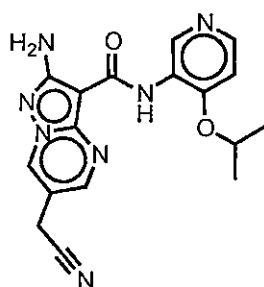
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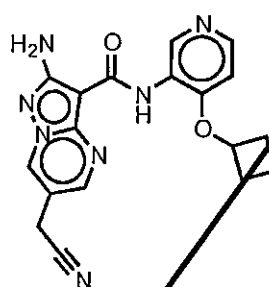
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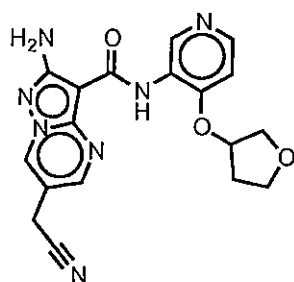
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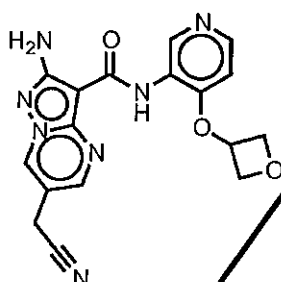
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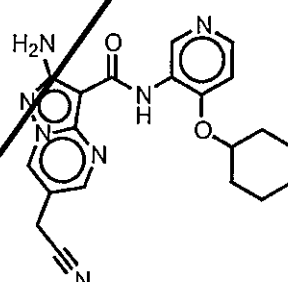
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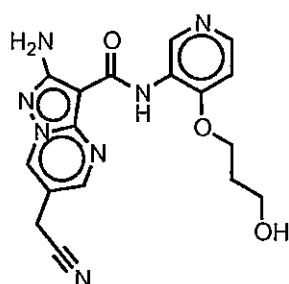
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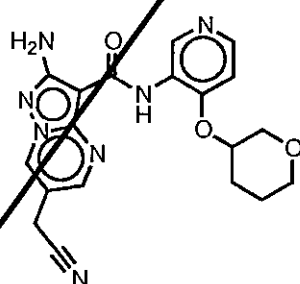
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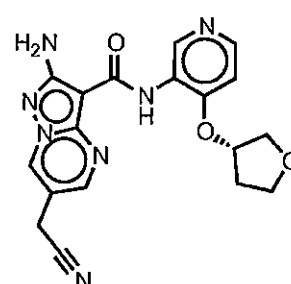
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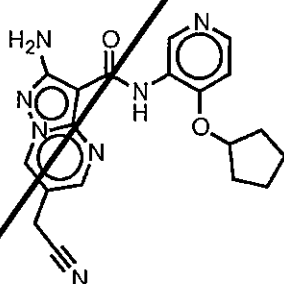
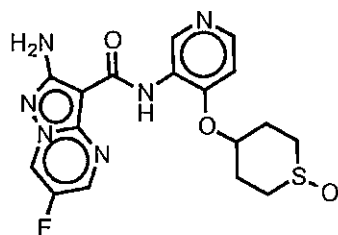
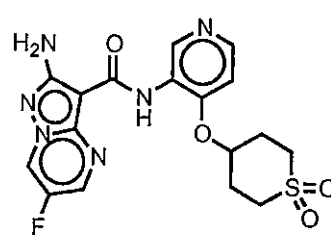
I-O-40



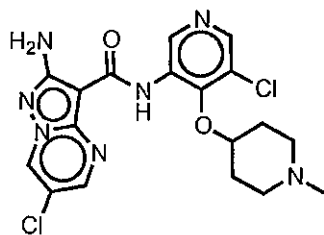
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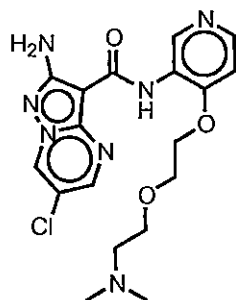
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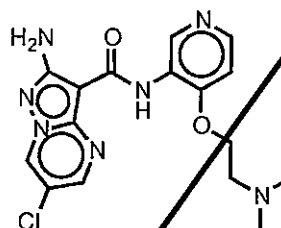
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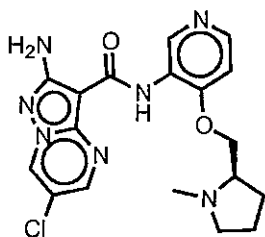
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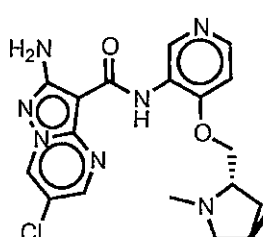
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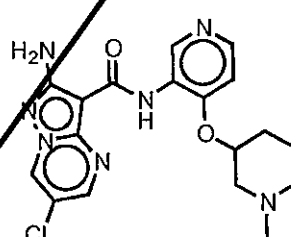
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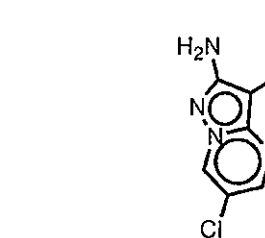
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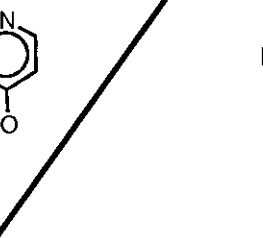
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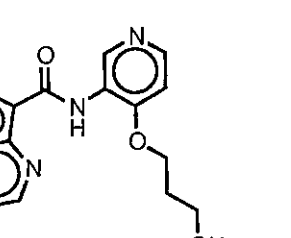
I-O-49



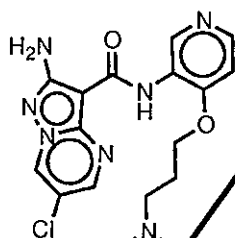
I-O-50



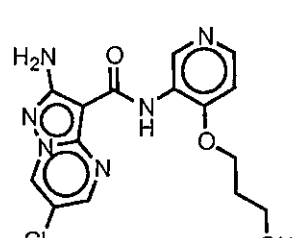
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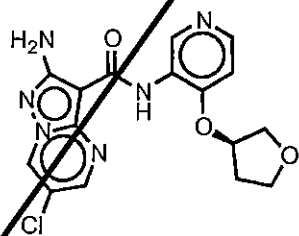
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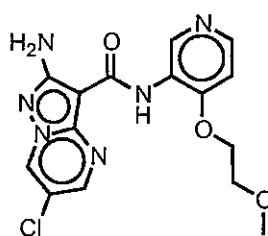
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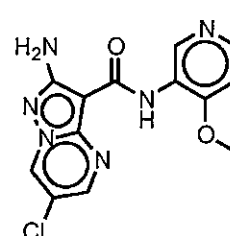
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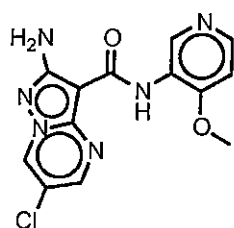


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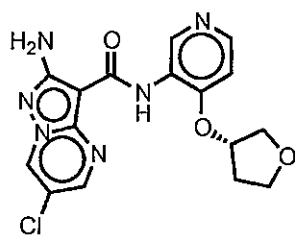


I-O-56

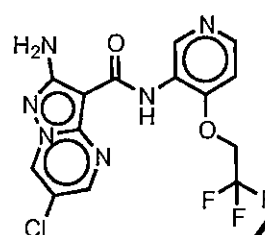




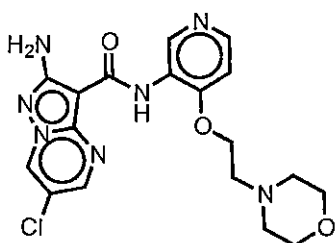
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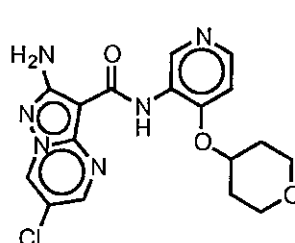
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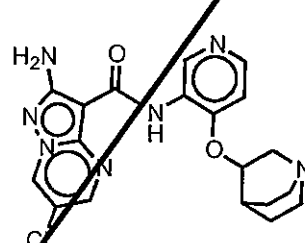
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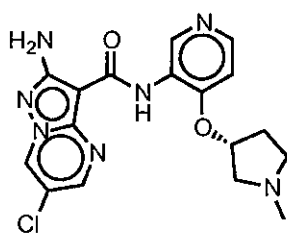
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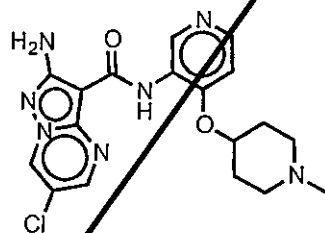
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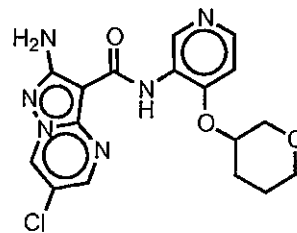
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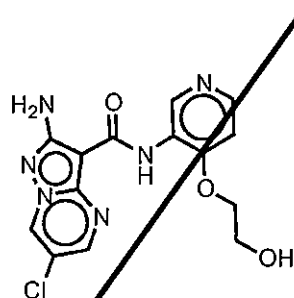
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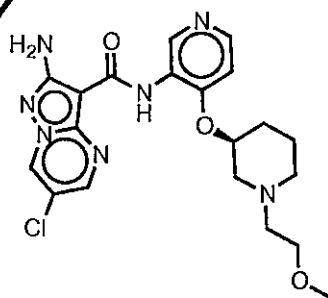
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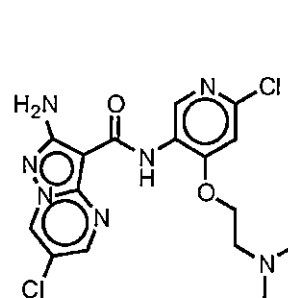
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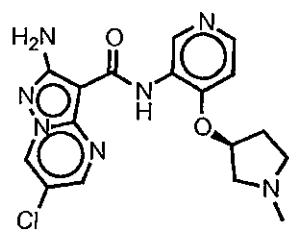
I-O-66



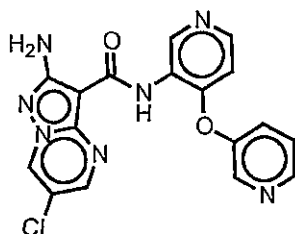
I-O-67



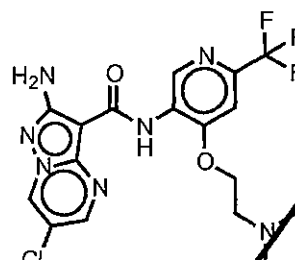
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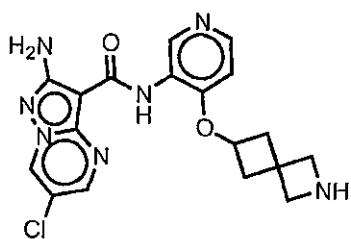
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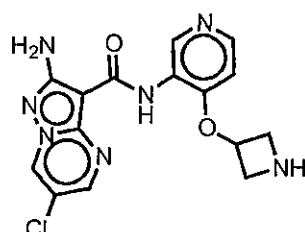
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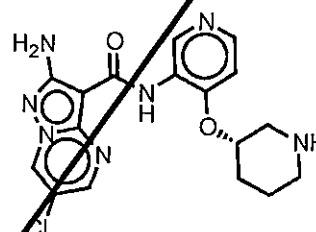
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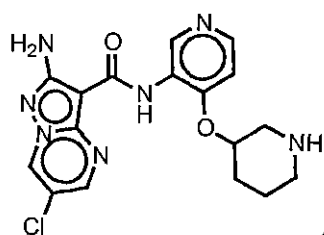
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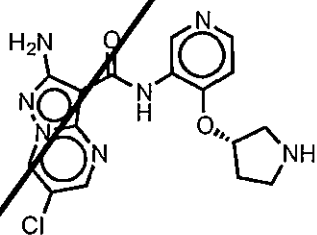
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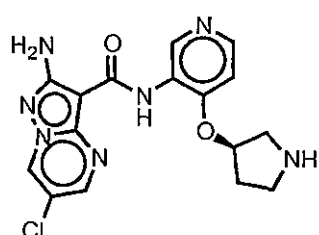
I-O-74



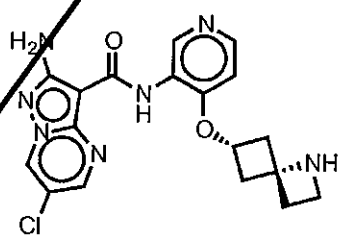
I-O-75



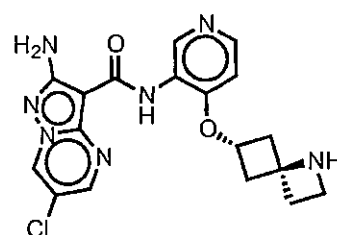
I-O-76



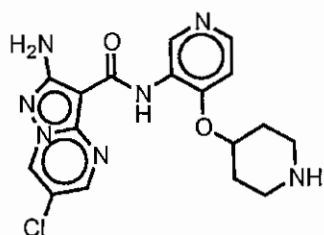
I-O-77



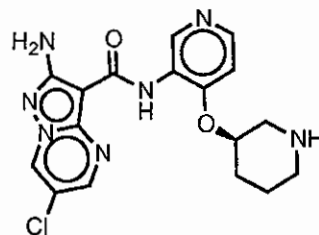
I-O-78



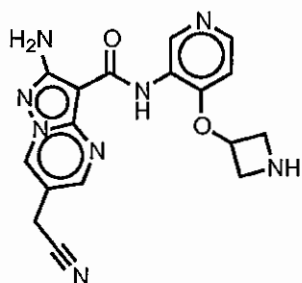
I-O-79



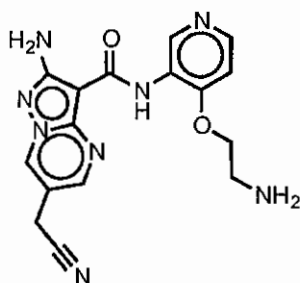
I-O-80



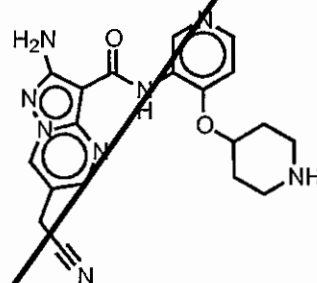
I-O-81



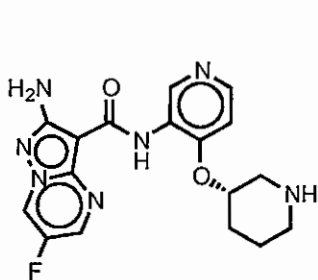
I-O-82



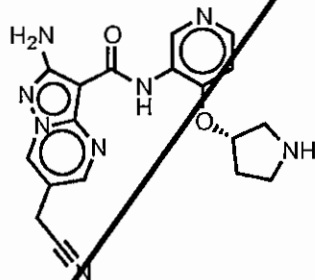
I-O-83



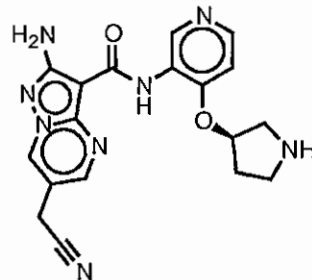
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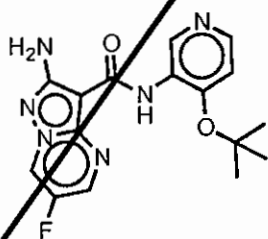
I-O-85



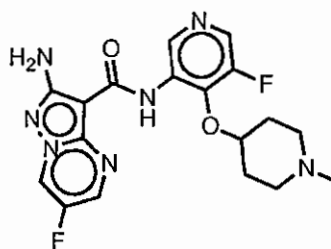
I-O-86



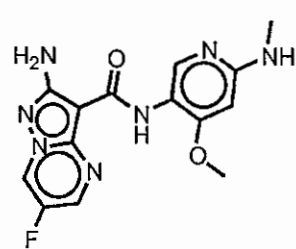
I-O-87



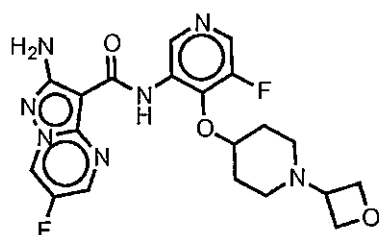
I-O-88



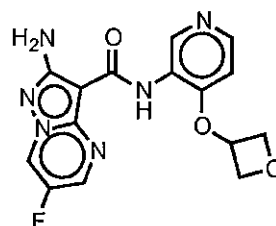
I-O-89



I-O-90

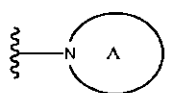


I-O-91



I-O-92

68. The compound of claim 34, wherein R⁴ is:



69. The compound of claim 68, 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.

70. The compound of claim 69, wherein Ring A is a 3-7 membered heterocyclyl.

71. The compound of claim 70, 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.

72. The compound of claim 71, wherein Ring A is independently selected from piperidinyl, piperazinyl, 1,4-diazepanyl, thiomorpholinyl, pyrrolidinyl, azepanyl, morpholinyl.

73. The compound of claim 72, wherein Ring A is independently selected from piperazinyl or piperidinyl.

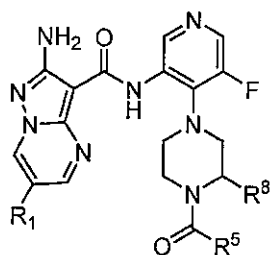
74. The compound of claim 69, wherein Ring A is a 5 membered heteroaryl.

75. The compound of claim 74, wherein Ring A is independently selected from pyrrolyl, imidazolyl, pyrazolyl, 1,2,3-triazolyl, or 1,2,4-triazolyl.

76. The compound of claim 75, wherein Ring A is independently selected from pyrazolyl or imidazolyl.
77. The compound of claim 68, 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.
78. The compound of claim 77, 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.
79. The compound of any one of claims 68-76, wherein J^P 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)-.
80. The compound of claim 79, wherein J^Q is independently selected from -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).
81. The compound of claim 80, wherein J^Q is C_{1-4} alkyl, -O-, or -C(O)-.
82. The compound of any one of claims 68-78, wherein J^Q is Q^2 .
83. The compound of claim 82, wherein Q^2 is a 3-7 membered heterocyclyl or carbocyclyl; the heterocyclyl having 1-3 heteroatoms selected from oxygen, nitrogen, or sulfur.
84. The compound of claim 83, wherein Q^2 is independently selected from selected from oxetanyl, tetrahydropyranyl, tetrahydrofuranyl, cyclopropyl, azetidiny, pyrrolidinyl, piperazinyl, cyclobutyl, thiomorpholinyl, or morpholinyl.
85. The compound of claim 84, wherein Q^2 is independently selected from oxetanyl, tetrahydropyranyl, or tetrahydrofuranyl.

86. The compound of claim 85, wherein Q^2 is oxetanyl.
87. The compound of claim 86, 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.
88. The compound of claim 87, wherein Q^2 is independently selected from 5,6,7,8-tetrahydroimidazo[1,5-a]pyrazinyl or 5,6,7,8-tetrahydroimidazo[1,2-a]pyrazinyl.
89. The compound of any one of claims 68-73, wherein two occurrences of J^Q , together with Ring A, form a bridged ring system.
90. The compound of any one of claims 68-78, wherein J^Q is $=O$ or $\rightarrow O$.
91. The compound of any one of claims 79-89, wherein J^R is a 3-6 membered heterocyclyl having 1-3 heteroatoms selected from oxygen, nitrogen, or sulfur.
92. The compound of claim 91, wherein J^R is independently selected from oxetanyl, piperadiny, azetidiny, piperazinyl, pyrrolidinyl, or morpholinyl.
93. The compound of claim 92, wherein J^R is a piperazinyl.
94. The compound of any one of claims 79-89, 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 $-(C_{0-4}alkyl)O(C_{1-4}alkyl)$.
95. The compound of any one of claims 82-89, 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.
96. The compound of claim 95, wherein J^R is independently selected from oxetanyl or azetidiny.
97. The compound of any one of claims 82-84, wherein two occurrences of J^R , together with Ring A, form a bridged ring system.

98. The compound of claim 93, wherein J^T is a 3-6 membered non-aromatic ring having 0-2 heteroatoms selected from oxygen, nitrogen, or sulfur.
99. The compound of claim 98, wherein J^T is oxytanyl.
100. The compound of claim 34 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.

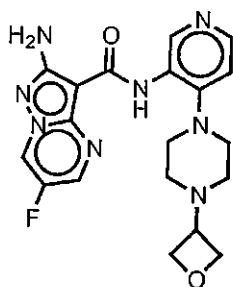
101. The compound of claim 100, wherein R^1 is fluoro.
102. The compound of claim 101, wherein R^5 is C_{1-4} aliphatic.
103. The compound of claim 102, wherein R^5 is independently selected from methyl or ethyl.
104. The compound of claim 100, wherein R^5 is a 3-6 membered cycloalkyl.
105. The compound of claim 104, wherein R^5 is cyclopropyl.
106. The compound of claim 100, wherein R^5 is a 3-6 membered heterocyclyl having 1-2 heteroatoms selected from oxygen or sulfur.
107. The compound of claim 106, wherein R^5 is tetrahydrofuranyl or oxytanyl.

108. The compound of claim 100, 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.

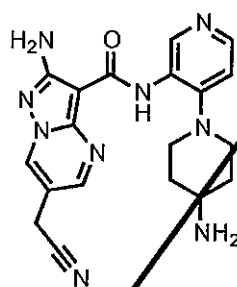
109. The compound of claim 108, wherein the ring formed by R^5 and R^6 is a five-membered ring.

110. The compound of claim 108, wherein the ring formed by R^5 and R^6 is a six-membered ring.

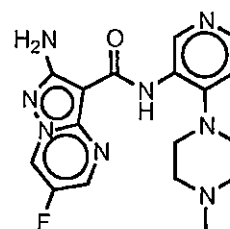
111. The compound of any one of claims 68-110 independently selected from:



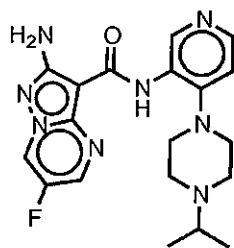
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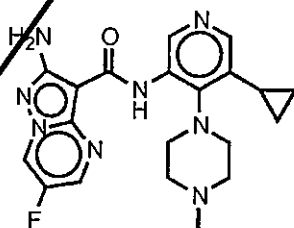
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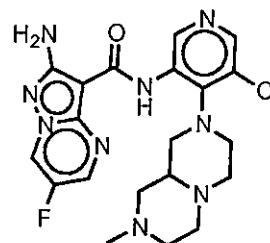
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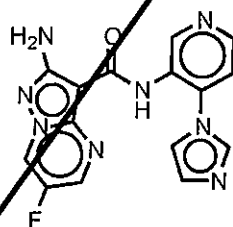
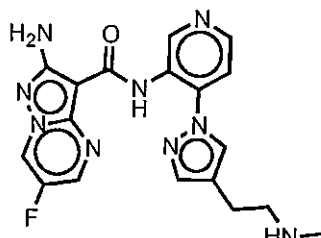
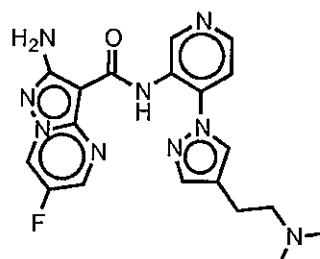
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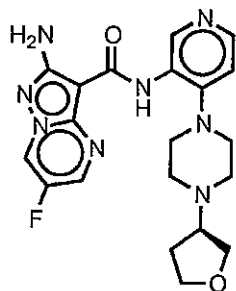
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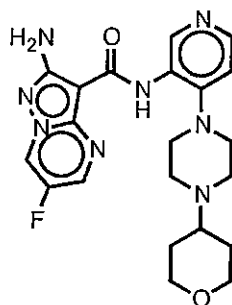
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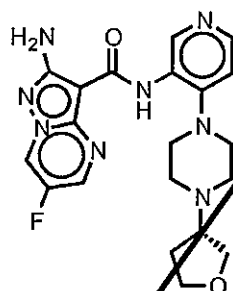
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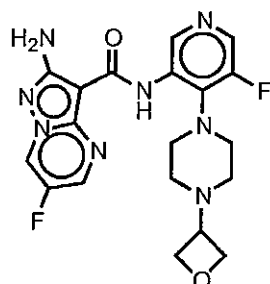
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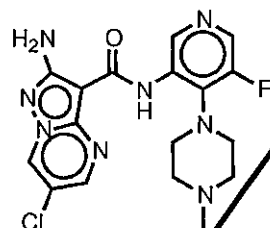
I-N-9



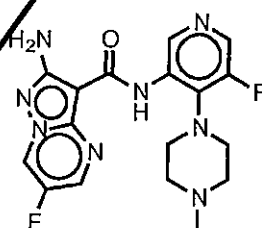
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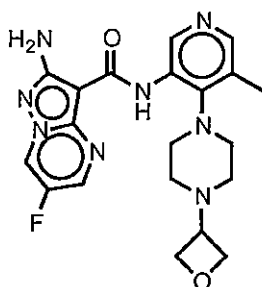
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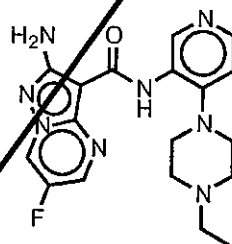
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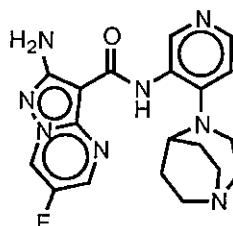
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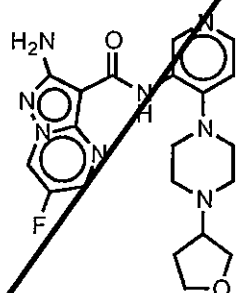
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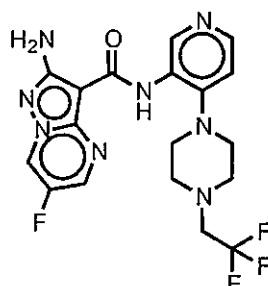
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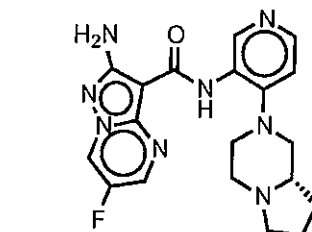
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I-N-17



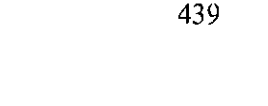
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I-N-19

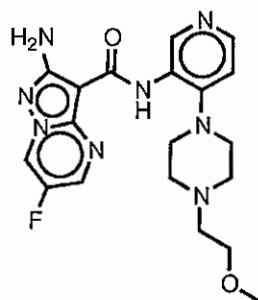


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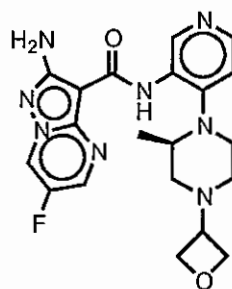


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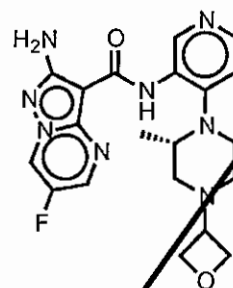




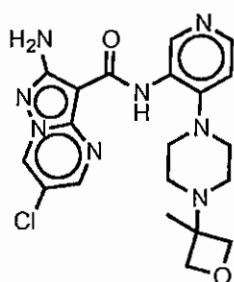
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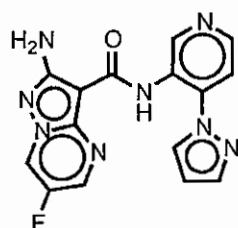
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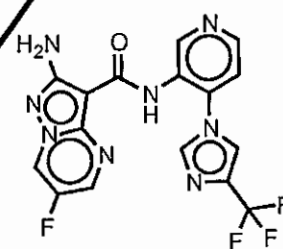
I-N-24



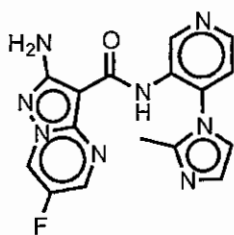
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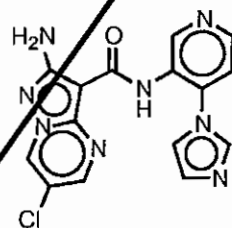
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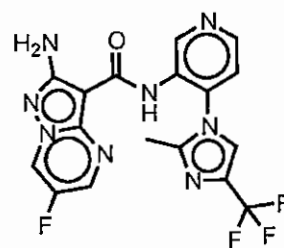
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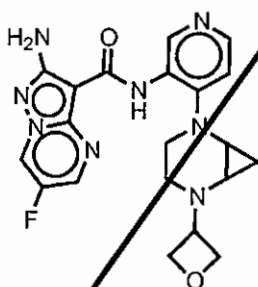
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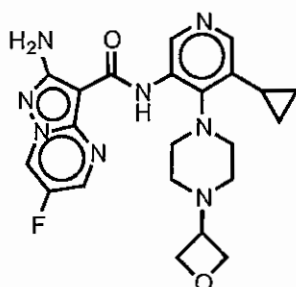
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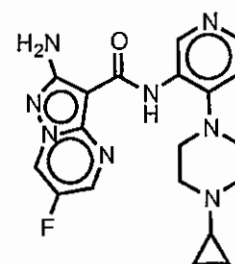
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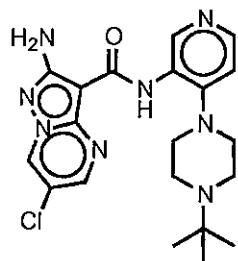
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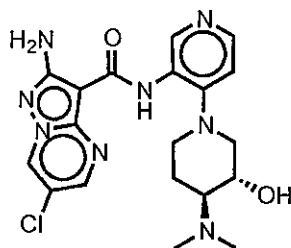
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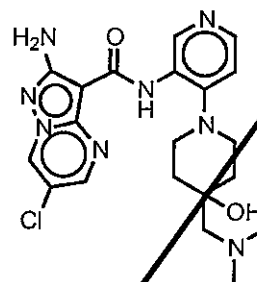
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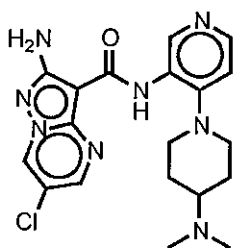
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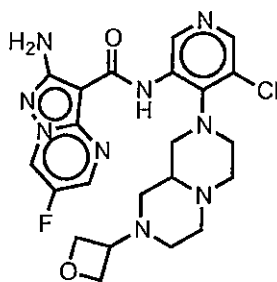
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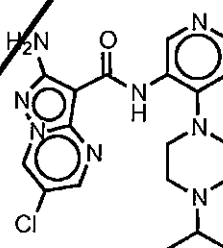
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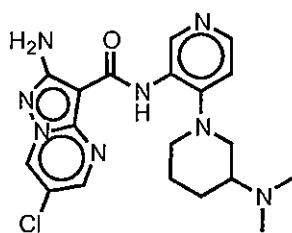
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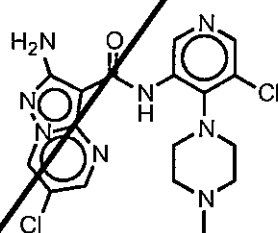
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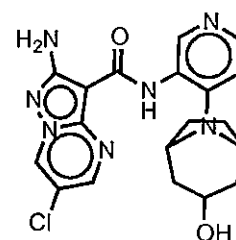
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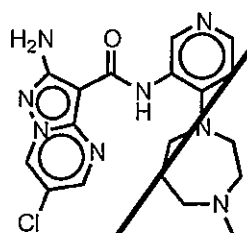
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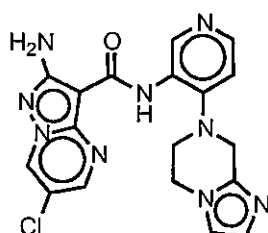
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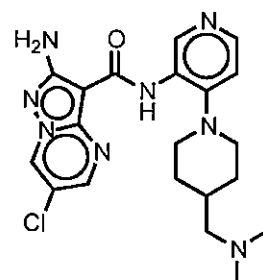
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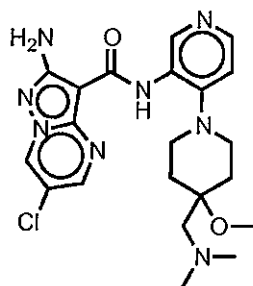
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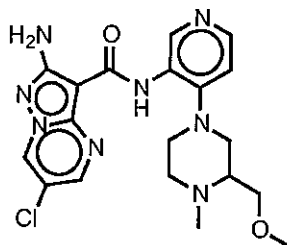
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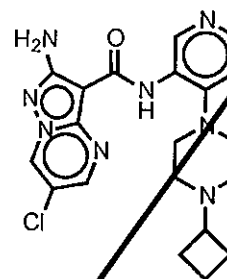
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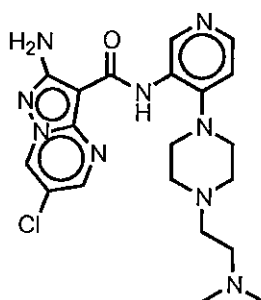
I-N-46



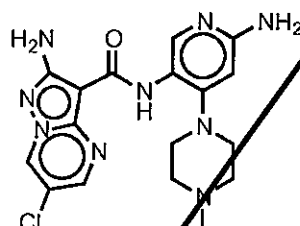
I-N-47



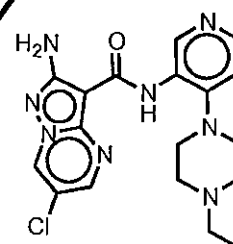
I-N-48



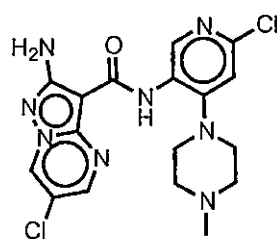
I-N-49



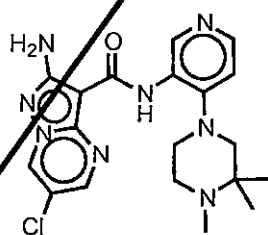
I-N-50



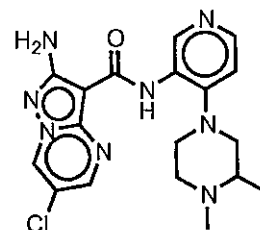
I-N-51



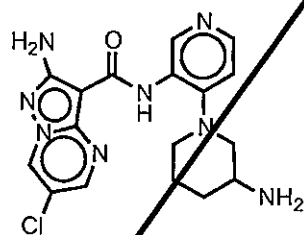
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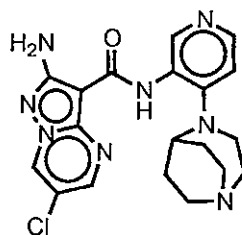
I-N-53



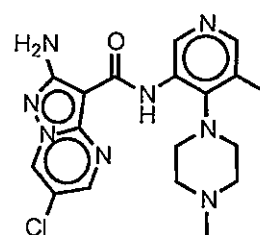
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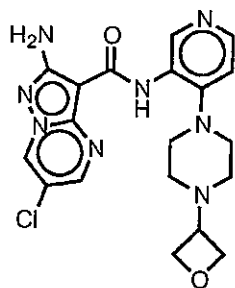
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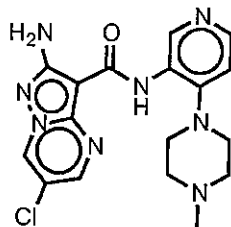
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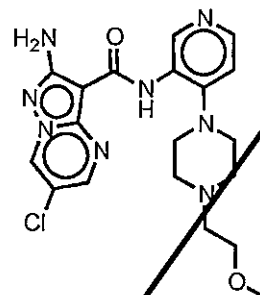
I-N-57



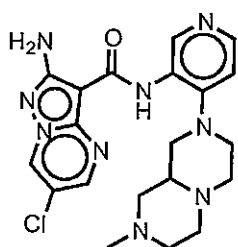
I-N-58



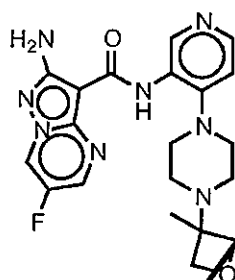
I-N-59



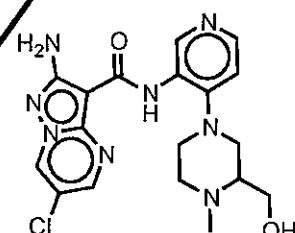
I-N-60



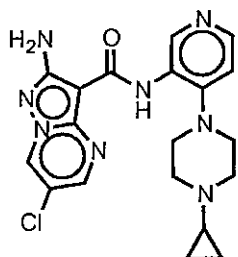
I-N-61



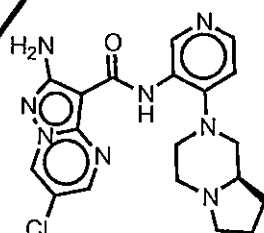
I-N-62



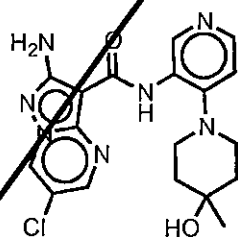
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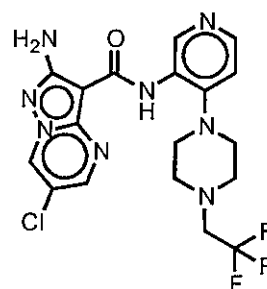
I-N-64



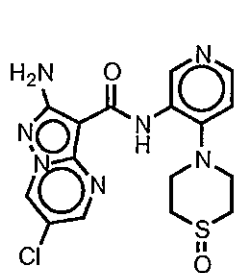
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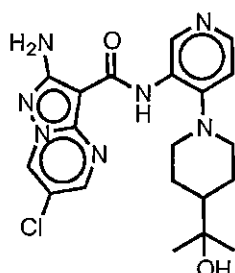
I-N-66



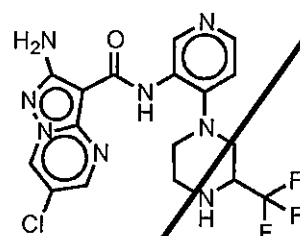
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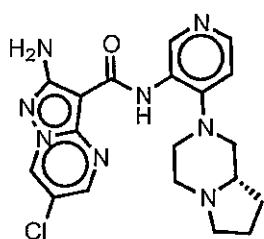
I-N-68



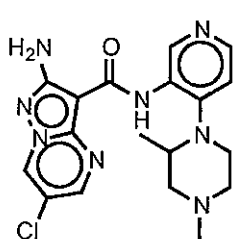
I-N-69



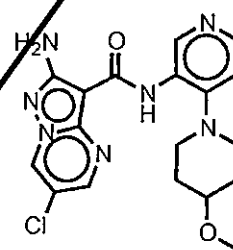
I-N-70



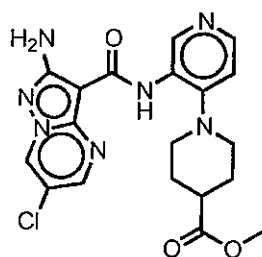
I-N-71



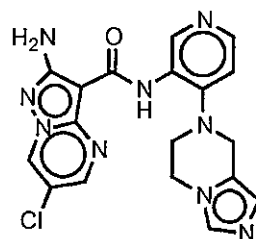
I-N-72



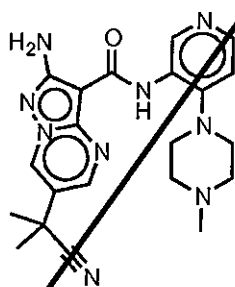
I-N-73



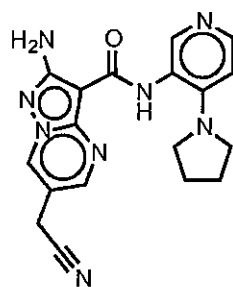
I-N-74



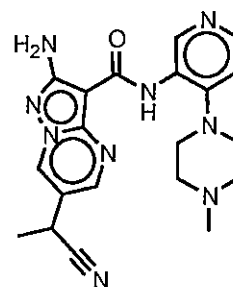
I-N-75



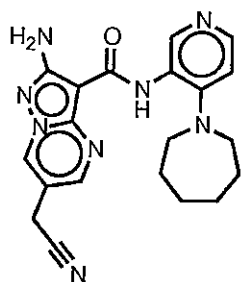
I-N-76



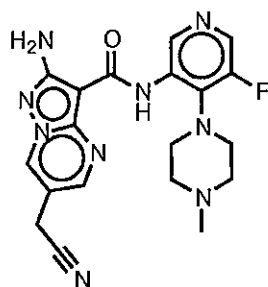
I-N-77



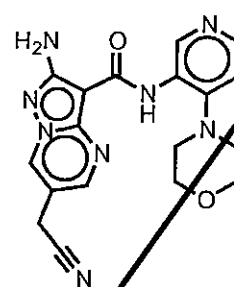
I-N-78



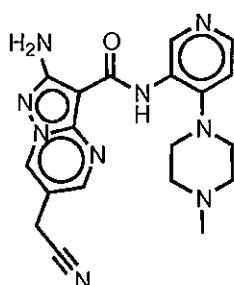
I-N-79



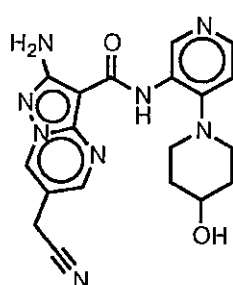
I-N-80



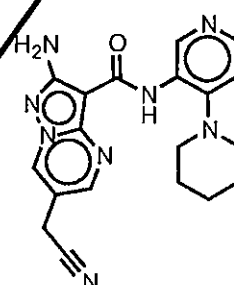
I-N-81



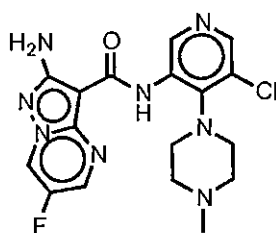
I-N-82



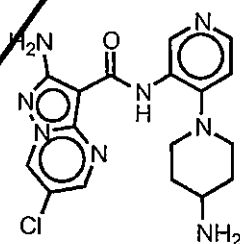
I-N-83



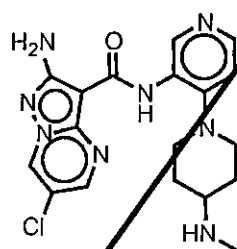
I-N-84



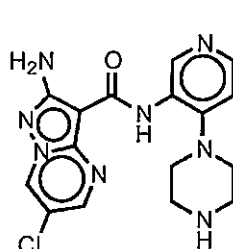
I-N-85



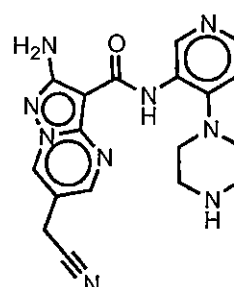
I-N-86



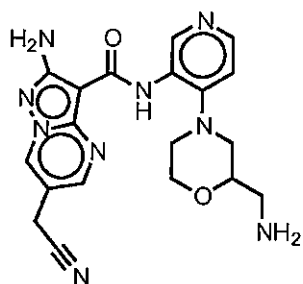
I-N-87



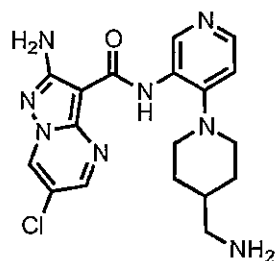
I-N-88



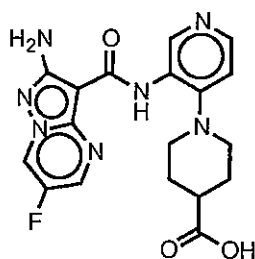
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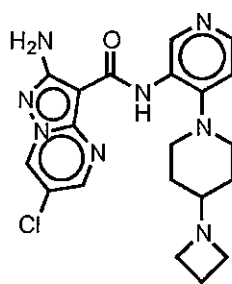
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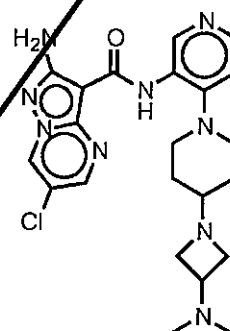
I-N-91



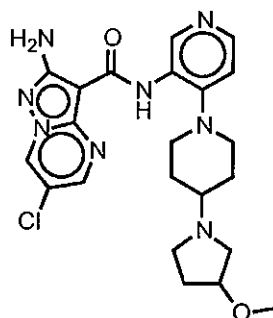
I-N-92



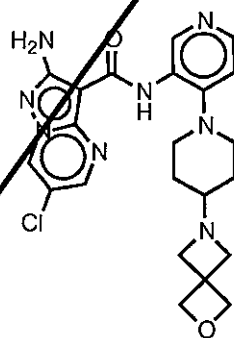
I-N-93



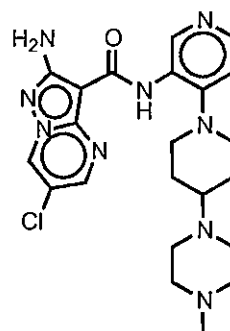
I-N-94



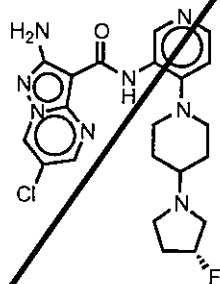
I-N-95



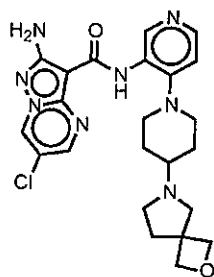
I-N-96



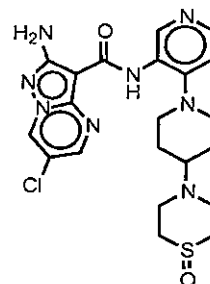
I-N-97



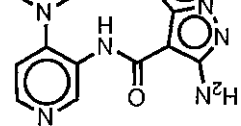
I-N-98



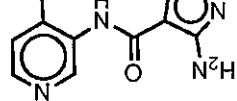
I-N-99



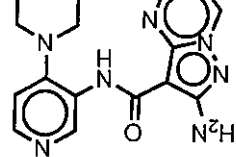
I-N-100



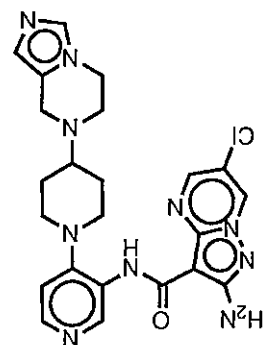
I-N-101



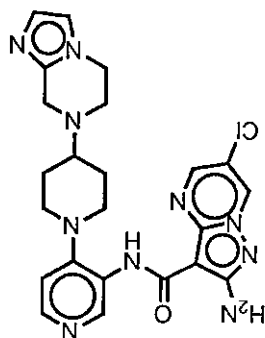
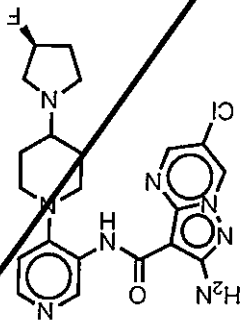
I-N-102



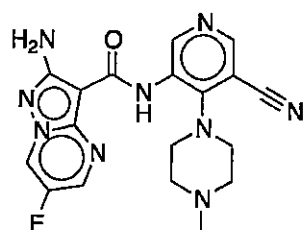
I-N-103



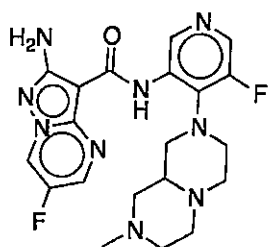
WO 2014/089379



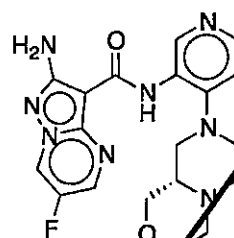
PCT/US2013/073457



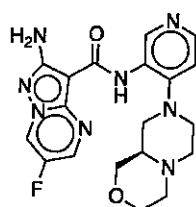
I-N-113



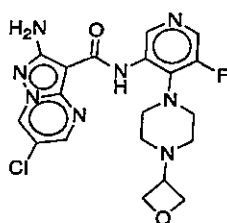
I-N-114



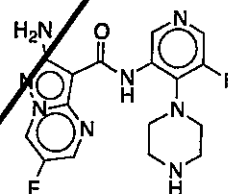
I-N-115



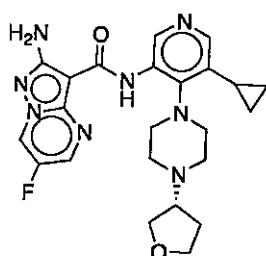
I-N-116



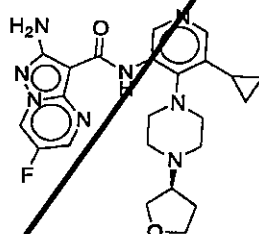
I-N-117



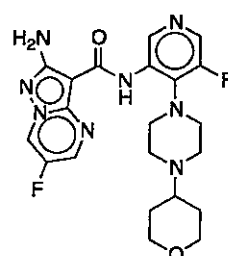
I-N-118



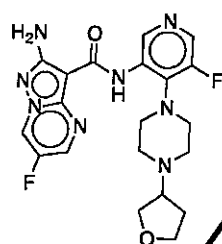
I-N-119



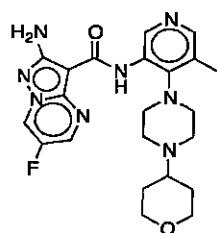
I-N-120



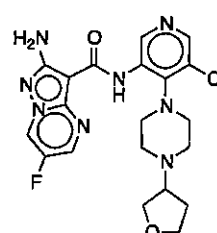
I-N-121



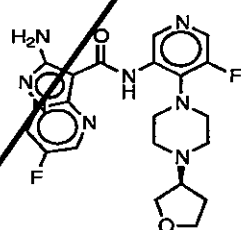
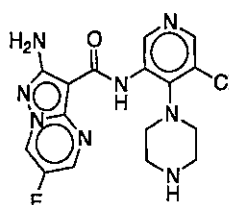
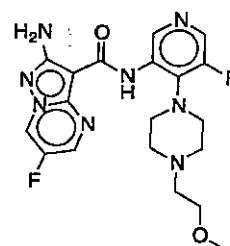
I-N-122



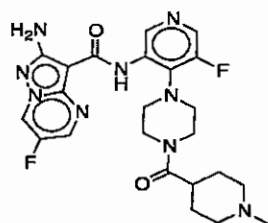
I-N-123



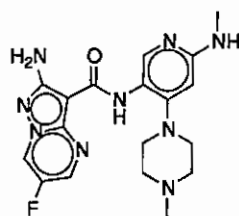
I-N-124



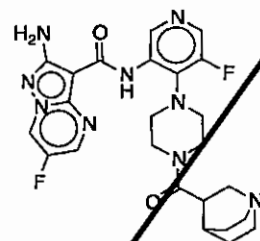
I-N-125



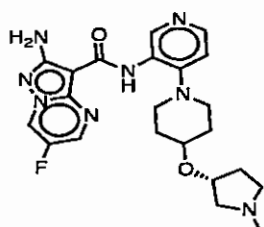
I-N-126



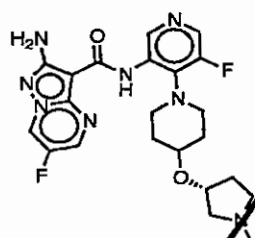
I-N-127



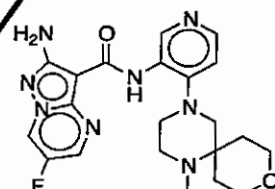
I-N-128



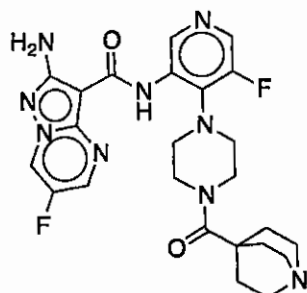
I-N-129



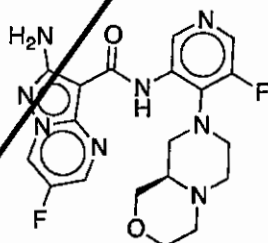
I-N-130



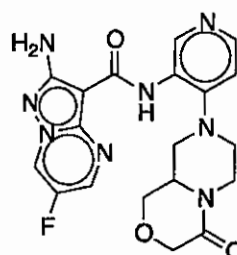
I-N-131



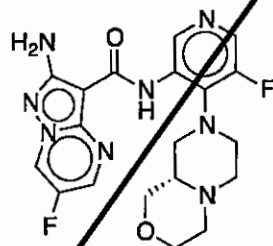
I-N-132



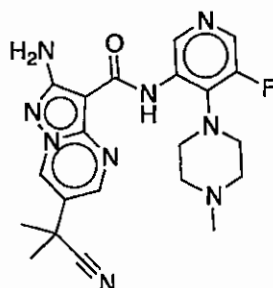
I-N-133



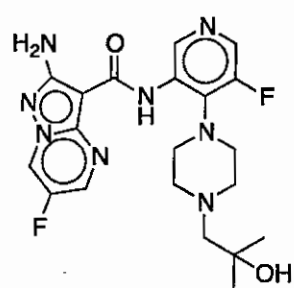
I-N-134



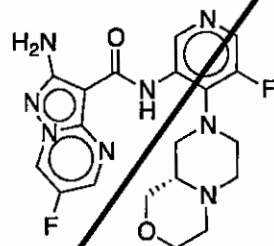
I-N-135



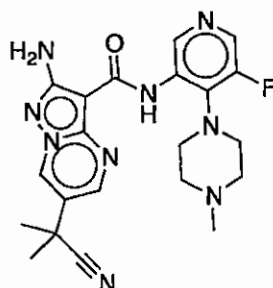
I-N-136



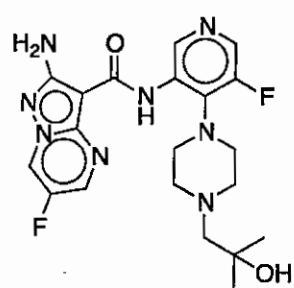
I-N-137

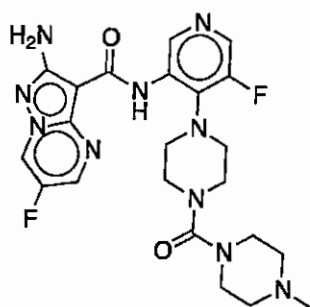


I-N-138

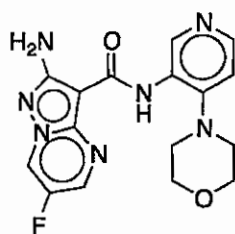


I-N-139

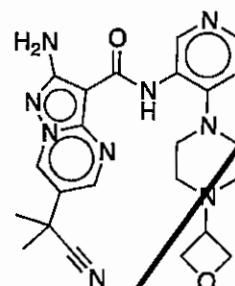




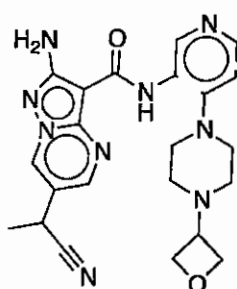
I-N-140



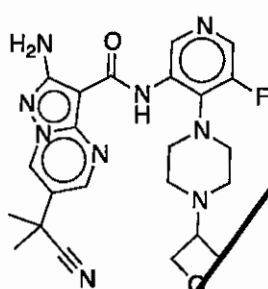
I-N-141



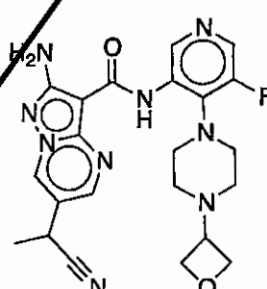
I-N-142



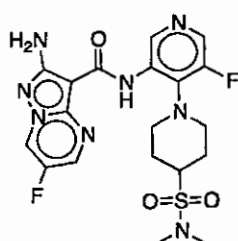
I-N-143



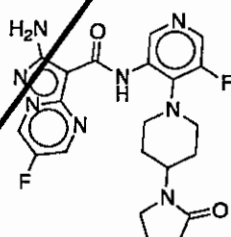
I-N-144



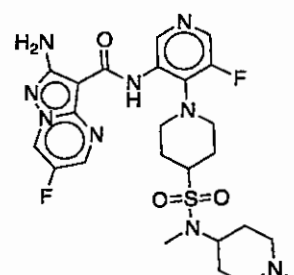
I-N-145



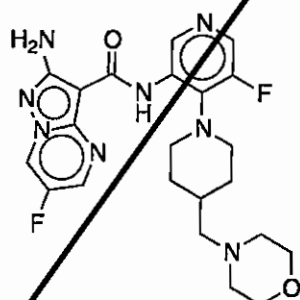
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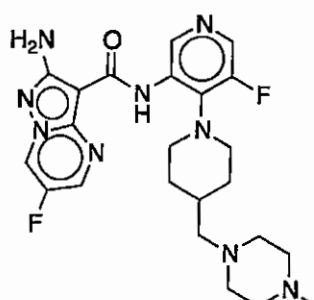
I-N-147



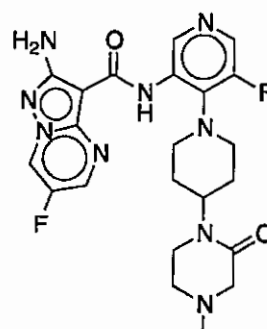
I-N-148



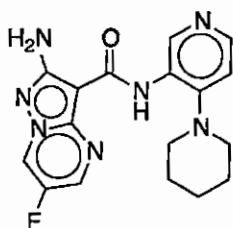
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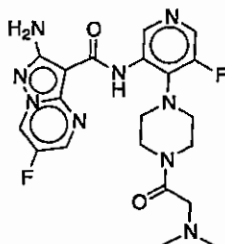
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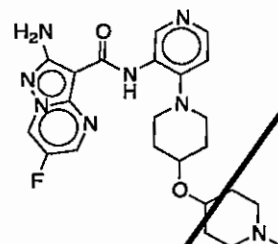
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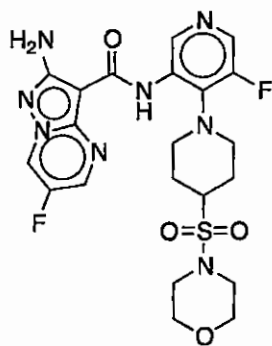
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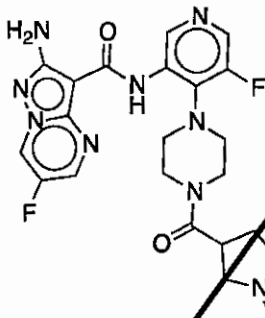
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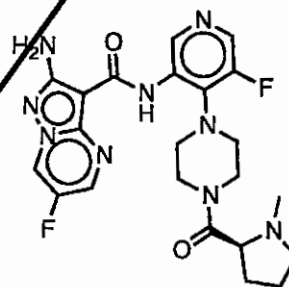
I-N-154



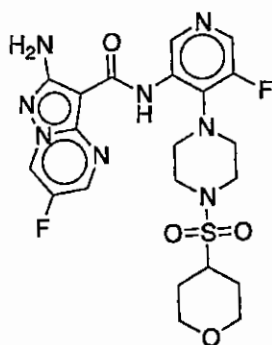
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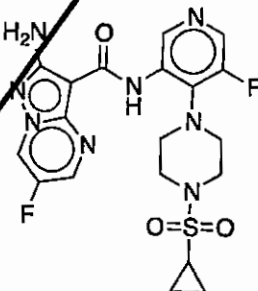
I-N-156



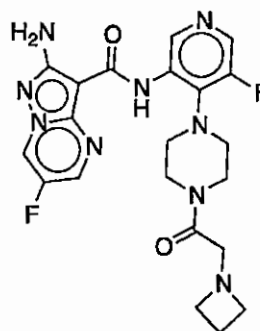
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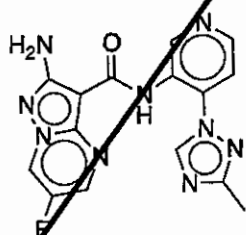
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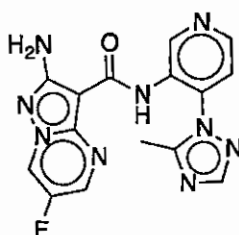
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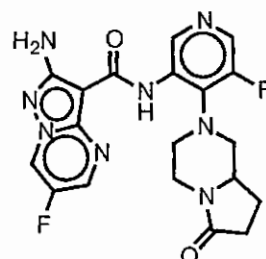
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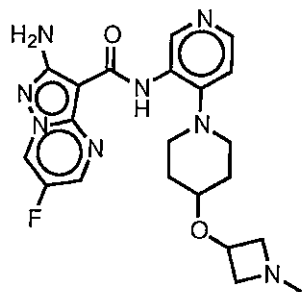
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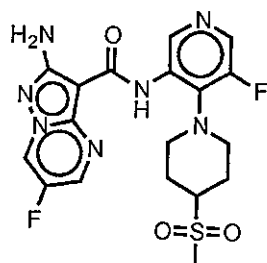
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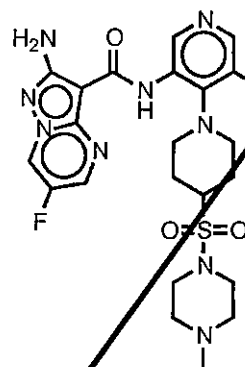
I-N-163



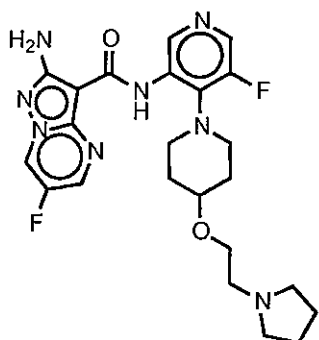
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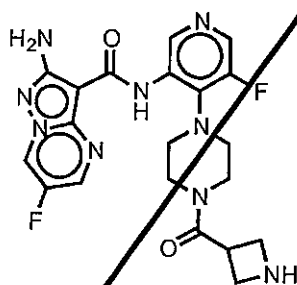
I-N-165



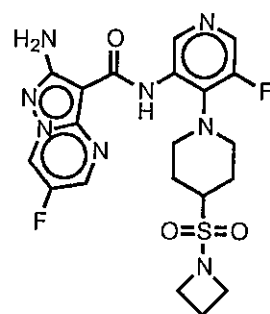
I-N-166



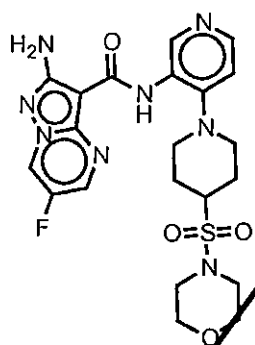
I-N-167



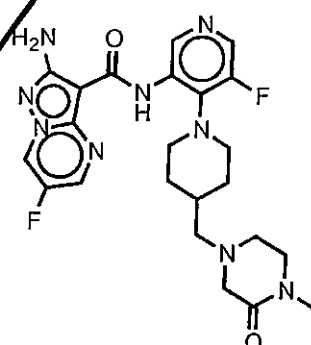
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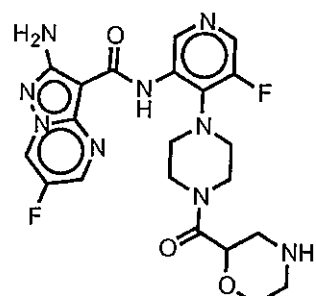
I-N-169



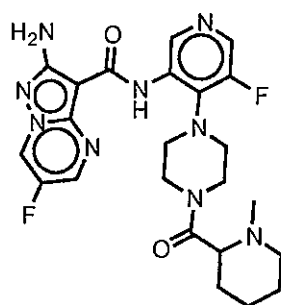
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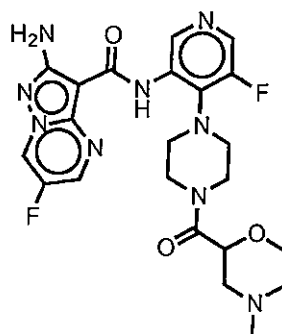
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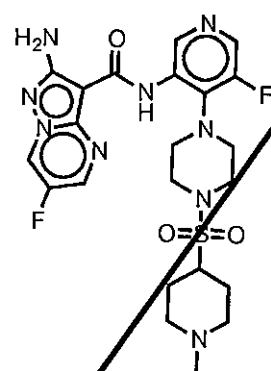
I-N-172



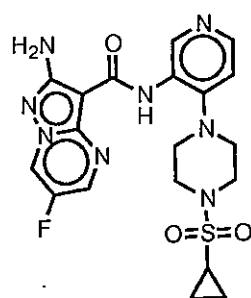
I-N-173



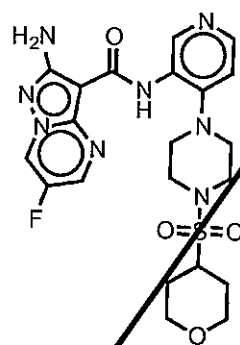
I-N-174



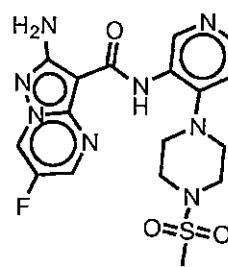
I-N-175



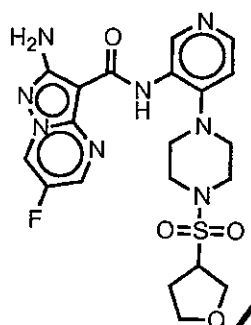
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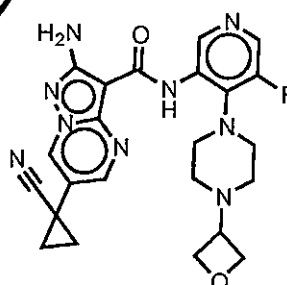
I-N-177



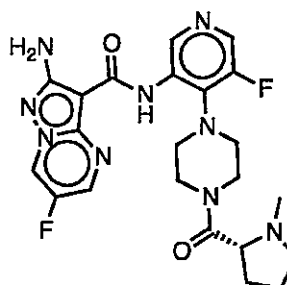
I-N-178



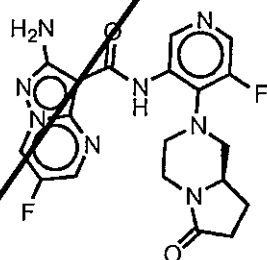
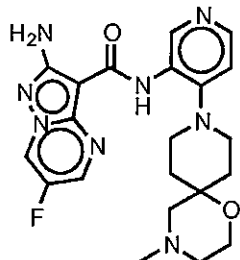
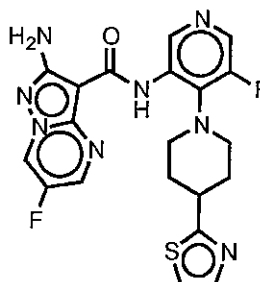
I-N-179



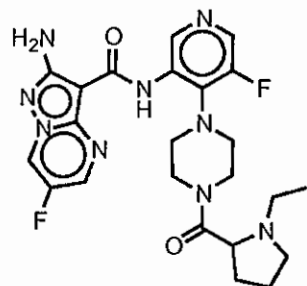
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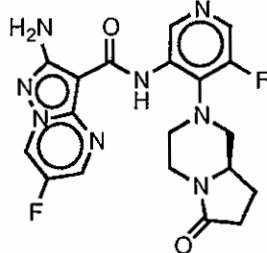
I-N-181



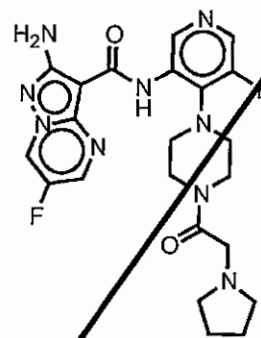
I-N-182



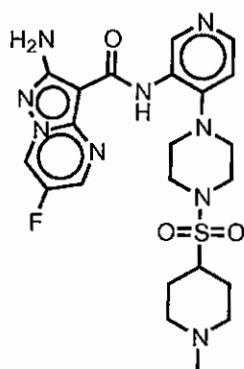
I-N-183



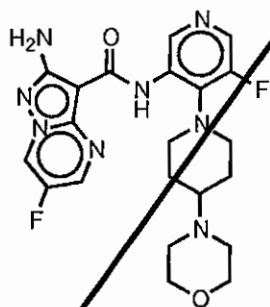
I-N-184



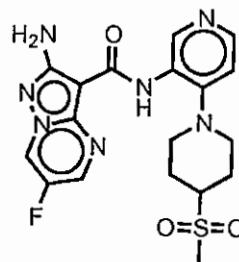
I-N-185



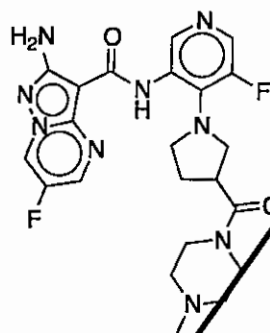
I-N-186



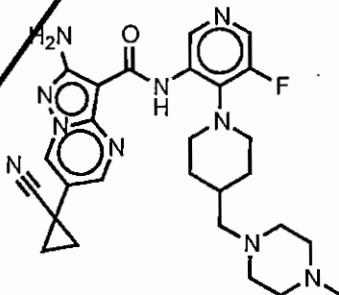
I-N-187



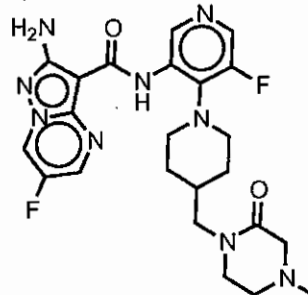
I-N-188



I-N-189



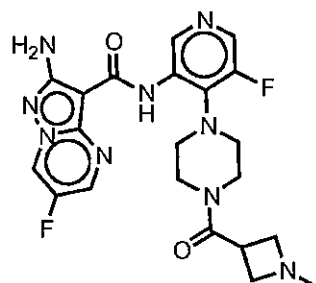
I-N-190



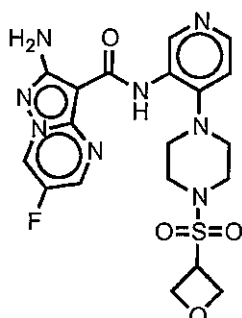
I-N-191

I-N-192

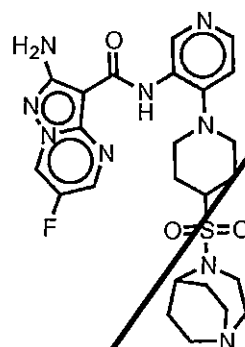
I-N-193



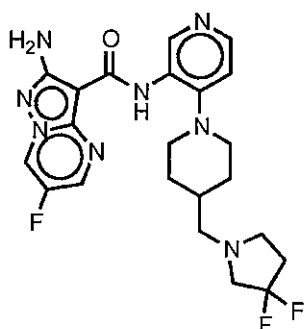
I-N-194



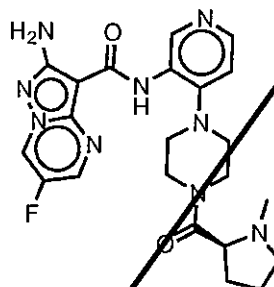
I-N-195



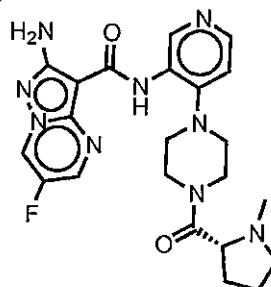
I-N-196



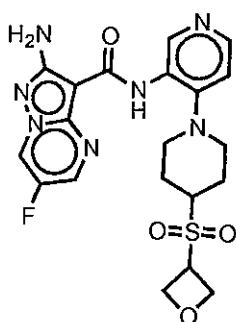
I-N-197



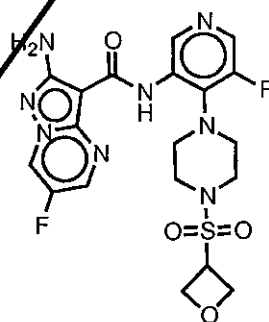
I-N-198



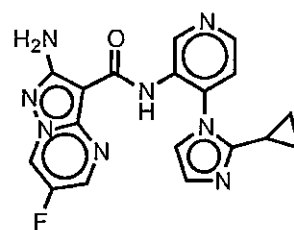
I-N-199



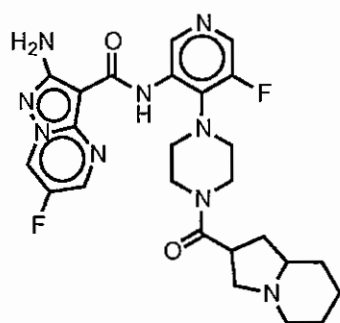
I-N-200



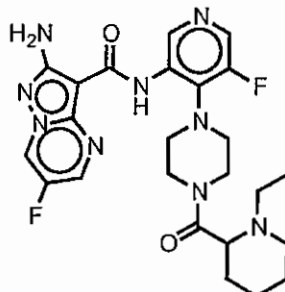
I-N-201



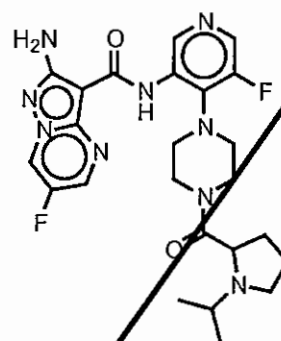
I-N-202



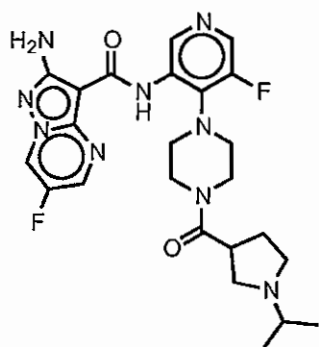
I-N-203



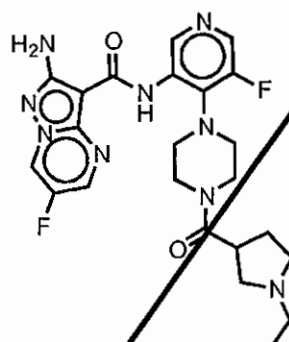
I-N-204



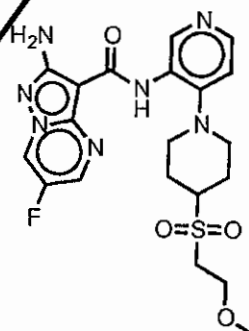
I-N-205



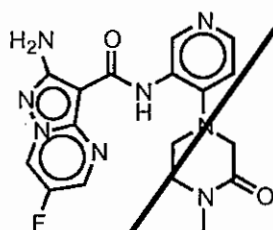
I-N-206



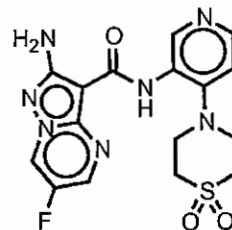
I-N-207



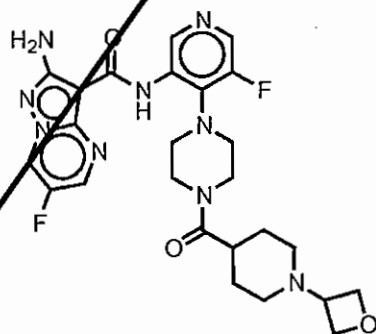
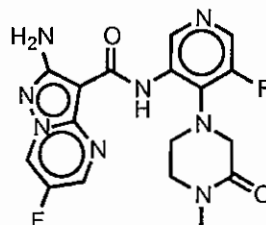
I-N-208



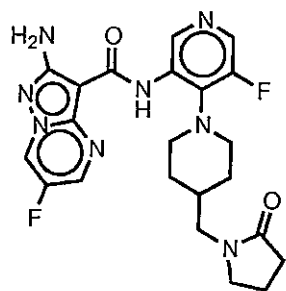
I-N-209



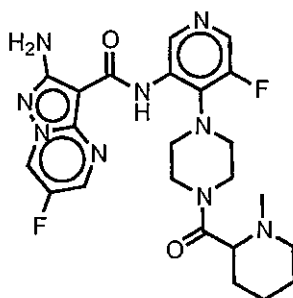
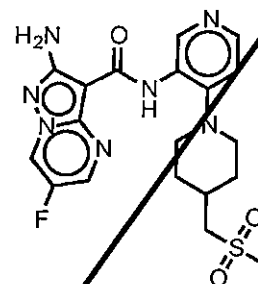
I-N-210



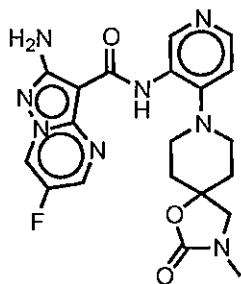
I-N-211



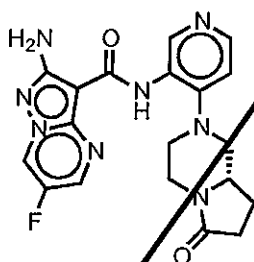
I-N-212



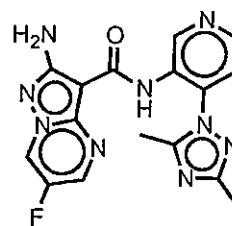
I-N-213



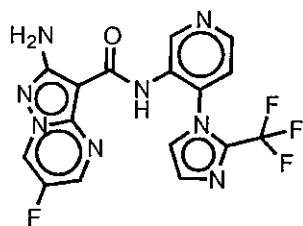
I-N-214



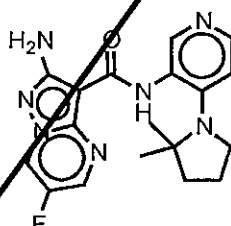
I-N-215



I-N-216

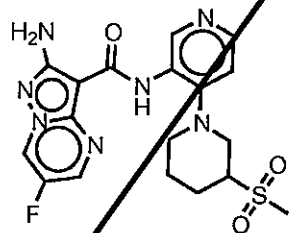


I-N-217

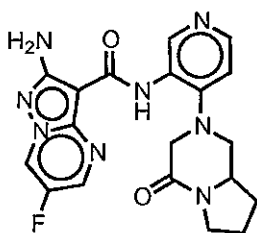
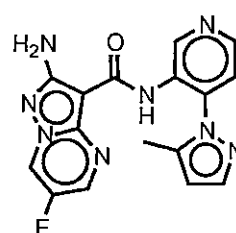


I-N-218

I-N-219



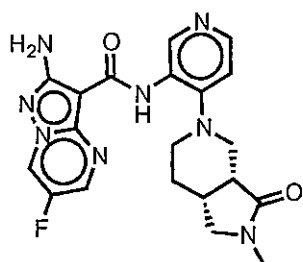
I-N-220



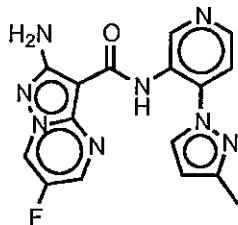
I-N-221

I-N-222

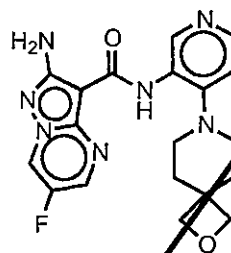
I-N-223



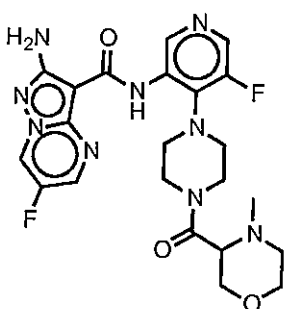
I-N-224



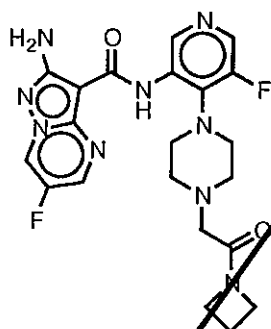
I-N-225



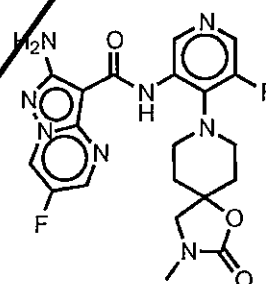
I-N-226



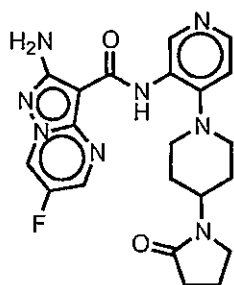
I-N-227



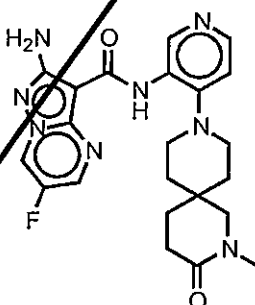
I-N-228



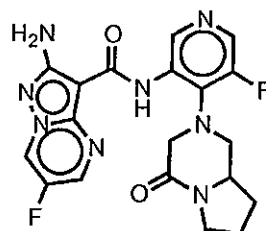
I-N-229



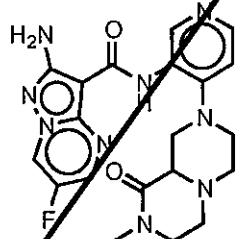
I-N-230



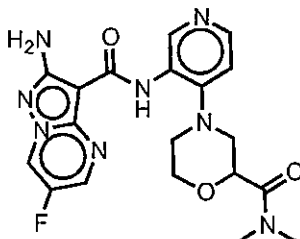
I-N-231



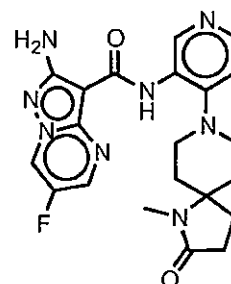
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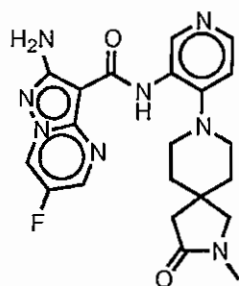
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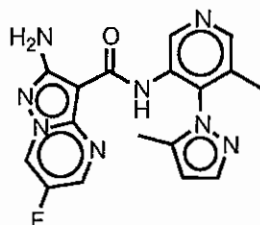
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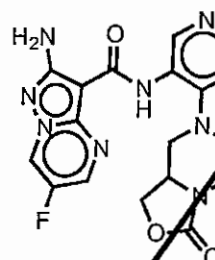
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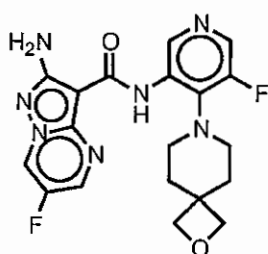
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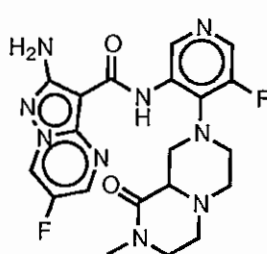
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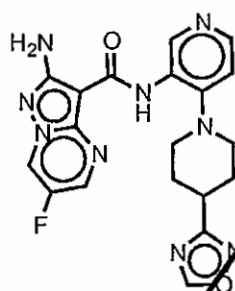
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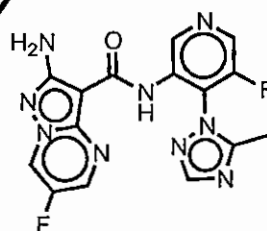
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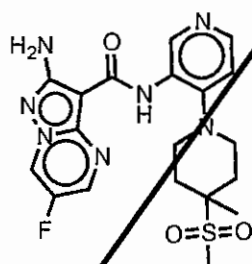
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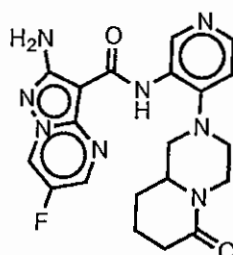
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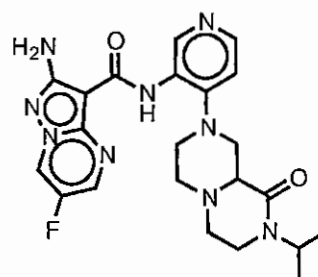
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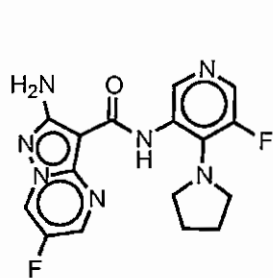
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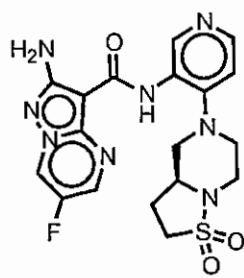
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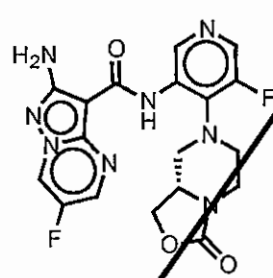
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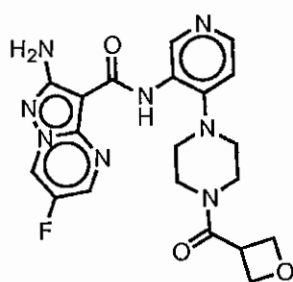
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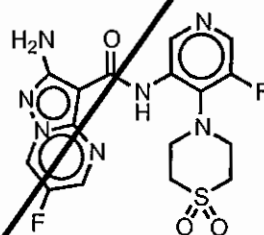
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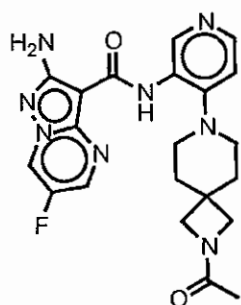
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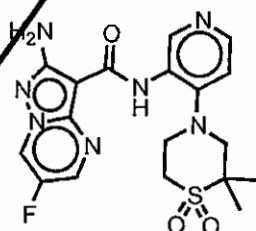
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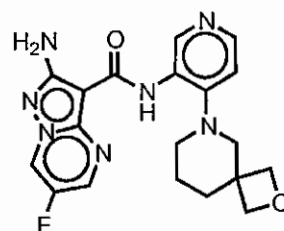
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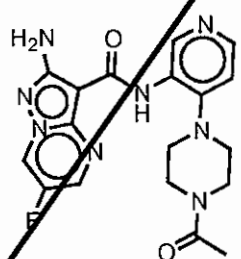
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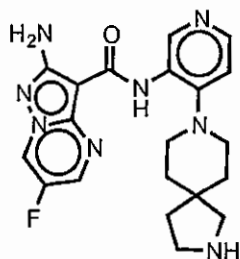
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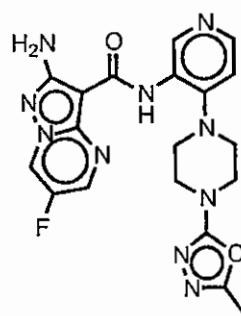
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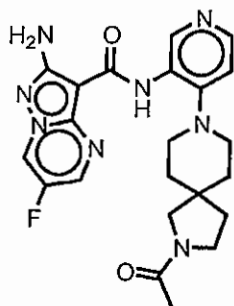
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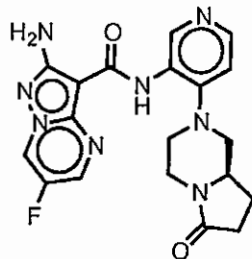
I-N-255



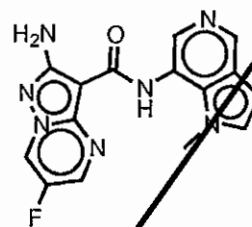
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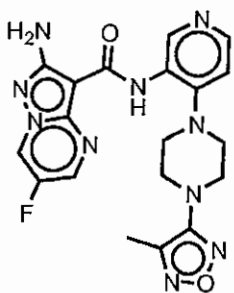
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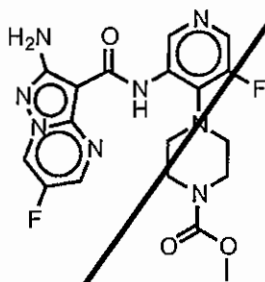
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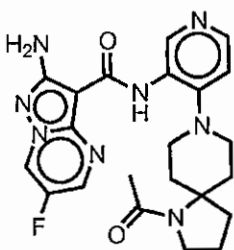
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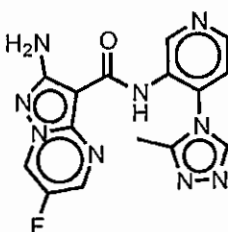
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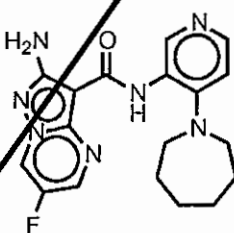
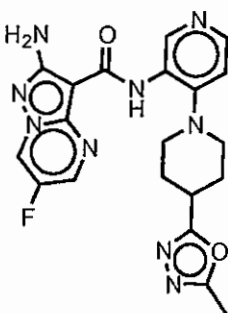
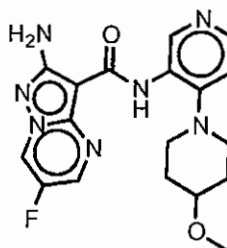
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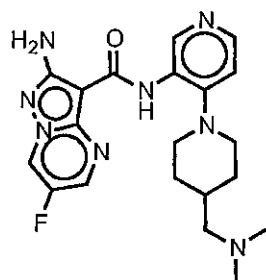
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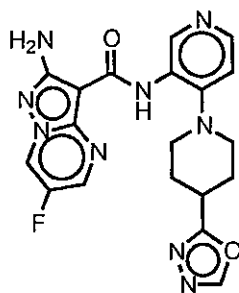
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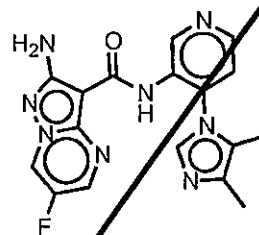
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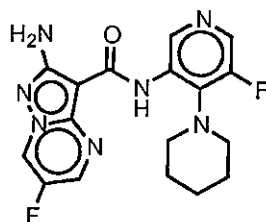
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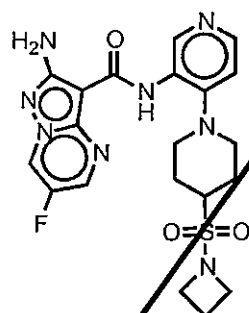
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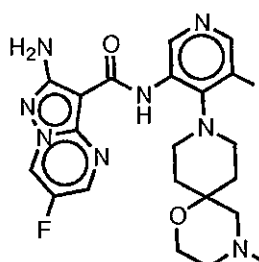
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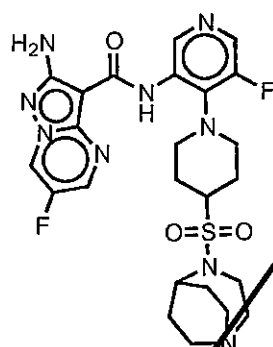
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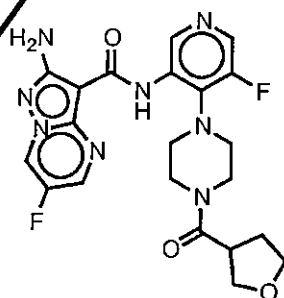
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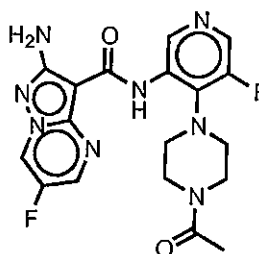
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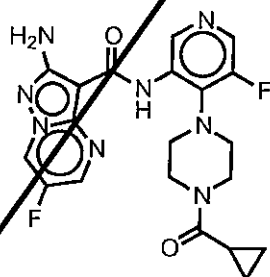
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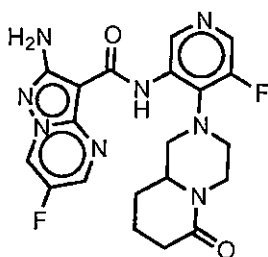
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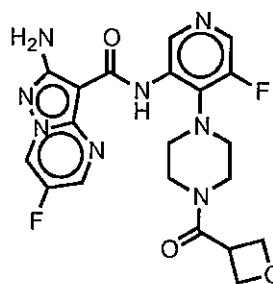
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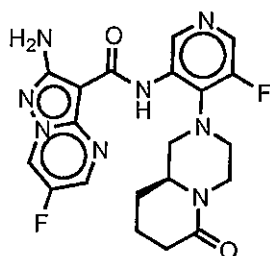
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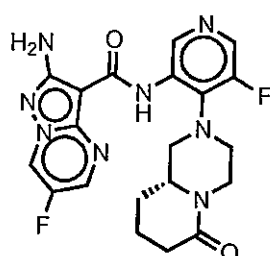
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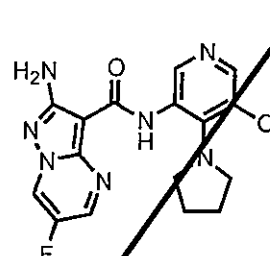
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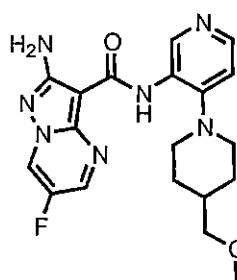
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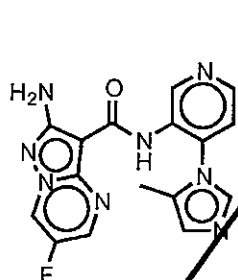
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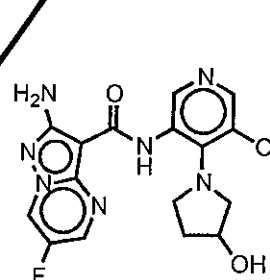
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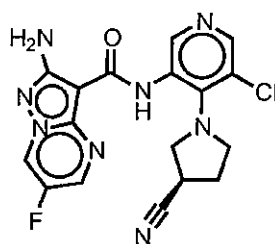
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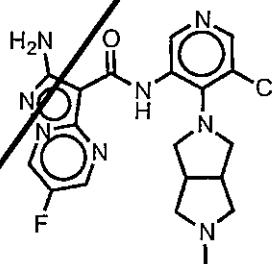
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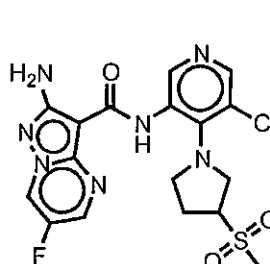
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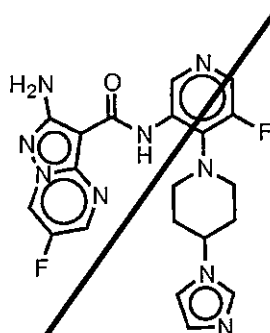
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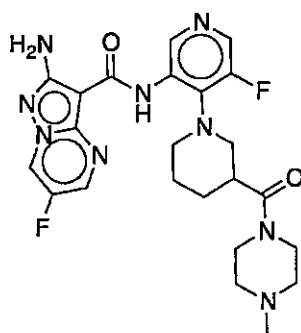
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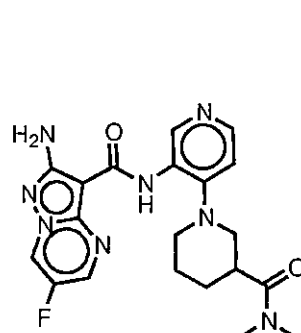
I-N-285



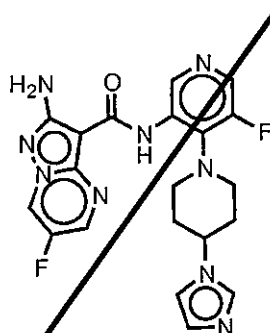
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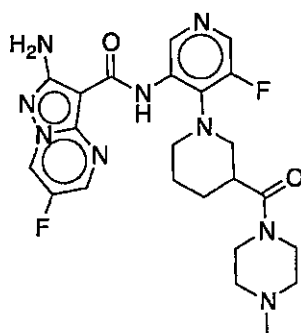
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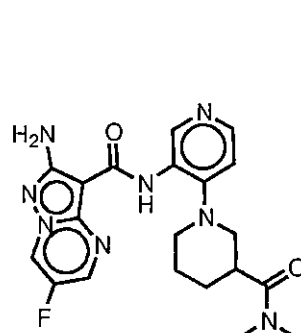
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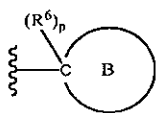
I-N-289



I-N-290.



112. The compound of claim 34, wherein R^4 is:



113. The compound of claim 112, wherein p is 1.

114. The compound of claim 113, wherein Ring B is a 3-7 membered cycloaliphatic or heterocyclyl ring having 1-2 heteroatoms selected from oxygen, nitrogen or sulfur.

115. The compound of claim 114, wherein Ring B is independently selected from selected from cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, 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, 1,2,3,6-tetrahydropyridine, and azetidiny.

116. The compound of claim 115, wherein Ring B is piperidinyl.

117. The compound of any one of claims 112-116, wherein J^Q is $-C(O)-$ or C_{1-4} alkyl.

118. The compound of any one of claims 112-116, wherein, J^Q is Q^2 .

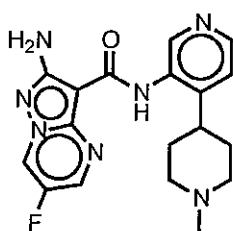
119. The compound of claim 118, wherein Q^2 is independently selected from oxetanyl, tetrahydropyranyl, tetrahydrofuranyl, cyclopropyl, azetidiny, pyrrolidinyl, piperazinyl, piperidinyl, cyclobutyl, thiomorpholinyl, or morpholinyl.

120. The compound of claim 119, wherein Q^2 is oxetanyl.

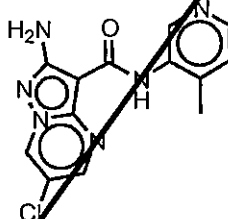
121. The compound of claim 112, wherein p is 0.

122. The compound of claim 121, wherein Ring B is independently selected from phenyl, pyridinyl, pyrazinyl, pyrimidinyl, tetrahydropyridinyl, pyridiziny, or pyrazolyl.

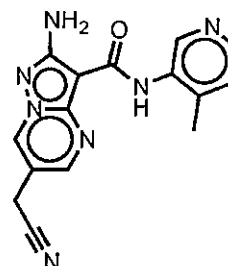
123. The compound of claim 122, wherein Ring B is independently selected from phenyl or pyridinyl.
124. The compound of claim 34, wherein R^4 is $-\text{CH}_2-\text{R}^7$.
125. The compound of claim 124, wherein R^7 is H.
126. The compound of any one of claims 22-29, wherein R^3 and R^4 , taken together with the atoms to which they are bound, form a 5-6 membered non-aromatic ring having 0-2 heteroatoms selected from oxygen.
127. The compound of claim 124, wherein the J^Z is independently selected from $\rightarrow\text{O}$ or $\text{C}_{1-4}\text{alkyl}$.
128. The compound of any one of claims 112-127, independently selected from:



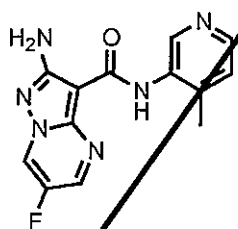
I-C-1



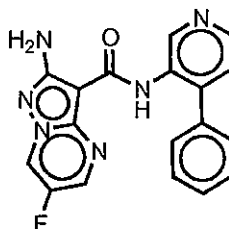
I-C-2



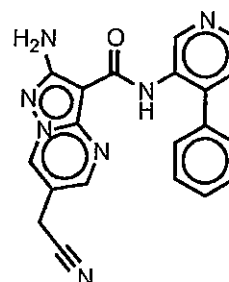
I-C-3



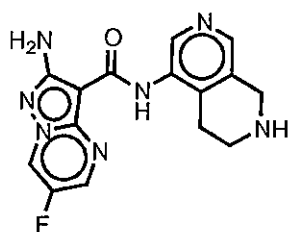
I-C-4



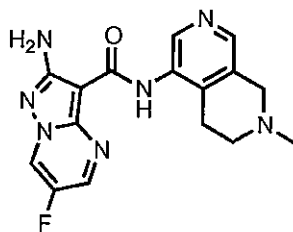
I-C-5



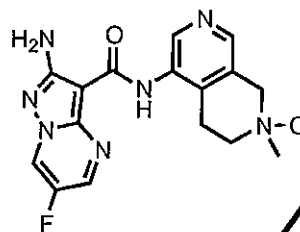
I-C-6



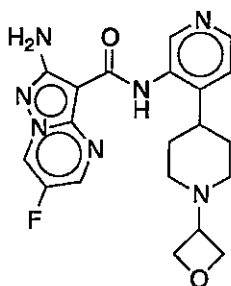
I-C-7



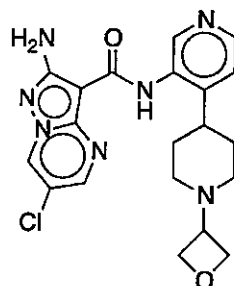
I-C-8



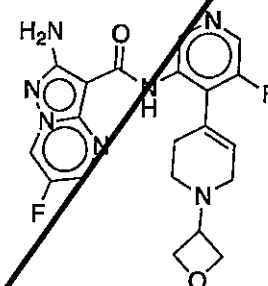
I-C-9



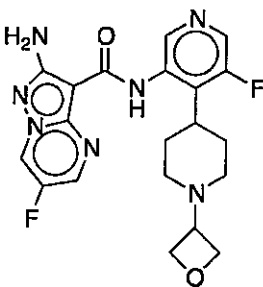
I-C-10



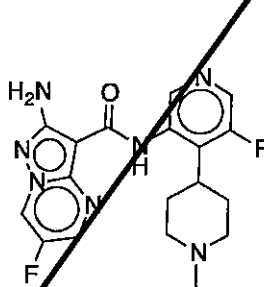
I-C-11



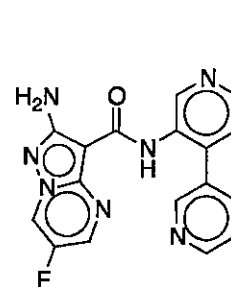
I-C-12



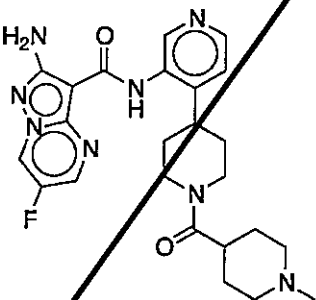
I-C-13



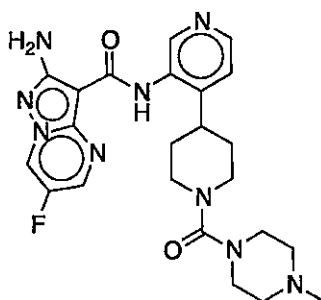
I-C-14



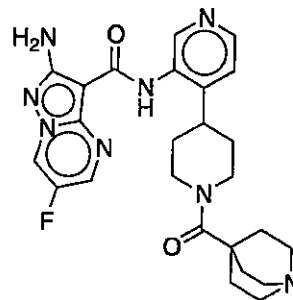
I-C-15



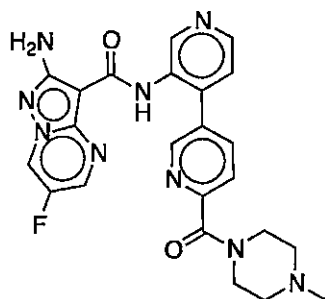
I-C-16



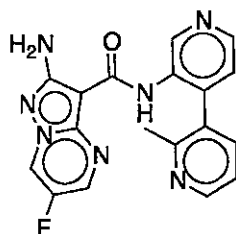
I-C-17



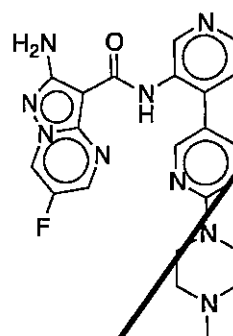
I-C-18



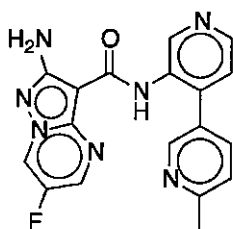
I-C-19



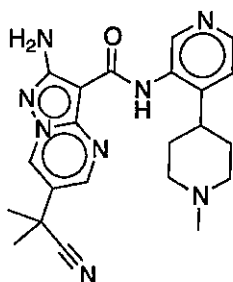
I-C-20



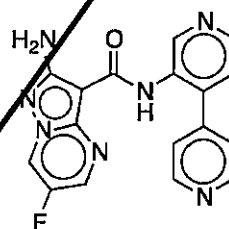
I-C-21



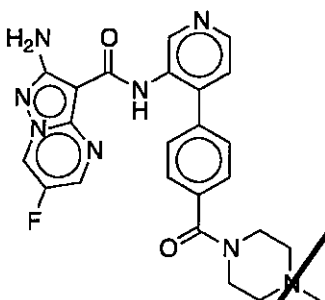
I-C-22



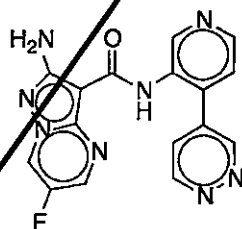
I-C-23



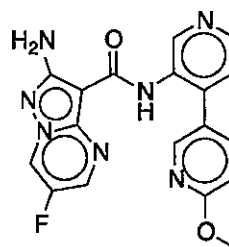
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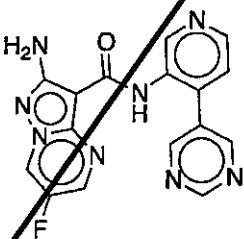
I-C-25



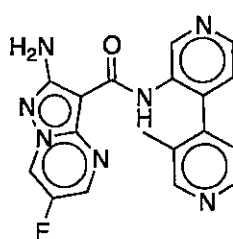
I-C-26



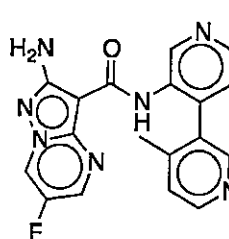
I-C-27



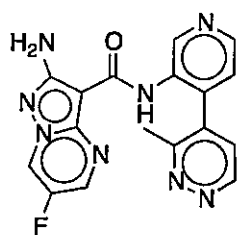
I-C-28



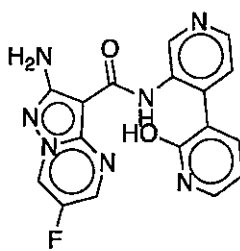
I-C-29



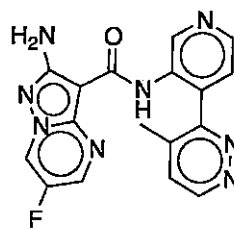
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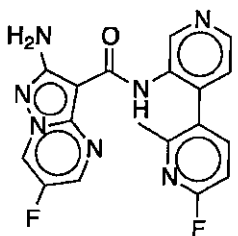
I-C-31



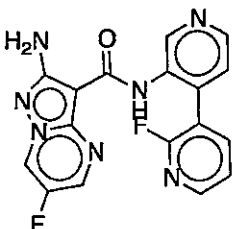
I-C-32



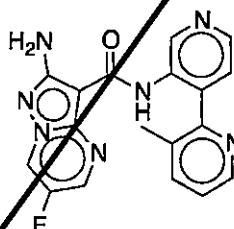
I-C-33



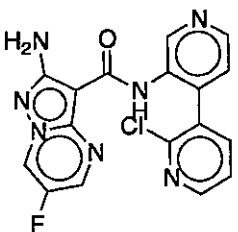
I-C-34



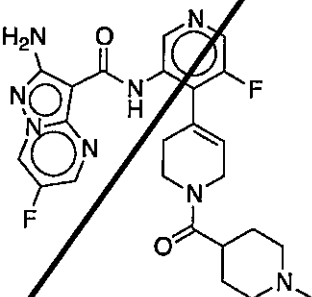
I-C-35



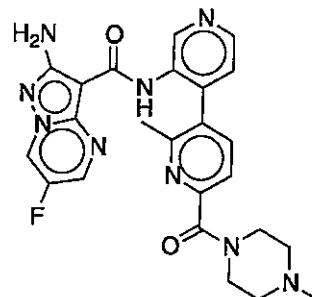
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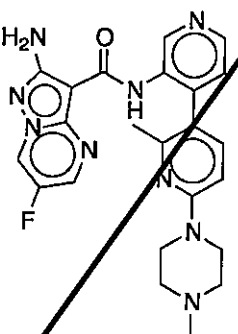
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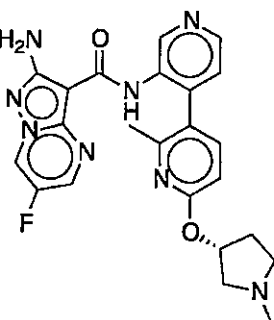
I-C-38



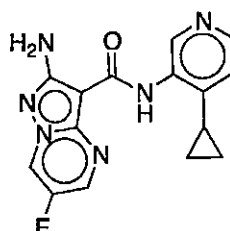
I-C-39



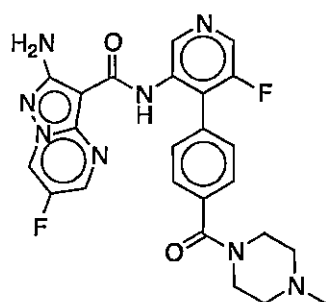
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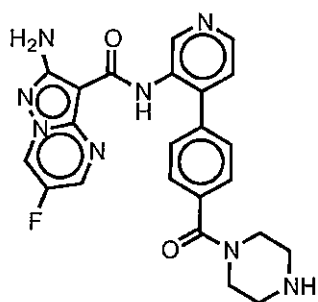
I-C-41



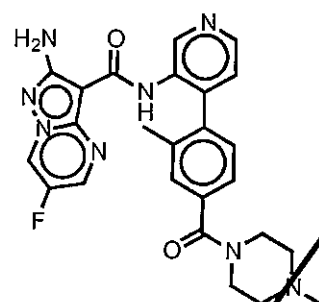
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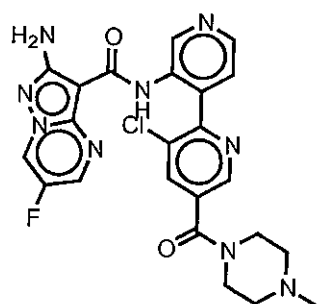
I-C-43



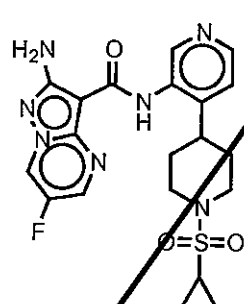
I-C-44



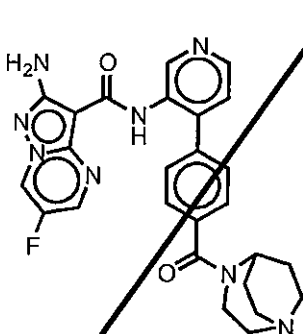
I-C-45



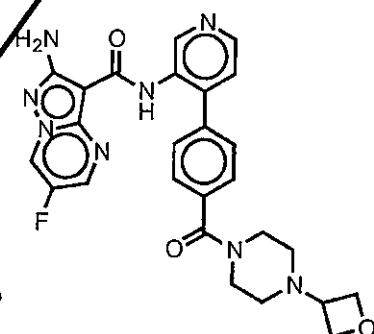
I-C-46



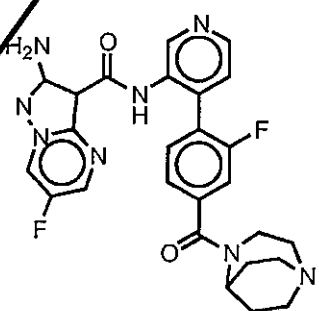
I-C-47



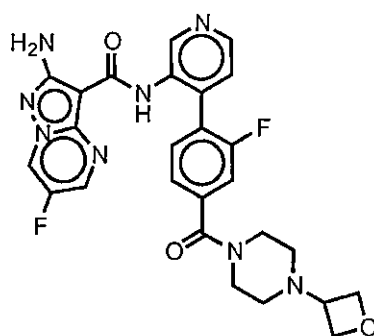
I-C-48



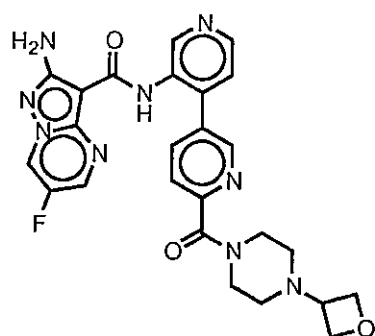
I-C-49



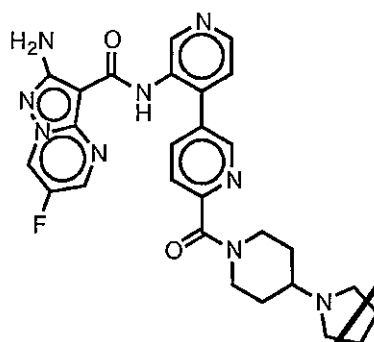
I-C-50



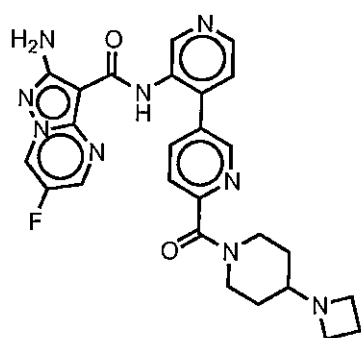
I-C-51



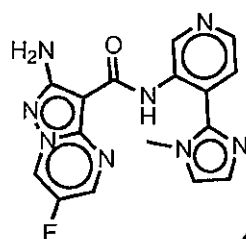
I-C-52



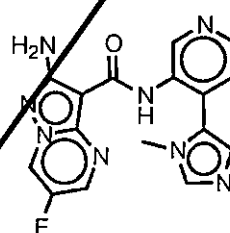
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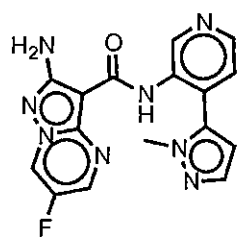
I-C-54



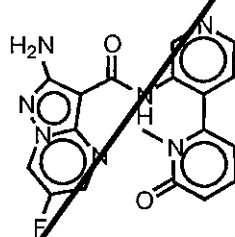
I-C-55



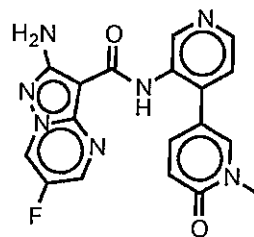
I-C-56



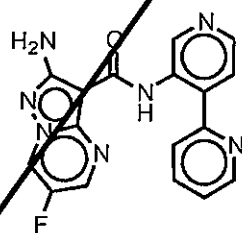
I-C-57



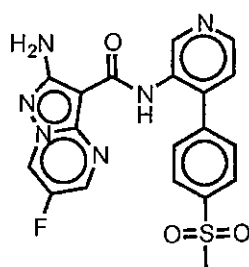
I-C-58



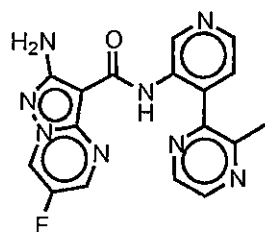
I-C-59



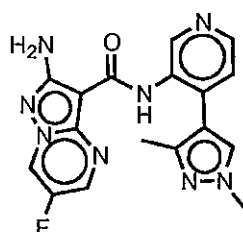
I-C-60



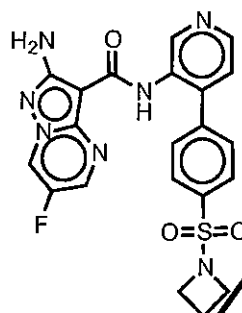
I-C-61



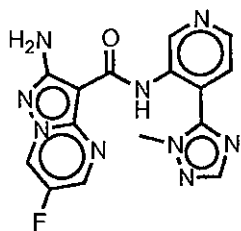
I-C-62



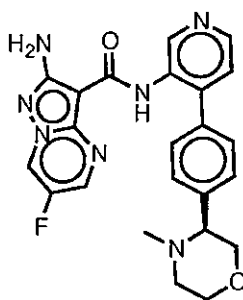
I-C-63



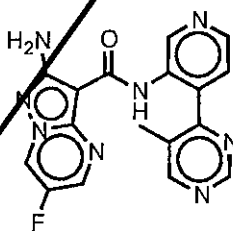
I-C-64



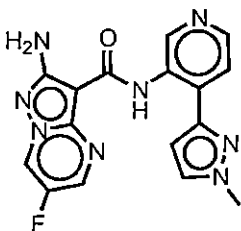
I-C-65



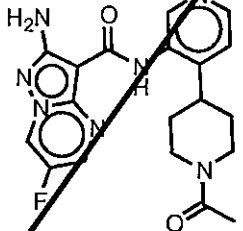
I-C-66



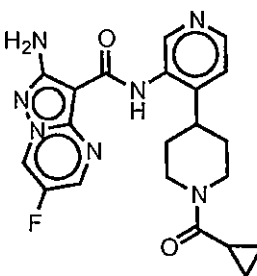
I-C-67



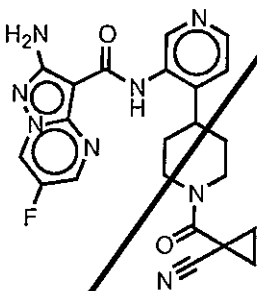
I-C-68



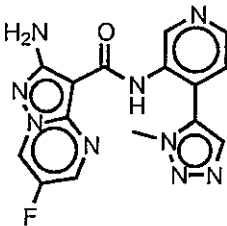
I-C-69



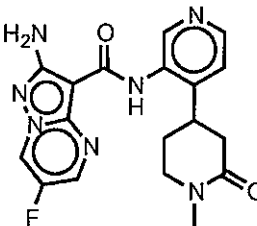
I-C-70



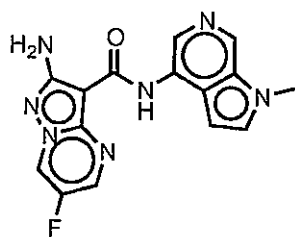
I-C-71



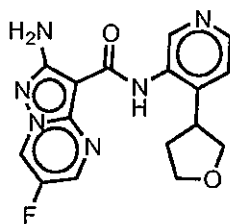
I-C-72



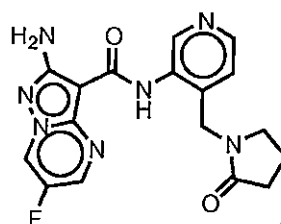
I-C-73



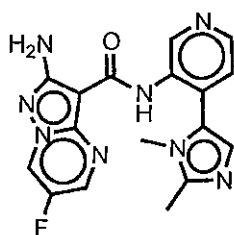
I-C-74



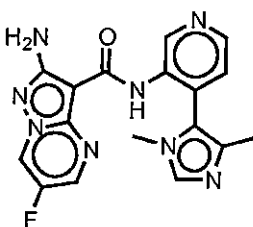
I-C-75



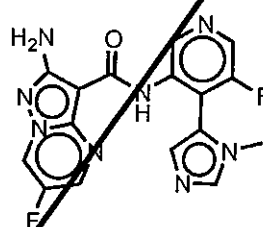
I-C-76



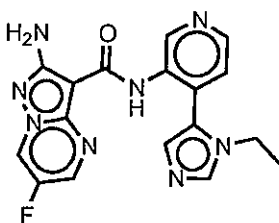
I-C-77



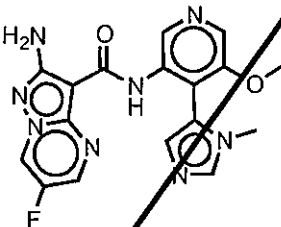
I-C-78



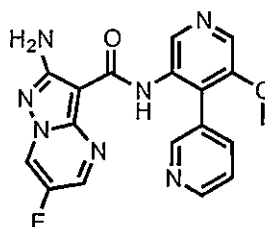
I-C-79



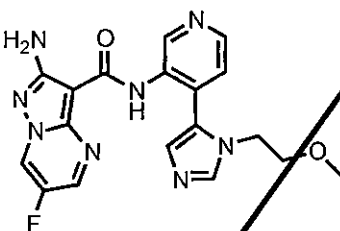
I-C-80



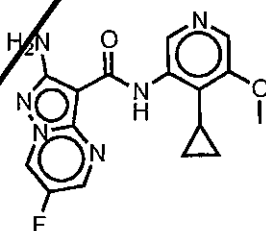
I-C-81



I-C-82

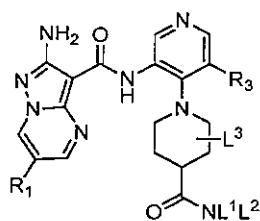


I-C-83



I-C-84

129. A compound having the formula I-B:



I-B

or a pharmaceutically acceptable salt or prodrug 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 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 selected from 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 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;

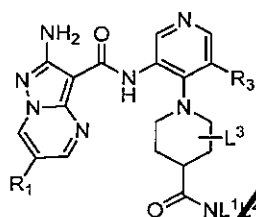
J^K is a 3-7 membered aromatic or non-aromatic ring having 0-2 heteroatoms selected from oxygen, nitrogen, or sulfur;

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

130. A compound having the formula **I-B**:



I-B

or a pharmaceutically acceptable salt or prodrug 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; $-N(R^\circ)_2$; $\rightarrow O$; 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;

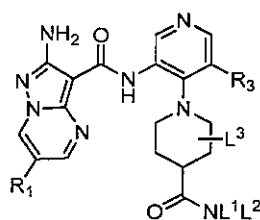
two occurrences of J^G , together with Ring D, form a 6-10 membered saturated or partially unsaturated bridged ring system;

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° are H or C_{1-4} alkyl.

131. A compound having the formula **I-B**:



I-B

or a pharmaceutically acceptable salt or prodrug 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^D ;

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;

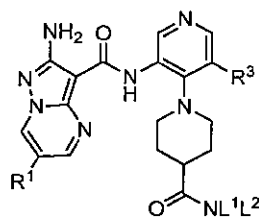
two occurrences of J^G , together with Ring D, form a 6-10 membered saturated or partially unsaturated bridged ring system;

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.

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



I-B

or a pharmaceutically acceptable salt or prodrug 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; $-N(R^G)_2$; a 3-6 membered carbocyclyl; a 3-6 membered heterocyclyl having 1-2 heteroatoms selected from oxygen nitrogen, or sulfur; or a

C₁₋₄alkyl chain wherein up to two methylene units of the alkyl chain are optionally replaced with -O-, -NR-, -C(O)-, or -S(O)_n; each J^G is optionally substituted with 0-2 occurrences of J^K.

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

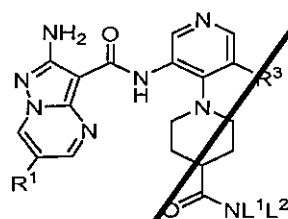
two occurrences of J^G, together with Ring D, form a 6-10 membered saturated or partially unsaturated bridged ring system;

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.

133. A compound of formula I-B:



I-B

or a pharmaceutically acceptable salt or prodrug 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; 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 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, $-N(R^o)_2$, or a 3-5 membered carbocycyl; 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 C_{1-4} alkyl.

134. The compound of any one of claims 129-132, wherein R^1 is fluoro.

135. The compound of any one of claims 129-132, wherein R^1 is $-\text{CH}_2\text{CN}$.

136. The compound of any one of claims 129-132, wherein R^1 is chloro.

137. The compound of any one of claims 129-135, wherein R^3 is independently selected from H, chloro, fluoro, cyclopropyl, or C_{1-4} alkyl.

138. The compound of claim 137, wherein R^3 is independently selected from H, chloro, or fluoro.

139. The compound of claim 137, wherein R^3 is H.

140. The compound of claim 137, wherein R^3 is chloro.

141. The compound of claim 137, wherein R^3 is fluoro.

142. The compound of any one of claims 138-141, 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} alkyl; azetidiny; piperidiny; oxytanyl; or pyrrolidinyl.

143. The compound of any one of claims 134-141, wherein L^1 and L^2 , together with the nitrogen to which they are attached, form Ring D.

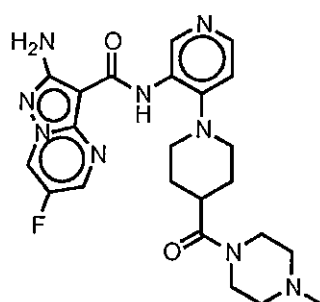
144. The compound of claim 143, wherein Ring D is a 3-7 membered heterocyclyl ring having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur.

145. The compound of claim 144, wherein Ring D is independently selected from piperaziny, piperidiny, morpholiny, tetrahydropyrany, azetidiny, pyrrolidinyl, or 1,4-diazepanyl.

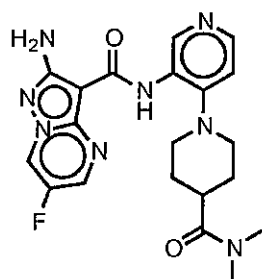
146. The compound of claim 145, wherein Ring D is piperazinyl, piperidinyl, 1,4-diazepanyl, pyrrolidinyl or azetidiny.
147. The compound of claim 146, wherein Ring D is piperazinyl or piperidinyl.
148. The compound of claim 144, wherein Ring D is an 8-12 membered fully saturated or partially unsaturated bicyclic ring having 0-5 heteroatoms selected from oxygen, nitrogen, or sulfur.
149. The compound of claim 148, wherein Ring D is octahydropyrrolo[1,2-a]pyrazine or octahydropyrrolo[3,4-c]pyrrole.
150. The compound of any one of claims 144-149, 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.
151. The compound of claim 150, wherein J^G is methyl, $-N(C_{1-4}$ alkyl)₂, ethyl, $-O(C_{1-3}$ alkyl), cyclopropyl, oxetanyl, cyclobutyl, pyrrolidinyl, piperidinyl, or azetidiny.
152. The compound of claim 151, wherein J^G is methyl, $-O(C_{1-3}$ alkyl), oxetanyl, pyrrolidinyl, piperidinyl, or azetidiny.
153. The compound of claim 152, wherein J^G is methyl.
154. The compound of any one of claims 145-148, wherein two occurrences of J^G , together with Ring D, form a 6-10 membered saturated or partially unsaturated bridged ring system.
155. The compound of claim 154, 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.
156. The compounds of any one of claims 144-147, 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.

157. The compound of claim 156, wherein the ring formed by the two occurrences of J^G on the same atom is selected from oxetanyl or cyclopropyl.

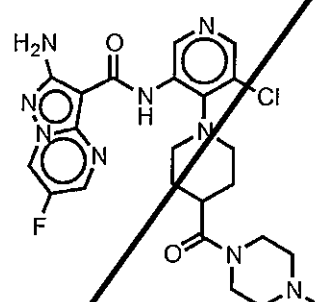
158. A compound of any one of claims 129-157 independently selected from:



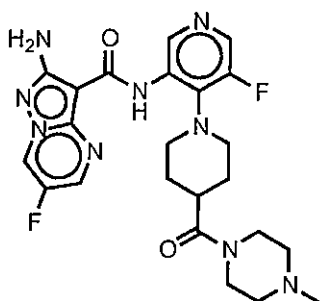
I-G-1



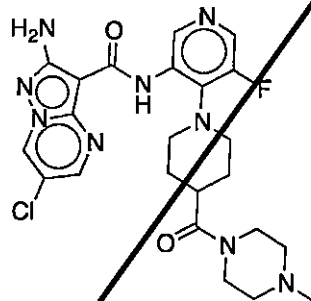
I-G-2



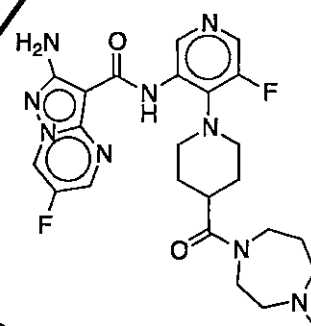
I-G-3



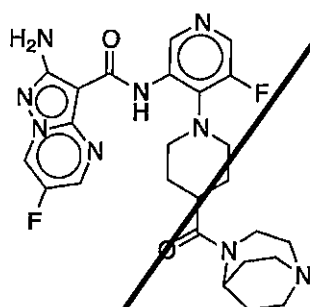
I-G-4



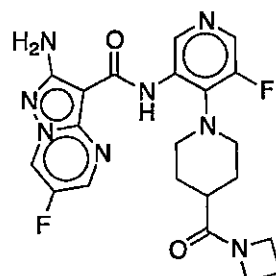
I-G-5



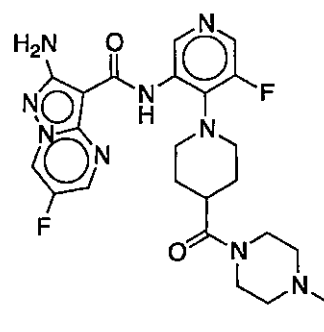
I-G-6



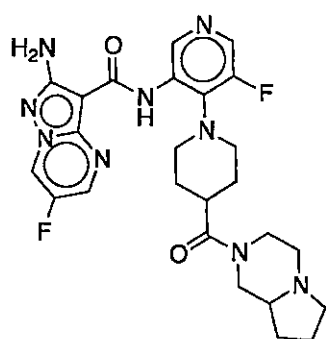
I-G-7



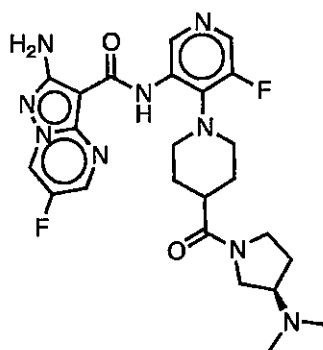
I-G-8



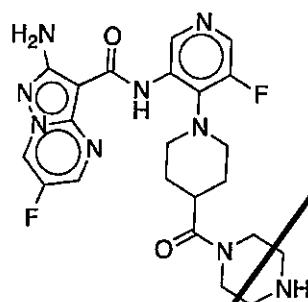
I-G-9



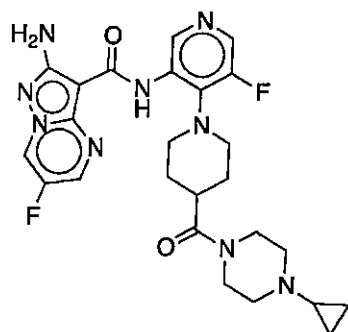
I-G-10



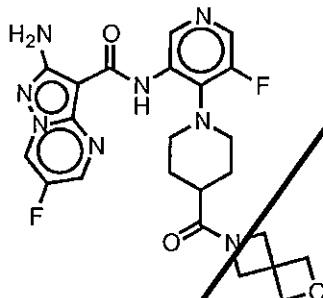
I-G-11



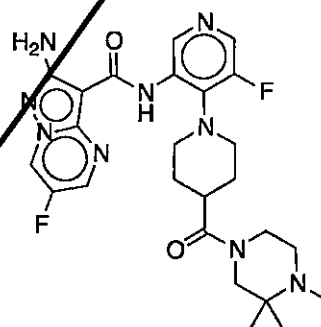
I-G-12



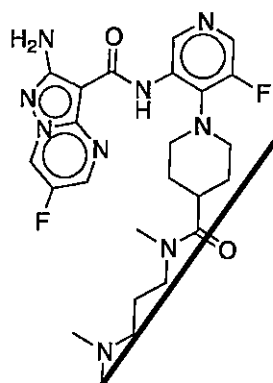
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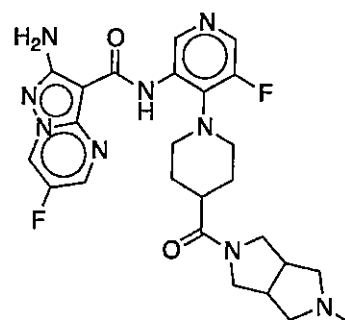
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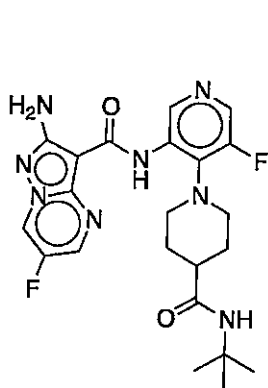
I-G-15



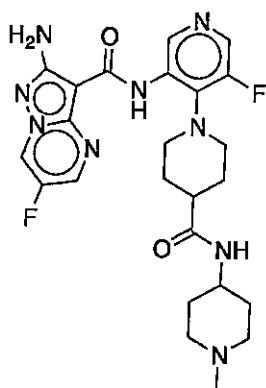
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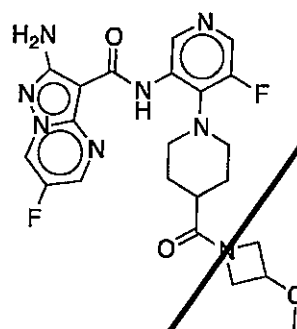
I-G-18



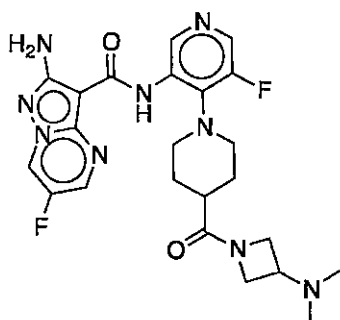
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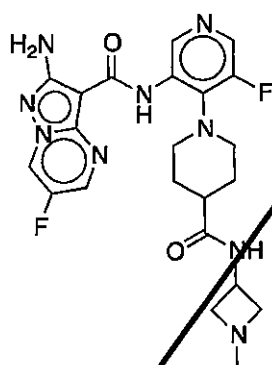
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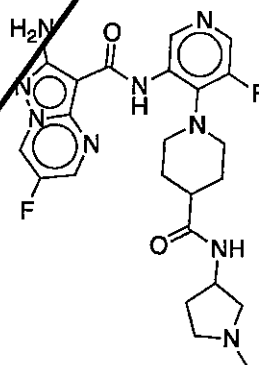
I-G-21



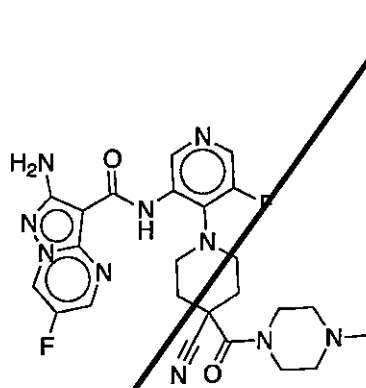
I-G-22



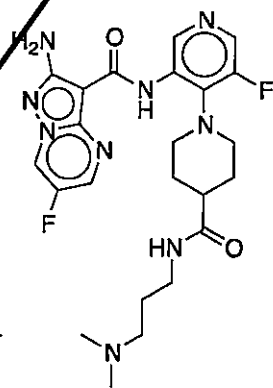
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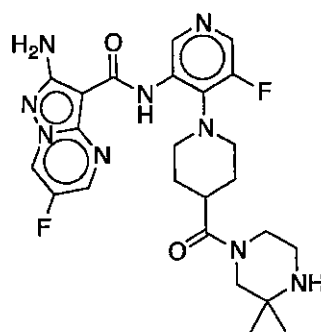
I-G-24



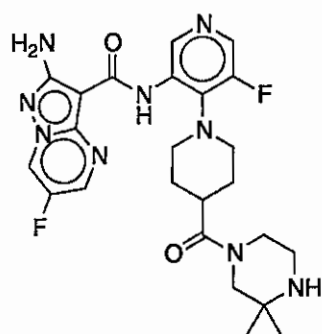
I-G-25



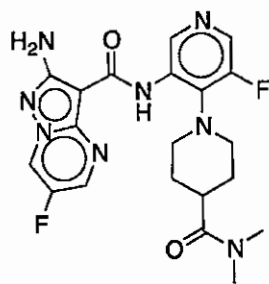
I-G-26



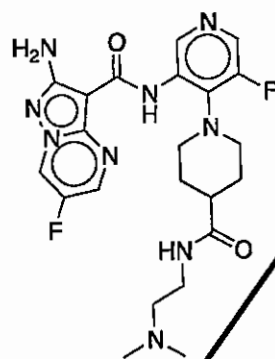
I-G-27



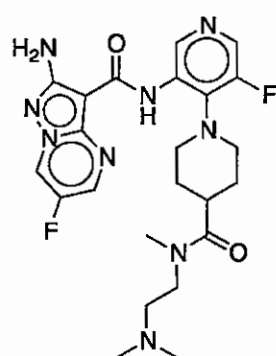
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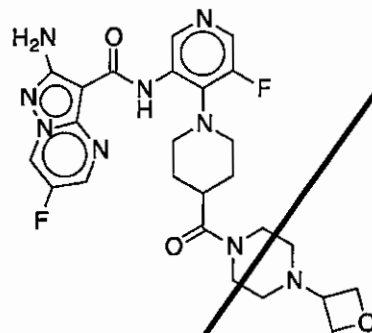
I-G-29



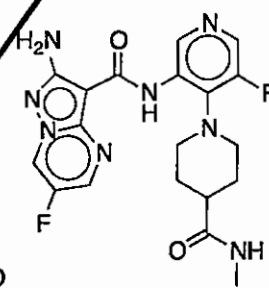
I-G-30



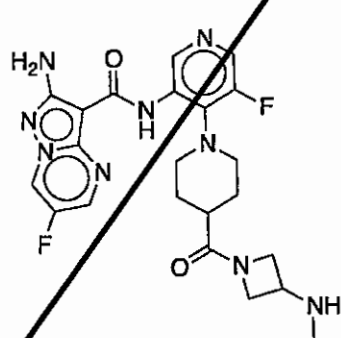
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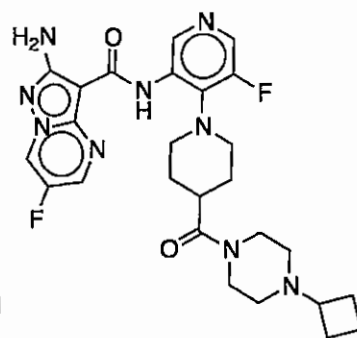
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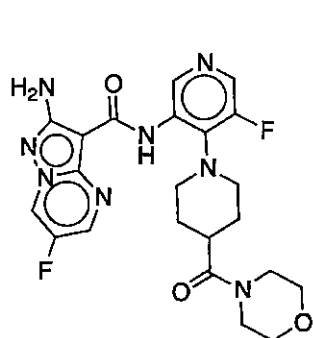
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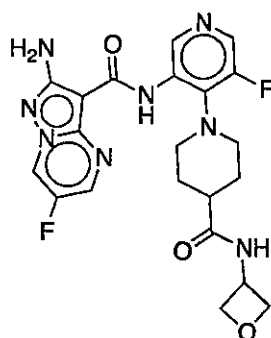
I-G-34



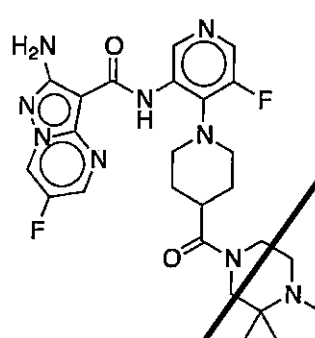
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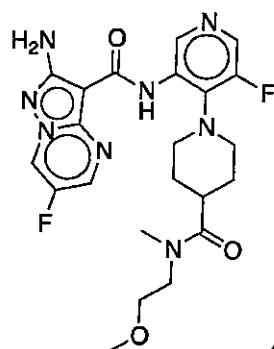
I-G-36



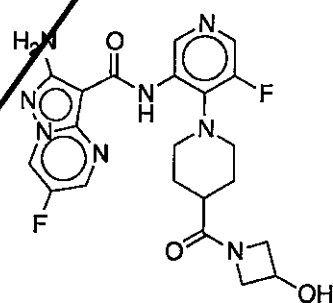
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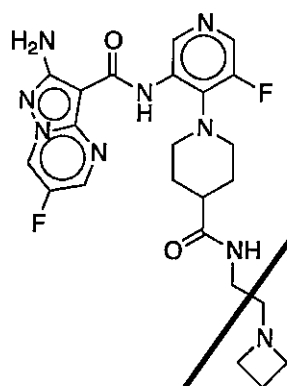
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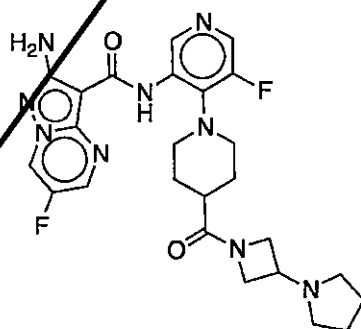
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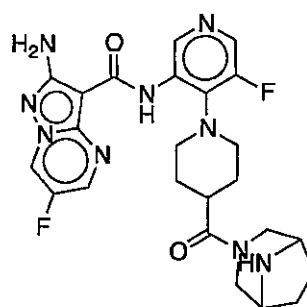
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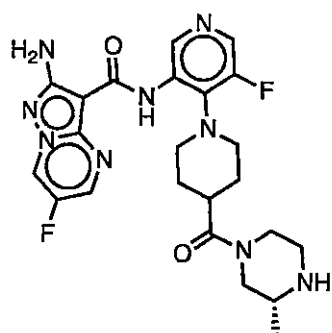
I-G-42



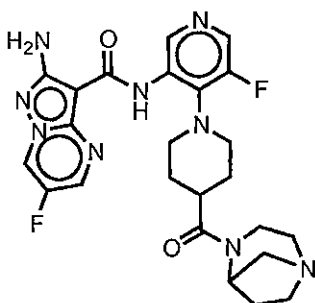
I-G-43



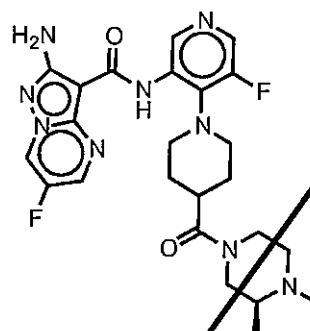
I-G-44



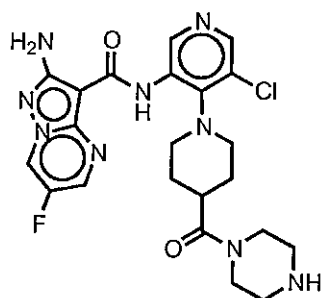
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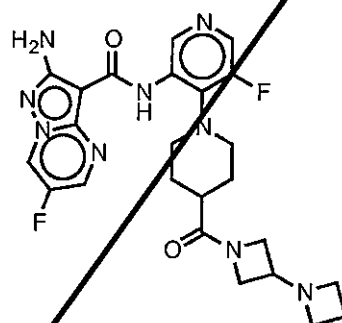
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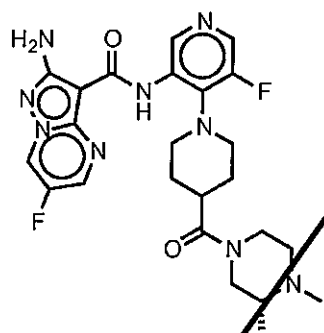
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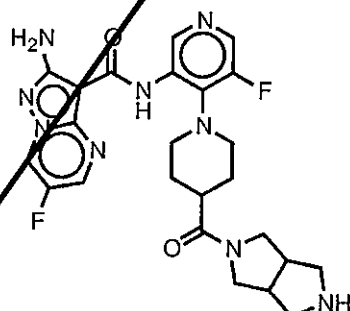
I-G-48



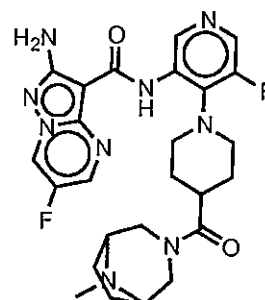
I-G-49



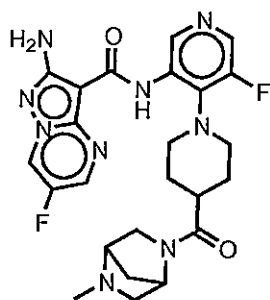
I-G-50



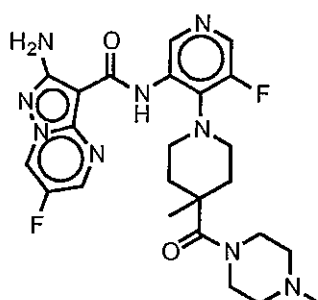
I-G-51



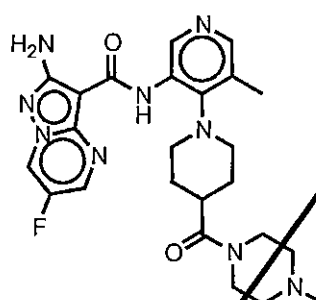
I-G-52



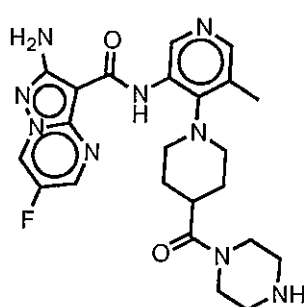
I-G-53



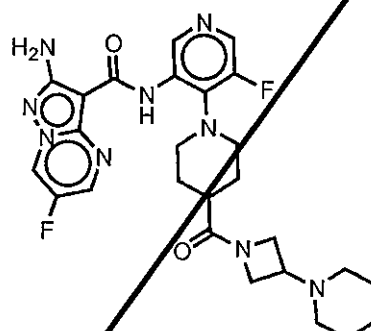
I-G-54



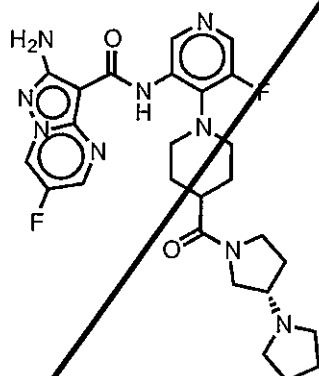
I-G-55



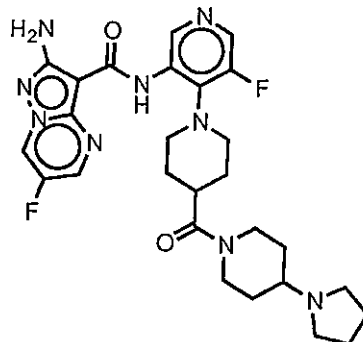
I-G-56



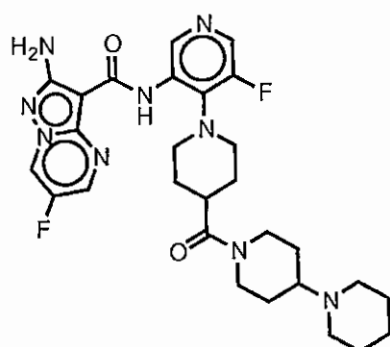
I-G-57



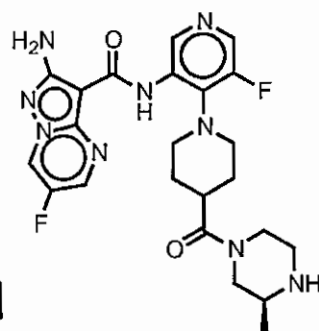
I-G-58



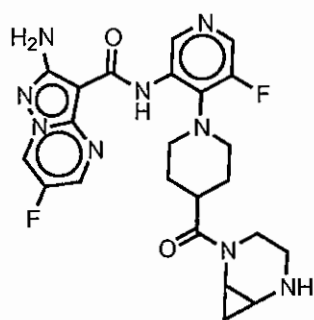
I-G-59



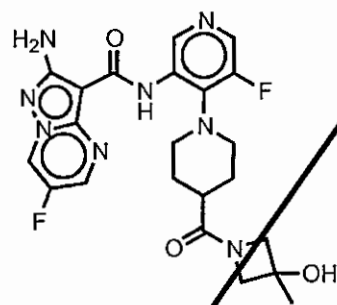
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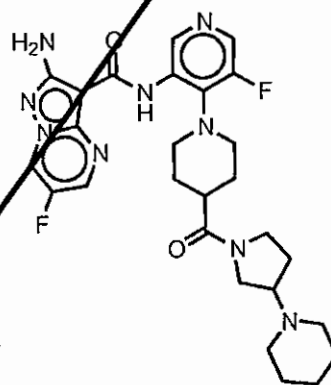
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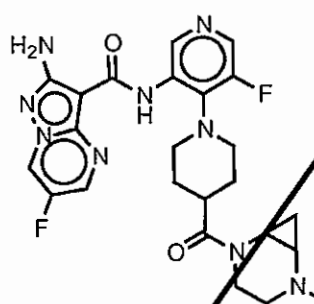
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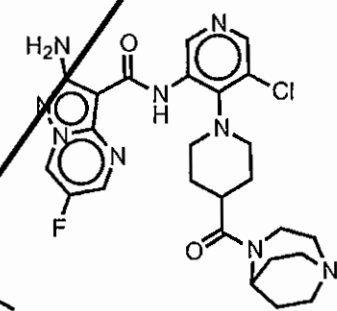
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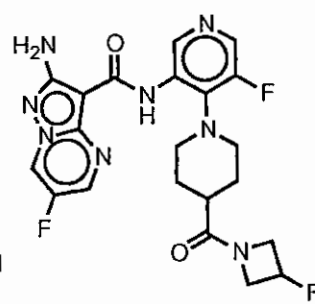
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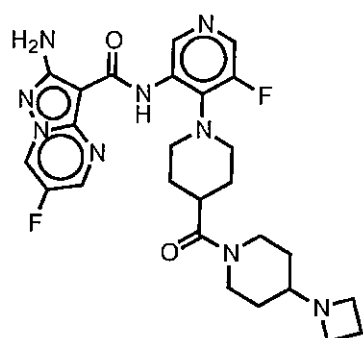
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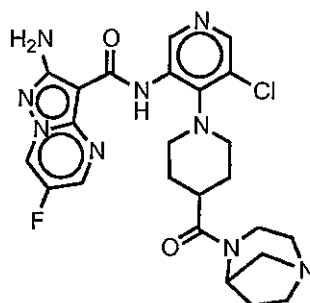
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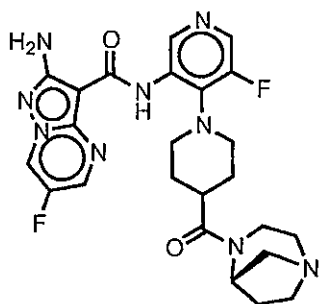
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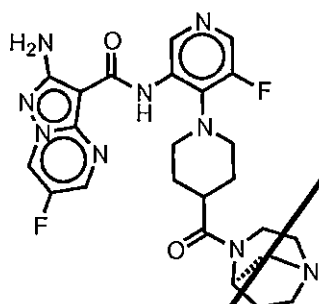
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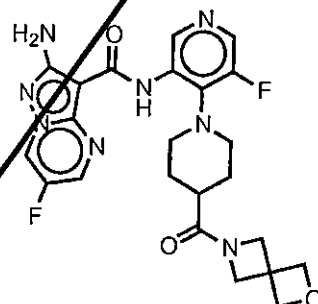
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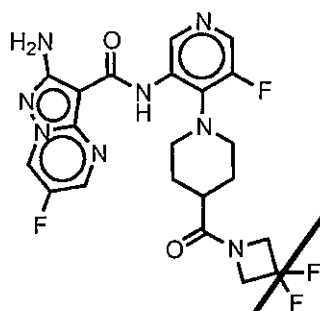
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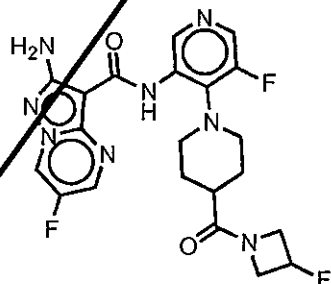
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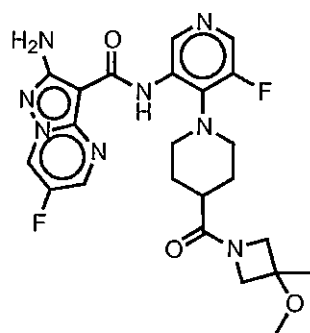
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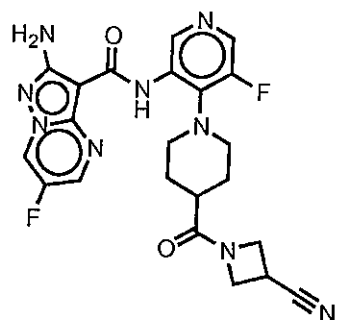
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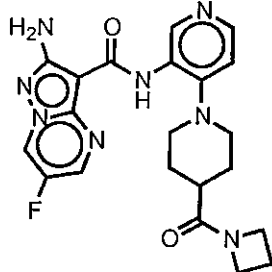
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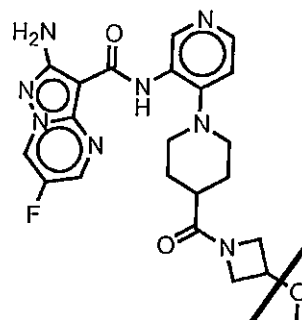
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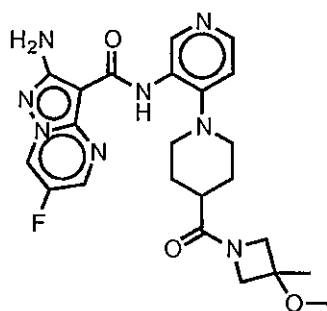
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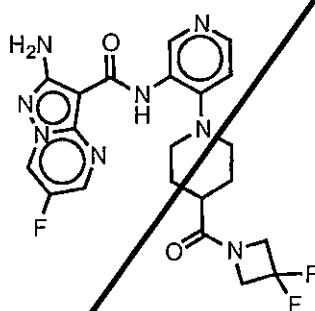
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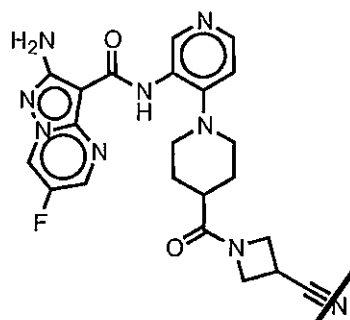
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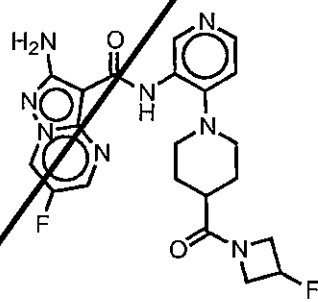
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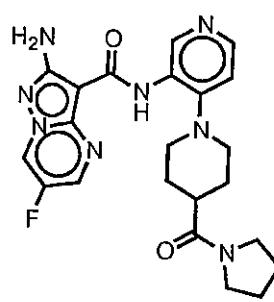
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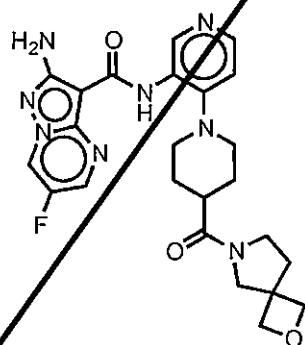
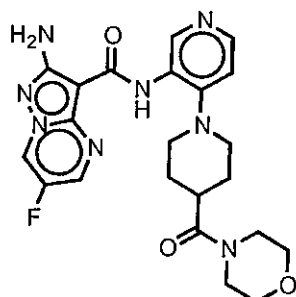
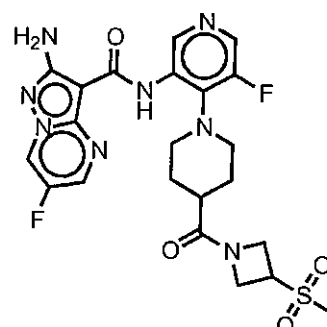
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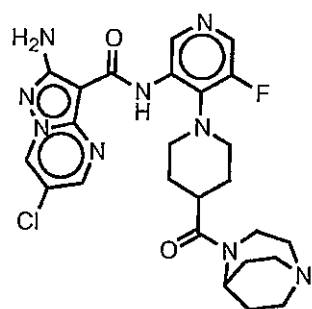
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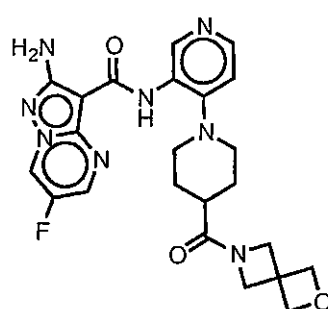
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I-G-84



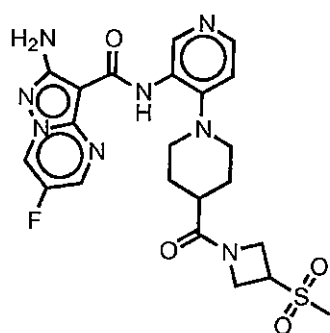
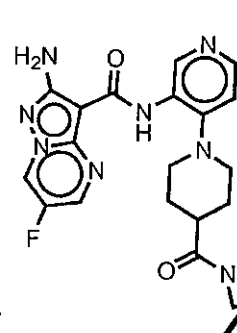
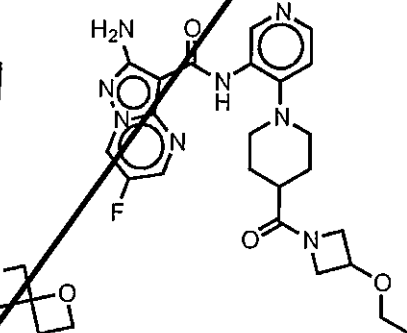
I-G-85



I-G-86

I-G-87

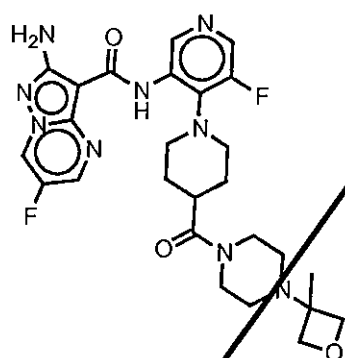
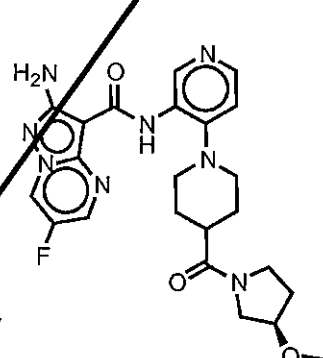
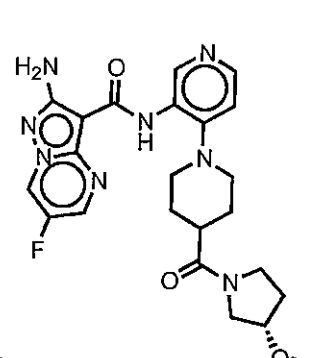
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I-G-89

I-G-90

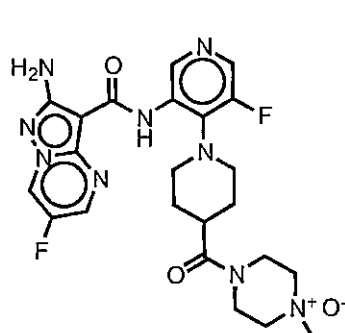
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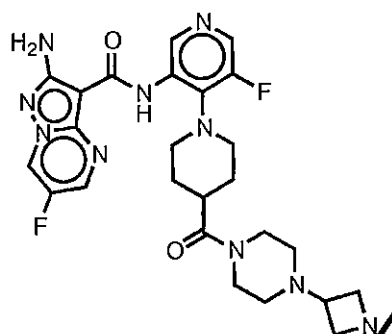
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I-G-93

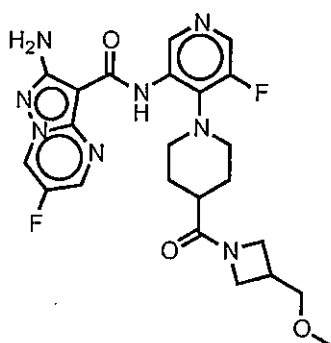
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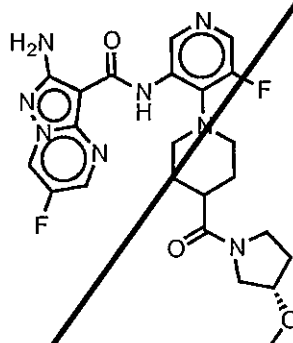
I-G-95



I-G-96



I-G-98



I-G-99.

159. A pharmaceutical composition comprising a compound of any one of claims 1-158 and a pharmaceutically acceptable carrier.
160. A method for treating cancer in a patient comprising administering a compound of any one of claims 1-159 or a pharmaceutically acceptable derivative thereof.
161. The method of claim 160, further comprising administering to said patient an additional therapeutic agent independently selected from a DNA-damaging agent; wherein said additional therapeutic agent is appropriate for the disease being treated; and said 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.
162. The method of claim 161, wherein said DNA-damaging agent is selected chemotherapy or radiation treatment.

163. The method of claim 161, 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.
164. The method of claim 163, 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.
165. The method of claim 163, 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.
166. The method of claim 164, 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.
167. The method of claim 166, 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.

168. The method of claim 166, wherein said DNA-damaging agent is independently selected from a platinating agent or ionizing radiation.
169. The method of claim 164, wherein the antimetabolite is gemcitabine.
170. The method of claim 164, wherein the DNA-damaging agent is ionizing radiation.
171. The method of claim 164, wherein the DNA-damaging agent is a platinating agent independently selected from Cisplatin or Carboplatin.
172. The method of claim 164, wherein the DNA-damaging agent is a Topo II inhibitor selected from Etoposide.
173. The method of claim 162, wherein the DNA-damaging agent is an alkylating agent selected from Temozolomide.
174. The method of claim 164, wherein the DNA-damaging agent is independently selected from one or more of the following: Cisplatin, Carboplatin, gemcitabine, Etoposide, Temozolomide, or ionizing radiation.
175. The method of claim 174, wherein the additional therapeutic agents are selected from one or more of the following: gemcitabine, cisplatin or carboplatin, and etoposide.
176. The method of any one of claims 160-175, 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, Karposi'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, Karposi'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.

177. The method of claim 176, wherein said cancer is selected from a cancer of the lung or the pancreas.

178. The method of claim 177, wherein said cancer is lung cancer.

179. The method of claim 178, wherein the lung cancer is non-small cell lung cancer or small cell lung cancer.

180. The method of claim 179, wherein the lung cancer is small cell lung cancer and the additional therapeutic agents are cisplatin and etoposide.

181. The method of claim 179, wherein the lung cancer is non-small cell lung cancer and the additional therapeutic agents are gemcitabine and cisplatin.

182. The method of claim 181, wherein the non-small cell lung cancer is squamous non-small cell lung cancer.

183. The method of any one of claims 160-175, wherein said cancer is selected from lung cancer, head and neck cancer, pancreatic cancer, gastric cancer, or brain cancer.

184. The method of any one of claims 160-175, 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.

185. The method of claim 184, wherein the cancer is breast cancer and the additional therapeutic agent is cisplatin.

186. The method of claim 185, wherein the cancer is triple negative breast cancer.

187. The method of claim 168, wherein the additional therapeutic agent is Gemcitabine and the cancer is pancreatic cancer.

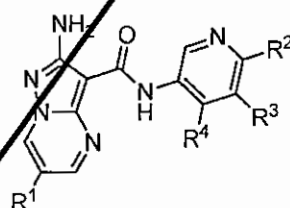
188. A method of treating pancreatic cancer comprising administering to a patient a compound of a compound of any one of claims 1-158 in combination with an additional therapeutic agent selected from Gemcitabine, radiation therapy, or both Gemcitabine and radiation therapy together.
189. A method of increasing the sensitivity of pancreatic cancer cells to a cancer therapy selected from chemotherapy or radiation therapy by administering to a patient a compound of any one of claims 1-158.
190. The method of claim 189, wherein the chemotherapy is gemcitabine.
191. The method of claim 189, wherein the cancer therapy is gemcitabine.
192. The method of claim 189, wherein the cancer therapy is radiation.
193. The method of claim 181, wherein the cancer therapy is gemcitabine and radiation.
194. A method of inhibiting phosphorylation of Chk1 (Ser 345) in a pancreatic cancer cell comprising administering a compound of any one of claims 1-159 in combination with gemcitabine (100 nM) and/or radiation (6 Gy).
195. A method of sensitizing pancreatic cancer cells to chemoradiation by administering a compound of any one of claims 1-158 in combination with chemoradiation.
196. The method of claim 166, wherein the chemoradiation is gemcitabine and radiation.
197. A method of radiosensitizing hypoxic pancreatic cancer cells by administering a compound of any one of claims 1-158 in combination with radiation therapy.
198. A method of sensitizing hypoxic pancreatic cancer cells by administering a compound of any one of claims 1-158 in combination with chemotherapy.
199. The method of any one of claims 195-198 wherein said cancer cell is a PSN-1, MiaPaCa-2 or PancM cancer cell.

200. A method of disrupting damage-induced cell cycle checkpoints by administering a compound of any one of claims 1-158 in combination with radiation therapy and/or gemcitabine.
201. A method of inhibiting repair of DNA damage by homologous recombination in a pancreatic cancer cell by administering a compound of any one of claims 1-156 in combination with radiation therapy and/or gemcitabine.
202. The method of any one of claims 195-201 wherein the compound is administered to a patient.
203. The method of any one of claims 196-201 wherein the compound is administered to a pancreatic cancer cell.
204. The method of claim 203, wherein the pancreatic cancer cells are derived from a pancreatic cell line selected from PSN-1, MiaPaCa-2 or Panc-1.
205. A method of treating non-small cell lung cancer comprising administering to a patient a compound of any one of claim 1-158 in combination with one or more of the following additional therapeutic agents: Cisplatin or Carboplatin, Etoposide, and ionizing radiation.
206. A method of promoting cell death in cancer cells comprising administering to a patient a compound of any one of claims 1-158.
207. A method of preventing cell repair from DNA damage comprising administering to a patient a compound of any one of claims 1-158.
208. A method of inhibiting ATR in a biological sample comprising the step of contacting a compound of any one of claims 1-158 with said biological sample.
209. The method of claim 208, wherein said biological sample is a cell.
210. A method of sensitizing cells to DNA damaging agents comprising administering to a patient a compound of any one of claims 1-158.

211. The method of any one of claims 161-210, wherein said cell is a cancer cell having defects in the ATM signaling cascade.
212. The method of claim 211, 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.
213. The method of claim 211, 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.
214. The method of any one of claims 160-210, wherein said cell is a cancer cell expressing DNA damaging oncogenes.
215. The method of claim 214, 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.
216. The method of any one of claims 161-210, wherein said cancer, cancer cell, or cell has a defect in a base excision repair protein.
217. The method of claim 216, 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.
218. The method of claim 217, wherein the base excision repair protein is PARP1, PARP2 or PolB.
219. The method of claim 218, wherein the base excision repair protein is PARP1 or PARP2.
220. The method of any one of claims 161-219, further comprising administering to said patient an additional therapeutic agent wherein said agent inhibits or modulates a base excision repair protein.

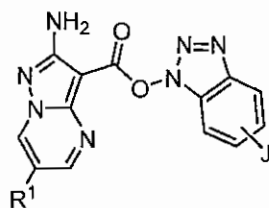
221. The method of claim 220, wherein the base excision repair protein is selected from UNG, SMUG1, MBD4, TDG, OGG1, MYH, NTH1, MPG, NEIL1, NEIL2, NEIL3 (DNA glycosylases); APE1, APEX2 (AP endonucleases); LIG1, LIG3 (DNA ligases I and III); XRCC1 (LIG3 accessory); PNK, PNKP (polynucleotide kinase and phosphatase); PARP1, PARP2 (Poly(ADP-Ribose) Polymerases); PolB, PolG (polymerases); FEN1 (endonuclease) or Aprataxin.
222. The method of claim 221, wherein the base excision repair protein is selected from PARP1, PARP2, or PolB.
223. The method of claim 222, wherein the base excision repair protein is selected from PARP1 or PARP2.
224. The method of claim 213, 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.

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



I-A

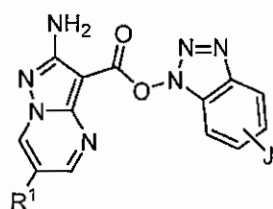
comprising reacting a compound of formula 6:



6

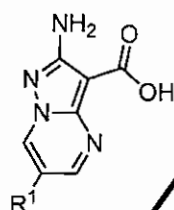
under suitable conditions to form an amide bond, wherein J, R¹, R², R³, and R⁴ are as defined in claims 1-158.

224. The process of claim 223, further comprising the step of preparing a compound of formula 6:



6

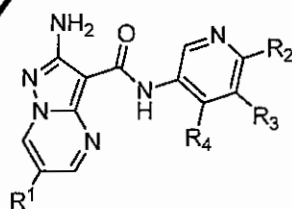
by reacting a compound of formula 5:



5

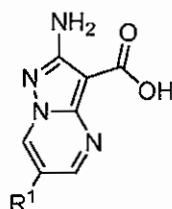
under suitable conditions to form an activated ester.

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



I-A

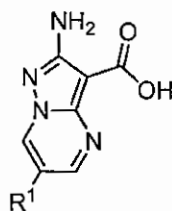
comprising reacting a compound of formula 5:



5

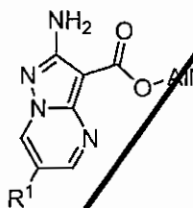
under suitable conditions to form an amide bond, wherein R^1 , R^2 , R^3 , and R^4 are as defined in claims 1-158.

226. The process of any one of claims 223-225, further comprising the step of preparing a compound of formula 5:



5

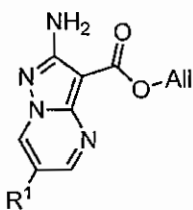
by reacting a compound of formula 4:



4

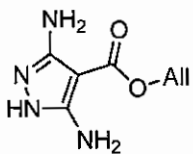
under suitable deprotection conditions.

227. The process of claim 226, further comprising the step of preparing a compound of formula 4:



4

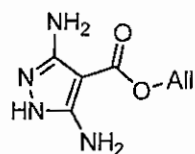
by reacting a compound of formula 3:



3

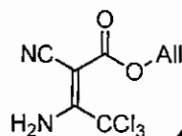
under suitable condensation conditions to form a pyrimidine ring.

228. The process of claim 227, further comprising the step of preparing the compound of formula 3:



3

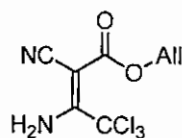
by reacting a compound of formula 2:



2

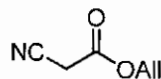
under suitable condensation conditions to form a pyrazole ring.

229. The process of claim 228, 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.

230. The process of any one of claims 223, wherein R^1 is independently selected from halo or $-\text{CH}_2\text{CN}$.
231. The process of claim 230, wherein R^1 is independently selected from fluoro or chloro.
232. The process of claim 223, 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.
233. The process of claim 232, wherein the aprotic solvent is selected from NMP, pyridine, or DMF.
234. The process of claim 232, wherein the aprotic solvent is optionally substituted pyridine.
235. The process of any one of claims 232-234, wherein the reaction is carried out at a temperature of at least 80°C .
236. The process of claim 235, wherein the reaction is carried out at a temperature of at least 100°C .
237. The process of any one of claims 224, 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.
238. The process of claim 237, wherein the organic base is an aliphatic amine.
239. The process of claim 238, wherein the organic base is independently selected from DIPEA or triethylamine.
240. The process of any one of claims 237-239, wherein the amide coupling agent is independently selected from EDCI, TBTU, TCTU, HATU, T3P, or COMU.
241. The process of claim 240, wherein the amide coupling agent is independently selected from TBTU or TCTU.
242. The process of claim 241, wherein the amide coupling agent is TCTU.

243. The process of claim 226, wherein suitable hydrolytic conditions comprise reacting the compound of formula 4 with a silane in the presence of a metal catalyst.
244. The process of claim 243, wherein the silane is phenylsilane.
245. The process of claim 244, wherein the metal catalyst is a palladium catalyst.
246. The process of claim 245, wherein the metal catalyst is Pd(PPh₃)₄.
247. The process of claim 226, wherein suitable hydrolytic conditions comprise reacting the compound of formula 4 with an aqueous alkali.
248. The process of claim 247, wherein the aqueous alkali is independently selected from LiOH, NaOH, or KOH.
249. The process of claim 227, 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.
250. The process of claim 249, wherein the 1,3-dielectrophilic species is 1,3-dialdehyde or 3-(dialkylamino)-prop-2-enal.
251. The process of any one of claims 249 or 250, wherein the solvent is selected from DMF or DMSO.
252. The process of claim 249, wherein the 1,3-dielectrophilic species is generated *in situ* from a protected 1,3-dielectrophilic species.
253. The process of claim 252, wherein the 1,3-dielectrophilic species is generated from a ketal in the presence of a sulfonic acid.
254. The process of claim 253, wherein the sulfonic acid is PTSA.
255. The process of claim 228, 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.
256. The process of claim 255, wherein the aprotic solvent is DMF.
257. The process of claim 255, wherein the basic conditions comprise reacting the compound of formula 2 in the presence of potassium acetate or sodium acetate.

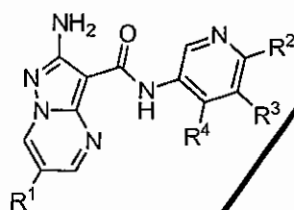
258. The process of claim 229, wherein suitable anion condensation conditions comprise
 1) reacting the compound of formula 1 with a base, in the presence of a solvent, to generate the anion of the compound of formula 1; and 2) reacting the anion of the compound of formula 1 with trichloroacetonitrile.

259. The process of claim 258, wherein the base is potassium acetate.

260. The process of claim 258, wherein the solvent is an alcohol.

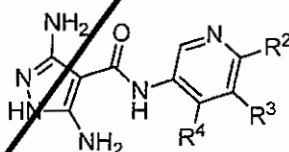
261. The process of claim 260, wherein the solvent is isopropylalcohol.

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



I-A

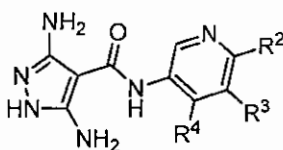
comprising reacting a compound of formula 9:



9

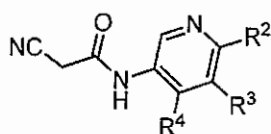
under suitable condensation conditions to form a pyrimidine ring, wherein R^1 , R^2 , R^3 and R^4 are as defined in claims 1-156.

263. The process of claim 262, further comprising the step of preparing a compound of formula 9:



9

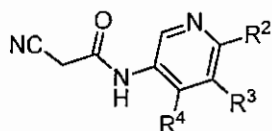
by reacting a compound of formula 8:



8

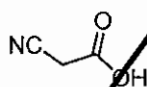
under suitable condensation conditions to form a pyrazole ring.

264. The process of claim 263, further comprising the step of preparing a compound of formula 8:



8

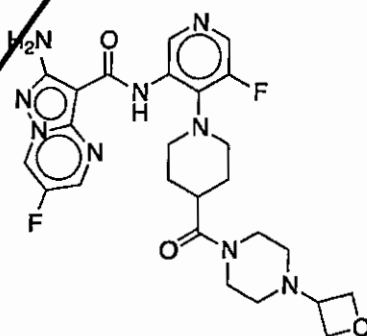
by reacting a compound of formula 7:



7

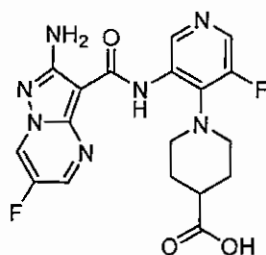
under suitable conditions to form an amide bond.

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



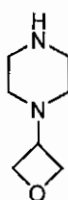
I-G-32

comprising the step of reacting the compound of formula 29:



29

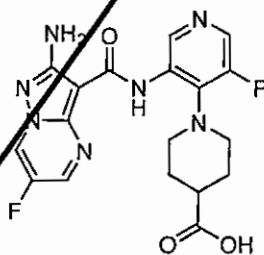
with a compound of formula 25:



25

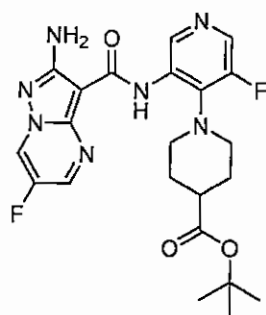
under suitable conditions to form an amide bond.

266. The process of claim 265, further comprising the step of preparing the compound of formula 29:



29

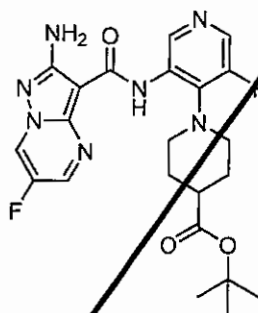
by reacting the compound of formula 28:



28

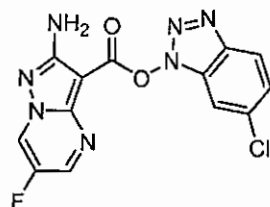
under suitable deprotection conditions to form the carboxylic acid.

267. The process of claim 266, further comprising the step of preparing a compound of formula 28:



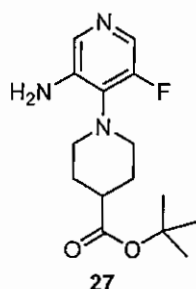
28

by reacting the compound of formula 6a*:



6a*

with a compound of formula 27:



27

under suitable conditions to form an amide bond.

268. The compound of claim 265, 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.

269. The compound of claim 268, wherein the aprotic solvent is independently selected from NMP, DMF, or tetrahydrofuran.

270. The process of claim 269, wherein the aprotic solvent is tetrahydrofuran.

271. The process of claim 269, wherein the base is an aliphatic amine.

272. The process of claim 271, wherein the base is DIPEA.

273. The process of any one of claims 268-272, wherein the amide coupling partner is independently selected from TBTU or TCTU.

274. The process of claim 273, wherein the amide coupling partner is TCTU.

275. The process of claim 266, wherein suitable deprotection conditions comprise reacting the compound of formula 28 with an acid in the presence of a solvent.

276. The process of claim 275, wherein the acid is HCl.

277. The process of claim 276, wherein the solvent is 1,4-dioxane.

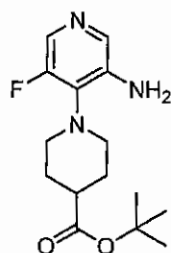
278. The process of claim 267, wherein the suitable conditions for forming the amide bond comprise reacting the compound of formula 6a* with the compound of formula 27 in an aprotic solvent under heat.

279. The process of claim 278, wherein the aprotic solvent is independently selected from NMP, pyridine, or DMF.

280. The process of claim 279, wherein the aprotic solvent is pyridine.

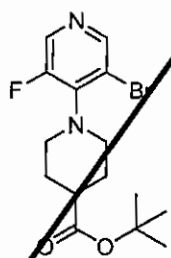
281. The process of any one of claims 278, wherein the reaction is carried out at a temperature of at least 80°C.

282. A process of preparing a compound of formula 27:



27

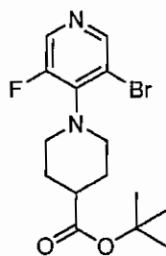
comprising the step of reacting a compound of formula 26:



26

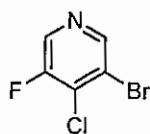
under suitable conditions to form an amine.

283. The process of claim 282, further comprising the step of preparing a compound of formula 26:

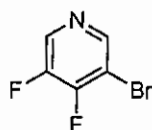


26

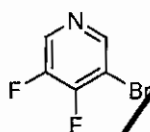
by 1) reacting a compound of formula 18:

**18**

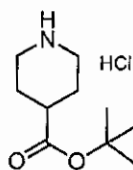
under suitable halogen exchange conditions to generate the compound of formula 32

**32**, and

2) reacting the compound of formula 32:

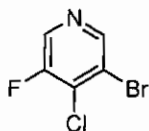
**32**

with a compound of formula 22:

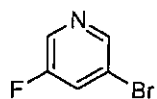
**22**

under suitable displacement conditions.

284. The process of claim 282, further comprising the step of preparing a compound of formula 18:

**18**

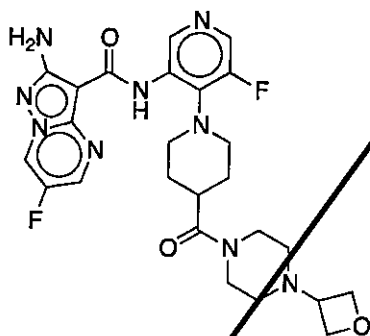
by reacting the compound of formula **31**:



31

under suitable halogenation conditions.

285. A compound having the structure **I-G-32**:

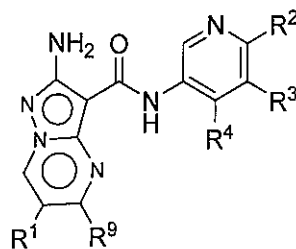


I-G-32

or a pharmaceutically acceptable salt.

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} ;

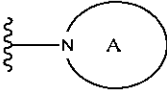
J^{LM} is independently selected from halo, $-CN$, or a $C_{1-4}aliphatic$ chain wherein up to two methylene units of the aliphatic chain are optionally replaced with $-O-$, $-NR-$, $-C(O)-$, or $-S(O)_n-$;

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_{1-8} 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;

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;

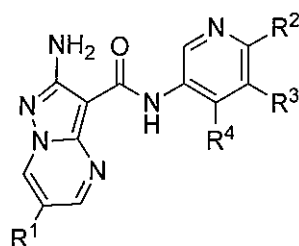
J^M is independently selected from halo or C₁₋₆aliphatic;

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 C₁₋₃aliphatic 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 0-3 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:

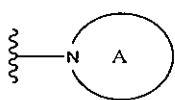
R^1 is independently selected from fluoro, chloro, or $-C(J^1)_2CN$;

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_{1-3} 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;

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

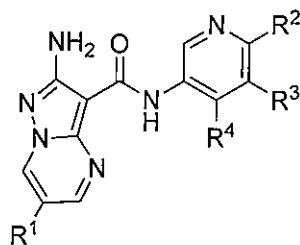
two occurrences of J^T , together with Q^3 , form a 6-10 membered saturated or partially unsaturated bridged ring system;

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:

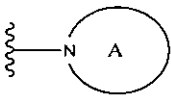
R^1 is independently selected from fluoro, chloro, or $-C(J^1)_2CN$;

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;

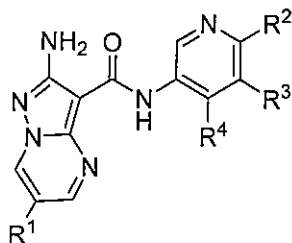
two occurrences of J^T , together with Q^3 , form a 6-10 membered saturated or partially unsaturated bridged ring system;

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:

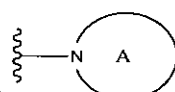
R^1 is independently selected from fluoro, chloro, or $-C(J^1)_2CN$;

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.

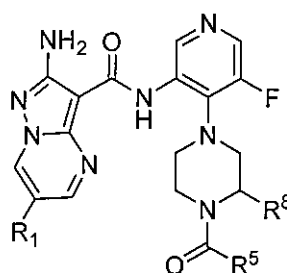
26. The compound of any one of claims 1-25, wherein R^2 is independently selected from $-CF_3$, $-NH(C_{1-2}alkyl)$, chloro, or H.

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 heterocyclyl.
- 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, pyrrolidinyl, piperazinyl, cyclobutyl, thiomorpholinyl, or morpholinyl.
- 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]pyrazinyl or 5,6,7,8-tetrahydroimidazo[1,2-a]pyrazinyl.
- 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, piperazinyl, pyrrolidinyl, or morpholinyl.
- 58 The compound of claim 57, wherein J^R is a piperazinyl.
- 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:

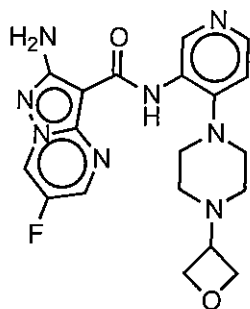
R^5 is selected from C_{1-4} aliphatic, a 3-6 membered cycloalkyl, or a 3-6 membered heterocyclyl having 1-2 heteroatoms selected from oxygen or sulfur;

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

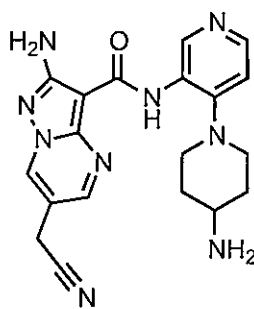
R^5 and R^8 , taken together with the atoms to which they are bound, form a 5-6 membered non-aromatic ring having 1-2 heteroatoms selected from oxygen, nitrogen or sulfur.

- 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.

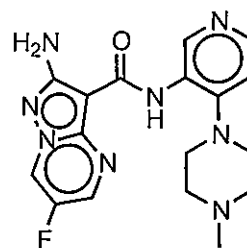
- 70 The compound of claim 69, wherein R^5 is cyclopropyl.
- 71 The compound of claim 65, wherein R^5 is a 3-6 membered heterocyclyl having 1-2 heteroatoms selected from oxygen or sulfur.
- 72 The compound of claim 71, wherein R^5 is tetrahydrofuranyl or oxytanyl.
- 73 The compound of claim 65, wherein 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:



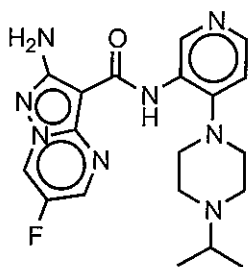
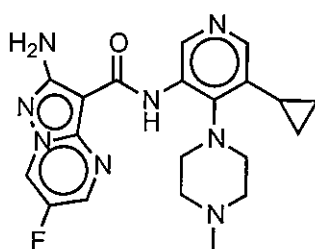
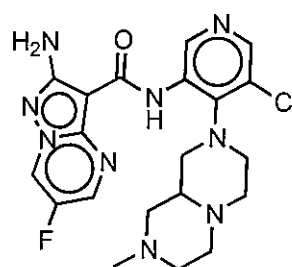
I-N-1



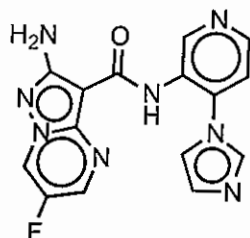
I-N-2



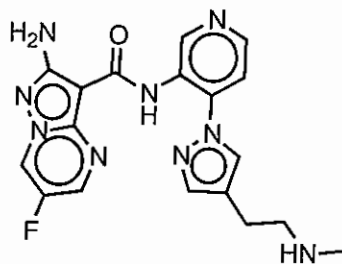
I-N-3



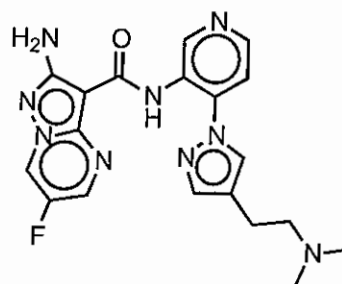
I-N-4



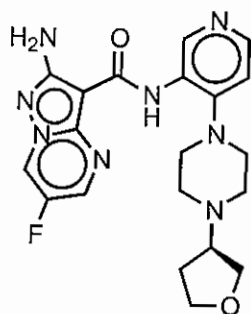
I-N-5



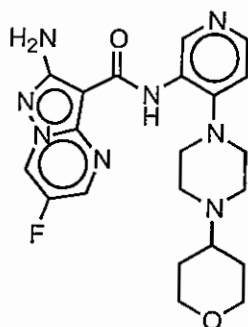
I-N-6



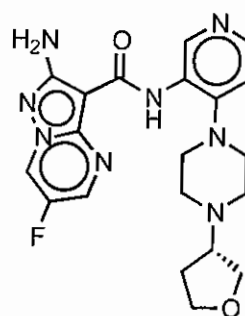
I-N-7



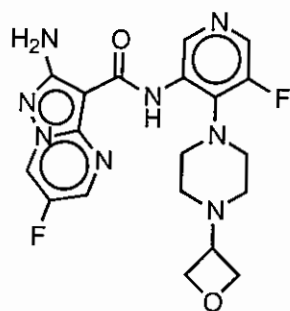
I-N-8



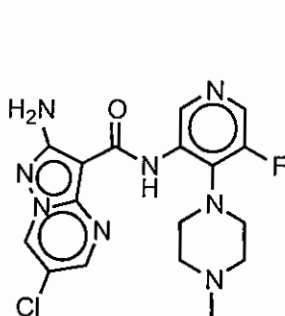
I-N-9



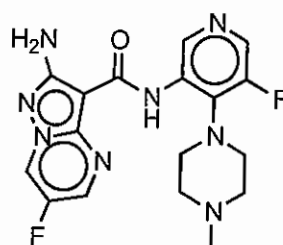
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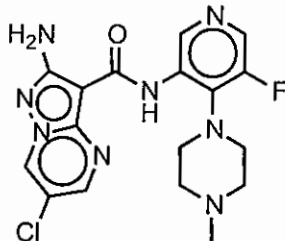
I-N-11



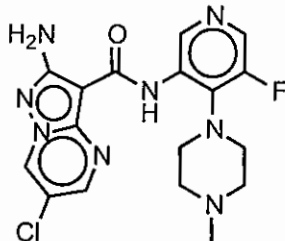
I-N-12



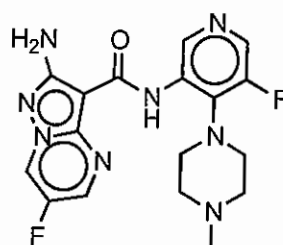
I-N-13

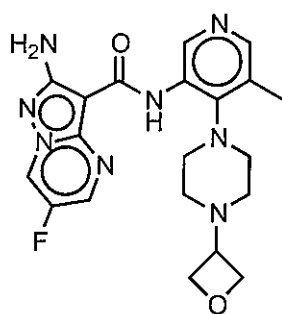


I-N-14

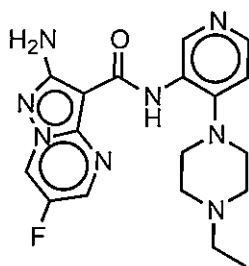


I-N-15

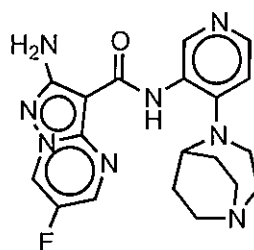




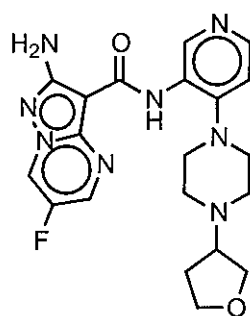
I-N-16



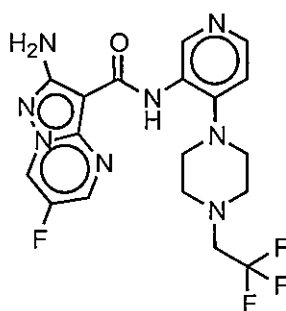
I-N-17



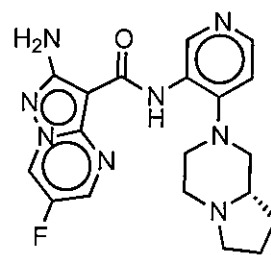
I-N-18



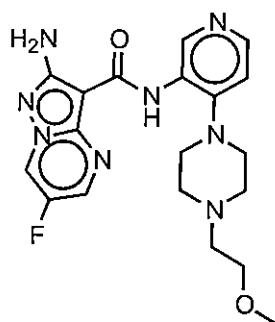
I-N-19



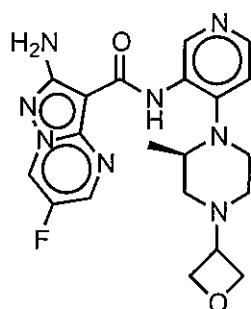
I-N-20



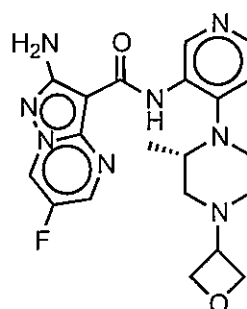
I-N-21



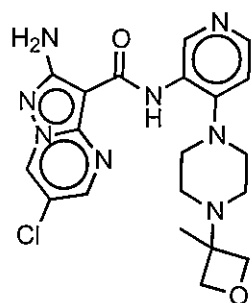
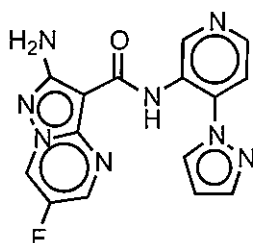
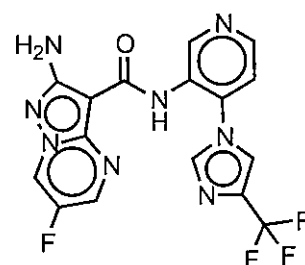
I-N-22



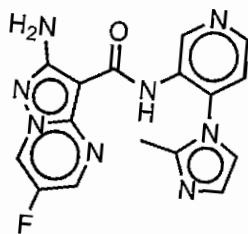
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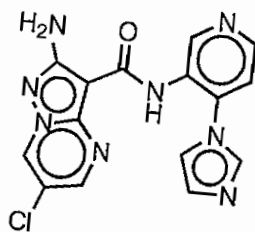
I-N-24



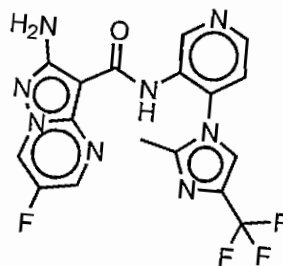
I-N-25



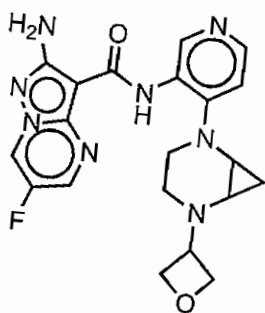
I-N-26



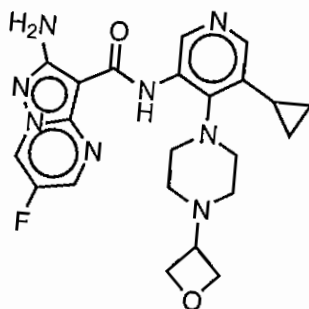
I-N-27



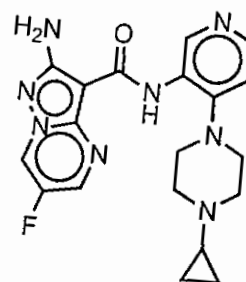
I-N-28



I-N-29



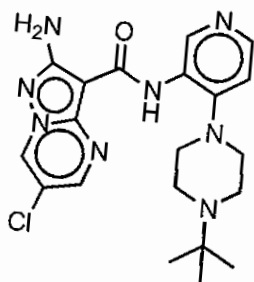
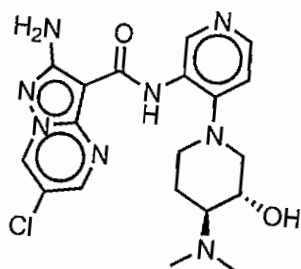
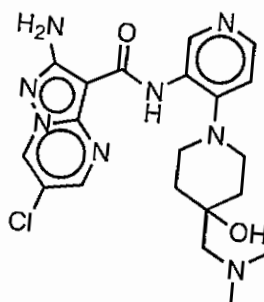
I-N-30



I-N-31

I-N-32

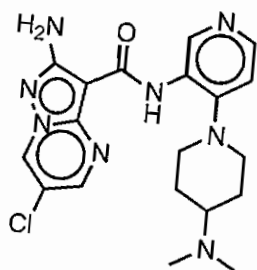
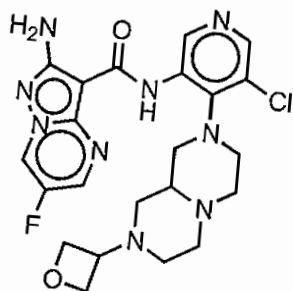
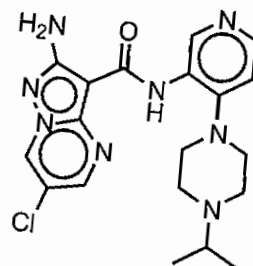
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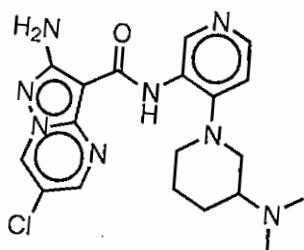
I-N-34

I-N-35

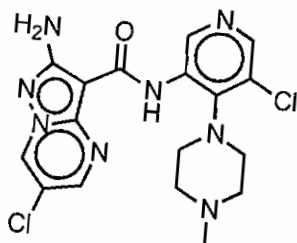
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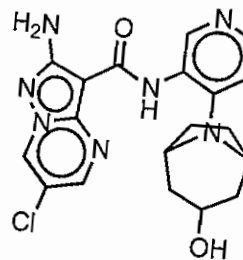
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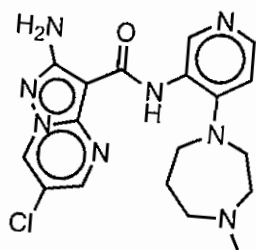
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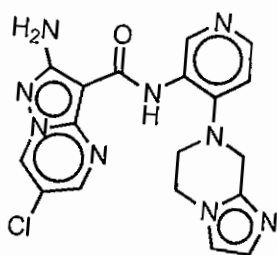
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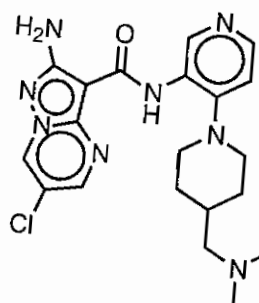
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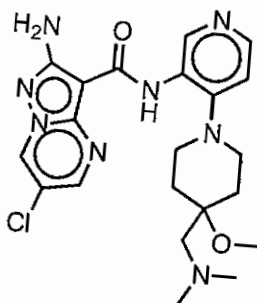
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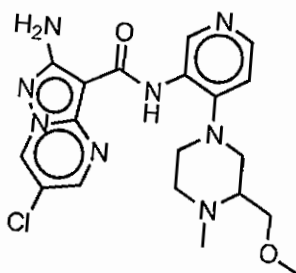
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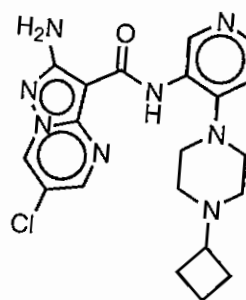
I-N-43



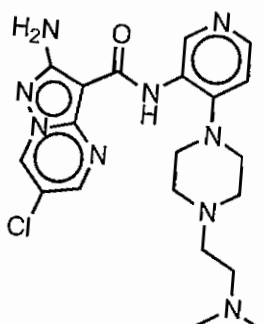
I-N-44



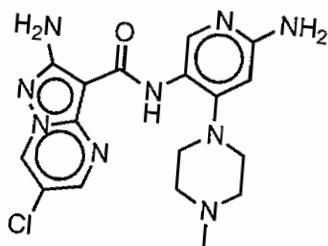
I-N-45



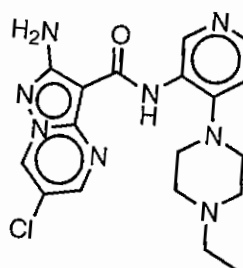
I-N-46

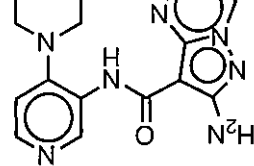


I-N-47

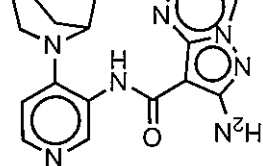


I-N-48

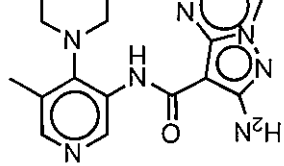




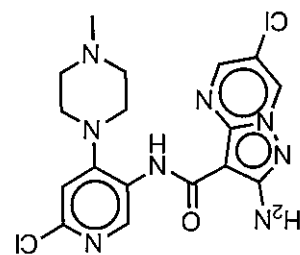
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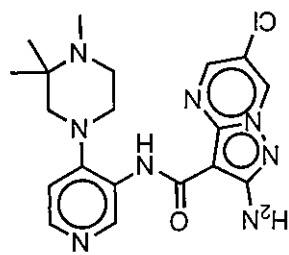
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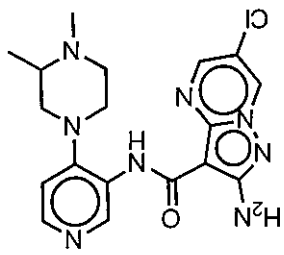
I-N-54



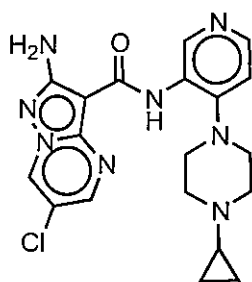
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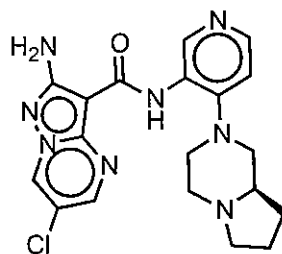
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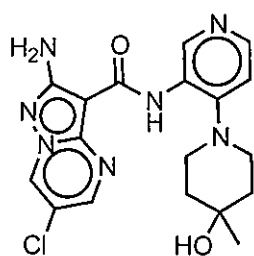
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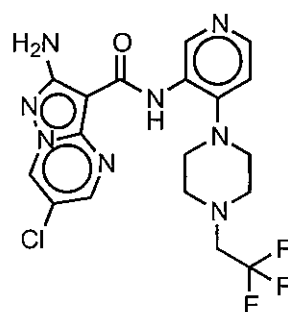
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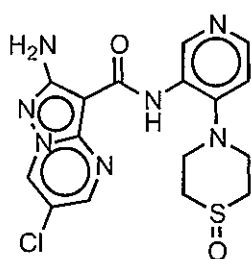
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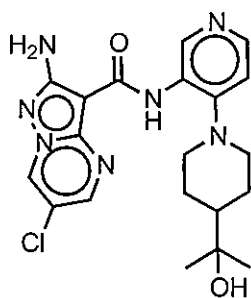
I-N-66



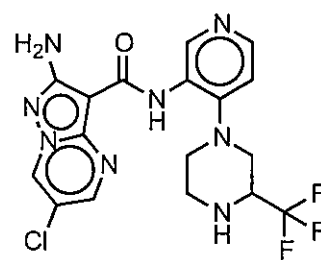
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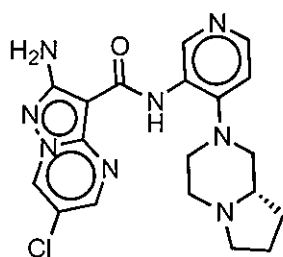
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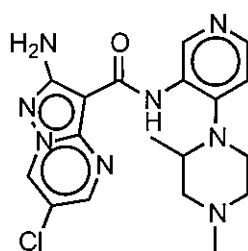
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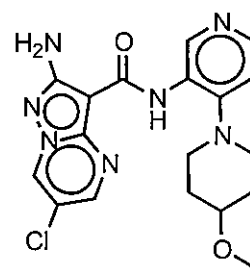
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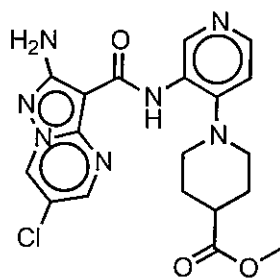
I-N-71



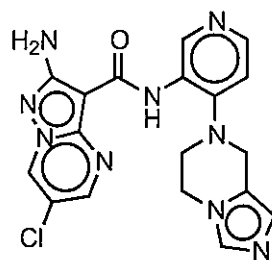
I-N-72



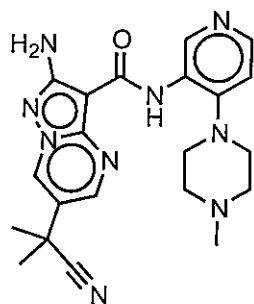
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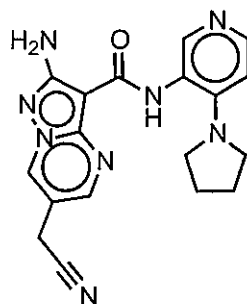
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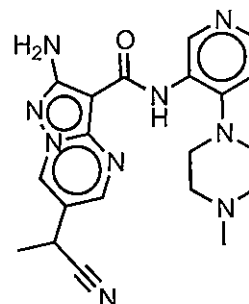
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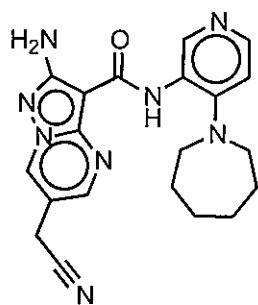
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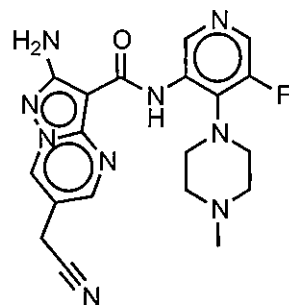
I-N-77



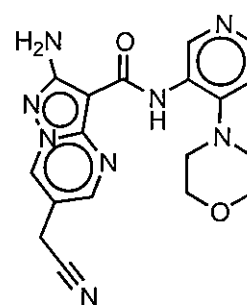
I-N-78



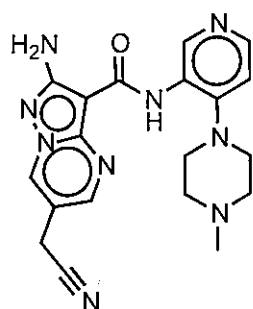
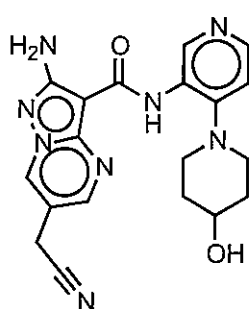
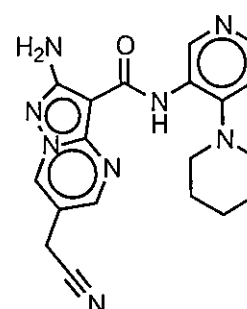
I-N-79



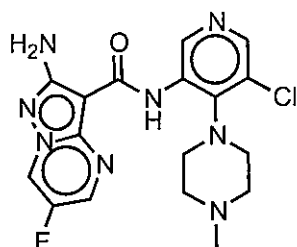
I-N-80



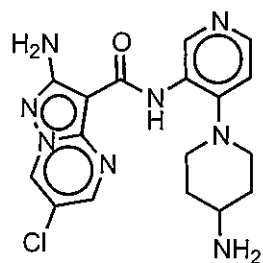
I-N-81



I-N-82

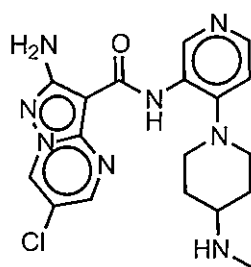


I-N-83

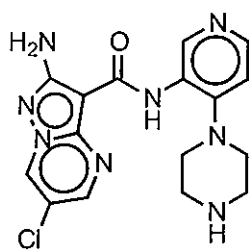
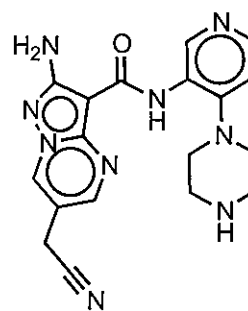


I-N-84

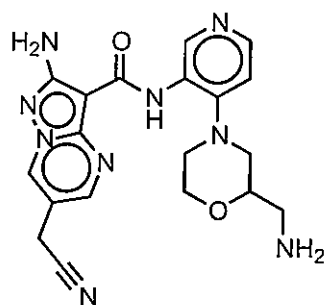
I-N-85



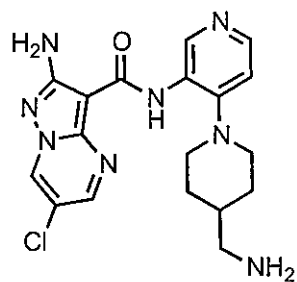
I-N-86



I-N-87



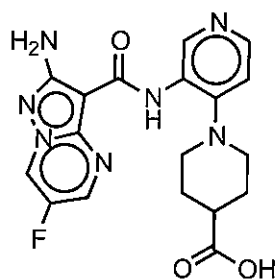
I-N-88



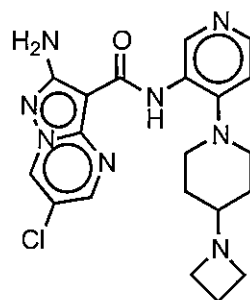
I-N-89

I-N-90

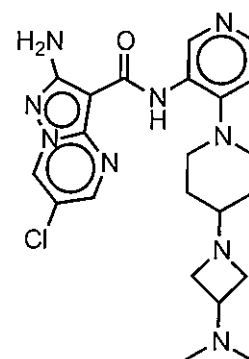
I-N-91



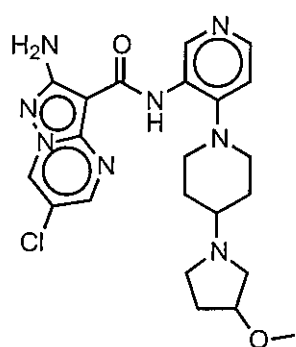
I-N-92



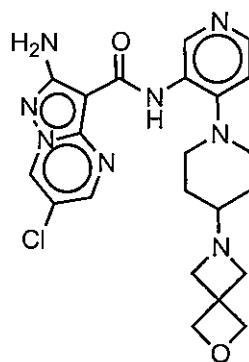
I-N-93



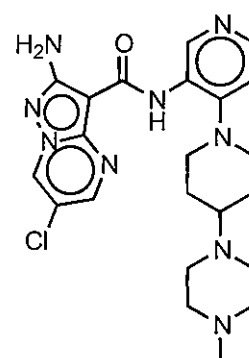
I-N-94



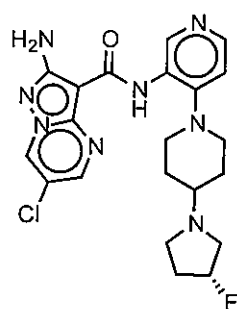
I-N-95



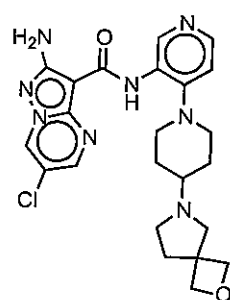
I-N-96



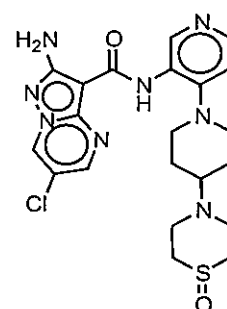
I-N-97



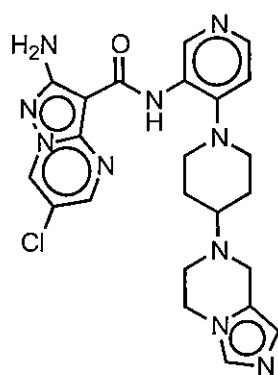
I-N-98



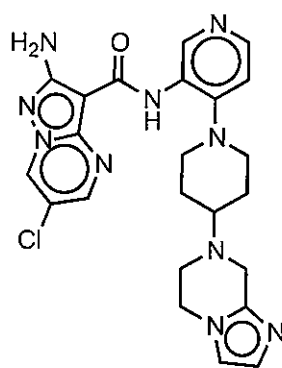
I-N-99



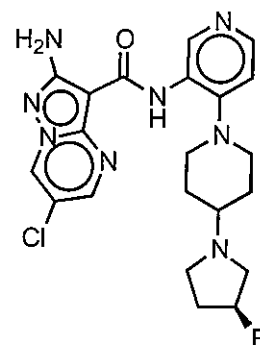
I-N-100



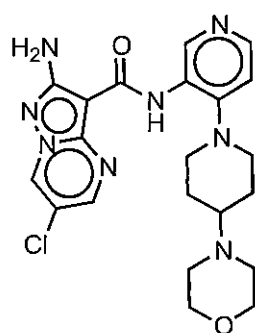
I-N-101



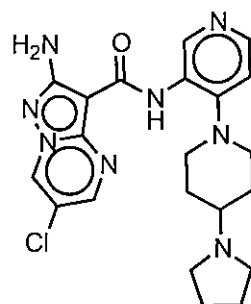
I-N-102



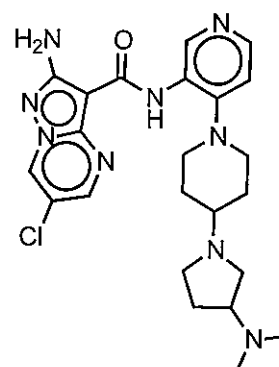
I-N-103



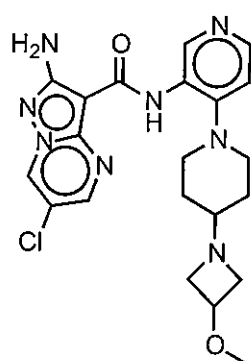
I-N-104



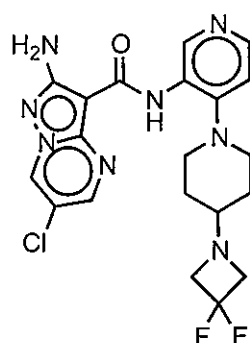
I-N-105



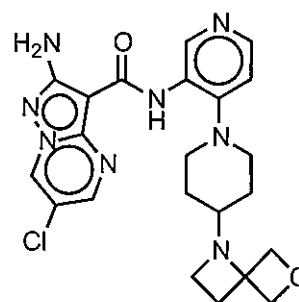
I-N-106



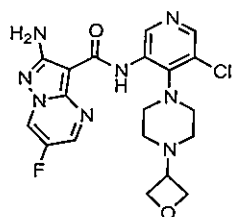
I-N-107



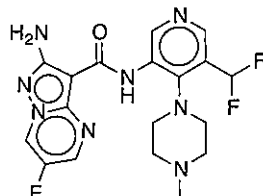
I-N-108



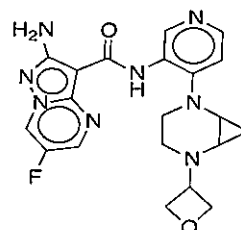
I-N-109



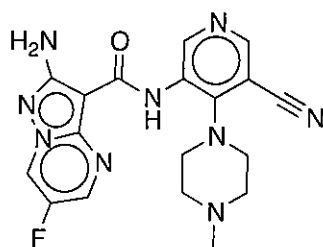
I-N-110



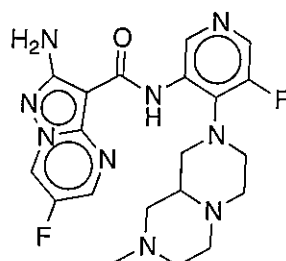
I-N-111



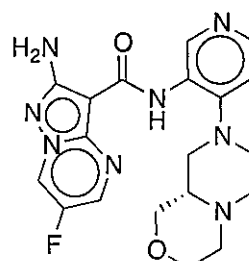
I-N-112



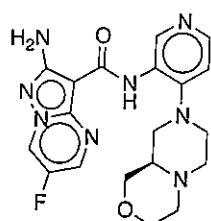
I-N-113



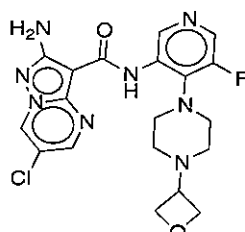
I-N-114



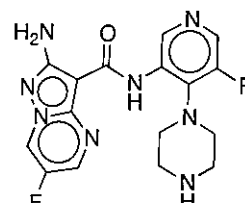
I-N-115



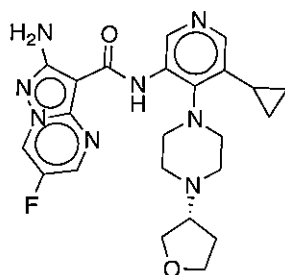
I-N-116



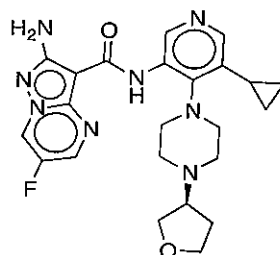
I-N-117



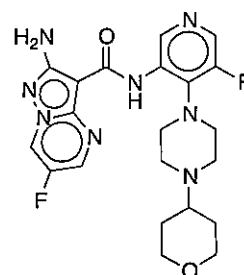
I-N-118



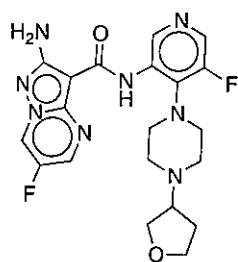
I-N-119



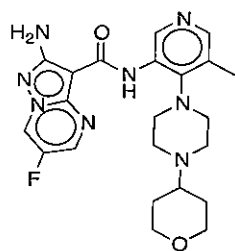
I-N-120



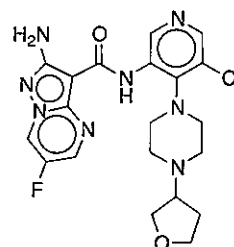
I-N-121



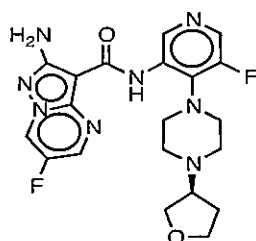
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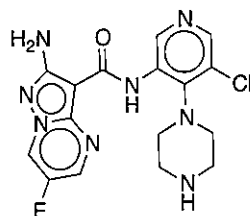
I-N-123



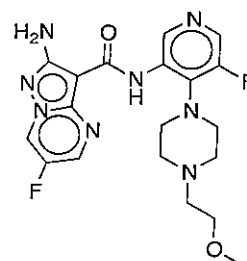
I-N-124



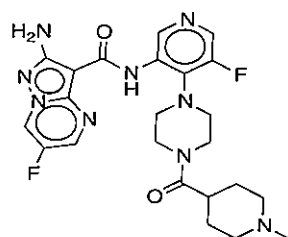
I-N-125



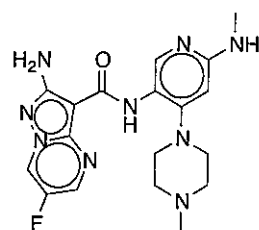
I-N-126



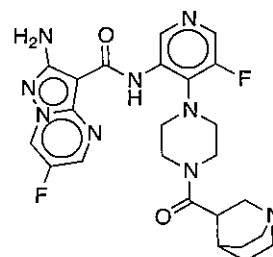
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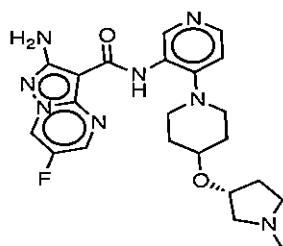
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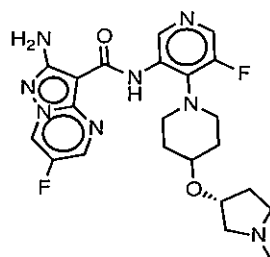
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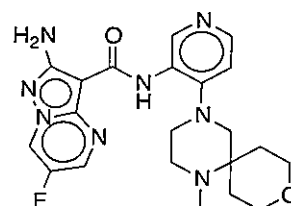
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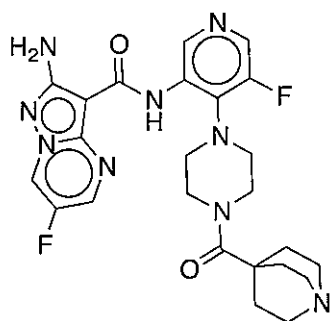
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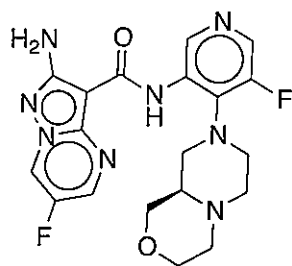
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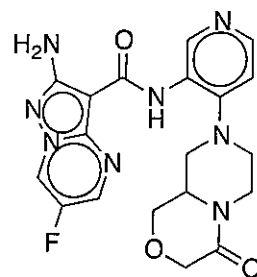
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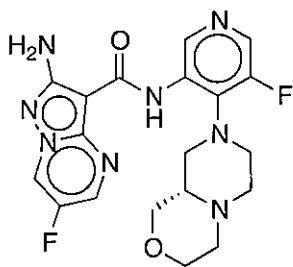
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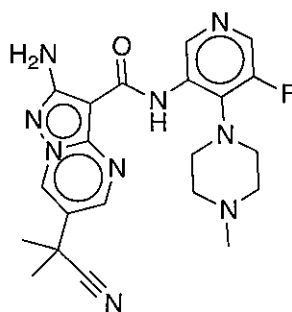
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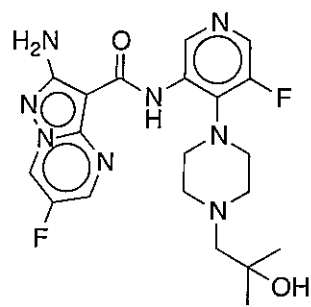
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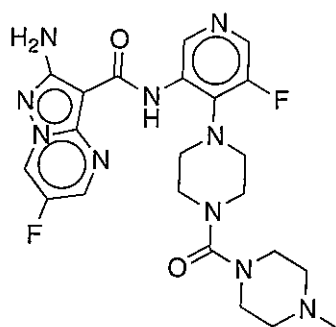
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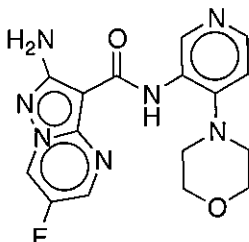
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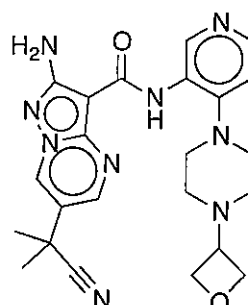
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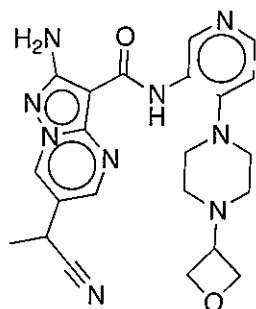
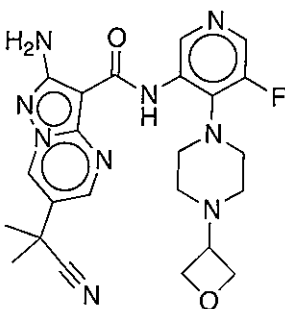
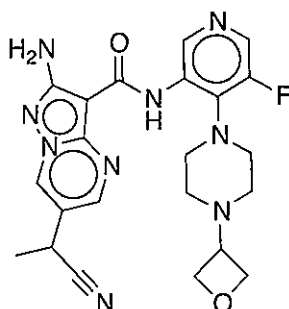
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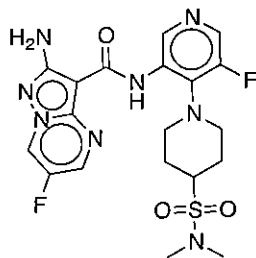
I-N-141



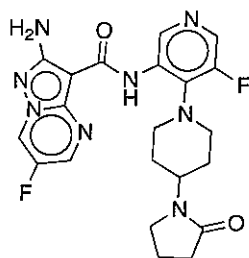
I-N-142



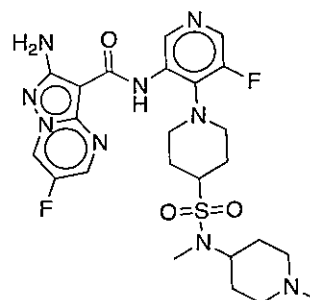
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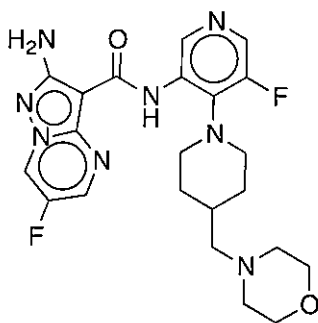
I-N-144



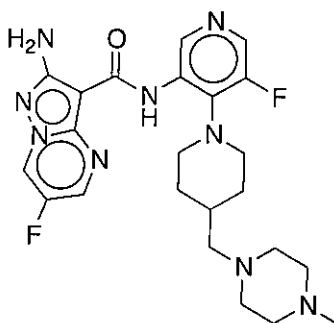
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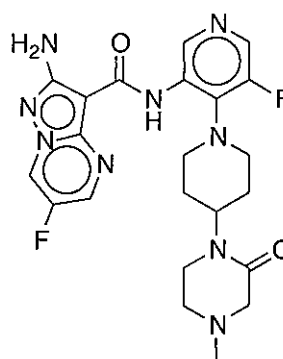
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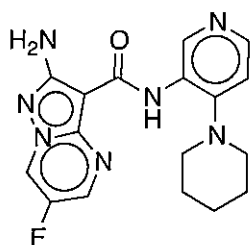
I-N-147



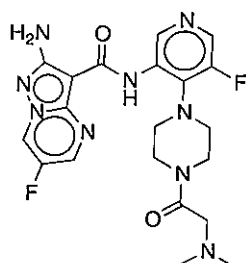
I-N-148



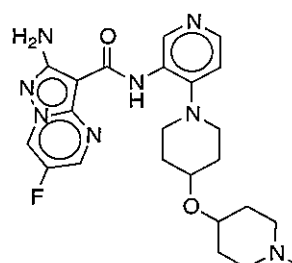
I-N-149



I-N-150



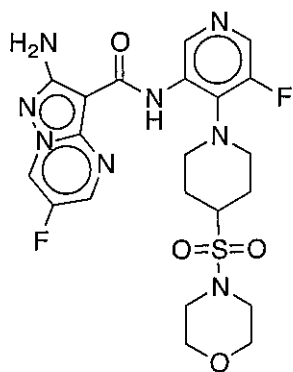
I-N-151



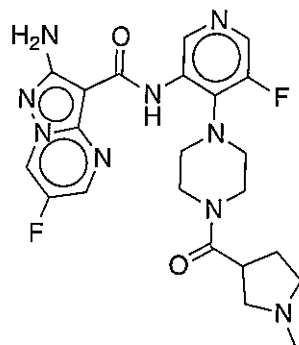
I-N-152

I-N-153

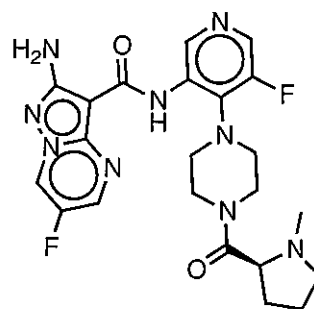
I-N-154



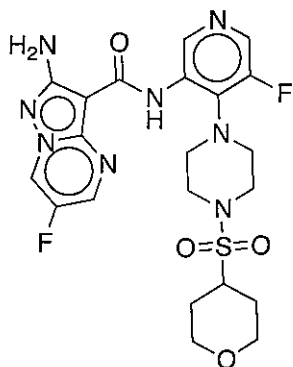
I-N-155



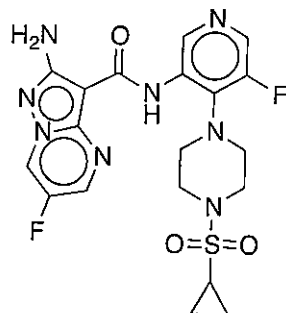
I-N-156



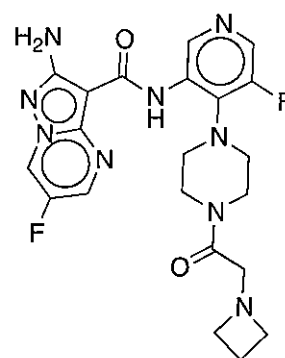
I-N-157



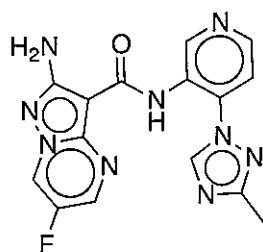
I-N-158



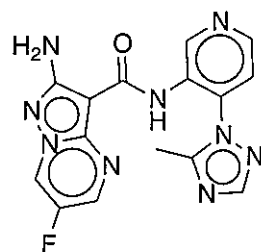
I-N-159



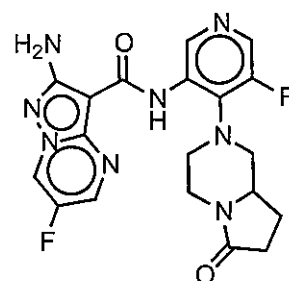
I-N-160



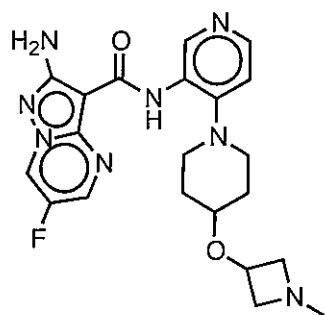
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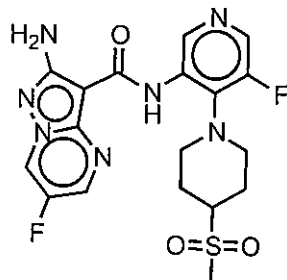
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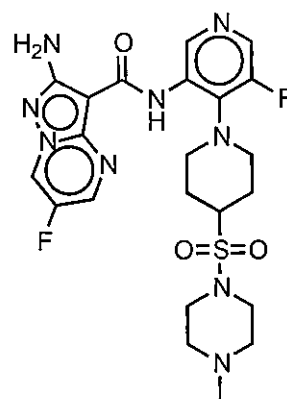
I-N-163



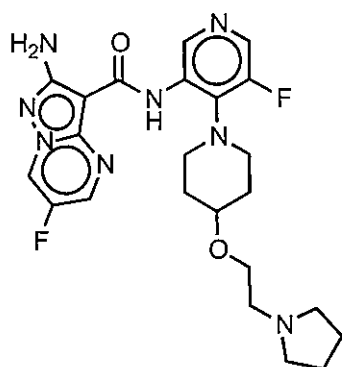
I-N-164



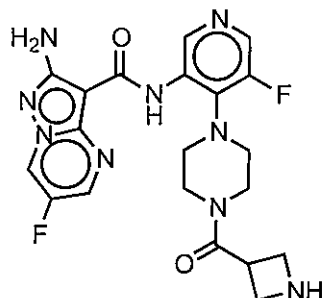
I-N-165



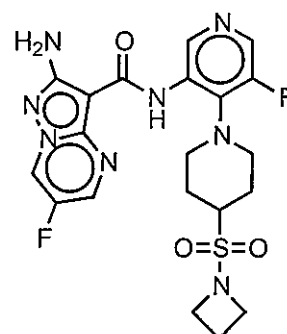
I-N-166



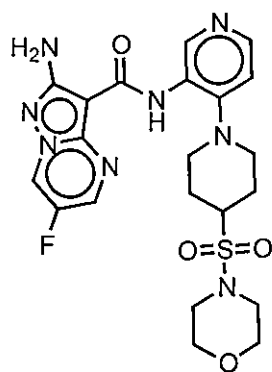
I-N-167



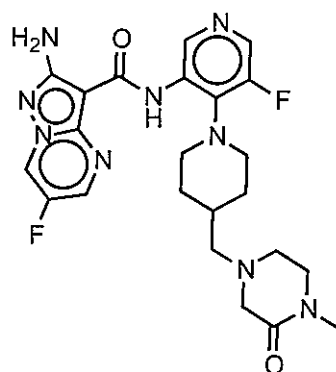
I-N-168



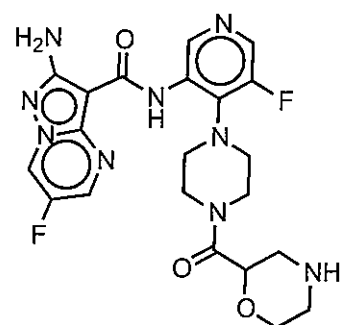
I-N-169



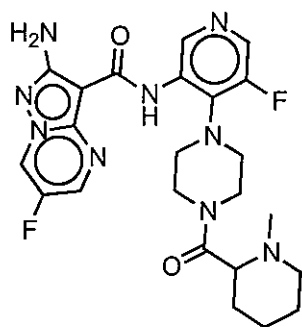
I-N-170



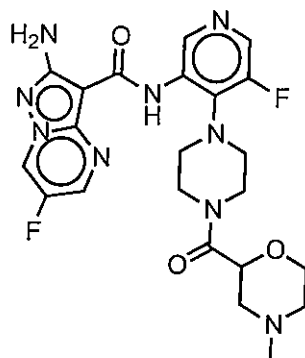
I-N-171



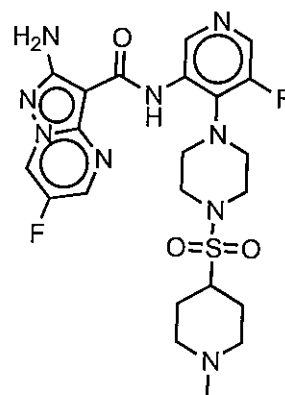
I-N-172



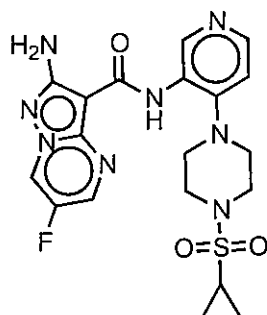
I-N-173



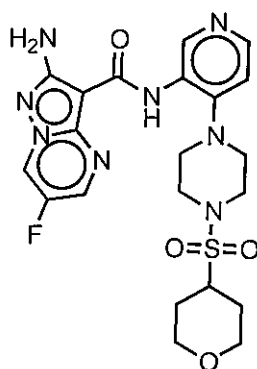
I-N-174



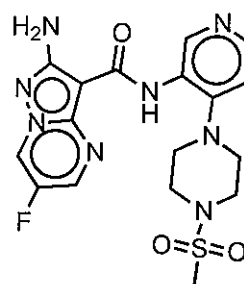
I-N-175



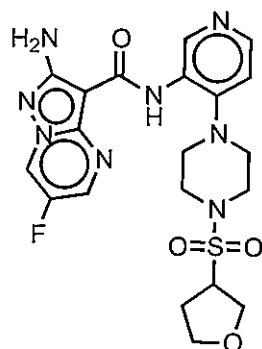
I-N-176



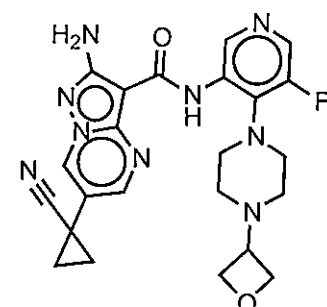
I-N-177



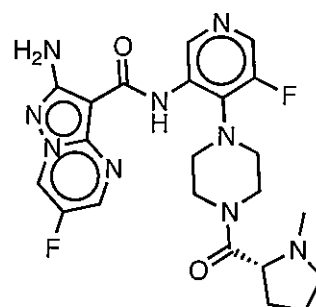
I-N-178



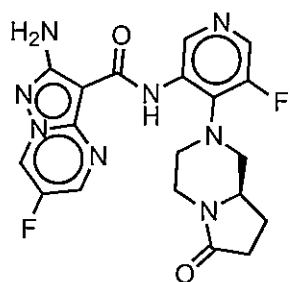
I-N-179



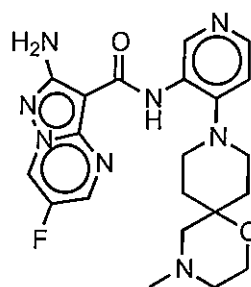
I-N-180



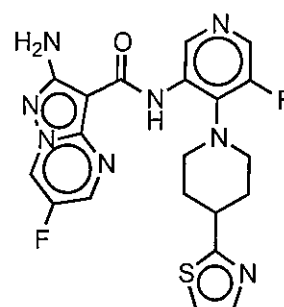
I-N-181



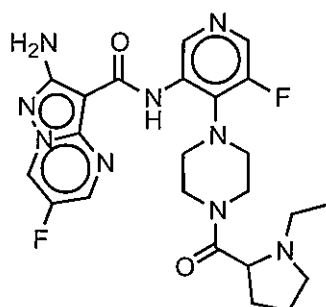
I-N-182



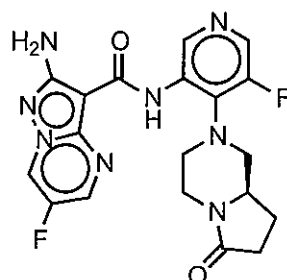
I-N-183



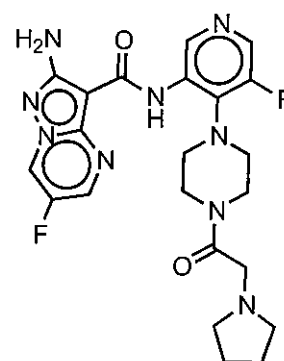
I-N-184



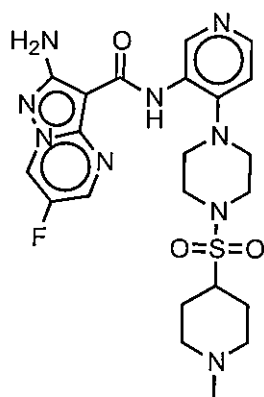
I-N-185



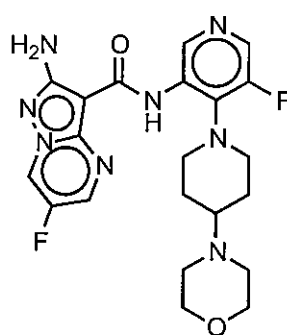
I-N-186



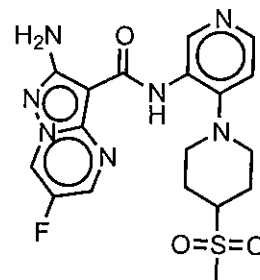
I-N-187



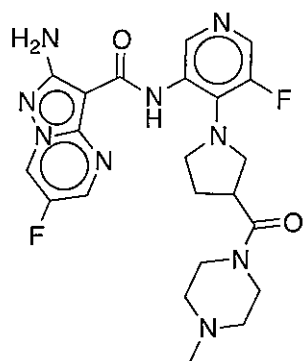
I-N-188



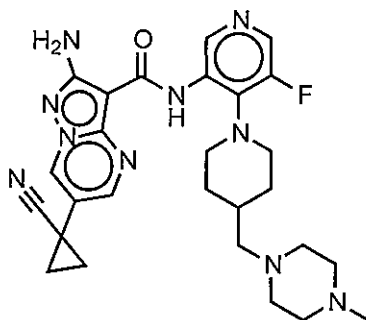
I-N-189



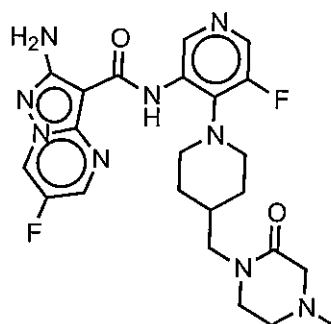
I-N-190



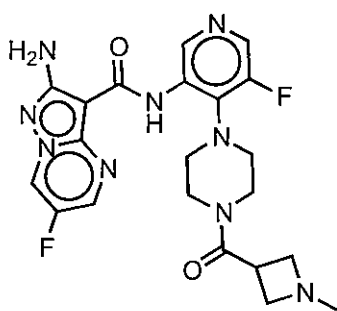
I-N-191



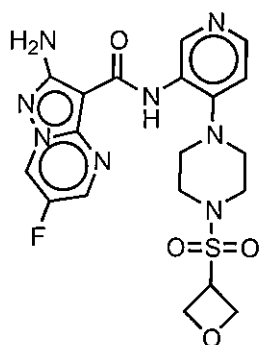
I-N-192



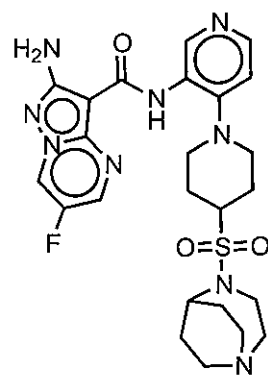
I-N-193



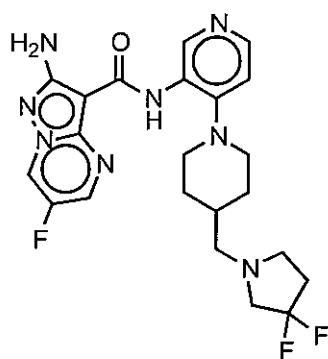
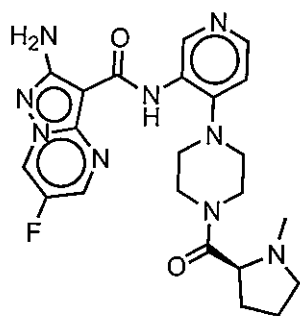
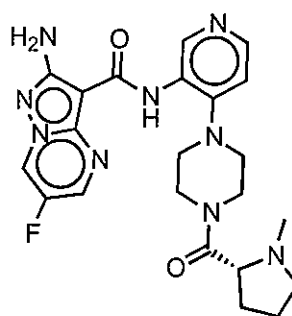
I-N-194

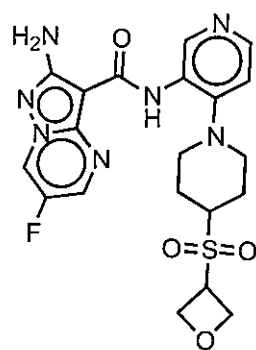
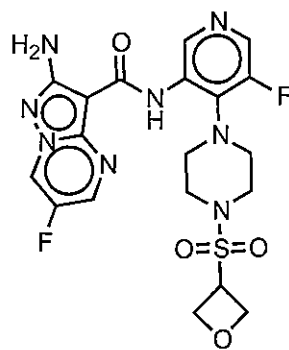
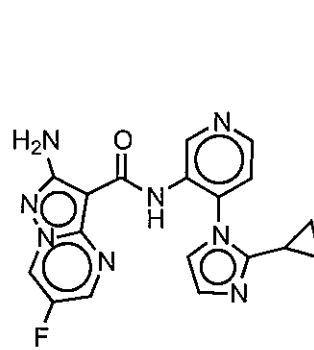
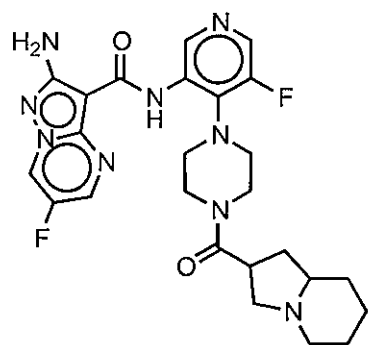
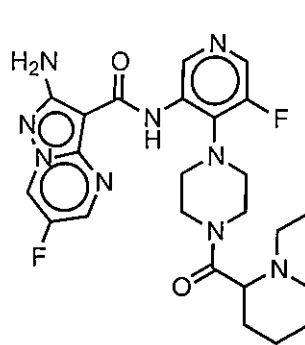
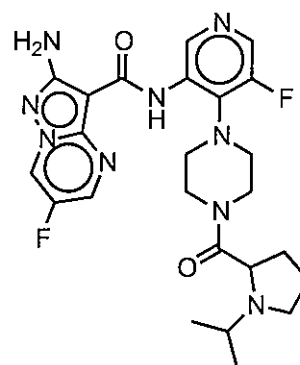
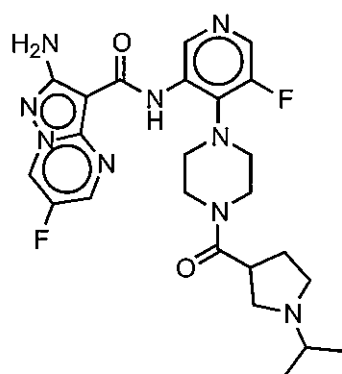
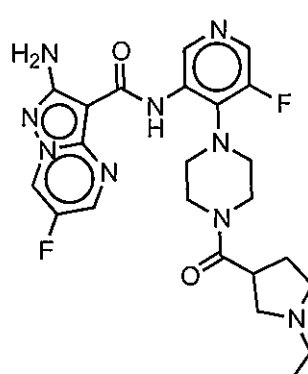
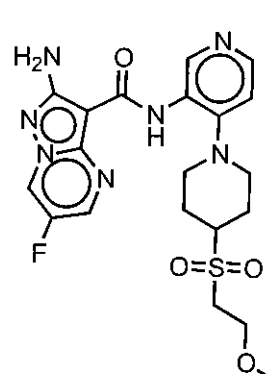


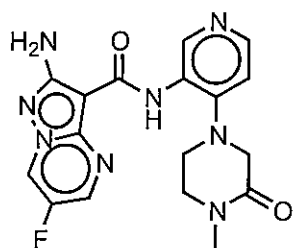
I-N-195



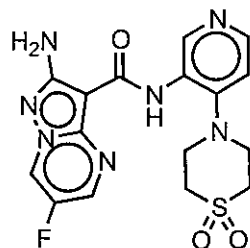
I-N-196



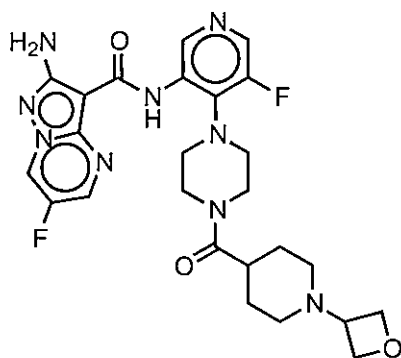
I-N-197**I-N-198****I-N-199****I-N-200****I-N-201****I-N-202****I-N-203****I-N-204****I-N-205****I-N-206****I-N-207****I-N-208**



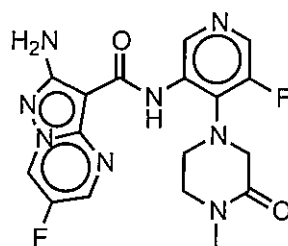
I-N-209



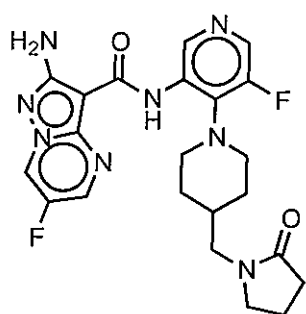
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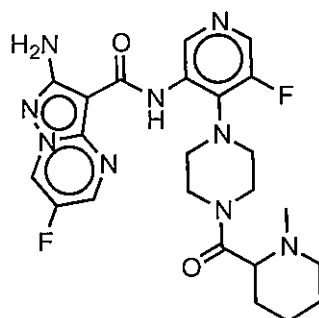
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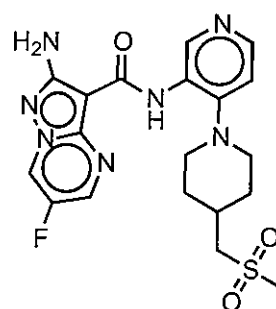
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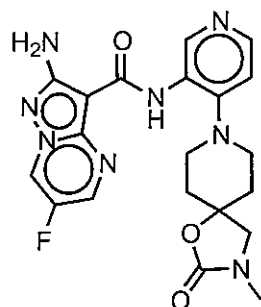
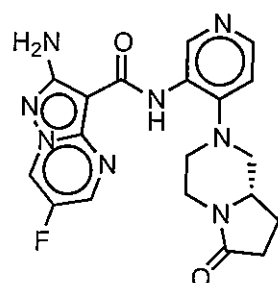
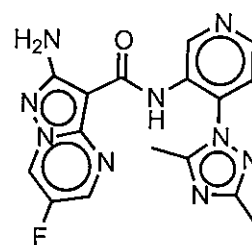
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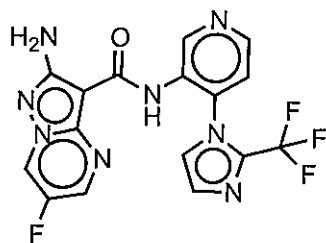
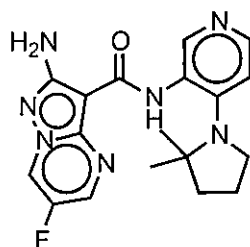
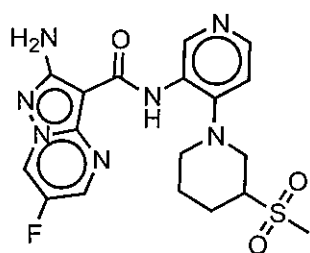
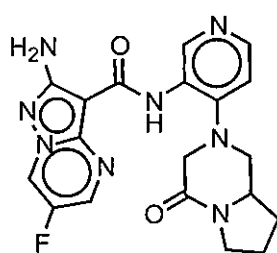
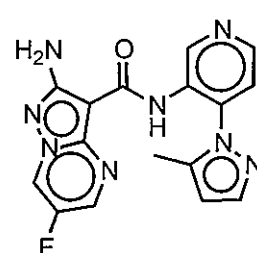
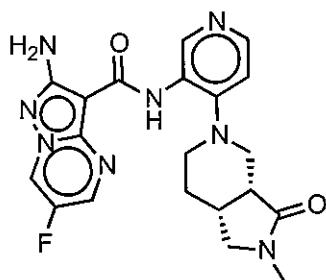
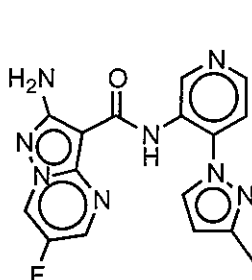
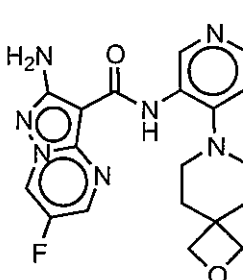
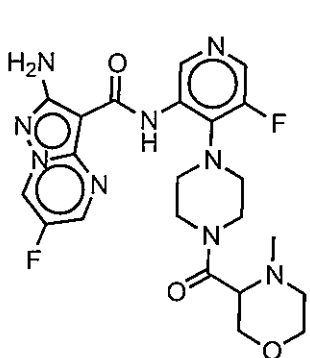
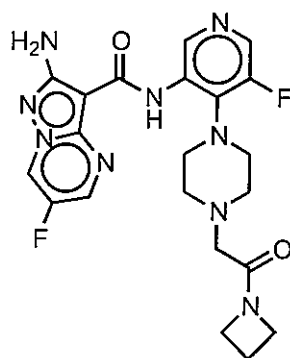
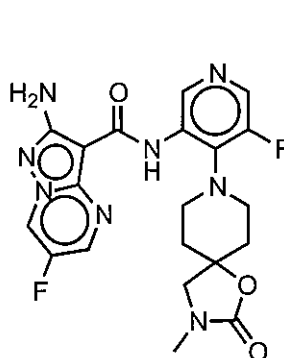


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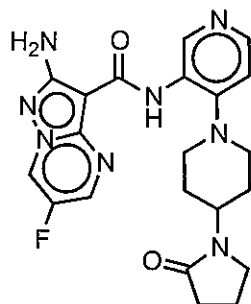


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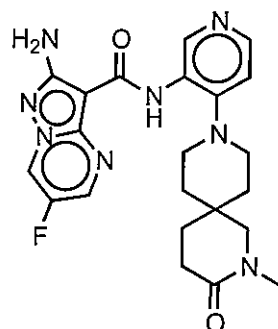


I-N-216**I-N-217****I-N-218****I-N-219****I-N-220****I-N-221****I-N-222****I-N-223****I-N-224****I-N-225****I-N-226**

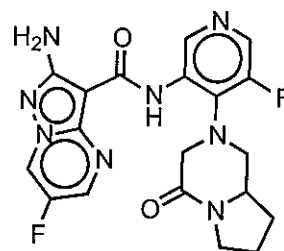
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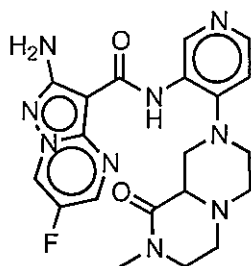
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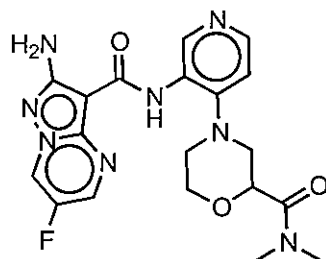
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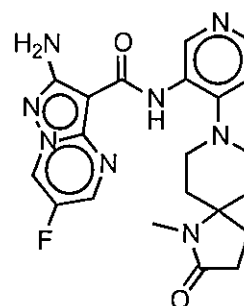
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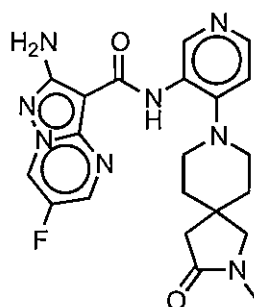
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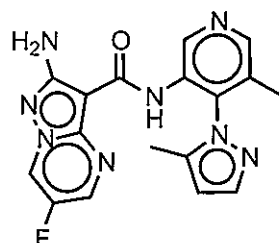
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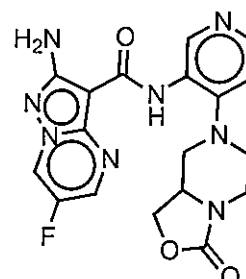
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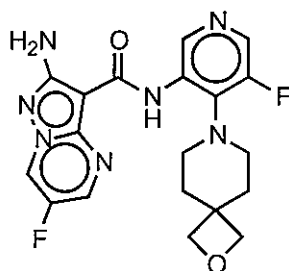
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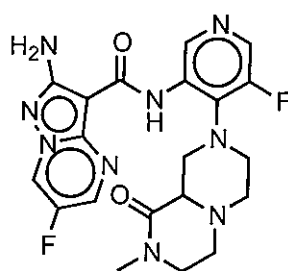
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I-N-236

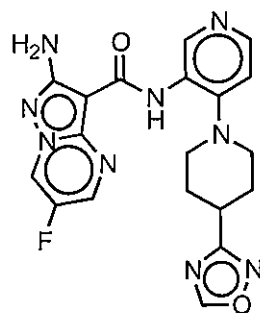


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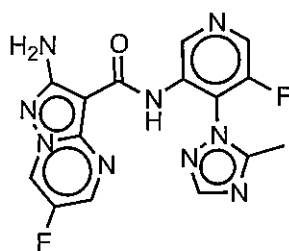


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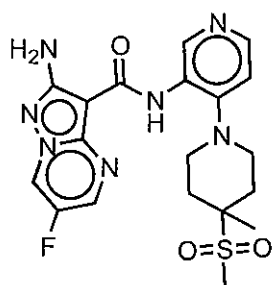
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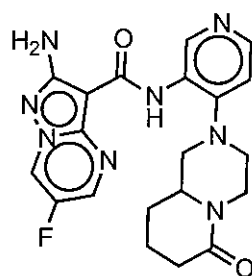
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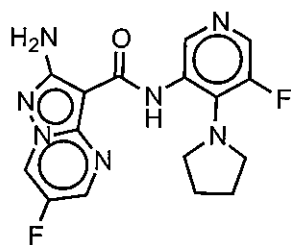
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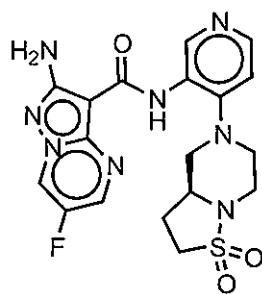
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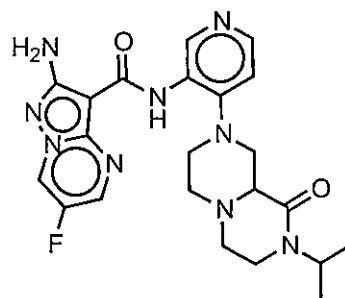
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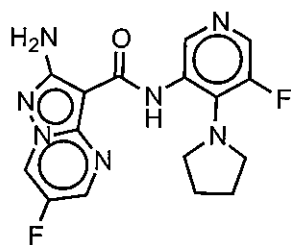
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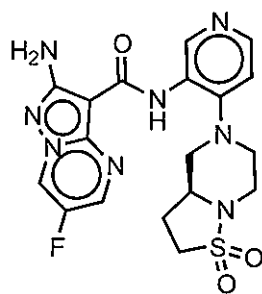
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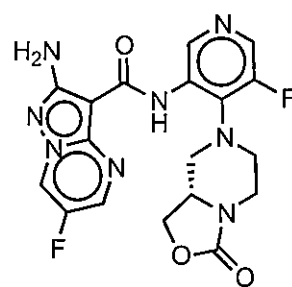
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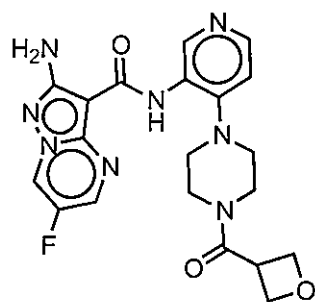


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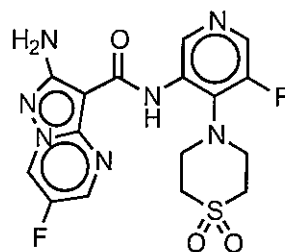


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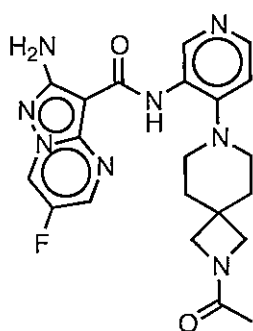




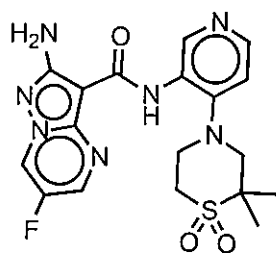
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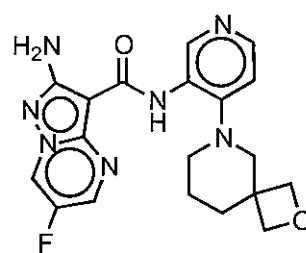
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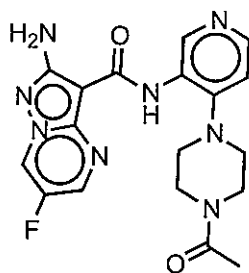
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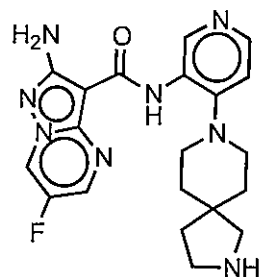
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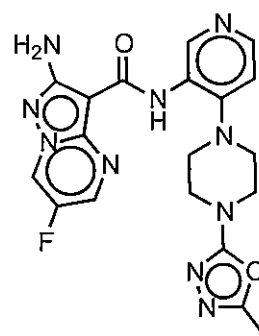
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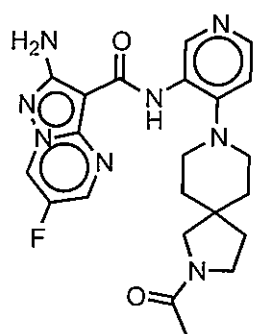
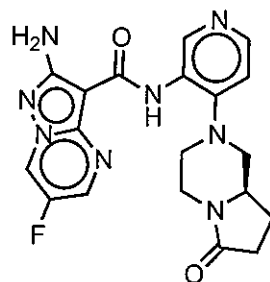
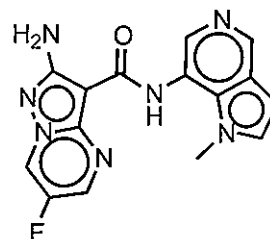
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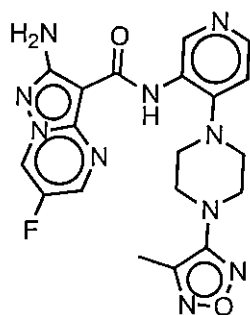
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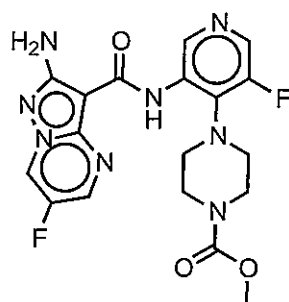
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I-N-257

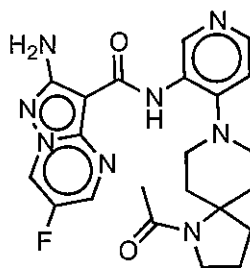


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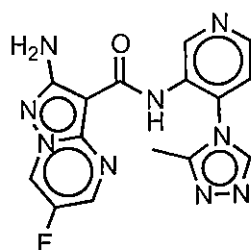


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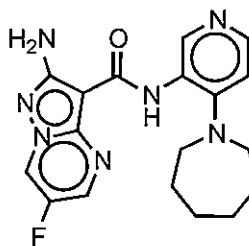
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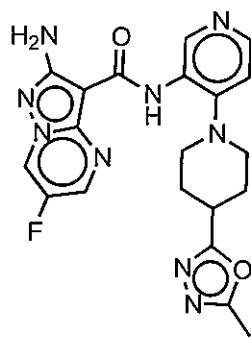
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I-N-262



I-N-263



I-N-264

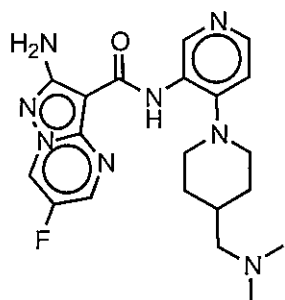


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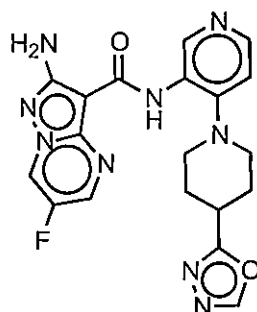


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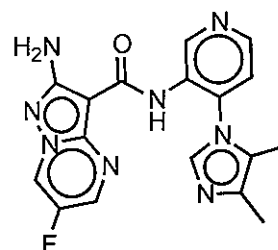




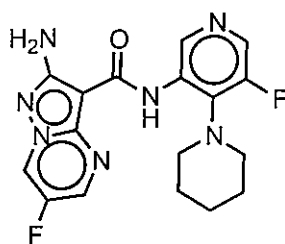
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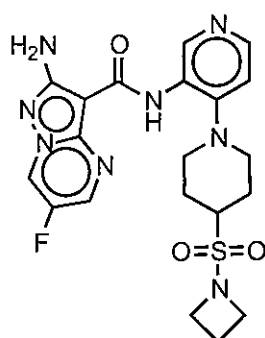
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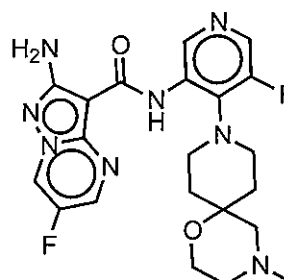
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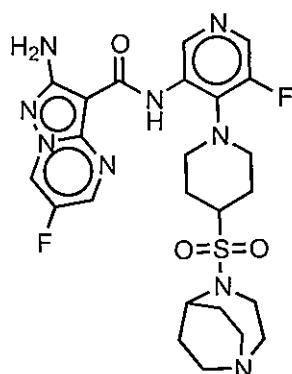
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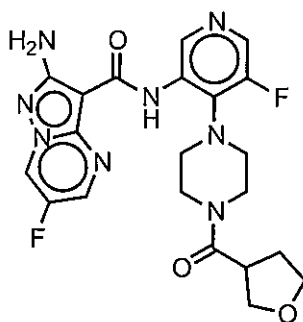
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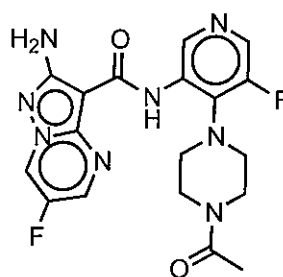
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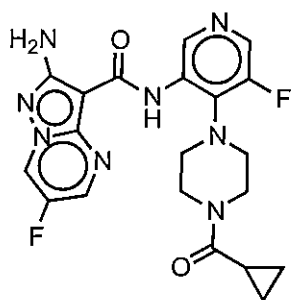
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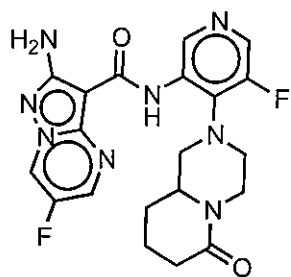
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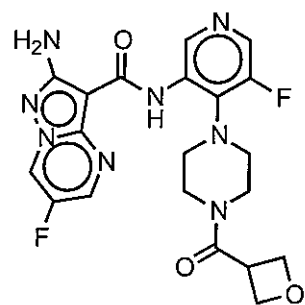
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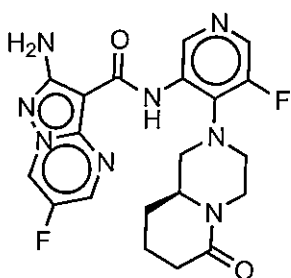
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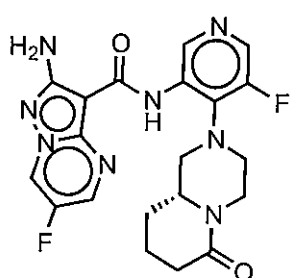
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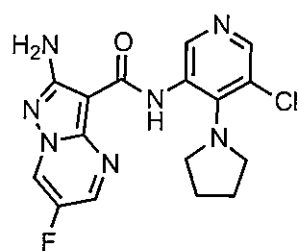
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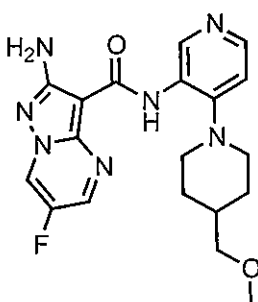
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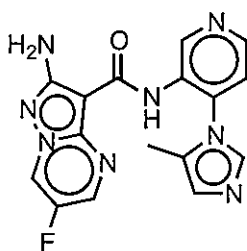
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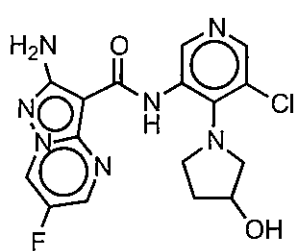
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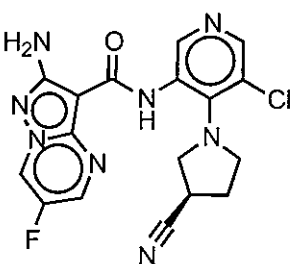
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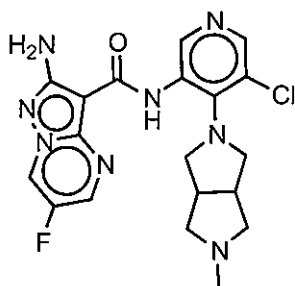
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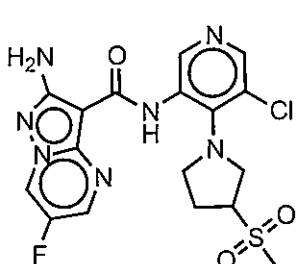
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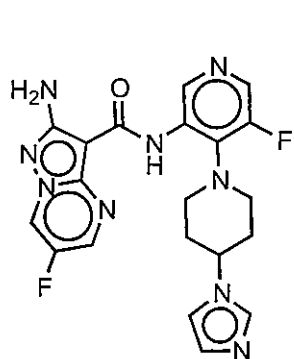
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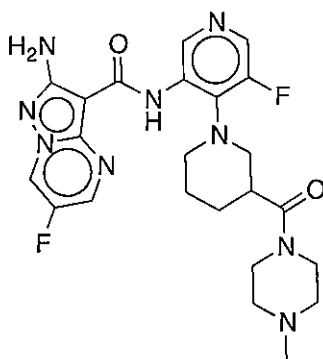
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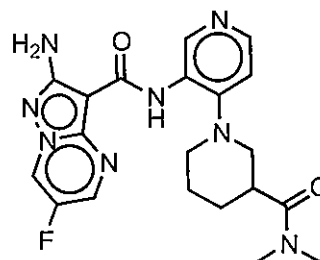
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I-N-288

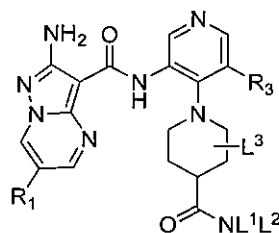


I-N-289



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;

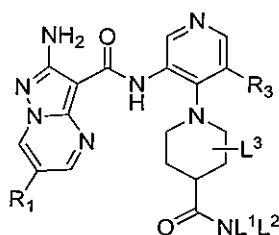
J^K is a 3-7 membered aromatic or non-aromatic ring having 0-2 heteroatoms selected from oxygen, nitrogen, or sulfur;

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 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 selected from halo; $-\text{CN}$; $-\text{N}(\text{R}^\circ)_2$; $\rightarrow\text{O}$; a 3-6 membered carbocycl; a 3-6 membered heterocycl; 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 $-\text{O}-$, $-\text{NR}-$, $-\text{C}(\text{O})-$, or $-\text{S}(\text{O})_n$; 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;

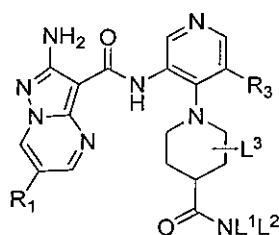
two occurrences of J^G , together with Ring D, form a 6-10 membered saturated or partially unsaturated bridged ring system;

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.

79. 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 $-\text{C}(\text{J}^1)_2\text{CN}$;

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; $-\text{CN}$; or a C_{1-3} 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 $-\text{S}(\text{O})_n$;

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;

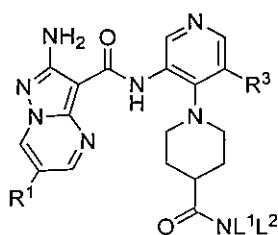
two occurrences of J^G , together with Ring D, form a 6-10 membered saturated or partially unsaturated bridged ring system;

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 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;

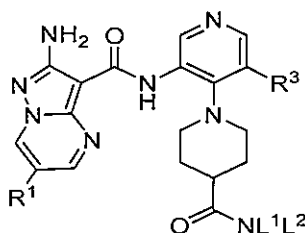
two occurrences of J^G , together with Ring D, form a 6-10 membered saturated or partially unsaturated bridged ring system;

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° 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 $-C(J^1)_2CN$;

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; 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 heterocyclcyl 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

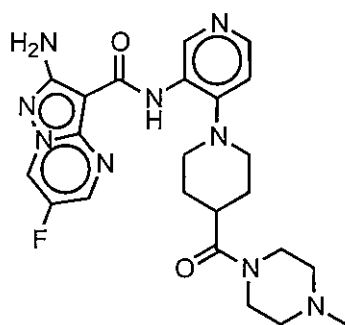
R° is H or C_{1-4} alkyl.

82. The compound of any one of claims 77-80, wherein R¹ is fluoro.
83. The compound of any one of claims 77-80, wherein R¹ is -CH₂CN.
84. The compound of any one of claims 77-80, wherein R¹ is chloro.
85. The compound of any one of claims 77-83, wherein R³ is independently selected from H, chloro, fluoro, cyclopropyl, or C₁₋₄alkyl.
86. The compound of claim 85, wherein R³ is independently selected from H, chloro, or fluoro.
87. The compound of claim 85, wherein R³ is H.
88. The compound of claim 85, wherein R³ is chloro.
89. The compound of claim 85, wherein R³ is fluoro.
90. The compound of any one of claims 86-89, wherein L¹ and L² are H; -(C₁₋₃alkyl)O(C₁₋₂alkyl); -(C₁₋₃alkyl)N(C₁₋₂alkyl)₂; C₁₋₄alkyl; azetidiny; piperidiny; oxytanyl; or pyrrolidiny.
91. The compound of any one of claims 82-89, wherein L¹ and L², 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 piperaziny, piperidiny, morpholiny, tetrahydropyranyl, azetidiny, pyrrolidiny, or 1,4-diazepanyl.
94. The compound of claim 93, wherein Ring D is piperaziny, piperidiny, 1,4-diazepanyl, pyrrolidiny or azetidiny.

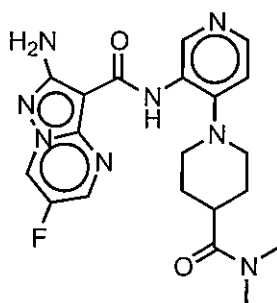
95. The compound of claim 94, wherein Ring D is piperazinyl or piperidinyl.
96. The compound of claim 92, wherein Ring D is an 8-12 membered fully saturated or partially unsaturated bicyclic ring having 0-5 heteroatoms selected from oxygen, nitrogen, or sulfur.
97. The compound of claim 96, wherein Ring 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, C₁₋₄alkyl, -O(C₁₋₃alkyl), C₃₋₆cycloalkyl, a 3-6 membered heterocyclyl, -NH(C₁₋₃alkyl), -OH, or -N(C₁₋₄alkyl)₂.
99. The compound of claim 98, wherein J^G is methyl, -N(C₁₋₄alkyl)₂, ethyl, -O(C₁₋₃alkyl), cyclopropyl, oxetanyl, cyclobutyl, pyrrolidinyl, piperidinyl, or azetidiny.
100. The compound of claim 99, wherein J^G is methyl, -O(C₁₋₃alkyl), 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.

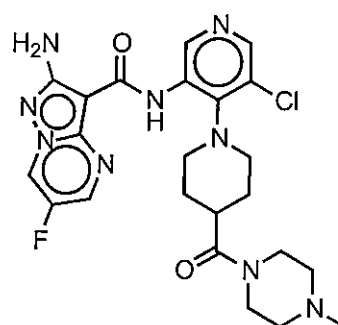
106. A compound of any one of claims 77-105 independently selected from:



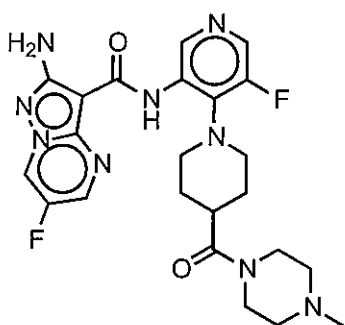
I-G-1



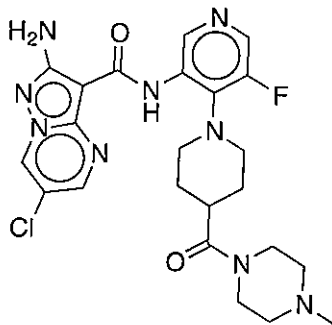
I-G-2



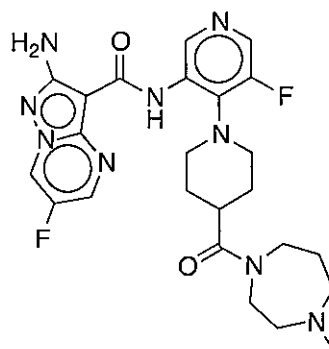
I-G-3



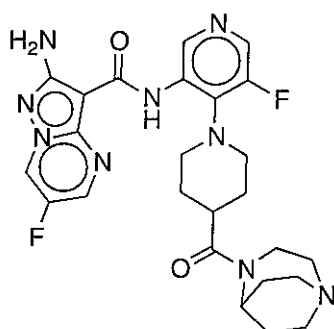
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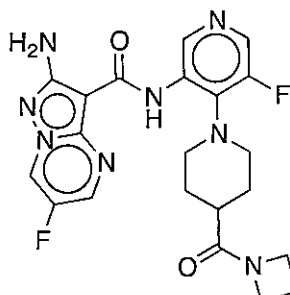
I-G-5



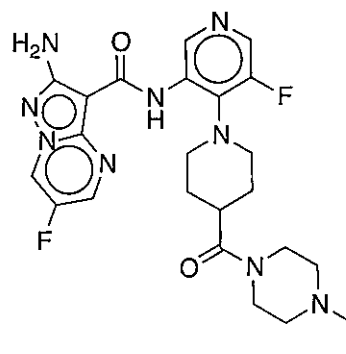
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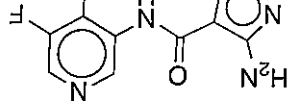
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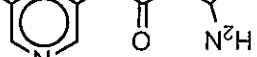
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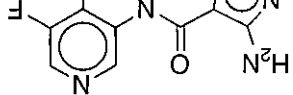
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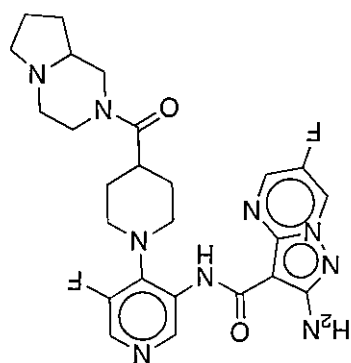
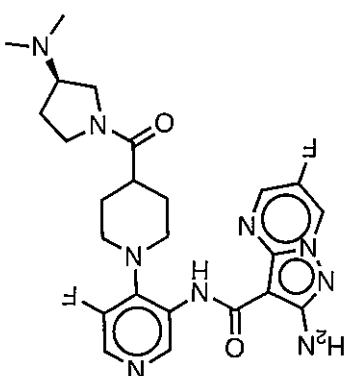
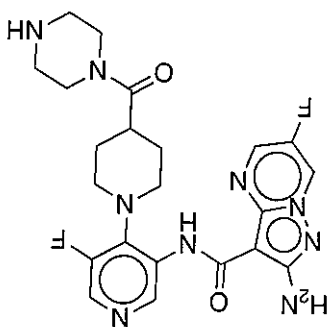
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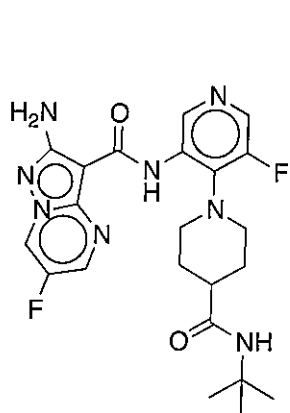


I-G-11

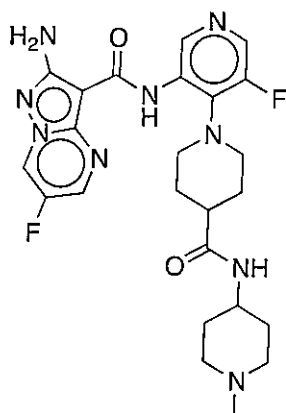


I-G-12

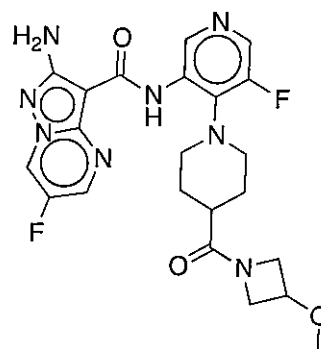




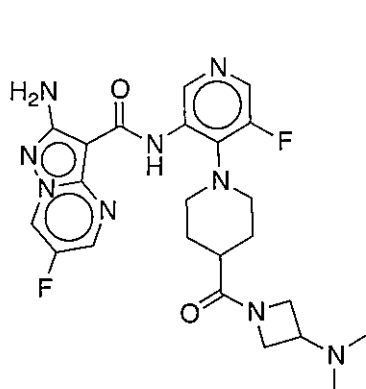
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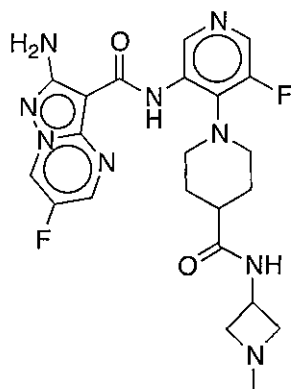
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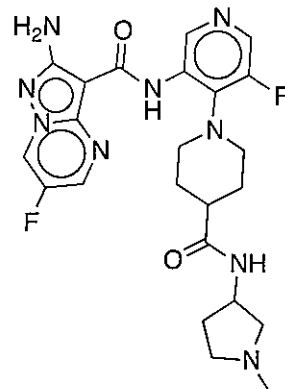
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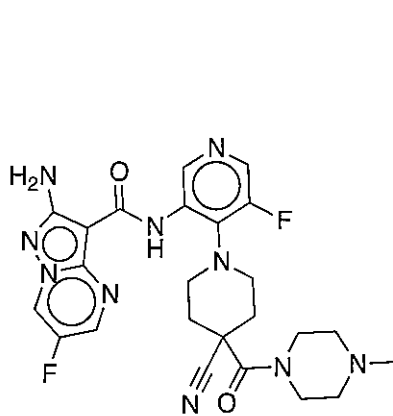
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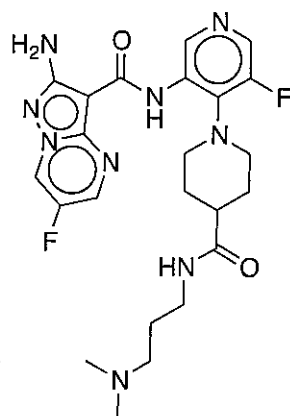
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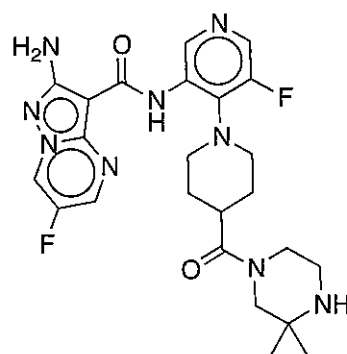
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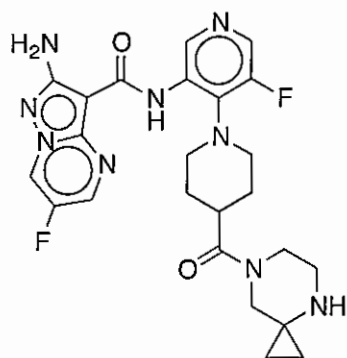
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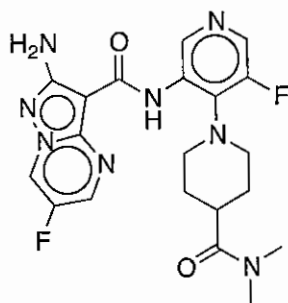
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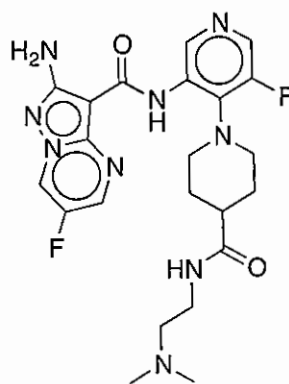
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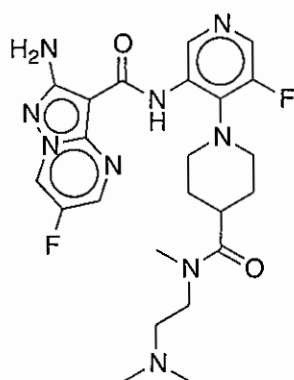
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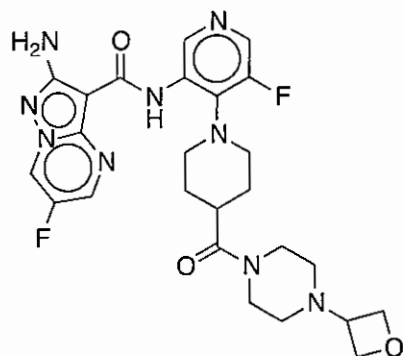
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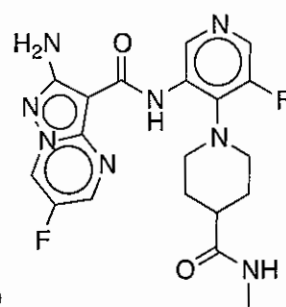
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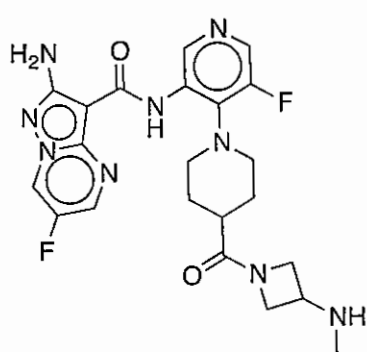
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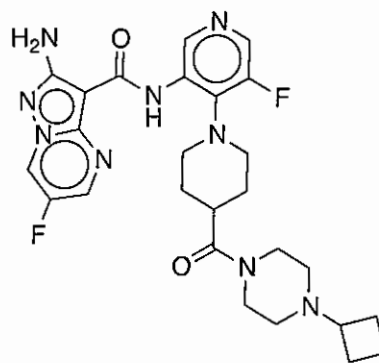
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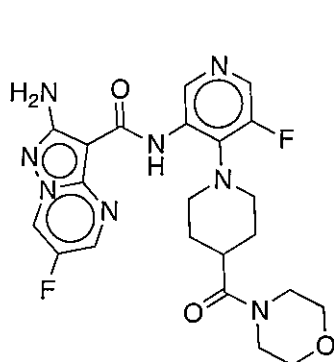
I-G-33



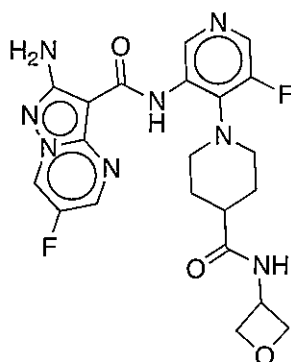
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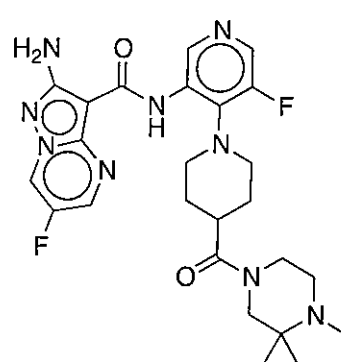
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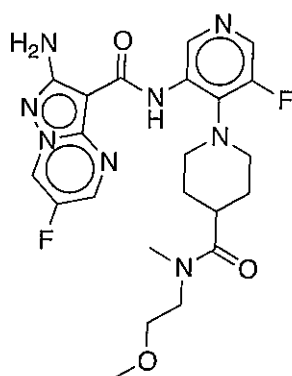
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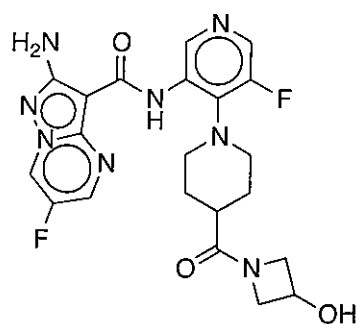
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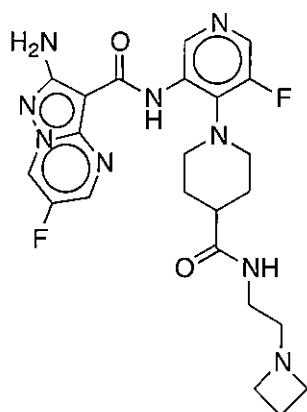
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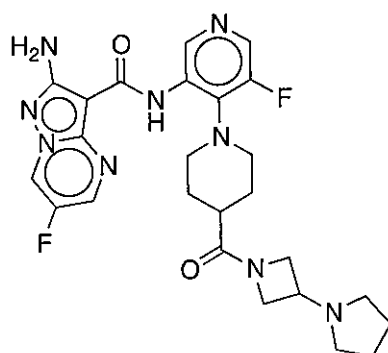
I-G-40



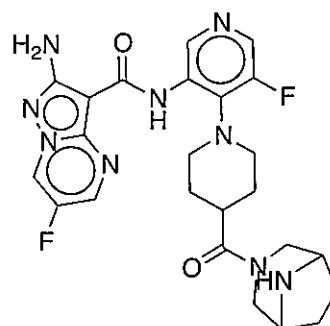
I-G-41



I-G-42

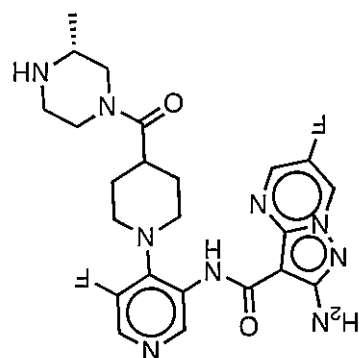


I-G-43

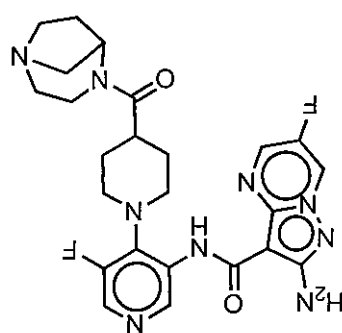


I-G-44

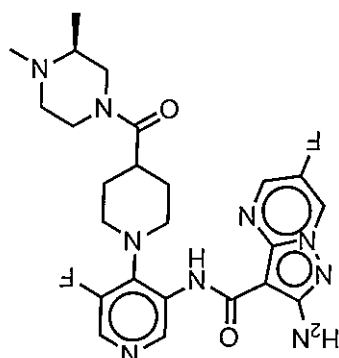
I-G-45

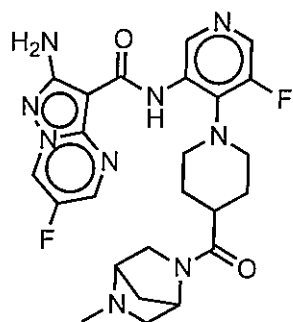


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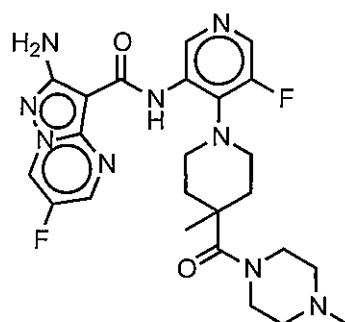


I-G-47

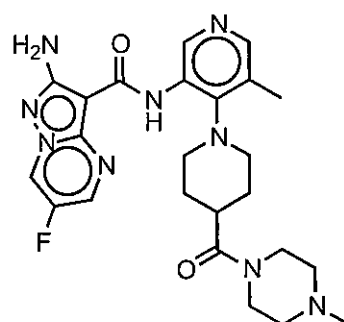




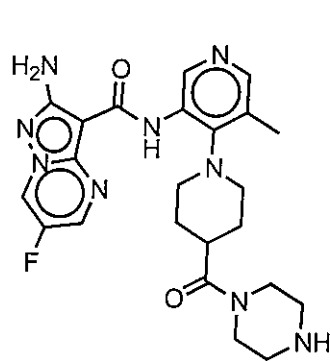
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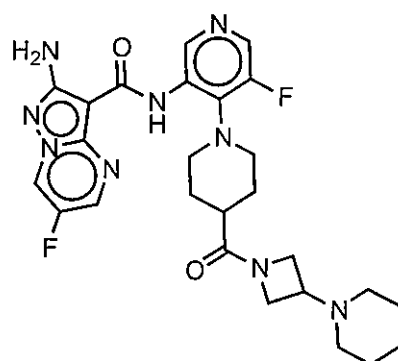
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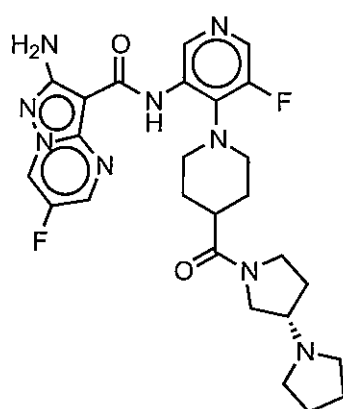
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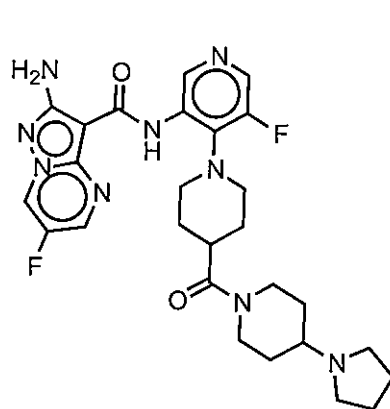
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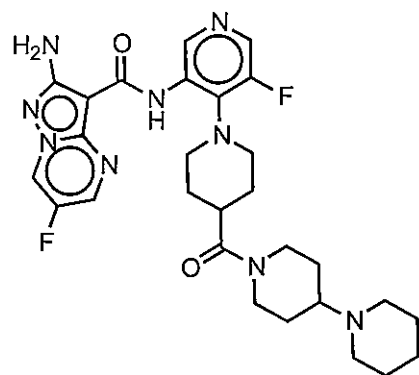
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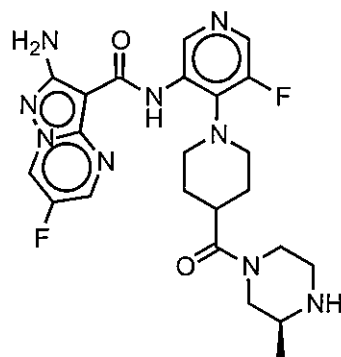
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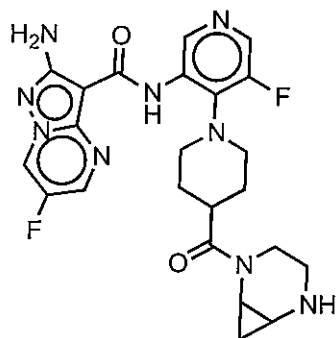
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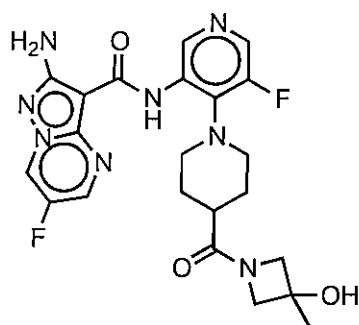
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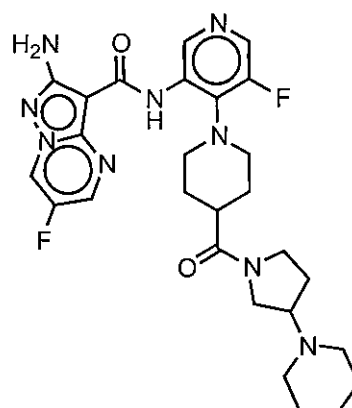
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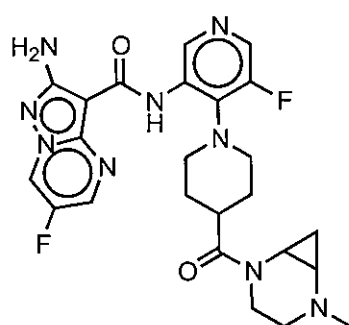
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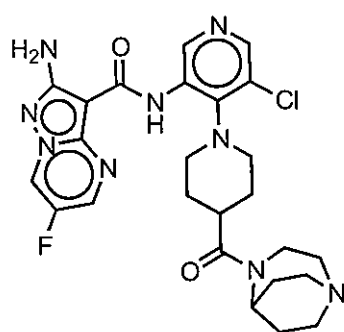
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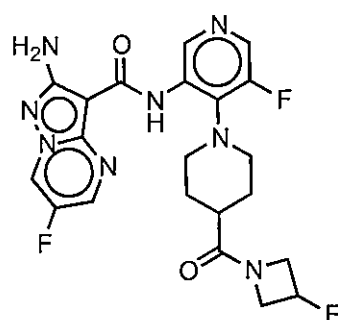
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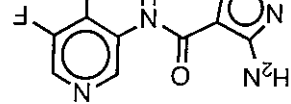
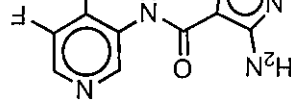
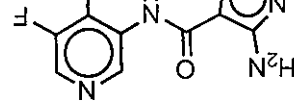
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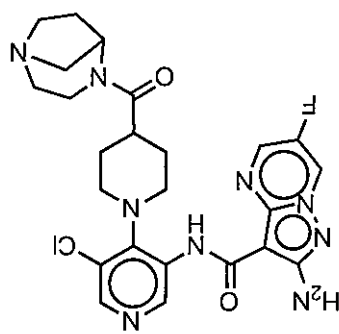
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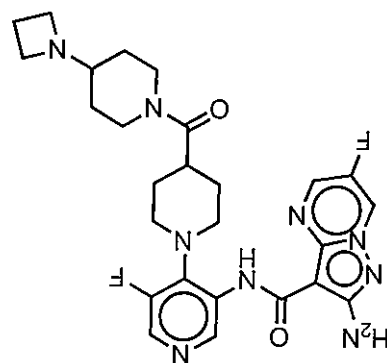
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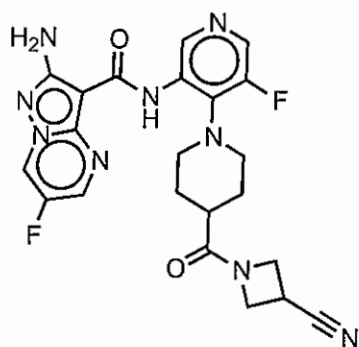


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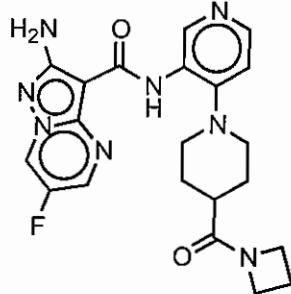


89-G-I

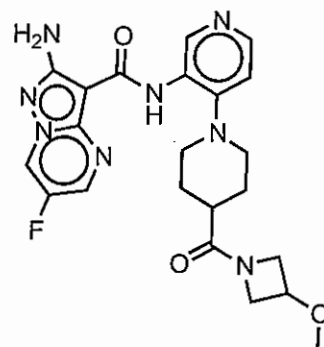




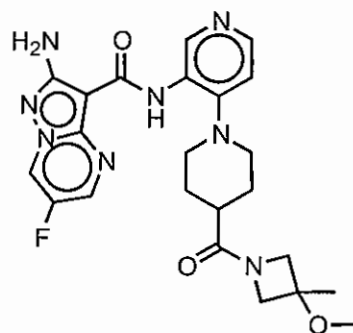
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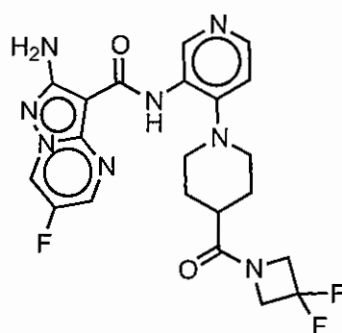
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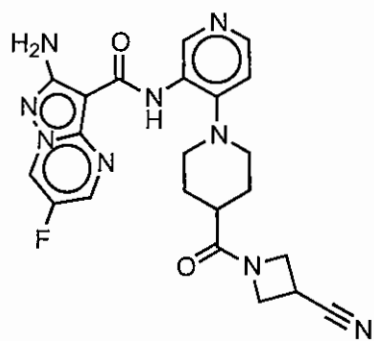
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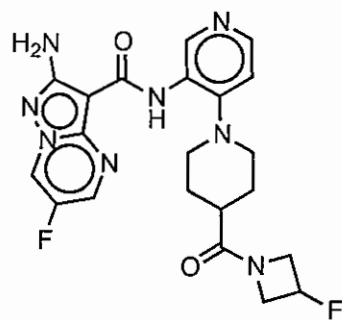
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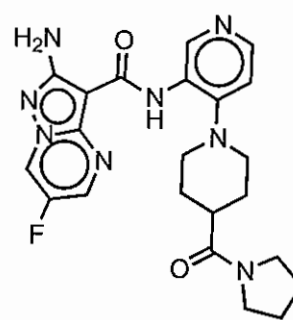
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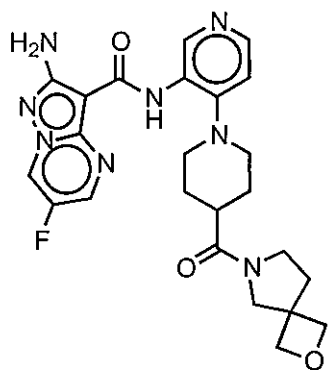
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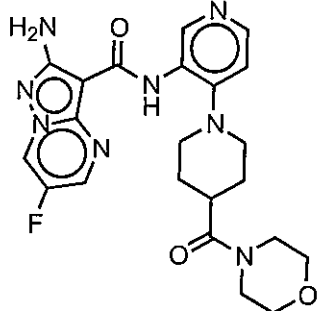
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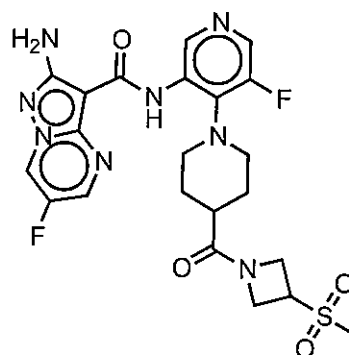
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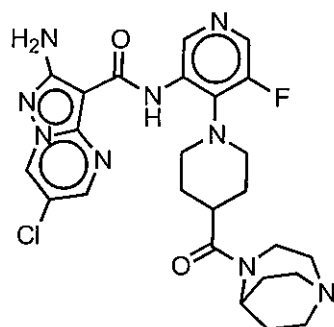
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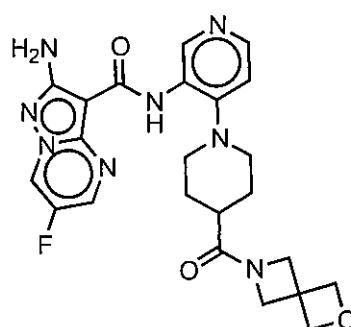
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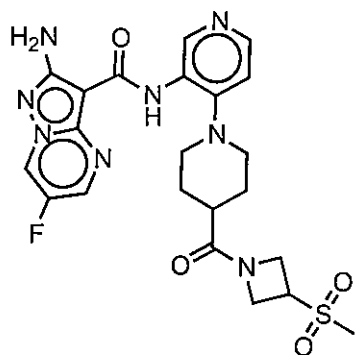
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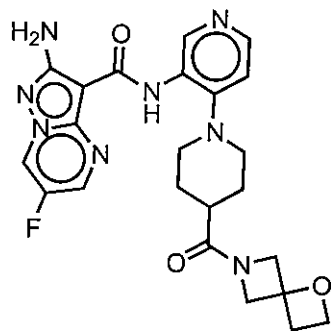
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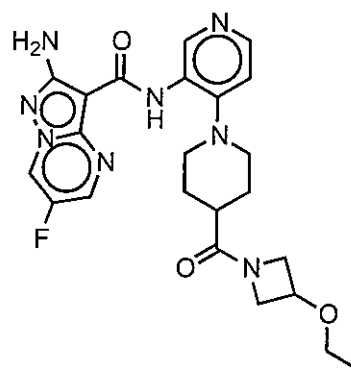
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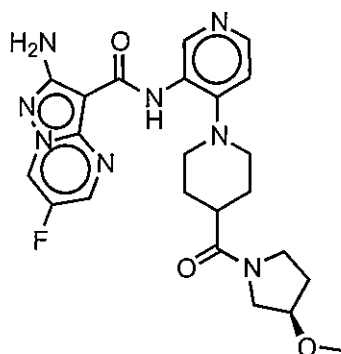
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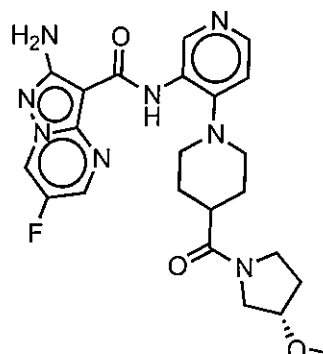
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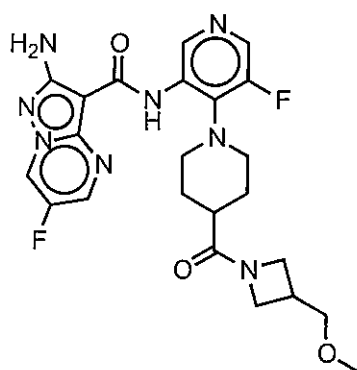
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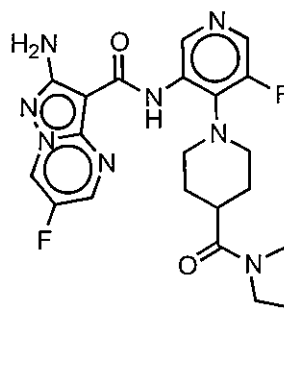
I-G-93



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.

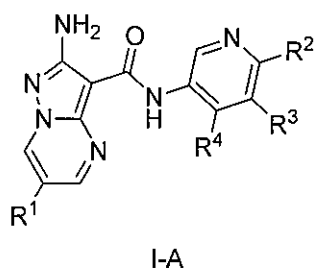
162. The use of any one of claims 108-158, wherein said cell is a cancer cell expressing DNA damaging oncogenes.
163. The use of claim 162, wherein said cancer cell has altered expression or activity of one or more of the following: K-Ras, N-Ras, H-Ras, Raf, Myc, Mos, E2F, Cdc25A, CDC4, CDK2, Cyclin 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.

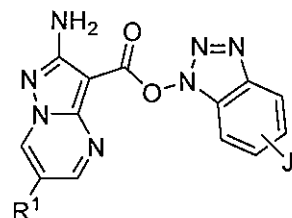
171. The use of claim 170, wherein the base excision repair protein is selected from PARP1 or PARP2.

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:

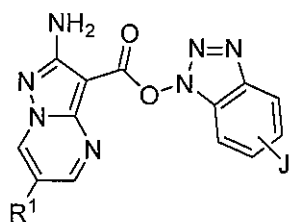


comprising reacting a compound of formula 6:



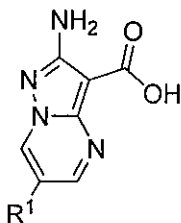
under suitable conditions to form an amide bond, wherein J, R¹, R², R³, and R⁴ are as defined in claims 1-33, 34-76, or 77-106.

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



6

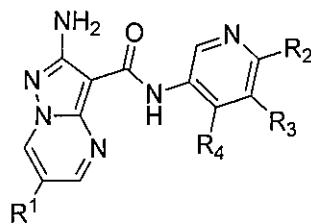
by reacting a compound of formula 5:



5

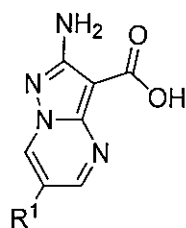
under suitable conditions to form an activated ester.

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



I-A

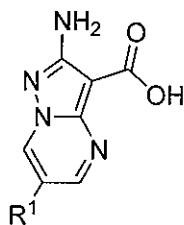
comprising reacting a compound of formula 5:



5

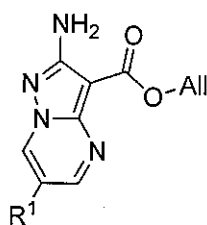
under suitable conditions to form an amide bond, wherein R^1 , R^2 , R^3 , and R^4 are as defined in claims 1-33, 34-76, or 77-106.

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



5

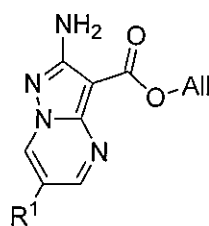
by reacting a compound of formula 4:



4

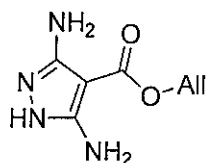
under suitable deprotection conditions.

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



4

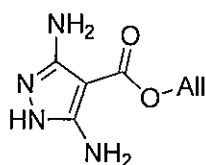
by reacting a compound of formula 3:



3

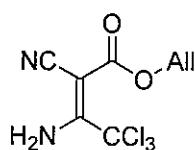
under suitable condensation conditions to form a pyrimidine ring.

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



3

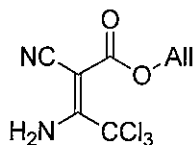
by reacting a compound of formula 2:



2

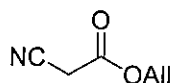
under suitable condensation conditions to form a pyrazole ring.

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.

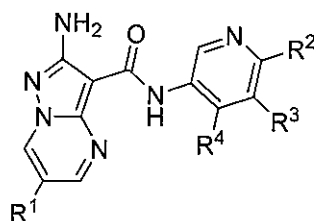
184. The process of claim 182, wherein the aprotic solvent is optionally substituted pyridine.

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 Pd(PPh₃)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.

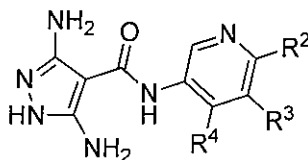
199. The process of claim 177, wherein suitable condensation conditions for forming a pyrimidine ring comprise reacting the compound of formula **3** with a 1,3-dielectrophilic species in the presence of a solvent.
200. The process of claim 199, wherein the 1,3-dielectrophilic species is 1,3-dialdehyde 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

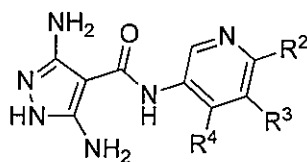
comprising reacting a compound of formula 9:



9

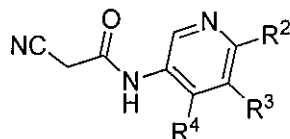
under suitable condensation conditions to form a pyrimidine ring, wherein R¹, R², R³ and R⁴ are as defined in claims 1-33, 34-76, or 77-104.

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



9

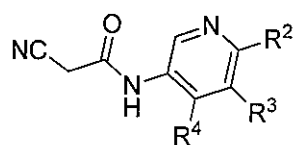
by reacting a compound of formula 8:



8

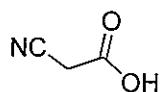
under suitable condensation conditions to form a pyrazole ring.

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



8

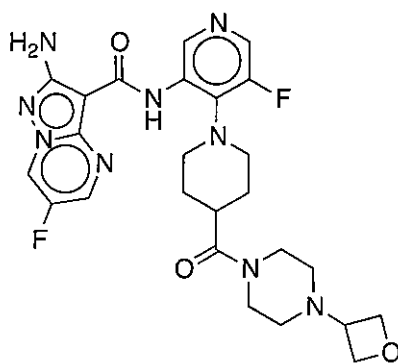
by reacting a compound of formula 7:



7

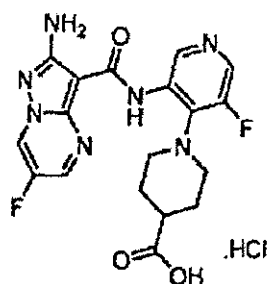
under suitable conditions to form an amide bond.

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



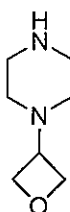
I-G-32

comprising the step of reacting the compound of formula 30:



30

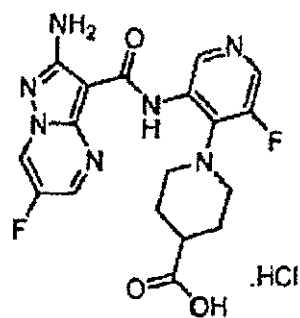
with a compound of formula 25:



25

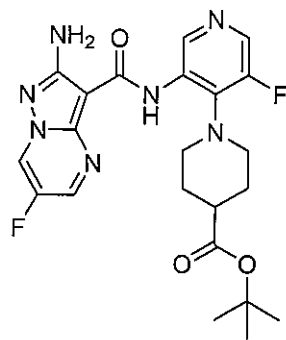
under suitable conditions to form an amide bond.

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



30

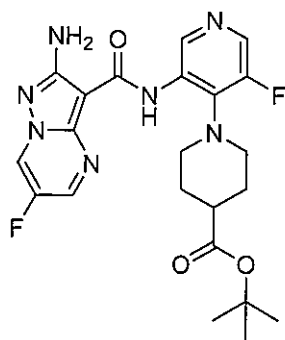
by reacting the compound of formula **28**:



28

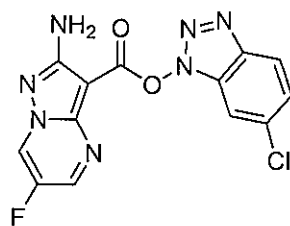
under suitable deprotection conditions to form the carboxylic acid.

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



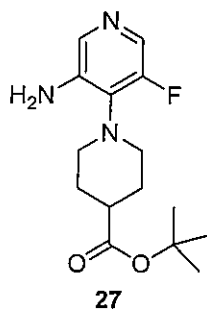
28

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.

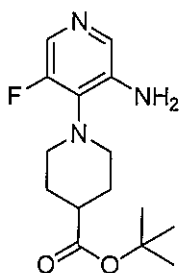
219. The compound of claim 218, wherein the aprotic solvent is independently selected from NMP, DMF, or tetrahydrofuran.

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.

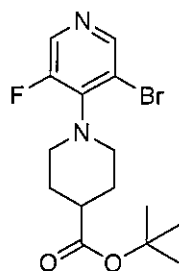
222. The process of claim 221, wherein the base is DIPEA.

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

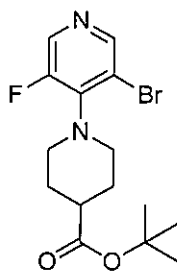
comprising the step of reacting a compound of formula **26**:



26

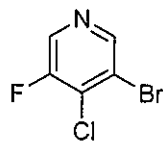
under suitable conditions to form an amine.

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



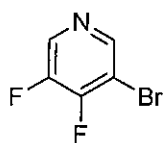
26

by 1) reacting a compound of formula 18:



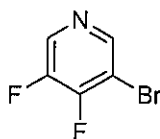
18

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



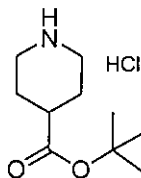
32 , and

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



32

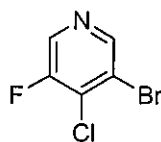
with a compound of formula **22**:



22

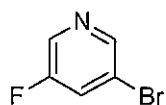
under suitable displacement conditions.

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



18

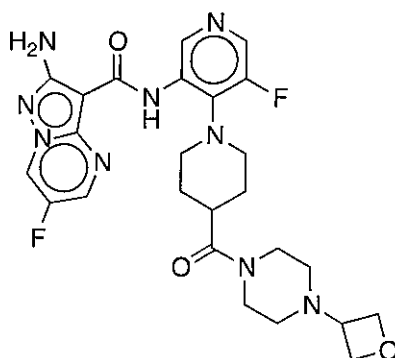
by reacting the compound of formula **31**:



31

under suitable halogenation conditions.

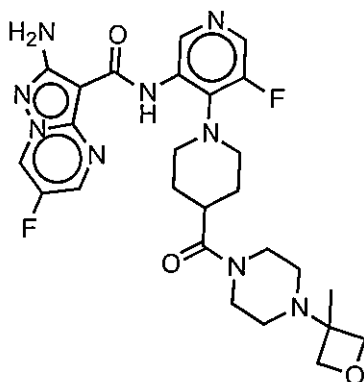
235. A compound having the structure **I-G-32**:



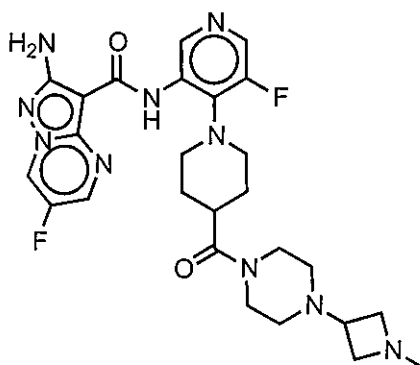
I-G-32

or a pharmaceutically acceptable salt thereof.

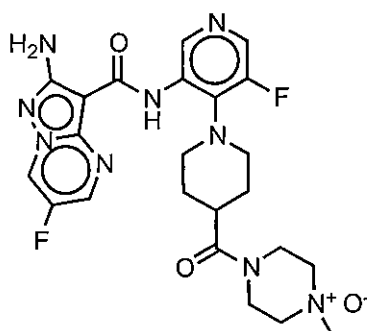
236. A compound selected from:



I-G-92

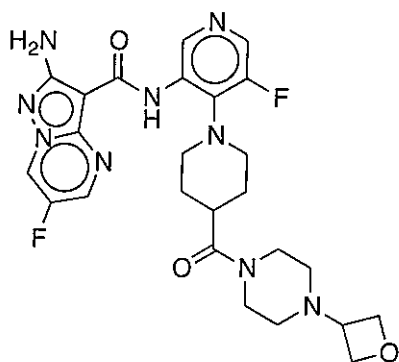


I-G-95



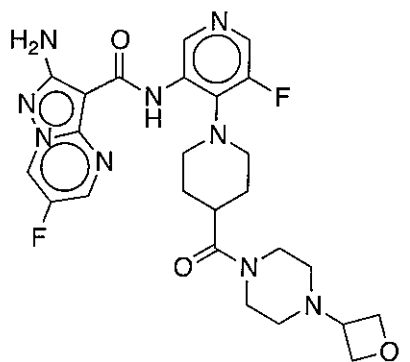
I-G-96

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



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

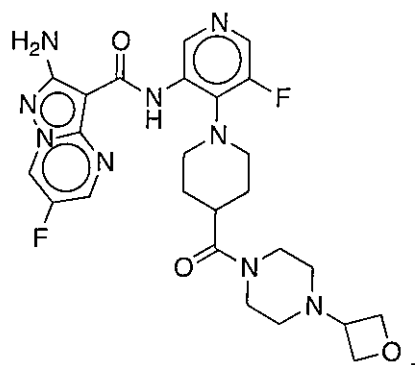
238. A compound of claim 235, wherein the compound is a pharmaceutically



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.