each of R_{72}, R_{82} and R_{92} is independently hydrogen, $-C_{1-10}$ alkyl, $-C_{2-10}$alkenyl, $-C_{2-10}$ alkynyl, $-C_{1-10}$heteroalkyl, $-C_{3-10}$aryl, $-C_{1-10}$hetaryl, $-C_{3-10}$cycloalkyl, $-C_{1-10}$heterocyclyl, -OH, $-CF_3$, $-C(O)R^{31}$, $-CO_2R^{31}$, $-C(=O)NR^{31}$, $-S(O)_{0-2}R^{31}$, $-C(=S)OR^{31}$, $-C(=O)SR^{31}$;

each of R_{10} and R_{14} is independently $-C_{1-10}$ alkyl, $-C_{2-10}$alkenyl, $-C_{2-10}$ alkynyl, $-C_{1-10}$heteroalkyl, $-C_{3-10}$aryl, $-C_{1-10}$hetaryl, $-C_{3-10}$cycloalkyl, $-C_{1-10}$heterocyclyl, optionally substituted by one or more independent R_{11} substituents;

each of R_{11}, R_{12}, R_{13} and R_{15} is independently hydrogen, halogen, $-C_{1-10}$ alkyl, $-C_{2-10}$alkenyl, $-C_{2-10}$ alkynyl, $-C_{1-10}$heteroalkyl, $-C_{3-10}$aryl, $-C_{1-10}$hetaryl, $-C_{3-10}$cycloalkyl, $-C_{1-10}$heterocyclyl, -OH, $-CF_3$, $-OCF_3$, $-OR^{31}$, $-NR^{31}R^{32}$, $-C(O)R^{31}$, $-CO_2R^{31}$, $-C(=O)NR^{31}$, $-NO_2$, -CN, $-S(O)_{0-2}R^{31}$, $-SO_2NR^{31}R^{32}$, $-NR^{31}C(=O)R^{32}$, $-NR^{31}C(=O)OR^{32}$, $-NR^{31}C(=O)NR^{32}R^{33}$, $-NR^{31}S(O)_{0-2}R^{32}$, $-C(=S)OR^{31}$, $-C(=O)SR^{31}$, $-NR^{31}C(=NR^{32})NR^{32}R^{33}$, $-NR^{31}C(=NR^{32})OR^{33}$, $-NR^{31}C(=NR^{32})SR^{33}$, $-OC(=O)OR^{33}$, $-OC(=O)NR^{31}R^{32}$, $-OC(=O)SR^{31}$, $-SC(=O)SR^{31}$, $-P(O)OR^{31}OR^{32}$, or $-SC(=O)NR^{31}NR^{32}$;

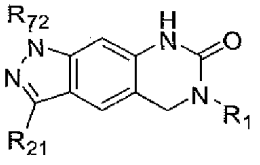
each of R^{31}, R^{32}, R^{33} and R^{34} is independently hydrogen, halogen, $-C_{1-10}$ alkyl, $-C_{2-10}$alkenyl, $-C_{2-10}$alkynyl, $-C_{1-10}$heteroalkyl, $-C_{3-10}$aryl, $-C_{1-10}$hetaryl, $-C_{3-10}$cycloalkyl, $-C_{1-10}$heterocyclyl, or wherein R^{31} together with R^{32} form a heterocyclic ring;

wherein ring A comprises one or more heteroatoms selected from N, O, or S;

wherein if X_7 is O or X_2-X_3 is $R_1C{=}CR_3$, ring A comprises at least two heteroatoms selected from N, O, or S; and

wherein if X_3 is O or N, or X_2-X_3 is $R_1C{=}N$, at least one of X_7 or X_9 is not N.

[0006a] In one embodiment, there is provided a compound of Formula II-E:



(II-E),

or a pharmaceutically acceptable salt thereof; wherein:

R_1 is $-C_{1-10}$heterocyclyl, $-C_{1-10}$heterocyclyl-C_{1-10}alkyl, or $-C_{1-10}$heterocyclyl-C_{3-10}aryl, each of which is unsubstituted or substituted by one or more independent R_{10} or R_{11} substituents;

R_{21} is $-L-C_{1-10}$heteroalkyl, $-L-C_{3-10}$aryl, $-L-C_{1-10}$hetaryl, $-L-C_{3-10}$cycloalkyl, or $-L-C_{1-10}$heterocyclyl, each of which is unsubstituted or substituted by one or more independent R_{12} substituents;

L is a bond, $-O-$, $-N(R^{31})-$, $-S(O)_{0-2}-$, $-C(=O)-$, $-C(=O)O-$, $-OC(=O)-$, $-C(=O)N(R^{31})-$, $-N(R^{31})C(=O)-$, $-NR^{31}C(=O)O-$, $-NR^{31}C(=O)NR^{32}-$, $-NR^{31}S(O)_{0-2}-$, $-S(O)_{0-2}N(R^{31})-$, $-C(=S)O-$, $-C(=O)S-$, $-NR^{31}C(=NR^{32})NR^{32}-$, $-NR^{31}C(=NR^{32})O-$, $-NR^{31}C(=NR^{32})S-$, $-OC(=O)O-$, $-OC(=O)NR^{31}-$, $-OC(=O)S-$, $-SC(=O)S-$, $-P(O)OR^{31}O-$, or $-SC(=O)NR^{31}-$;

R_{72} is hydrogen;

R_{10} is $-C_{1-10}$ alkyl, $-C_{2-10}$alkenyl, $-C_{2-10}$ alkynyl, $-C_{1-10}$heteroalkyl, $-C_{3-10}$aryl, $-C_{1-10}$hetaryl, $-C_{3-10}$cycloalkyl, or $-C_{1-10}$heterocyclyl, each of which is unsubstituted or substituted by one or more independent R_{11} substituents;

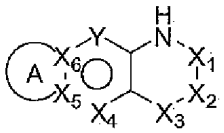
R_{11} and R_{12} are independently hydrogen, halogen, $-C_{1-10}$ alkyl, $-C_{2-10}$alkenyl, $-C_{2-10}$ alkynyl, $-C_{1-10}$heteroalkyl, $-C_{3-10}$aryl, $-C_{1-10}$hetaryl, $-C_{3-10}$cycloalkyl, $-C_{1-10}$heterocyclyl, -OH, $-CF_3$, $-OCF_3$, $-OR^{31}$, $-NR^{31}R^{32}$, $-C(O)R^{31}$, $-CO_2R^{31}$, $-C(=O)NR^{31}$, $-NO_2$, -CN, $-S(O)_{0-2}R^{31}$, $-SO_2NR^{31}R^{32}$, $-NR^{31}C(=O)R^{32}$, $-NR^{31}C(=O)OR^{32}$, $-NR^{31}C(=O)NR^{32}R^{33}$, $-NR^{31}S(O)_{0-2}R^{32}$, $-C(=S)OR^{31}$, $-C(=O)SR^{31}$, $-NR^{31}C(=NR^{32})NR^{32}R^{33}$, $-NR^{31}C(=NR^{32})OR^{33}$, $-NR^{31}C(=NR^{32})SR^{33}$, $-OC(=O)OR^{33}$, $-OC(=O)NR^{31}R^{32}$, $-OC(=O)SR^{31}$, $-SC(=O)SR^{31}$, $-P(O)OR^{31}OR^{32}$, or $-SC(=O)NR^{31}NR^{32}$;

each of R^{31}, R^{32}, and R^{33} is independently hydrogen, halogen, $-C_{1-10}$ alkyl, $-C_{2-10}$alkenyl, $-C_{2-10}$ alkynyl, $-C_{1-10}$heteroalkyl, $-C_{3-10}$aryl, $-C_{1-10}$hetaryl, $-C_{3-10}$cycloalkyl, or $-C_{1-10}$heterocyclyl, or R^{31} together with R^{32} form a heterocyclic ring.

[0006b] In one embodiment, there is provided use of the compound as described herein in the manufacture of a medicament for inhibiting activity of a protein kinase present in a cell.

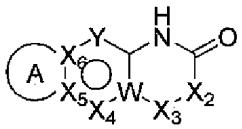
[0006c] In one embodiment, there is provided use of the compound as described herein in the manufacture of a medicament for treatment of cancer, optionally wherein the cancer is selected from the group consisting of breast cancer, pancreatic cancer, non-small cell lung cancer (NSCLC), thyroid cancer, seminomas, melanoma, bladder cancer, liver cancer, kidney cancer, myelodysplastic syndrome (MDS), acute myelogenous leukemia (AML), and colorectal cancer.

[0007] In some embodiments, the invention provides a compound of Formula I-A:



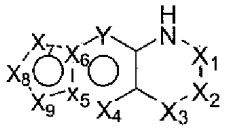
or a pharmaceutically acceptable salt or prodrug thereof.

[0008] In some embodiments, the invention provides a compound of Formula I-B:



or a pharmaceutically acceptable salt or prodrug thereof.

[0009] In some cases, the invention provides a compound of Formula II:

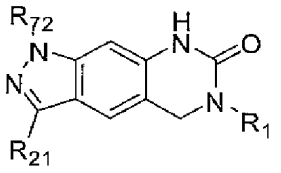


or a pharmaceutically acceptable salt or prodrug thereof.

[0010] In some embodiments, X_1 is C=O. In some embodiments, X_2 is NR_1. In some embodiments, X_5 is N and X_6 is C. In other embodiments, X_5 is C and X_6 is C. In some embodiments, X_9 is CR_{21}.

CLAIMS

1. A compound of Formula II-E:



(II-E),

or a pharmaceutically acceptable salt thereof; wherein:

R_1 is $-C_{1-10}$heterocyclyl, $-C_{1-10}$heterocyclyl-C_{1-10}alkyl, or $-C_{1-10}$heterocyclyl-C_{3-10}aryl, each of which is unsubstituted or substituted by one or more independent R_{10} or R_{11} substituents;

R_{21} is $-L-C_{1-10}$heteroalkyl, $-L-C_{3-10}$aryl, $-L-C_{1-10}$hetaryl, $-L-C_{3-10}$cycloalkyl, or $-L-C_{1-10}$heterocyclyl, each of which is unsubstituted or substituted by one or more independent R_{12} substituents;

L is a bond, $-O-$, $-N(R^{31})-$, $-S(O)_{0-2}-$, $-C(=O)-$, $-C(=O)O-$, $-OC(=O)-$, $-C(=O)N(R^{31})-$, $-N(R^{31})C(=O)-$, $-NR^{31}C(=O)O-$, $-NR^{31}C(=O)NR^{32}-$, $-NR^{31}S(O)_{0-2}-$, $-S(O)_{0-2}N(R^{31})-$, $-C(=S)O-$, $-C(=O)S-$, $-NR^{31}C(=NR^{32})NR^{32}-$, $-NR^{31}C(=NR^{32})O-$, $-NR^{31}C(=NR^{32})S-$, $-OC(=O)O-$, $-OC(=O)NR^{31}-$, $-OC(=O)S-$, $-SC(=O)S-$, $-P(O)OR^{31}O-$, or $-SC(=O)NR^{31}-$;

R_{72} is hydrogen;

R_{10} is $-C_{1-10}$ alkyl, $-C_{2-10}$alkenyl, $-C_{2-10}$ alkynyl, $-C_{1-10}$heteroalkyl, $-C_{3-10}$aryl, $-C_{1-10}$hetaryl, $-C_{3-10}$cycloalkyl, or $-C_{1-10}$heterocyclyl, each of which is unsubstituted or substituted by one or more independent R_{11} substituents;

R_{11} and R_{12} are independently hydrogen, halogen, $-C_{1-10}$ alkyl, $-C_{2-10}$alkenyl, $-C_{2-10}$ alkynyl, $-C_{1-10}$heteroalkyl, $-C_{3-10}$aryl, $-C_{1-10}$hetaryl, $-C_{3-10}$cycloalkyl, $-C_{1-10}$heterocyclyl, -OH, $-CF_3$, $-OCF_3$, $-OR^{31}$, $-NR^{31}R^{32}$, $-C(O)R^{31}$, $-CO_2R^{31}$, $-C(=O)NR^{31}$, $-NO_2$, -CN, $-S(O)_{0-2}R^{31}$, $-SO_2NR^{31}R^{32}$, $-NR^{31}C(=O)R^{32}$, $-NR^{31}C(=O)OR^{32}$, $-NR^{31}C(=O)NR^{32}R^{33}$, $-NR^{31}S(O)_{0-2}R^{32}$, $-C(=S)OR^{31}$, $-C(=O)SR^{31}$, $-NR^{31}C(=NR^{32})NR^{32}R^{33}$, $-NR^{31}C(=NR^{32})OR^{33}$, $-NR^{31}C(=NR^{32})SR^{33}$, $-OC(=O)OR^{33}$, $-OC(=O)NR^{31}R^{32}$, $-OC(=O)SR^{31}$, $-SC(=O)SR^{31}$, $-P(O)OR^{31}OR^{32}$, or $-SC(=O)NR^{31}NR^{32}$;

each of R^{31}, R^{32}, and R^{33} is independently hydrogen, halogen, $-C_{1-10}$ alkyl, $-C_{2-10}$alkenyl, $-C_{2-10}$ alkynyl, $-C_{1-10}$heteroalkyl, $-C_{3-10}$aryl, $-C_{1-10}$hetaryl, $-C_{3-10}$cycloalkyl, or $-C_{1-10}$heterocyclyl, or R^{31} together with R^{32} form a heterocyclic ring.

2. The compound of claim 1, wherein R_{21} is selected from the group consisting of $-L-C_{1-10}$heteroalkyl, $-L-C_{3-10}$aryl, $-L-C_{1-10}$hetaryl, $-L-C_{3-10}$cycloalkyl, and $-L-C_{1-10}$heterocyclyl, each of which is unsubstituted or substituted by one or more independent R_{12} substituents; and wherein L is a bond.

3. The compound of claim 2, wherein R_{21} is $-L-C_{1-10}$hetaryl unsubstituted or substituted by one or more independent R_{12} substituents; and wherein L is a bond.

4. The compound of claim 3, wherein the C_{1-10}hetaryl of R_{21} comprises one or more nitrogen atoms.

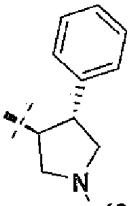
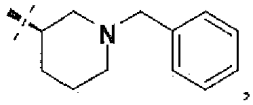
5. The compound of claim 4, wherein the C_{1-10}hetaryl of R_{21} is selected from the group consisting of pyrazolyl, pyridinyl, pyrazinyl, pyrimidinyl, and pyridazinyl.

6. The compound of claim 5, wherein the C_{1-10}hetaryl of R_{21} is unsubstituted.

7 The compound of claim 5, wherein the C_{1-10}hetaryl or R_{21} is substituted with one, two, or three independent R_{12} substituents.

8. The compound of any one of claims 2-5 or 7, wherein each R_{12} substituent is independently selected from the group consisting of $-C_{1-10}$ alkyl, $-C_{2-10}$alkenyl, $-C_{2-10}$ alkynyl, $-C_{1-10}$heteroalkyl, $-C_{3-10}$aryl, $-C_{1-10}$hetaryl, $-C_{3-10}$cycloalkyl, $-C_{1-10}$heterocyclyl, -OH, $-CF_3$, $-OCF_3$, and $-OR^{31}$; wherein each R^{31} is independently hydrogen or $-C_{1-10}$ alkyl.

9. The compound of claim 8, wherein each R_{12} substituent is independently selected from the group consisting -Me, -Et, -*i*-Pr, -*n*-Pr, -OH, -OMe, -OEt, and -OPr.

10. The compound of any one of claims 1-9, wherein R_1 is , , or , each of which is unsubstituted or substituted by one or more independent R_{10} or R_{11} substituents.

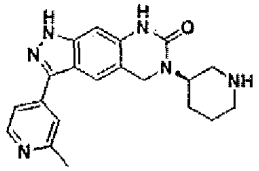
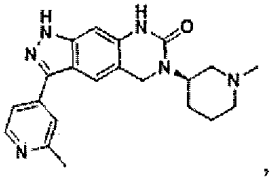
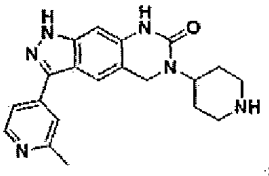
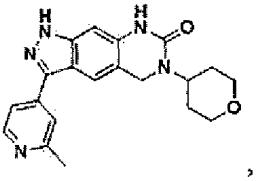
11. Use of the compound of any one of claims 1-10 in the manufacture of a medicament for inhibiting activity of a protein kinase present in a cell.

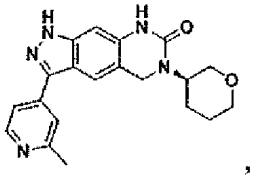
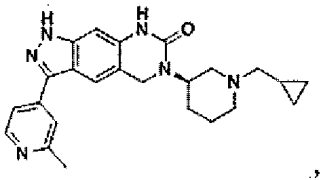
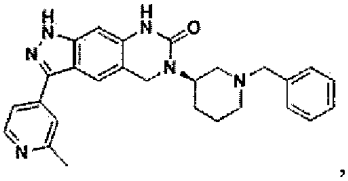
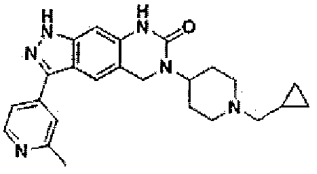
12. The use of claim 11, wherein the protein kinase is ERK.

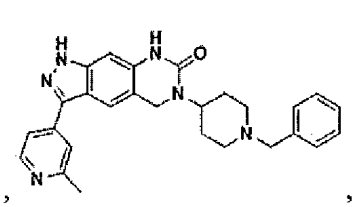
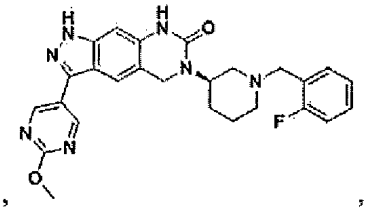
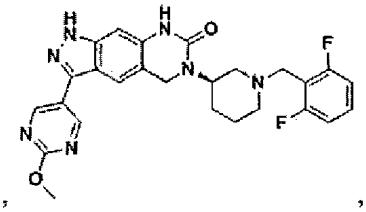
13. Use of the compound of any one of claims 1-10 in the manufacture of a medicament for treatment of cancer, optionally wherein the cancer is selected from the group consisting of breast cancer, pancreatic cancer, non-small cell lung cancer (NSCLC), thyroid cancer, seminomas, melanoma, bladder cancer, liver cancer, kidney cancer, myelodysplastic syndrome (MDS), acute myelogenous leukemia (AML), and colorectal cancer.

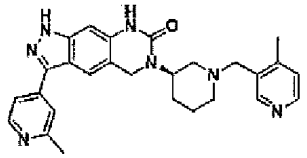
14. A pharmaceutical composition comprising the compound of any one of claims 1-10 and a pharmaceutically acceptable excipient, optionally wherein the composition is formulated in an oral dosage.

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

, , , ,

, , , ,

, , ,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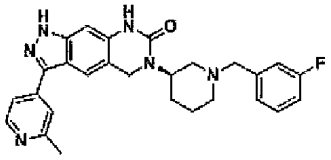
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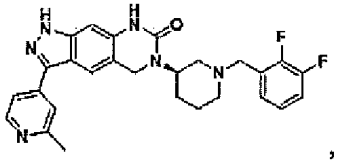
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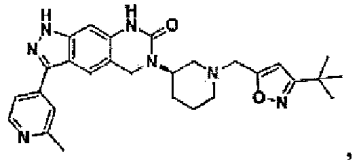
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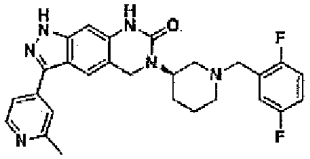
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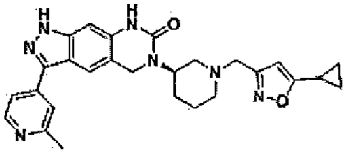
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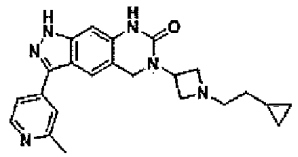
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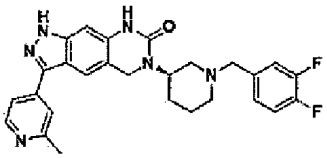
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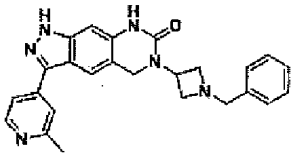
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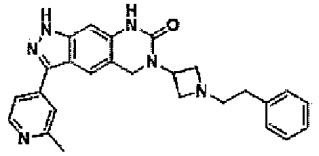
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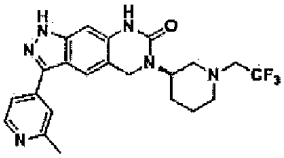
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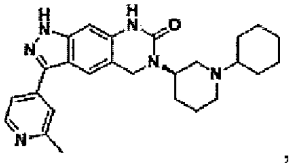
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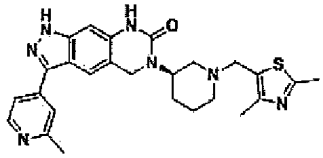
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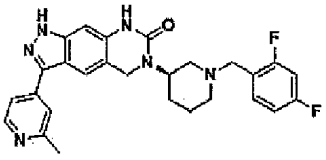
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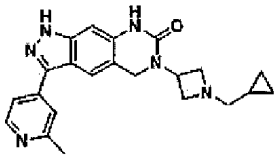
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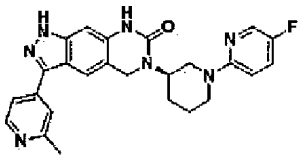
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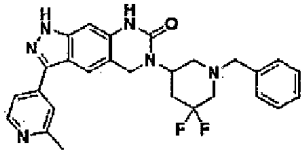
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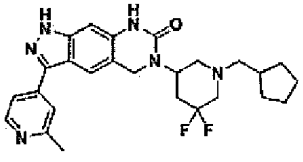
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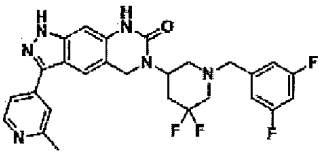
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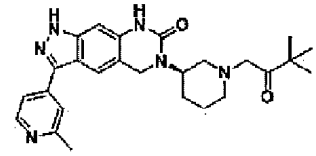
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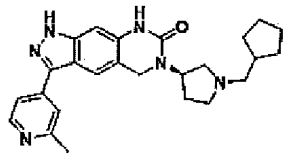
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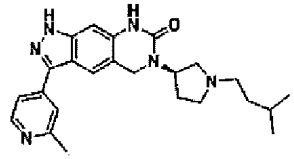
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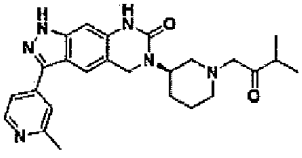
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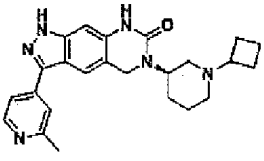
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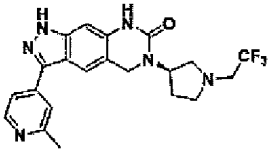
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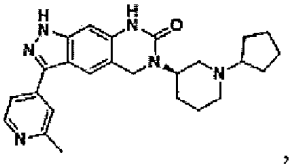
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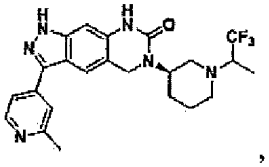
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