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(54) Title **COMPOUNDS AND METHODS FOR KINASE MODULATION, AND INDICATIONS THEREFOR**

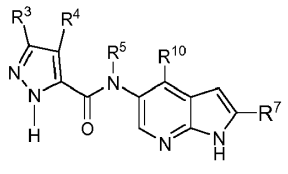
(56) References Cited: EP-A1- 2 522 658, WO-A1-00/27394, WO-A1-2005/094805, WO-A1-2008/144253, US-A1- 2006 035 921, DATABASE REGISTRY [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 22 November 2010 (2010-11-22), XP002724645, Database accession no. 1253912-

30-9, US-B2- 7 846 941, DAVID L SELWOOD ET AL: "Solution-phase parallel synthesis of 5-carboxamido 1-benzyl-3-(3-dimethylaminopropyloxy)-1H-p yrazoles as activators of soluble guanylate cyclase with improved oral bioavailability", BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, vol. 11, no. 8, 1 April 2001 (2001-04-01), pages 1089-1092, XP055118885, ISSN: 0960-894X, DOI: 10.1016/S0960-894X(01)00141-X, FRANCOIS CLEMENCE ET AL: "4-Hydroxy-3-quinolinecarboxamides with antiarthritic and analgesic activities", JOURNAL OF MEDICINAL CHEMISTRY, vol. 31, no. 7, 1 July 1988 (1988-07-01), pages 1453-1462, XP055118870, ISSN: 0022-2623, DOI: 10.1021/jm00402a034, KISELYOV ET AL: "Novel inhibitors of VEGF receptors -1 and -2 based on azole-5-carboxamide templates", BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, PERGAMON, AMSTERDAM, NL, vol. 17, no. 13, 1 July 2007 (2007-07-01), pages 3550-3557, XP022114537, ISSN: 0960-894X, DOI: 10.1016/J.BMCL.2007.04.042, US-A1- 2007 072 862

Enclosed is a translation of the patent claims in Norwegian. Please note that as per the Norwegian Patents Acts, section 66i the patent will receive protection in Norway only as far as there is agreement between the translation and the language of the application/patent granted at the EPO. In matters concerning the validity of the patent, language of the application/patent granted at the EPO will be used as the basis for the decision. The patent documents published by the EPO are available through Espacenet (http://worldwide.espacenet.com) or via the search engine on our website here: https://search.patentstyret.no/

Patentkrav

1. Forbindelse med formel (IVa-2):



(IVa-2)

eller et farmasøytisk akseptabelt salt, en oppløsning, en tautomer, en stereoisomer, eller en deuterert analog av samme, hvori:

R^7 er halogen, -CN, C_{1-6}alkyl, C_{1-6}alkoksy, C_{2-6}alkenyl, C_{2-6} alkynyl, C_{3-6} sykloalkyl, C_{3-6}sykloalkyl-C_{1-4}alkyl, aryl, aryl-C_{1-4}alkyl, heteroaryl, heteroaryl-C_{1-4} alkyl, heterosyklyl, heterosyklyl-C_{1-4}alkyl, -C(O)-R^a, -C(O)NHR^a, -C(O)NR^{a}R^a, -NHC(O)R^a, -NHC(O)NHR^a, -NHC(O)NR^{a}R^a, -NR^{a}R^a, -NHR^a, -C(O)OR^a, -OC(O)R^a, -SO_2R^a, -NHSO_2R^a, -NHSO_2NHR^a, -NHSO_2NR^{a}R^a, -SO_2NHR^a, eller -SO_2NR^{a}R^a;

hver R^a er uavhengig valgt fra C_{1-6}alkyl, aryl, aryl-C_{1-2}alkyl, C_{3-6}sykloalkyl, C_{3-6}sykloalkyl-C_{1-4}alkyl, heteroaryl, heteroaryl-C_{1-4}alkyl, heterosykloalkyl, og heterosykloalkyl-C_{1-4}alkyl;

hvori hver R^a er videre valgfritt substituert med 1-3 R^b-substituenter uavhengig valgt fra C_{1-6}alkyl, C_{1-6}alkoksy, halogen, C_{1-6}haloalkyl, og C_{1-6}haloalkoksy;

R^7 er valgfritt substituert med fra 1-4 R^9-komponenter valgt fra halogen, -CN, C_{1-6}alkyl, C_{1-6}alkoksy, C_{1-6} haloalkyl, C_{1-6} haloalkoksy, C_{3-6}sykloalkyl, C_{3-6} sykloalkyl-C_{1-4}alkyl, aryl, aryl-C_{1-4}alkyl, heteroaryl, heteroaryl-C_{1-4}alkyl, heterosyklyl, heterosyklyl-C_{1-4}alkyl, og R^8;

eller de to tilgrensende R^9-substituenter på en aromatisk ring er tatt sammen for å danne en 5- eller 6-leddet ring med fra 0-2 heteroatomer valgt fra O, N, og S;

R^8 er valgt fra halogen, CN, -OH, -NH_2, -NO_2, -C(O)OH, -C(S)OH, -C(O)NH_2, -C(S)NH_2, -S$(O)_2NH_2$, -NHC(O)NH_2, -NHC(S)NH_2, -NHS$(O)_2NH_2$, -C(NH)NH_2, -OR^a, -SR^a, -OC(O)R^a, -OC(S)R^a, -C(O)R^a, -C(S)R^a, -C(O)OR^a, -C(S)OR^a, -S(O)R^a, -S$(O)_2$R^a, -C(O)NHR^a, -C(S)NHR^a, -C(O)NR^{a}R^a, -C(S)NR^{a}R^a, -S$(O)_2$NHR^a, -S$(O)_2$NR^{a}R^a, -C(NH)NHR^a, -C(NH)NR^{a}R^a, -NHC(O)R^a, -NHC(S)R^a, -NR^{a}C(O)R^a, -NR^{a}C(S)R^a, -NHS$(O)_2$R^a, -NR^{a}S$(O)_2$R^a, -NHC(O)NHR^a, -NHC(S)NHR^a, -NR^{a}C(O)NH_2, -NR^{a}C(S)NH_2, -NR^{a}C(O)NHR^a, -NR^{a}C(S)NHR^a, -NHC(O)NR^{a}R^a, -NHC(S)NR^{a}R^a, -NR^{a}C(O)NR^{a}R^a, -NR^{a}C(S)NR^{a}R^a, -NHS$(O)_2$NHR^a, -NR^{a}S$(O)_2$$NH_2$, -NR^{a}S$(O)_2$NHR^a, -NHS$(O)_2$NR^{a}R^a, -NR^{a}S$(O)_2$NR^{a}R^a, -NHR^a, og -NR^{a}R^a;

R^{10} er H, -CN, C_{1-4}alkyl, halogen, C_{1-4}haloalkyl, C_{1-4}haloalkoksy, eller C_{1-4}alkoksy;

R^3 og R^4 er hver uavhengig valgt fra H, halogen, C_{1-4}alkyl, C_{1-4}haloalkyl, C_{1-4}haloalkoksy, syklopropyl, fenyl, -CN, CN-CH_2-, C_{1-4}alkoksy, R^g, og et enkelt par med elektroner; eller

R^3 og R^4 er tatt sammen med atomene som de er festet til for å danne en valgfritt substituert 5- til 8-leddet ring med fra 0-2 heteroatomer som ring-medlemmer valgt fra O, N, og S;

R^g er -OH, -NH_2, -NO_2, -C(O)OH, -C(S)OH, -C(O)NH_2, -C(S)NH_2, -S(O)$_2NH_2$, -NHC(O)NH_2, -NHC(S)NH_2, -NHS(O)$_2NH_2$, -C(NH)NH_2, -OR^h, -SR^h, -OC(O)R^h, -OC(S)R^h,-C(O)R^h, -C(S)R^h, -C(O)OR^h, -C(S)OR^h, -S(O)R^h, -S(O)$_2R^h$, -C(O)NHR^h, -C(S)NHR^h, -C(O)NR^hR^h, -C(S)NR^hR^h, -S(O)$_2NHR^h$, -S(O)$_2NR^hR^h$, -C(NH)NHR^h, -C(NH)NR^hR^h, -NHC(O)R^h, -NHC(S)R^h, -NR^hC(O)R^h, -NR^hC(S)R^h, -NHS(O)$_2R^h$, -NR^hS(O)$_2R^h$, -NHC(O)NHR^h, -NHC(S)NHR^h, -NR^hC(O)NH_2, -NR^hC(S)NH_2, -NR^hC(O)NHR^h, -NR^hC(S)NHR^h, -NHC(O)NR^hR^h, -NHC(S)NR^hR^h, -NR^hC(O)NR^hR^h, -NR^hC(S)NR^hR^h, -NHS(O)$_2NHR^h$, -NR^hS(O)$_2NH_2$, -NR^hS(O)$_2NHR^h$, -NHS(O)$_2NR^hR^h$, -NR^hS(O)$_2NR^hR^h$, -NHR^h, eller -NR^hR^h;

hver R^h er uavhengig H eller C_{1-2}alkyl; og

hver R^5 er uavhengig H eller C_{1-4}alkyl.

2. Forbindelse ifølge krav 1, hvori R^{10} er H.

3. Forbindelse ifølge et av kravene 1 eller 2, hvori R^3 og R^4 er hver uavhengig H, halogen, C_{1-4}alkyl, C_{1-4}alkoksy, syklopropyl, -CN, C_{1-4}haloalkyl, eller C_{1-4}haloalkoksy; eller R^3 og R^4 er tatt sammen med atomene som de er festet til for å danne en valgfritt substituert kondensert 5- til 8-leddet ring med fra 0-2 heteroatomer valgt fra N og S.

4. Forbindelse ifølge krav 1 eller 2, hvori R^3 og R^4 hver er uavhengig valgt fra H, Br, Cl, metyl, etyl, syklopropyl, -CN, CF_3, CHF_2, CH_2F, -OCH_3, -OCF_3, -$OCHF_2$ eller -OCH_2F, CNCH_2-, NH_2C(O)-, CH_3NHCO-, og CH_3C(O)NH-; eller R^3 og R^4 er tatt sammen med atomene som de er festet til for å danne en kondensert ring valgt fra benzen, pyridin, pyrimidin, pyrazin, pyridazin, syklobutan, syklopentan, sykloheksan, sykloheptan, syklopenten, sykloheksen, syklooktan, og syklooktatrien.

5. Forbindelse ifølge et av kravene 1-4, hvori hver R^9 er uavhengig valgt fra halogen, -CN, C_{1-6}alkyl, C_{1-6}alkoksy, C_{1-6} haloalkyl, C_{1-6} haloalkoksy, C_{3-6}sykloalkyl, C_{3-6} sykloalkyl-C_{1-4}alkyl, aryl, aryl-C_{1-4}alkyl, heteroaryl, heteroaryl-C_{1-2}alkyl, heterosyklyl, og heterosyklyl-C_{1-4}alkyl.

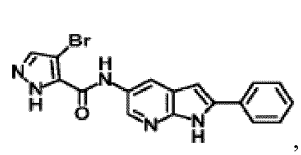
6. Forbindelse ifølge et av kravene 1-4, hvori R^7 er vinyl, etynyl, deuterert C_{1-6}alkyl, C_{1-6}alkyl, halogen, C_{1-6}alkoksy, 2-syklopropyletynyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, fenyl, benzyl, 1-pyrazolyl, 3-pyrazolyl, 4-pyrazolyl, 2-oksazolyl, 4-oksazolyl, 5-oksazolyl, 3-isoksazolyl, 4-isoksazolyl, 5-isoksazolyl, 2-thiozolyl, 4-thiozolyl, 5-thiozolyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 2-pyrazinyl, 3-pyridazinyl, 4-pyridazinyl, syklopropyl, syklopropylmetyl, syklopropylkarbonyl, syklobutyl,

syklobutylmetyl, syklopentyl, syklopentylmetyl, sykloheksyl, sykloheksylmetyl, benzoyl, fenylkarbamoyl, 1-piperidinyl, 2-piperidinyl, 3-piperidinyl, 4-piperidinyl, 1-piperazinyl, 2-piperazinyl, 4-morfolinyl, 4-thiomorfolinyl, 1-syklopentenyl, 1-sykloheksenyl, 1,2,3,6-tetrahydropyridin-4-yl, 1,2,3,6-tetrahydropyridin-5-yl, 2,5-dihydro-1H-pyrrol-3-yl, eller 2,5-dihydro-pyrrol-1-yl, som hver er valgfritt substituert med fra 1-4 R^{11}-komponenter uavhengig valgt fra halogen, -OH, $-NH_2$, $-CH_3$, etyl, propyl, isopropyl, 2-metylpropyl, $-CD_3$, $-OCH_3$, -CN, $-CH_2F$, $-CF_2H$, $-CF_3$, CF_2O-, CHF_2O-, CH_2FO-, $-N(C_{1-4}alkyl)_2$, $-NH(C_{1-4}alkyl)$, CH_3CONH-, $NH_2C(O)$-, $CH_3NHC(O)$-, $(CH_3)_2NC(O)$-, syklopropyl, $-SO_2NHR^{13}$, $-NHSO_2R^{13}$, $-SO_2R^{13}$, $-C(O)NHR^{13}$, $-C(O)R^{13}$, og $-OR^{13}$, hvori hver R^{13} er uavhengig C_{1-6}alkyl, C_{3-6}sykloalkyl, fenyl, C_{4-5} heterosykloalkyl, eller C_{4-5}heterosykloalkyl-C_{1-2}alkyl, hvori hver R^{13} er videre valgfritt substituert med fra 1-2 substituenter valgt fra C_{1-4}alkyl og C_{1-4}alkoksy.

7. Forbindelse ifølge et av kravene 1-4, hvori R^7 er valgt fra Cl, Br, fenyl, 4-fluorfenyl, 2-fluorfenyl, 3-fluorfenyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 1-syklopropylkarbonyl-1,2,3,6-tetrahydropyridin-4-yl, 1-morfolinokarbonyl, 1,2,3,6-tetrahydropyridin-4-yl, 1,2,3,6-tetrahydropyridin-5-yl, 1,3-dimetyl-pyrazol-4-yl, 1-(4-piperidinyl)pyrazol-4-yl, 3,4-dimetyl-1H-pyrazol-5-yl, 1-(syklopropylkarbonyl)-2,5-dihydro-pyrrol-3-yl, 3-fluor-propynyl, 3,5-dimetyl-isoksazol-4-yl, og 5-thiazolyl.

8. Forbindelse ifølge et av kravene 1-7, hvori R^5 er H.

9. Forbindelse ifølge krav 1, hvori forbindelsen er valgt fra: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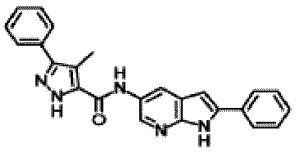
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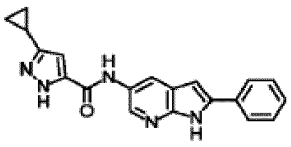
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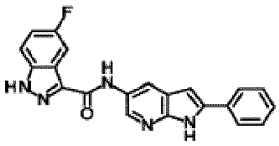
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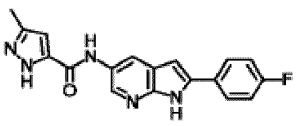
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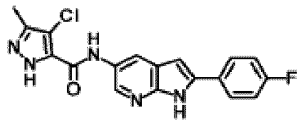
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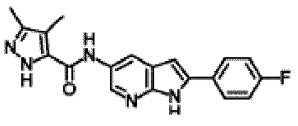
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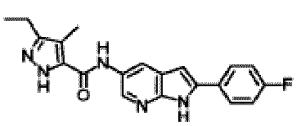
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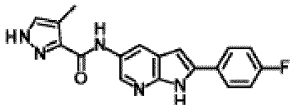
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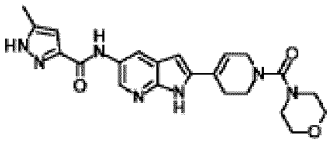
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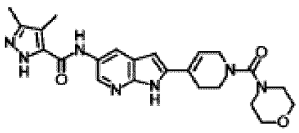
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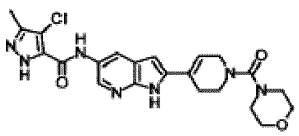
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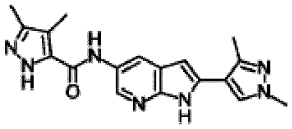
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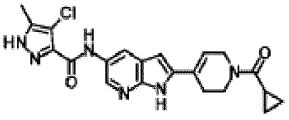
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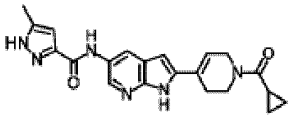
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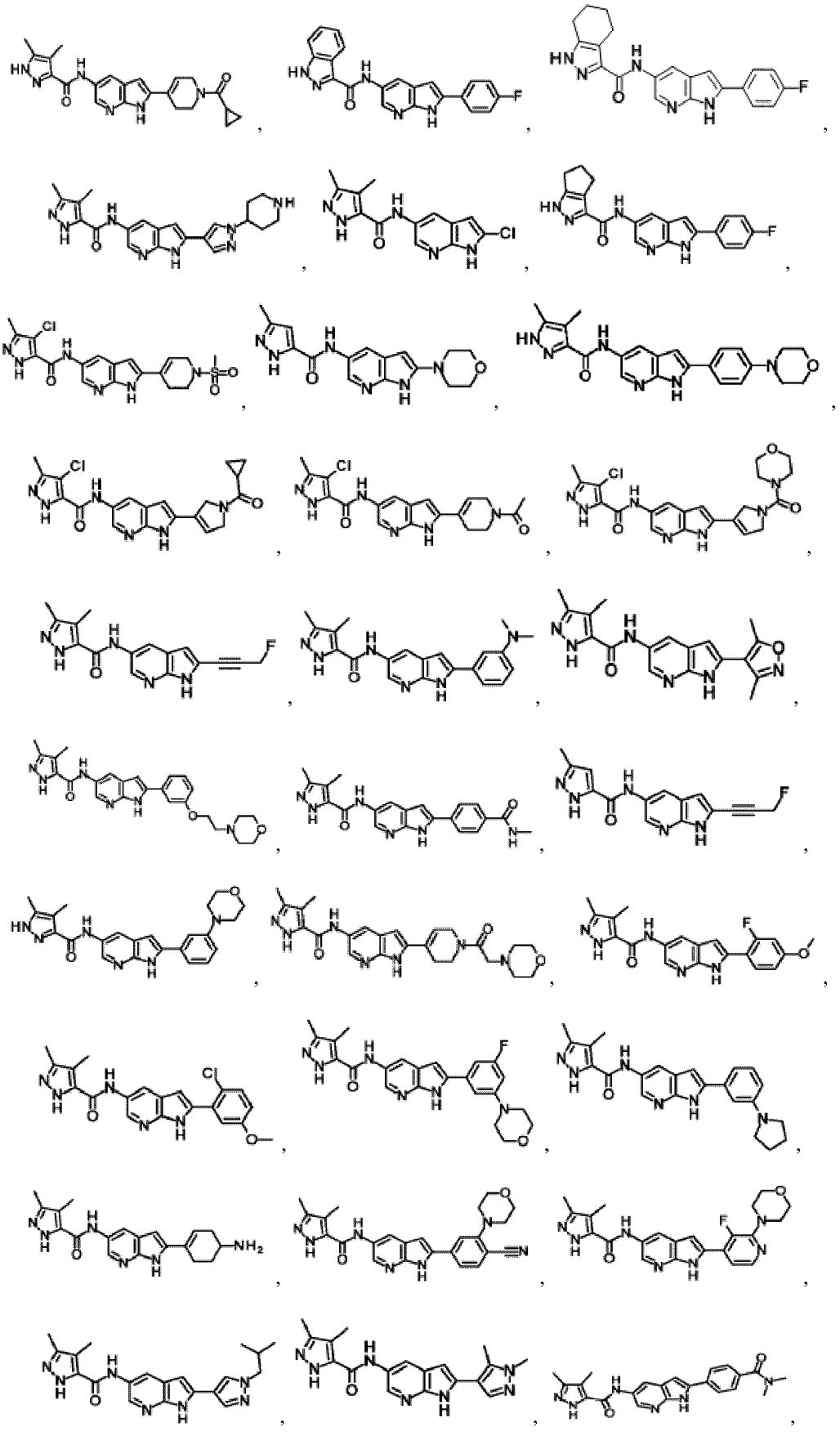
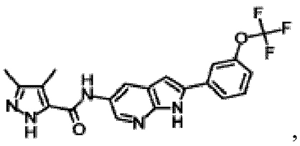
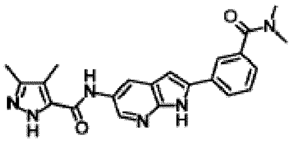
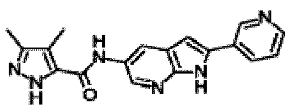
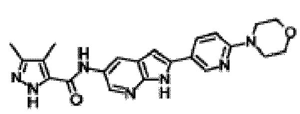
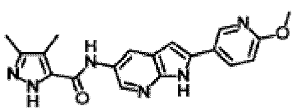
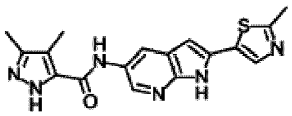
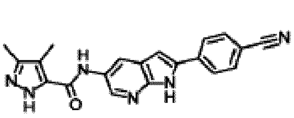
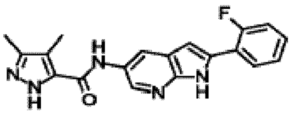
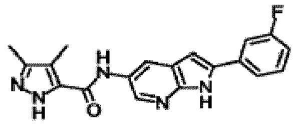
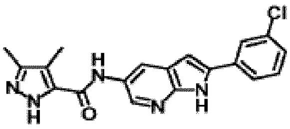
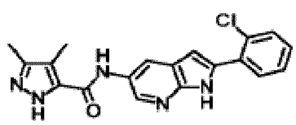
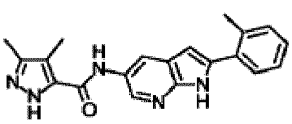
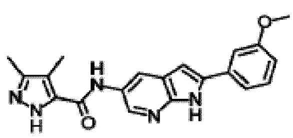
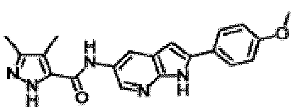
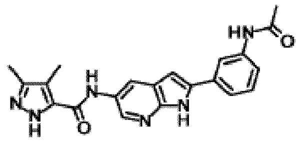


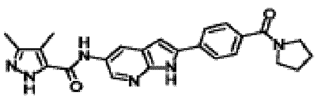
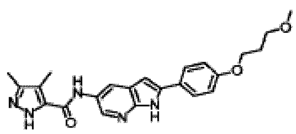
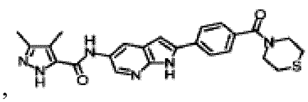
 ,  ,  ,

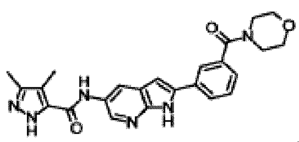
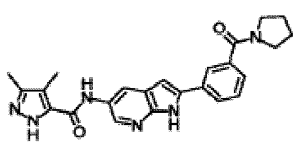
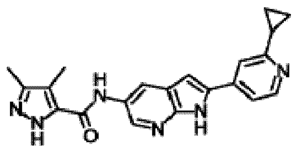
 ,  ,  ,

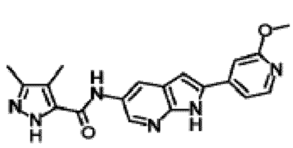
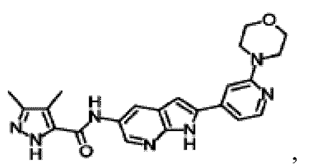
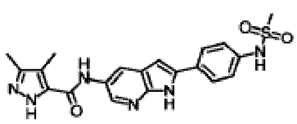
 ,  ,  ,

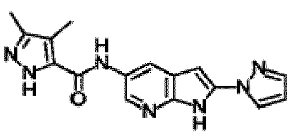
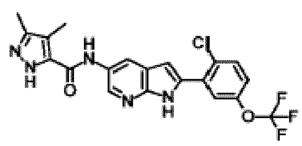
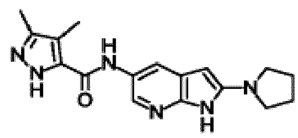
 ,  ,  ,

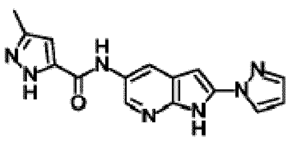
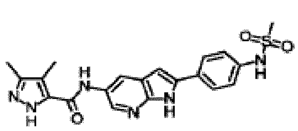
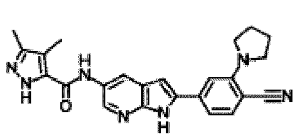
 ,  ,  ,

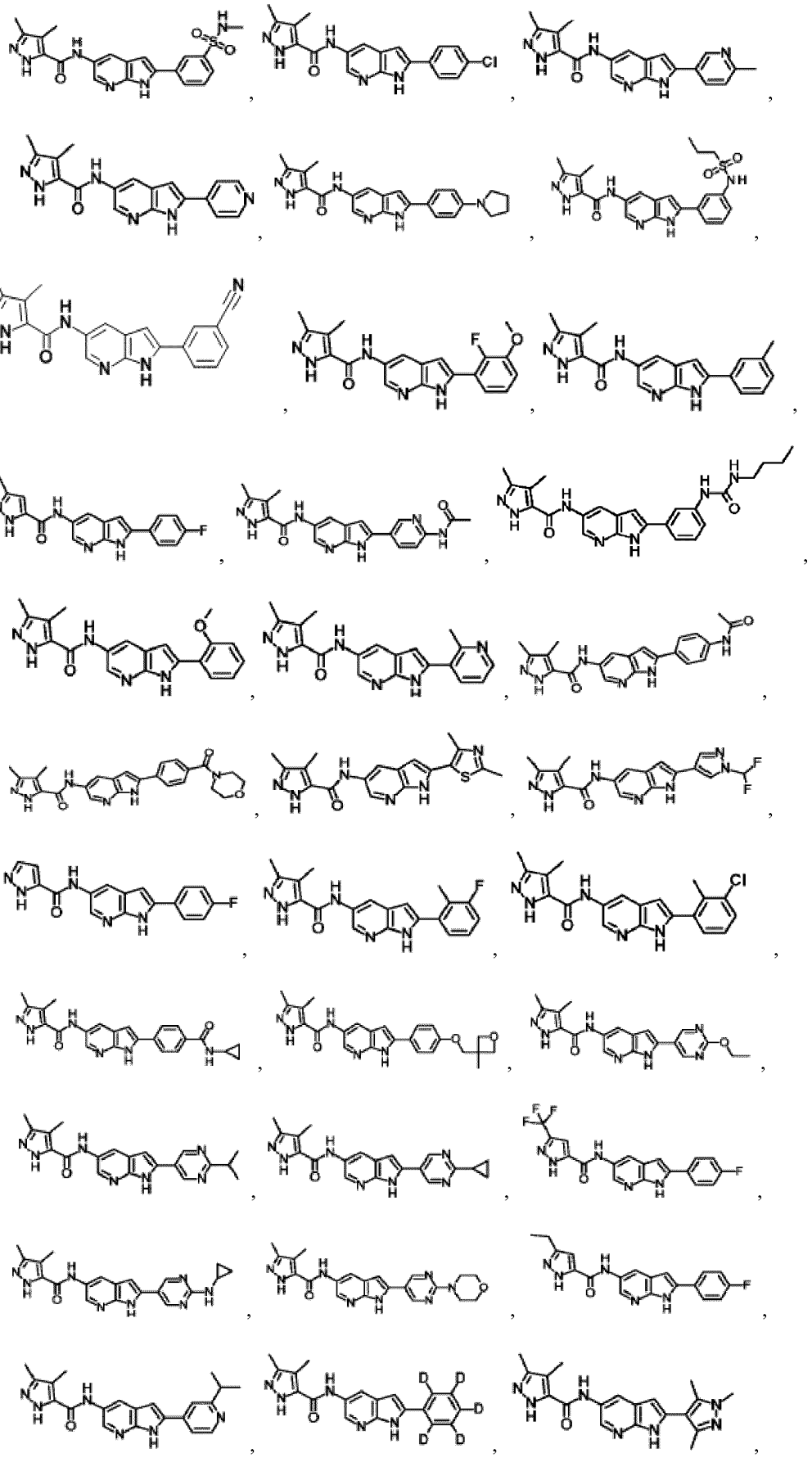
 ,  ,  ,

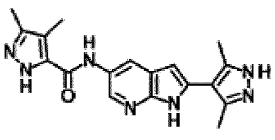
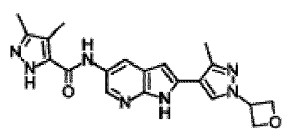
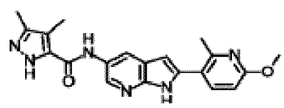
 ,  ,  ,

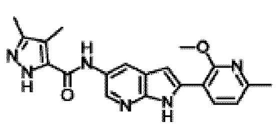
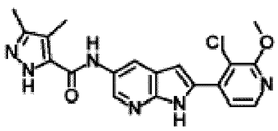
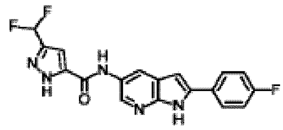
 ,  ,  ,

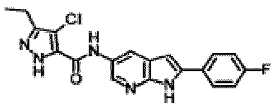
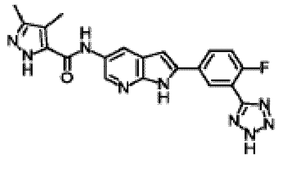
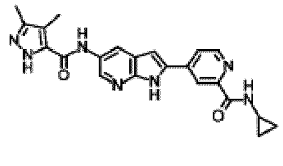
 ,  ,  ,

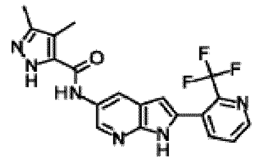
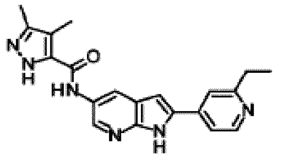
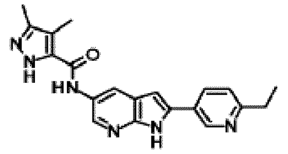
 ,  ,  ,

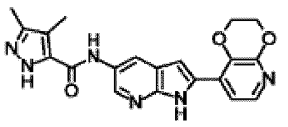
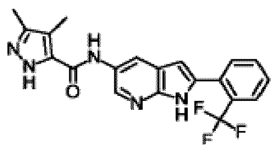
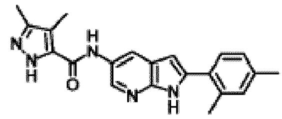


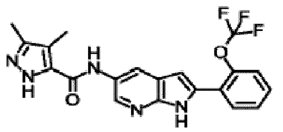
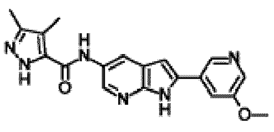
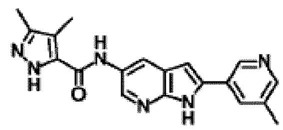
 ,  ,  ,

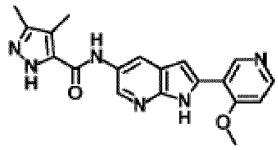
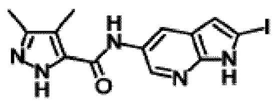
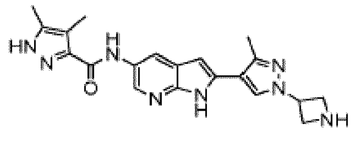
 ,  ,  ,

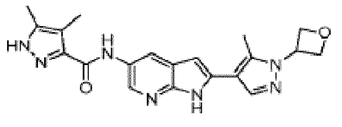
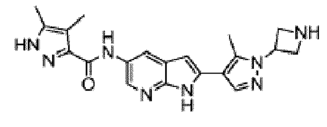
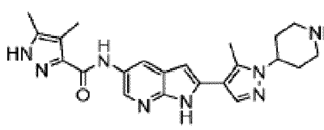
 ,  ,  ,

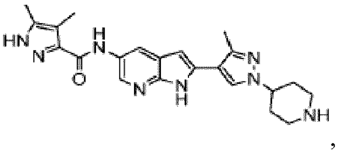
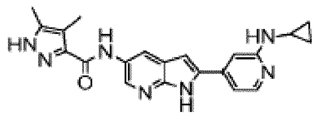
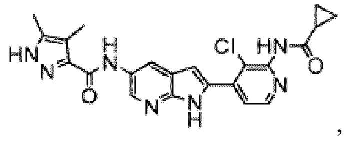
 ,  ,  ,

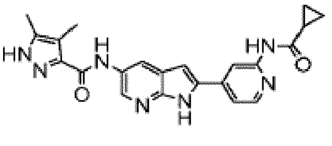
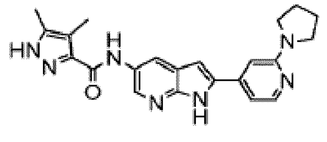
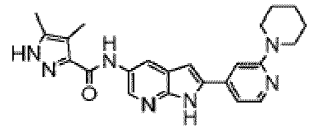
 ,  ,  ,

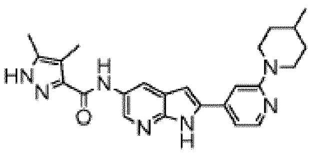
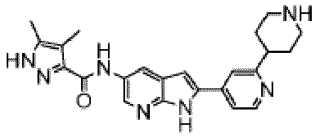
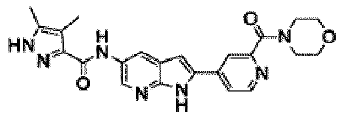
 ,  ,  ,

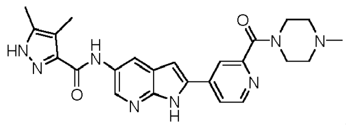
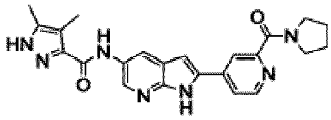
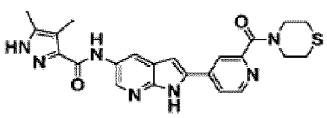
 ,  ,  ,

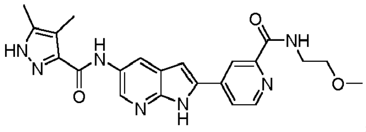
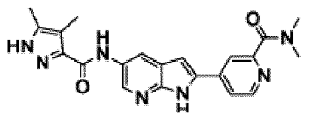
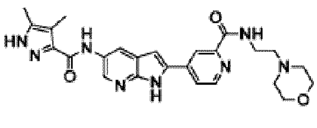
 ,  ,  ,

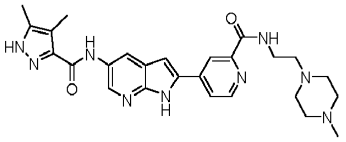
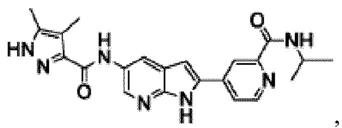
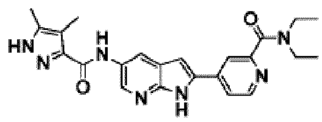
 ,  ,  ,

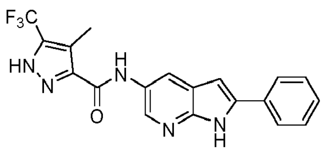
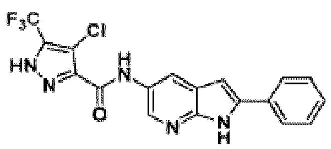
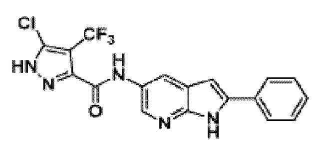
 ,  ,  ,

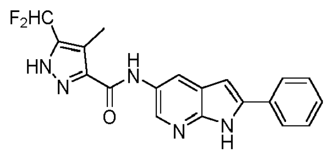
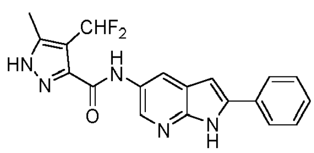
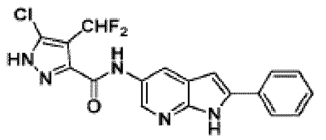
 ,
 ,
 ,

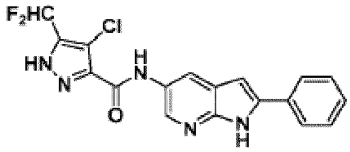
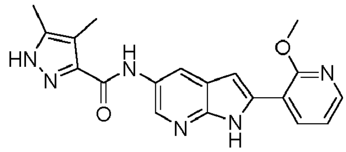
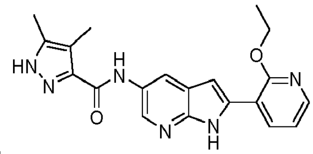
 ,
 ,
 ,

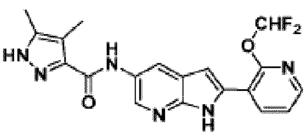
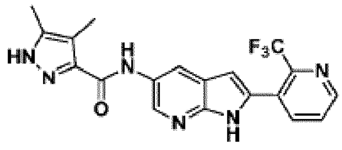
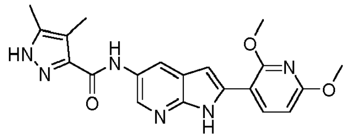
 ,
 ,
 ,

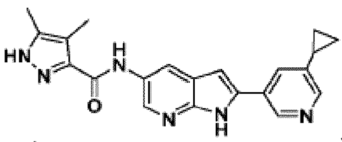
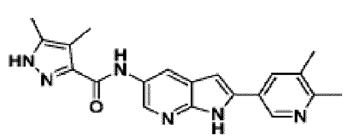
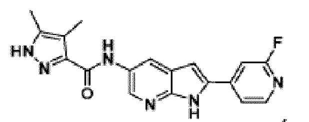
 ,
 ,
 ,

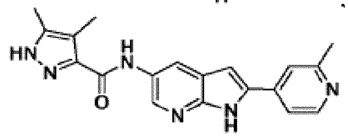
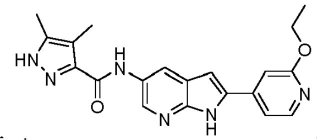
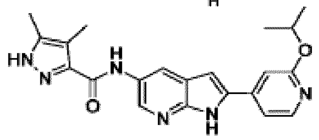
 ,
 ,
 ,

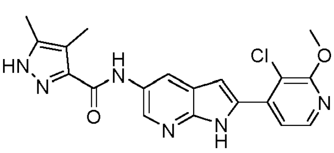
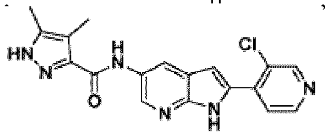
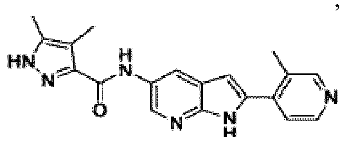
 ,
 ,
 ,

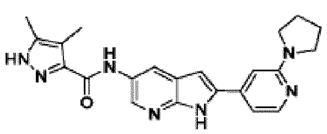
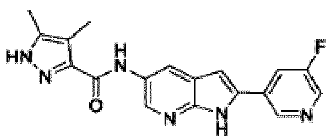
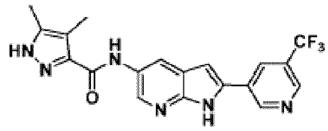
 ,
 ,
 ,

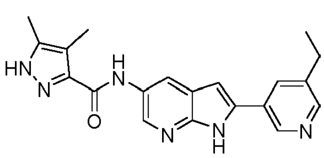
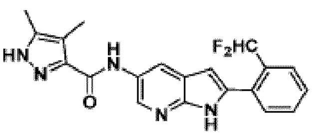
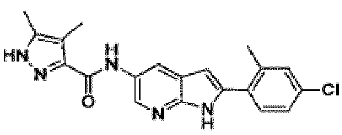
 ,
 ,
 ,

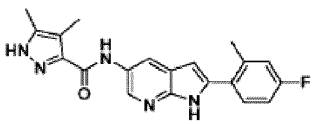
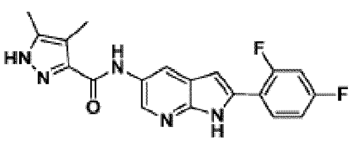
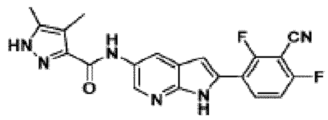
 ,   ,

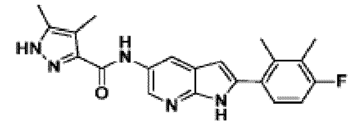
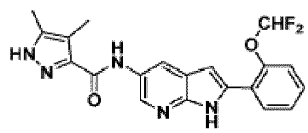
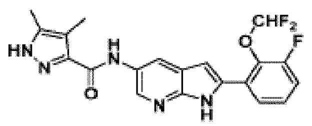
 .  ,  ,

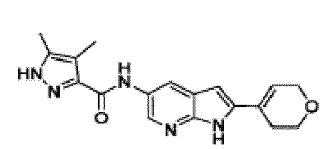
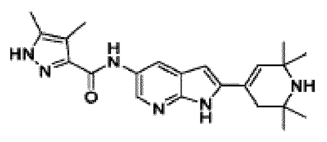
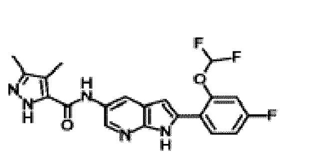
 ,  ,  ,

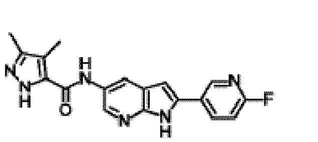
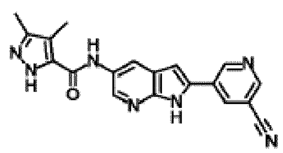
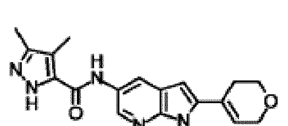
 ,  ,  ,

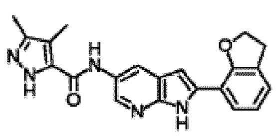
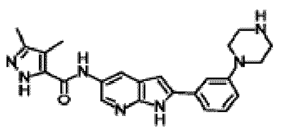
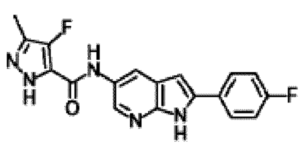
 ,  ,  ,

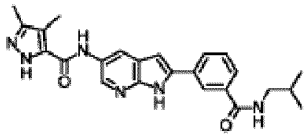
 ,  ,  ,

 ,  ,  ,

 ,  ,  ,

 ,  ,  ,

 ,  ,  ,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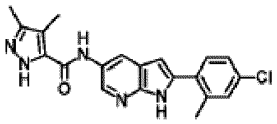
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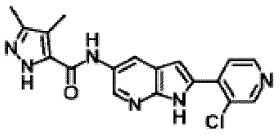
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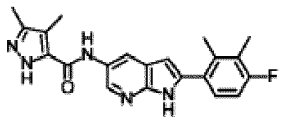
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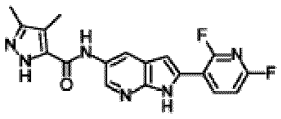
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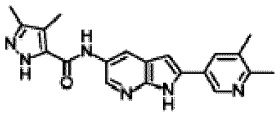
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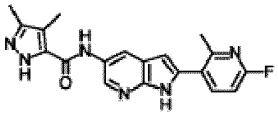
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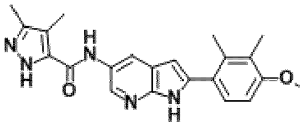
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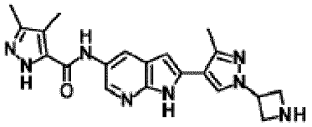
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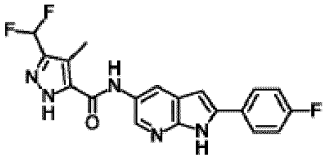
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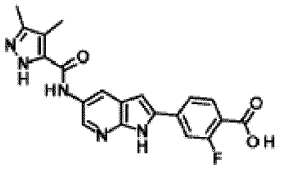
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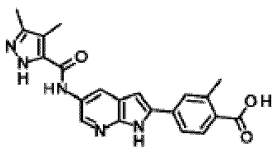
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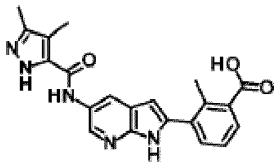
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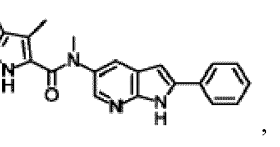
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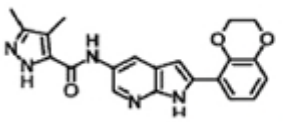
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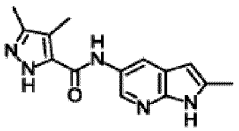
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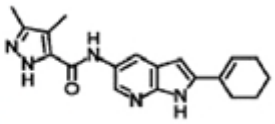
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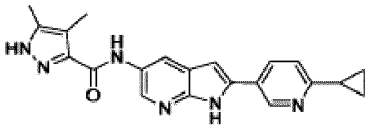
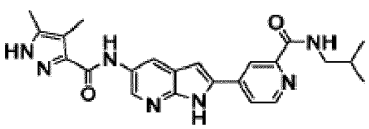
eller et farmasøytisk akseptabelt salt, hydrat, oppløsning, tautomer, eller stereoisomer av samme.

10. Forbindelse ifølge krav 1, hvori forbindelsen er:



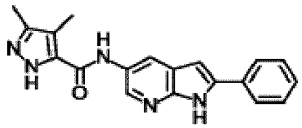
eller et farmasøytisk akseptabelt salt, et hydrat, en oppløsning, en tautomer, eller en stereoisomer av samme.

11. Forbindelse ifølge krav 1, hvori forbindelsen er:



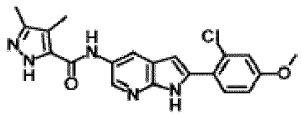
eller et farmasøytisk akseptabelt salt, et hydrat, en oppløsning, en tautomer, eller en stereoisomer av samme.

12. Forbindelse ifølge krav 1, hvori forbindelsen er:



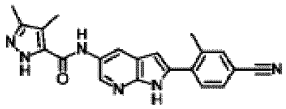
eller et farmasøytisk akseptabelt salt, et hydrat, en oppløsning, et tautomer, eller en stereoisomer av samme.

13. Forbindelse ifølge krav 1, hvori forbindelsen er:



eller et farmasøytisk akseptabelt salt, et hydrat, en oppløsning, en tautomer, eller en stereoisomer av samme.

14. Forbindelse ifølge krav 1, hvori forbindelsen er:



eller et farmasøytisk akseptabelt salt, et hydrat, en oppløsning, en tautomer, eller en stereoisomer av samme.

15. Forbindelse som definert i et av kravene 1-14, for anvendelse i behandlingen av melanom, hjernesvulst, glioblastom multiforme, pilocytisk astrocytom, sarkom, leverkreft, gallekanalkreft, kolangiokarsinom, kolorektal kreft, lungekreft, galleblærekreft, brystkreft, pankreaskreft, skjoldbruskkjertelkreft, nyrekreft, eggstokkreft, adrenokortikal kreft, prostatakreft, histiosytisk lymfom, nevrofibromatose, gastrointestinale stromale tumorer, akutt myeloid leukemi, myelodysplastisk syndrom, leukemi, tumor-angiogenese, medullær skjoldbruskkjertelkreft, karsinoid, småcellet lungekreft, Kaposis sarkom, feokromocytom, akutt smerte, kronisk smerte, eller polysystisk nyresykdom.

16. Farmasøytisk blanding som omfatter en forbindelse ifølge et av kravene 1-14, og en farmasøytisk akseptabel bærer eller bindemiddel.

17. Farmasøytisk blanding som omfatter en forbindelse ifølge krav et av kravene 1-14, eller en blanding ifølge krav 16, og et annet terapeutisk middel.

18. Forbindelse ifølge et av kravene 1-14, eller en blanding ifølge krav 16 eller 17, for anvendelse i behandlingen av kreft, akutt myelocytisk leukemi (AML), gastrointestinale stromale tumorer, eller mastocytose.

19. Forbindelse ifølge et av kravene 1-14, eller en blanding ifølge krav 16 eller 17, for anvendelse i behandlingen av gastrointestinale stromale tumorer.