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C07D 417/04 (2006.01)

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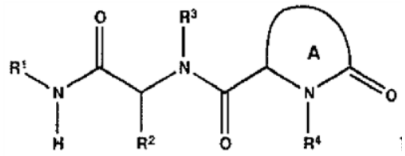
(54) Title **LACTAM DERIVATES USEFUL AS INHIBITORS OF MUTANT IDH1**

(56) References Cited:

JANETA POPOVICI-MULLER ET AL: "Discovery of the First Potent Inhibitors of Mutant IDH1 That Lower Tumor 2-HG in Vivo", ACS MEDICINAL CHEMISTRY LETTERS, vol. 3, no. 10, 11 October 2012 (2012-10-11), pages 850-855, XP055159509, ISSN: 1948-5875, DOI: 10.1021/ml300225h, WO-A1-2011/072174, WO-A1-01/16097, WO-A1-2009/150248

Patentkrav:

1. Forbindelse med formel I eller et farmasøytisk akseptabelt salt, tautomer, isotopolog eller hydrat derav, hvor:



formel I

R^1 er eventuelt substituert C_4-C_6-karbocyclyl;

hver R^2 og R^3 er uavhengig valgt fra eventuelt substituert aryl eller eventuelt substituert heteroaryl;

R^4 er alkyl, eventuelt substituert aryl, eventuelt substituert heteroaryl, eventuelt substituert aralkyl eller eventuelt substituert heteroaralkyl;

ring A er 4-6 leddet ikke-aromatisk ring som har 0-1 ytterligere heteroatomer valgt fra N, O eller S, hvor ring A eventuelt er substituert med en eller to R^5 -grupper;

hver R^5 er uavhengig halo; CF_3; CN; OR^6; $N(R^6)_2$; $C(O)C_1$-C_4-alkyl; C_1-C_4-haloalkyl; C_1-C_4-alkyl eventuelt substituert med OR^6 eller $N(R^6)_2$; -O-C_1-C_4-alkyl eventuelt substituert med halogen, OR^6 eller $N(R^6)_2$; -$SO_2N(R^6)_2$; -SO_2(C_1-C_4-alkyl); $NR^6SO_2R^6$; C_3-C_5-karbocyklyl eventuelt substituert med en eller to R^6-grupper; -O-(C_3-C_6-karbocyklyl) eventuelt substituert med en eller to R^6-grupper; 5-6 leddet heteroaryl; -C_1-C_4 alkyl-C(O)O-C_1-C_4-alkyl; eller -C(O)O-C_1-C_4-alkyl; eller

hver R^6 er uavhengig H eller C_1-C_3-alkyl.

2. Forbindelse eller farmasøytisk akseptabelt salt derav ifølge krav 1, hvor:

R^1 er C_4-C_6-karbocyklyl eventuelt substituert med en til tre R^7 -grupper;

hver R^2 og R^3 er uavhengig valgt fra aryl eller heteroaryl, hvor nevnte aryl eller heteroaryl er uavhengig eventuelt substituert med en til tre R^7-grupper;

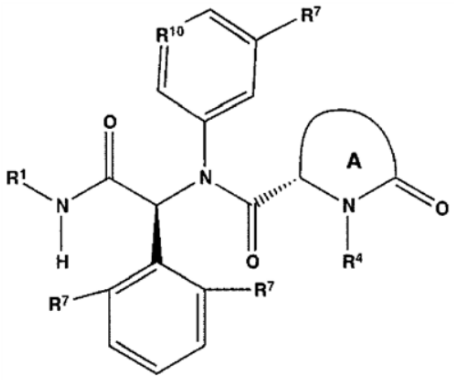
R^4 er alkyl, aryl, heteroaryl, aralkyl eller heteroaralkyl, hvor nevnte aryl, heteroaryl, aralkyl og heteroaralkyl er hver uavhengig eventuelt substituert med en til tre R^7 -grupper;

hver R^5 og R^7 er uavhengig halo; CF_3; CN; OR^6; $N(R^6)_2$; $C(O)C_1$-C_4-alkyl; C_1-C_4-haloalkyl; C_1-C_4-alkyl eventuelt substituert med OR^6 eller $N(R^6)_2$; -O-C_1-C_4-alkyl eventuelt substituert med halogen, OR^6 eller $N(R^6)_2$; $SO_2N(R^6)_2$; -S(O)-C_{1-4}-alkyl; SO_2(C_1-C_4-alkyl); $NR^6SO_2R^6$; C_3-C_5-karbocyklyl eventuelt substituert med en eller to R^6-grupper; -O-(C_3-C_6-karbocyklyl) eventuelt substituert med en eller to R^6-grupper; 5-6 leddet heteroaryl; C_1-C_4-alkyl-C(O)O-C_1-C_4-alkyl; eller -C(O)O-C_1-C_4-alkyl; eller

hver R^6 er uavhengig H eller C_1-C_4-alkyl.

3. Forbindelse eller farmasøytisk akseptabelt salt derav ifølge krav 1 eller 2, hvor hver R^2 og R^3 er uavhengig aryl eventuelt substituert med en til tre R^7 grupper.

4. Forbindelse eller farmasøytisk akseptabelt salt derav ifølge krav 1 med formel II-a,

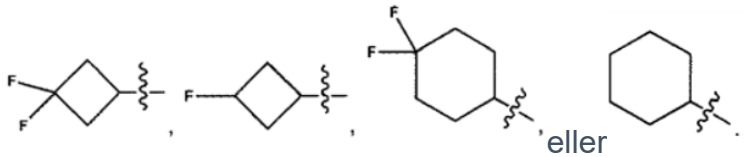


formel II-a

hvor R^{10} er OR^{11} eller N; og R^{11} er -F, $-SO_2NH_2$, $-SO_2CH_3$, $-S(O)CH_3$, -CN, metoksy, $-OCH_2OH$, $-CH_2OH$, $-SO_2N(CH_3)_2$, $-SO_2NHCH_3$, $-NHSO_2CH_3$, $-CH_2CH_2OH$, $-N(CH_3)_2$, t-butyl, cyklopropyl, $-C(OH)(CH_3)_2$, $-OCF_3$, $-OCHF_2$, -O-cyklopropyl, -1-metyl-cyklopropyl eller pyrazolyl.

5. Forbindelse eller farmasøytisk akseptabelt salt derav ifølge et hvilket som helst av kravene 1-4, hvor R^1 er C_4 eller C_6-cykloalkyl eventuelt substituert med en til to R^7-grupper og R^7 assosiert med R^1 er halo.

6. Forbindelse eller farmasøytisk akseptabelt salt derav ifølge krav 5, hvor R^1 er



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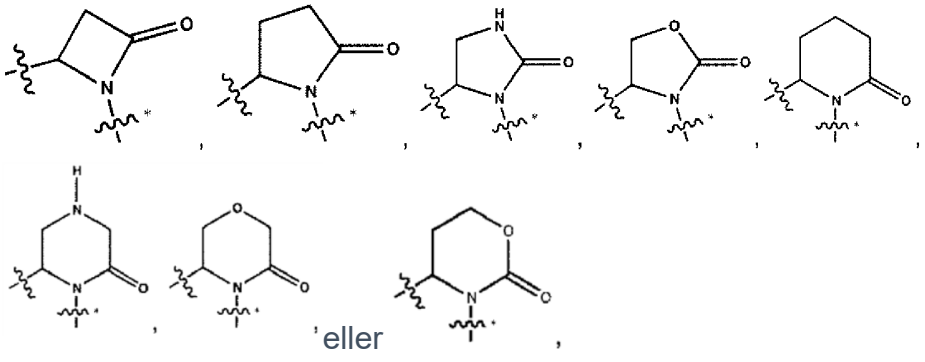
7. Forbindelse eller farmasøytisk akseptabelt salt derav ifølge krav 5, hvor ring A er:



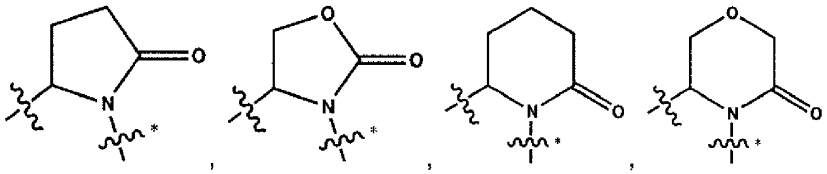
eller

hvori

betegner ring As kobling til amiddelen av formelen og

betegner ring As kobling til R^4; og hvor hvert medlem av ring A eventuelt er substituert med en eller to R^5-grupper.

8. Forbindelse eller farmasøytisk akseptabelt salt derav ifølge krav 7, hvor ring A er:



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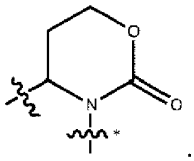
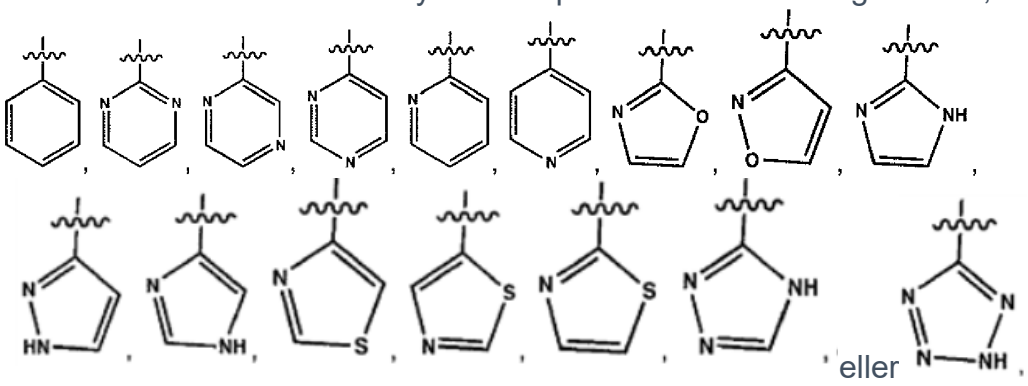


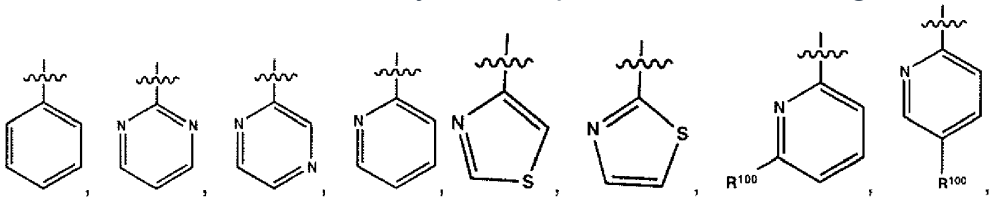
9. Forbindelse eller farmasøytisk akseptabelt salt derav ifølge krav 7, hvor R^4 er aryl eller heteroaryl, hver aryl eller heteroaryl er eventuelt substituert med en til tre R^7 grupper.

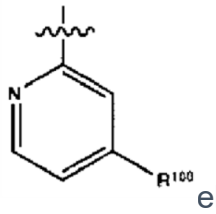
10. Forbindelse eller farmasøytisk akseptabelt salt derav ifølge krav 9, hvor R^4 er:



hvor hvert medlem av R^4 er eventuelt substituert med en eller to R^7-grupper og hver R^7 er uavhengig F, Cl, metyl, CF_3, CN, OMe eller $N(R^6)_2$.

11. Forbindelse eller farmasøytisk akseptabelt salt derav ifølge krav 10, hvor R^4 er:

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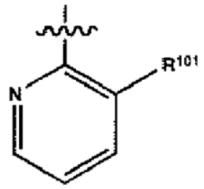
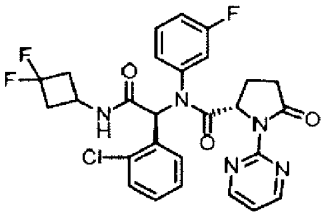


hvor R^{100} er H, metyl, Cl, CF_3, CN, OCH_3, eller N $(R^6)_2$; og R^{101} er H, F eller metyl.

12. Forbindelse eller farmasøytisk akseptabelt salt derav ifølge krav 1 valgt fra: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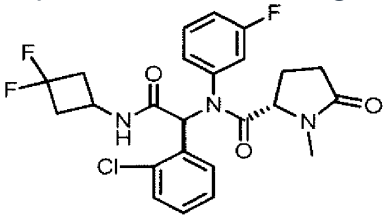
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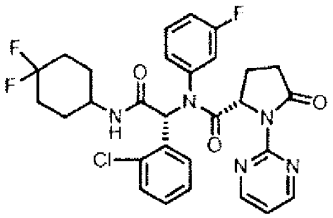
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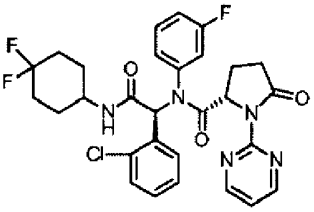
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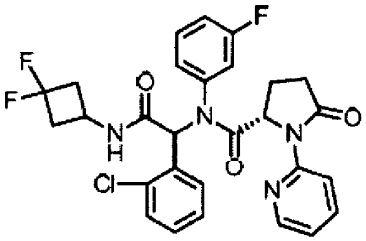
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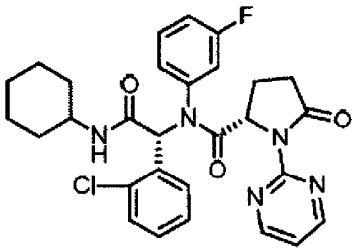
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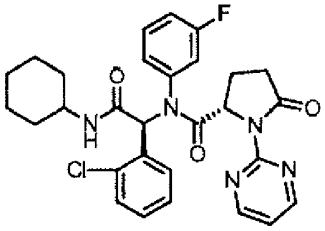
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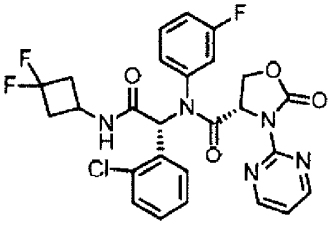
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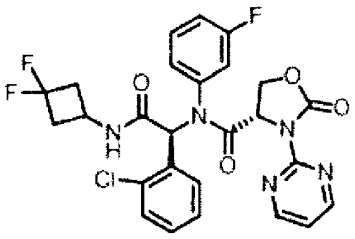

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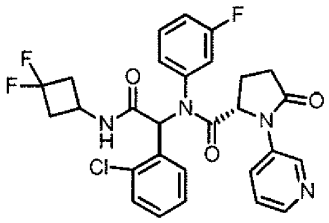

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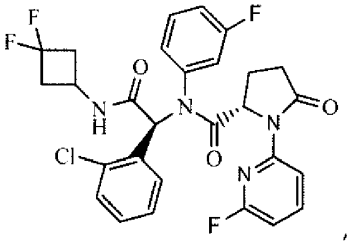

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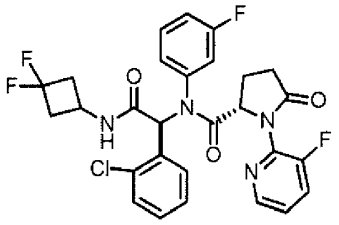

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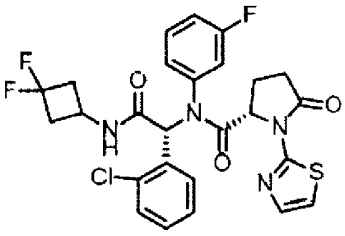

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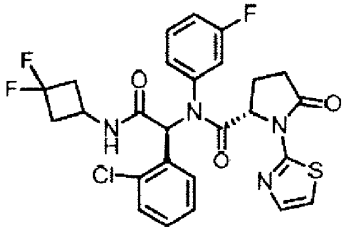

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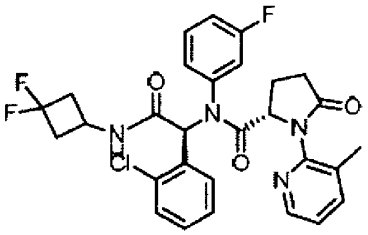

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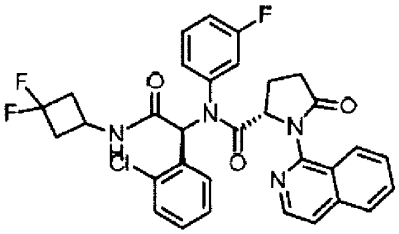

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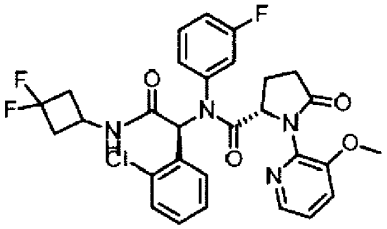

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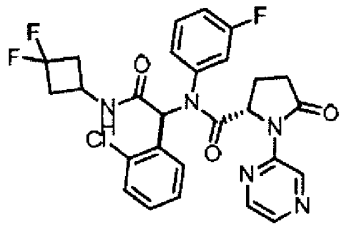

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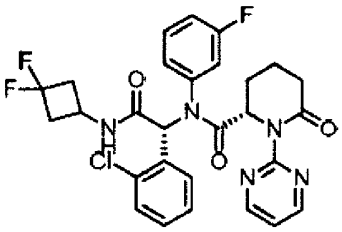

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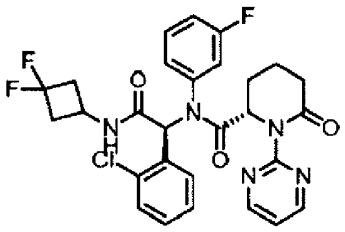

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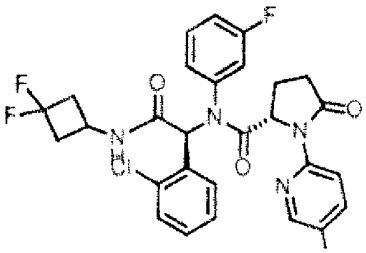

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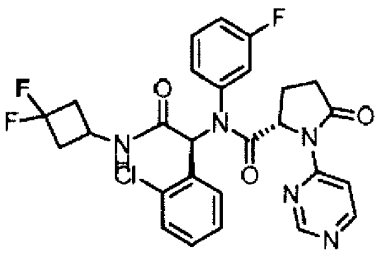

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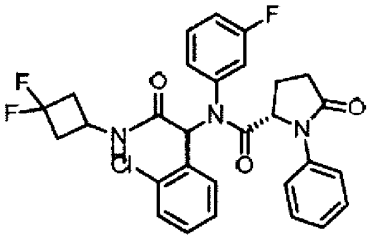

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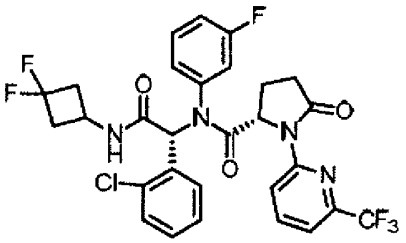

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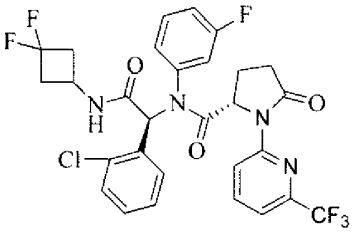

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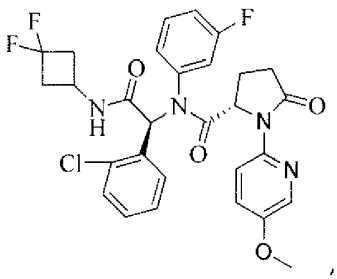

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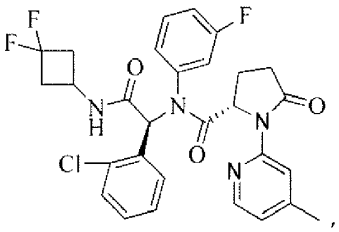

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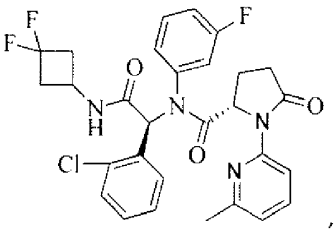

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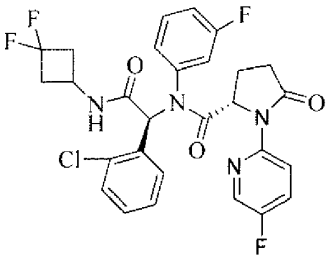

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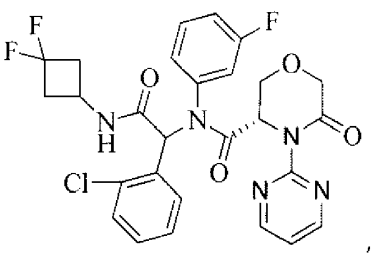

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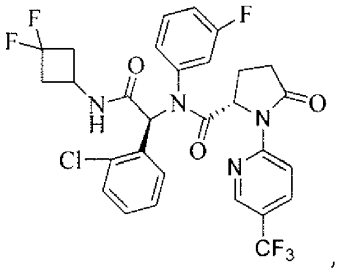

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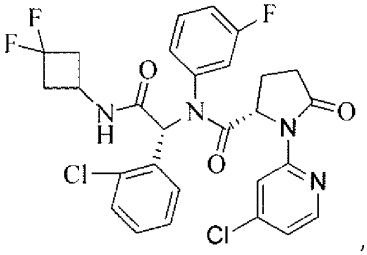

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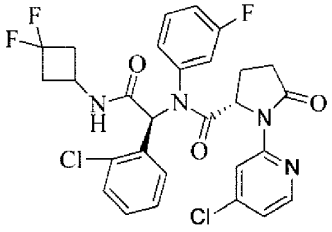

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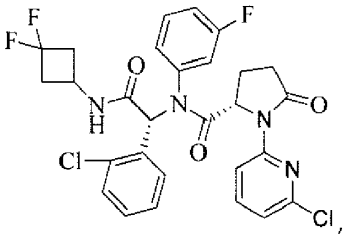

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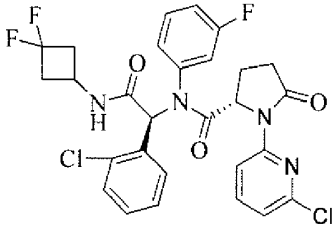

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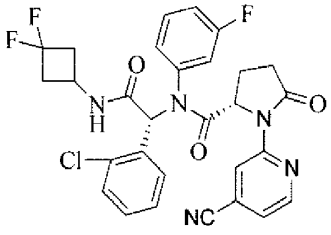

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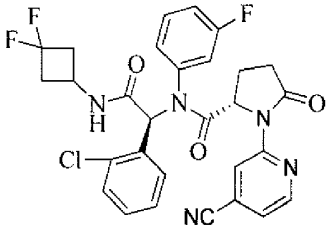

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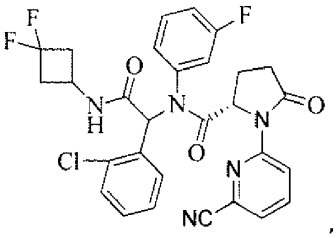

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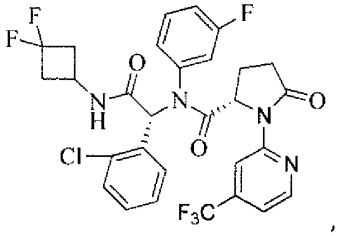

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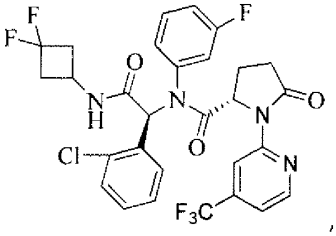

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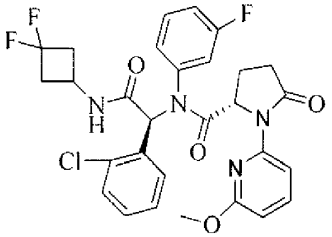

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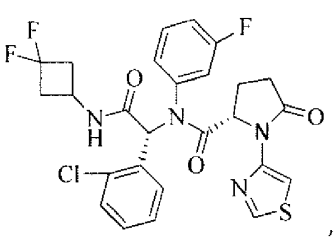

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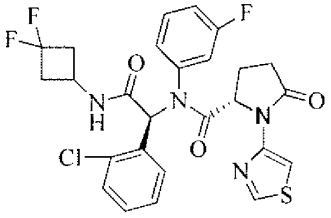

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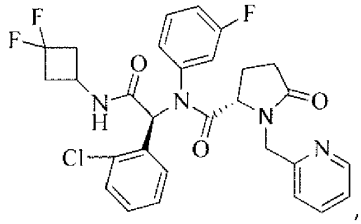

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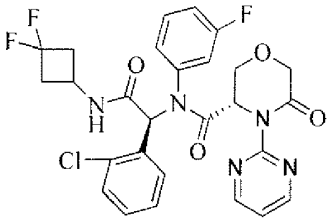

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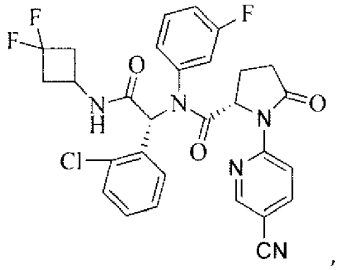

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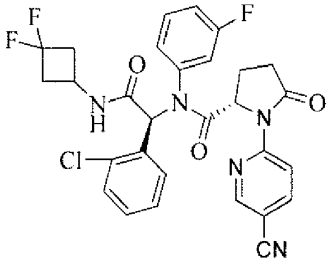

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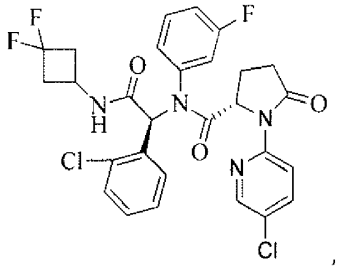

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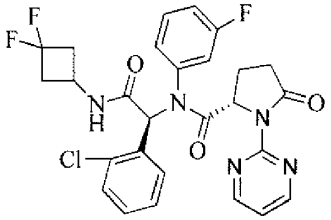

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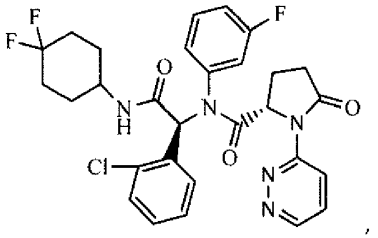

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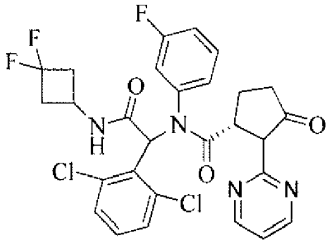

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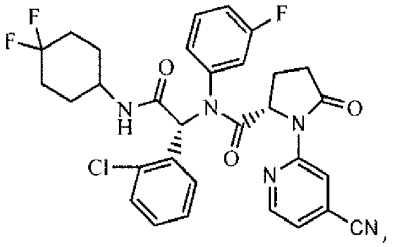

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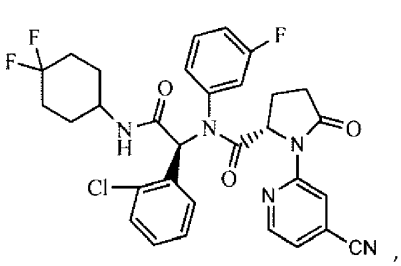

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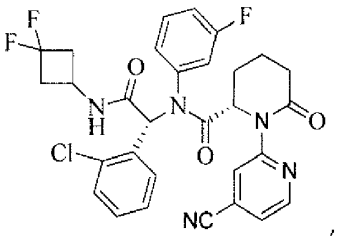

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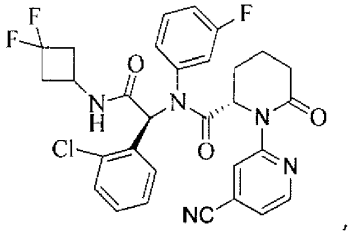

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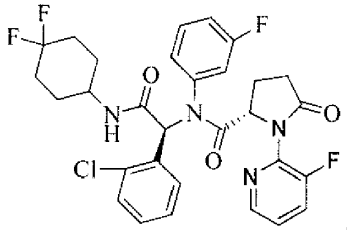

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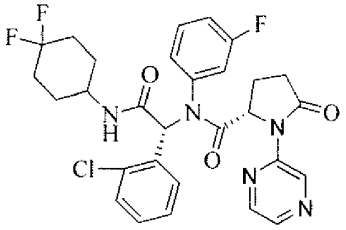

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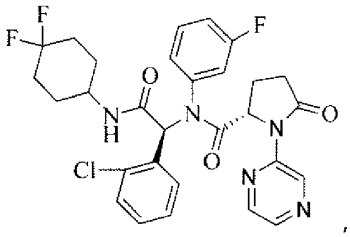

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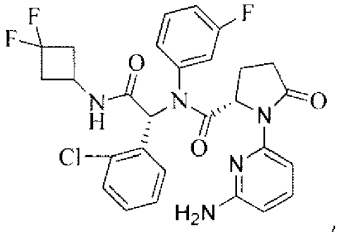

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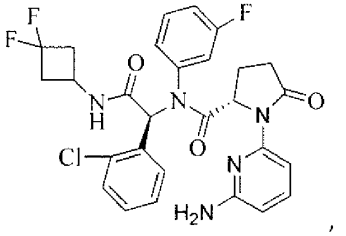

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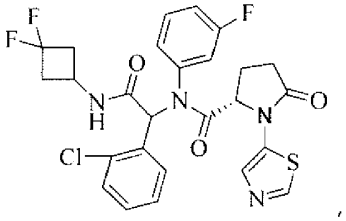

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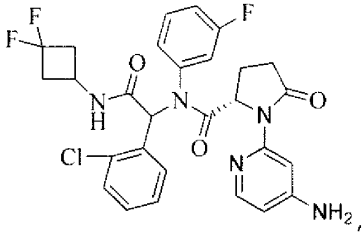

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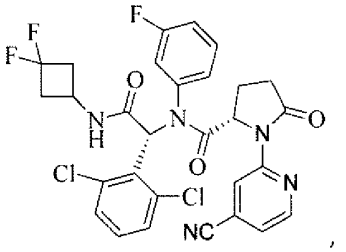

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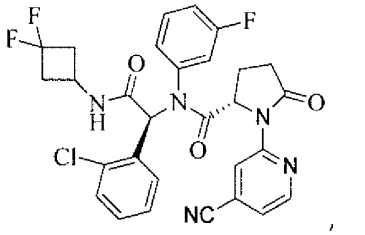

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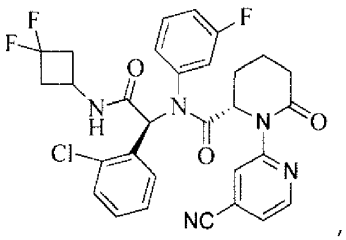

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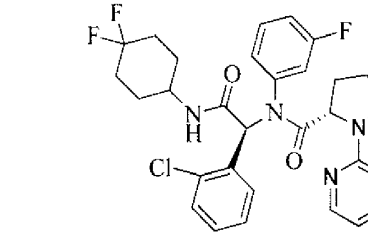

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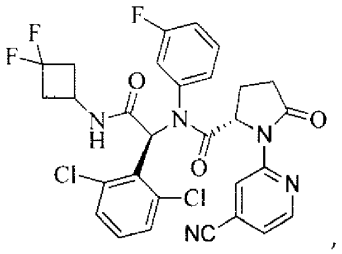

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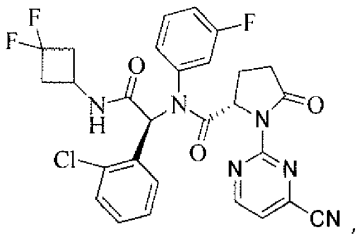

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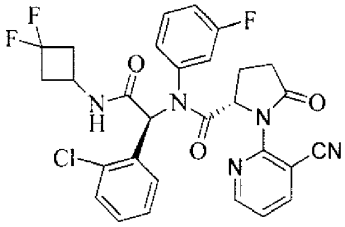

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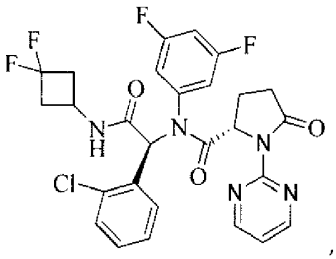

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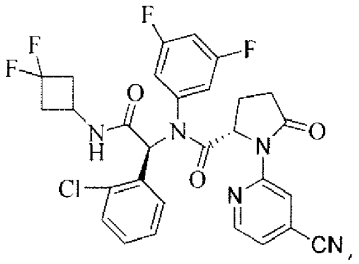

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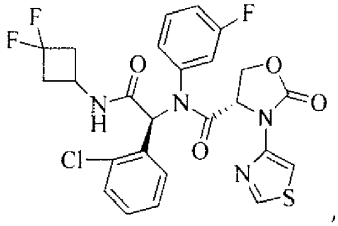

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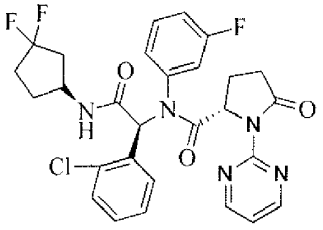

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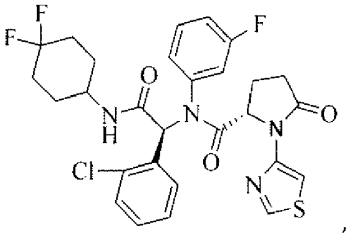

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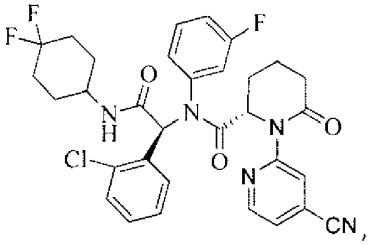

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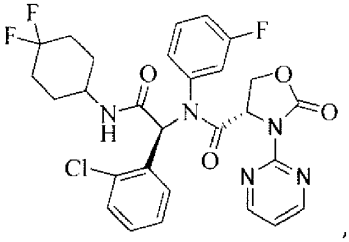

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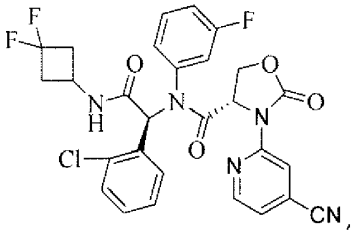

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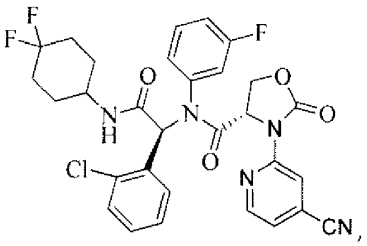

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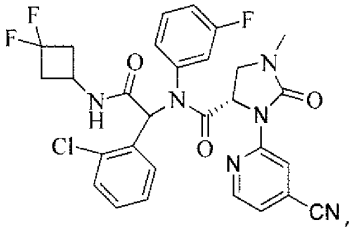

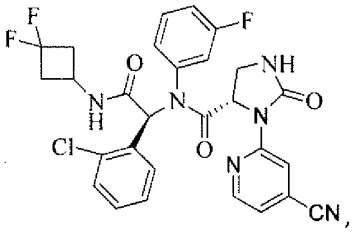

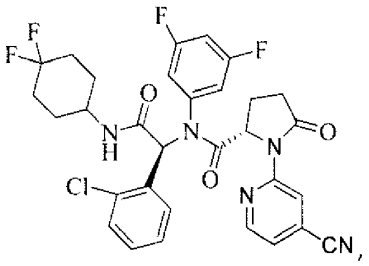

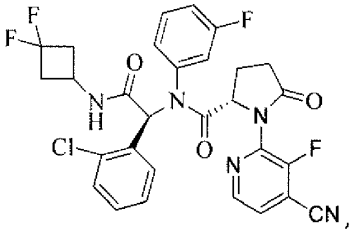

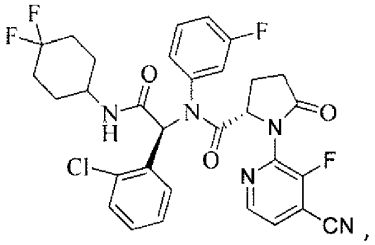

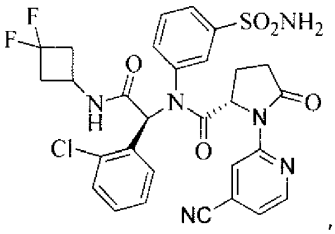

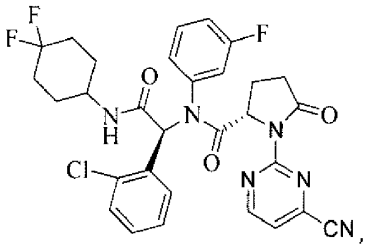

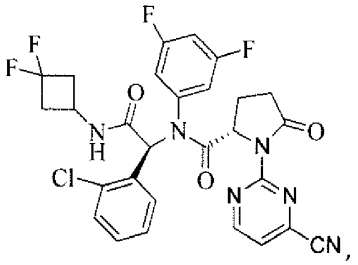

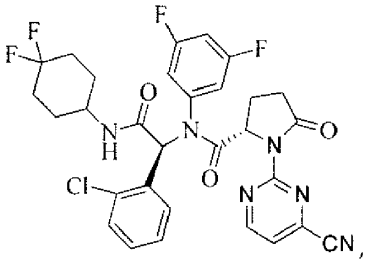

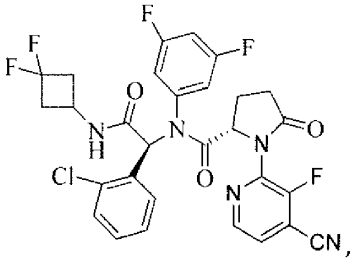

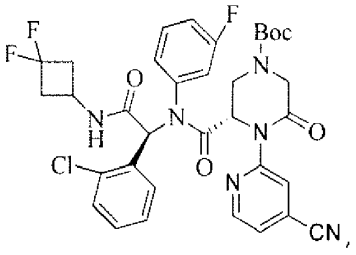

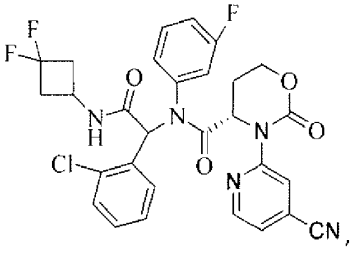

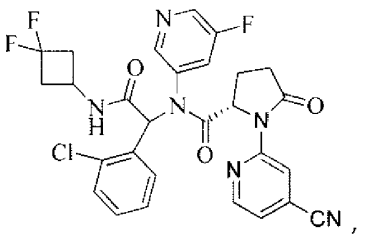

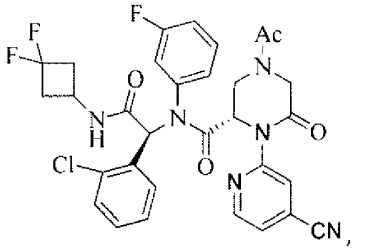

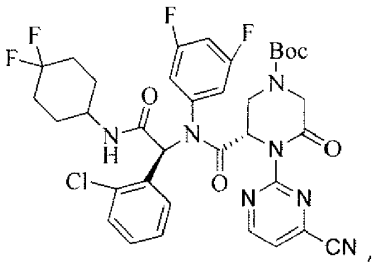

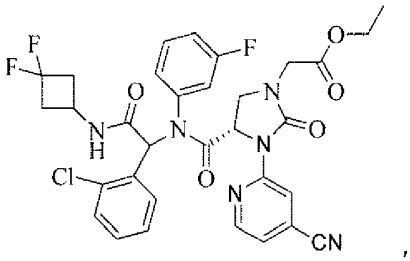

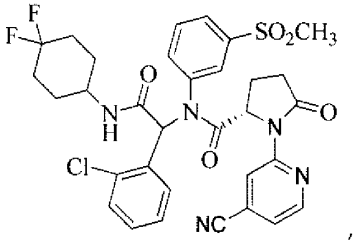

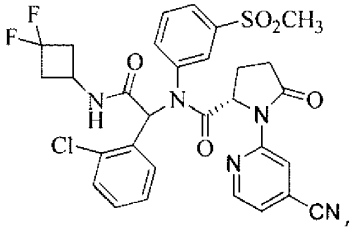

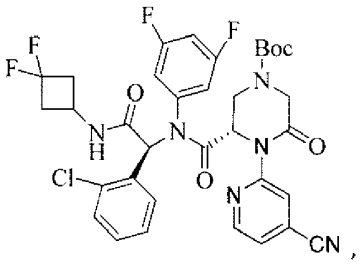

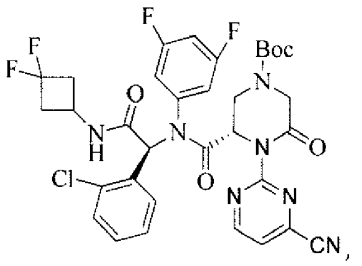

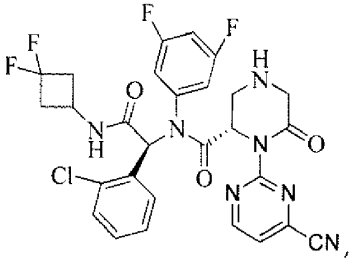

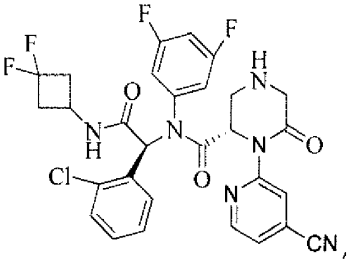

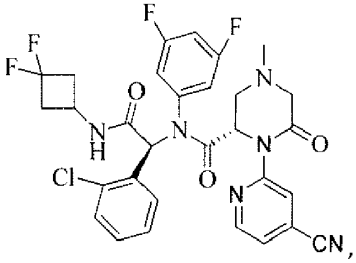

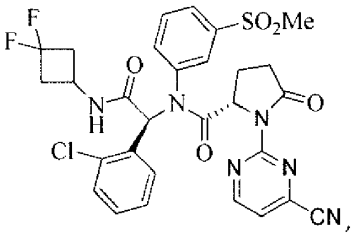

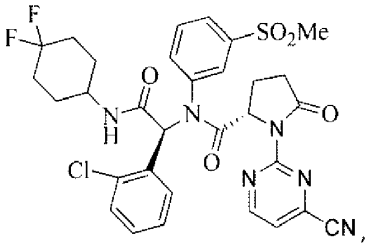

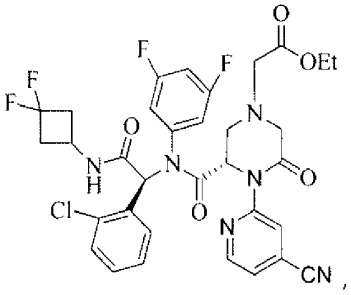

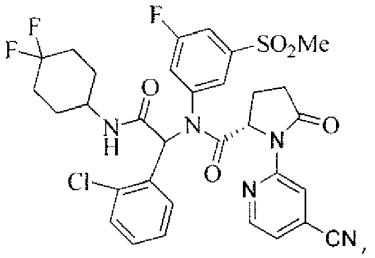

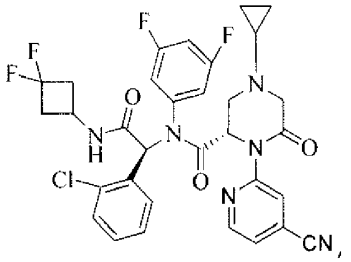

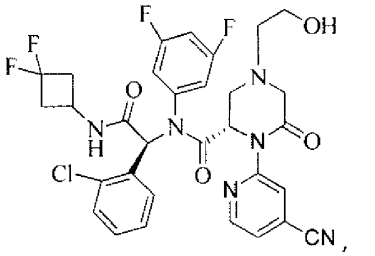

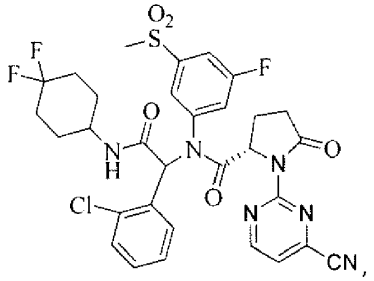

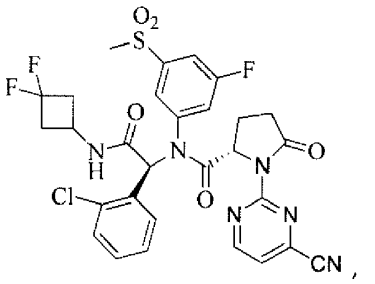

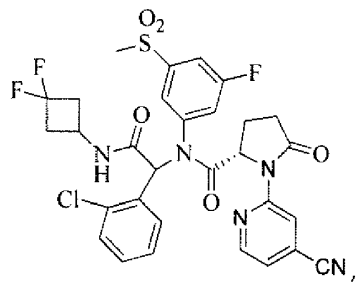

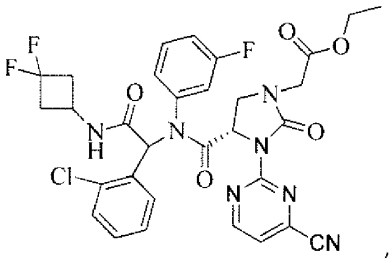

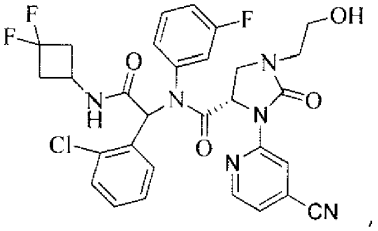

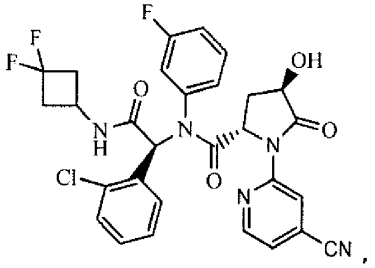

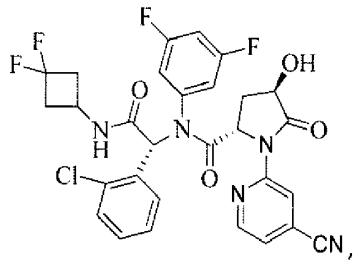

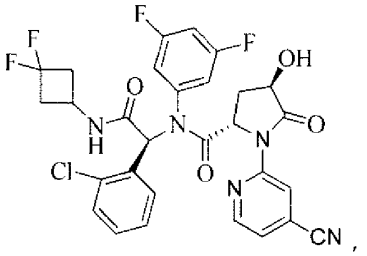

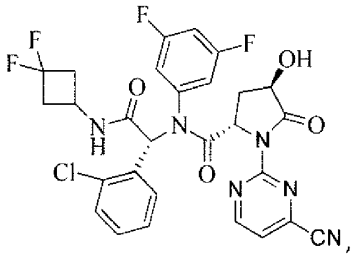

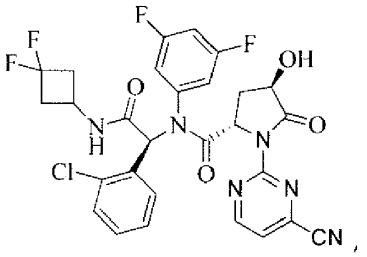

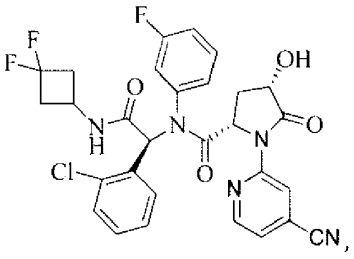

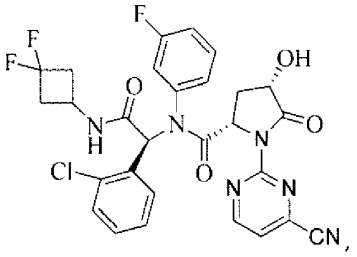

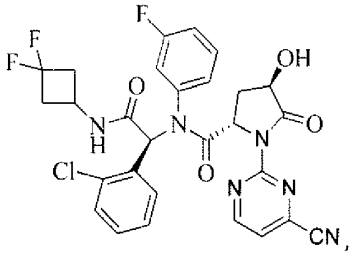

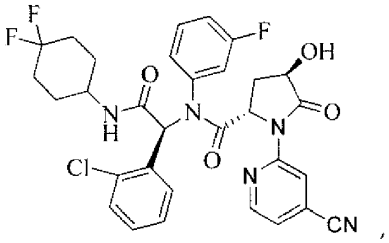

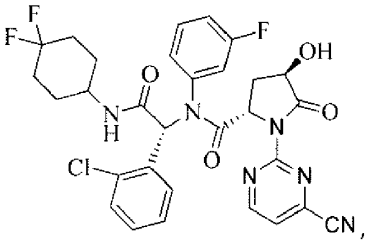

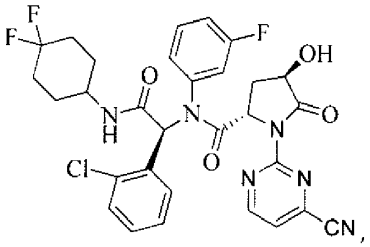

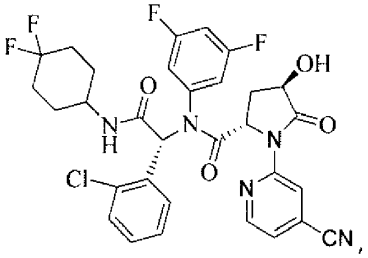

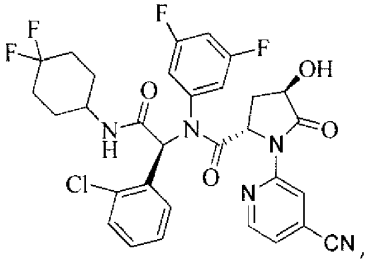

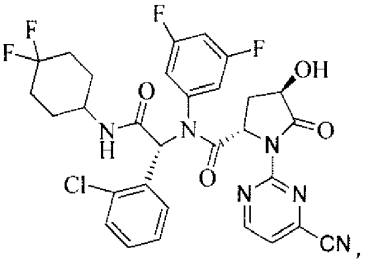

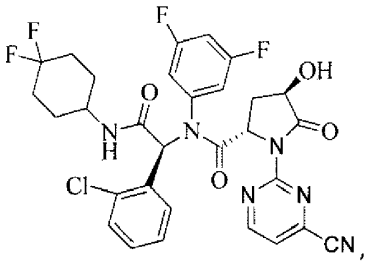

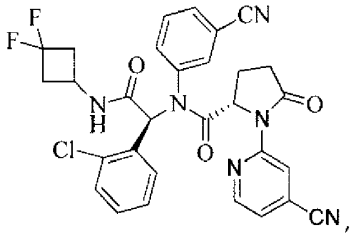

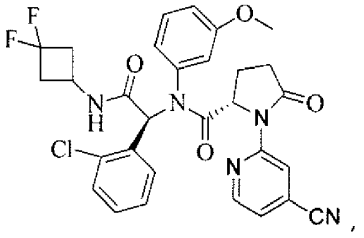

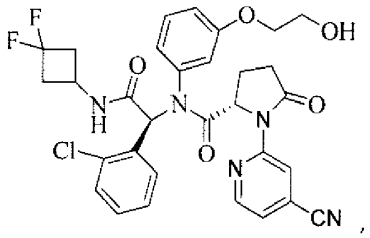

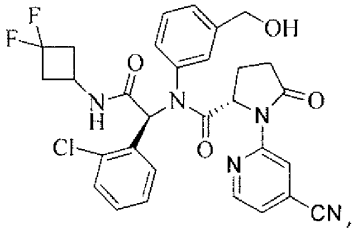

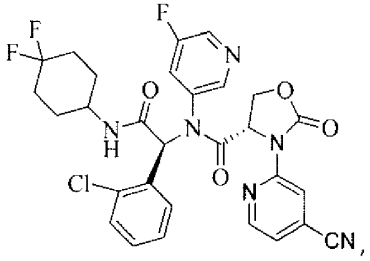

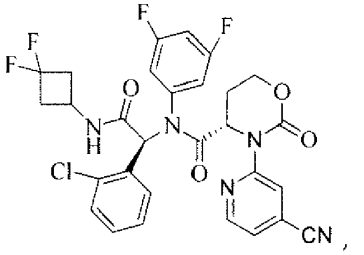

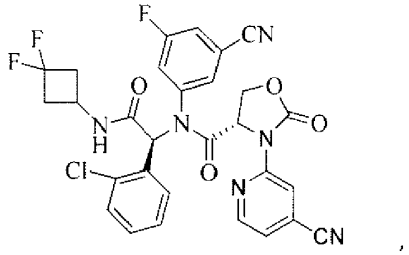

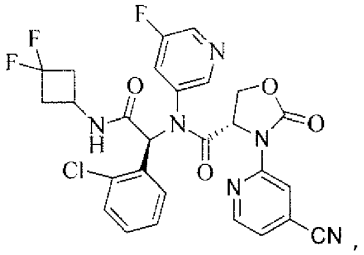

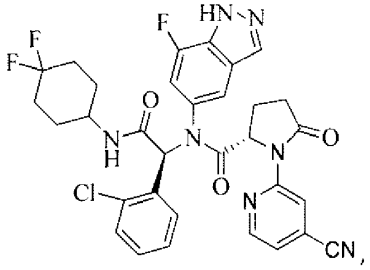

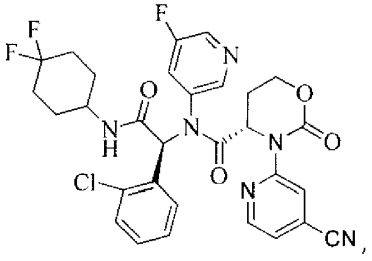

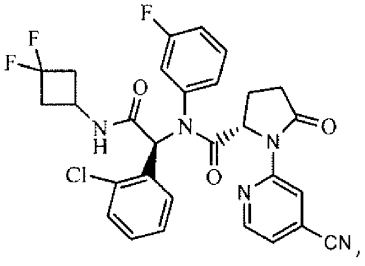

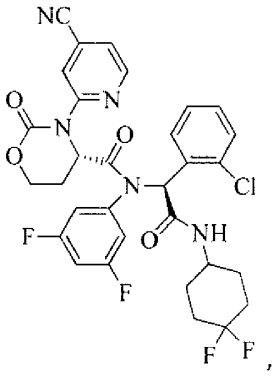

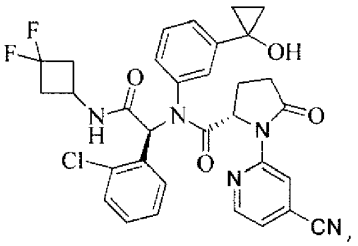

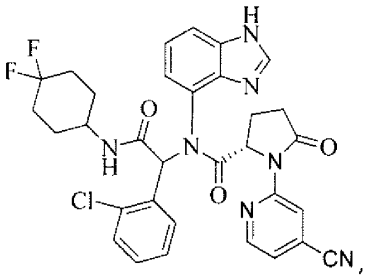

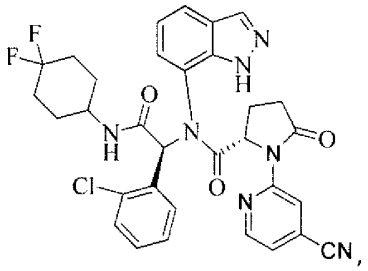

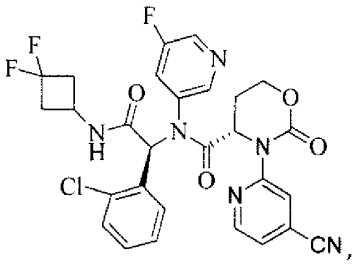

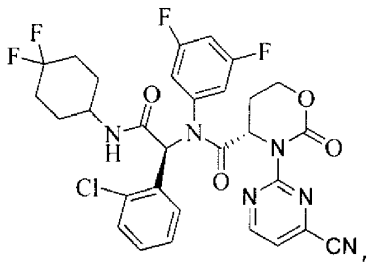

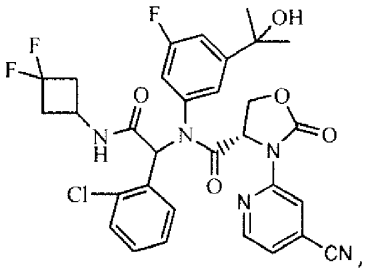

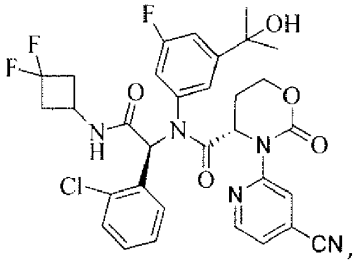

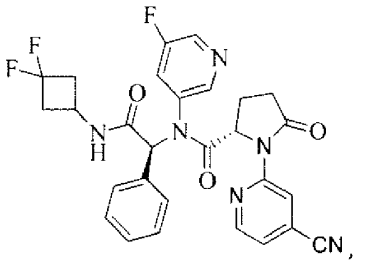

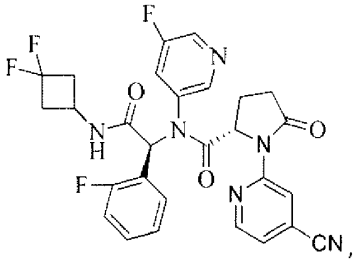

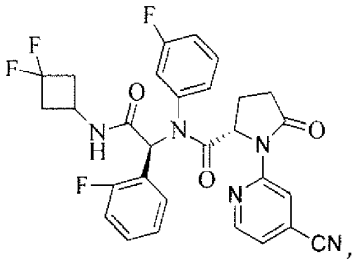

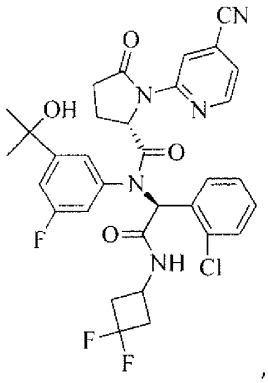

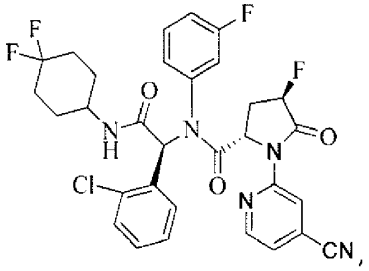

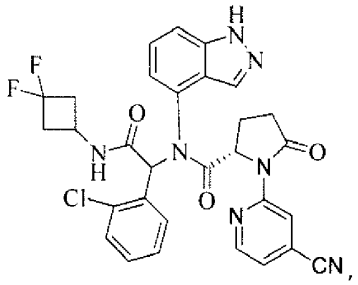

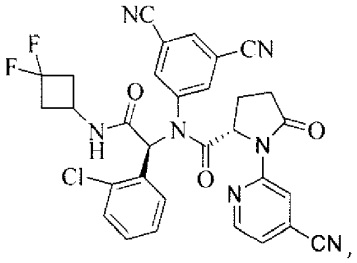

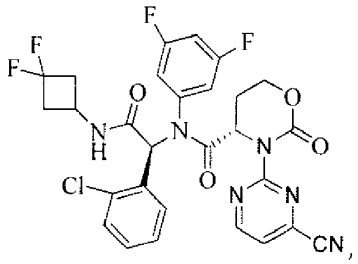

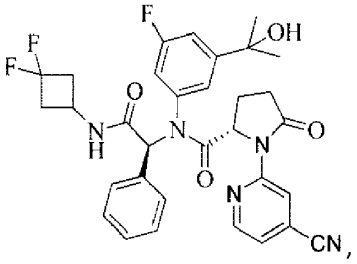

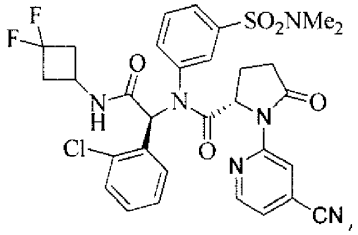

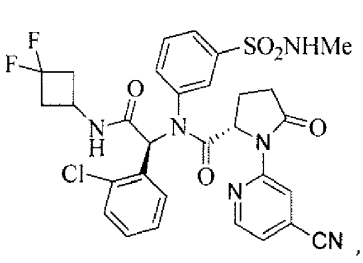

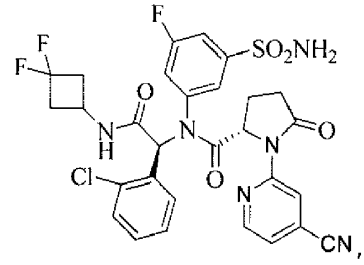

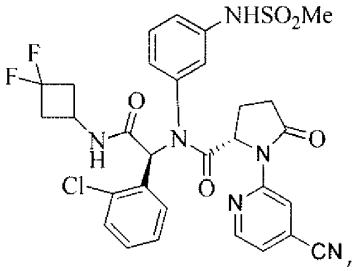

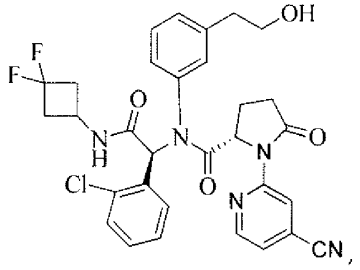

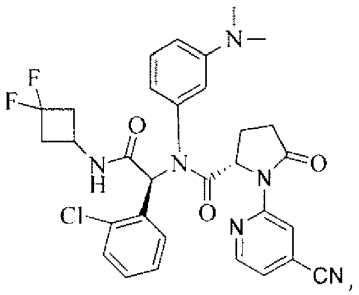

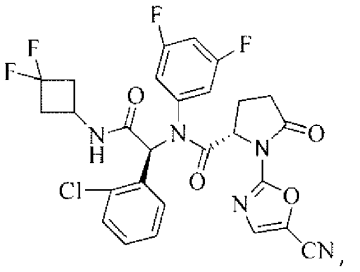

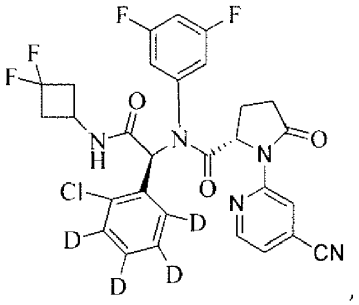

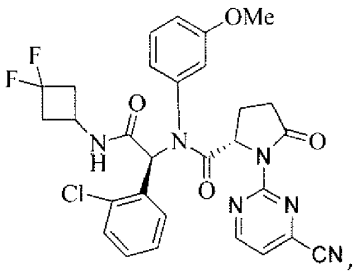

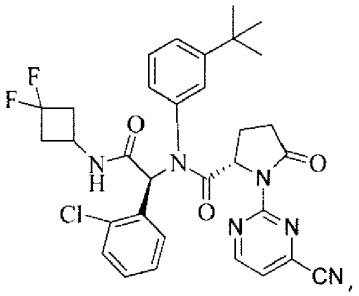

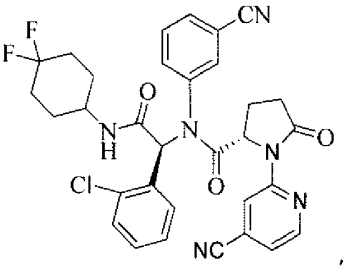

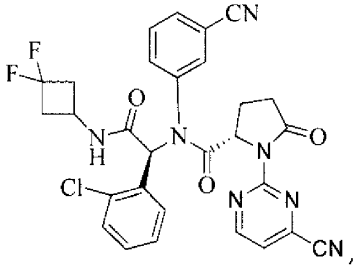

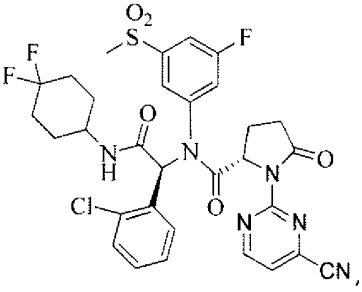

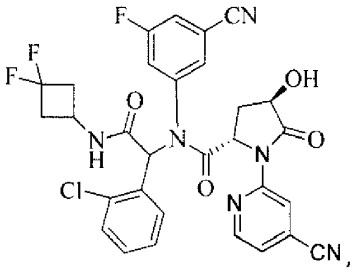

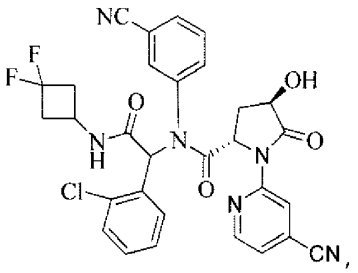

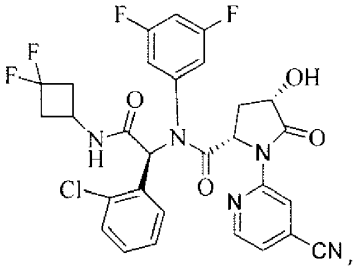

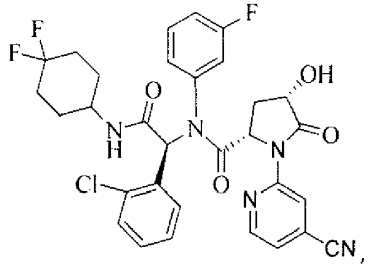

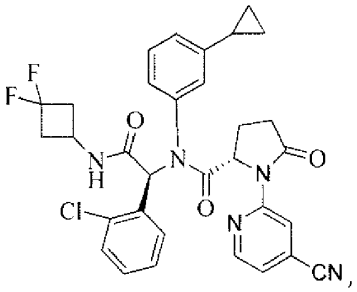

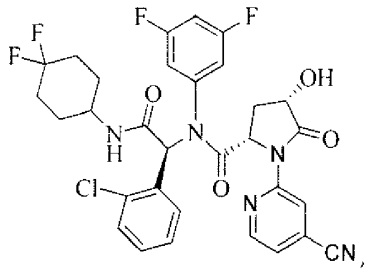

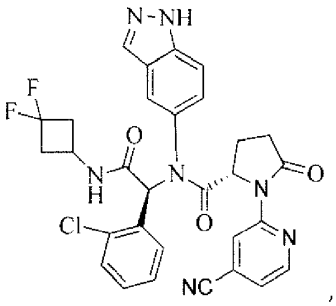

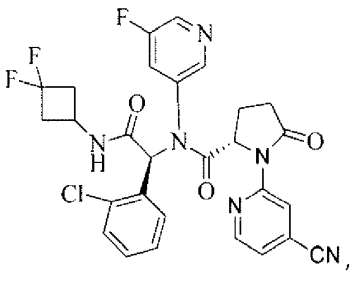

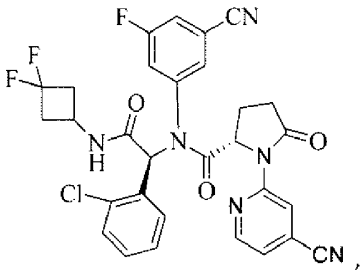

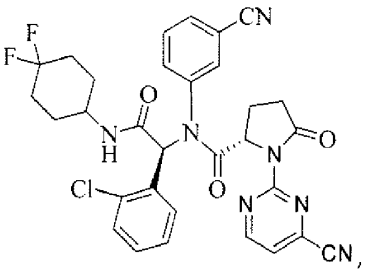

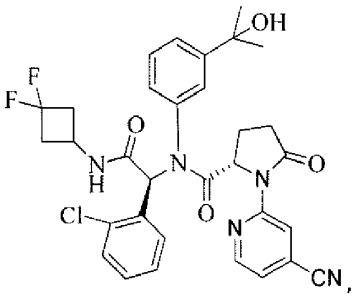

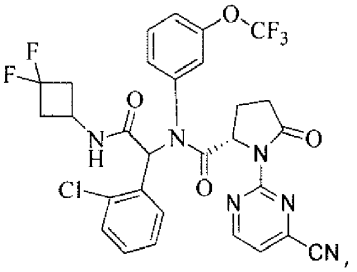

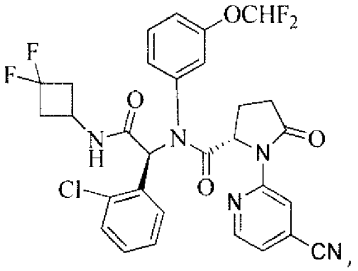

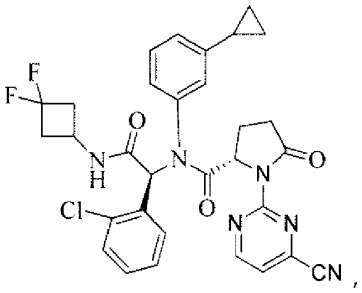

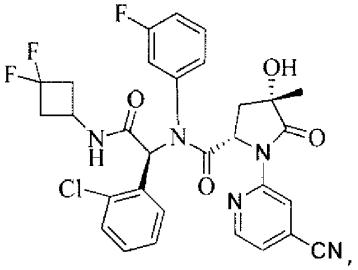

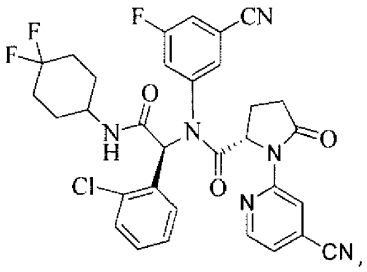

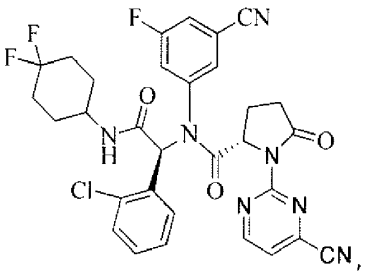

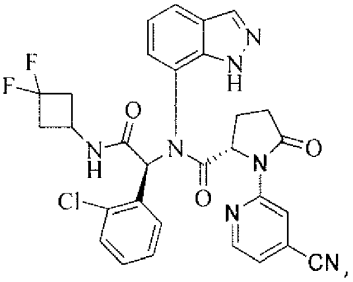

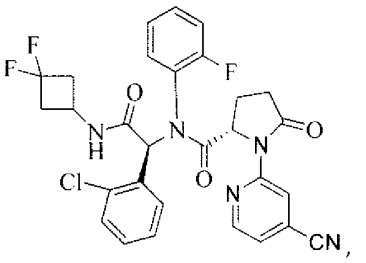

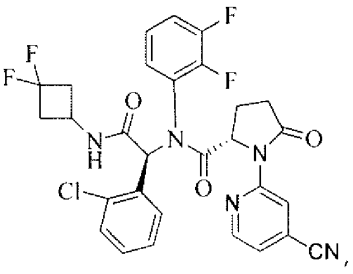

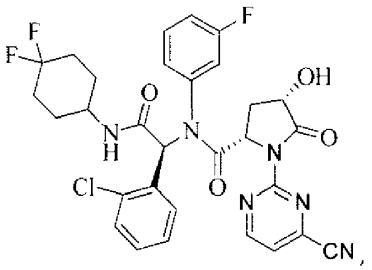

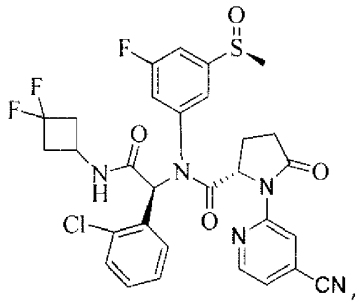

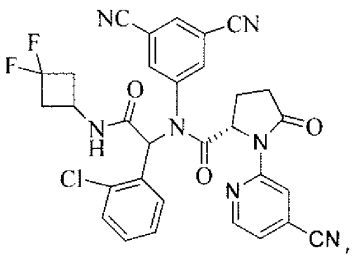

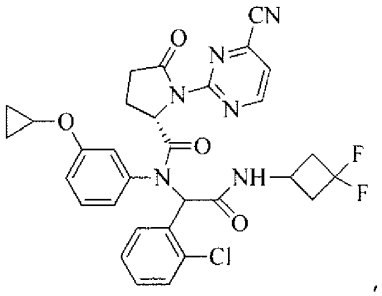

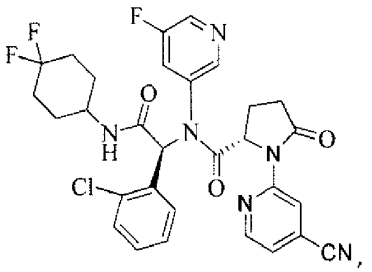

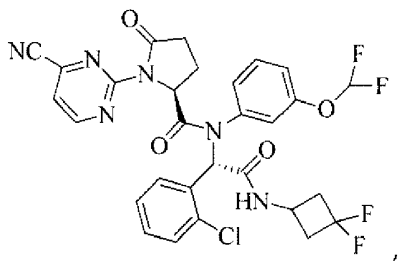

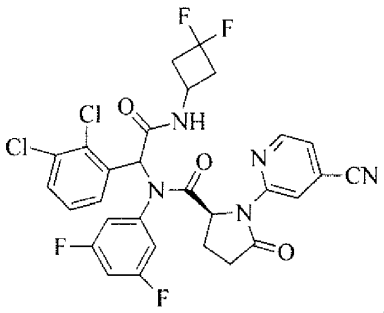

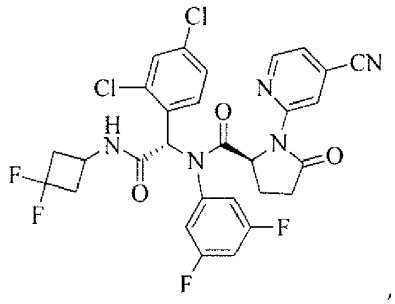

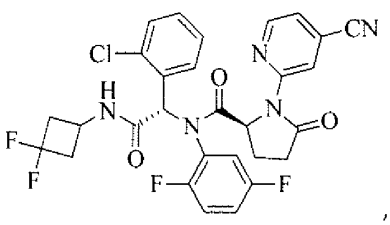

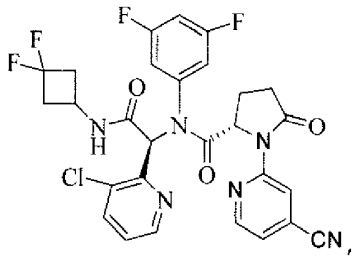

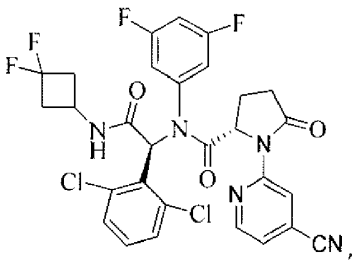

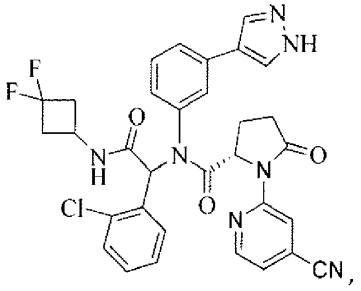

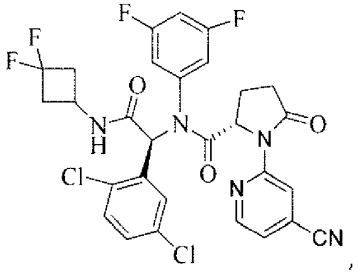

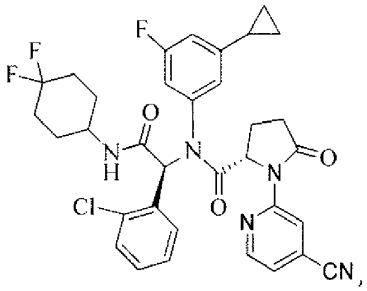

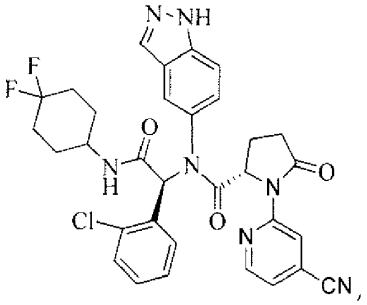

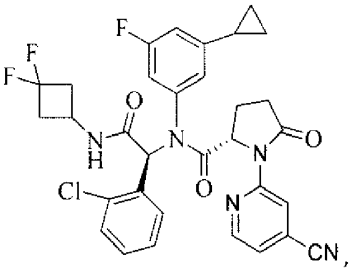

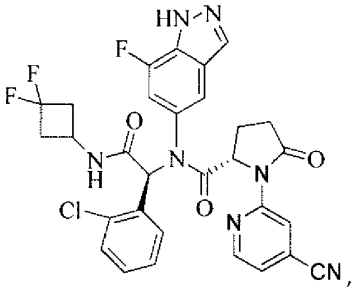

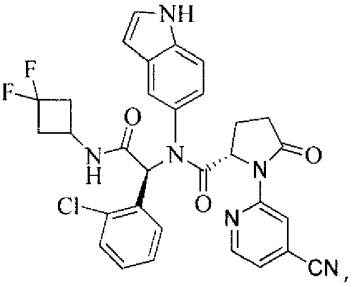

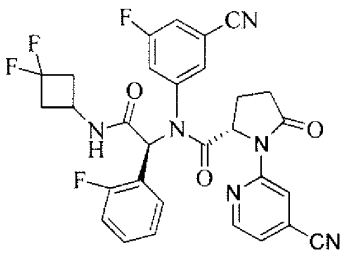

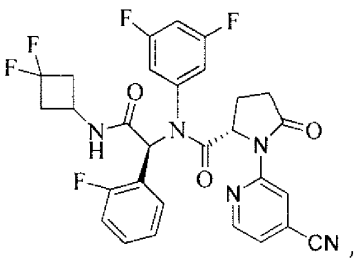

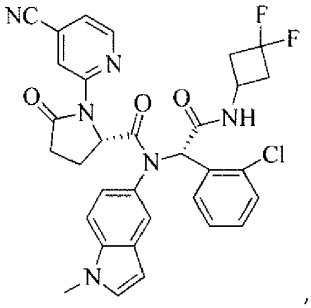

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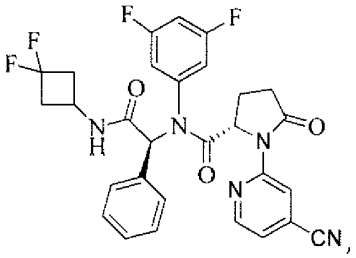

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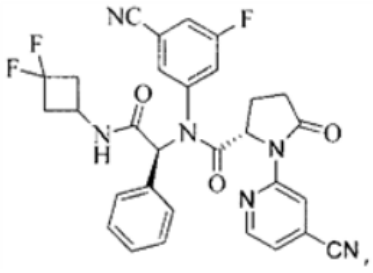

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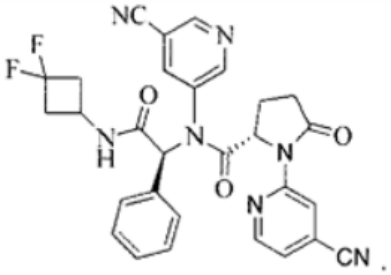

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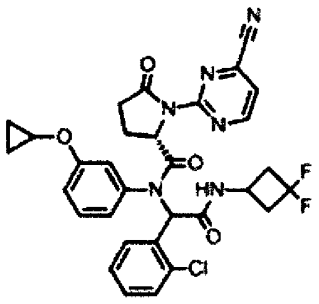
13. Farmasøytisk sammensetning omfattende en forbindelse eller farmasøytisk akseptabelt salt derav ifølge hvilket som helst av kravene 1 til 12; og en farmasøytisk akseptabel bærer, eventuelt ytterligere omfattende et andre terapeutisk middel som er nyttig ved behandling av kreft.

14. Forbindelse med formel I eller farmasøytisk akseptabelt salt derav ifølge krav 1 eller en farmasøytisk sammensetning ifølge krav 13 for anvendelse ved behandling av kreft *karakterisert av* nærværet av en IDH1-mutasjon, hvor IDH1-mutasjonen resulterer i en ny evne for enzymet til å katalysere den NADPH-avhengige reduksjonen av α-ketoglutarat til R(-)-2-hydroksyglutarat.

15. Forbindelsen eller farmasøytisk akseptabelt salt derav eller farmasøytisk sammensetning for anvendelse ifølge krav 14, hvor IDH1-mutasjonen er en IDH1 R132H- eller R132C-mutasjon, eller
hvor kreft er valgt fra hjernesvulst (glioblastom), akutt myelogen leukemi, melanom, ikke-småcellet lungekreft (NSCLC), kolangiokarcinom, kondrosarkom, myelodysplastisk syndrom (MDS), myeloproliferativ neoplasma (MPN) og tykktarmskreft, eventuelt videre omfattende et annet terapeutisk middel som er nyttig ved behandling av kreft.

16. Forbindelse eller farmasøytisk akseptabelt salt derav ifølge krav 12, som er



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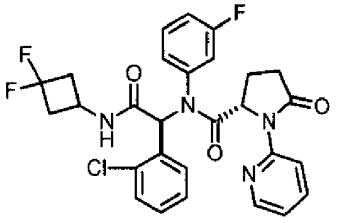
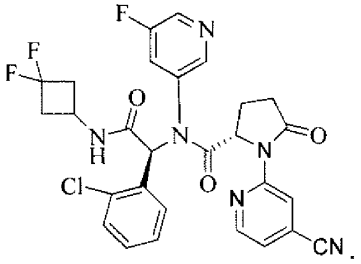
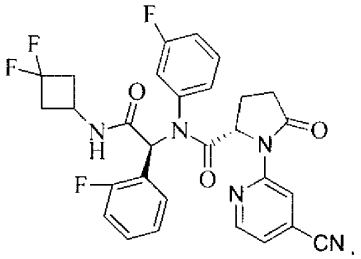
17. Forbindelse eller farmasøytisk akseptabelt salt derav ifølge krav 12, som er



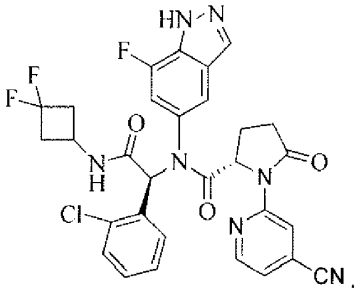
18. Forbindelse eller farmasøytisk akseptabelt salt derav ifølge krav 12, som er



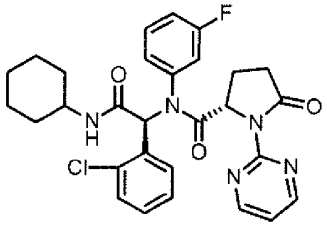
19. Forbindelse eller farmasøytisk akseptabelt salt derav ifølge krav 12, som er



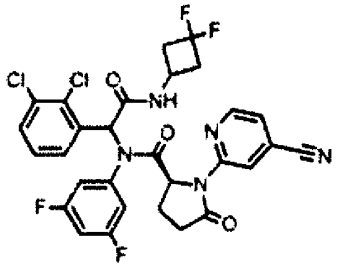
20. Forbindelse eller farmasøytisk akseptabelt salt derav ifølge krav 12, som er



21. Forbindelse eller farmasøytisk akseptabelt salt derav ifølge krav 12, som er



22. Forbindelse eller farmasøytisk akseptabelt salt derav ifølge krav 12, som er



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