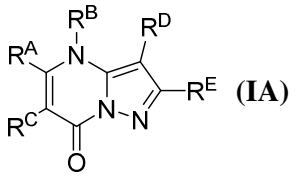
WE CLAIM:

1. A compound according to formula IA or a pharmaceutically acceptable salt thereof:



(IA)

wherein

R^A is selected from the group consisting of H, C_1-C_6-alkyl, C_2-C_6-alkenyl, C_1-C_6-alkoxy, C_3-C_{14}-carbocycle, (C_3-C_{14}-carbocyclo)-C_1-C_6-alkyl-, 3- to 14-membered heterocycle or heterocyclo-C_1-C_6-alkyl- (wherein 1 to 4 heterocycle ring members are heteroatoms selected from N, O, and S), (3- to 14-membered heterocyclo)oxy-, C_6-C_{14}-aryl, (C_6-C_{14}-aryl)-C_1-C_6-alkyl-, C_6-C_{14}-aryloxy-, -$(CH_2)_{0-6}NR^1(CH_2)_{0-6}C(O)R^2$, NR^1R^2, $C(O)NR^1R^2$, $NR^1C(NR^2)NR^1R^2$, $NR^1C(NR^2)(=NR^1)$, SR^1, -CN, and -OH;

wherein each alkyl, alkenyl, alkoxy, aryl, and heterocycle is optionally substituted with one or more of R^1, OR^1, halo, -N=N-R^1, NR^1R^2, -(C_1-C_6-alkyl)NR^1R^2, -$C(O)OR^1$, -$C(O)NR^1R^2$, -$OC(O)R^1$, -CN, -$OP(O)(OR^1)_{1-2}$, or oxo;

R^B is selected from the group consisting of H, C_2-C_6-alkenyl, and C_1-C_6-alkyl, wherein R^B is optionally substituted by one or more of R^1;

R^C, R^D, and R^E are independently selected from the group consisting of C_3-C_{14}-carbocycle, C_6-C_{14}-aryl, and 3- to 14-membered heterocycle (wherein 1 to 4 heterocycle ring members are heteroatoms selected from N, O, and S),

wherein R^C, R^D, and R^E are optionally substituted with one or more of R^1, -OR^1, halo, -NR^1R^2, -(C_1-C_6-alkyl)-NR^1R^2, -$C(O)OR^1$, -$C(O)NR^1R^2$, -NO_2, -CN, or oxo; and

R^1 and R^2 are independently selected from the group consisting of H, D (^{2}H), -CN, -OH, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_2-C_6-alkenyl, C_2-C_6-alkynyl, NH_2, -$S(O)_{0-2}$-(C_1-C_6-alkyl), -$S(O)_{0-2}$-(C_6-C_{14}-aryl), -$C(O)$(C_1-C_6-alkyl), -$C(O)$(C_3-C_{14}-carbocyclo), -C_3-C_{14}-carbocycle, C_6-C_{14}-aryl, and 3- to 14-membered heterocycle or heterocyclo(C_1-C_6-alkyl)- (wherein 1 to 4 heterocycle ring members are heteroatoms selected from N, O, and S),

wherein each alkyl, alkoxy, alkenyl, alkynyl, aryl, carbocycle, and heterocycle moiety of R^1 and R^2 is optionally substituted with one or more of hydroxy, halo,

$-NH_2$, $-NHC(O)(OC_1-C_6\text{-alkyl})$, $-NO_2$, -CN, oxo, $-C(O)OH$, $-C(O)O(C_1-C_6\text{-alkyl})$, $-C_1-C_6\text{-alkyl}(C_1-C_6\text{-alkoxy})$, $-C(O)NH_2$, $C_1-C_6\text{-alkyl}$, $-C(O)C_1-C_6\text{-alkyl}$, $-OC_1-C_6\text{-alkyl}$, $-Si(C_1-C_6\text{-alkyl})_3$, $C_6-C_{14}\text{-aryl}$, $-(C_1-C_6\text{-alkyl})(C_6-C_{14}\text{-aryl})$, 3- to 14-membered heterocycle or heterocyclo(C_1-C_6-alkyl)- (wherein 1 to 4 heterocycle ring members are heteroatoms selected from N, O, and S), or $-O(C_6-C_{14}\text{-aryl})$,

wherein each alkyl, aryl, and heterocyclo in R^1 and R^2 is optionally substituted with one or more of hydroxy, $-OC_1-C_6\text{-alkyl}$, halo, $-NH_2$, $-(C_1-C_6\text{-alkyl})NH_2$, $-C(O)OH$, CN, or oxo;

and wherein the compound according to formula IA is not 4-(3-adamantyl-7-oxo-2-cyclopropyl-5-(4-(trifluoromethyl)phenyl)-4,7- dihydropyrazolo[1,5-a]pyrimidin-6-yl)benzonitrile).

2. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein R^D and R^E are independently selected from C_3-C_{14}-carbocycle, C_6-C_{14}-aryl, and 3- to 14-membered heterocycle (wherein 1 to 4 heterocycle ring members are heteroatoms selected from N, O, and S).

3. The compound according to claim 1 or 2, or a pharmaceutically acceptable salt thereof, wherein R^D and R^E are independently selected from C_3-C_{14}-carbocycle and C_6-C_{14}-aryl.

4. The compound according to any one of claims 1-3, or a pharmaceutically acceptable salt thereof, wherein R^D and R^E are independently selected from C_5-C_7-carbocycle and C_6-C_{10}-aryl.

5. The compound according to any one of claims 1-4, or a pharmaceutically acceptable salt thereof, wherein R^D and R^E are independently selected from cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, and phenyl.

6. The compound according to any one of claims 1-5, or a pharmaceutically acceptable salt thereof, wherein one of R^D and R^E is cyclohexyl or cyclohexenyl and the other is phenyl.

7. The compound according to any one of claims 1-6, or a pharmaceutically acceptable salt thereof, wherein

R^A is selected from the group consisting of C_1-C_6-alkyl, C_2-C_6-alkenyl, C_1-C_6-alkoxy, C_3-C_{14}-carbocycle, (C_3-C_{14}-carbocyclo)-C_1-C_6-alkyl-, 3- to 14-membered heterocycle or heterocyclo(C_1-C_6-alkyl)- (wherein 1 to 4 heterocycle ring members are heteroatoms selected from N, O, and S), C_6-C_{14}-aryl, (C_6-C_{14}-aryl)-C_1-C_6-alkyl-, C_6-C_{14}-aryloxy, $-(CH_2)_{0-6}NR^1(CH_2)_{0-6}C(O)R^2$, NR^1R^2, $NR^1C(NR^2)NR^1R^2$, -CN, and -OH.

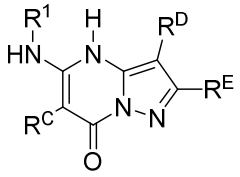
8. The compound according to any one of claims 1-7, or a pharmaceutically acceptable salt thereof, wherein R^A is selected from the group consisting of C_1-C_6-alkyl, $-(CH_2)_{0-6})NR^1(CH_2)_{0-6})C(O)R^2$, NR^1R^2, and $NR^1C(NR^2)NR^1R^2$.

9. The compound according any one of claims 1-8, or a pharmaceutically acceptable salt thereof, wherein R^A is C_1-C_6-alkyl or NR^1R^2.

10. The compound according any one of claims 1-9, or a pharmaceutically acceptable salt thereof, wherein R^A is NR^1R^2.

11. The compound according to claim 10, or a pharmaceutically acceptable salt thereof, wherein R^1 is H.

12. A compound or a pharmaceutically acceptable salt thereof, wherein the compound is one according to formula IB:



(IB)

wherein

R^C is a C_3-C_{14}-carbocycle or a 3- to 14-membered heterocycle (wherein 1 to 4 heterocycle ring members are heteroatoms selected from N, O, and S),

each optionally substituted with one or more of hydroxy, halogen, -NH_2, C_6-C_{14}-aryl, (C_6-C_{14}-aryl)-C_1-C_6-alkyl-, carboxy, -CN, oxo, C_1-C_6-alkyl, C_1-C_6-alkoxy, or -NH(C_1-C_6-alkyl),

wherein the C_1-C_6-alkyl, C_1-C_6-alkoxy, and NH(C_1-C_6-alkyl) are independently and optionally substituted with one or more of hydroxy, halogen, -NH_2, carboxy, -CN, or oxo;

R^D and R^E are independently a C_3-C_{14}-carbocycle or a 3- to 14-membered heterocycle (wherein 1 to 4 heterocycle ring members are heteroatoms selected from N, O, and S),

each optionally substituted with one or more of hydroxy, halogen, -NH_2, C_6-C_{14}-aryl, (C_6-C_{14}-aryl)-C_1-C_6-alkyl-, carboxy, -CN, oxo, C_1-C_6-alkyl, C_1-C_6-alkoxy, or -NH(C_1-C_6-alkyl),

wherein the C_1-C_6-alkyl, C_1-C_6-alkoxy, and NH(C_1-C_6-alkyl) are independently and optionally substituted with one or more of hydroxy, halogen, -NH_2, carboxy, -CN, or oxo; and

R_1 is selected from the group consisting of H, C_1-C_6-alkyl, C_3-C_{14}-carbocycle, and 3- to 14-membered heterocycle (wherein 1 to 4 heterocycle ring members are heteroatoms selected from N, O, and S),

each optionally substituted with one or more of hydroxy, halogen, -NH_2, -NO_2, -CN, oxo, carboxy, -C(O)OC_1-C_6-alkyl, (C_1-C_6-alkyl)OC_1-C_6-alkyl-, -C(O)NH_2, C_1-C_6-alkyl, -C(O)H, C_1-C_6-alkoxy, (C_1-C_6-alkyl)N(H)-aryl-, (C_6-C_{14}-aryl)C_1-C_6-alkyl-, 5- to 7-membered heteroaryl, (5- to 7-membered heteroaryl)-C_1-C_6-alkyl-, C_6-C_{14}-aryloxy, (C_6-C_{14}-aryl)(C_1-C_6-alkoxy)-, (5- to 7-membered heteroaryl)oxy-, or (5- to 7-membered heteroaryl)(C_1-C_6-alkoxy)-,

wherein the C_1-C_6-alkyl, C_1-C_6-alkoxy, (C_1-C_6-alkyl)N(H)-, -C(O)OC_1-C_6-alkyl, (C_1-C_6-alkyl)OC_1-C_6-alkyl-, -C(O)NH_2, C_6-C_{14}-aryl, (C_6-C_{14}-aryl)C_1-C_6-alkyl-, 5- to 7-membered heteroaryl, (5- to 7-membered heteroaryl)-C_1-C_6-alkyl-, C_6-C_{14}-aryloxy, (C_6-C_{14}-aryl)(C_1-C_6-alkoxy)-, (5- to 7-membered heteroaryl)oxy-, and (5- to 7-membered heteroaryl)(C_1-C_6-alkoxy)-, are optionally substituted with one or more of hydroxy, halogen, -NH_2, (C_1-C_6-alkyl)N(H)-, -COOH, -CN, or oxo,

wherein each heteroaryl in R^1 has 1 to 4 heteroaryl ring members that are heteroatoms selected from N, O, and S.

13. The compound according to any one of claims 1-3 or 7-12, or a pharmaceutically acceptable salt thereof, wherein R^D is C_3-C_{14}-carbocycle optionally substituted with one or moreof hydroxy, halogen, -NH_2, -C(O)OH, -CN, oxo, C_1-C_6-alkyl, C_1-C_6-alkoxy, or (C_1-C_6-alkyl)N(H)-, wherein the C_1-C_6-alkyl, C_1-C_6-alkoxy, and (C_1-C_6-alkyl)N(H)- are optionally substituted with one or more of hydroxy, halogen, -NH_2, -C(O)OH, -CN, and oxo.

14. The compound according to any one of claims 1-11, or a pharmaceutically acceptable salt thereof, wherein R^D is phenyl.

15. The compound according any one of claims 1-12, or a pharmaceutically acceptable salt thereof, wherein R^D is cyclohex-1-en-1-yl.

16. The compound according any one of claims 1-3 or 7-12, or a pharmaceutically acceptable salt thereof, wherein R^E is C_3-C_{14}-carbocycle optionally substituted with one or more of hydroxy, halogen, -NH_2, -C(O)OH, -CN, oxo, C_1-C_6-alkyl, C_1-C_6-alkoxy, or (C_1-C_6-alkyl)N(H)-,
wherein the C_1-C_6-alkyl, C_1-C_6-alkoxy, and (C_1-C_6-alkyl)N(H)- are optionally substituted with one or more of hydroxy, halogen, -NH_2, -C(O)OH, -CN, and oxo.

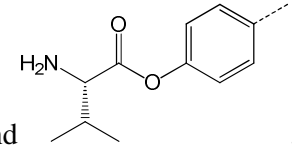
17. The compound according to any one of claims 1-2 or 7-12, or a pharmaceutically acceptable salt thereof, wherein R^E is selected from the group consisting of cyclohex-1-en-1-yl, ($^2H_9$)cyclohex-1-en-1-yl, cyclohexan-1,3-dien-1-yl, 4,4-difluorocyclohex-1-en-1-yl, cyclopent-1-en-1yl, cyclopentyl, pyridin-3-yl, pyridin-2-yl, 4-methoxypyridin-3-yl, pyridin-2-yl, 1H-pyrazol-4-yl, 1H-pyrrol-3-yl, 4,4-difluoropiperidin-1-yl, 5,6-dihydro-2H-pyran-3-yl, 3,6-dihydro-2H-pyran-4-yl, 1H-pyrrol-3-yl, 1H-pyrrol-1-yl, tetrahydrofuran-3-yl, 3,3-difluoropyrrolidin-1-yl, and 3,6-dihydro-2H-pyran-4-yl.

18. The compound according to any one of claims 1-11, or a pharmaceutically acceptable salt thereof, wherein R^E is phenyl.

19. The compound according to claim 18, or a pharmaceutically acceptable salt thereof, wherein R^D is cyclohex-1-en-1-yl.

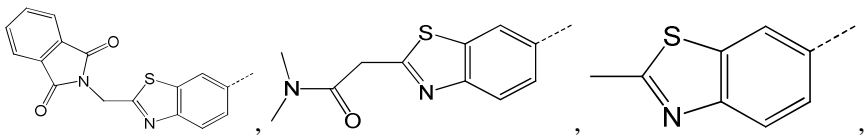
20. The compound according to any one of claims 1-12, or a pharmaceutically acceptable salt thereof, wherein R^C is C_3-C_{14}-carbocycle or 3- to 14-membered heterocycle (wherein 1 to 4 heterocycle ring members are heteroatoms selected from N, O, and S) and that is optionally substituted with one or moreof hydroxy, halogen, -NH_2, -C(O)OH, -CN, oxo, C_1-C_6-alkyl, C_1-C_6-alkoxy, or (C_1-C_6-alkyl)N(H)-,
wherein the C_1-C_6-alkyl, C_1-C_6-alkoxy, and (C_1-C_6-alkyl)N(H)- are optionally substituted with hydroxy, halogen, -NH_2, -C(O)OH, -CN and oxo.

21. The compound according to any one of claims 1-11, or a pharmaceutically acceptable salt thereof, wherein R^C is selected from the group consisting of 4-hydroxyphenyl, 4-chlorophenyl, 4-fluorophenyl, 4-methoxyphenyl, 4-ethoxyphenyl, 4-trifluoromethoxyphenyl, 4-hydroxy-2-methylphenyl, 4-hydroxy-2-methoxyphenyl,3,4-dihydroxyphenyl, 4-(2,2,2-trifluoroethoxy)phenyl, 4-(2-(dimethylamino)ethoxy)phenyl, 3-fluoro-4-hydroxyphenyl, 3-fluoro-4-methoxyphenyl, 2-chloro-4-hydroxyphenyl, 2-fluoro-4-methoxyphenyl, 3-amino-4-hydroxyphenyl, 3-amino-4-fluorophenyl, 3-(N,N-dimethylaminoethoxy)-4-hydroxyphenyl, 3-chloro-2-hydroxyphenyl, 3-hydroxyethoxy-4-hydroxyphenyl,

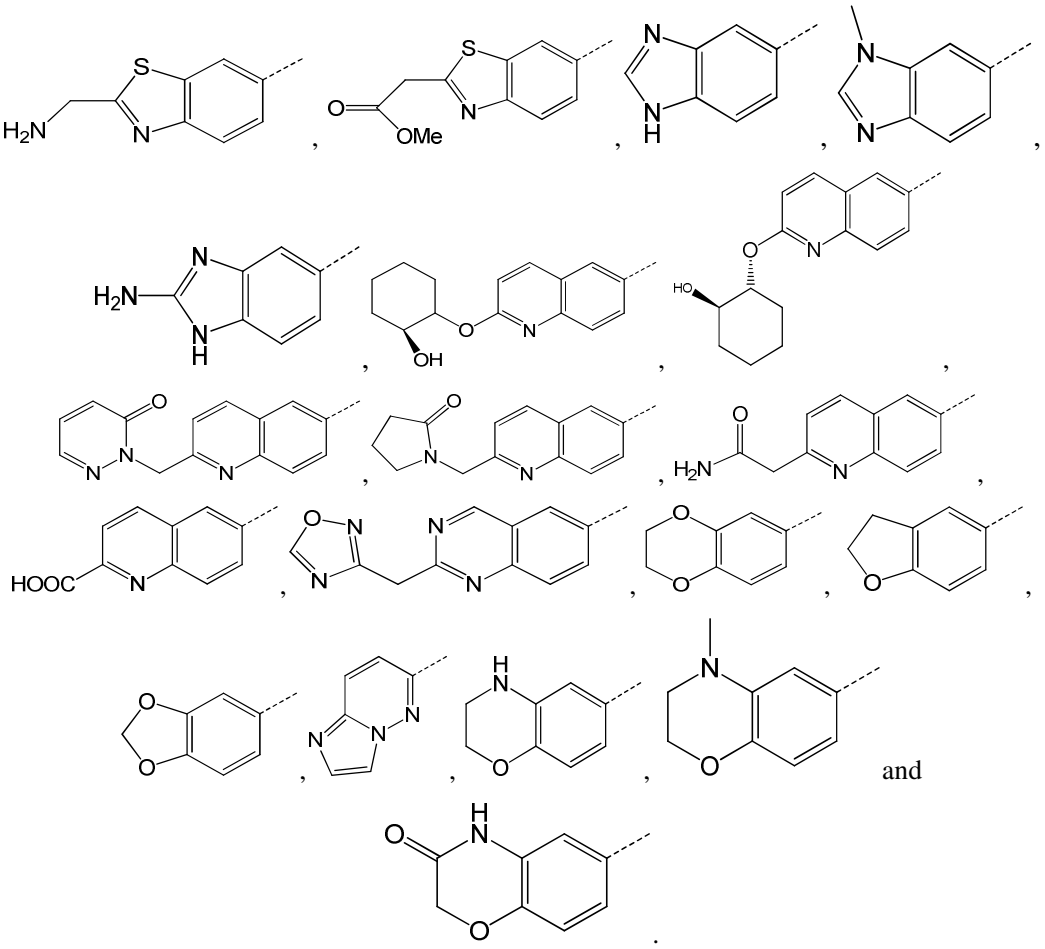


and .

22. The compound according to any one of claims 1-12, or a pharmaceutically acceptable salt thereof, wherein R^C is selected from the group consisting of 6-methoxypyridin-3-yl, 2-methoxypyridin-4-yl, 1H-pyrazol-4-yl, quinolin-6-yl, 2-methylquinolin-6-yl, 2-methoxyquinolin-6-yl, 2-hydroxymethylquinolin-6-yl, 3-hydroxy-2-methylquinolin-6-yl, 2-aminoquniazolin-6-yl,4-aminoquinazolin-6-yl, cinnolin-6-yl, quinoxalin-6-yl, 2-chloroquinoxalin-6-yl, 3-chloroquinoxalin-6-yl, 3-aminoquinoxalin-6-yl, 3-hydroxyquinoxalin-6-yl,3-methoxyquinoxalin-6-yl, 1,8-naphthyridin-3-yl, imidazo[1,2-a]pyridin-6-yl,



,



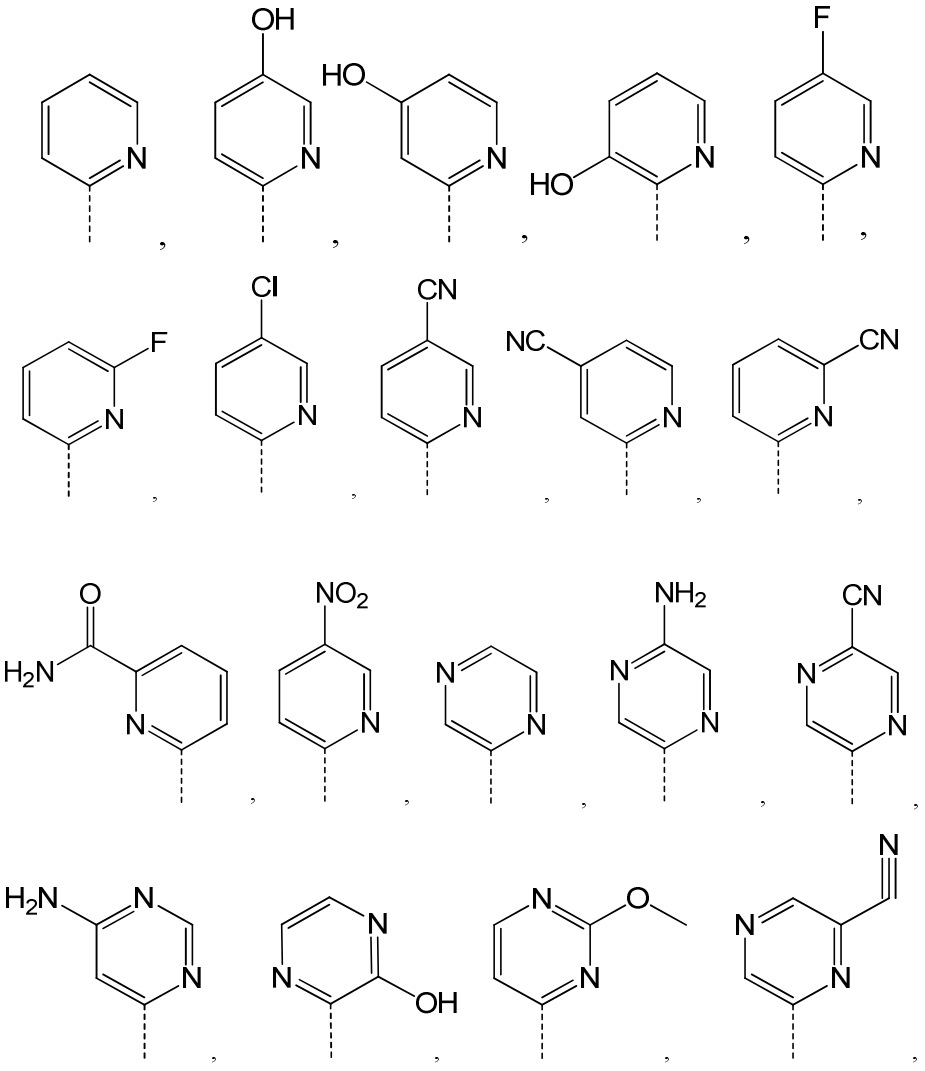
23. The compound according any one of claims 1-11, or a pharmaceutically acceptable salt thereof, wherein R^C is 4-methoxyphenyl.

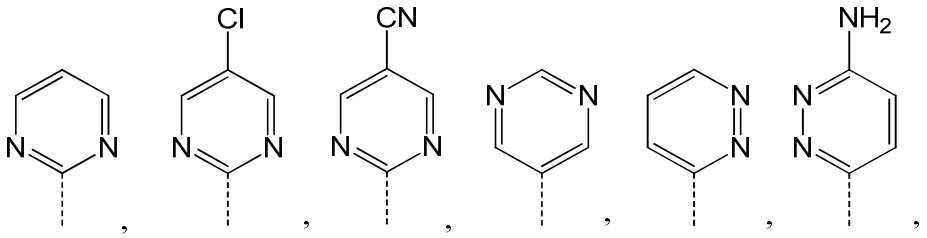
24. The compound according any one of claims 1-10 or 12, or a pharmaceutically acceptable salt thereof, wherein R^1 is a 3- to 14-membered heterocycle optionally substituted with one or more of hydroxy, halogen, -NH_2, -NO_2, -C(O)OH, -C(O)OC_1-C_6-alkyl, (C_1-C_6-alkyl)N(H)C(O)-, -CN, oxo, C_1-C_6-alkyl, -C(O)H, C_1-C_6-alkoxy, or (C_1-C_6-alkyl)N(H)-,

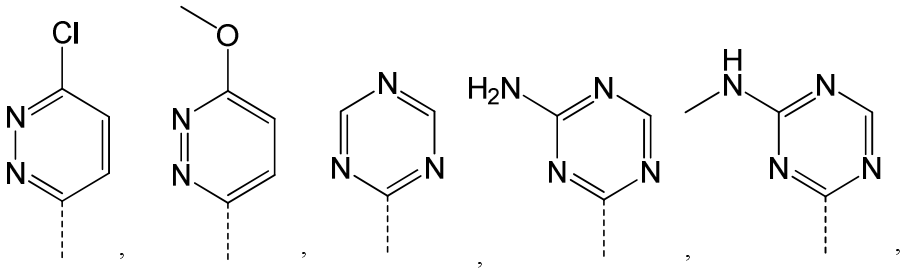
wherein the C_1-C_6-alkyl, C_1-C_6-alkoxy, and (C_1-C_6-alkyl)N(H)-, C(O)OC_1-C_6-alkyl, and (C_1-C_6-alkyl)N(H)C(O)- are optionally substituted with one or more of hydroxy, halogen, -NH_2, (C_1-C_6-alkyl)N(H)-, -C(O)H, -CN, and oxo.

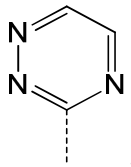
25. The compound according any one of claims 1-12, or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from the group consisting of pyridin-2-yl, pyrazin-2-yl, pyrimidin-2-yl, pyrimidin-4-yl, pyrimidin-5-yl, pyridazin-3-yl, 1,3,5-triazin-2-yl, 1,2,4-triazin-3-yl, each of which is optionally substituted with one or more of F, Cl, CN, OH, $-NO_2$, $-NH_2$, -NHMe, $-C(O)NH_2$, and methoxy.

26. The compound according any one of claims 1-10 or 12, or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from the group consisting of:



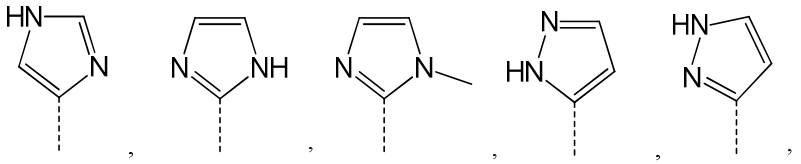


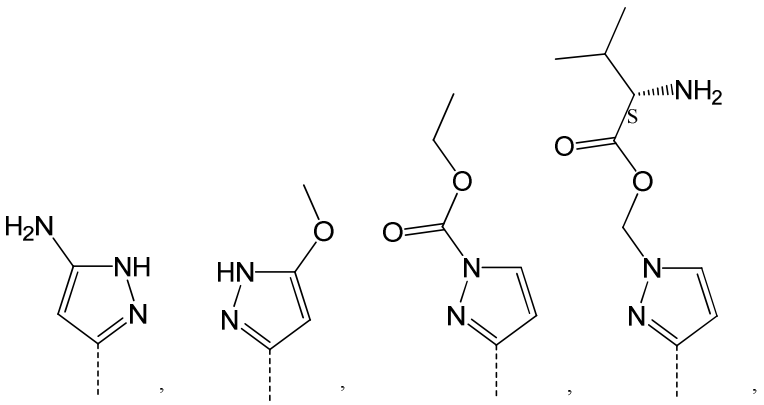


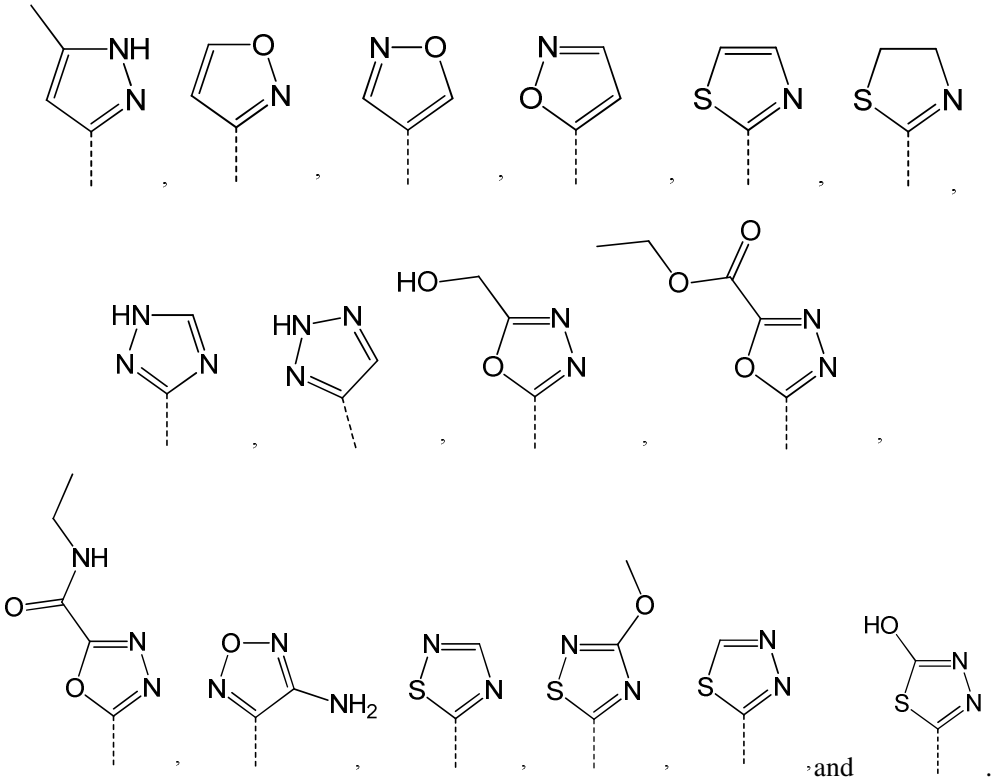


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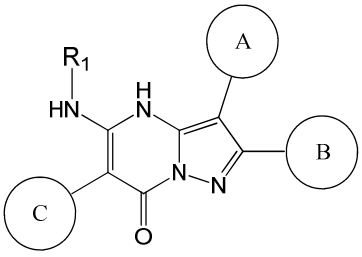
27. The compound according any one of claims 1-10 or 12, or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from the group consisting of:







28. A compound of formula (I) or a pharmaceutically acceptable salt thereof:



(I)

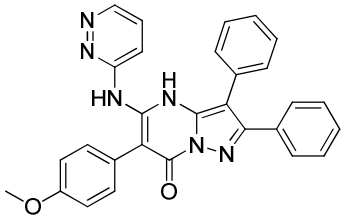
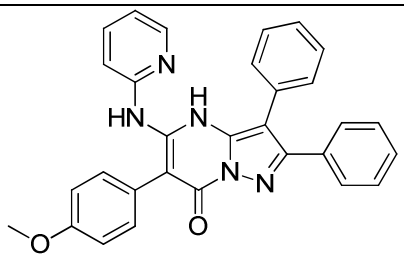
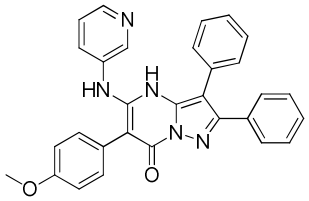
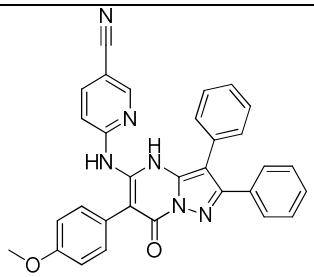
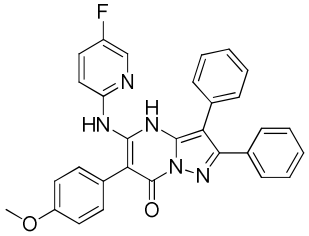
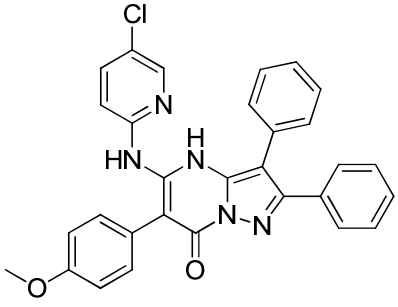
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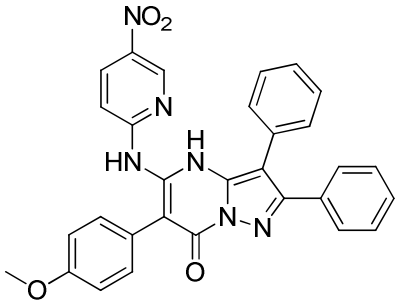
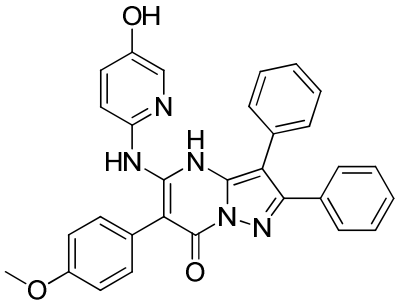
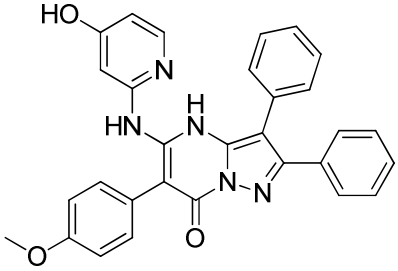
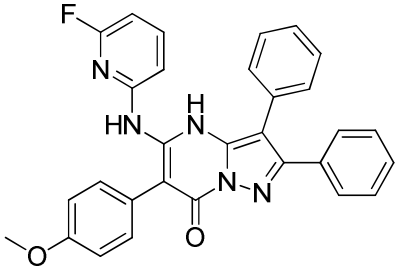
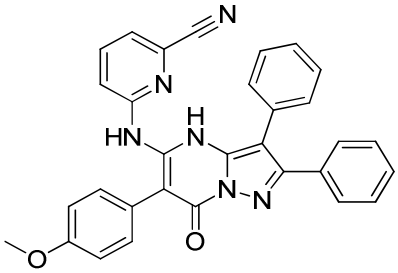
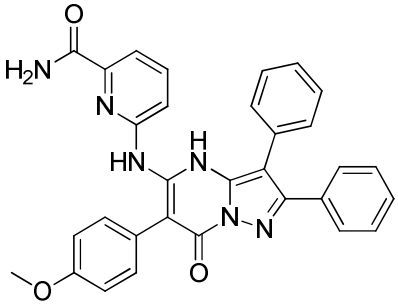
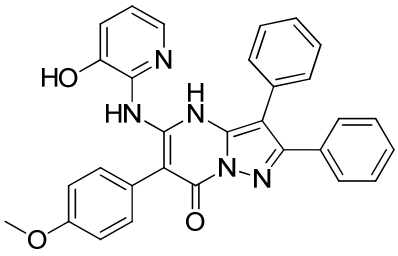
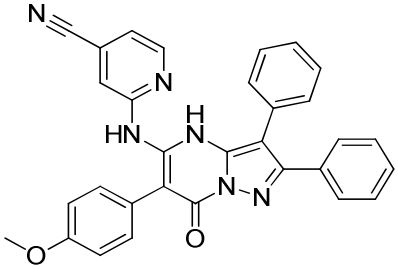
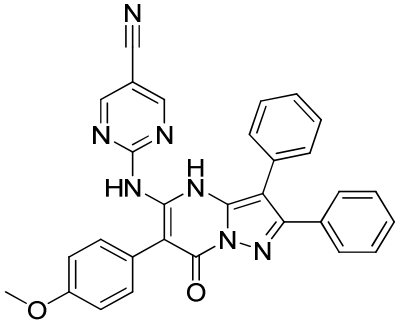
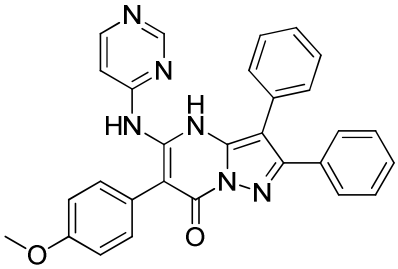
ring A and ring B are independently a carbocycle or a heterocycle each optionally substituted with one or more substituents selected from the group consisting of hydroxy, halogen, amino, carboxy, CN, oxo, alkyl, alkoxy and alkylamino wherein said alkyl, alkoxy and alkylamino are optionally substituted with hydroxy, halogen, amino, carboxy, CN and oxo;

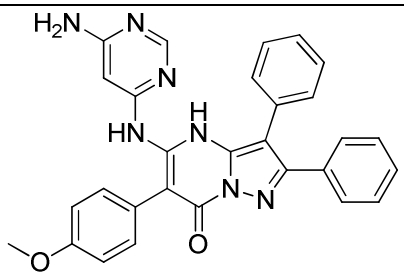
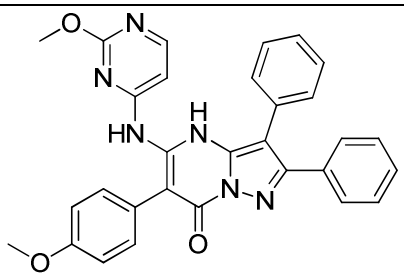
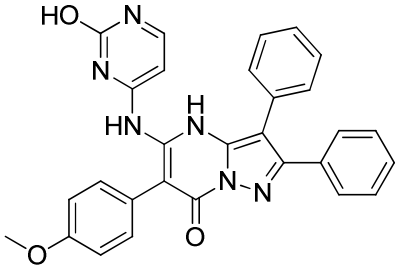
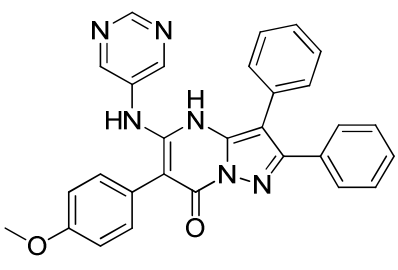
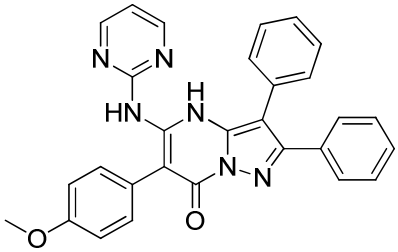
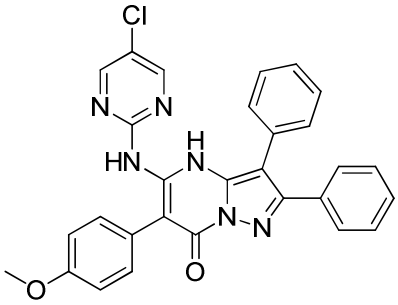
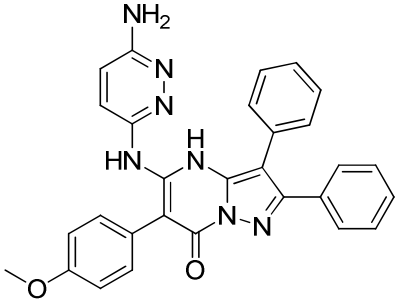
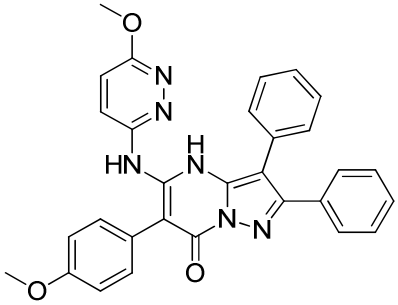
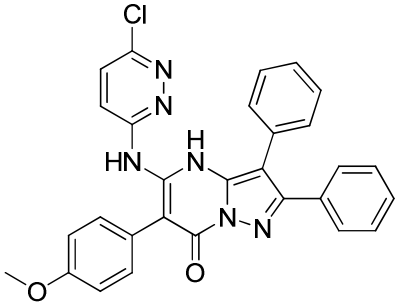
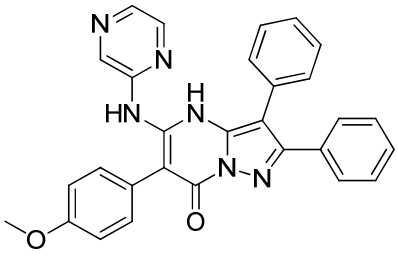
ring C is a carbocycle or a heterocycle each optionally substituted with one or more substituents selected from the group consisting of hydroxy, halogen, amino, carboxy, CN, oxo, alkyl, alkoxy and alkylamino wherein said alkyl, alkoxy and alkylamino are optionally substituted with hydroxy, halogen, amino, carboxy, CN and oxo; and

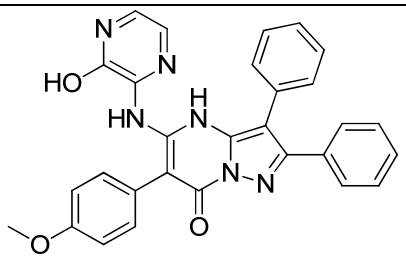
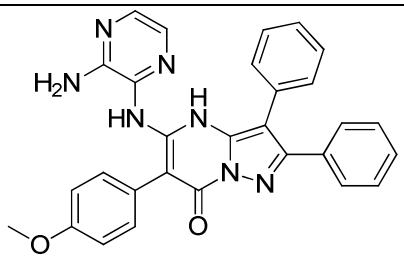
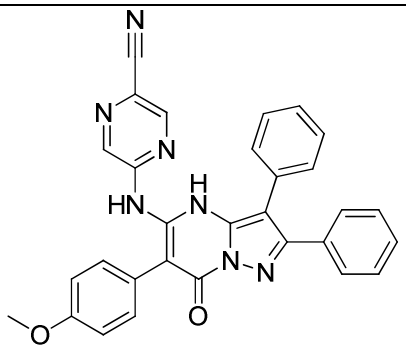
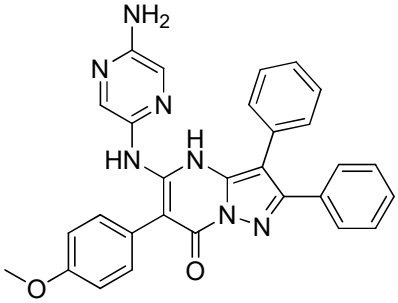
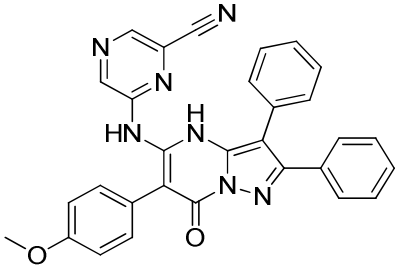
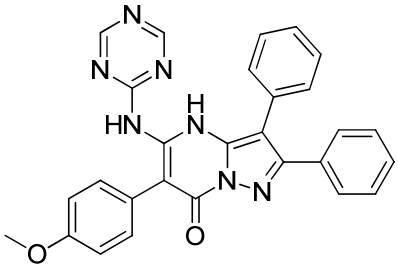
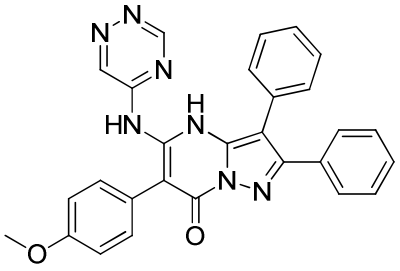
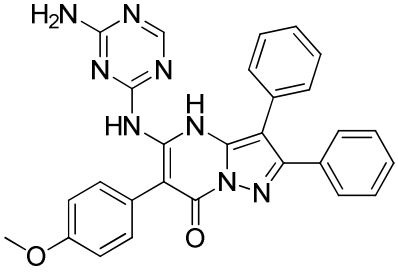
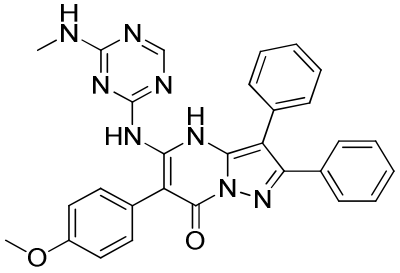
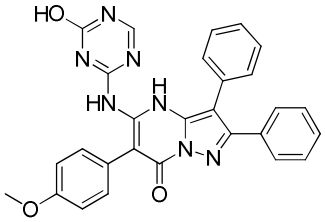
R_1 is H or alkyl, a carbocycle or a heterocycle each optionally substituted with one or more substituents selected from the group consisting of hydroxy, halogen, amino, NO_2, CN, oxo, carboxy, alkoxycarbonyl, alkoxyalkyl, aminocarbonyl, alkyl, acyl, alkoxy, alkylamino aryl, aralkyl, heteroaryl, heteroaralkyl, aryloxy, aralkoxy, heteroaryloxy and heteroaralkoxy wherein said alkyl, alkoxy, alkylamino, alkoxycarbonyl, alkoxyalkyl, aminocarbonyl, aryl, aralkyl, heteroaryl, heteroaralkyl, aryloxy, aralkoxy, heteroaryloxy and heteroaralkoxy are optionally substituted with hydroxy, halogen, amino, alkylamino, carboxy, CN or oxo.

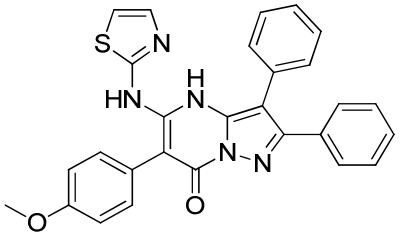
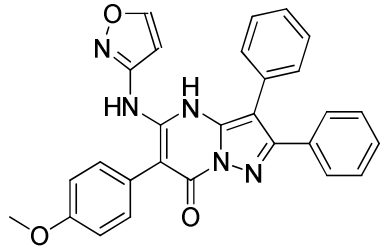
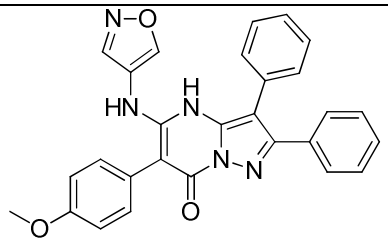
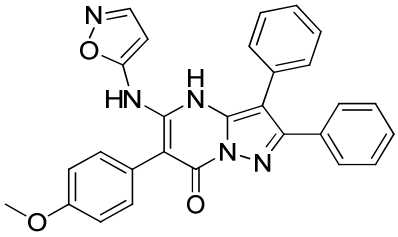
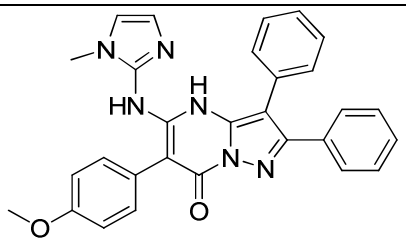
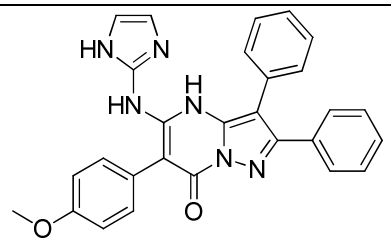
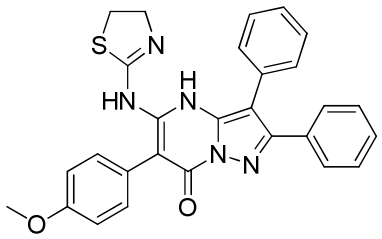
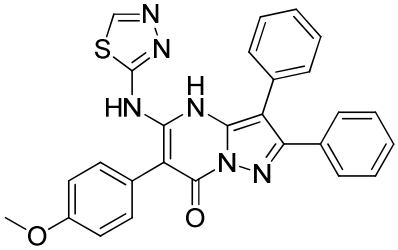
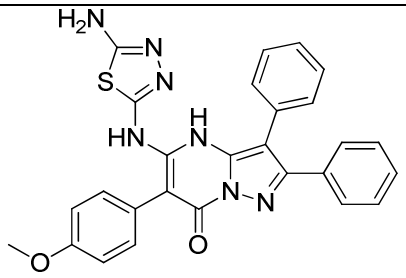
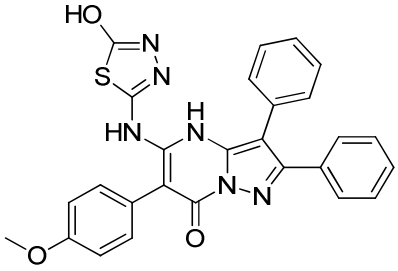
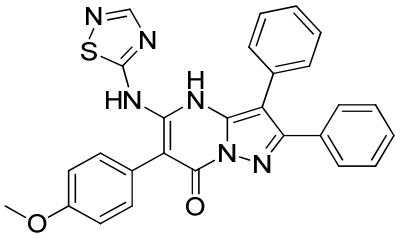
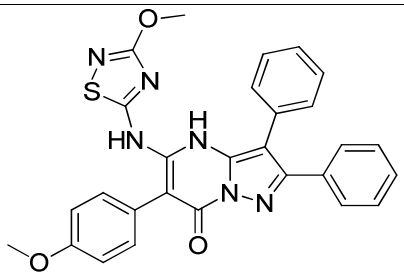
29. A compound according to claim 1 or claim 28, or a pharmaceutically acceptable salt thereof, that is selected from the following table:

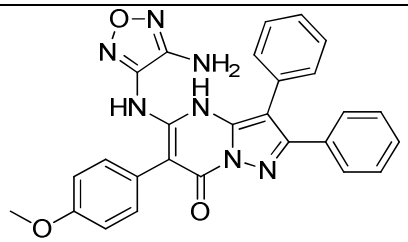
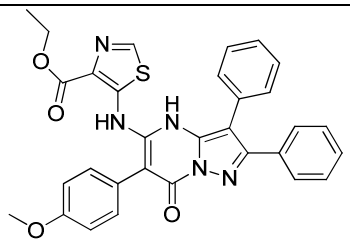
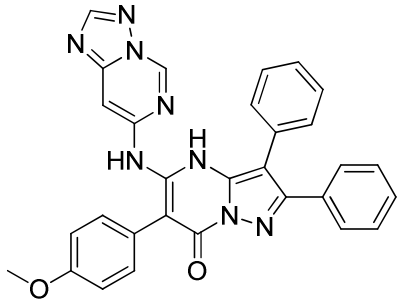
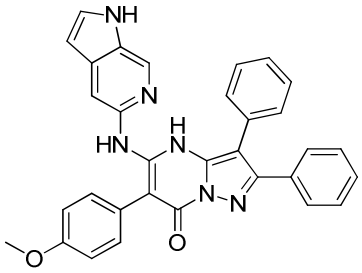
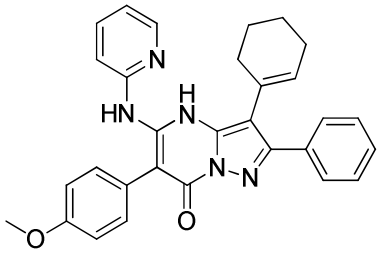
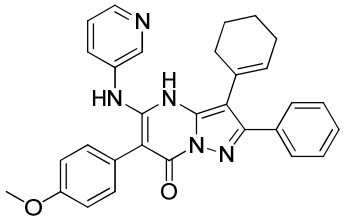
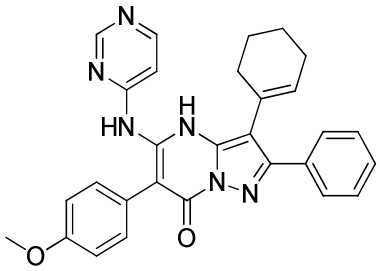
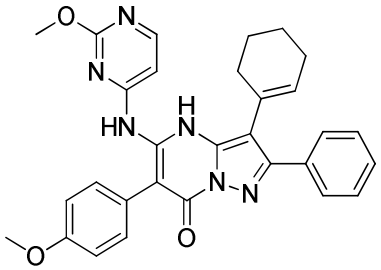
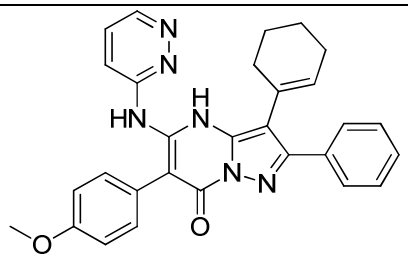
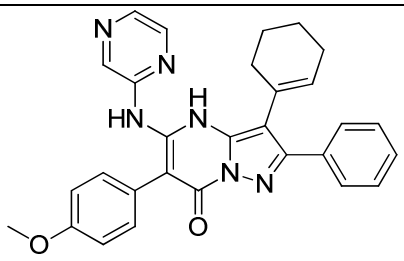
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103		**104**	
105		**106**	

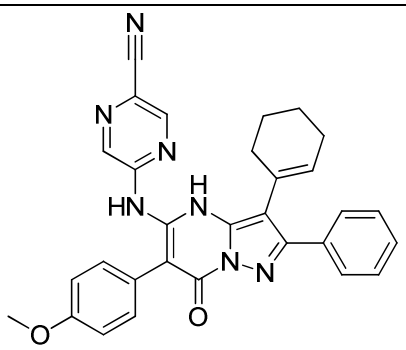
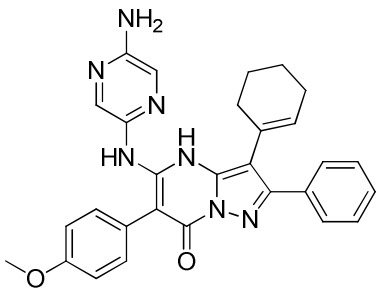
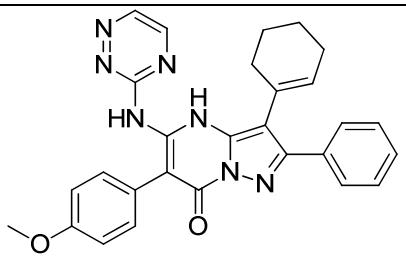
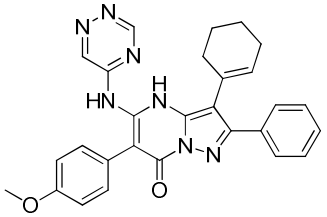
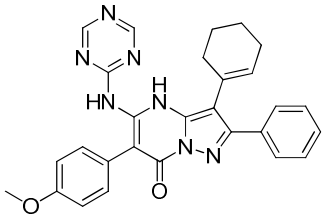
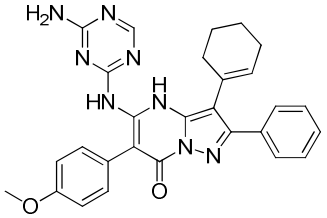
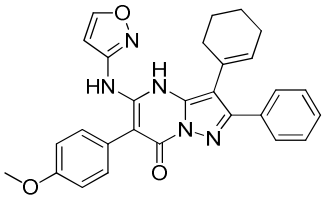
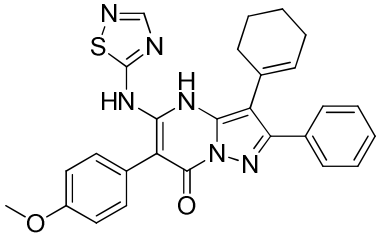
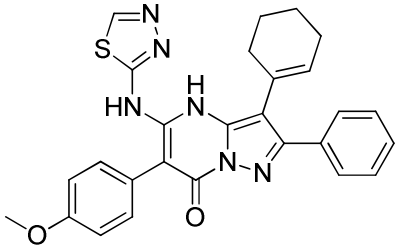
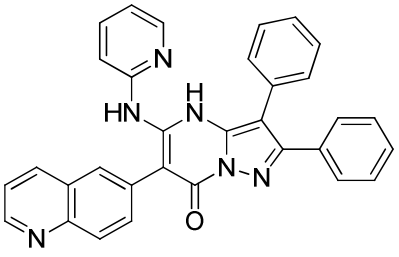
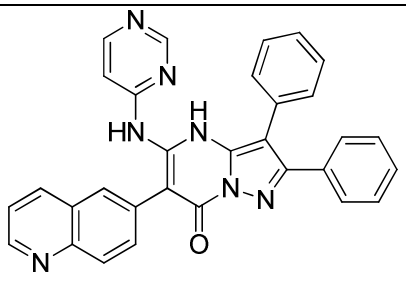
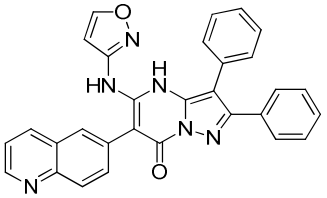
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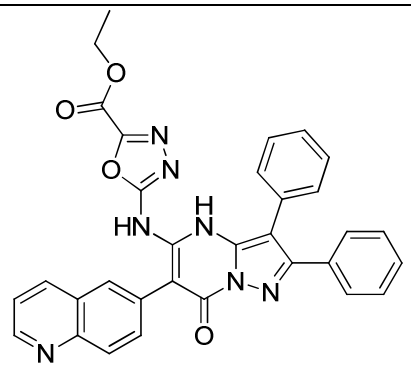
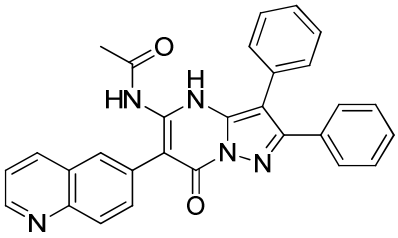
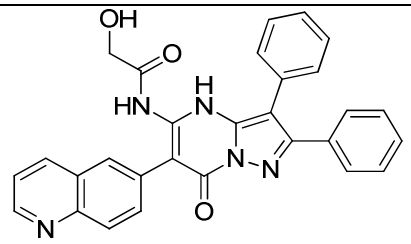
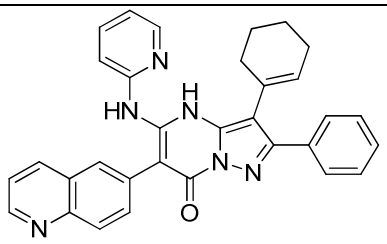
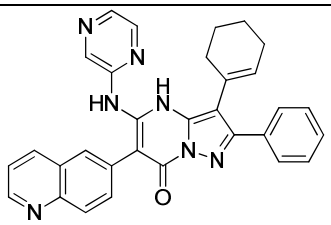
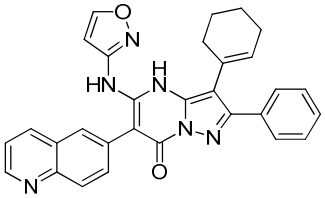
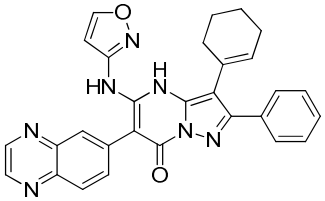
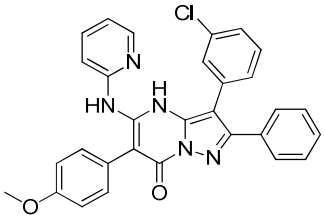
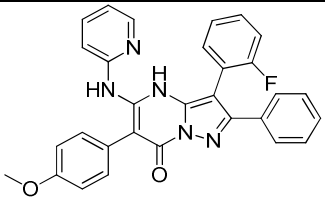
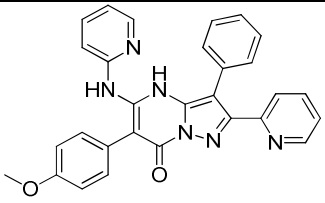
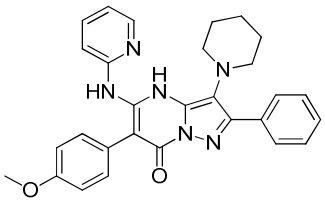
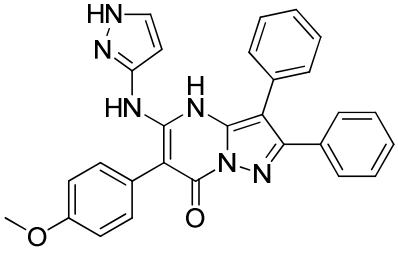
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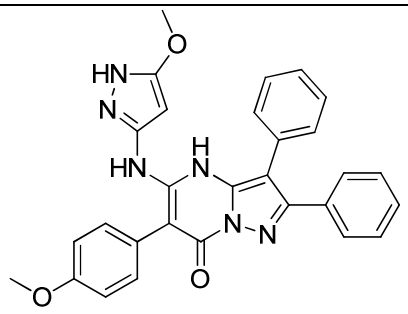
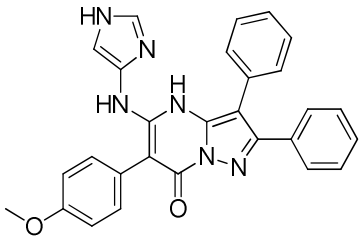
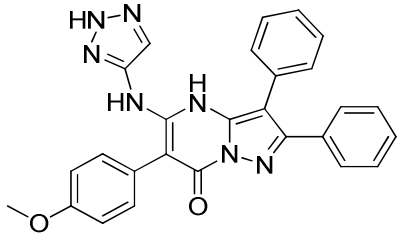
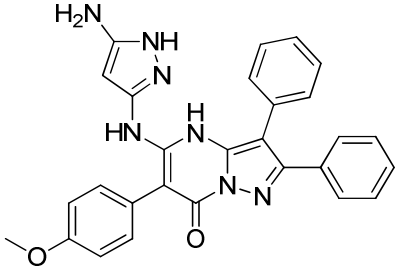
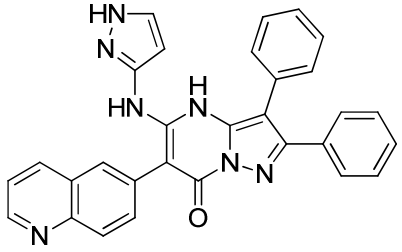
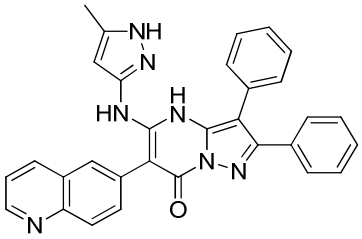
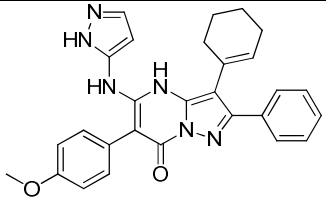
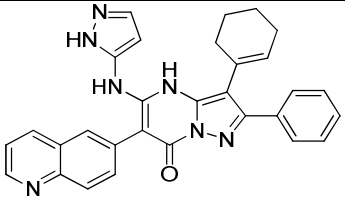
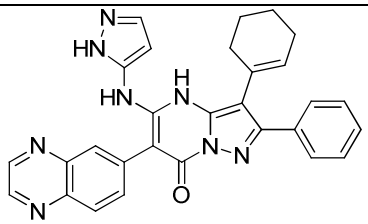
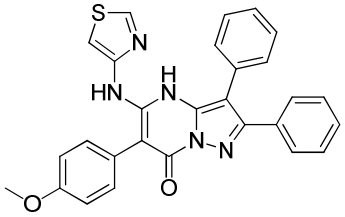
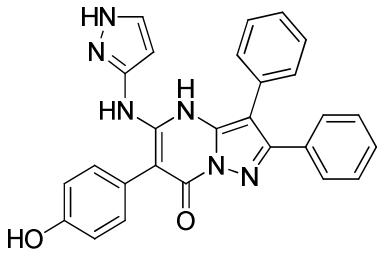
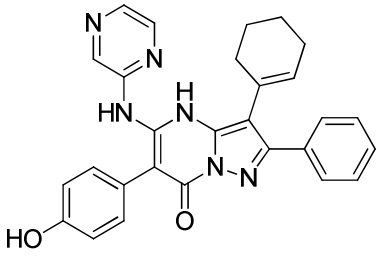
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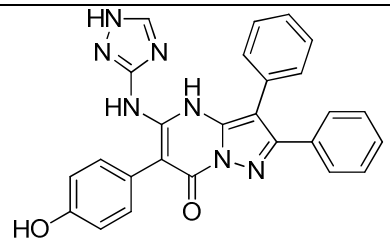
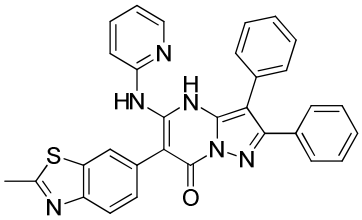
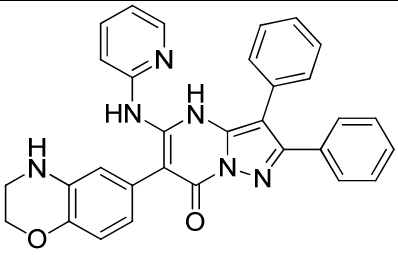
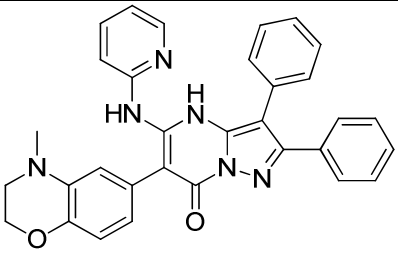
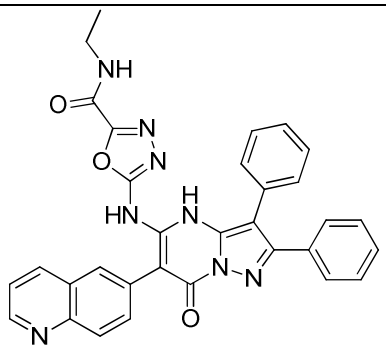
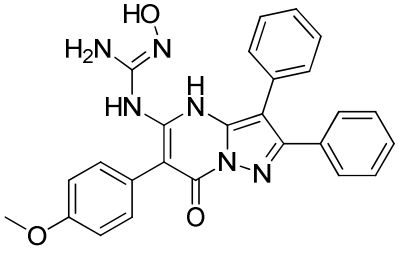
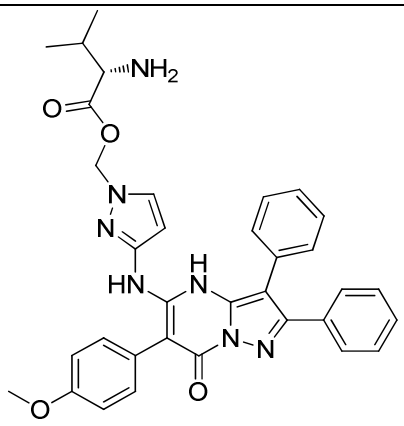
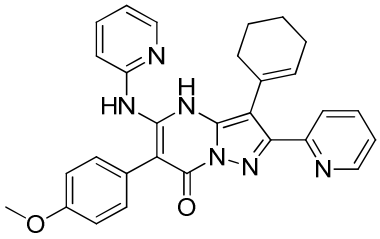
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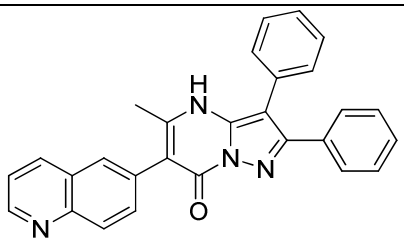
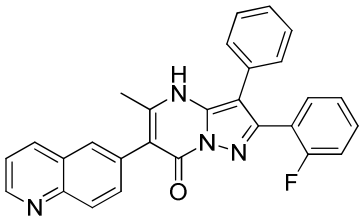
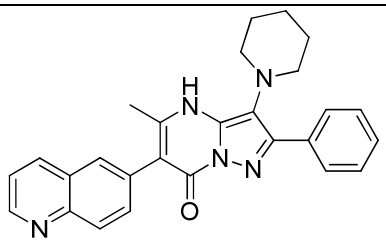
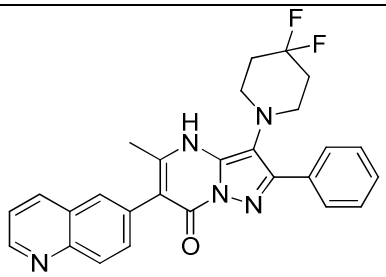
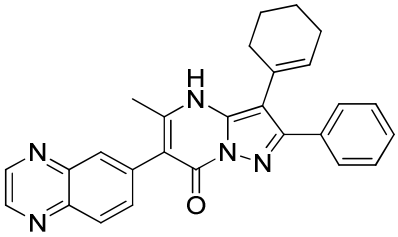
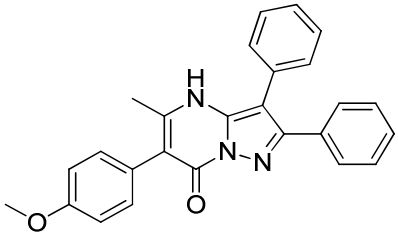
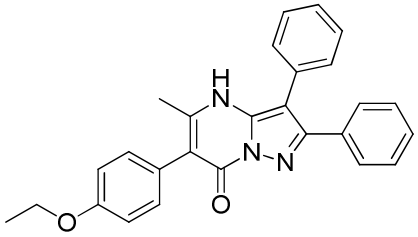
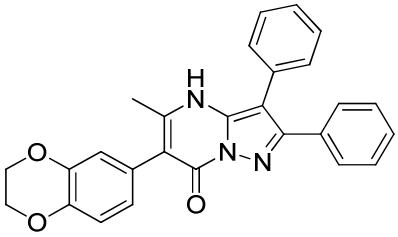
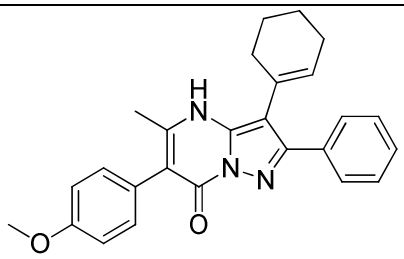
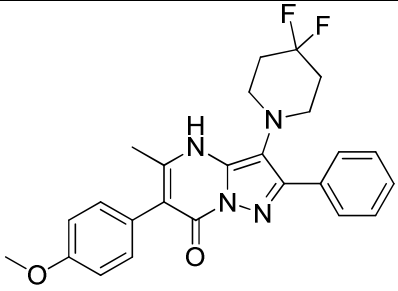
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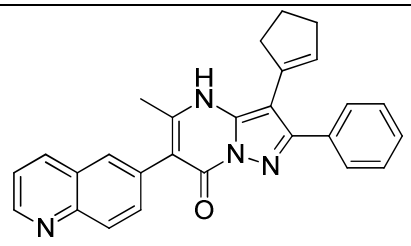
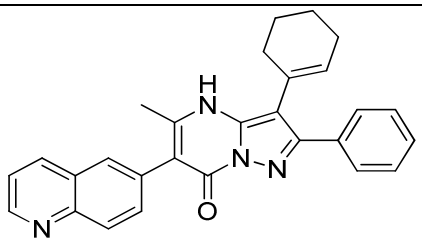
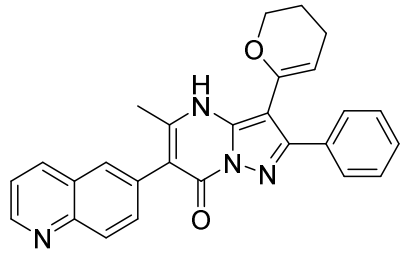
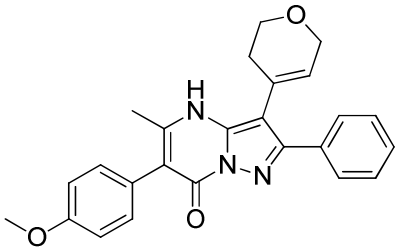
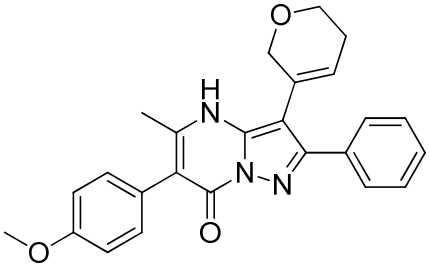
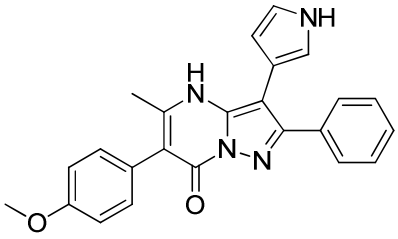
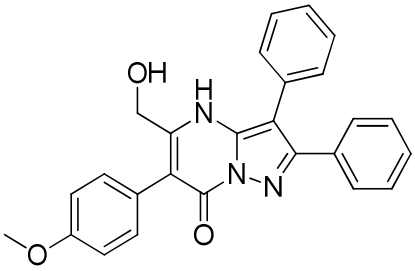
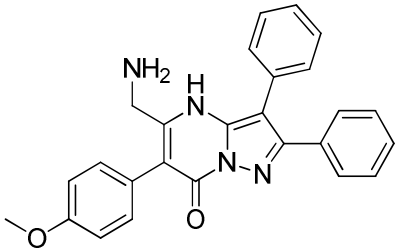
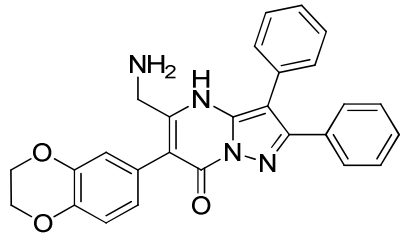
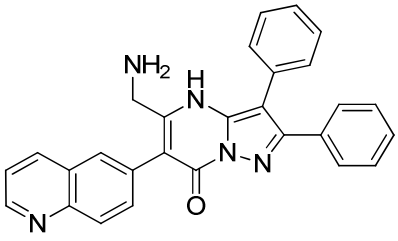
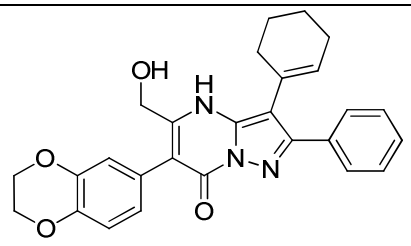
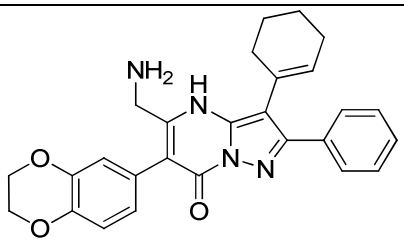
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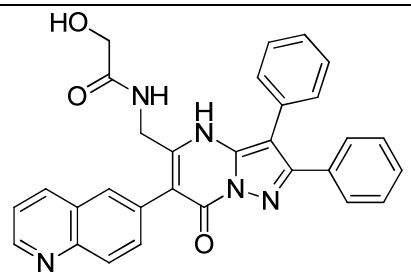
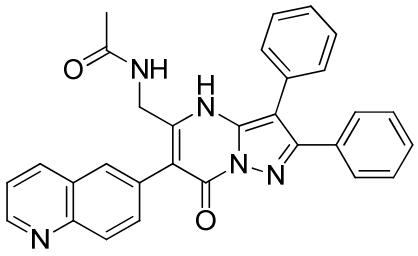
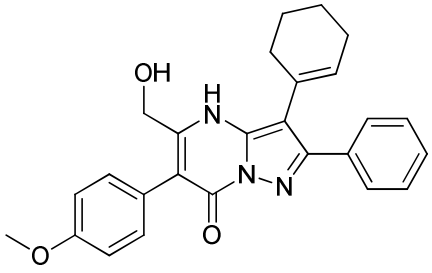
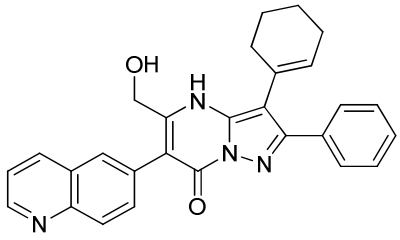
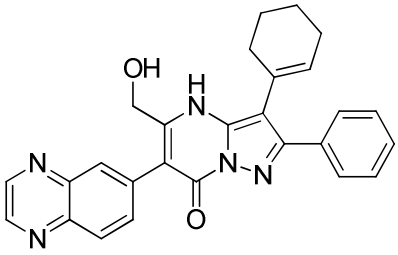
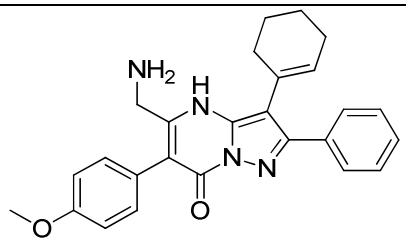
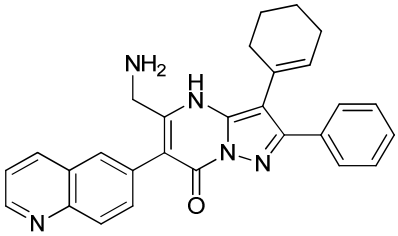
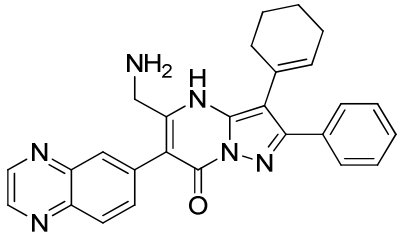
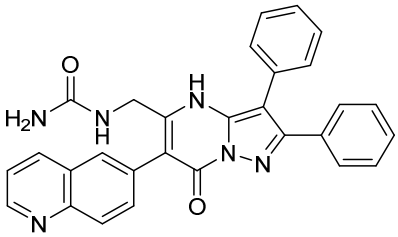
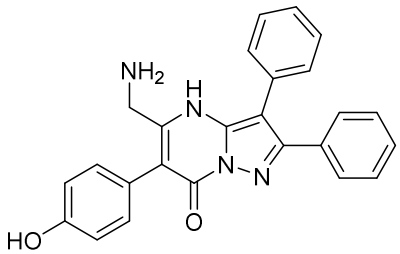
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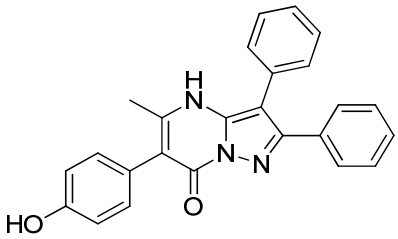
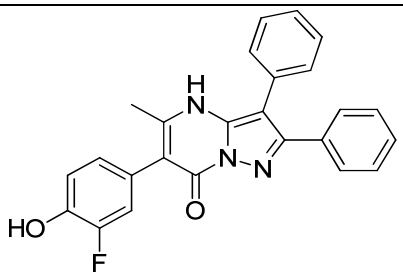
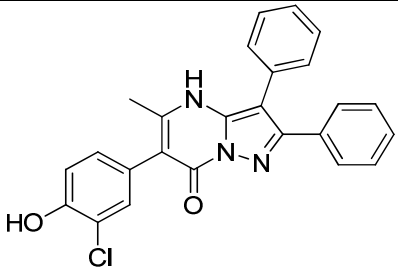
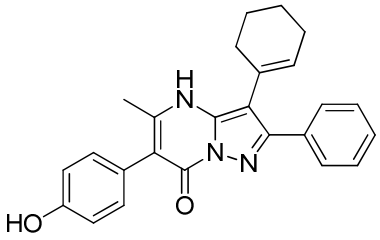
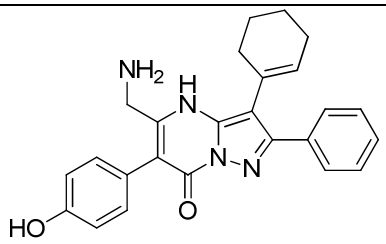
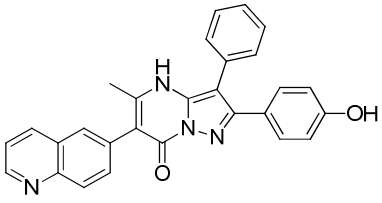
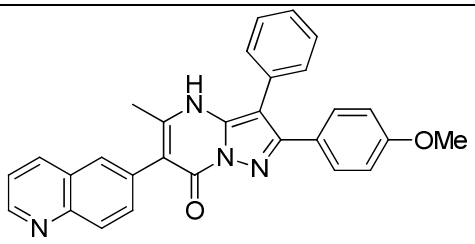
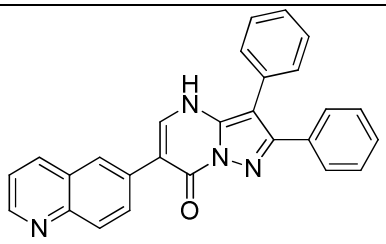
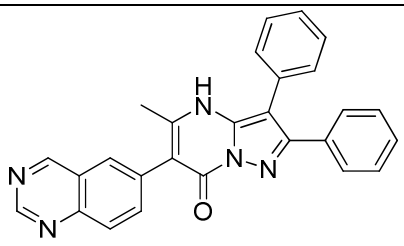
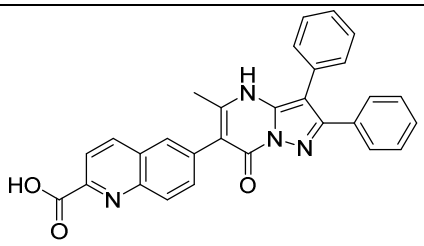
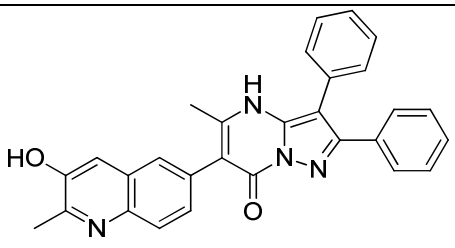
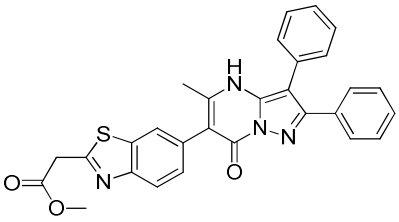
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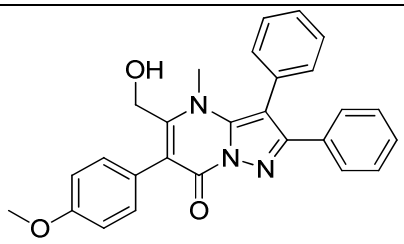
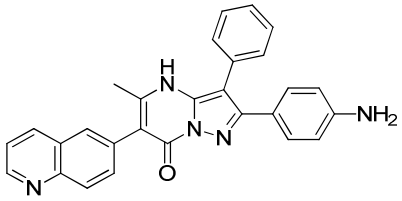
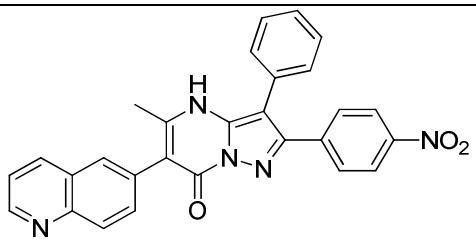
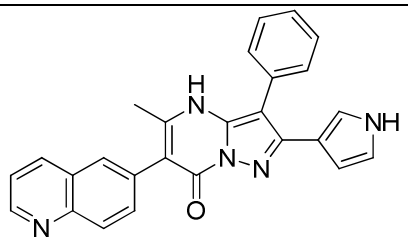
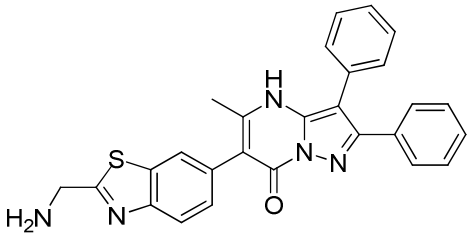
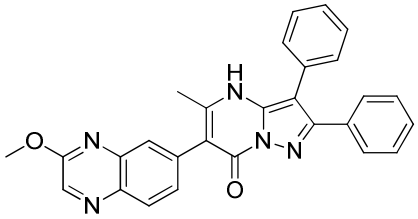
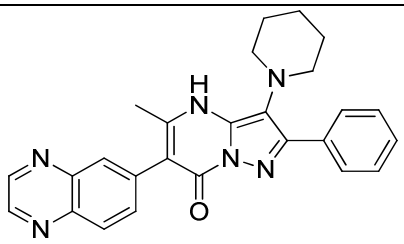
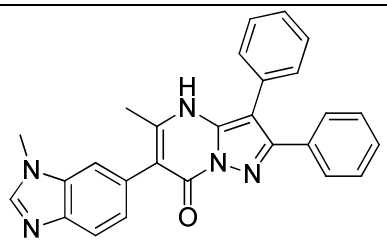
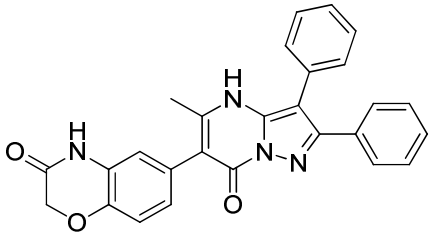
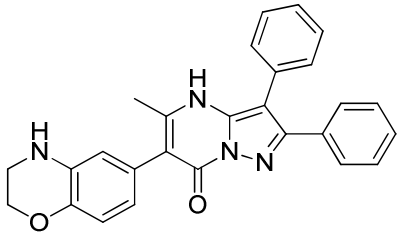
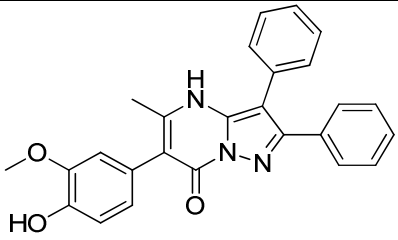
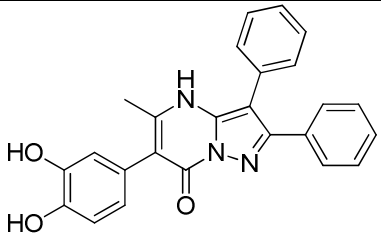
30. The compound, or a pharmaceutically acceptable salt thereof, of claim 1 that is selected from the following table:

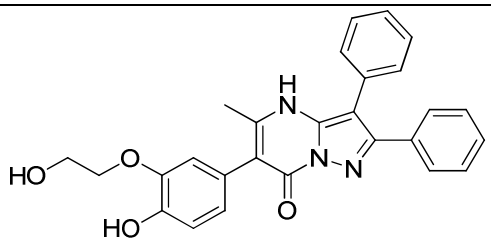
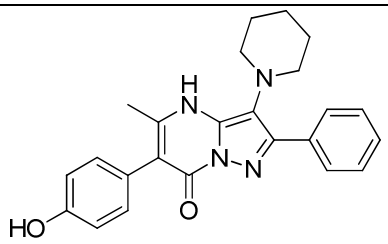
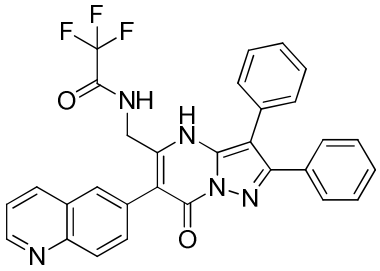
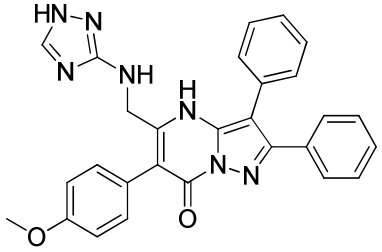
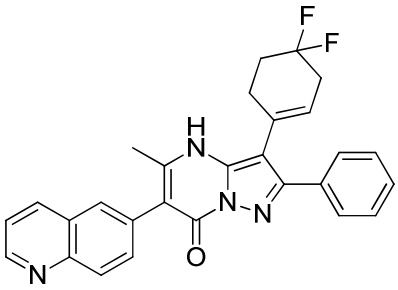
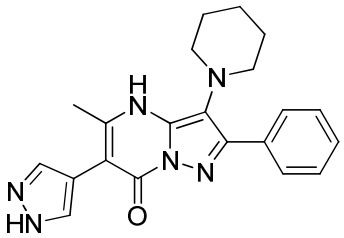
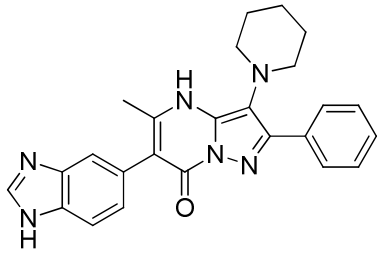
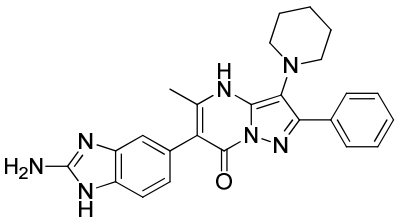
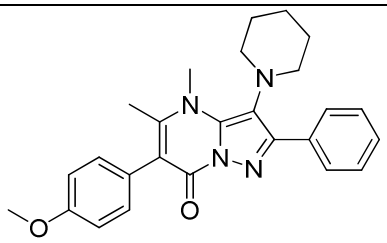
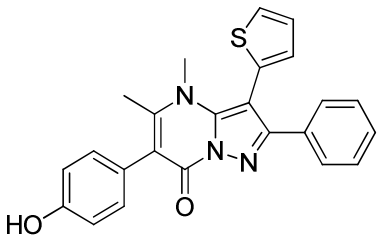
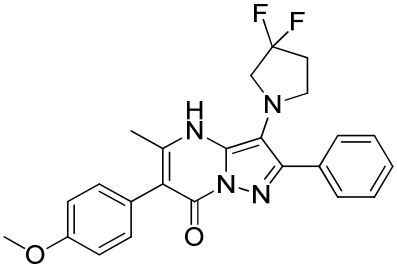
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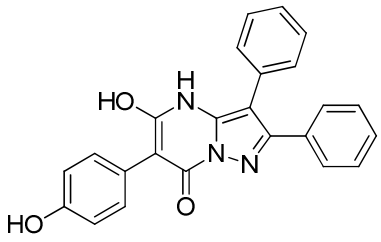
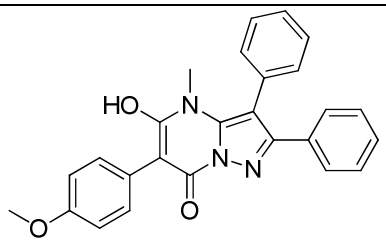
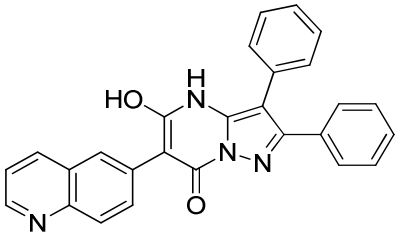
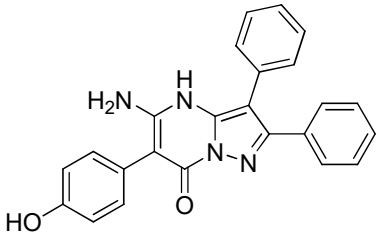
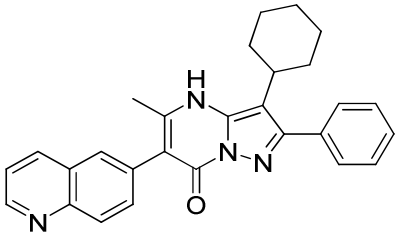
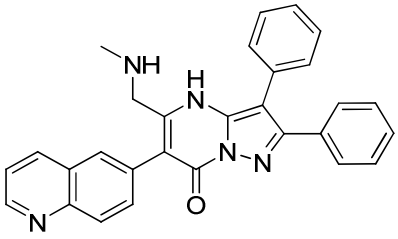
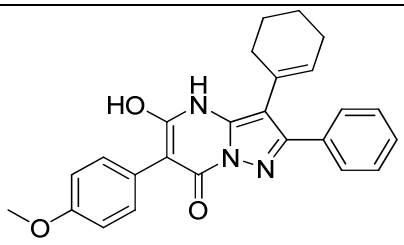
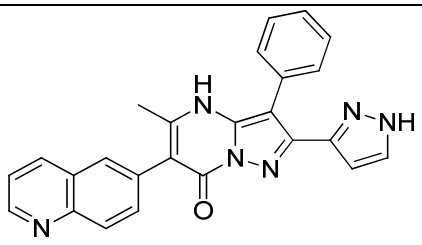
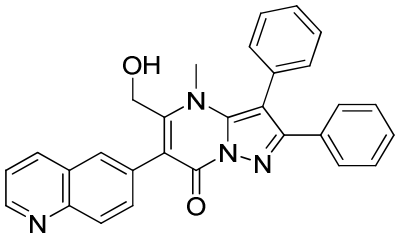
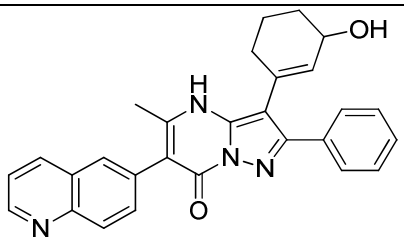
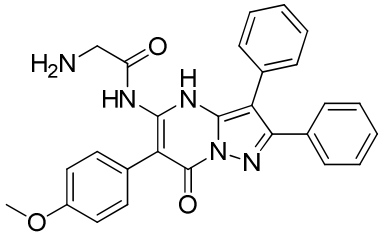
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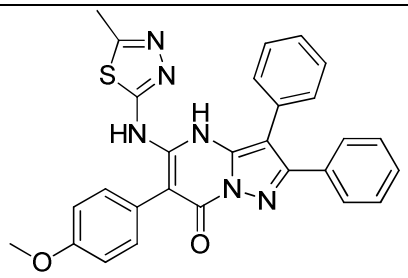
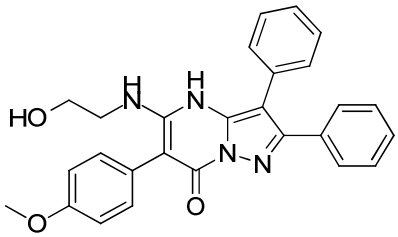
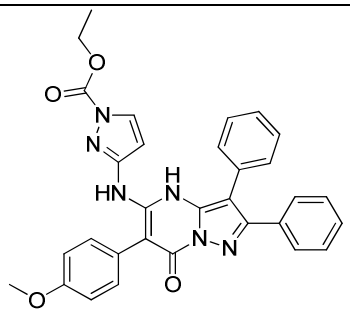
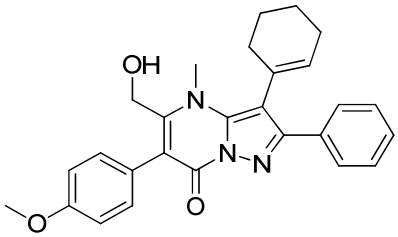
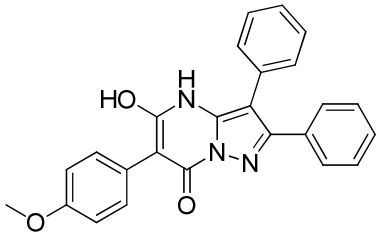
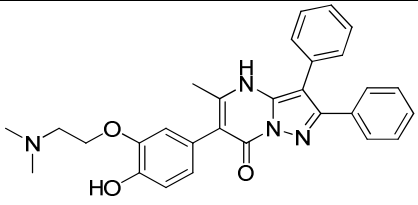
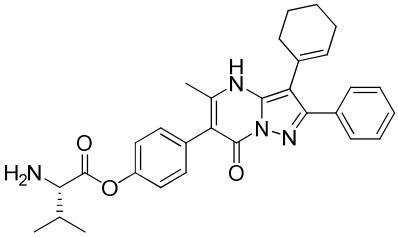
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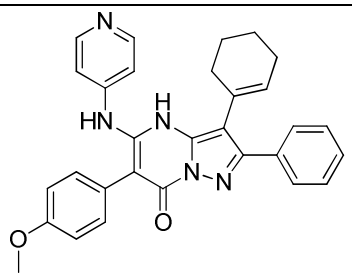
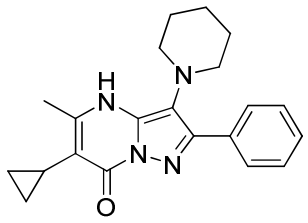
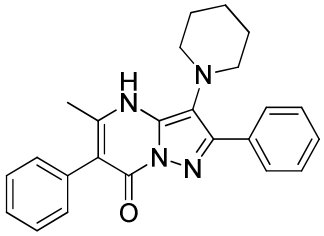
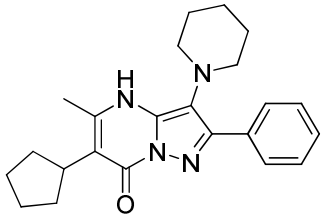
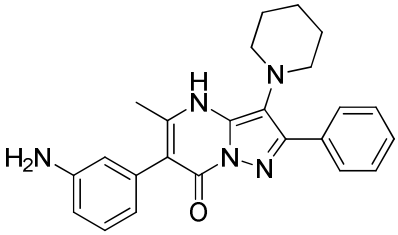
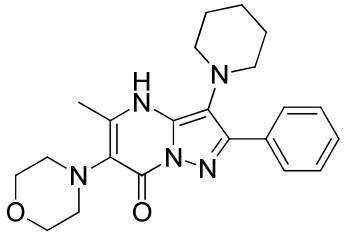
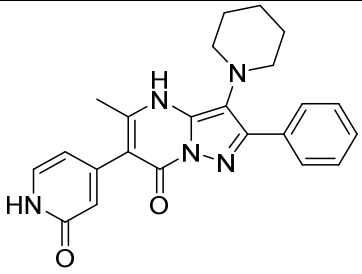
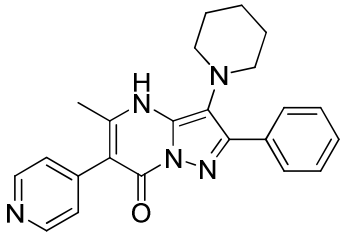
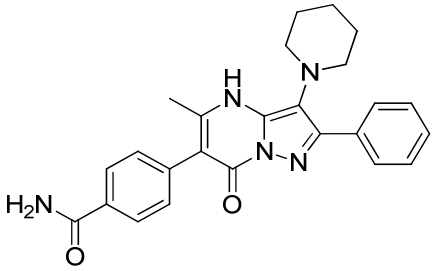
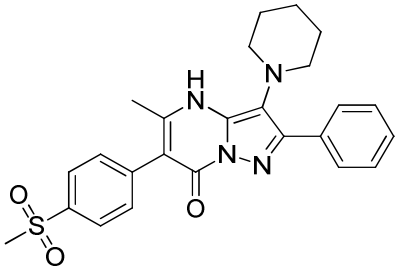
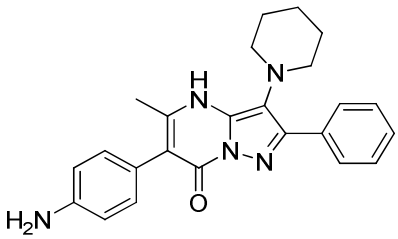
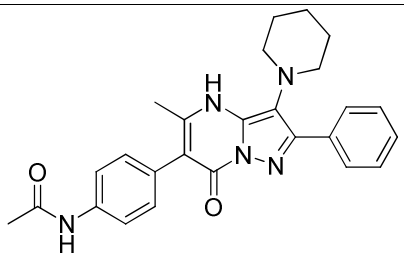
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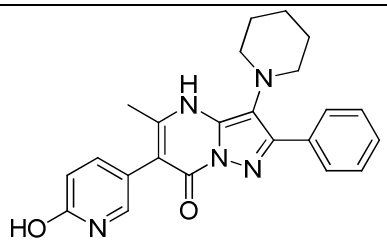
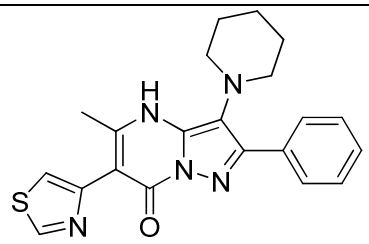
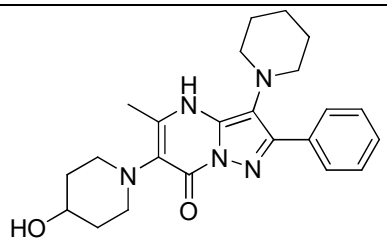
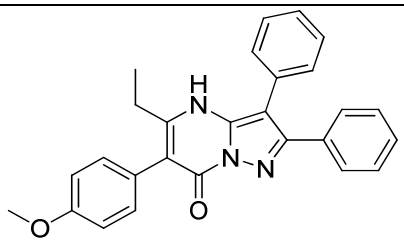
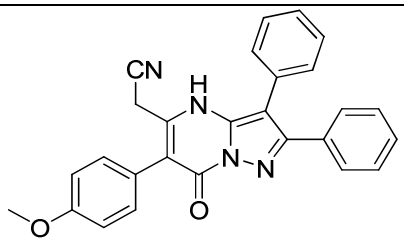
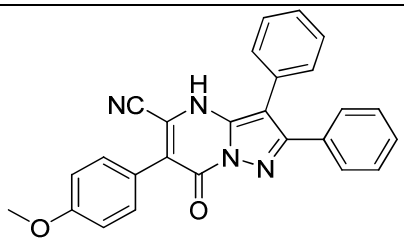
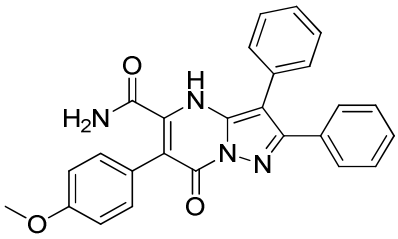
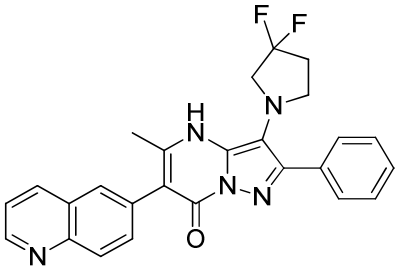
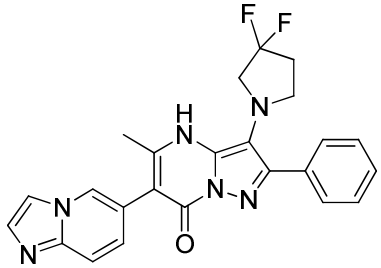
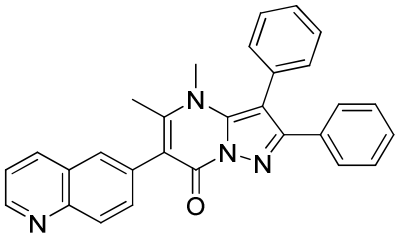
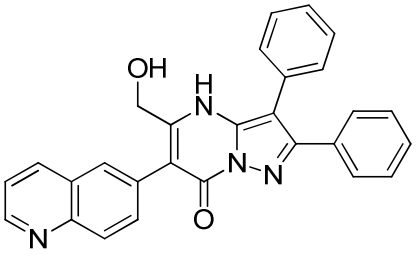
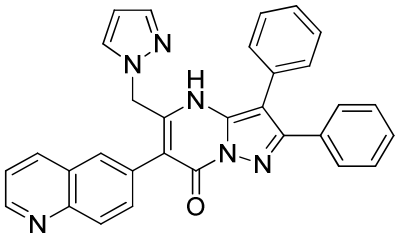
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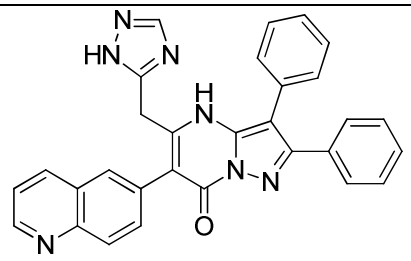
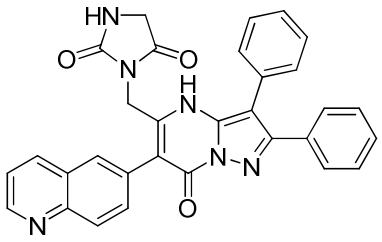
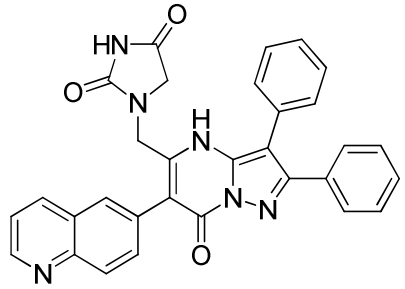
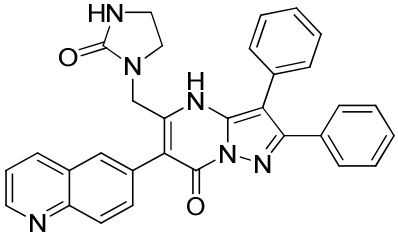
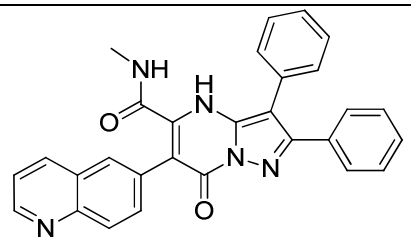
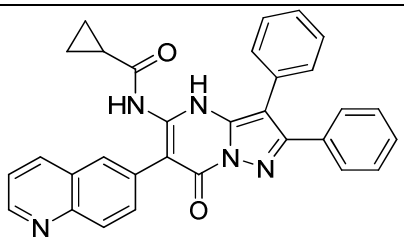
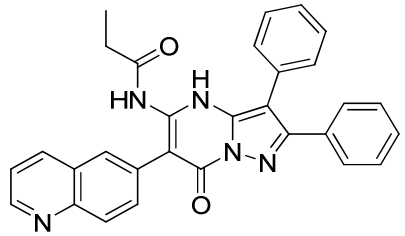
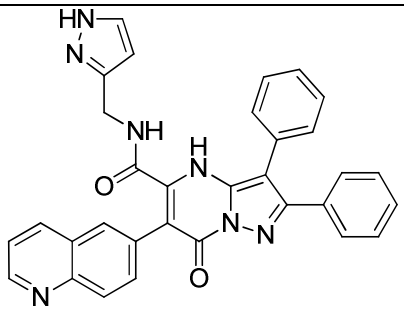
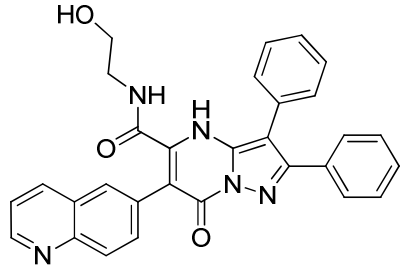
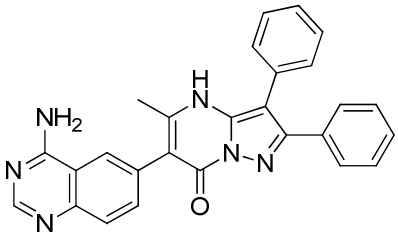
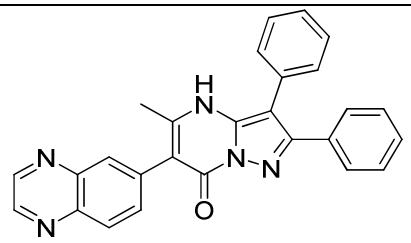
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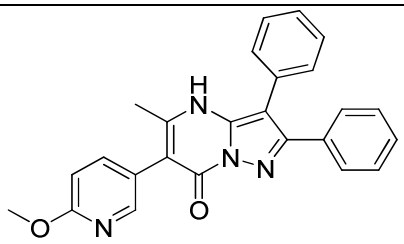
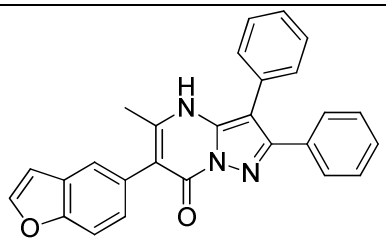
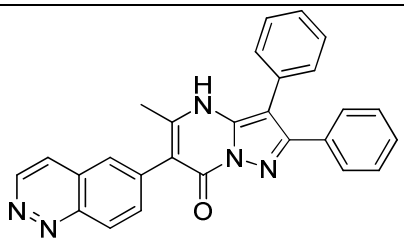
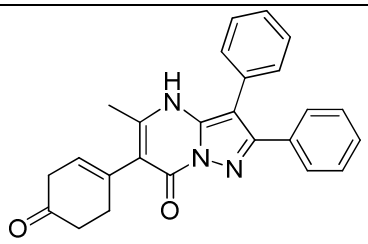
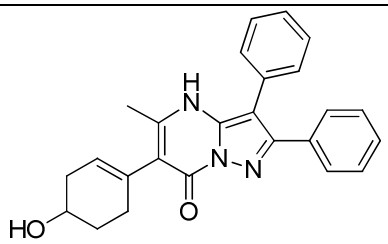
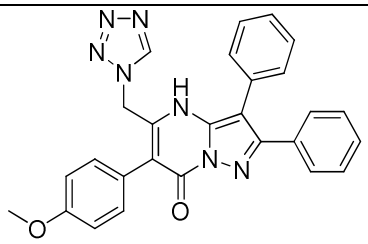
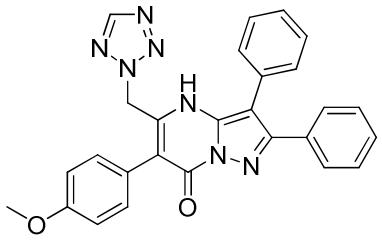
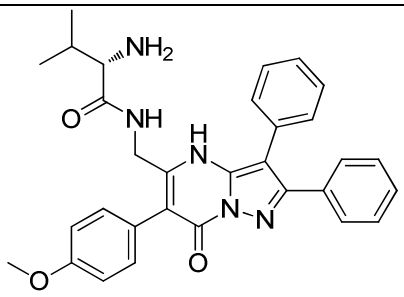
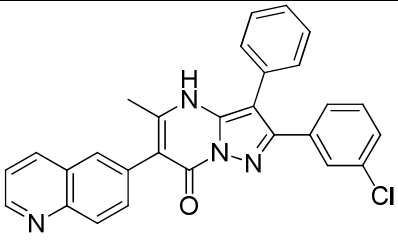
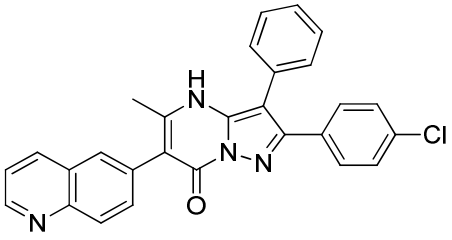
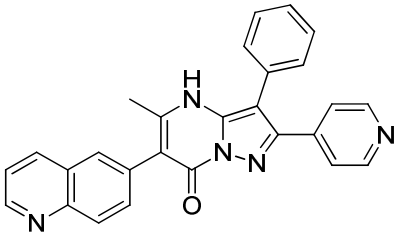
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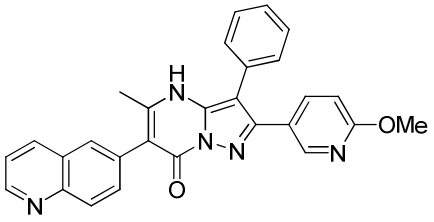
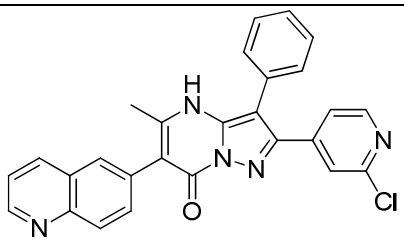
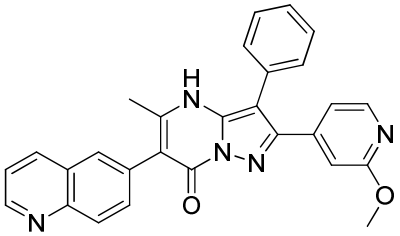
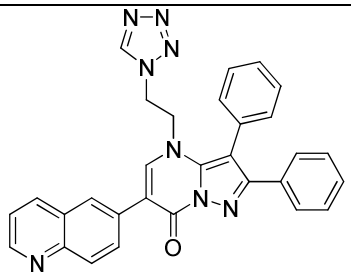
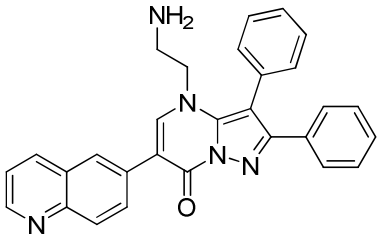
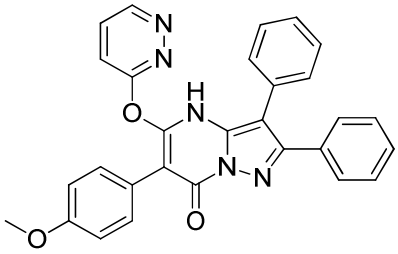
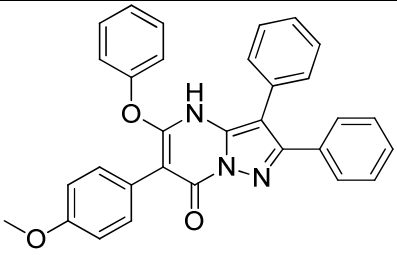
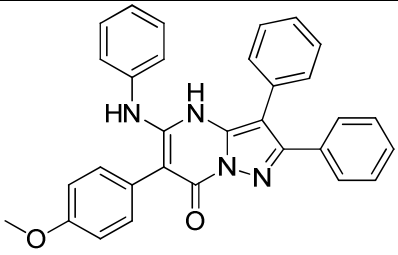
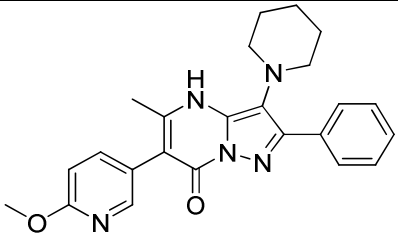
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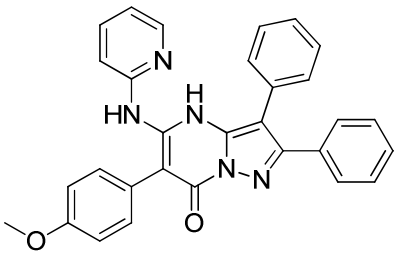
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329		**330**	
331			

333		**334**	
335		**336**	
337		**338**	
339		**340**	
		346	
347		**348**	

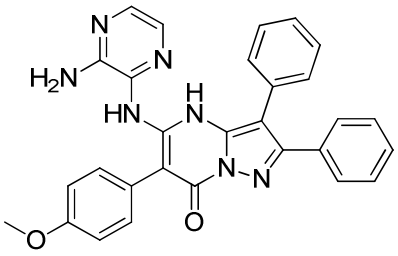
349		**350**	
351		**352**	
353		**354**	
355		**356**	
		358	

31. A compound according to claim 1, that is:



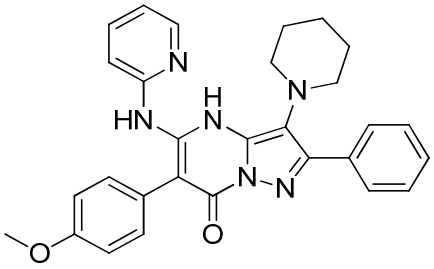
or a pharmaceutically acceptable salt thereof.

32. A compound according to claim 1, that is:



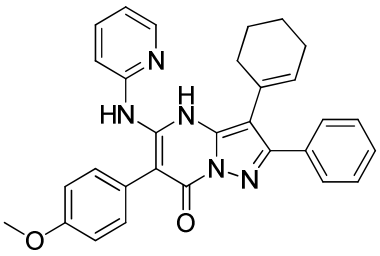
or a pharmaceutically acceptable salt thereof.

33. A compound according to claim 1, that is:



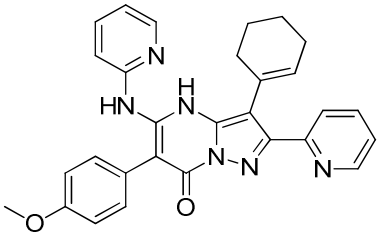
or a pharmaceutically acceptable salt thereof.

34. A compound according to claim 1, that is:



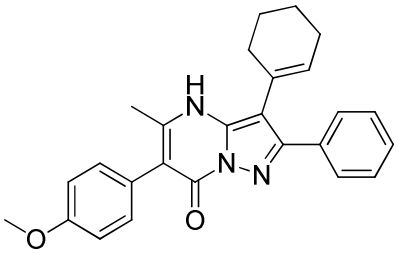
or a pharmaceutically acceptable salt thereof.

35. A compound according to claim 1, that is:



or a pharmaceutically acceptable salt thereof.

36. A compound according to claim 1, that is:



or a pharmaceutically acceptable salt thereof.

37. A pharmaceutical composition comprising a compound, or a pharmaceutically acceptable salt thereof, according to any one of claims 1-36, and a pharmaceutically acceptable carrier.

38. A compound according to any one of claims 1-36, or a pharmaceutically acceptable salt thereof, for inhibiting the synthesis of S-adenosyl methionine (SAM) from methionine and ATP by MAT2A in a cell.

39. A compound according to any one of claims 1-36, or a pharmaceutically acceptable salt thereof, for treating a disease or condition in a subject suffering therefrom, wherein the disease or condition is mediated by the overexpression of MAT2A.

40. A compound according to any one of claims 1-36, or a pharmaceutically acceptable salt thereof, for treating a cancer in a subject suffering therefrom, wherein the cancer is characterized by a reduction or absence of methylthioadenosine phosphorylase (MTAP) expression, the absence of the MTAP gene, or reduced function of MTAP protein.