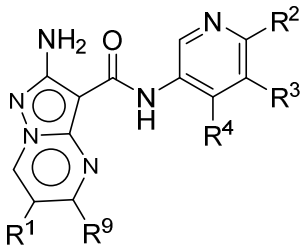
CLAIMS

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 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 →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; →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; =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 claim 1,

wherein (I) R^9 is H; or:

wherein (II) R^9 is M; optionally wherein M is a C_{1-8}aliphatic wherein up to three methylene units are optionally replaced with -O- or -NR-; optionally thereto 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); optionally thereto wherein M is C_{1-4}alkyl.

3. The compound of any one of claims 1-2, wherein R^9 is -$(L^1)_k$-W; optionally:

wherein (I) k is 0; or:

wherein (II) k is 1; optionally wherein L is a C_{1-8}aliphatic wherein up to three methylene units are optionally replaced with -O- or -NR-; optionally thereto wherein L is -O-, -O(C_{1-4}aliphatic)-, or -NR(C_{1-3}alkyl)-.

4. The compound of claim 3,

wherein (I) W is a 3-7 membered fully saturated, partially unsaturated, or aromatic monocyclic ring having 0-3 heteroatoms selected from oxygen, nitrogen or sulfur; optionally wherein W is a 3-7 membered heterocyclyl, optionally thereto wherein W is independently selected from pyrrolidinyl, piperidinyl, piperazinyl, oxetanyl, or azetidinyl; or:

wherein (II) W is a 7-12 membered fully saturated, partially unsaturated, or aromatic bicyclic ring having 0-5 heteroatoms selected from oxygen, nitrogen, or sulfur.

5. The compound of claim 3 or claim 4,

wherein (I) J^W is selected from C_{1-3}alkyl or CF_3; or:

wherein (II) 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; optionally wherein the ring formed by the two occurrences of J^W on the same atom is oxetanyl.

6. The compounds of any one of claims 1 to 5,

wherein (I) R^1 is fluoro; or:

wherein (II) R^1 is $–CH_2CN$, $-C(CH_3)_2CN$ or $–CH(C_{1-2}alkyl)CN$; or:

wherein (III) R^1 is chloro.

7. The compound of any one of claims 1 to 6, wherein R^2 is independently selected from $–CF_3$, $-NH(C_{1-2}alkyl)$, chloro, or H; optionally:

wherein (I) R^2 is H; or:

wherein (II) R^2 is -chloro.

8. The compound of any one of claims 1 to 7, wherein R^3 is independently selected from H, chloro, fluoro, CHF_2, -CN, cyclopropyl, or C_{1-4}alkyl; optionally:

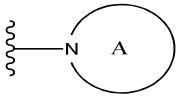
wherein R^3 is independently selected from H, chloro, or fluoro; optionally thereto:

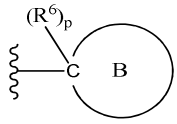
wherein (I) R^3 is H; or:

wherein (II) R^3 is chloro; or:

wherein (III) R^3 is fluoro.

9. The compound of any one of claims 1 to 8, wherein R^4 is independently selected from:

-O-; 

; 

; or $-CH_2-R^7$, wherein:

-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;

R^6 is H;

R^7 is independently selected from H or a C_{1-8}aliphatic chain wherein up to three methylene units of the aliphatic chain are optionally replaced with -O-, -NR-, -S-, -C(O)-, or $-S(O)_n-$; and

p is 0 or 1.

10. The compound of claim 9, wherein R^4 is -O-: optionally:

wherein (I) J^Q is independently selected from $-(C_{1\ 4}alkyl)$, $-(C_{1-4}alkyl)N(C_{1-4}alkyl)_2$, $-(C_{1-3}alkyl)O(C_{1-2}alkyl)N(C_{1-3}alkyl)_2$, $(C_{1\ 4}alkyl)OH$, $-(C_{1-4}alkyl)NH_2$, or $-(C_{1-4}alkyl)O(C_{1-4}alkyl)$; or:

wherein (II) J^Q is Q^2; optionally:

wherein (i) Q^2 is a 3-7 membered fully saturated, partially unsaturated, or aromatic monocyclic ring having 0-3 heteroatoms selected from oxygen, sulfur, or nitrogen; optionally:wherein Q^2 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; optionally thereto:

wherein (a) Q^2 is independently selected from a 4-7 membered cycloaliphatic or a 3-7 membered heterocyclyl; optionally wherein Q^2 is a 3-7 membered heterocyclyl; optionally thereto: wherein Q^2 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, azetidinyl, and oxetanyl; optionally thereto wherein Q^2 is independently selected from tetrahydrothiopyranyl, pyrrolidinyl, piperidinyl, piperazinyl, tetrahydrofuranyl, tetrahydropyranyl, or azetidinyl; or:

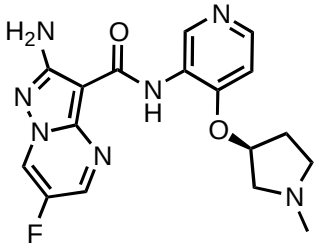
wherein (b) Q^2 is a 5-6 membered heteroaryl; optionally wherein Q^2 is independently selected from imidazolyl, pyrrolyl, pyridinyl, pyrazinyl, pyrimidinyl, pyrazolyl, 1,2,3-triazolyl, or 1,2,4-triazolyl; optionally thereto wherein Q^2 is pyridinyl; or:

wherein (c) Q^2 is a 4-6 membered cycloaliphatic; optionally wherein Q^2 is independently selected from cyclobutyl or cyclohexyl; or:

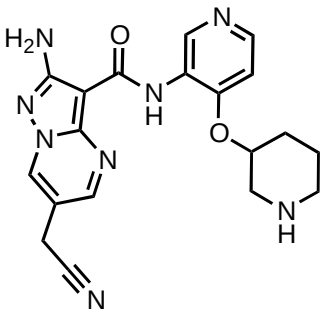
wherein (d) Q^2 is phenyl; or:

wherein (ii) 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; optionally wherein Q^2 is 6,7-dihydro-5H-pyrrolo[1,2-a]imidazole.

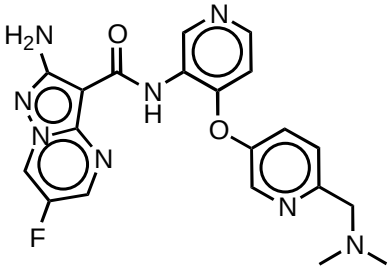
11. The compound of any one of claims 9 and 10 independently selected from:



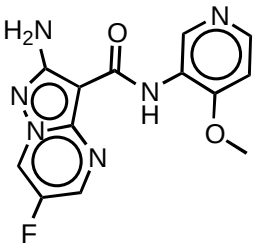
I-O-1



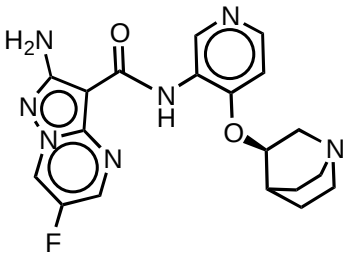
I-O-2



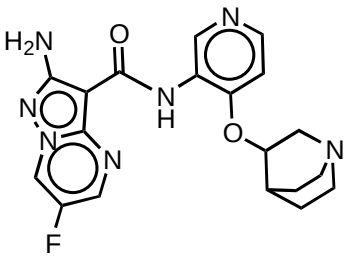
I-O-3



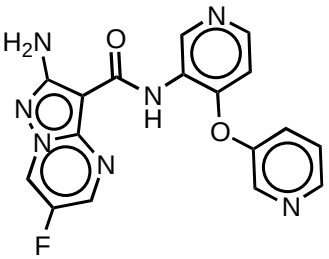
I-O-4



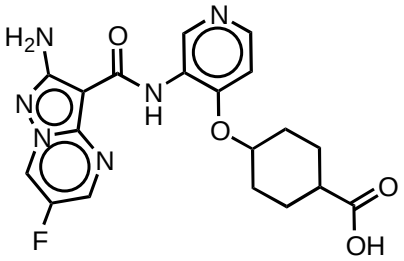
I-O-5



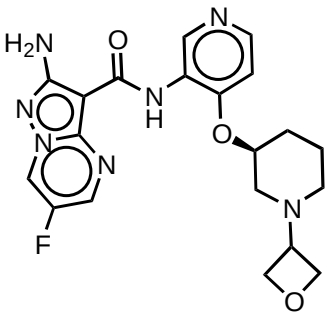
I-O-6



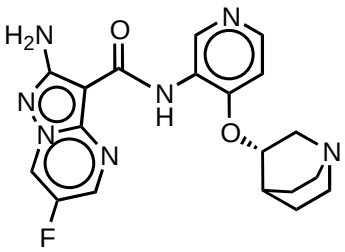
I-O-7



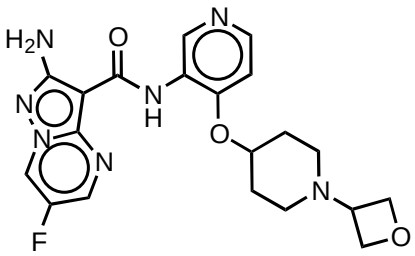
I-O-8



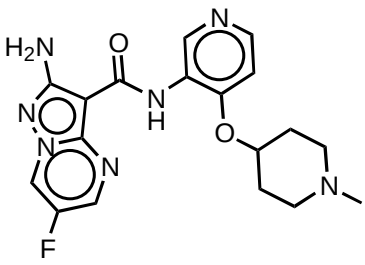
I-O-9



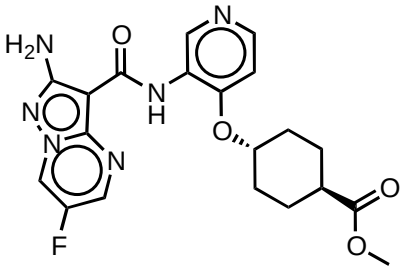
I-O-10



I-O-11



I-O-12



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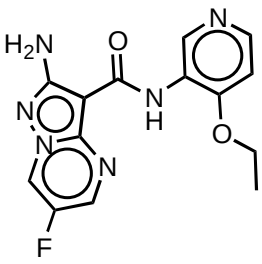

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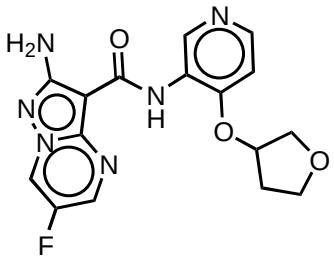

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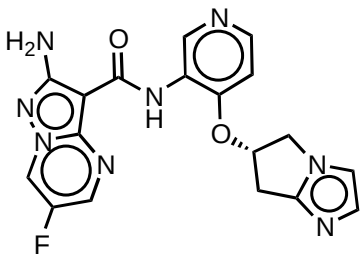
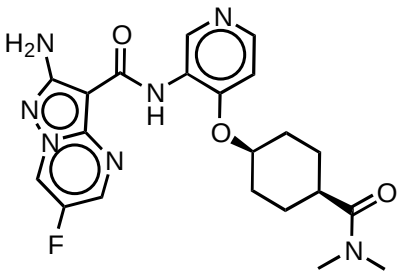


I-O-16



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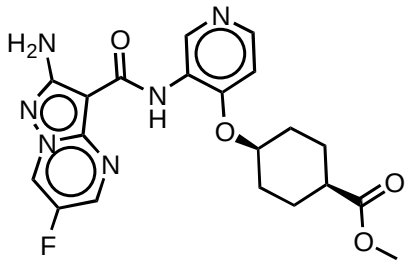

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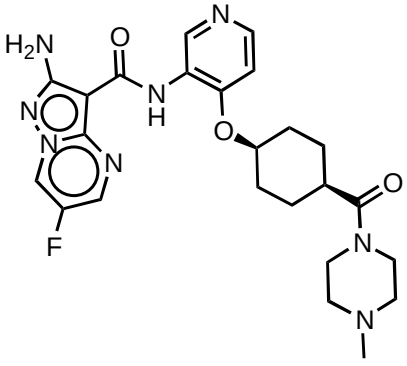
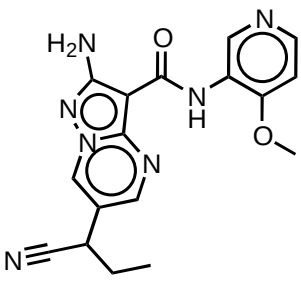
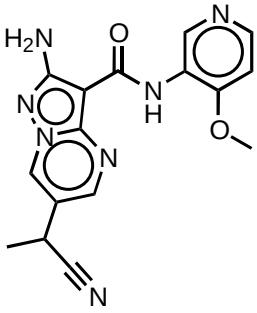


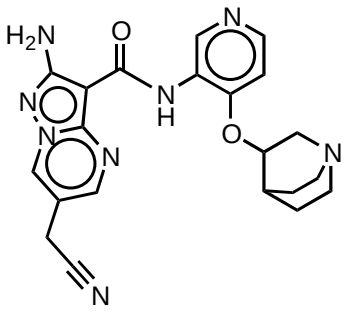
I-O-19



I-O-20



I-O-21



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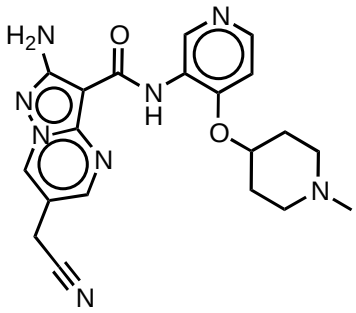

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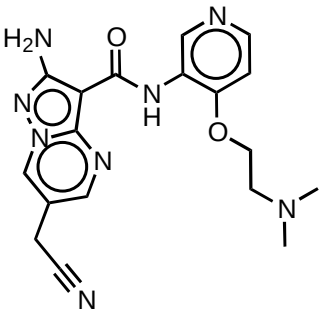
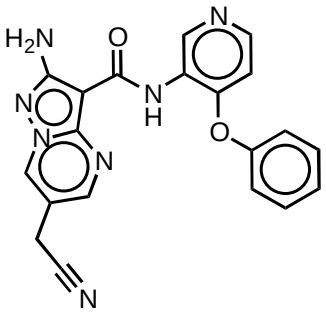
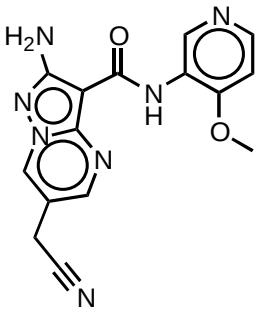


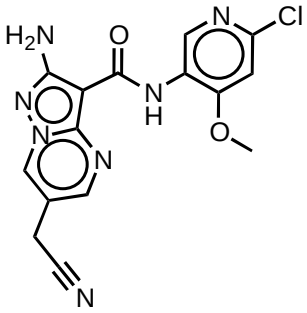
I-O-24



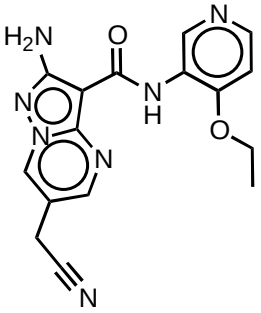
I-O-25



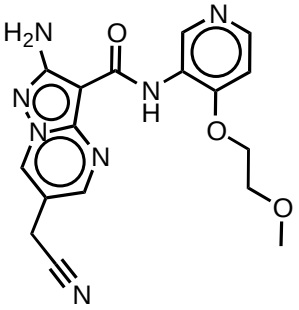
I-O-26



I-O-27



I-O-28



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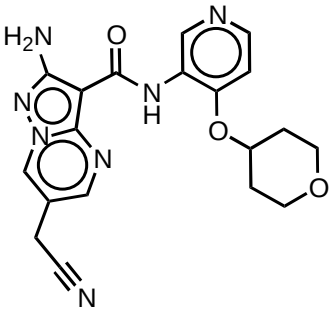

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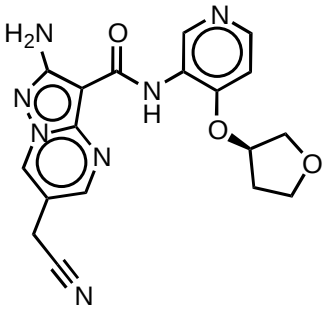

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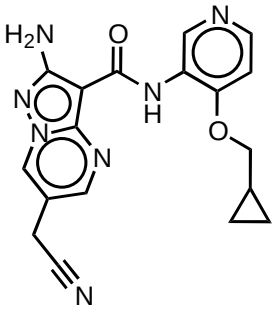

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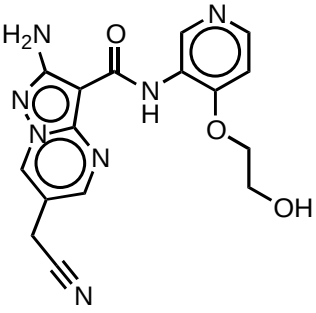

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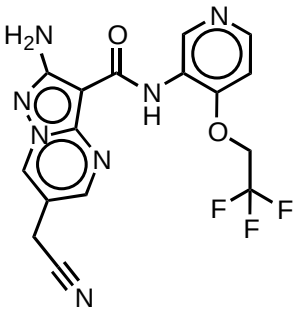

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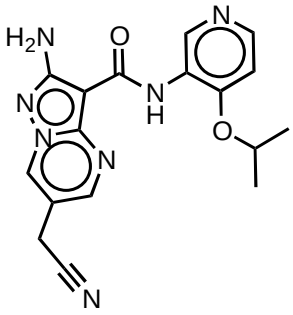

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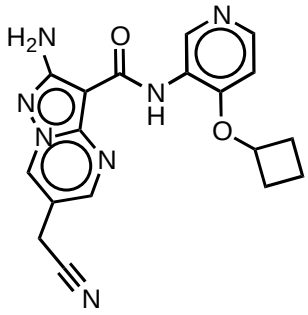

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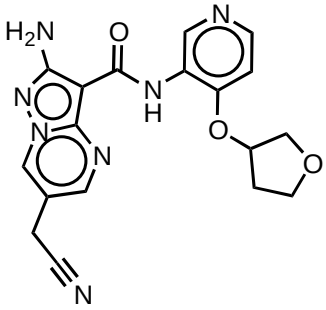

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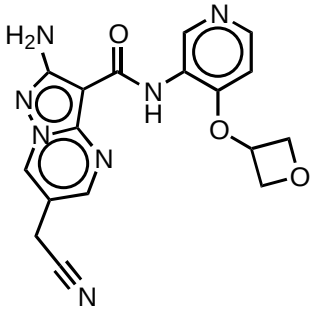

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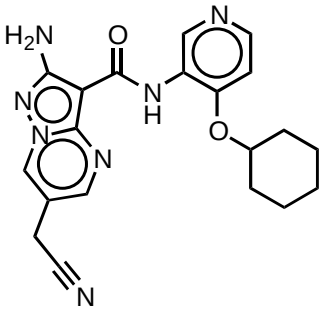

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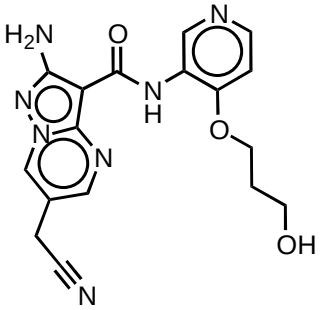

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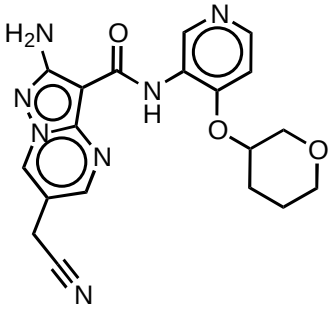

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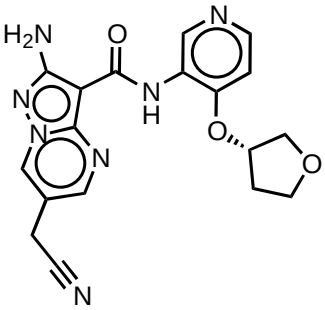

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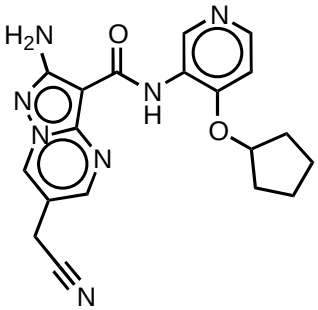

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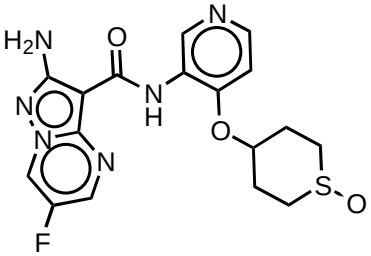

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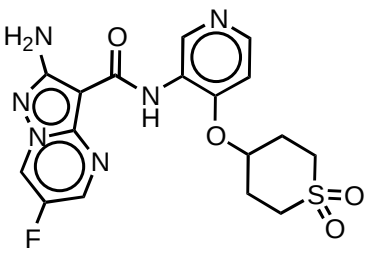

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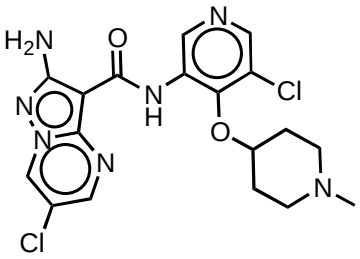

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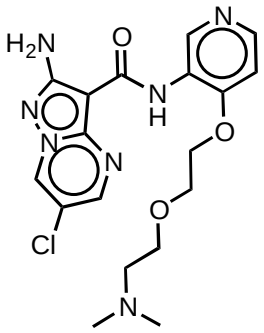

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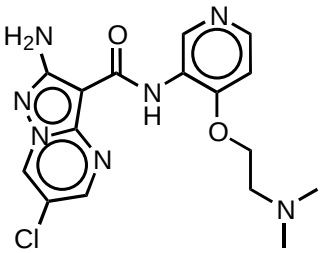

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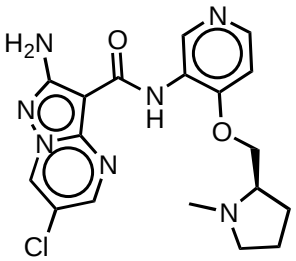

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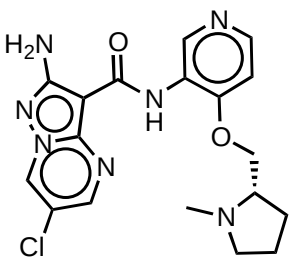

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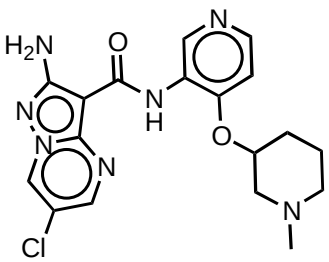

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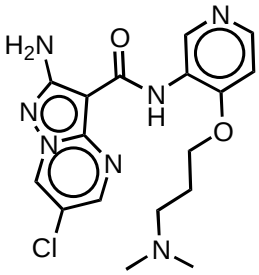

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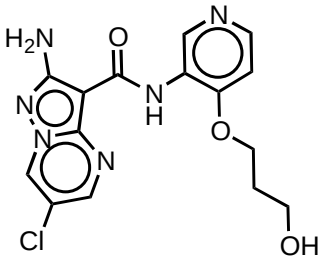

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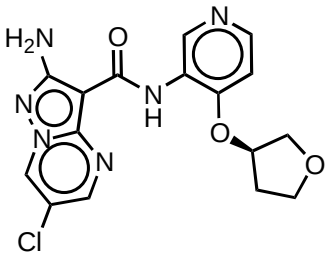

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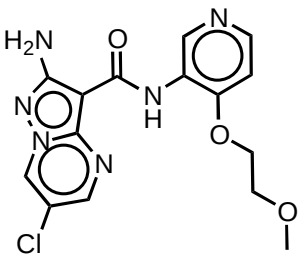

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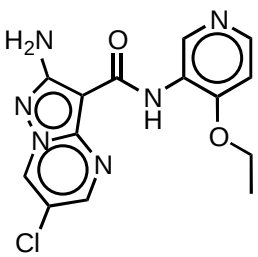

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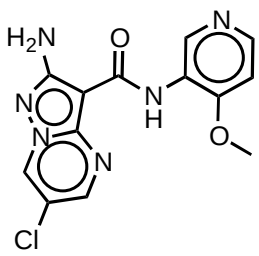

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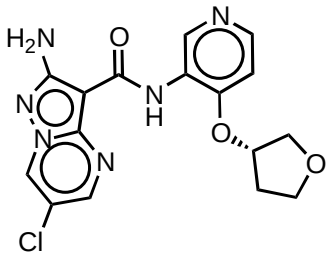

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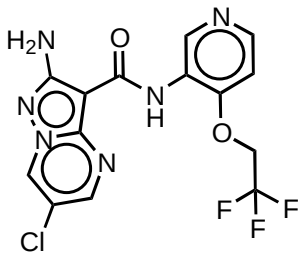

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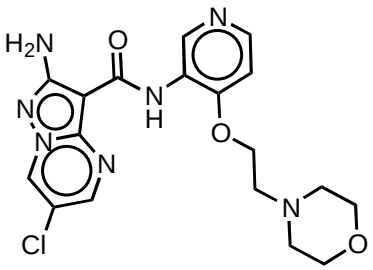

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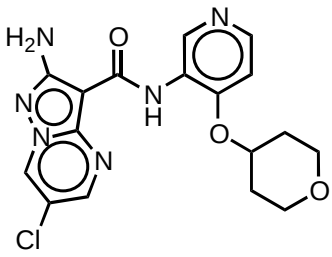

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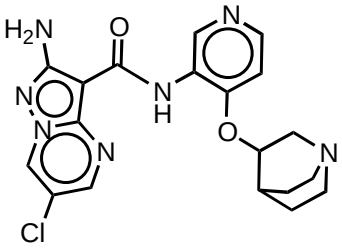

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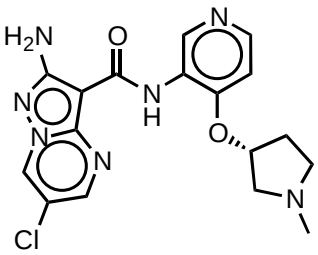

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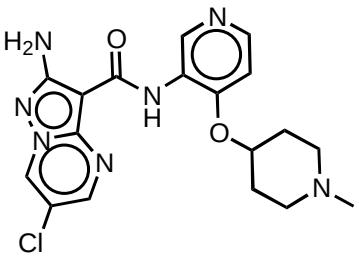

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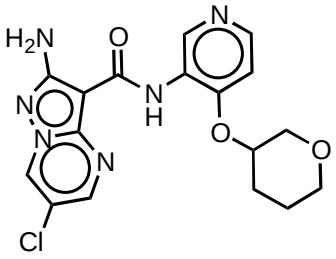

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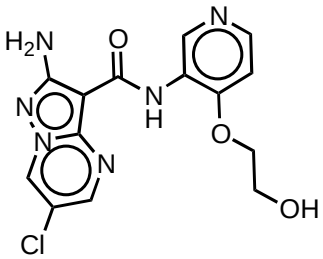
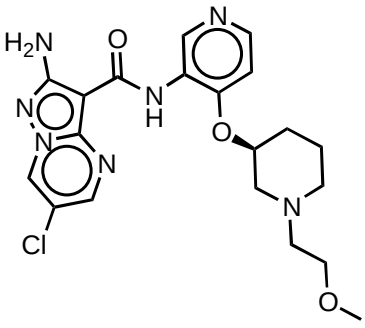
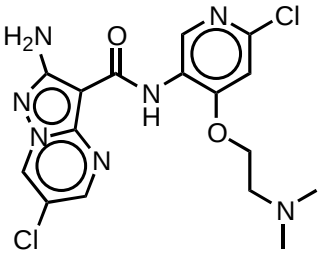


I-O-66



I-O-67



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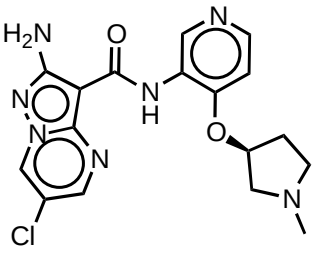
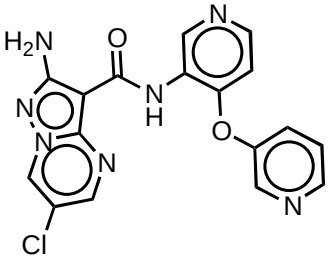
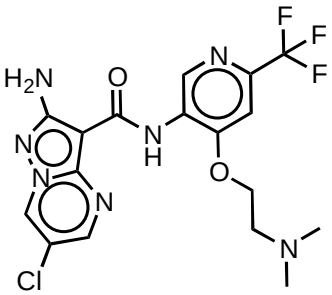


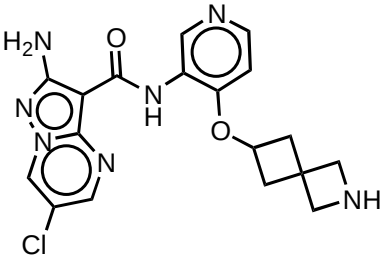
I-O-69



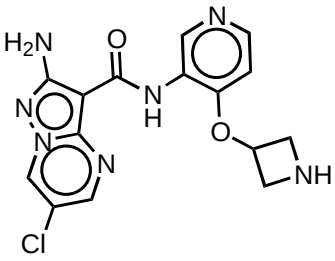
I-O-70



I-O-71



I-O-72



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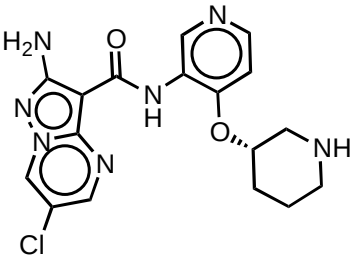
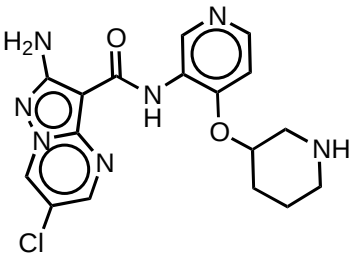
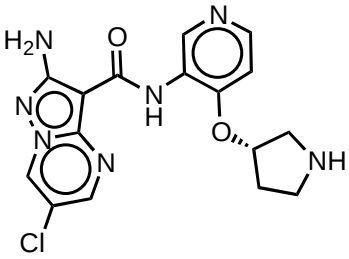


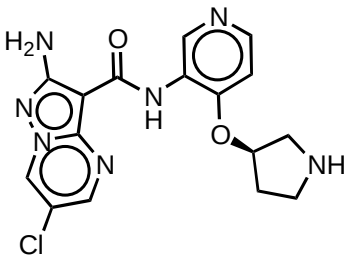
I-O74



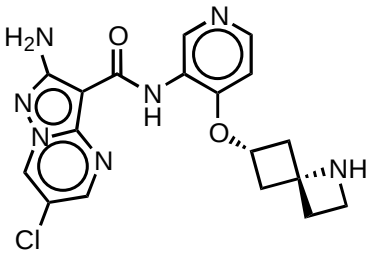
I-O-75



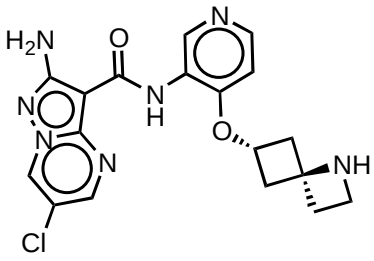
I-O-76



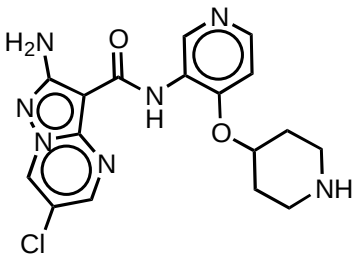
I-O-77



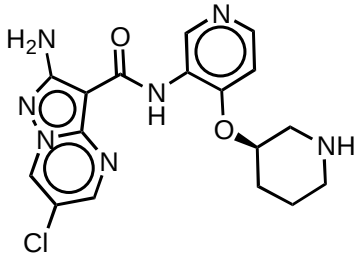
I-O-78



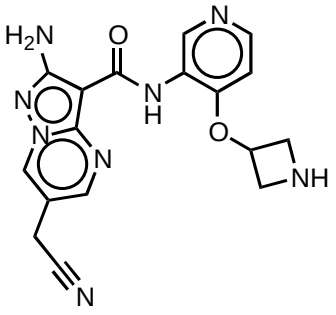
I-O-79



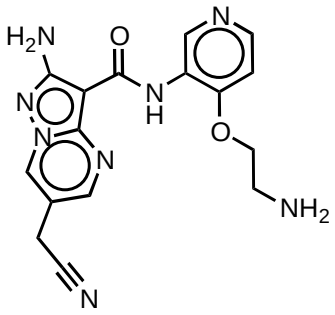
I-O-80



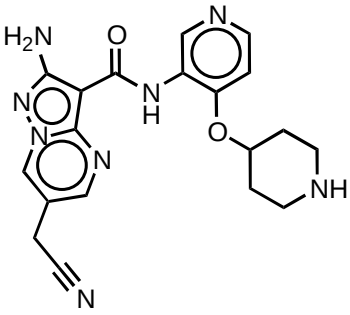
I-O-81



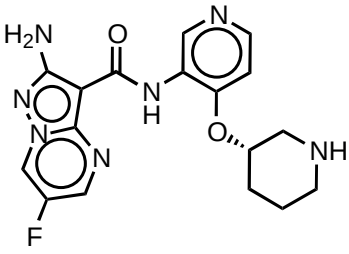
I-O-82



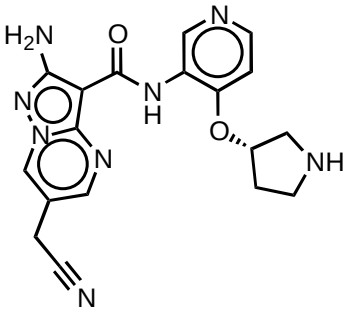
I-O-83



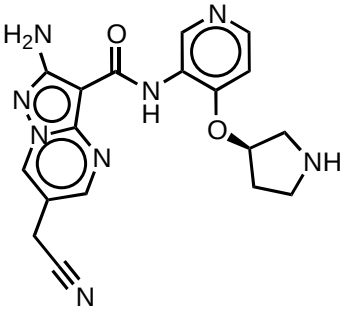
I-O-84



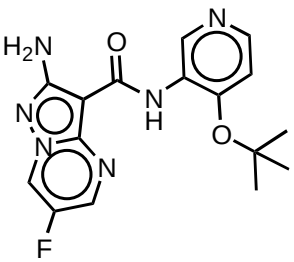
I-O-85



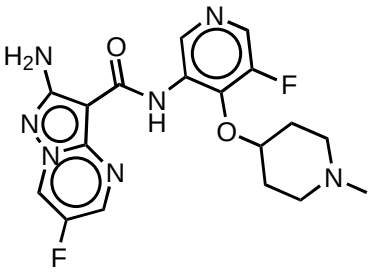
I-O-86



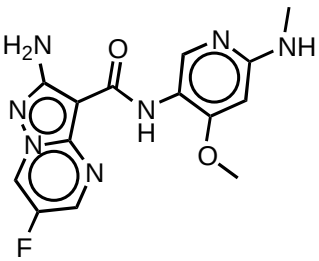
I-O-87



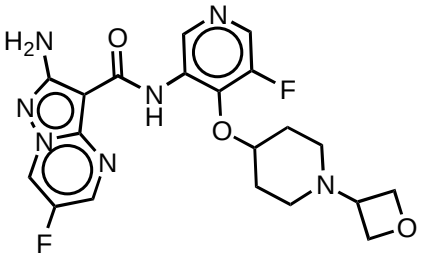
I-O-88



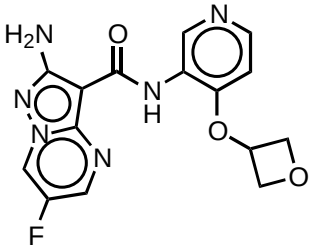
I-O-89



I-O-90

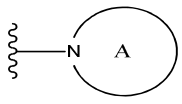


I-O-91



I-O-92.

12. The compound of claim 9, wherein R^4 is:



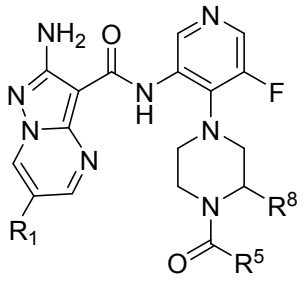
;

optionally wherein Ring A is a is a 3-7 membered fully saturated, partially unsaturated, or aromatic monocyclic ring having 1-3 heteroatoms selected from oxygen, nitrogen or sulfur; optionally thereto

wherein (I) Ring A is a 3-7 membered heterocyclyl; optionallywherein 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 azetidinyl; optionally thereto wherein Ring A is independently selected from piperidinyl, piperazinyl, 1,4-diazepanyl, thiomorpholinyl, pyrrolidinyl, azepanyl, morpholinyl; optionally thereto wherein Ring A is independently selected from piperazinyl or piperidiny; or:

wherein (II) Ring A is a 5 membered heteroaryl; optionally wherein Ring A is independently selected from pyrrolyl, imidazolyl, pyrazolyl, 1,2,3-triazolyl, or 1,2,4-triazolyl; optionally thereto wherein Ring A is independently selected from pyrazolyl or imidazolyl.

13. The compound of claim 9 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; optionally:

wherein (I) R^1 is fluoro; optionally wherein R^5 is C_{1-4}aliphatic; optionally thereto wherein R^5 is independently selected from methyl or ethyl; or:

wherein (II) R^5 is a 3-6 membered cycloalkyl; optionally wherein R^5 is cyclopropyl; or:

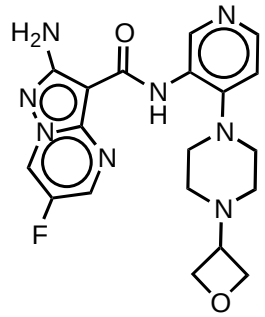
. wherein (III) R^5 is a 3-6 membered heterocyclyl having 1-2 heteroatoms selected from oxygen or sulfur; optionally wherein R^5 is tetrahydrofuranyl or oxytanyl; or:

wherein (IV) 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 form oxygen, nitrogen or sulfur; optionally:

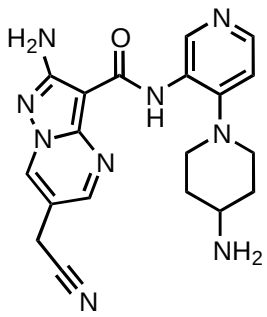
wherein (i) the ring formed by R^5 and R^6 is a five-membered ring; or:

wherein (ii) the ring formed by R^5 and R^6 is a six-membered ring.

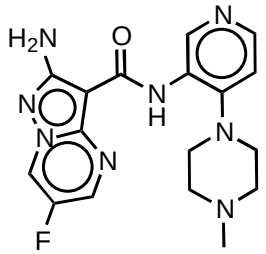
14. The compound of any one of claims 12 and 13, independently selected from:



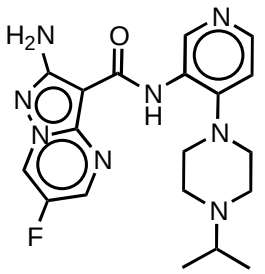
I-N-1



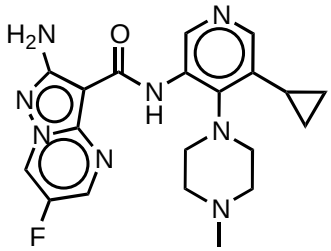
I-N-2



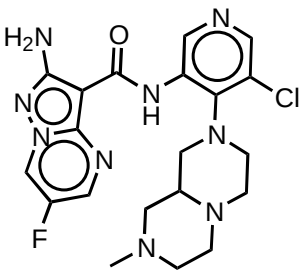
I-N-3



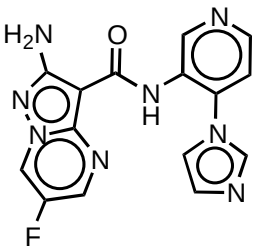
I-N-4



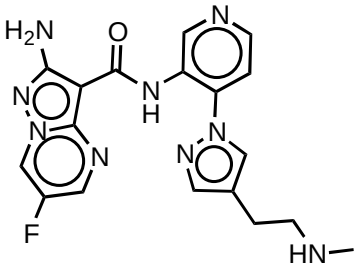
I-N-5



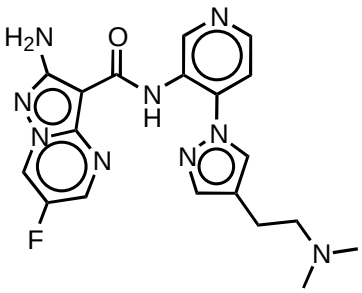
I-N-6



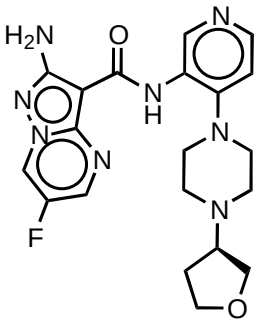
I-N-7



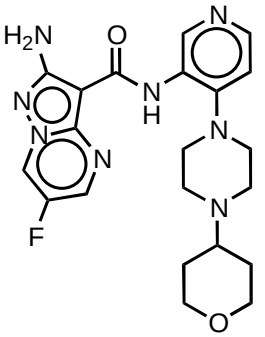
I-N-8



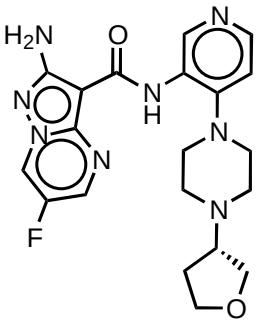
I-N-9



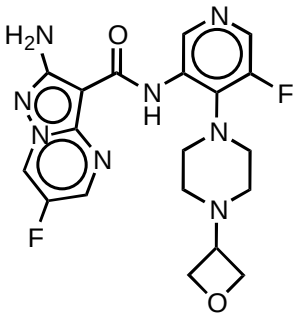
I-N-10



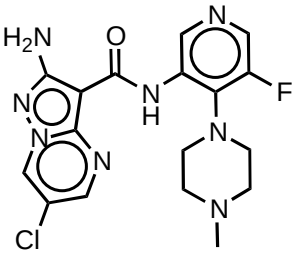
I-N-11



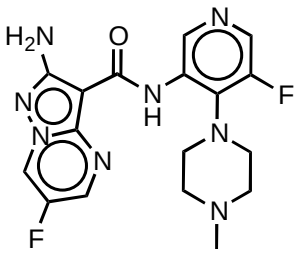
I-N-12



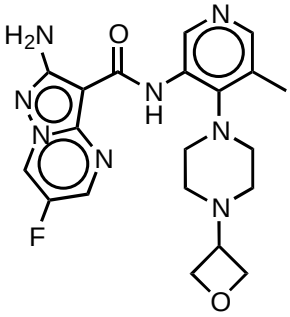
I-N-13



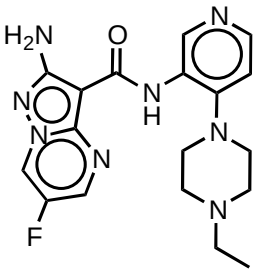
I-N-14



I-N-15



I-N-16



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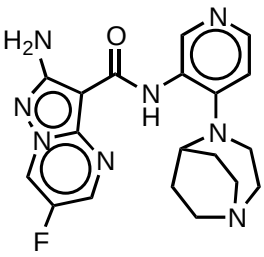
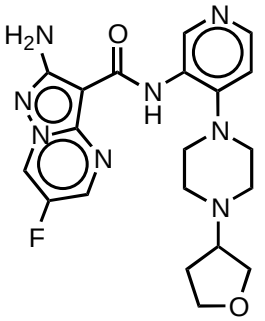
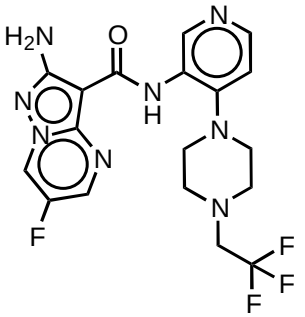


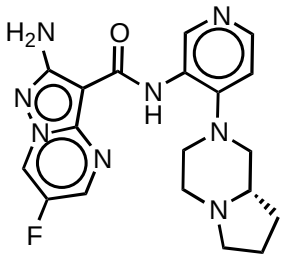
I-N-18



I-N-19



I-N-20



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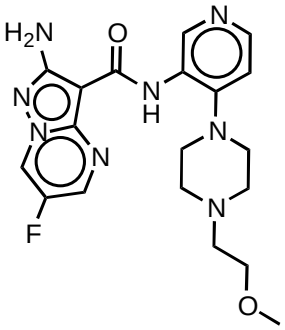

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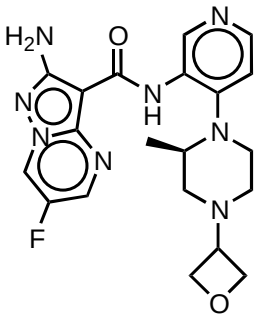

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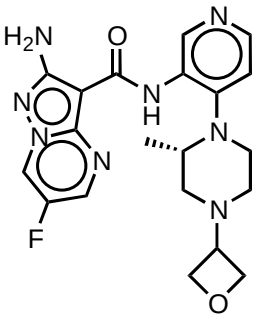
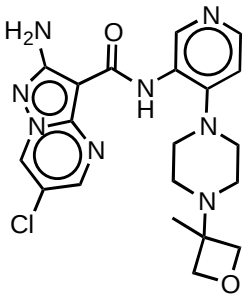


I-N-24



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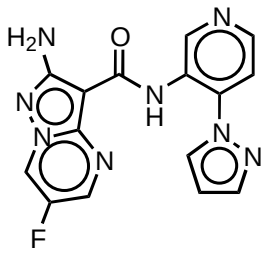
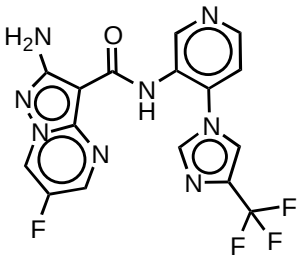


I-N-26



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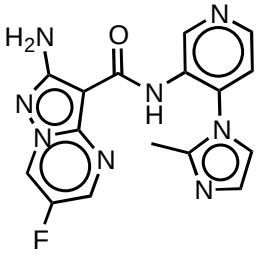
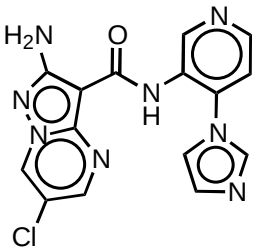
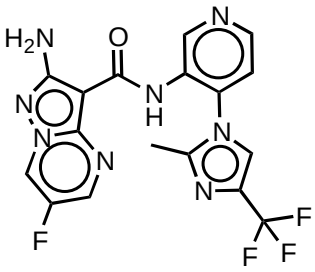


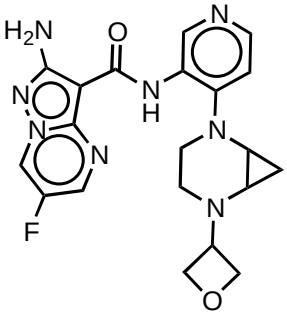
I-N-28



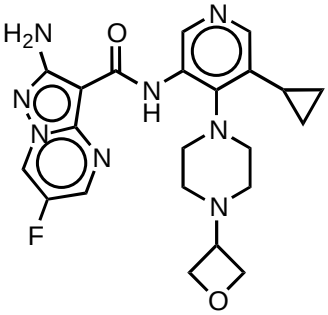
I-N-29



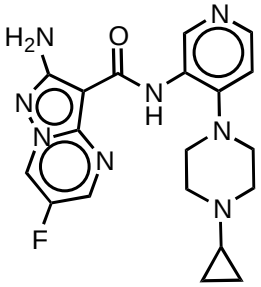
I-N-30



I-N-31



I-N-32



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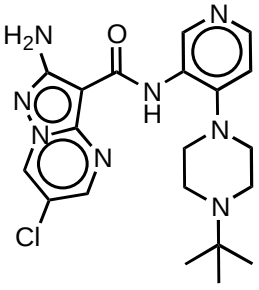
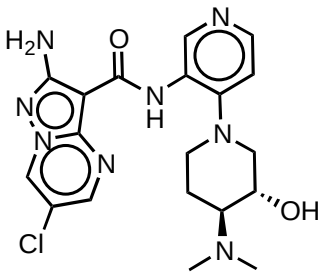
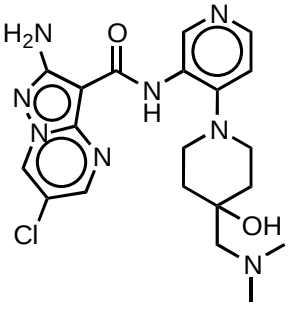


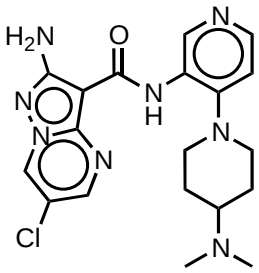
I-N-34



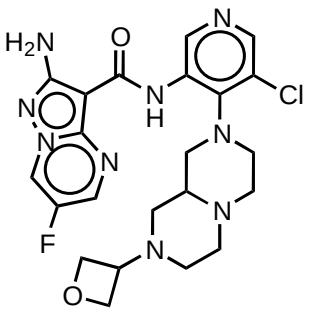
I-N-35



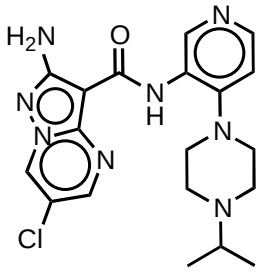
I-N-36



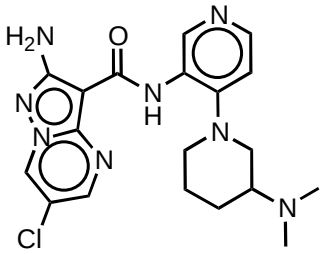
I-N-37



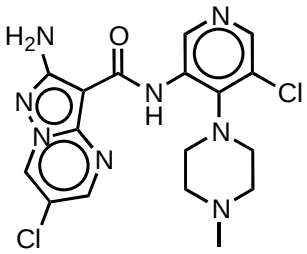
I-N-38



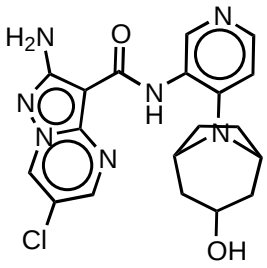
I-N-39



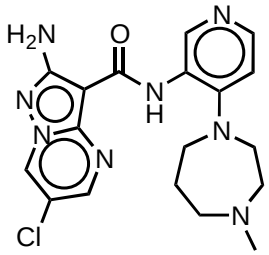
I-N-40



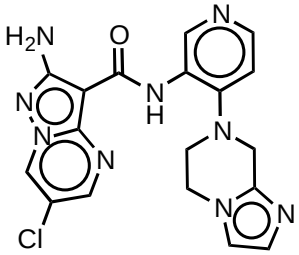
I-N-41



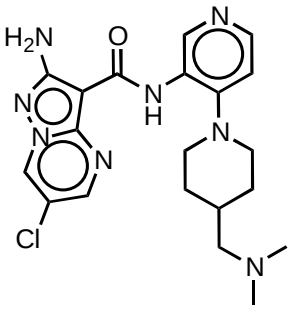
I-N-42



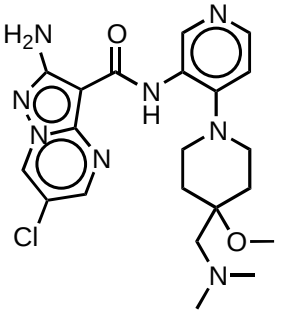
I-N-43



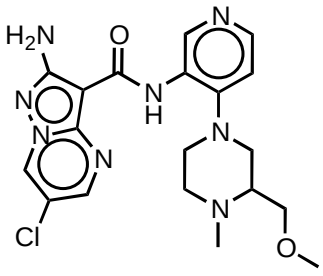
I-N-44



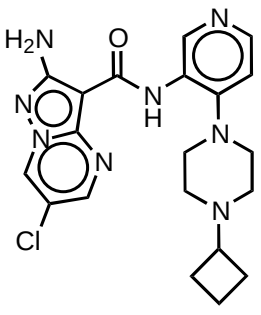
I-N-45



I-N-46



I-N-47



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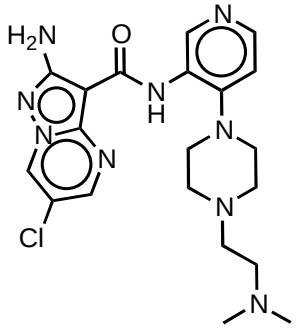
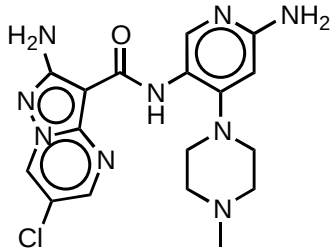


I-N-49



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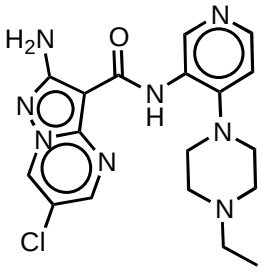

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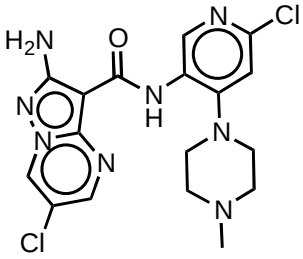
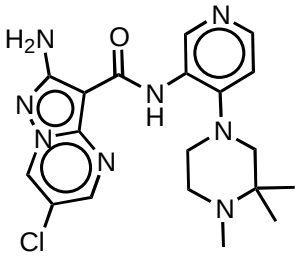
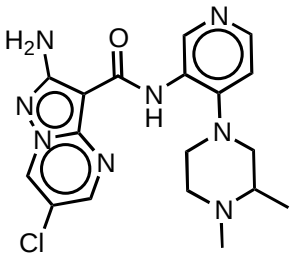


I-N-52



I-N-53



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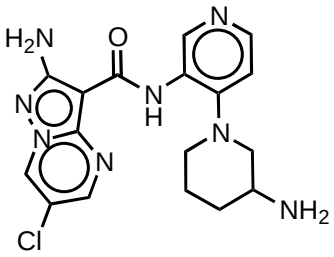

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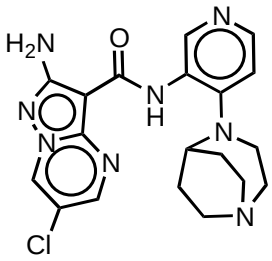
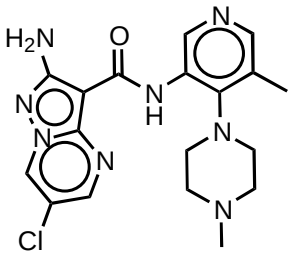
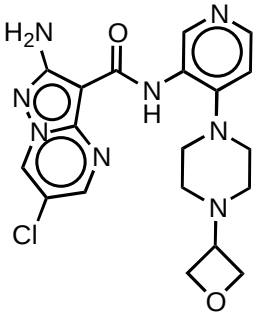


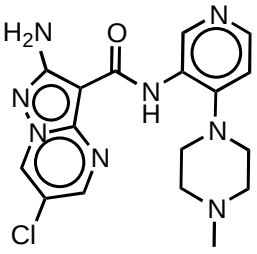
I-N-56



I-N-57



I-N-58



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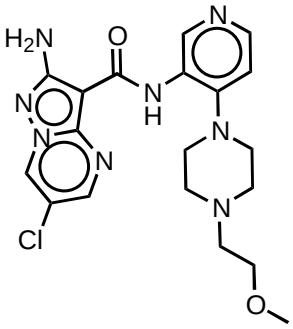

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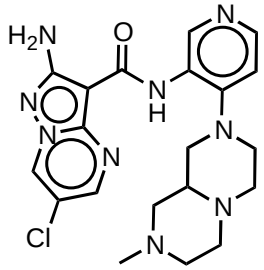

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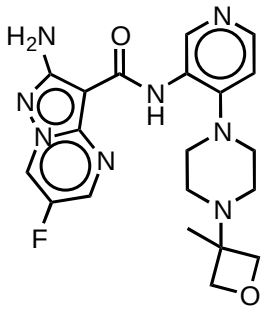
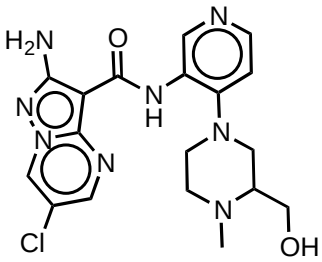


I-N-62



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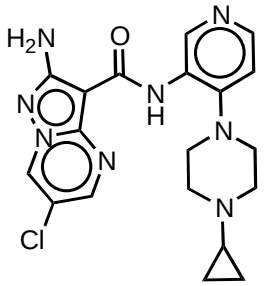
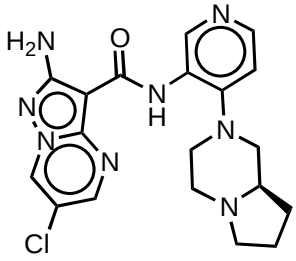


I-N-64



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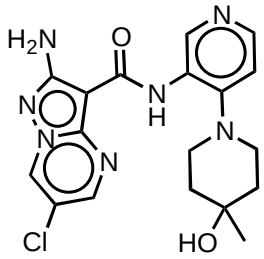
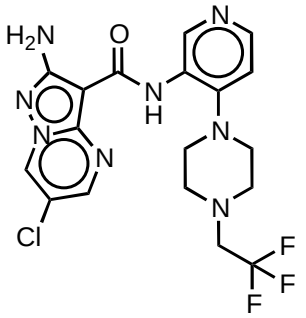
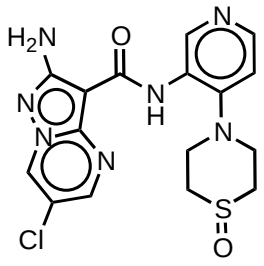


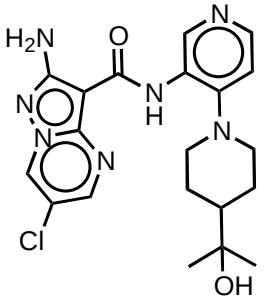
I-N-66



I-N-67



I-N-68



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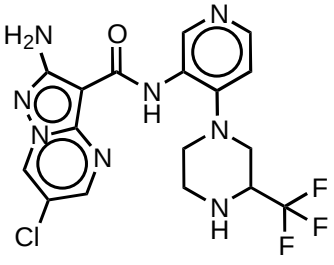

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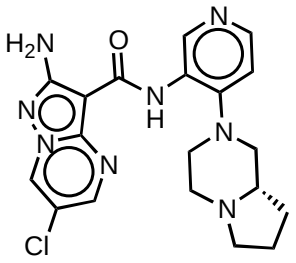

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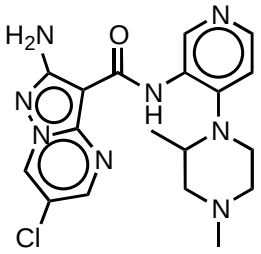
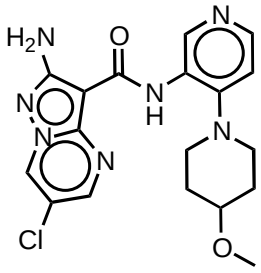
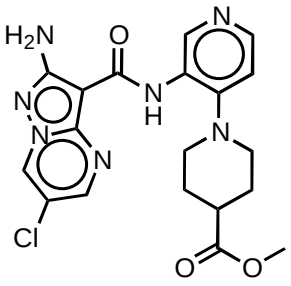


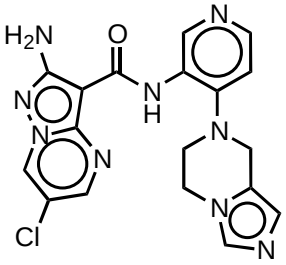
I-N-72



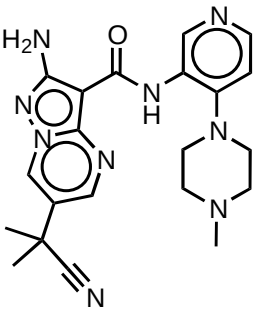
I-N-73



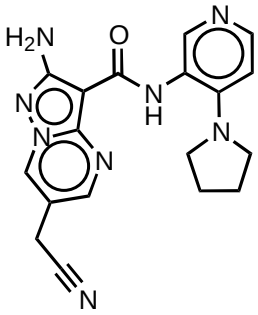
I-N-74



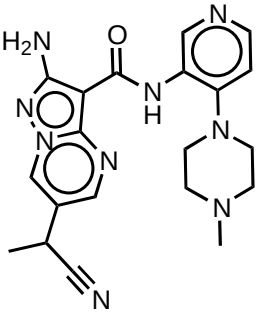
I-N-75



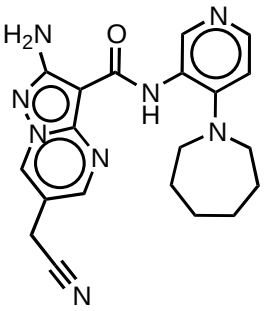
I-N-76



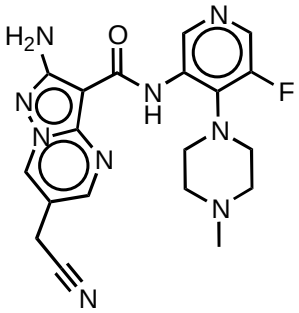
I-N-77



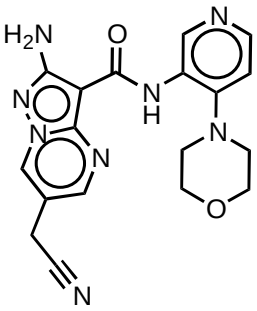
I-N-78



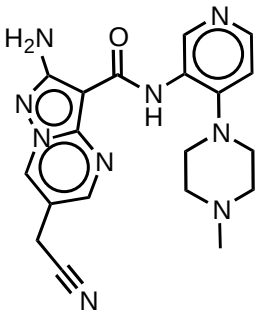
I-N-79



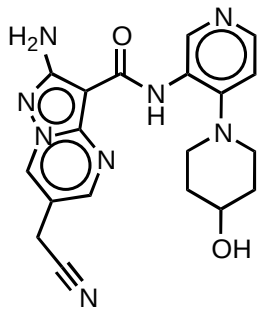
I-N-80



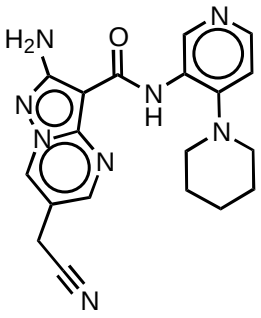
I-N-81



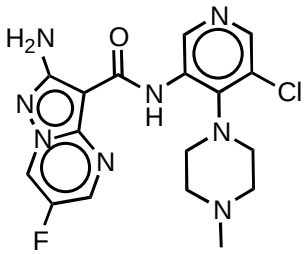
I-N-82



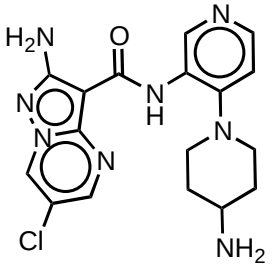
I-N-83



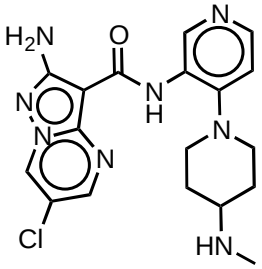
I-N-84



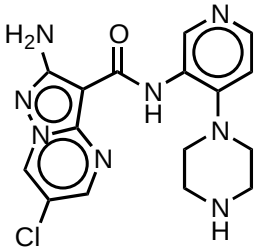
I-N-85



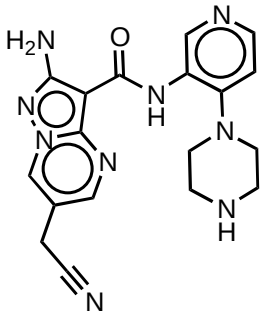
I-N-86



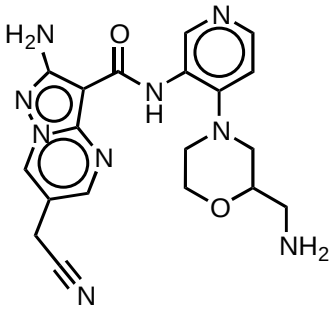
I-N-87



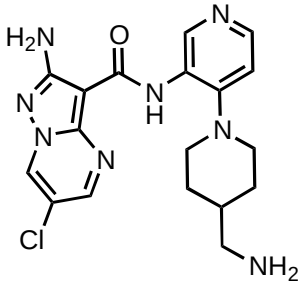
I-N-88



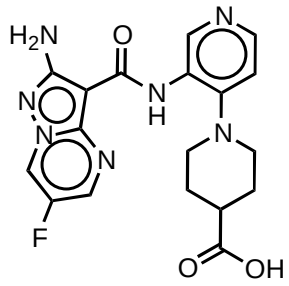
I-N-89



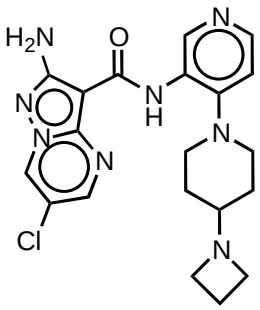
I-N-90



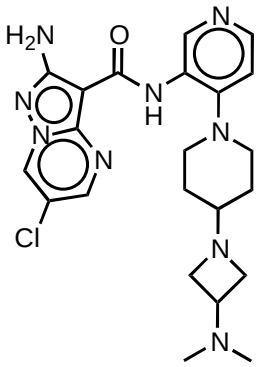
I-N-91



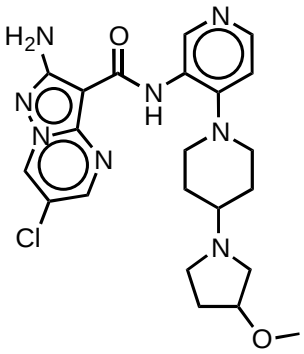
I-N-92



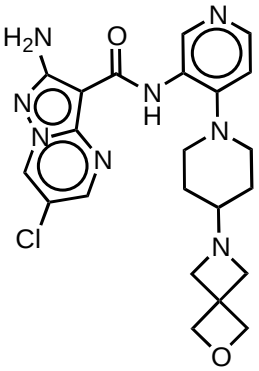
I-N-93



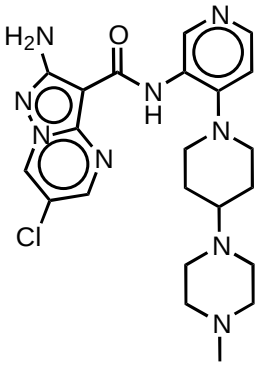
I-N-94



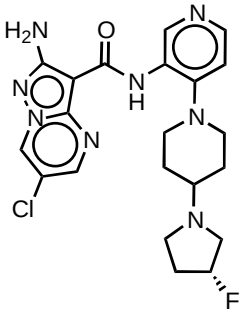
I-N-95



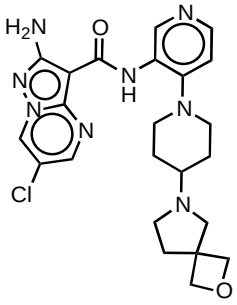
I-N-96



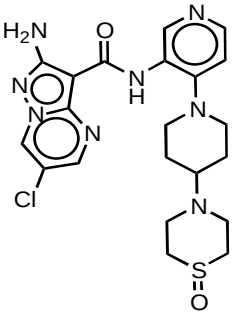
I-N-97



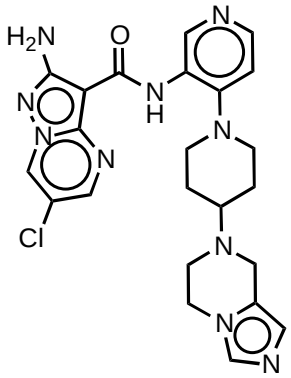
I-N-98



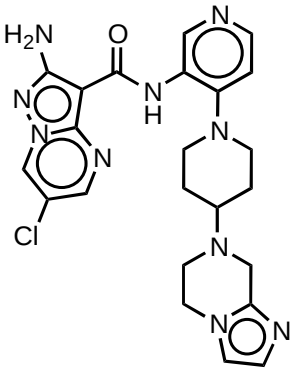
I-N-99



I-N-100



I-N-101



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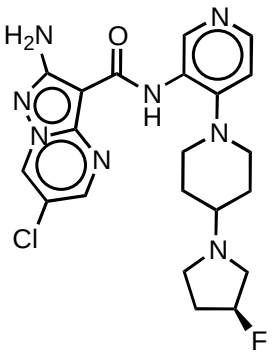

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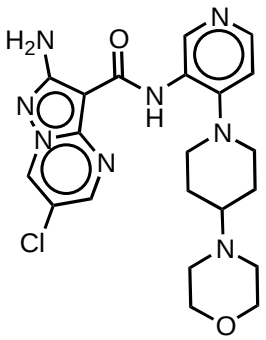

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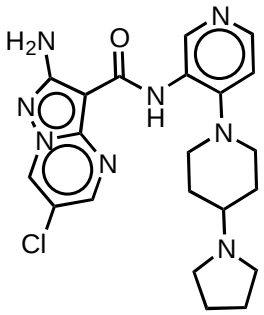

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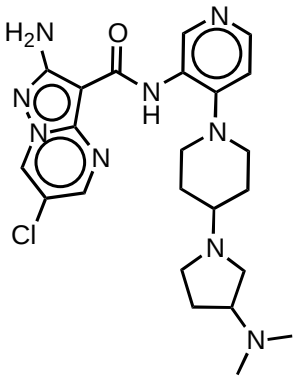

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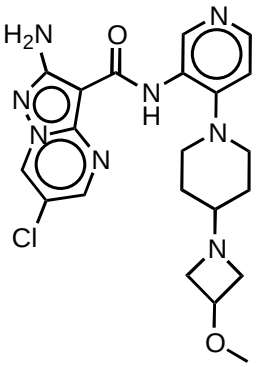

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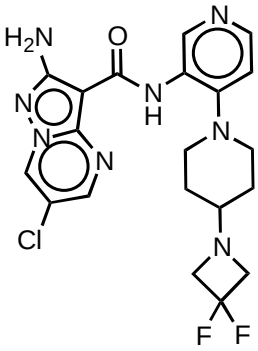

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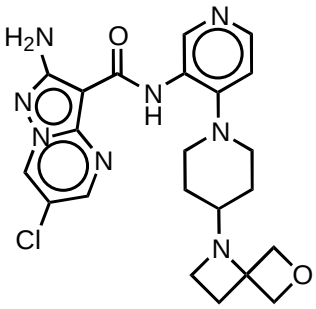

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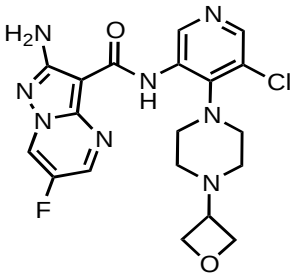

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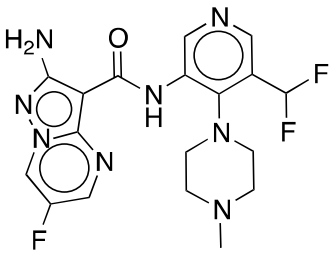

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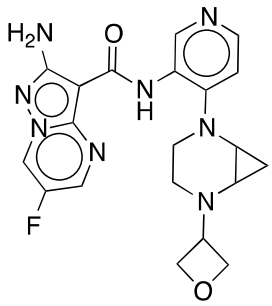

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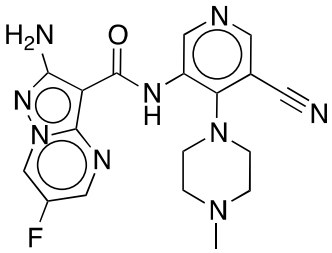
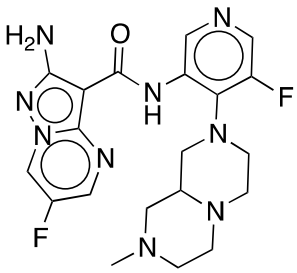


I-N-113



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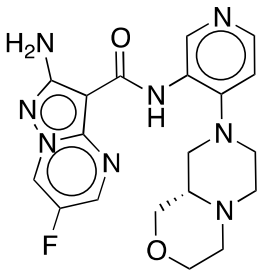

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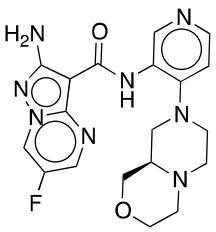

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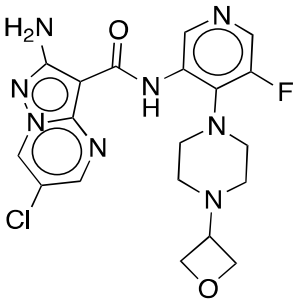

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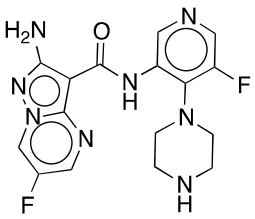

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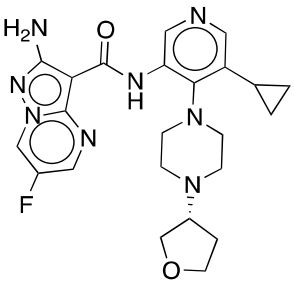

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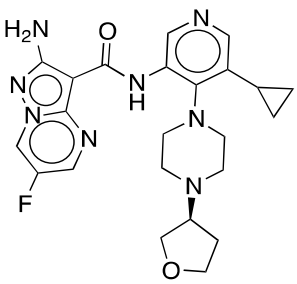

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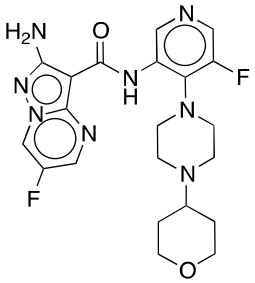

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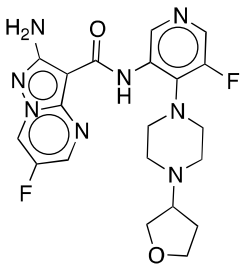

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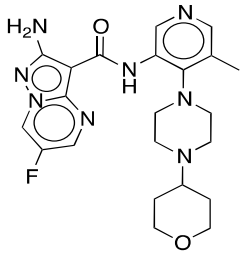

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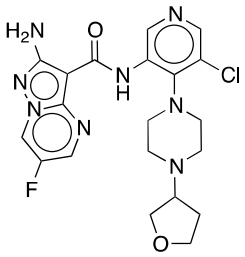

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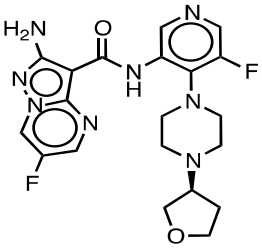

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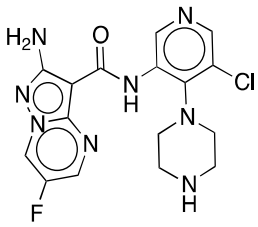

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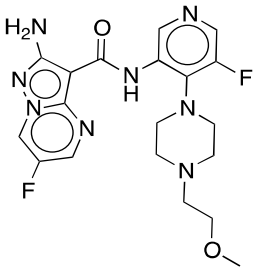

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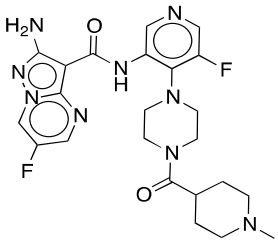

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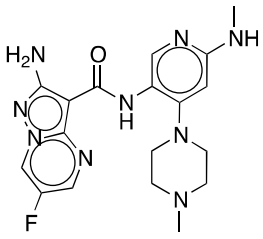

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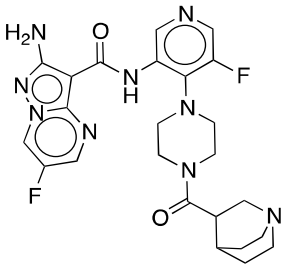

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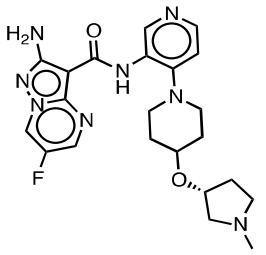
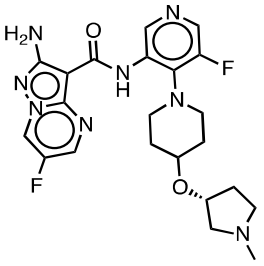


I-N-131



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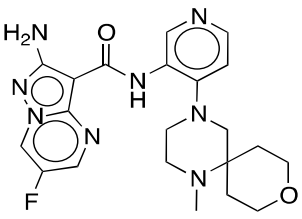
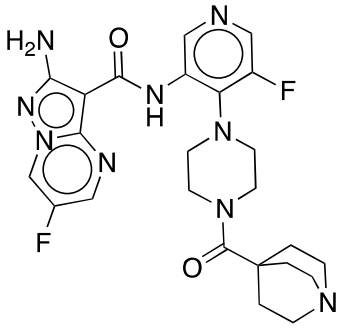


I-N-133



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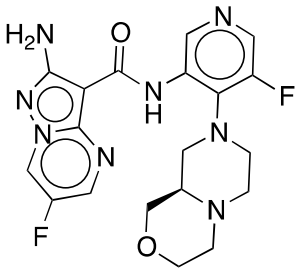

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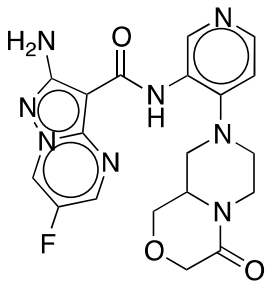
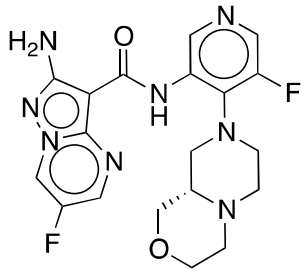
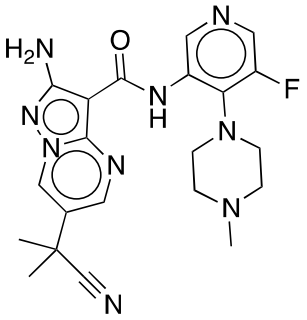


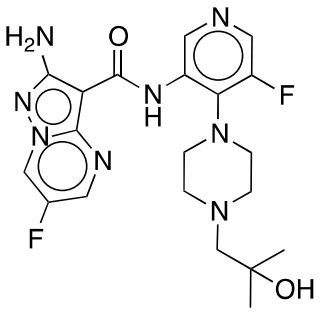
I-N-136



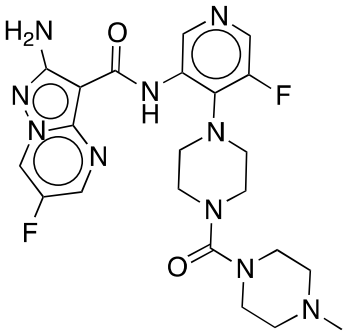
I-N-137



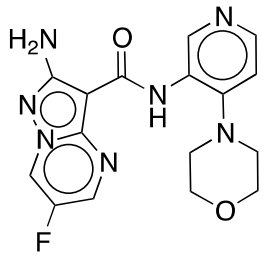
I-N-138



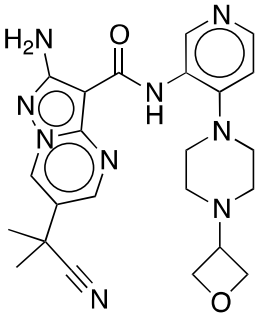
I-N-139



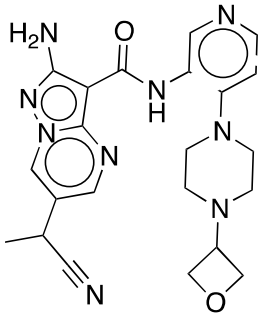
I-N-140



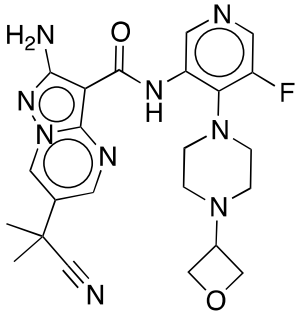
I-N-141



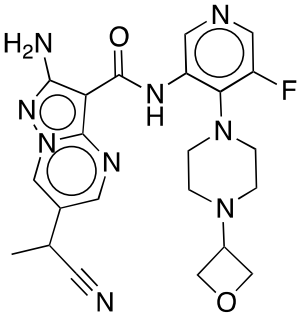
I-N-142



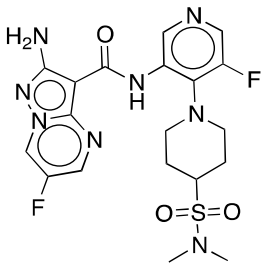
I-N-143



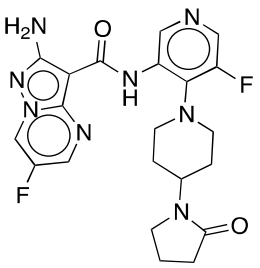
I-N-144



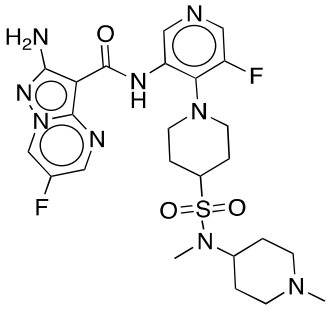
I-N-145



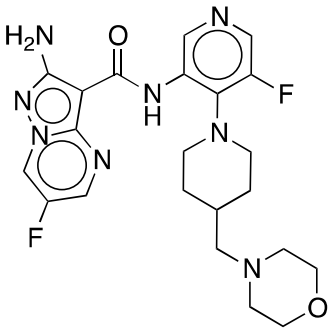
I-N-146



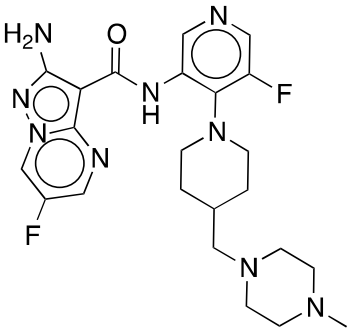
I-N-147



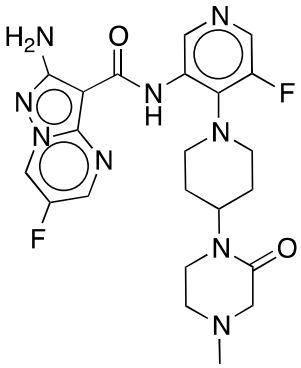
I-N-148



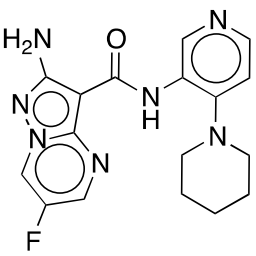
I-N-149



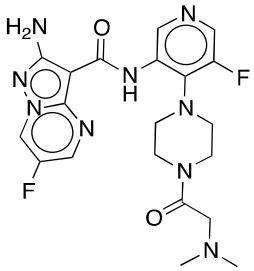
I-N-150



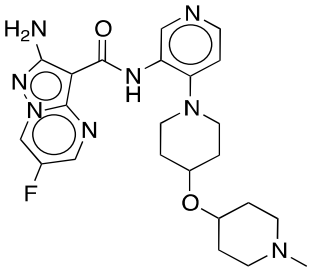
I-N-151



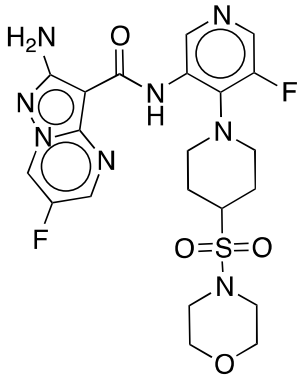
I-N-152



I-N-153



I-N-154



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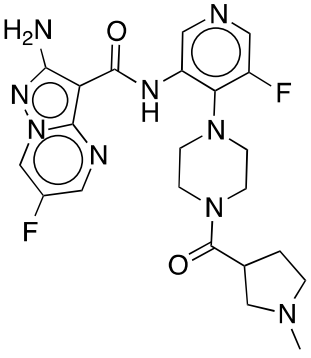

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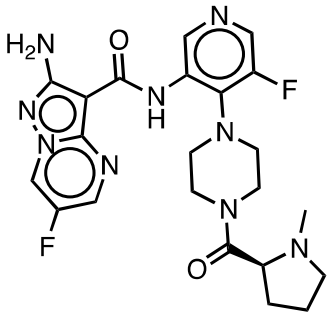

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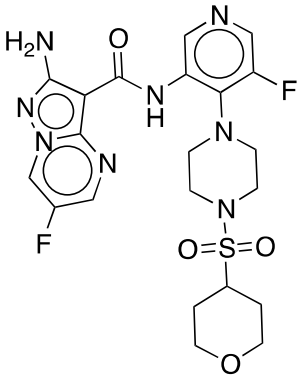

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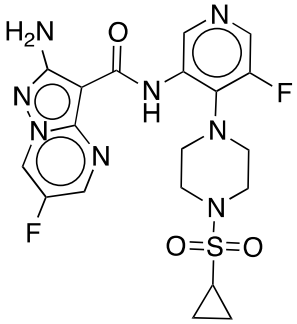

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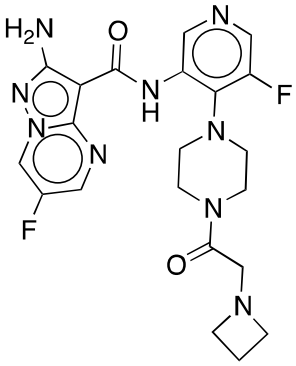

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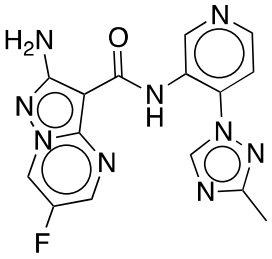

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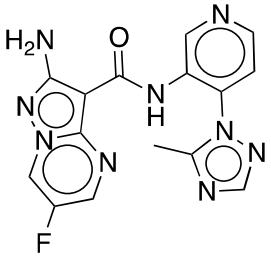

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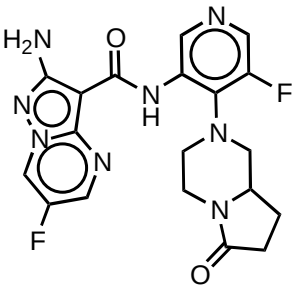

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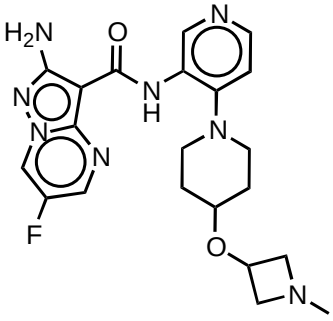

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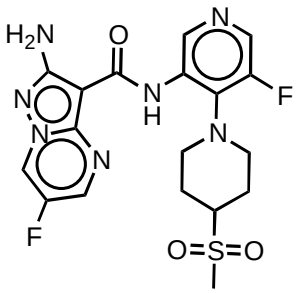

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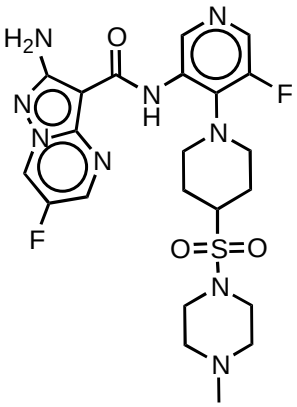

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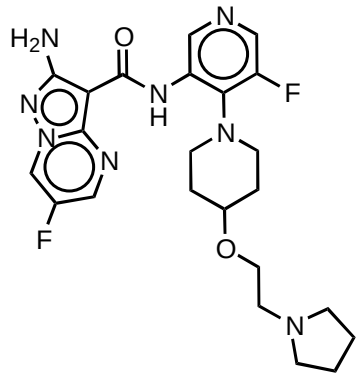

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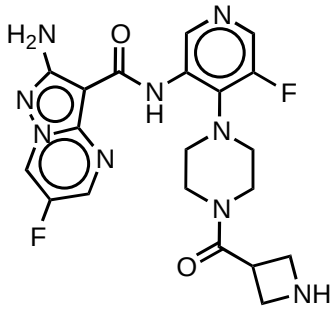

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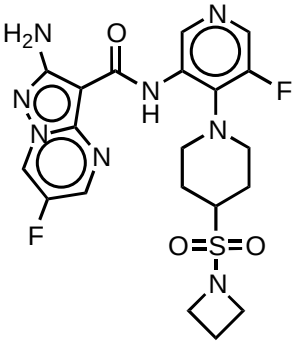

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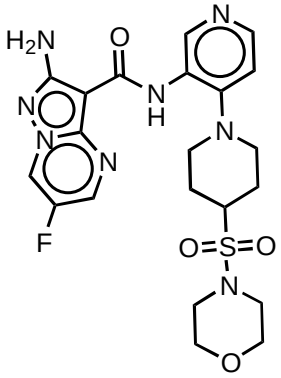

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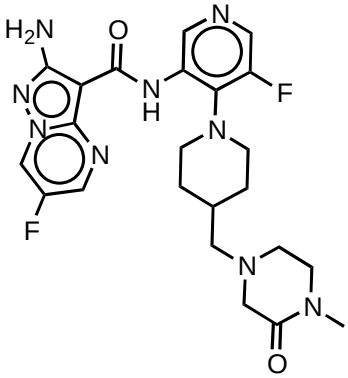

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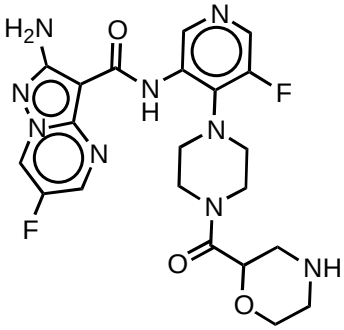

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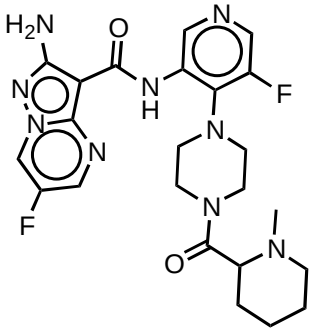

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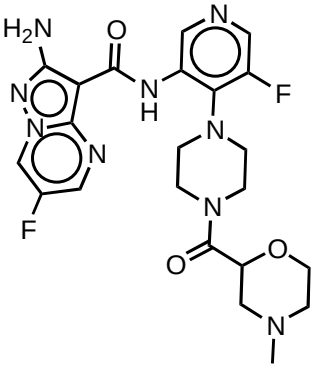

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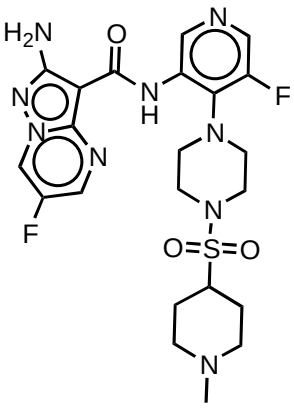

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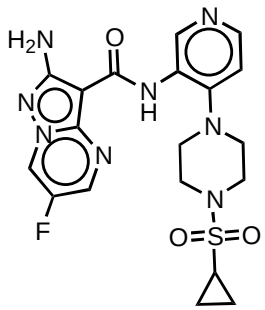

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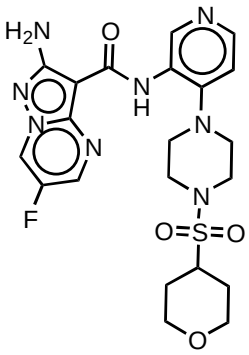

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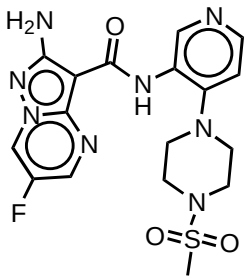

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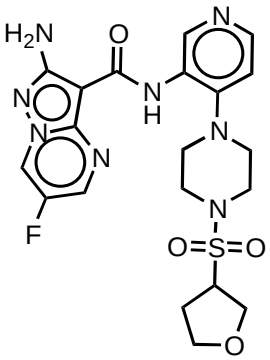

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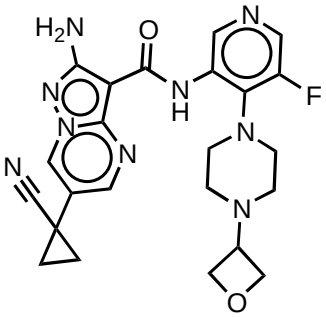

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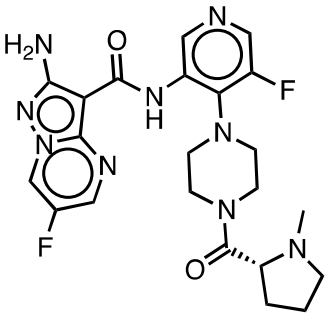

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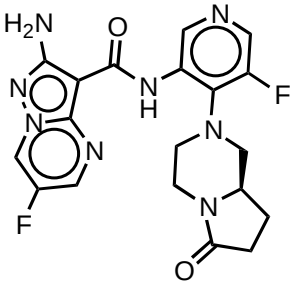

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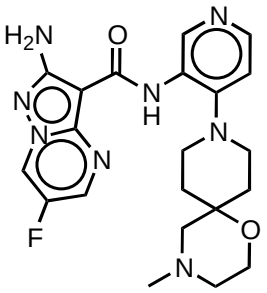

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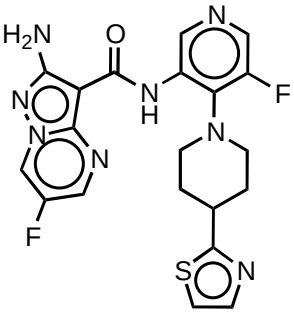

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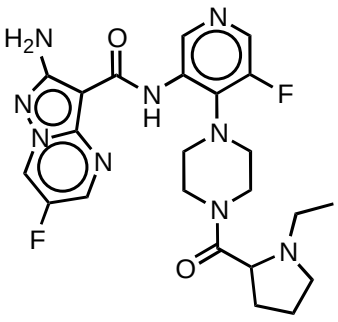

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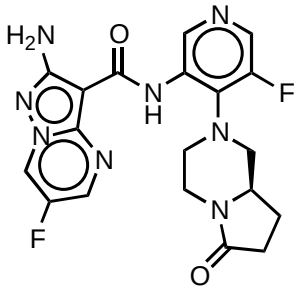

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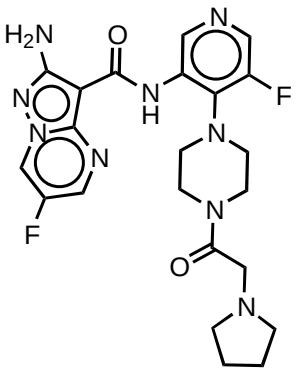

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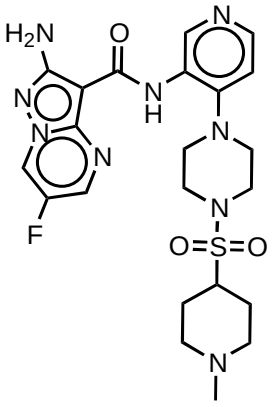

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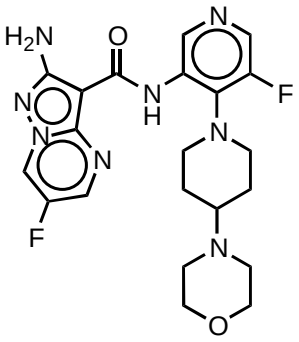

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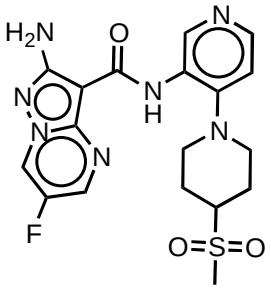

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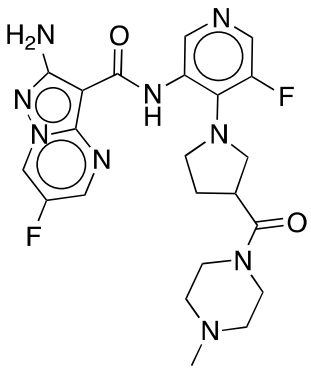

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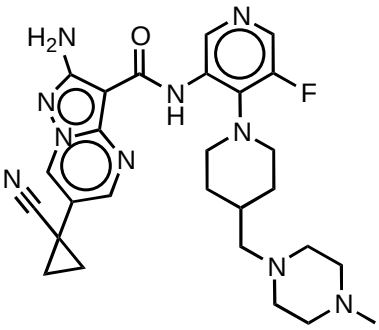
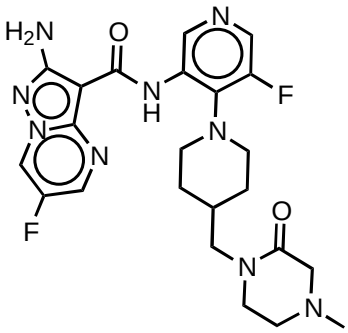


I-N-192



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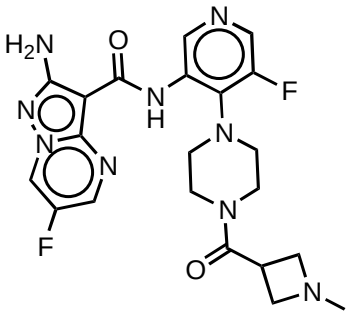

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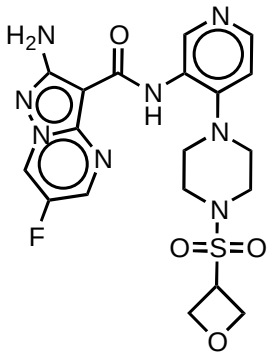

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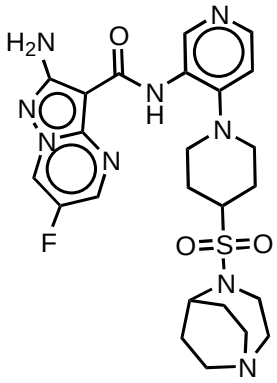

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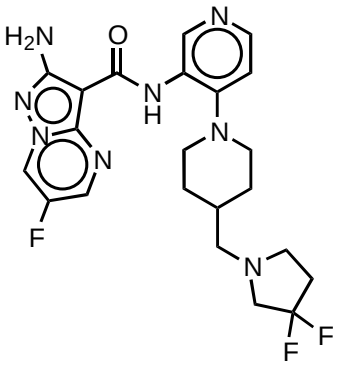
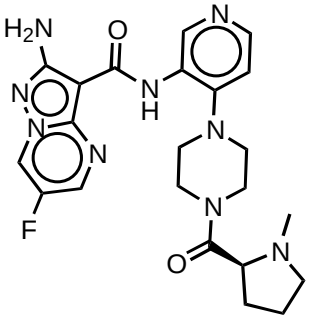


I-N-197



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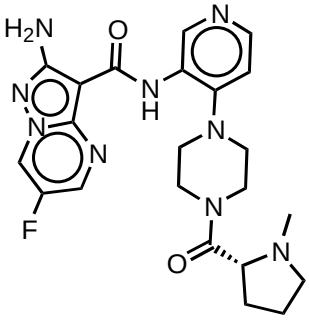

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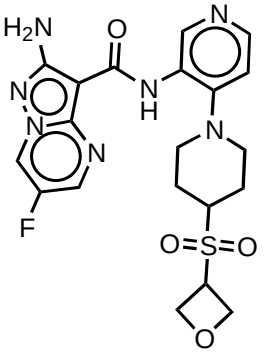
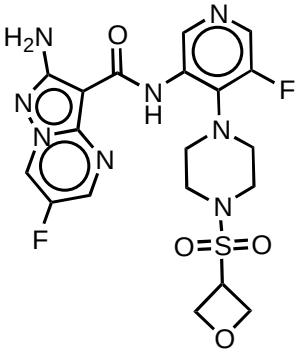
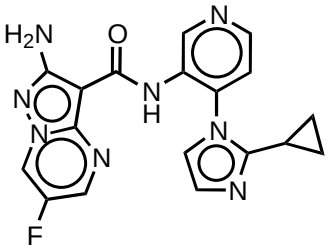


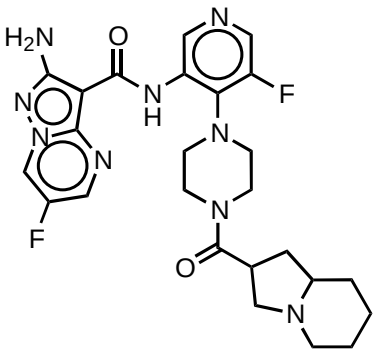
I-N-200



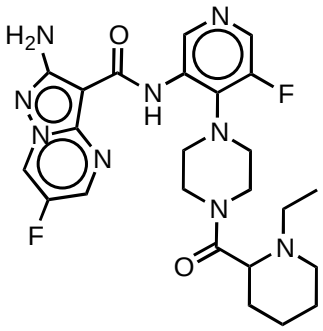
I-N-201



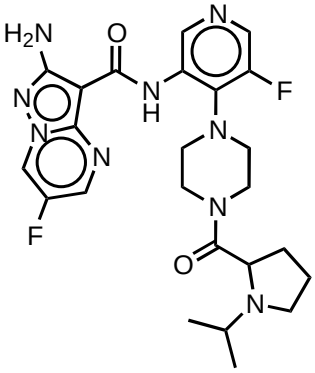
I-N-202



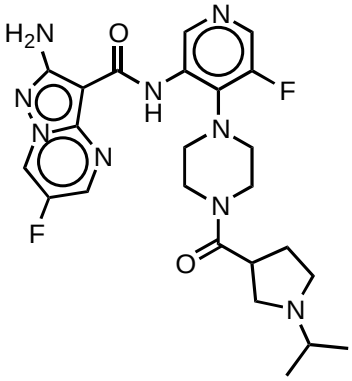
I-N-203



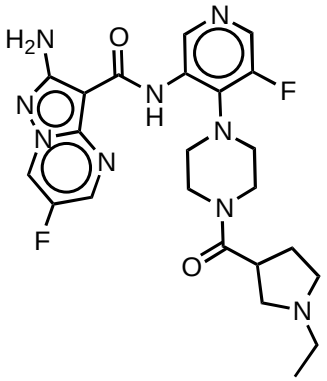
I-N-204



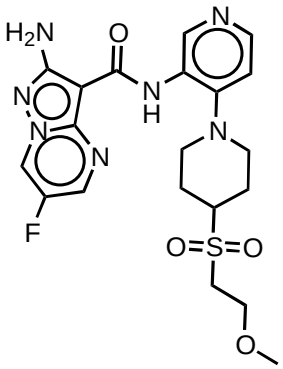
I-N-205



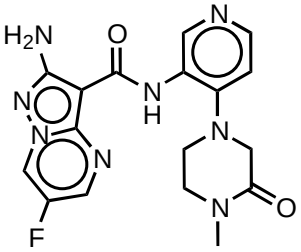
I-N-206



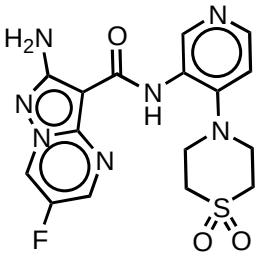
I-N-207



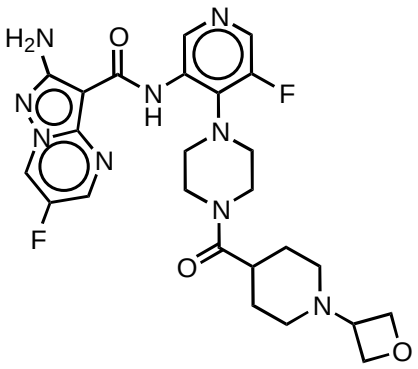
I-N-208



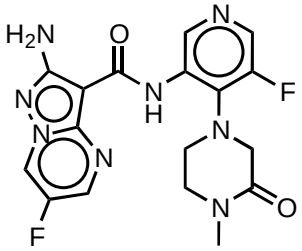
I-N-209



I-N-210



I-N-211



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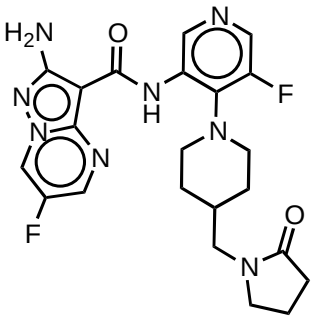

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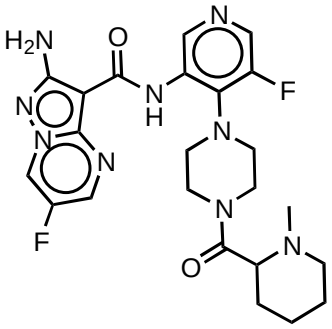

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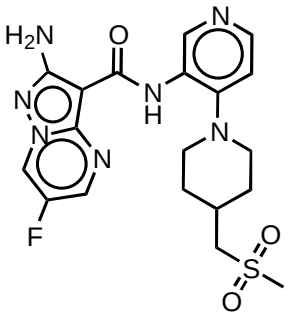

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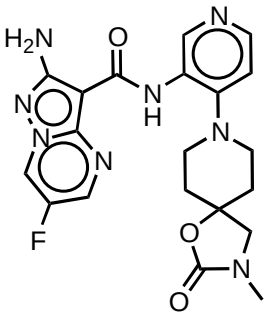

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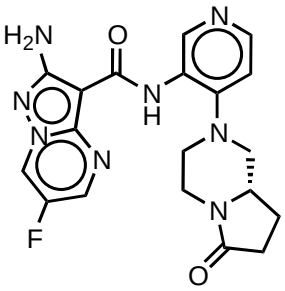

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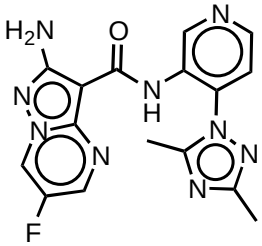

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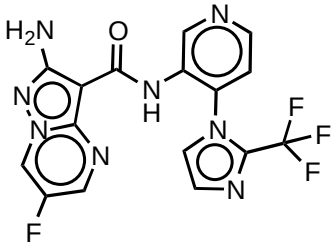

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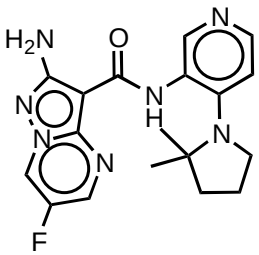

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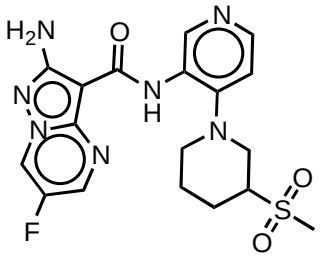

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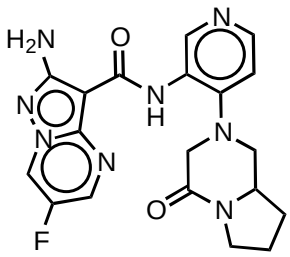

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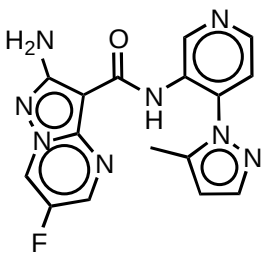

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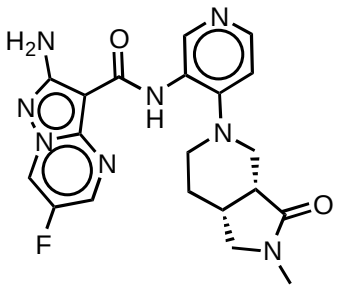

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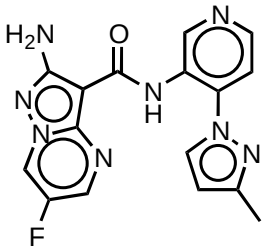

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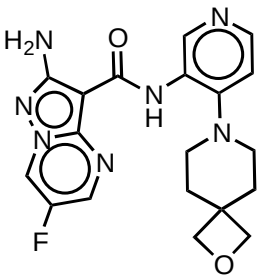

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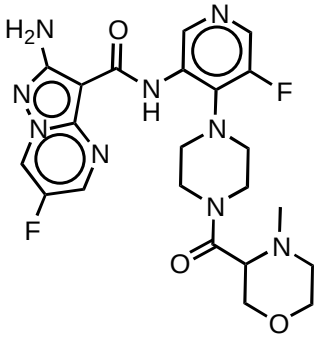

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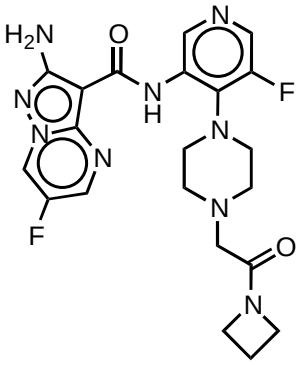

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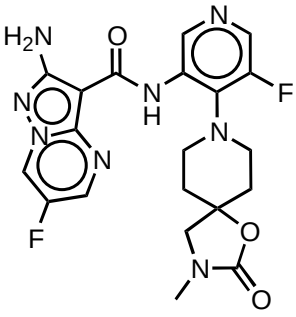

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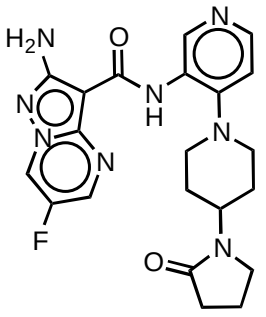

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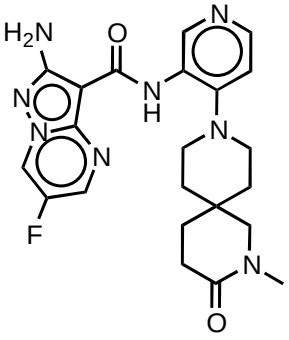

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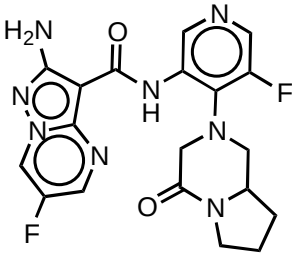

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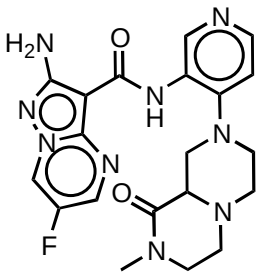

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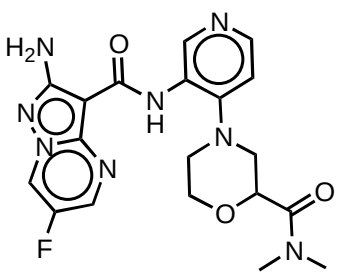

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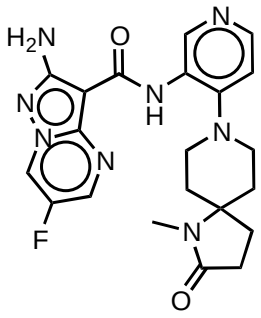

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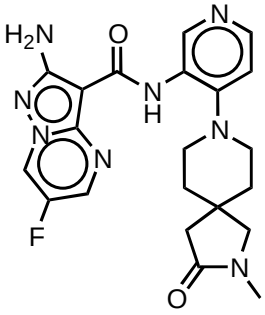

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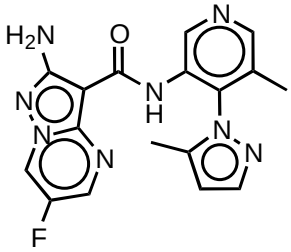

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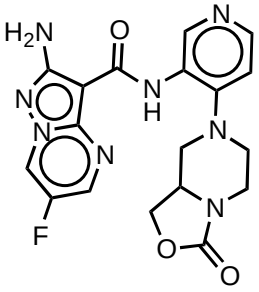

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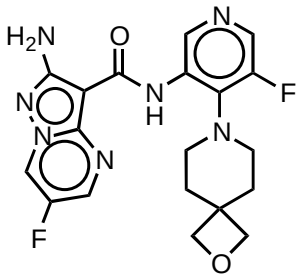

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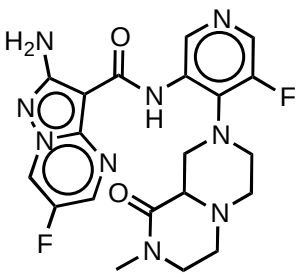

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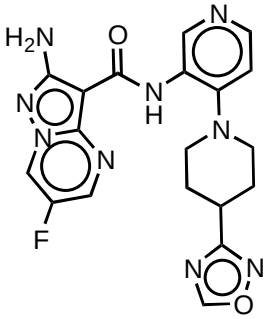

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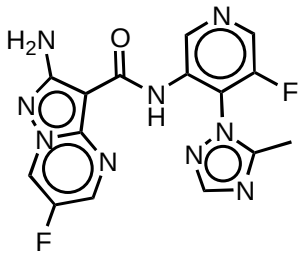

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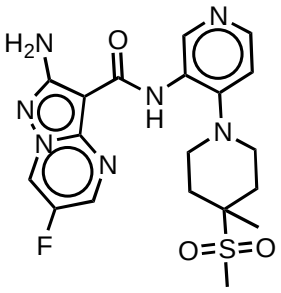
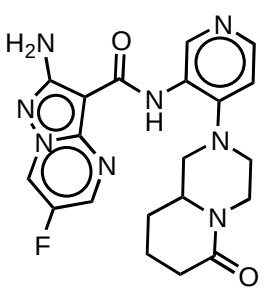


I-N-243



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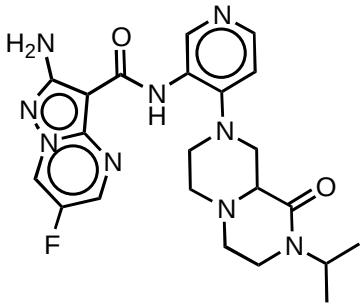

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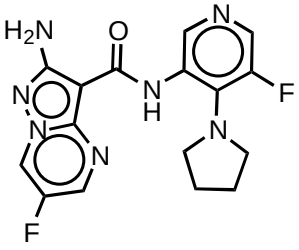

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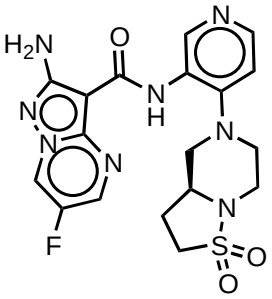

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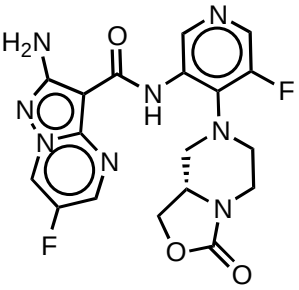

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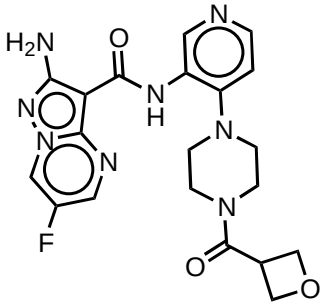

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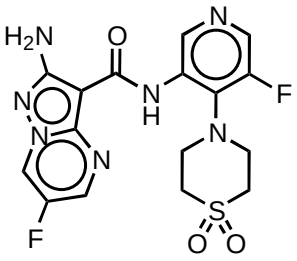

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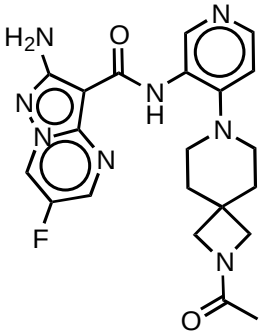

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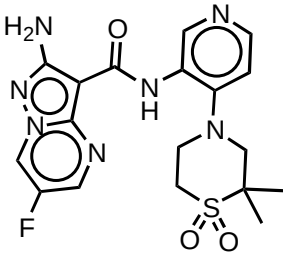

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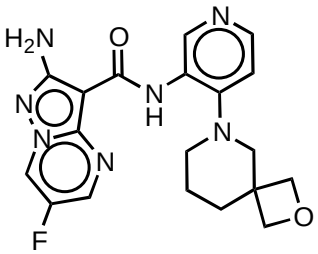

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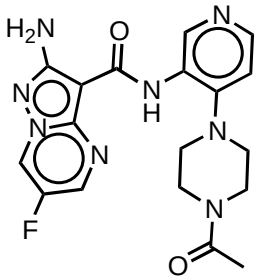

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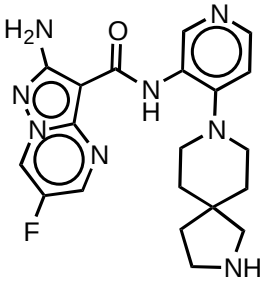

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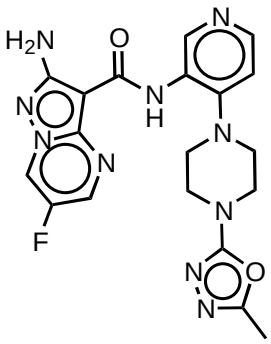
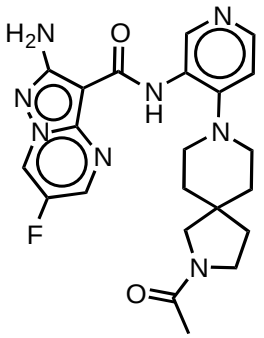
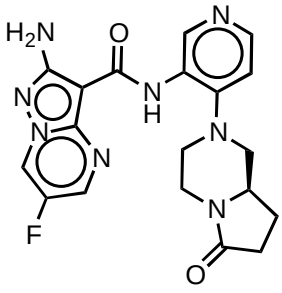


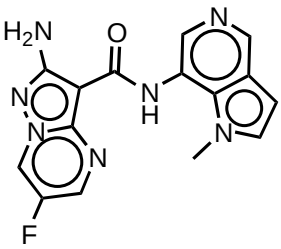
I-N-256



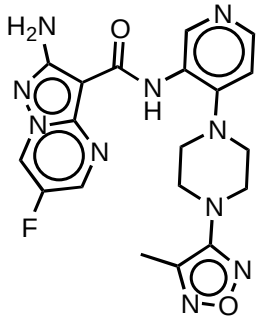
I-N-257



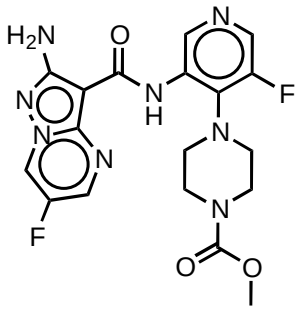
I-N-258



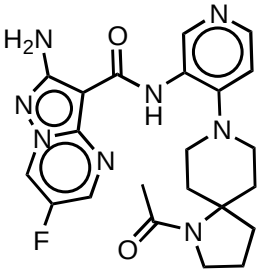
I-N-259



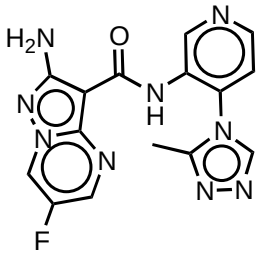
I-N-260



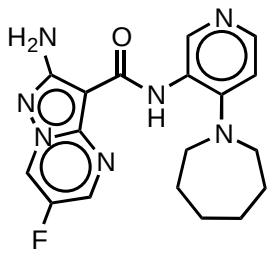
I-N-261



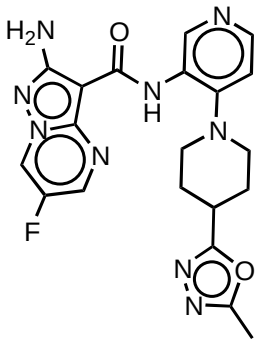
I-N-262



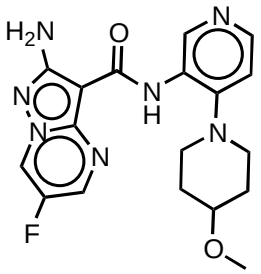
I-N-263



I-N-264



I-N-265



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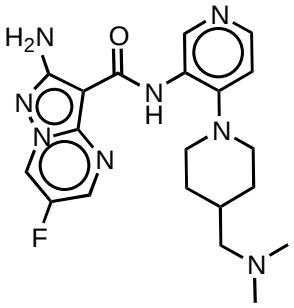

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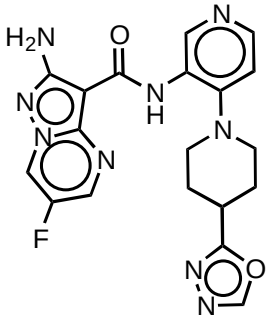

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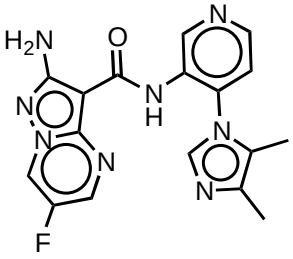

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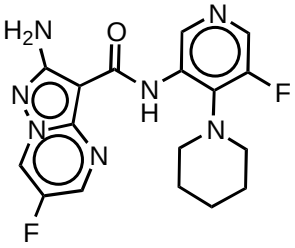

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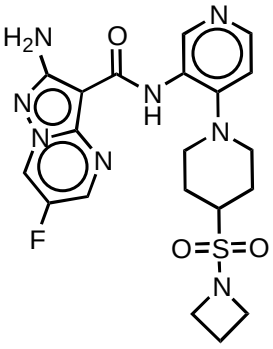

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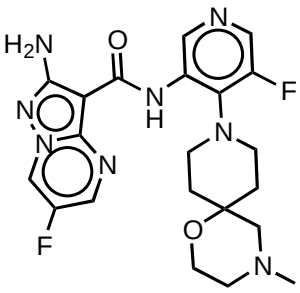

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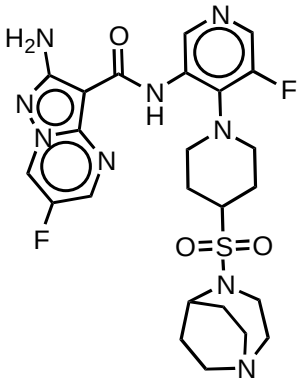

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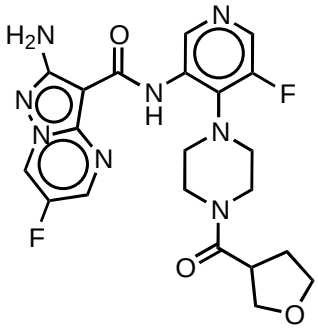

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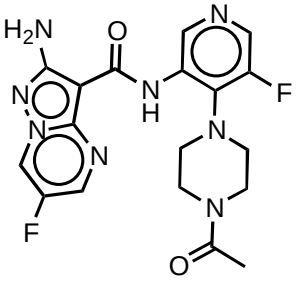

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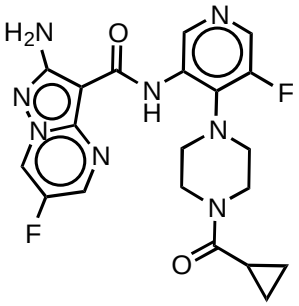

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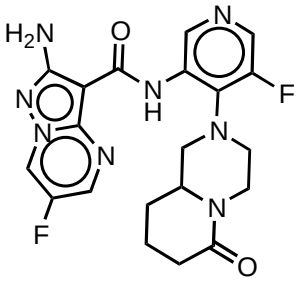

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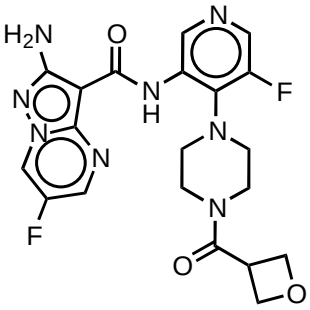

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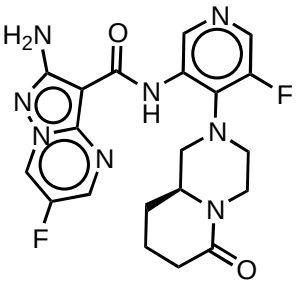

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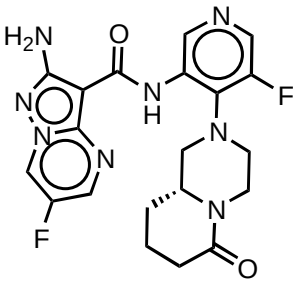

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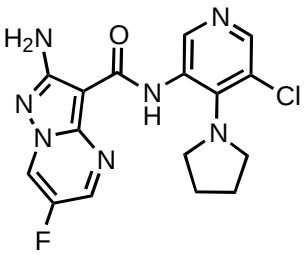

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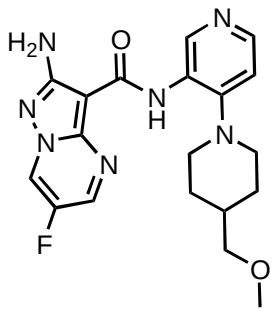

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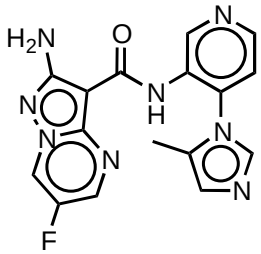

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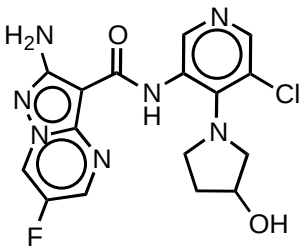

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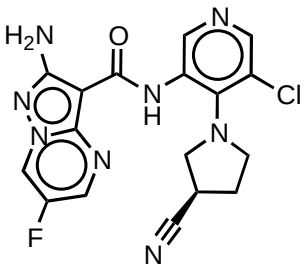

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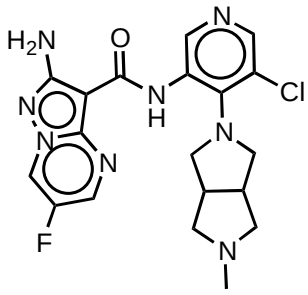
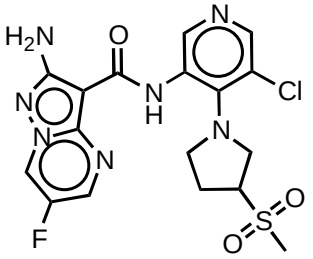


I-N-286



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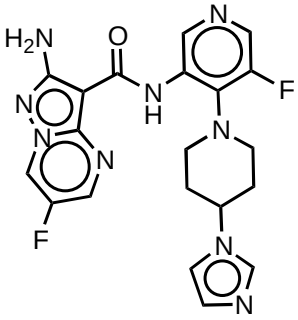
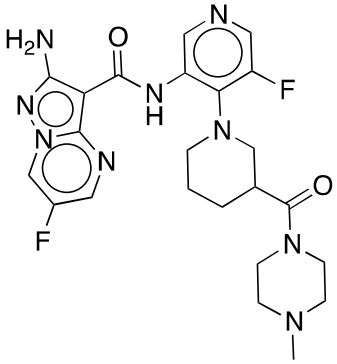


I-N-288



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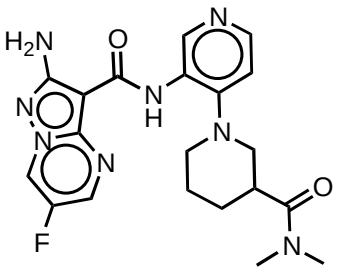
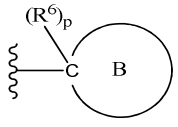


I-N-290.

15. The compound of claim 9, wherein R^4 is:



; optionally:

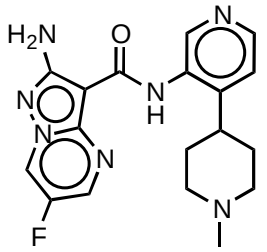
wherein p is 1; optionally thereto:

wherein Ring B is a 3-7 membered cycloaliphatic or heterocyclyl ring having 1-2 heteroatoms selected from oxygen, nitrogen or sulfur; optionally thereto:

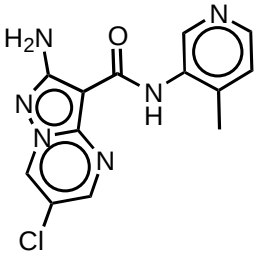
wherein Ring B is independently selected from selected from cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, pyrrolidinyl, piperidinyl, azepanyl, pyrazolidinyl, isoxazolidinyl, oxazolidinyl, thiazolidinyl, imidazolidinyl, piperazinyl, morpholinyl, thiomorpholinyl, 1,3-oxazinanyl, 1,3-thiazinanyl, dihydropyridinyl, dihydroimidazolyl, 1,3-tetrahydropyrimidinyl, dihydropyrimidinyl, 1,4-diazepanyl, 1,4-oxazepanyl, 1,4-thiazepanyl, 1,2,3,6-tetrahydropyridine, and azetidinyl; optionally thereto:

wherein Ring B is piperidinyl.

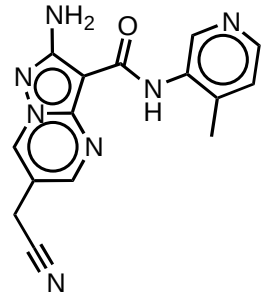
16. The compound of any one of claim 15 independently selected from:



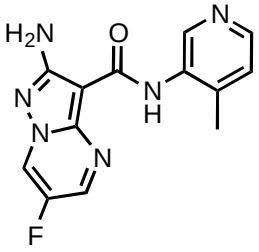
I-C-1



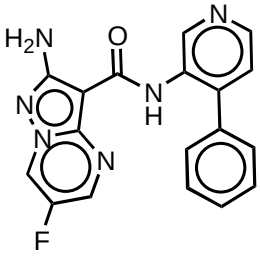
I-C-2



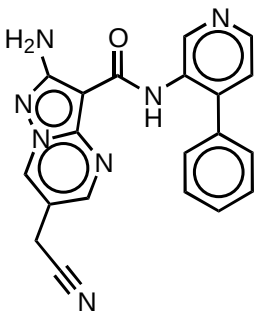
I-C-3



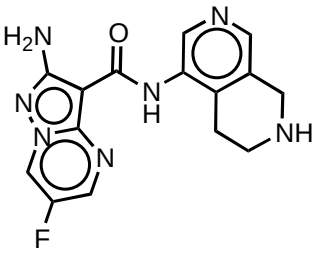
I-C-4



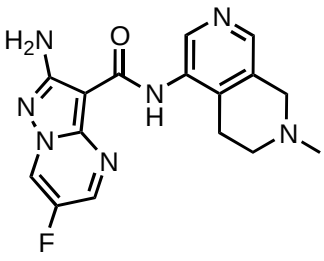
I-C-5



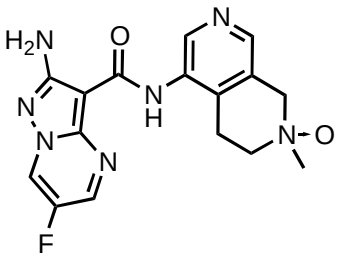
I-C-6



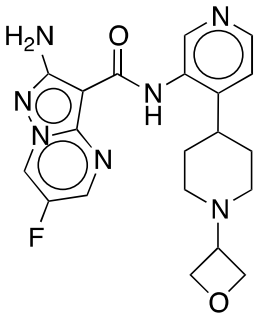
I-C-7



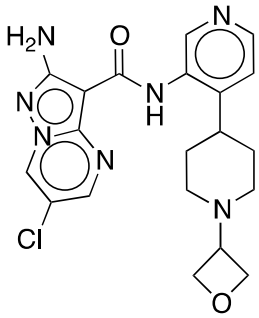
I-C-8



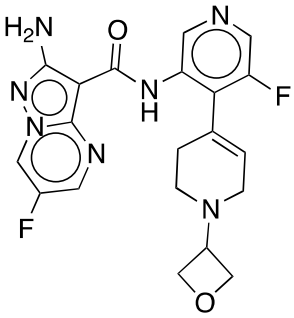
I-C-9 .



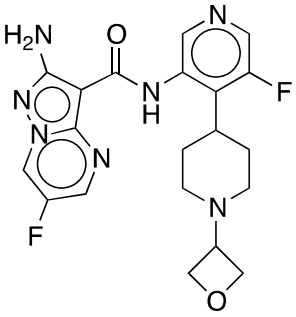
I-C-10



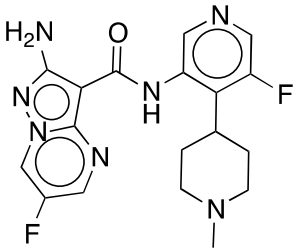
I-C-11



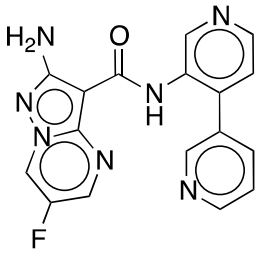
I-C-12



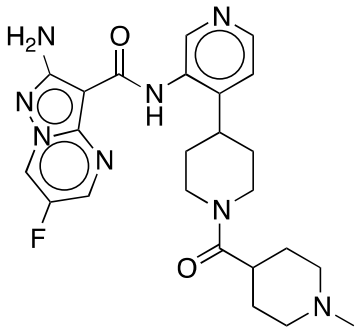
I-C-13



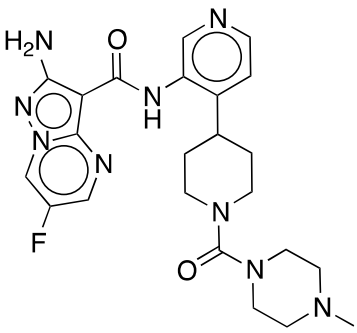
I-C-14



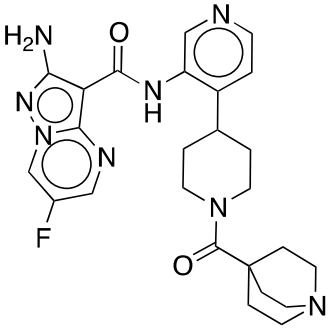
I-C-15



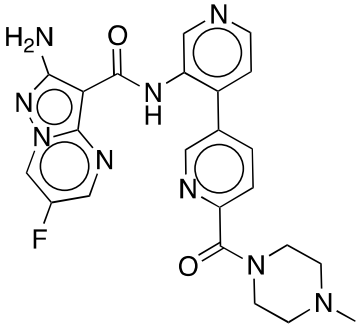
I-C-16



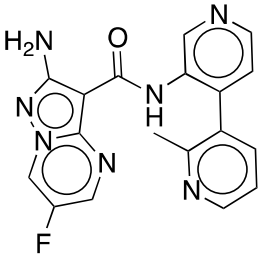
I-C-17



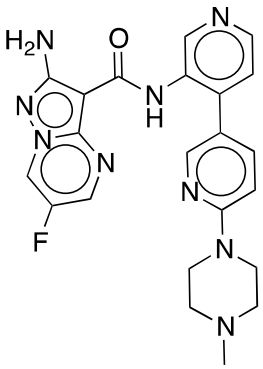
I-C-18



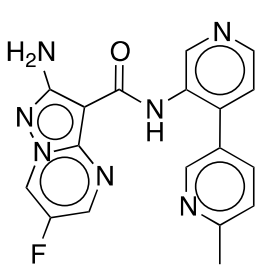
I-C-19



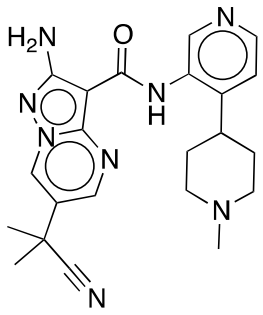
I-C-20



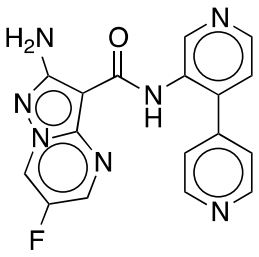
I-C-21



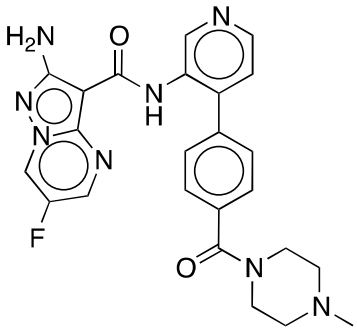
I-C-22



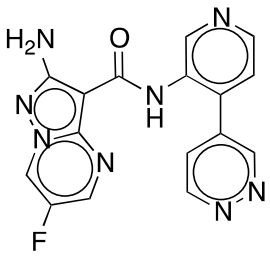
I-C-23



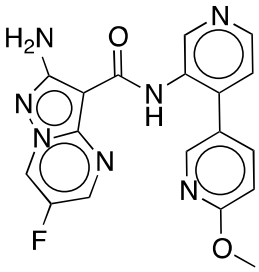
I-C-24



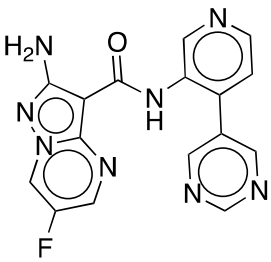
I-C-25



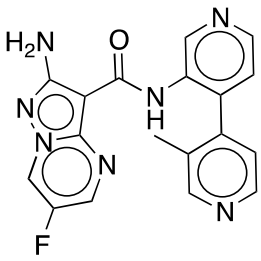
I-C-26



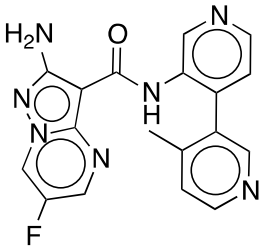
I-C-27



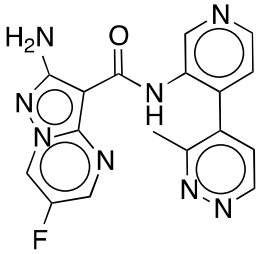
I-C-28



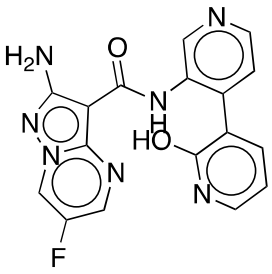
I-C-29



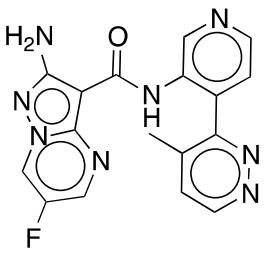
I-C-30



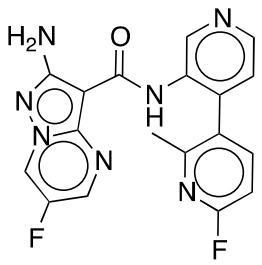
I-C-31



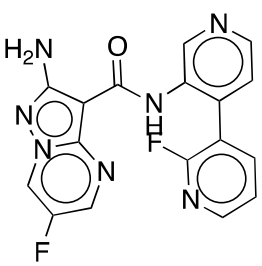
I-C-32



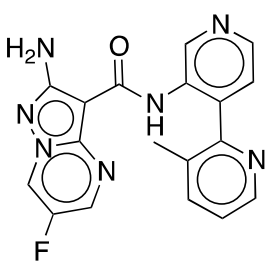
I-C-33



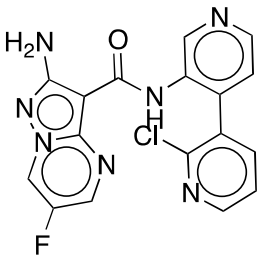
I-C-34



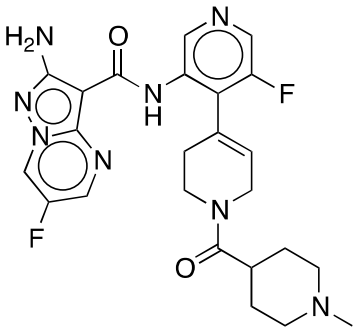
I-C-35



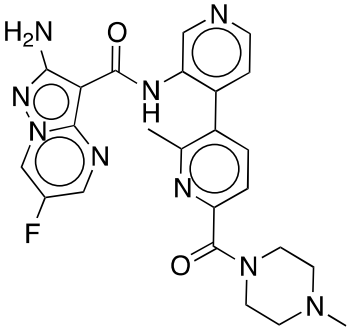
I-C-36



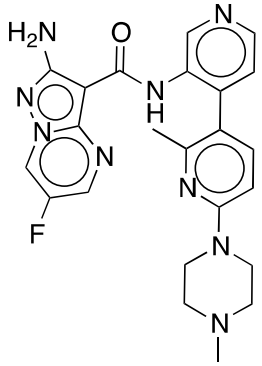
I-C-37



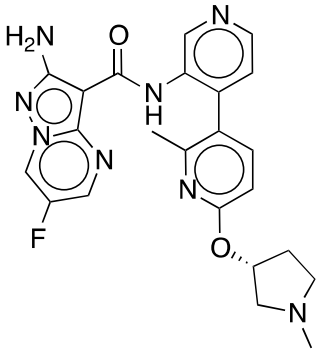
I-C-38



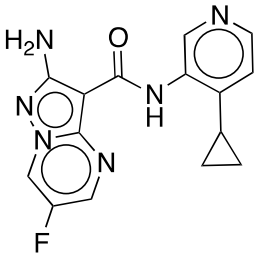
I-C-39



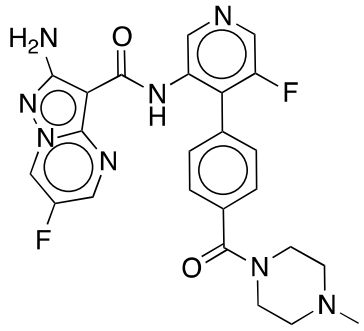
I-C-40



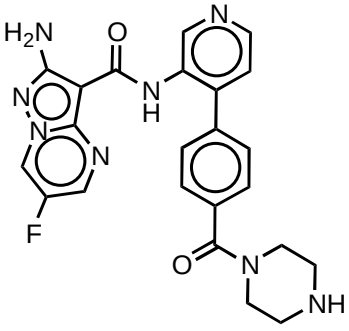
I-C-41



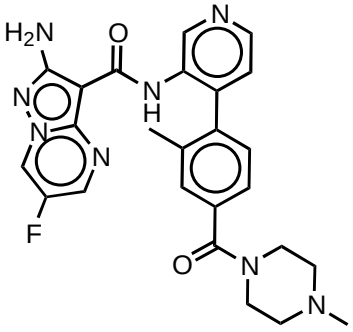
I-C-42



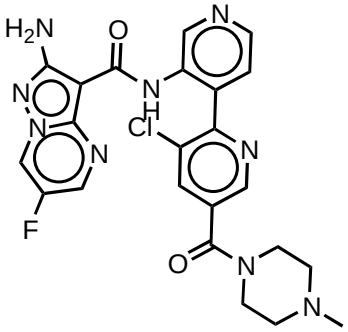
I-C-43



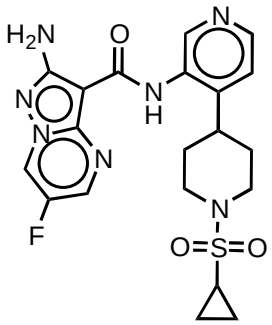
I-C-44



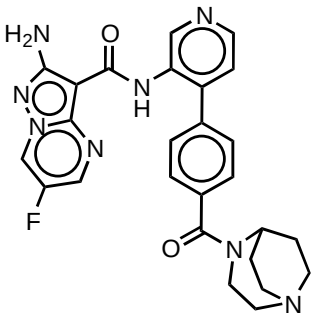
I-C-45



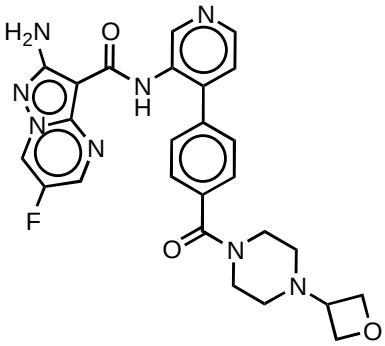
I-C-46



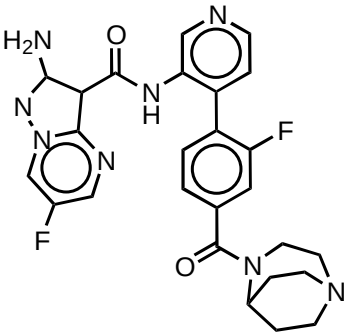
I-C-47



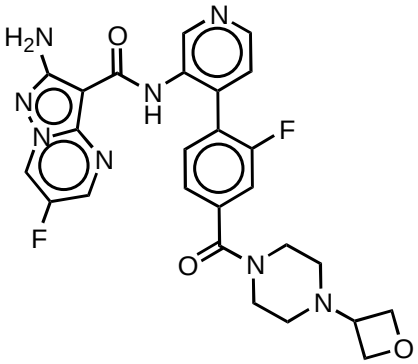
I-C-48



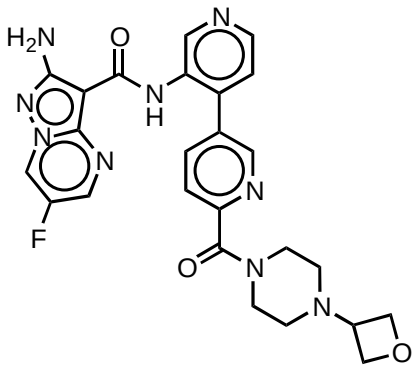
I-C-49



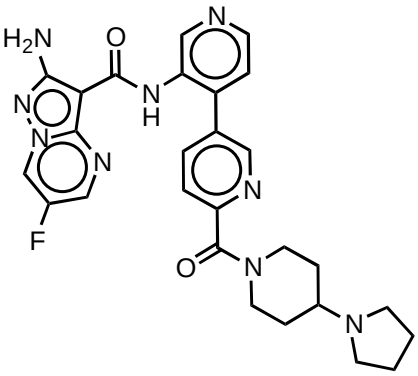
I-C-50



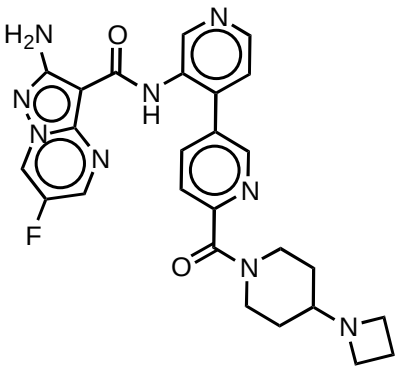
I-C-51



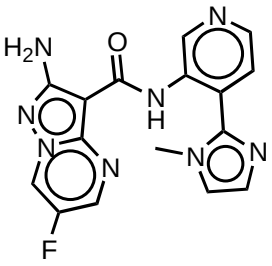
I-C-52



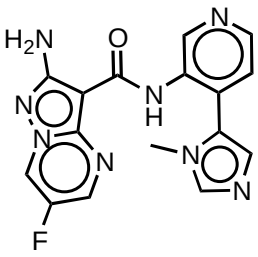
I-C-53



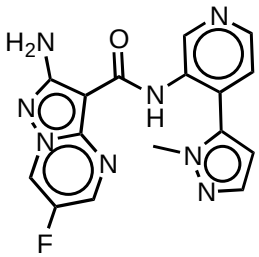
I-C-54



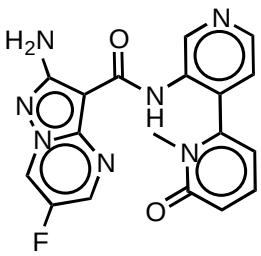
I-C-55



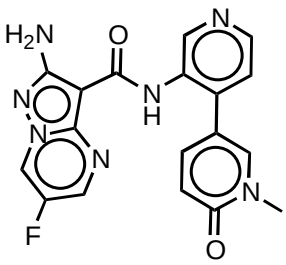
I-C-56



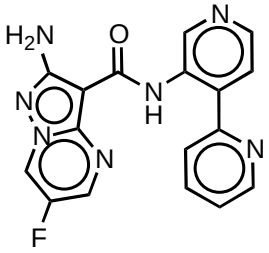
I-C-57



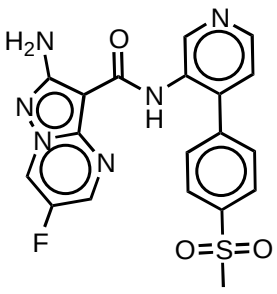
I-C-58



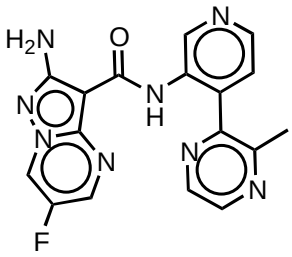
I-C-59



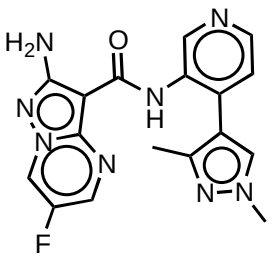
I-C-60



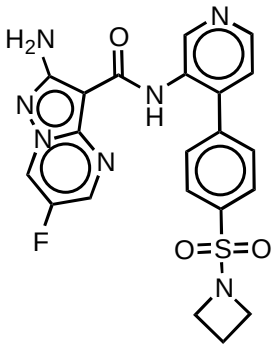
I-C-61



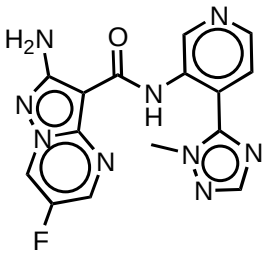
I-C-62



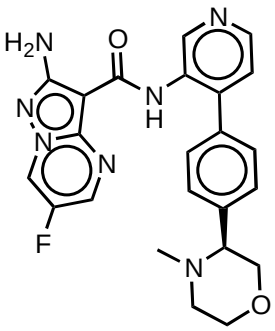
I-C-63



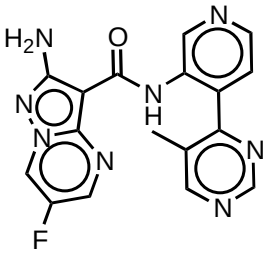
I-C-64



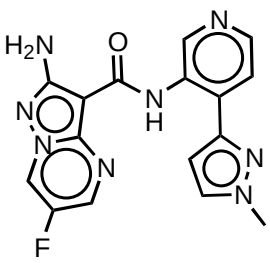
I-C-65



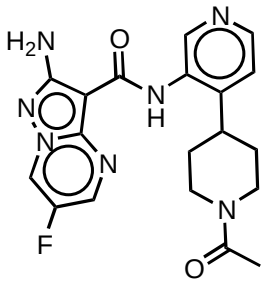
I-C-66



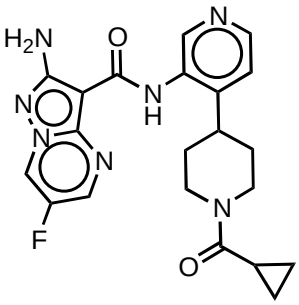
I-C-67



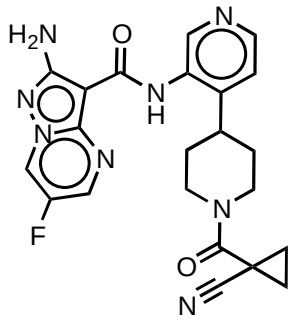
I-C-68



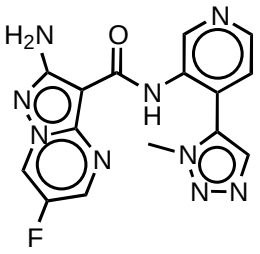
I-C-69



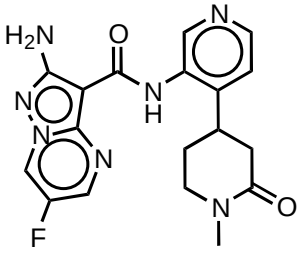
I-C-70



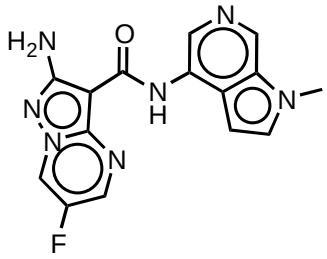
I-C-71



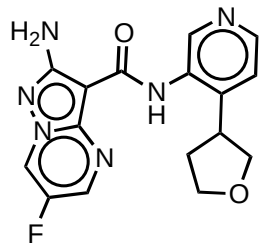
I-C-72



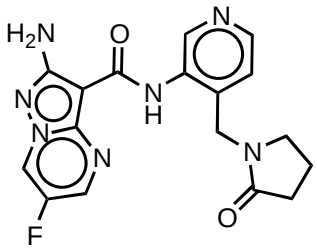
I-C-73



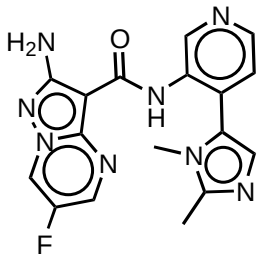
I-C-74



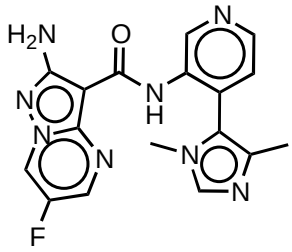
I-C-75



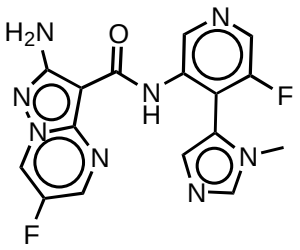
I-C-76



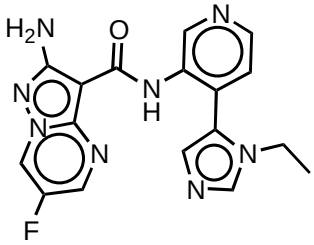
I-C-77



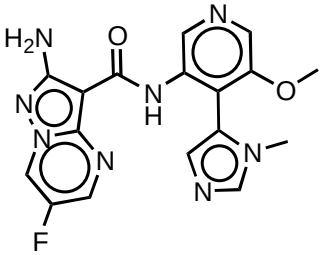
I-C-78



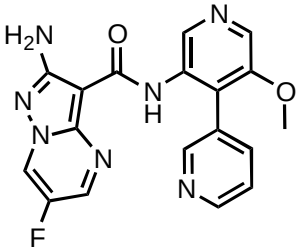
I-C-79



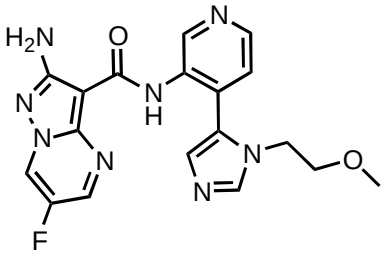
I-C-80



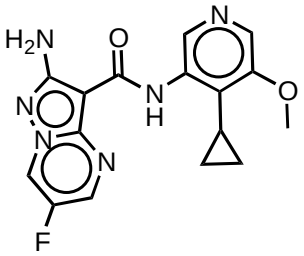
I-C-81



I-C-82



I-C-83



I-C-84

17. A pharmaceutical composition comprising a compound of any one of claims 1 to 16 and a pharmaceutically acceptable carrier.

18 A compound, or a pharmaceutically acceptable salt thereof, of any one of claims 1 to 16 or a pharmaceutical composition according to claim 17 for use in the treatment of cancer in a patient

19. The compound, or a pharmaceutical acceptable salt thereof, of any one of claims 1 to 16, or a pharmaceutical composition according to claim 17 for use as claimed in claim 18, 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; optionally:

wherein (I) said DNA-damaging agent is selected chemotherapy or radiation treatment; optionally wherein the DNA-damaging agent is an alkyating agent selected from Temozolomide; or:

wherein (II) 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; optionally

wherein (i) said DNA-damaging agent is independently selected from ionizing radiation, a platinating agent, a Topo I inhibitor, a Topo II inhibitor, or an antibiotic; or:

wherein (ii) 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; optionally:

wherein (a) 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; optionally:

wherein (aa) 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; or:

wherein (bb) said DNA-damaging agent is independently selected from a platinating agent or ionizing radiation; optionally wherein the additional therapeutic agent is Gemcitabine and the cancer is pancreatic cancer; or:

wherein (cc) the chemoradiation is gemcitabine and radiation; or:

wherein (b) the antimetabolite is gemcitabine; or:

wherein (c) the DNA-damaging agent is ionizing radiation; or:

wherein (d) the DNA-damaging agent is a platinating agent independently selected from Cisplatin or Carboplatin; or:

wherein (e) the DNA-damaging agent is a Topo II inhibitor selected from Etoposide; or:

wherein (f) the DNA-damaging agent is independently selected from one or more of the following: Cisplatin, Carboplatin, gemcitabine, Etoposide, Temozolomide, or ionizing radiation; optionally thereto wherein the additional therapeutic agents are selected from one or more of the following: gemcitabine, cisplatin or carboplatin, and etoposide.

20. The compound, or a pharmaceutical acceptable salt thereof, of any one of claims 1 to 16, or a pharmaceutical composition according to claim 17 for use as claimed in claim 18 or claim 19, 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, osteochronfroma (osteocartilaginous 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: optionally: wherein said cancer is selected from a cancer of the lung or the pancreas; optionally thereto:

wherein said cancer is lung cancer; optionally thereto:

wherein the lung cancer is non-small cell lung cancer or small cell lung cancer; optionally thereto:

wherein (I) the lung cancer is small cell lung cancer and the additional therapeutic agents are cisplatin and etoposide; or

wherein (II) the lung cancer is non-small cell lung cancer and the additional therapeutic agents are gemcitabine and cisplatin; optionally:

wherein (i) the non-small cell lung cancer is squamous non-small cell lung cancer; or:

wherein (ii) the cancer therapy is gemcitabine and radiation.

21. The compound, or a pharmaceutical acceptable salt thereof, of any one of claims 1 to 16, or a pharmaceutical composition according to claim 17 for use as claimed in claim 18 or claim 19,

wherein (I) said cancer is selected from lung cancer, head and neck cancer, pancreatic cancer, gastric cancer, or brain cancer; or:

wherein (II) 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; optionally wherein the cancer is breast cancer and the additional therapeutic agent is cisplatin; optionally theretowherein the cancer is triple negative breast cancer.

22. A compound, or a pharmaceutically acceptable salt thereof, of any one of claims 1 to 16 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.

23. A compound, or a pharmaceutically acceptable salt thereof, of any one of claims 1 to 16 for use in a treatment that increases the sensitivity of pancreatic cancer cells to a cancer therapy selected from chemotherapy or radiation; optionally:

wherein (I) the chemotherapy is gemcitabine; or:

wherein (II) the cancer therapy is gemcitabine; or:

wherein (III) the cancer therapy is radiation.

24. A compound, or a pharmaceutical acceptable salt thereof, of any one of claims 1 to 16, or a pharmaceutical composition according to claim 17 in combination with gemcitabine (100 nM) and/or radiation (6 Gy) for use in a treatment that inhibits phosphorylation of Chk1 (Ser 345) in a pancreatic cancer cell.

25. A compound, or a pharmaceutically acceptable salt thereof, of any one of claims 1 to 16 for use in a treatment that sensitizes pancreatic cancer cells to chemoradiation in combination with chemoradiation.

26. A compound, or a pharmaceutically acceptable salt thereof, of any one of claims 1 to 16 for use in a treatment

comprising (I) radiosensitizing hypoxic pancreatic cancer cells in combination with radiation therapy; or:

comprising (II) sensitizing hypoxic pancreatic cancer cells in combination with chemotherapy.

27. The compound, or a pharmaceutically acceptable salt thereof, of claims 25 or 26, wherein said cancer cell is a PSN-1, MiaPaCa-2 or PancM cancer cell.

28. A compound, or a pharmaceutically acceptable salt thereof, of claims 1 to 16, for use in a treatment comprising disrupting damage-induced cell cycle checkpoints in combination with radiation therapy and/or gemcitabine.

29. The compound, or a pharmaceutically acceptable salt thereof, of claims 1 to 16, for use in a treatment comprising inhibiting repair of DNA damage by homologous recombination in a pancreatic cancer cell in combination with radiation therapy and/or gemcitabine.

30. The compound for use, or a pharmaceutically derivative thereof, of claims 26 to 29, wherein the compound is administered to a pancreatic cancer cell; optionally wherein the pancreatic cancer cells are derived from a pancreatic cell line selected from PSN-1, MiaPaCa-2 or Panc-1.

31. A compound, or a pharmaceutically acceptable salt thereof, of any one of claims 1 to 16 for use in a treatment comprising

(I) treating non-small cell lung cancer in combination with one or more of the following additional therapeutic agents: Cisplatin or Carboplatin, Etoposide, and ionizing radiation; or:

(II) promoting cell death in cancer cells; or:

(III) preventing cell repair from DNA damage; or:

(IV) inhibiting ATR in a biological sample comprising the step of contacting a compound of any one of claims 1 to 31 with said biological sample; optionally wherein said biological sample is a cell; or:

(V) sensitizing cells to DNA damaging agents.

32. The compound, or a pharmaceutical acceptable salt thereof, of any one of claims 1 to 16, or a pharmaceutical composition according to claim 17 for use as claimed in claims 19 to 31,

wherein (I) said cell is a cancer cell having defects in the ATM signaling cascade; optionally:

wherein (i) 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; or:

wherein (ii) said defect is altered expression or activity of one or more of the following: ATM, p53, CHK2, MRE11, RAD50, NBS1, 53BP1, MDC1 or H2AX; optionally 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; or:

wherein (II) said cell is a cancer cell expressing DNA damaging oncogenes; optionally 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; or:

wherein (III) said cancer, cancer cell, or cell has a defect in a base excision repair protein; optionally 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; optionally thereto wherein the base excision repair protein is PARP1, PARP2, or PolB; optionally thereto wherein the base excision repair protein is PARP1 or PARP2.

33. The compound, or a pharmaceutical acceptable salt thereof, of any one of claims 1 to 16, or a pharmaceutical composition according to claim 17 for use as claimed in claims 19 to 32, further comprising administering to said patient an additional therapeutic agent wherein said agent inhibits or modulates a base excision repair protein; optionally 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; optionally thereto wherein the base excision repair protein is selected from PARP1, PARP2, or PolB; optionally thereto wherein the base excision repair protein is selected from PARP1 or PARP2.