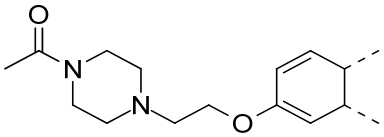
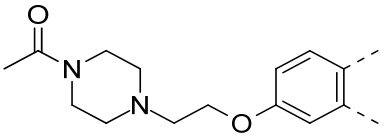
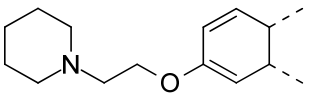
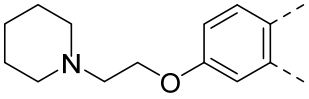
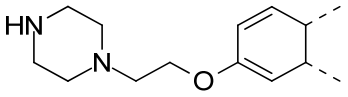
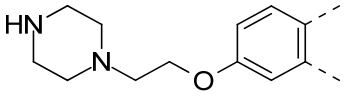
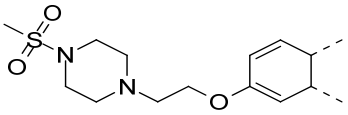
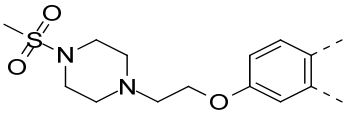
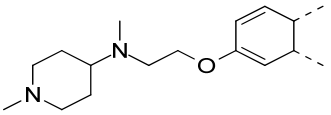
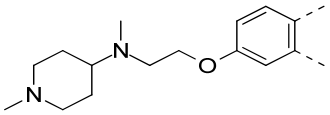
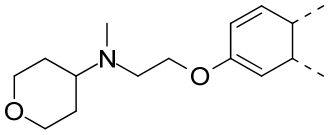
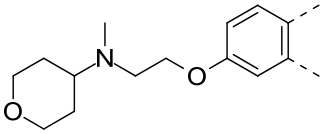
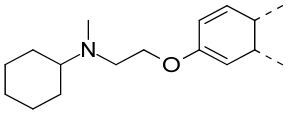
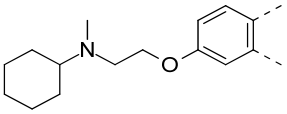
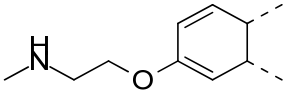
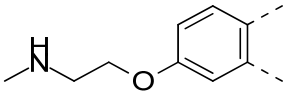
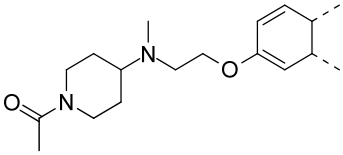
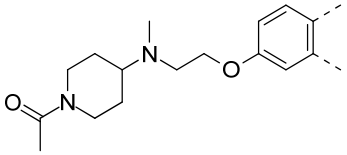
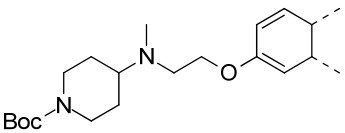
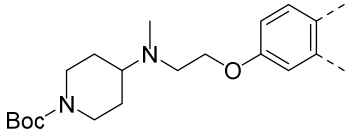
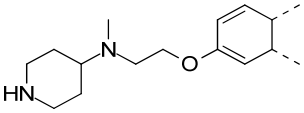
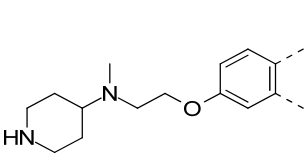
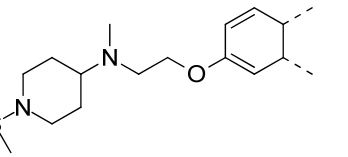
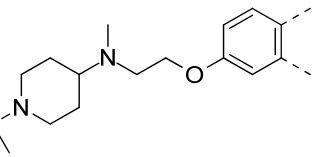
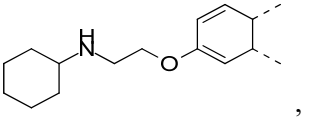
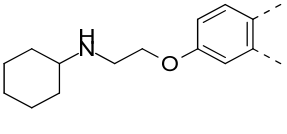
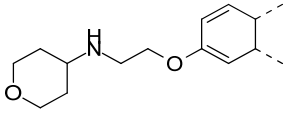
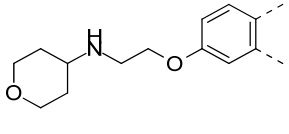
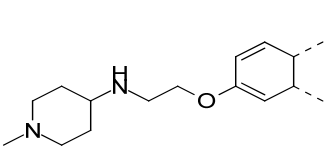
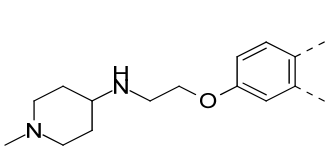
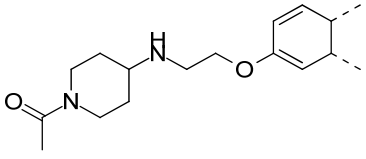
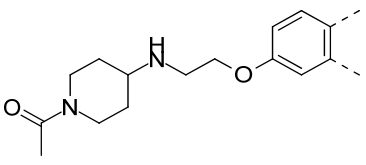
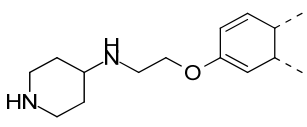
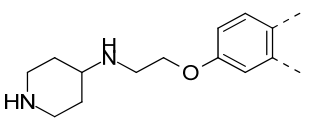
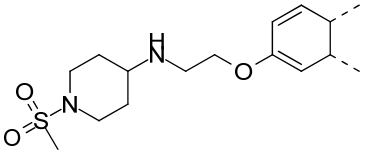
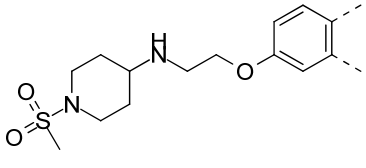
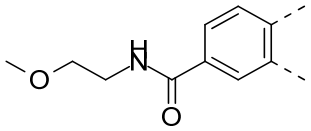
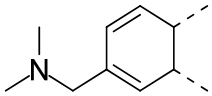
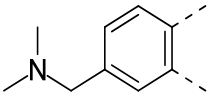
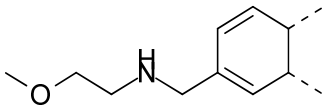
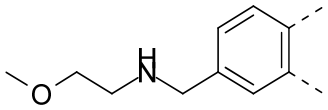
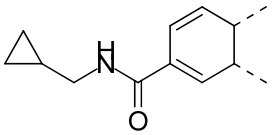
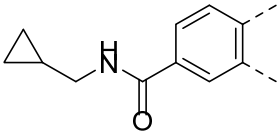
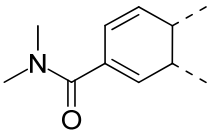
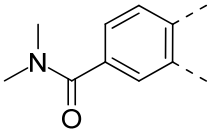
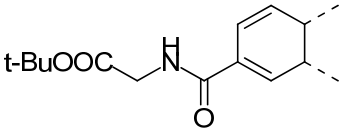
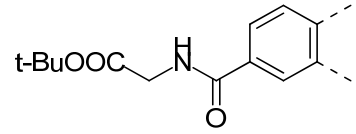
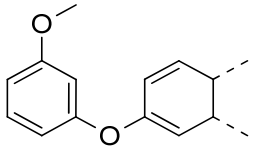
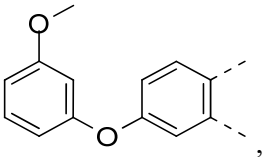
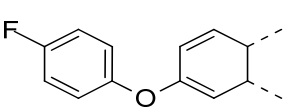
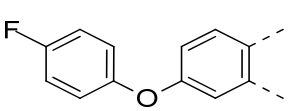
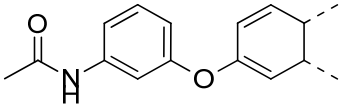
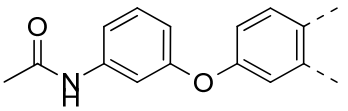
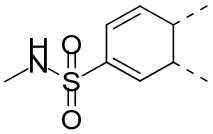
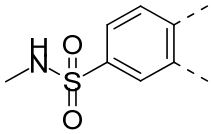
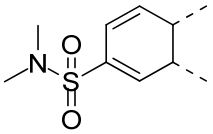
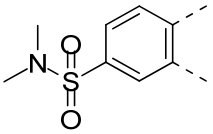
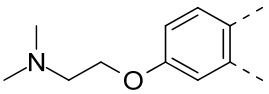
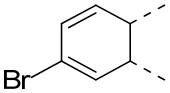
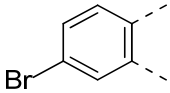
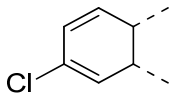
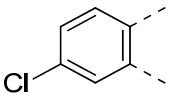
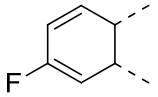
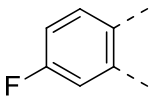
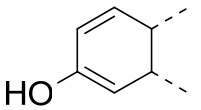
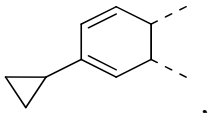
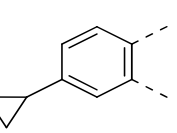
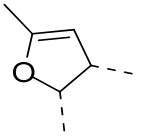
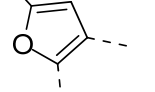
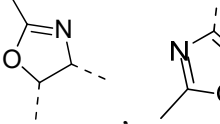
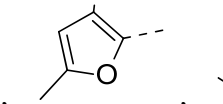
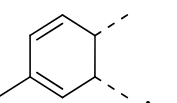
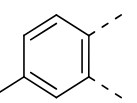
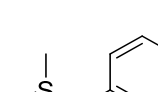
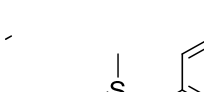
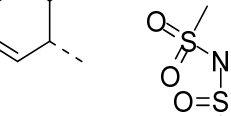

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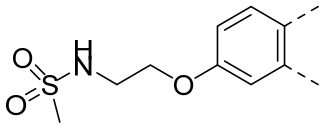
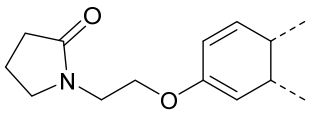
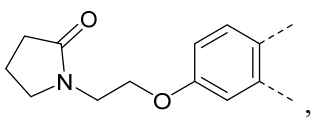
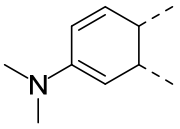
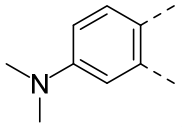
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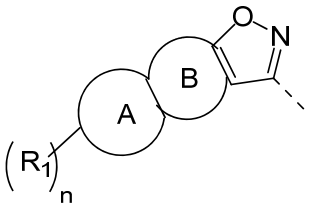
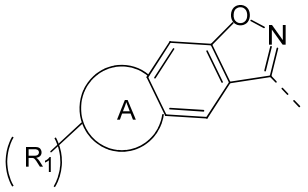
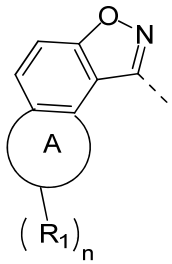
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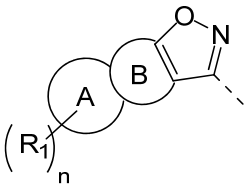
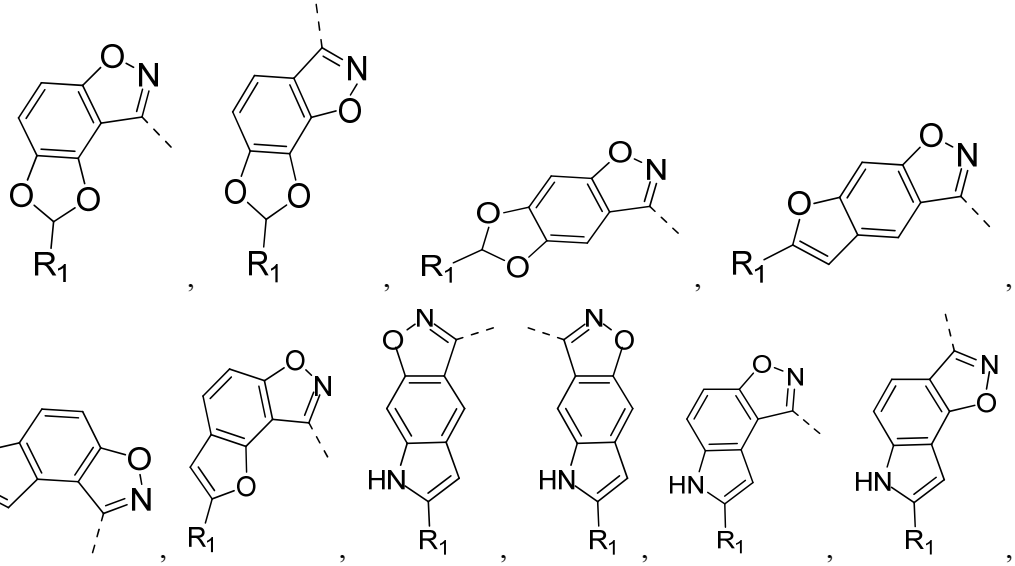
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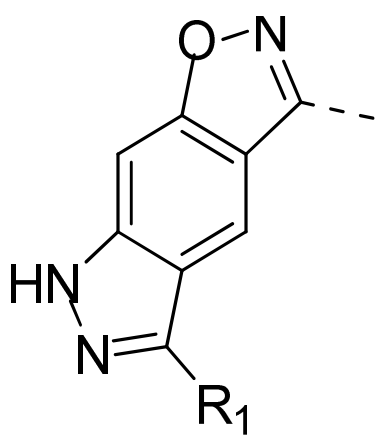
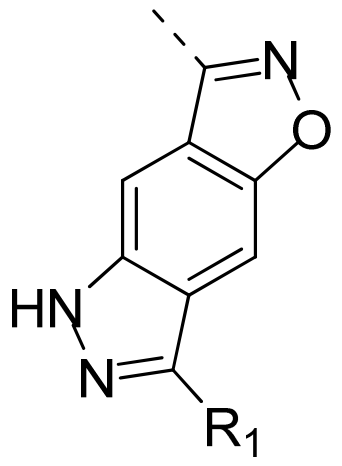
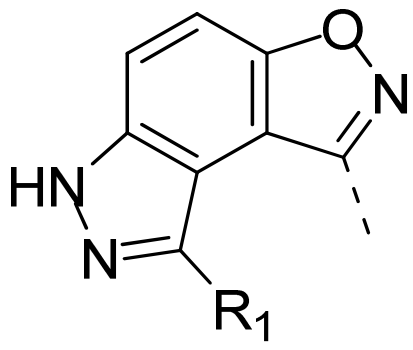
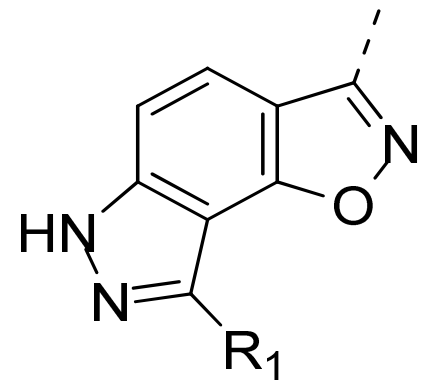
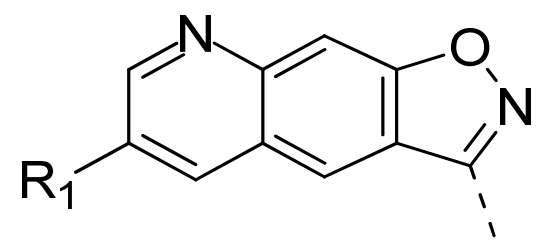









































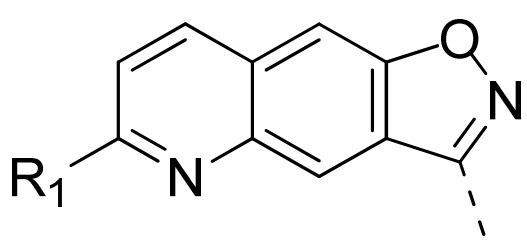
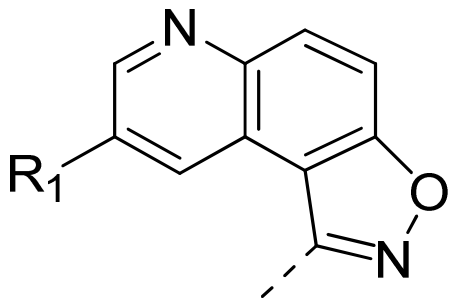
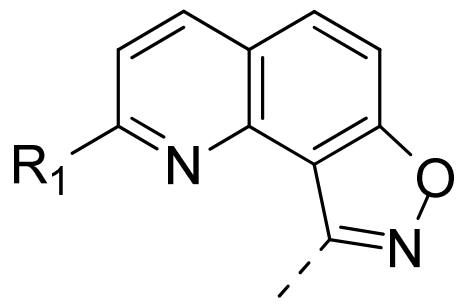
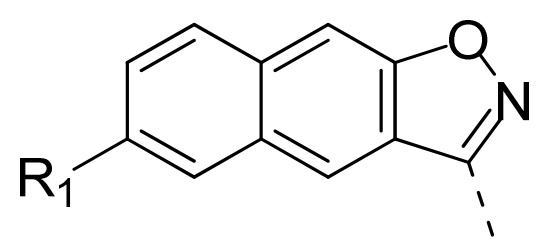




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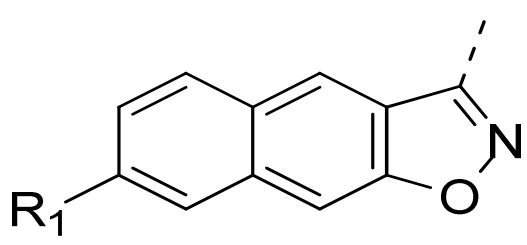
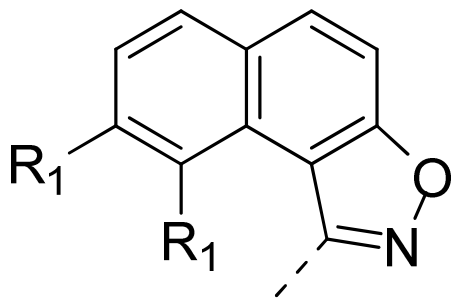
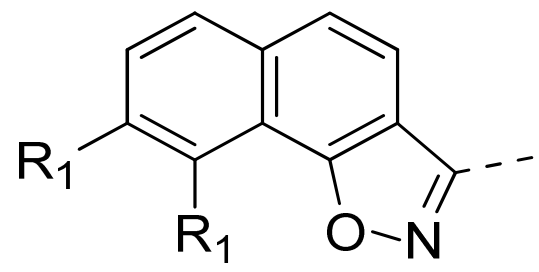
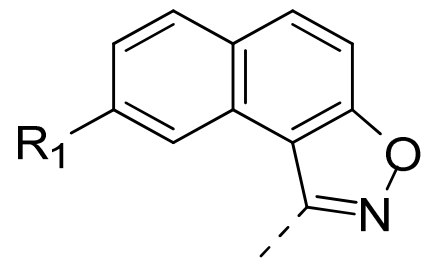
In some embodiments of the present invention, ring B is selected from phenyl.

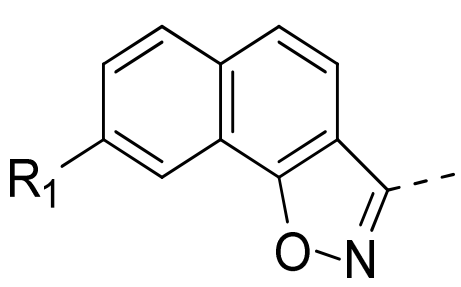
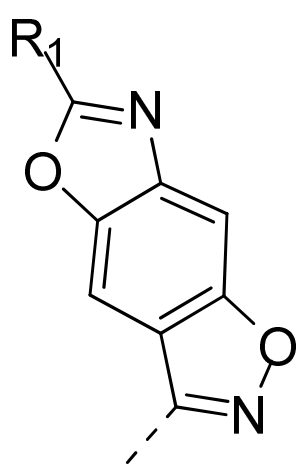
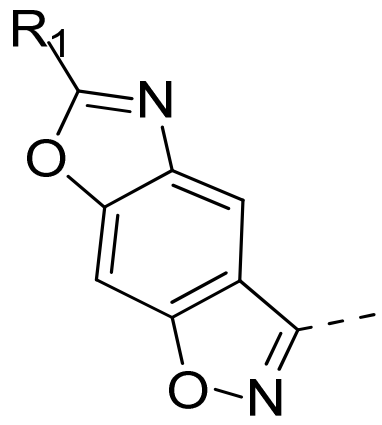
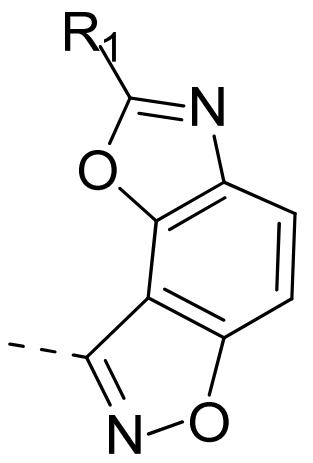
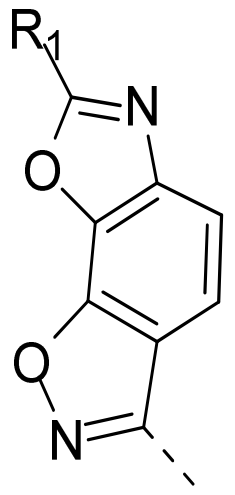
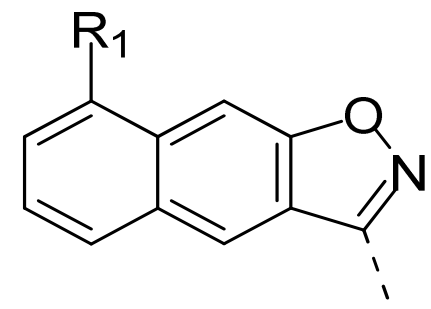
In some embodiments of the present invention, the structural unit  is selected from the group consisting of  and  , while the other variables are defined as herein.

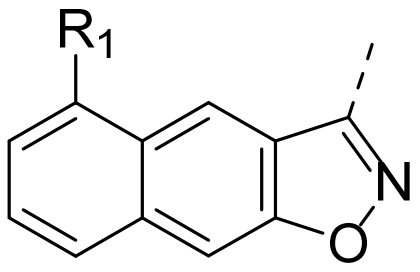
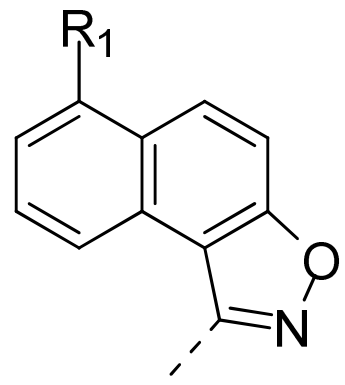
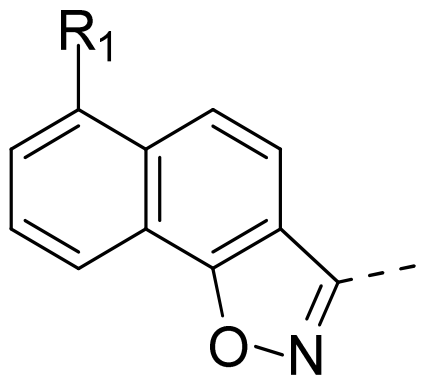
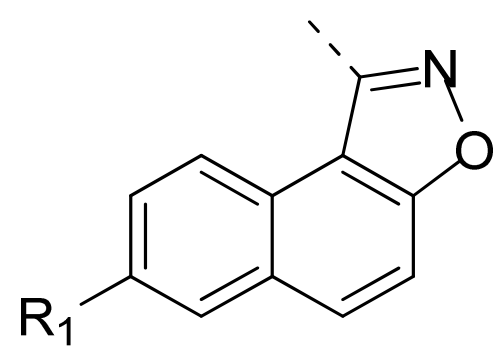
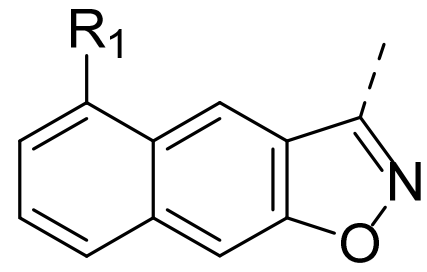
In some embodiments of the present invention, the structural unit  is selected from the group consisting of  , ,

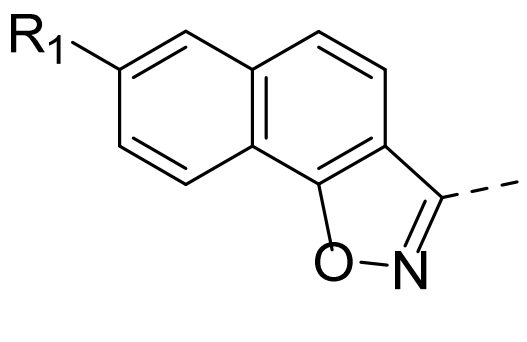
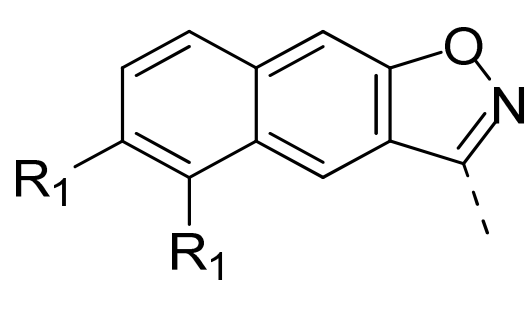
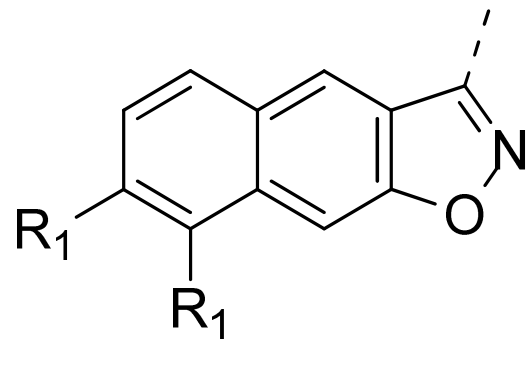
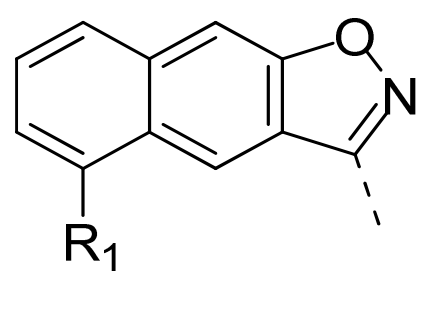
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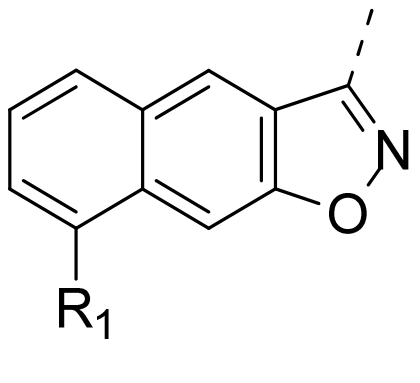
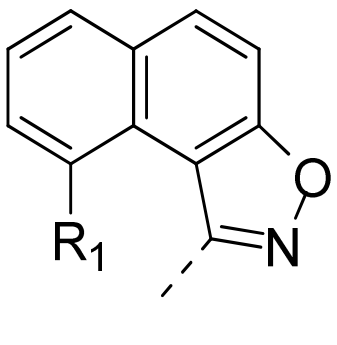
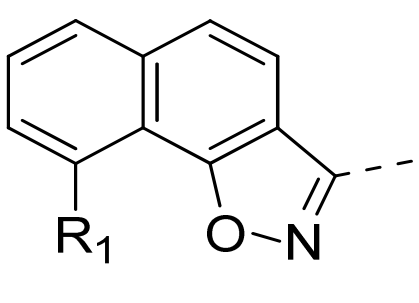
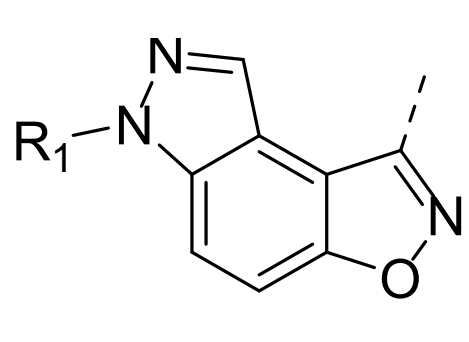
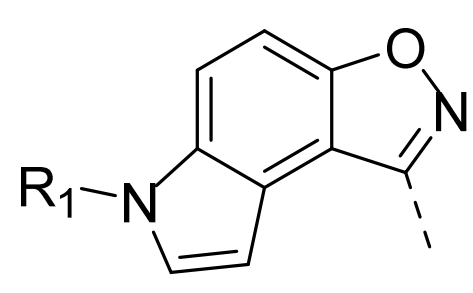
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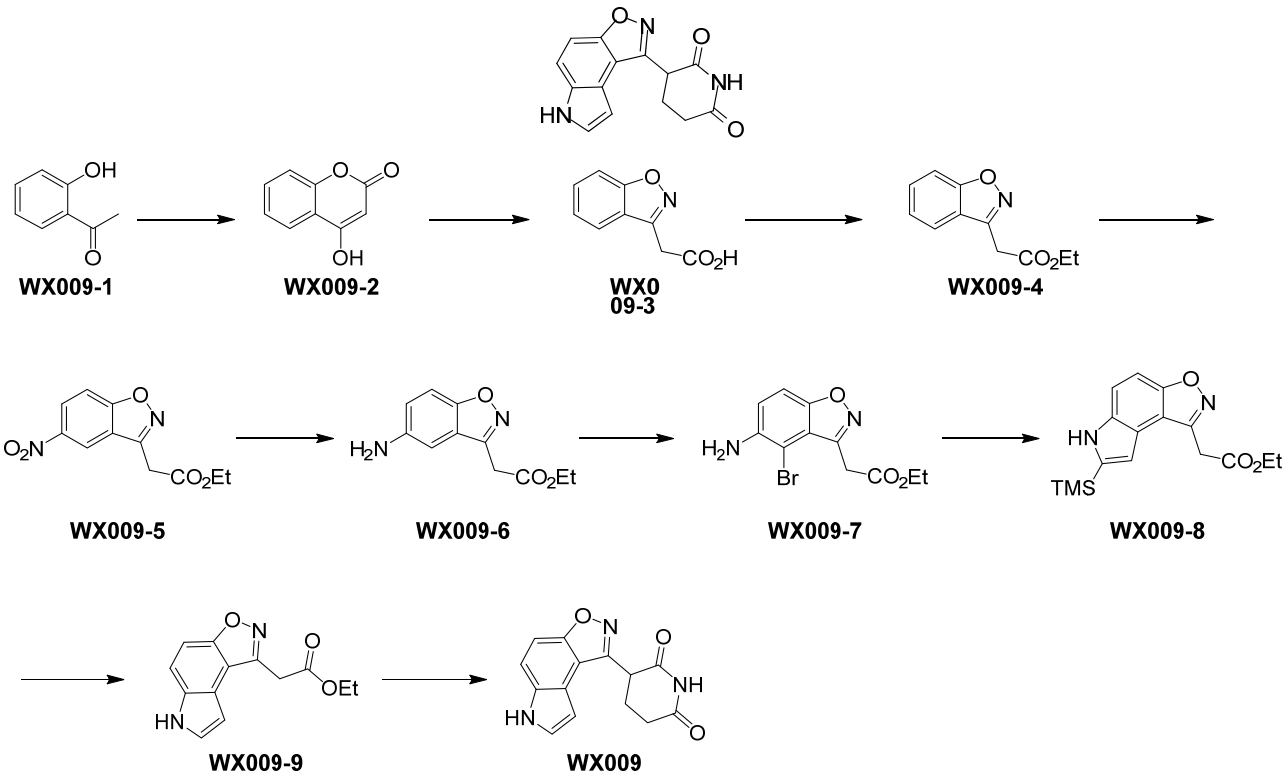
 ,  ,  ,  and  , while the other variables are defined as herein.

chromatography (eluent: petroleum ether/ethyl acetate = 5/1-3/1, volume ratio), thus giving intermediate **WX008-10**.

Step **10**: synthesis of **WX008**

Intermediate **WX008-10** (0.3 g, 908.17 μmol) was dissolved in tetrahydrofuran (5 mL) at 0 °C under nitrogen atmosphere, and then acrylamide (64.55 mg, 908.17 μmol, 62.67 μL) and potassium *tert*-butoxide (101.91 mg, 908.17 μmol) were added sequentially. The reaction mixture was stirred at room temperature (10 °C) for 14 h. After the reaction was completed, the reaction mixture was added into water (10 mL), and a mixed solution (ethyl acetate/2-methyltetrahydrofuran = 1/1) (10 mL × 3) was added for extraction. The organic phases were combined, dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure to remove the solvent. The resulting residue was separated by prep-HPLC (mobile phase: acetonitrile/water; acidic system: 0.05% HCl) to give target compound **WX008**. MS–ESI *m/z*: 356.1 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ: 8.34 (d, *J*=8.8 Hz, 1H), 8.24 (d, *J*=9.2 Hz, 1H), 8.02 (s, 1H), 7.90 (d, *J*=9.2 Hz, 1H), 7.22 (d, *J*=8.8 Hz, 1H), 4.76 (t, *J*=4.6 Hz, 2H), 4.67–4.58 (m, 1H), 3.85 (t, *J*=4.4 Hz, 2H), 3.48 (s, 3H), 3.10–2.99 (m, 1H), 2.87–2.72 (m, 2H), 2.62–2.56 (m, 1H).

Example 9: WX009



Step **1**: synthesis of intermediate **WX009-2**

WX009-1 (25.00 g, 183.62 mmol) was dissolved in a mixed solution of diethyl carbonate (250 mL) and toluene (250 mL) at room temperature. After the reaction mixture was cooled to 0 °C, sodium hydride (36.72 g, 918.12 mmol, purity: 60%) was added in batches. The reaction mixture was heated to 120 °C and stirred for 12 h. After the reaction was completed, the reaction mixture was cooled to room temperature and poured slowly into ice water (500 mL), and ethyl acetate (500 mL × 2) was added for extraction. The organic phase was discarded, and the aqueous phase was adjusted to pH 3 with 3 N hydrochloric acid and extracted with ethyl acetate (1 L × 3). The organic phases were combined, dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure to remove the solvent, thus giving intermediate **WX009-2**. ^{1}H NMR (400 MHz, DMSO_d_6) δ: 12.52 (s, 1H), 7.82 (dd, *J*=1.6, 7.6 Hz, 1H), 7.68–7.62 (m, 1H), 7.40–7.32 (m, 2H), 5.59 (s, 1H).

Step **2**: synthesis of intermediate **WX009-3**

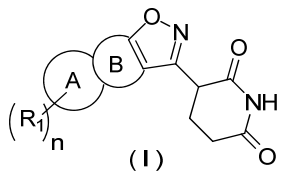
Intermediate **WX009-2** (25.00 g, 154.19 mmol) was dissolved in methanol (300 mL) at room temperature, and then sodium acetate (44.27 g, 539.65 mmol) and hydroxylamine hydrochloride (37.50 g, 539.65 mmol) were added sequentially. The reaction mixture was stirred at 15 °C for 1.5 h and then heated to 80 °C and stirred for 12 h. After the reaction was completed, the reaction mixture was cooled to room temperature, adjusted to pH = 5 with 3 N hydrochloric acid, and then concentrated under reduced pressure to remove the solvent. Water (200 mL) was added, and the reaction flask was placed in an ice-water bath to cool while 3 N hydrochloric acid was added to adjust the pH to 3. After being stirred for 30 min, the reaction mixture was filtered, and the filter cake was collected and concentrated under reduced pressure to remove the solvent, thus giving intermediate **WX009-3**.

Step **3**: synthesis of intermediate **WX009-4**

Intermediate **WX009-3** (28.00 g, 158.05 mmol) was dissolved in ethanol (600 mL) at room temperature, and then

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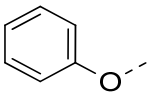
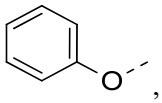
1. A compound of formula (I) or a pharmaceutically acceptable salt thereof,



(I)

wherein,

n is selected from the group consisting of 0, 1, 2 and 3;

each R_1 is independently selected from the group consisting of H, F, Cl, Br, I, OH, NH_2, CN, C_{1-6} alkyl, C_{3-10} cycloalkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl,  , $-S(=O)_2NH_2$, $-NHS(=O)_2-C_{1-6}$ alkyl, $-N[S(=O)_2-C_{1-6}$ alkyl$]_2$, $-N[C(=O)-C_{1-6}$ alkyl$]_2$, $-NHC(=O)-C_{1-6}$ alkyl and $-C(=O)NH_2$, wherein the OH, NH_2, C_{1-6} alkyl, C_{3-10} cycloalkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl,  , $-S(=O)_2NH_2$, $-NHS(=O)_2-C_{1-6}$ alkyl, $-N[S(=O)_2-C_{1-6}$ alkyl$]_2$, $-N[C(=O)-C_{1-6}$ alkyl$]_2$, $-NHC(=O)-C_{1-6}$ alkyl and $-C(=O)NH_2$ are optionally substituted with 1, 2 or 3 R_a;

ring A is selected from the group consisting of 5-6 membered heteroaryl, phenyl, C_{4-6} cycloalkyl, 4-7 membered heterocycloalkyl and 4-7 membered heterocycloalkenyl;

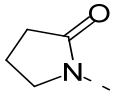
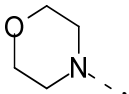
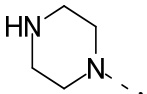
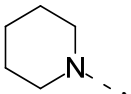
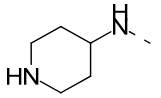
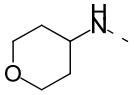
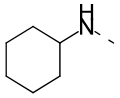
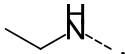
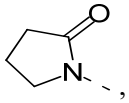
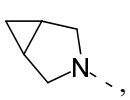
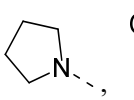
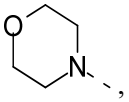
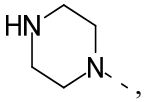
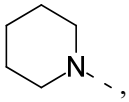
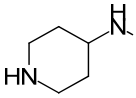
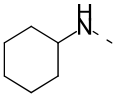
ring B is selected from the group consisting of 5-6 membered heteroaryl and phenyl;

each R_a is independently selected from the group consisting of F, Cl, Br, I, OH, NH_2, C_{1-10} alkyl, C_{1-10} alkoxy, C_{1-10} alkylamino, $-C(=O)NH-C_{1-10}$ alkyl, $-NHC(=O)-C_{1-10}$ alkyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkylamino, 4-10 membered heterocycloalkyl, 4-10 membered heterocycloalkylamino and 4-10 membered heterocycloalkyl substituted with one carbonyl, wherein the OH, NH_2, C_{1-10} alkyl, C_{1-10} alkoxy, C_{1-10} alkylamino, $-C(=O)NH-C_{1-10}$ alkyl, $-NHC(=O)-C_{1-10}$ alkyl, $-COOC_{1-10}$ alkyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkylamino, 4-10 membered heterocycloalkyl and 4-10 membered heterocycloalkylamino are optionally substituted with 1, 2 or 3 R;

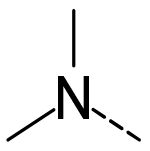
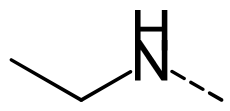
each R is independently selected from the group consisting of F, Cl, Br, I, OH, NH_2, C_{1-3} alkyl, C_{1-3} alkoxy, C_{1-3} alkylamino, C_{3-5} cycloalkyl, $-C(=O)-C_{1-3}$ alkyl, $-C(=O)O-C_{1-6}$ alkyl, $-S(=O)_2-C_{1-3}$ alkyl,  and  ;

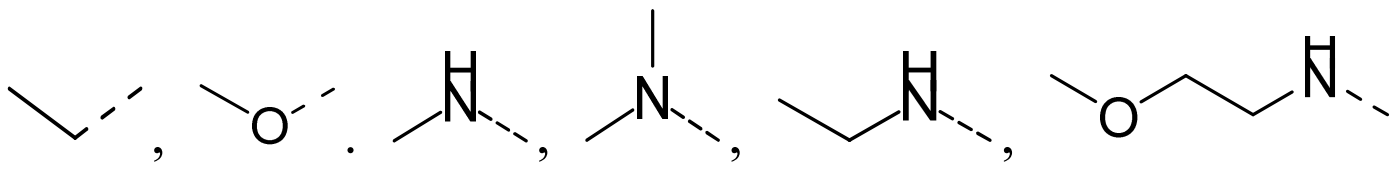
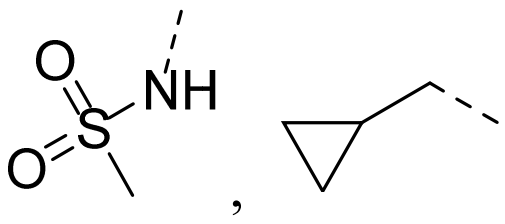
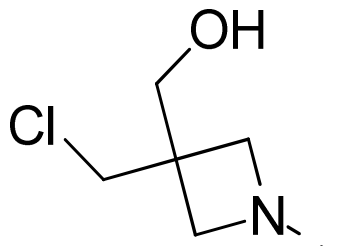
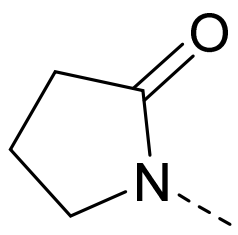
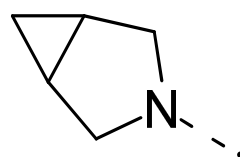
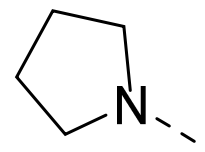
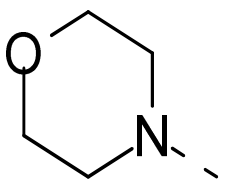
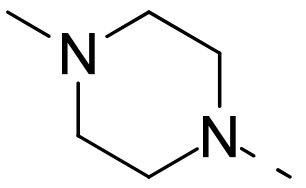
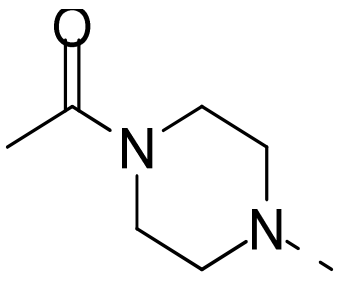
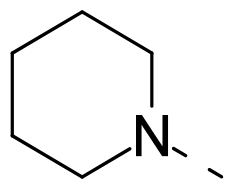
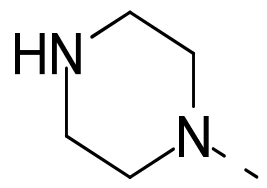
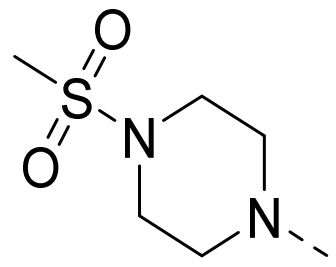
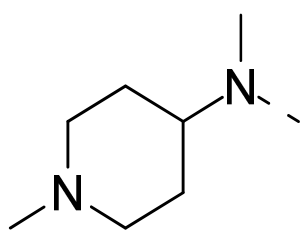
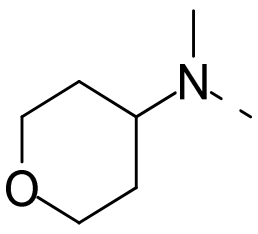
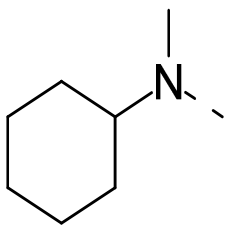
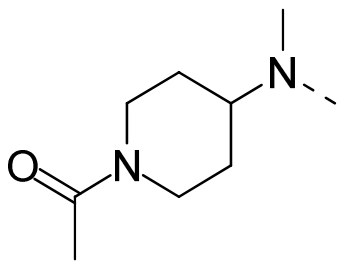
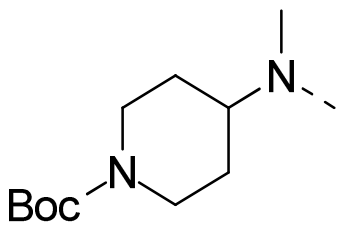
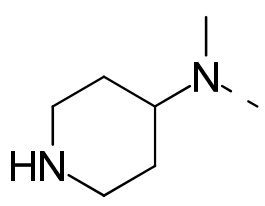
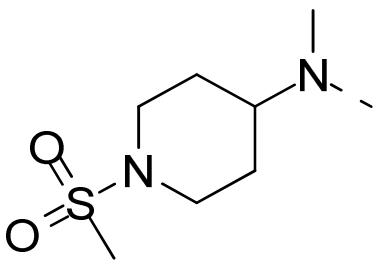
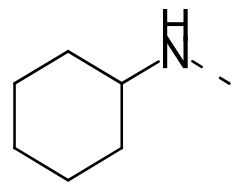
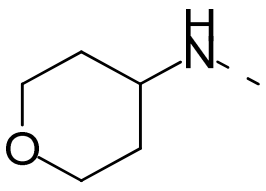
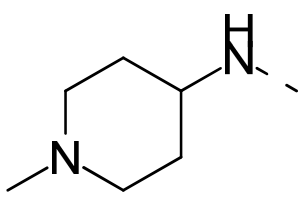
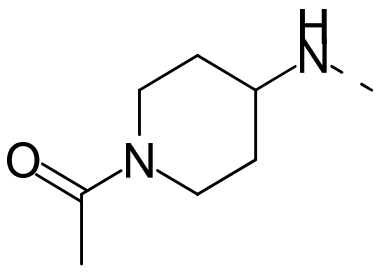
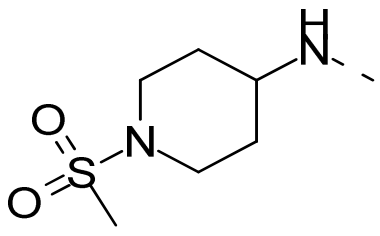
the 5-6 membered heteroaryl, 4-7 membered heterocycloalkyl, 4-10 membered heterocycloalkyl, 4-10 membered heterocycloalkylamino, 4-7 membered heterocycloalkenyl and 4-10 membered heterocycloalkyl substituted with one carbonyl each contain 1, 2, 3 or 4 heteroatoms or heteroatom groups independently selected from the group consisting of -NH-, -O-, -S- and N.

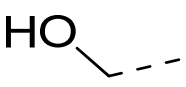
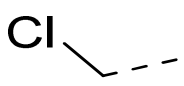
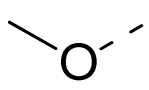
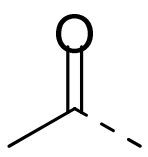
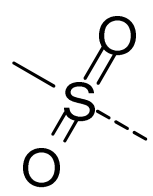
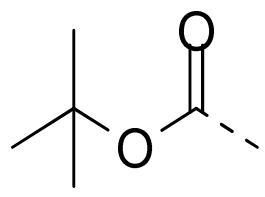
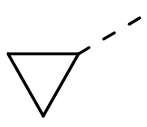
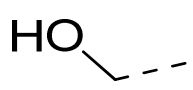
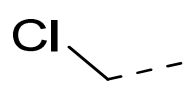
2. The compound according to claim 1, wherein ring A is selected from the group consisting of 5-6 membered heteroaryl, phenyl and 4-7 membered heterocycloalkenyl.

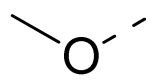
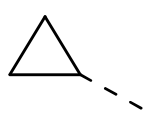
3. The compound according to claim 1 or 2, wherein each R_a is independently selected from F, Cl, Br, I, OH, NH_2, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, -C(=O)NH-C_{1-6} alkyl, -NHC(=O)-C_{1-6} alkyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkylamino, 4-6 membered heterocycloalkyl, 4-6 membered heterocycloalkylamino and 4-10 membered heterocycloalkyl substituted with one carbonyl, wherein the C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, -C(=O)NH-C_{1-6} alkyl, -NHC(=O)-C_{1-6} alkyl, -$COOC_{1-6}$ alkyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkylamino, 4-6 membered heterocycloalkyl and 4-6 membered heterocycloalkylamino are optionally substituted with 1, 2 or 3 R; preferably, each R_a is independently selected from the group consisting of F, Cl, Br, I, OH, NH_2, C_{1-3} alkyl, C_{1-3} alkoxy, C_{1-3} alkylamino, -C(=O)NH-C_{1-3} alkyl, -NHC(=O)-C_{1-3} alkyl, C_{3-6} cycloalkyl, cyclohexylamino, azetidinyl, pyrrolidin-2-one, tetrahydropyrrolyl, piperidinyl, piperazinyl, morpholinyl, tetrahydropyranyl, 3-azabicyclo[3,1,0]hexyl, azetidinylamino, tetrahydropyrrolylamino, tetrahydropyrrolyl, piperidinylamino, piperazinylamino, morpholinylamino, tetrahydropyranylamino and 3-azabicyclo[3,1,0]hexylamino, wherein the C_{1-3} alkyl, C_{1-3} alkoxy, C_{1-3} alkylamino, -C(=O)NH-C_{1-3} alkyl, -NHC(=O)-C_{1-3} alkyl, -$COOC_{1-4}$ alkyl, C_{3-6} cycloalkyl, cyclohexylamino, azetidinyl, tetrahydropyrrolyl, piperidinyl, piperazinyl, morpholinyl, tetrahydropyranyl, 3-azabicyclo[3,1,0]hexyl, azetidinylamino, tetrahydropyrrolylamino, piperidinylamino, piperazinylamino, morpholinylamino, tetrahydropyranylamino, and 3-azabicyclo[3,1,0]hexylamino are optionally substituted with 1, 2 or 3 R; more preferably, each R_a is independently selected from the group consisting of F, Cl, Br, I, OH, NH_2, $-CH_3$, $-CH_2CH_3$,  , ,  ,  , -C(=O)NHCH$_3$, -NHC(=O)CH$_3$,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , and  , wherein the -CH$_3$, -CH$_2$CH$_3$,  ,  ,  , -C(=O)NHCH$_3$, -NHC(=O)CH$_3$, -COOt-Bu,  ,  ,  ,  ,  ,  ,  ,  ,  , and  are optionally substituted with 1, 2 or 3 R.

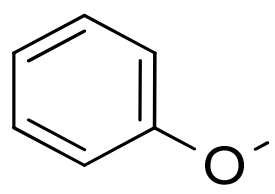
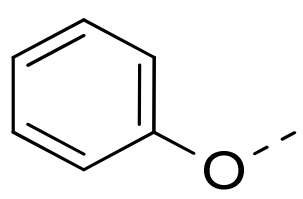
4. The compound according to claim 1 or 2, wherein each R_a is selected from the group consisting of F, Cl, Br, I, OH, NH_2, -CH_2-, -CH_2CH_2-,  ,  and  , wherein the -CH_2-, -CH_2CH_2-,  ,

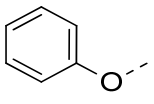
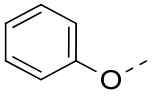
 and  are optionally substituted with 1, 2 or 3 R.

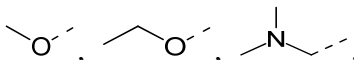
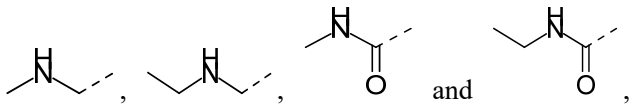
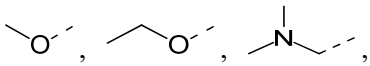
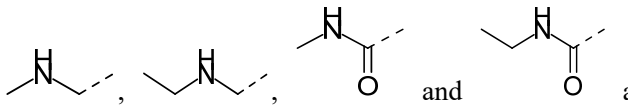
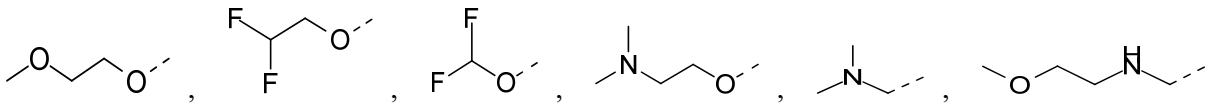
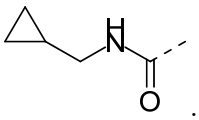
5. The compound according to claim 1 or 2, wherein each R_a is independently selected from the group consisting of F, Cl, Br, I, Me, OH, NH_2,  , -C(=O)NHCH$_3$, -NHC(=O)CH$_3$, -CH$_2$COOt-Bu,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  and  .

6. The compound according to claim 1 or 2, wherein each R is independently selected from the group consisting of C_{1-3} alkyl, C_{1-3} alkoxy, -C(=O)-C_{1-3} alkyl, C_{3-5} cycloalkyl, -C(=O)O-C_{1-4} alkyl, -S(=O)$_2$-C_{1-3} alkyl,  , and  ; preferably, each R is independently selected from the group consisting of -CH$_3$,  ,  ,  ,  ,  ,  and  .

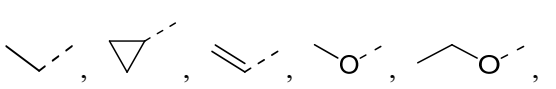
7. The compound according to claim 1 or 2, wherein each R is independently selected from the group consisting of F, Cl, Br, I, OH, NH_2, -CH$_2$-, -CH$_2$CH$_2$-,  and  .

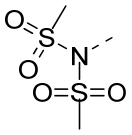
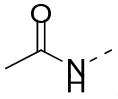
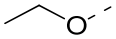
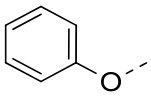
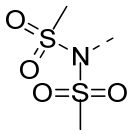
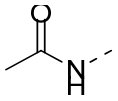
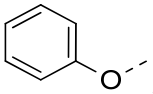
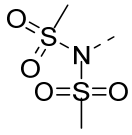
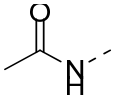
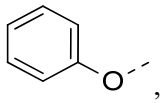
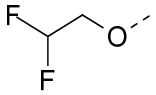
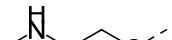
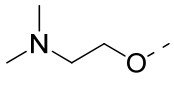
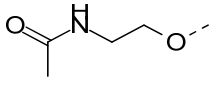
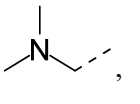
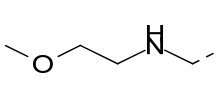
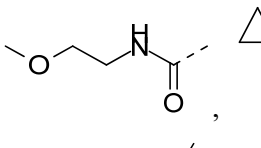
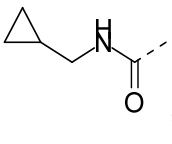
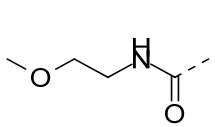
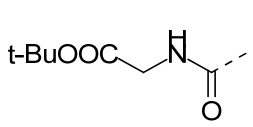
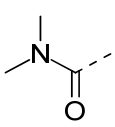
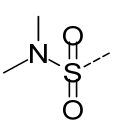
8. The compound according to claim 1 or 2, wherein each R_1 is independently selected from the group consisting of H, F, Cl, Br, I, OH, NH_2, CN, C_{1-3} alkyl, C_{3-5} cycloalkyl, C_{1-3} alkoxy, C_{1-3} alkylamino, C_{2-4} alkenyl,  , -S(=O)$_2$NH$_2$, -S(=O)$_2$NH-C_{1-3} alkyl, -NHS(=O)$_2$-C_{1-3} alkyl, -N[S(=O)$_2$-C_{1-3} alkyl]$_2$, -N[C(=O)-C_{1-3} alkyl]$_2$, -NHC(=O)-C_{1-3} alkyl, -C(=O)NH$_2$ and -C(=O)NH-C_{1-3} alkyl, wherein the C_{1-3} alkyl, C_{3-5} cycloalkyl, C_{1-3} alkoxy, C_{1-3} alkylamino, C_{2-4} alkenyl,  , -S(=O)$_2$NH$_2$, -S(=O)$_2$NH-C_{1-3} alkyl, -NHS(=O)$_2$-C_{1-3} alkyl, -N[S(=O)$_2$-C_{1-3} alkyl]$_2$, -N[C(=O)-C_{1-3} alkyl]$_2$, -NHC(=O)-C_{1-3} alkyl, -C(=O)NH$_2$ and -C(=O)NH-C_{1-3} alkyl are optionally substituted with 1, 2 or 3 R_a; preferably, each R_1 is

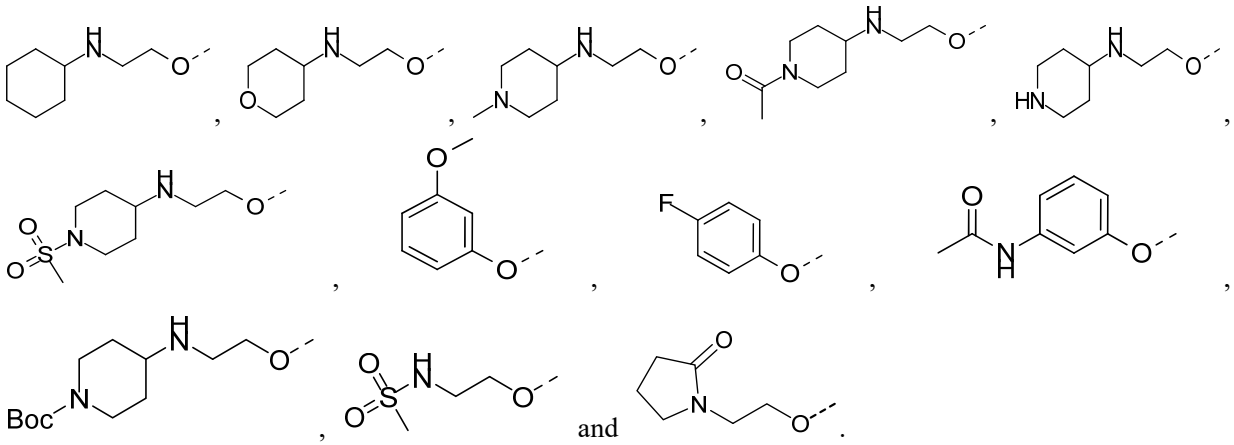
independently selected from the group consisting of H, F, Cl, Br, I, OH, NH_2, CN, C_{1-3} alkyl, C_{3-5} cycloalkyl, C_{1-3} alkoxy, C_{1-3} alkylamino, C_{2-4} alkenyl,  , $-S(=O)_2NH_2$, $-S(=O)_2NH-C_{1-3}$ alkyl, $-NHS(=O)_2-C_{1-3}$ alkyl, $-N[S(=O)_2-C_{1-3}$ alkyl$]_2$, $-N[C(=O)-C_{1-3}$ alkyl$]_2$, $-NHC(=O)-C_{1-3}$ alkyl, $-C(=O)NH_2$ and $-C(=O)NH-C_{1-3}$ alkyl, wherein the C_{1-3} alkyl, C_{3-5} cycloalkyl, C_{1-3} alkoxy, C_{1-3} alkylamino, C_{2-4} alkenyl,  , $-S(=O)_2NH_2$, $-S(=O)_2NH-C_{1-3}$ alkyl, $-NHS(=O)_2-C_{1-3}$ alkyl, $-N[S(=O)_2-C_{1-3}$ alkyl$]_2$, $-N[C(=O)-C_{1-3}$ alkyl$]_2$, $-NHC(=O)-C_{1-3}$ alkyl, $-C(=O)NH_2$ and $-C(=O)NH-C_{1-3}$ alkyl are optionally substituted with 1, 2 or 3 R_a.

9. The compound according to claim 1 or 2, wherein each R_1 is independently selected from the group consisting of H, F, Cl, Br, I, OH, NH_2, CN, C_{1-3} alkyl, C_{1-3} alkoxy and $-C(=O)NH_2$, wherein the C_{1-3} alkyl, C_{1-3} alkoxy and $-C(=O)NH_2$ are optionally substituted with 1, 2 or 3 R_a; preferably, each R_1 is independently selected from the group consisting of H, F, Cl, Br, I, OH, NH_2, CN, Me,  ,  and , wherein the Me,  ,  and are optionally substituted with 1, 2 or 3 R_a; more preferably, each R_1 is independently selected from the group consisting of H, Me, OH,  ,  and  .

10. The compound according to claim 1 or 2, wherein each R_1 is independently selected from the group consisting of F, Cl, Br, I, OH, NH_2 and C_{1-3} alkyl, wherein the C_{1-3} alkyl is optionally substituted with 1, 2 or 3 R_a; preferably, each R_1 is independently selected from the group consisting of F, Cl, Br, I, OH, NH_2 and Me, wherein the Me is optionally substituted with 1, 2 or 3 R_a; more preferably, each R_1 is independently selected from Me.

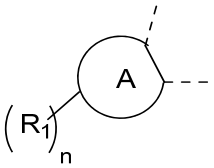
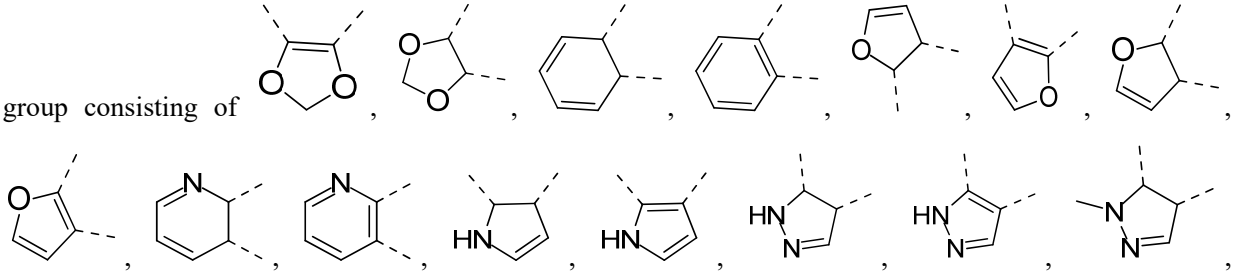
11. The compound according to claim 1 or 2, wherein each R_1 is independently selected from the group consisting of H, F, Cl, Br, I, OH, NH_2, CN, Me,  ,

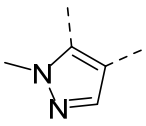
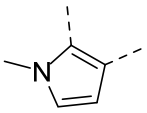
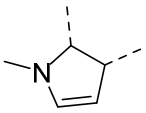
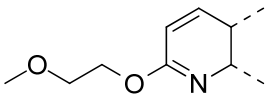
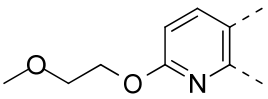
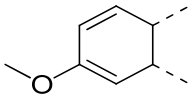
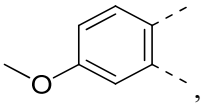
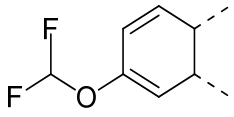
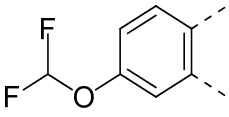
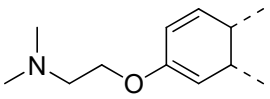
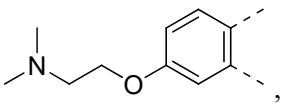
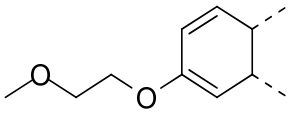
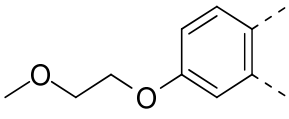
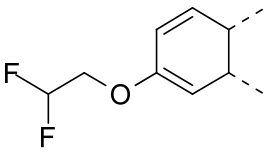
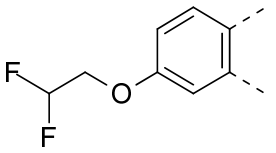
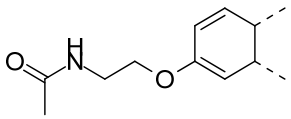
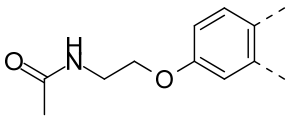
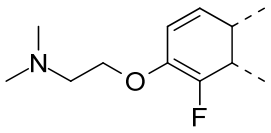
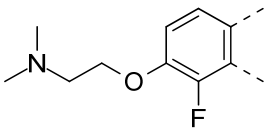
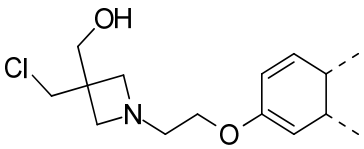
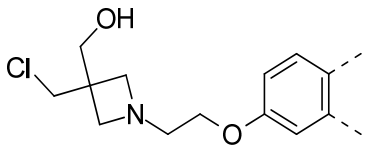
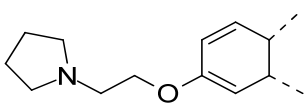
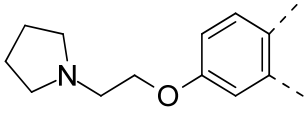
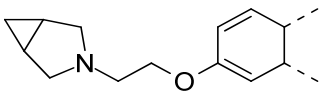
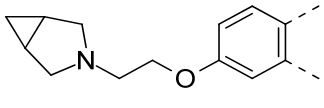
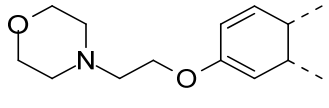
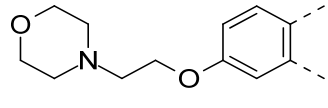
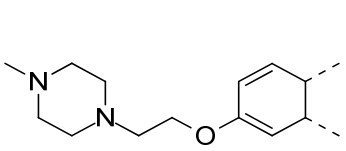
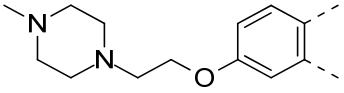
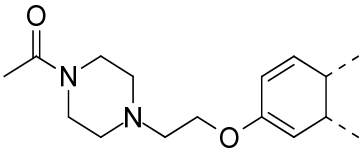
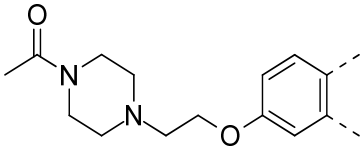
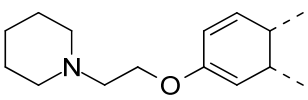
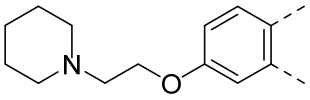
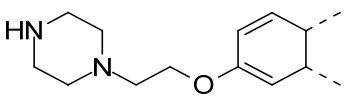
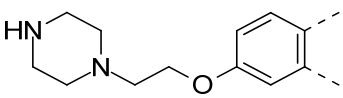
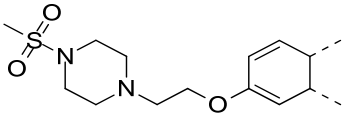
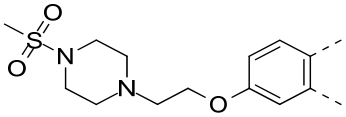
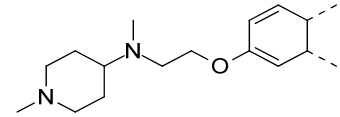
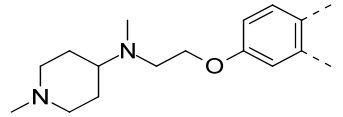
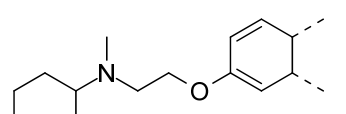
-$S(=O)_2NH_2$,  ,  , -$NHCH_3$ and -$C(=O)NH_2$, wherein the Me,  ,  ,  ,  ,  ,  , -$S(=O)_2NH_2$,  ,  , -$NHCH_3$ and-$C(=O)NH_2$ are optionally substituted with 1, 2 or 3 R_a; preferably, each R_1 is independently selected from the group consisting of H, F, Cl, Br, I, OH, NH_2, Me,  ,  ,  ,  ,  ,  , -$S(=O)_2NH_2$,  ,  , -$NHCH_3$ and -$C(=O)NH_2$, wherein the Me,  ,  ,  , -$S(=O)_2NH_2$, -$NHCH_3$ and -$C(=O)NH_2$ are optionally substituted with 1, 2 or 3 R_a; more preferably, each R_1 is independently selected from the group consisting of H, F, Cl, Br, I, Me, OH, NH_2,  ,  , ,  , , ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,



12. The compound according to claim 1 or 2, wherein ring A is selected from the group consisting of 5-6 membered heteroaryl, phenyl, 4-7 membered heterocycloalkyl and 4-7 membered heterocycloalkenyl; preferably, ring A is selected from the group consisting of 5-6 membered heteroaryl, phenyl and 4-7 membered heterocycloalkenyl; more preferably, ring A is selected from the group consisting of phenyl, 1,3-cyclohexadienyl, 1,3-dioxolanyl, 1,3-dioxolyl, morpholinyl, oxazolyl, cyclobutyl, oxapanyl, thiazolyl, tetrahydrothiazolyl, furanyl, 2,3-dihydrofuranyl, 1,4-oxazepanyl, pyridinyl, 2,3-dihydropyridinyl, pyrazolyl, 4,5-dihydro-1*H*-pyrazolyl, oxazolyl, 4,5-dihydrooxazolyl, pyrrolyl and 2,3-dihydro-1*H*-pyrrolyl; even more preferably, ring A is selected from the group consisting of phenyl, 1,3-dioxolanyl, morpholinyl, oxazolyl, cyclobutyl, oxapanyl, thiazolyl, tetrahydrothiazolyl, furanyl, tetrahydrofuranyl and 1,4-oxazepanyl; still more preferably, ring A is selected from the group consisting of phenyl, 1,3-dioxolanyl, morpholinyl, oxazolyl, cyclobutyl, oxapanyl and 1,4-oxazepanyl.

13. The compound according to claim 1 or 2, wherein ring A is selected from the group consisting of phenyl, 1,3-dioxolanyl, morpholinyl, oxazolyl, cyclobutyl, oxapanyl, thiazolyl, tetrahydrothiazolyl, furanyl, 1,4-oxazepanyl, pyridinyl and pyrrolyl; preferably, ring A is selected from the group consisting of phenyl, 1,3-dioxolanyl, furanyl, pyridinyl and pyrrolyl; more preferably, ring A is selected from the group consisting of phenyl, 1,3-dioxolanyl and furanyl.

14. The compound according to claim 1 or 2, wherein the structural unit  is selected from the group consisting of 


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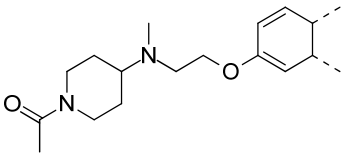
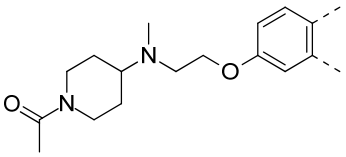
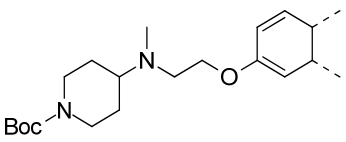
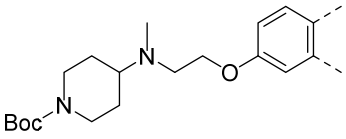
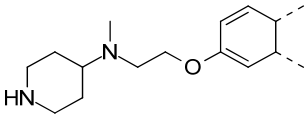
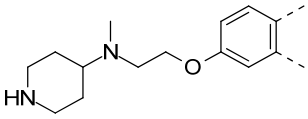
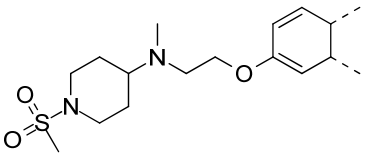
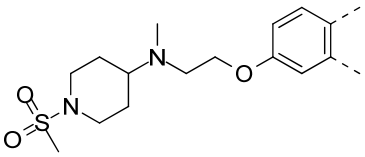
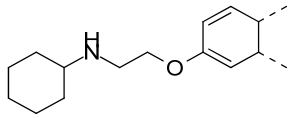
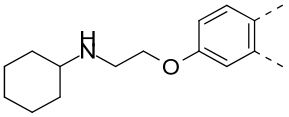
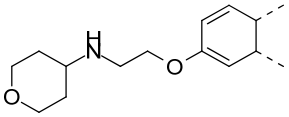
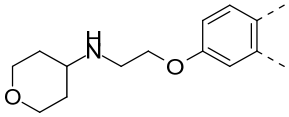
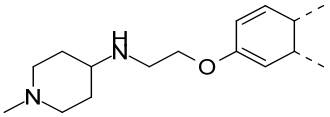
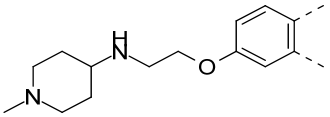
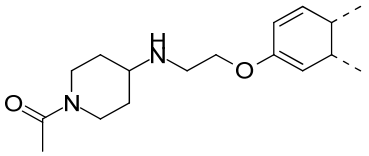
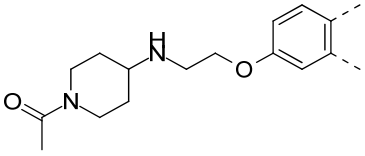
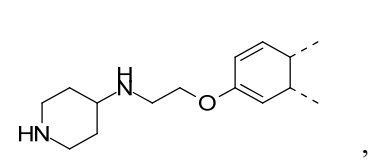
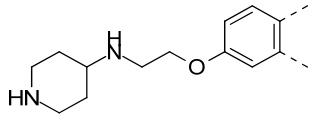
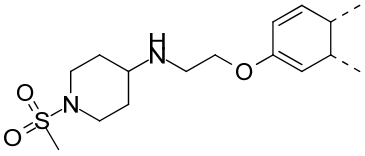
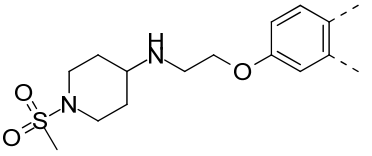
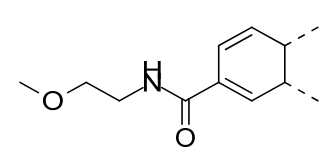
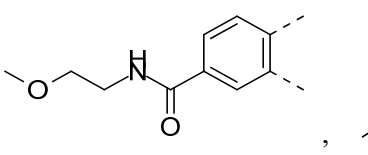
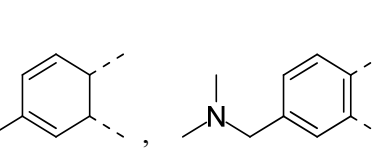
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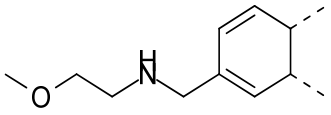
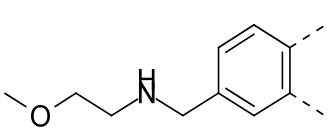
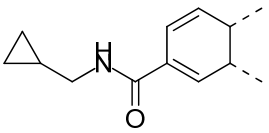
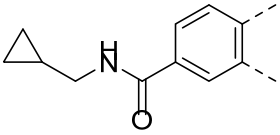
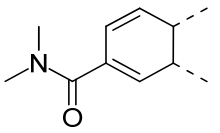
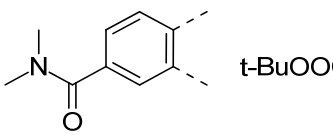
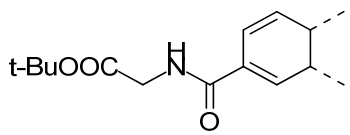
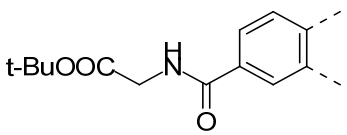
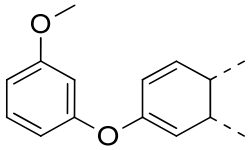
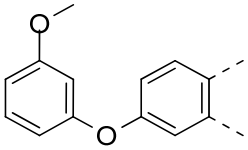
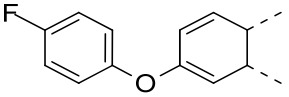
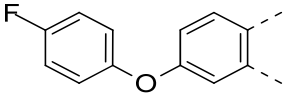
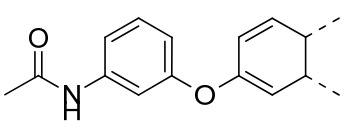
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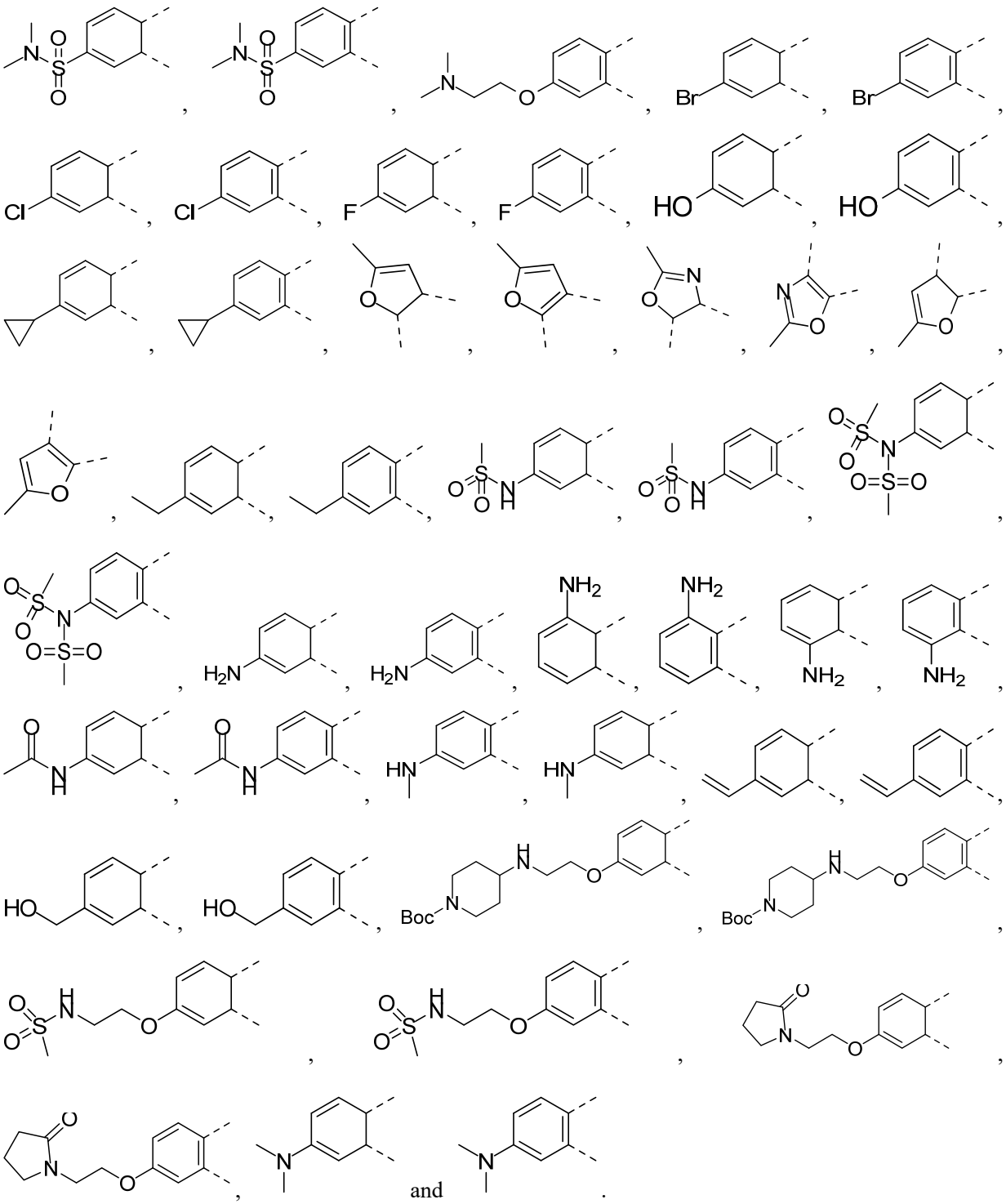
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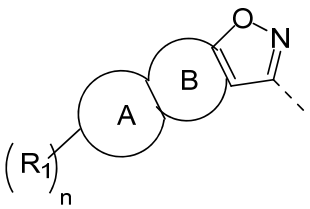
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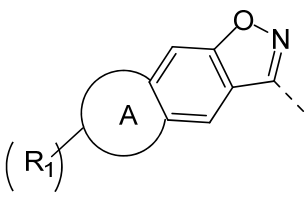
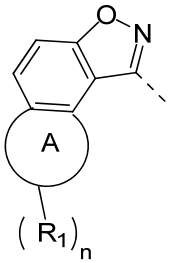
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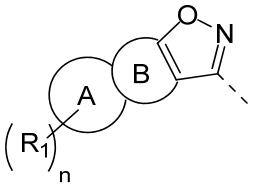
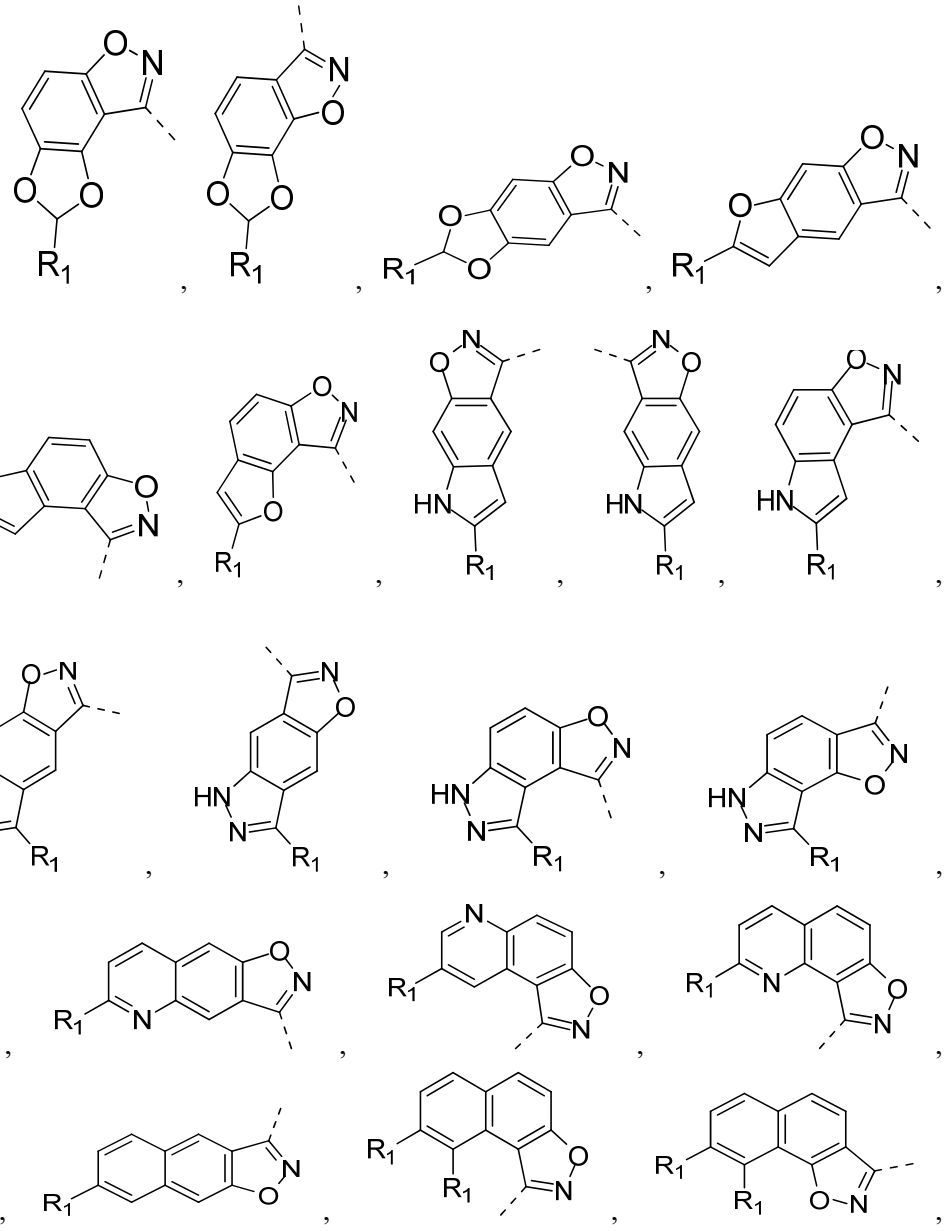
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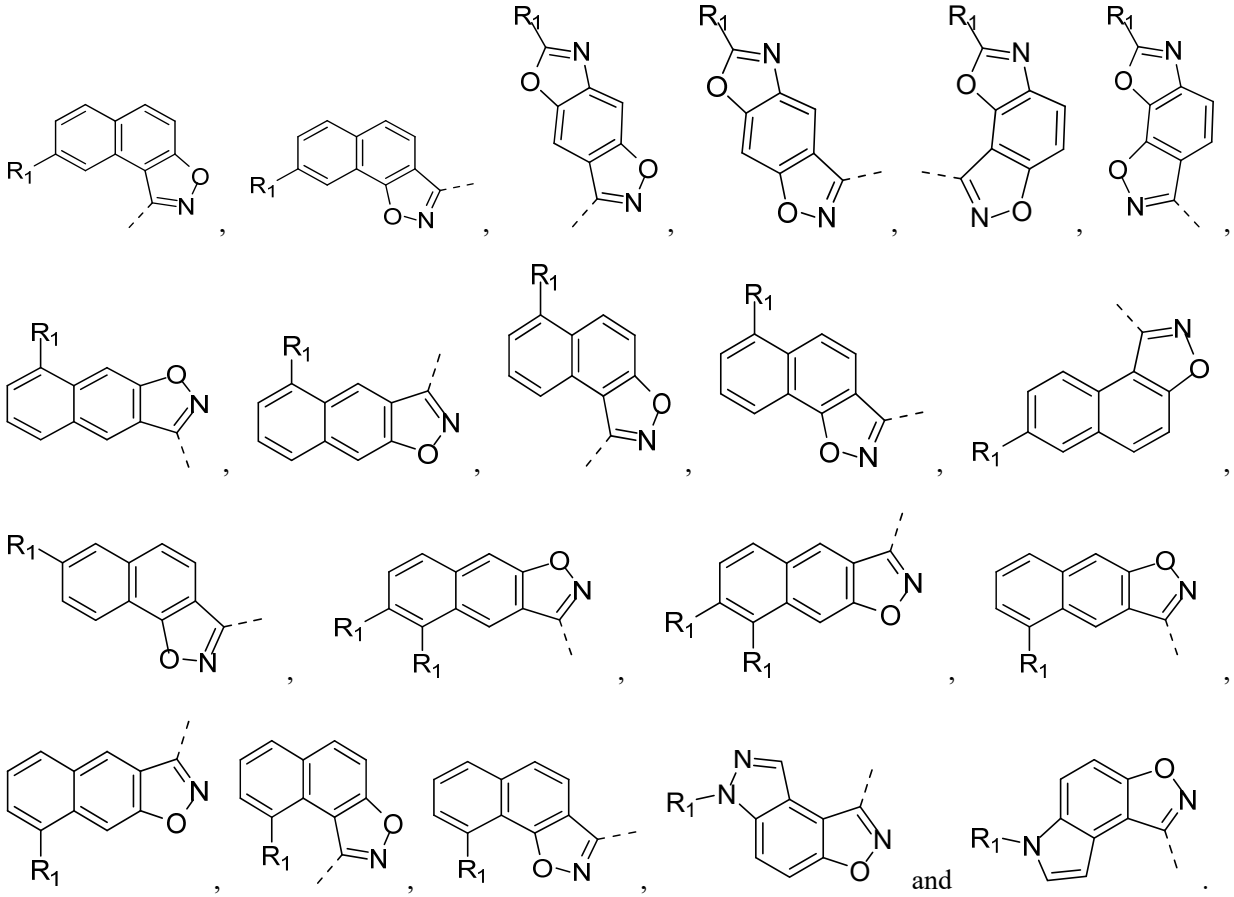
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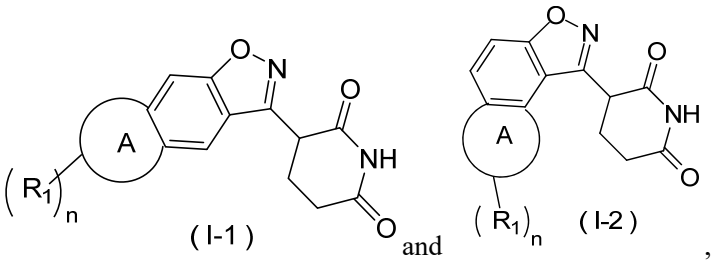
15. The compound according to claim 1 or 2, wherein the structural unit  is selected

from the group consisting of  and  .

16. The compound according to claim 1 or 2, wherein the structural unit  is selected from the group consisting of 

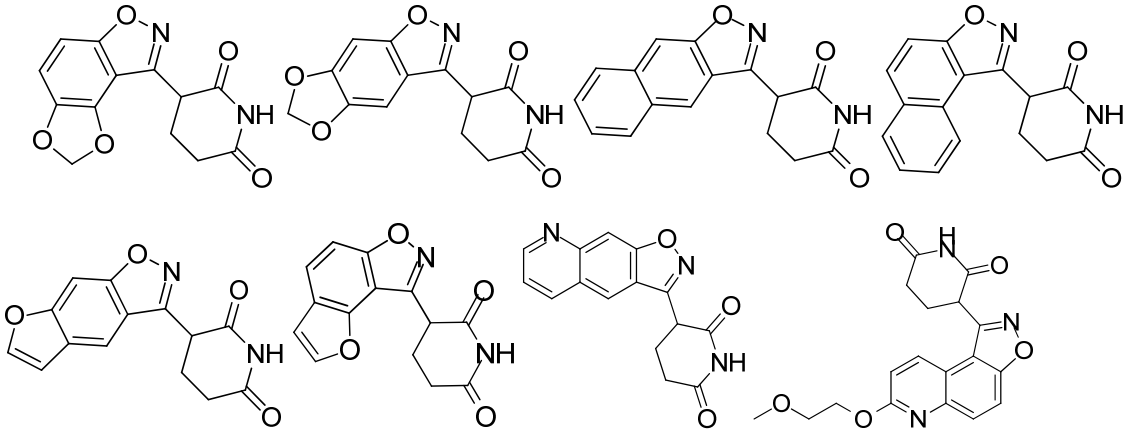


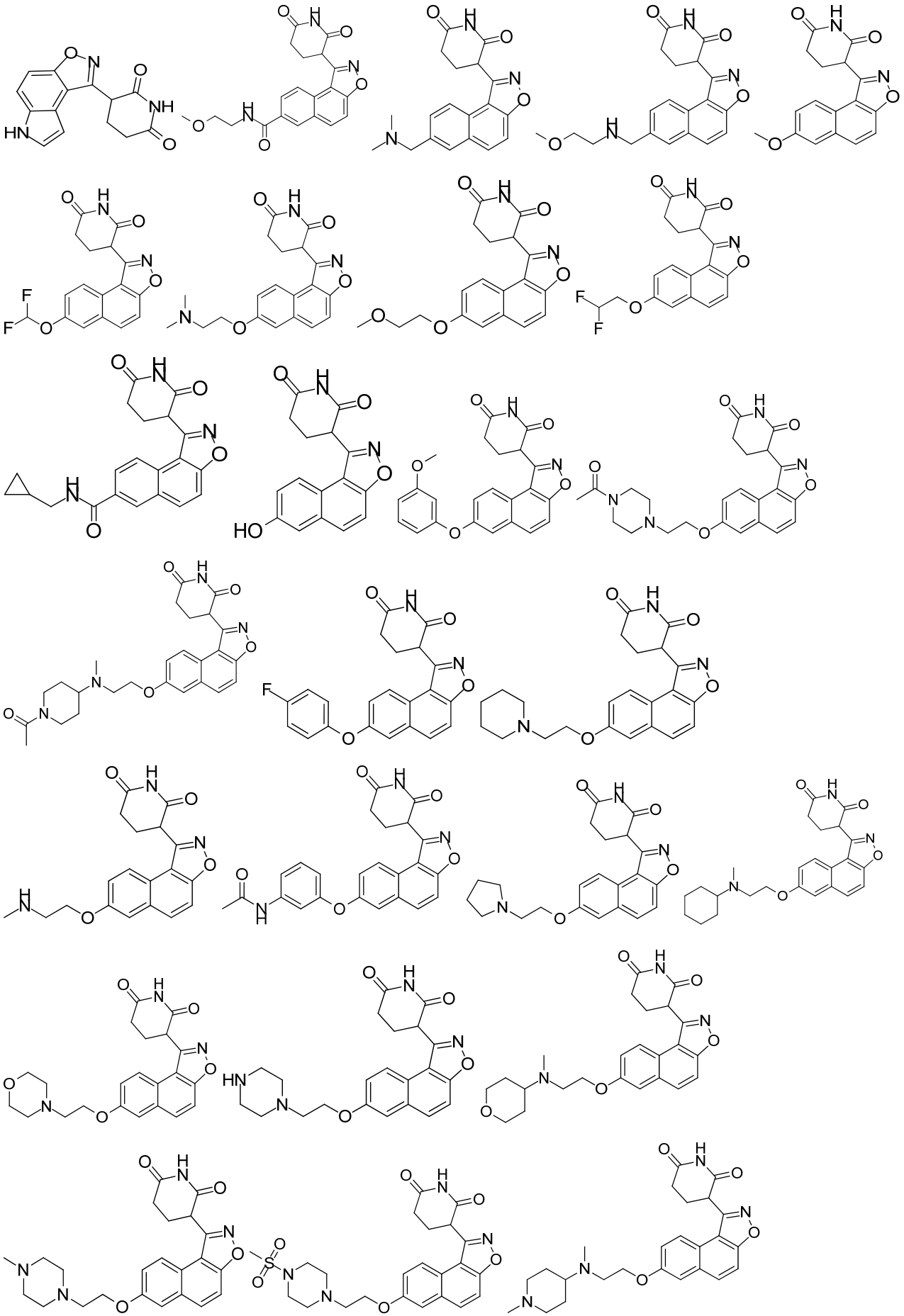
17. The compound according to claim 1 or 2, selected from the group consisting of

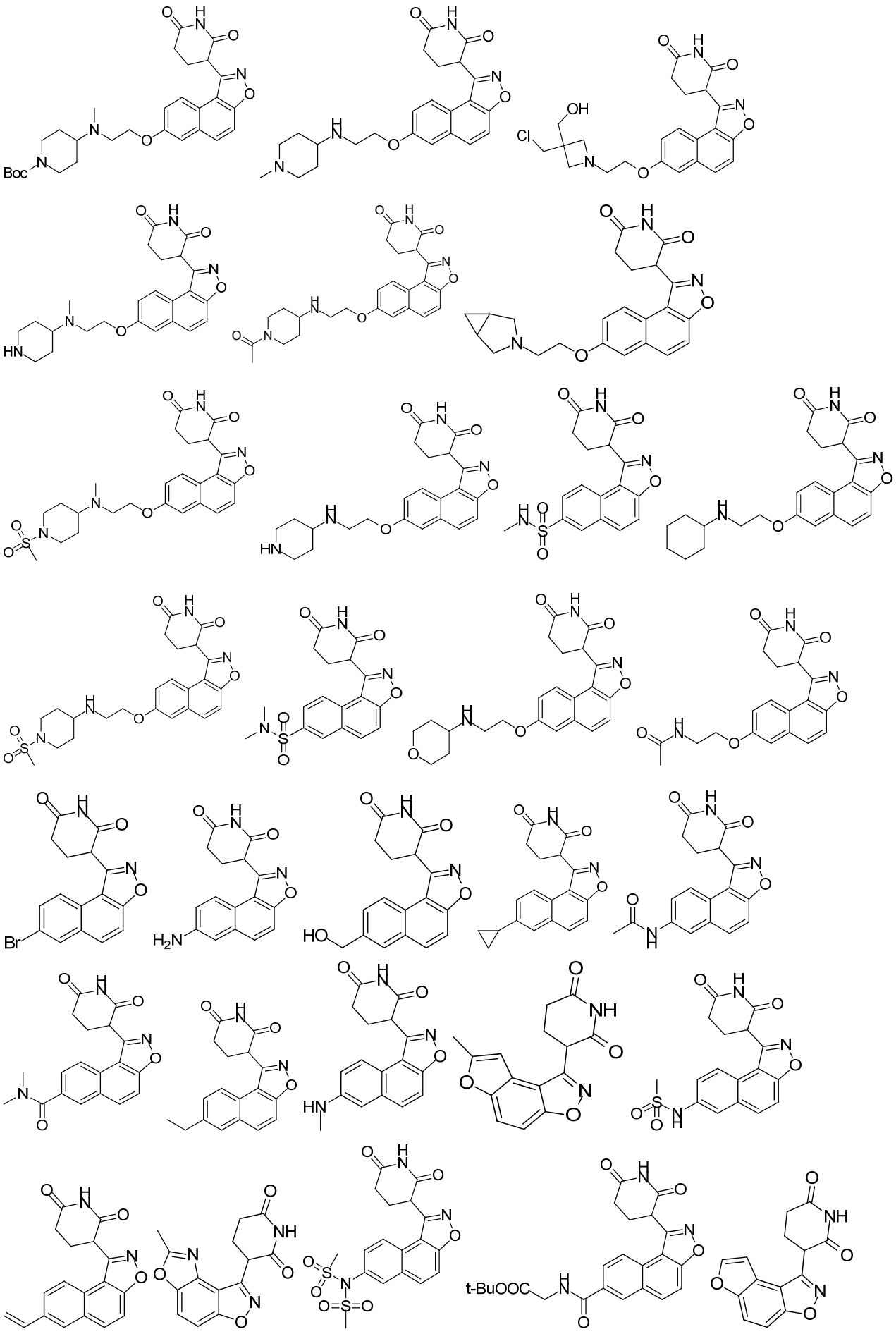


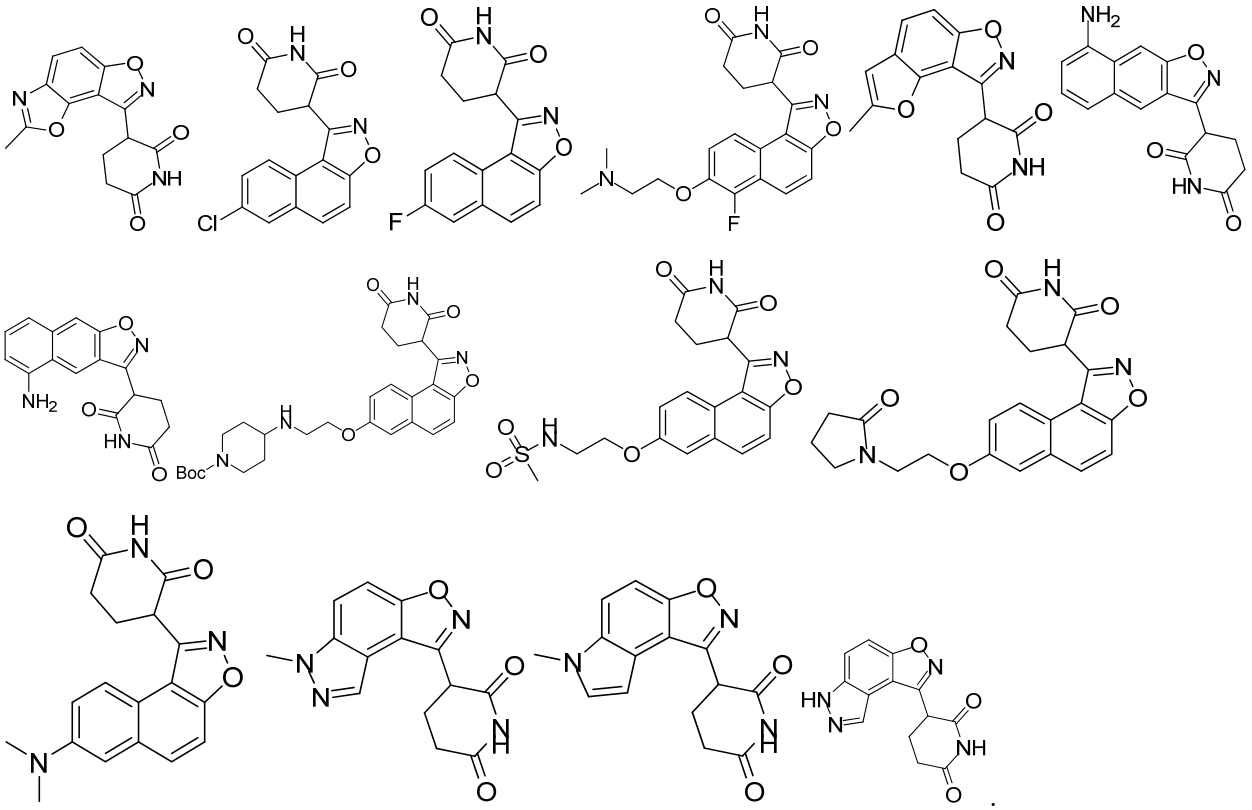
wherein n, ring A and R_1 are defined as in claim 1.

18. A compound of a formula below and a pharmaceutically acceptable salt thereof, selected from the group consisting of:









19. A pharmaceutical composition, comprising a therapeutically effective amount of the compound or the pharmaceutically acceptable salt thereof according to any one of claims 1-18 as an active ingredient, and a pharmaceutically acceptable carrier.

20. Use of the compound or the pharmaceutically acceptable salt thereof according to any one of claims 1-18 and the pharmaceutical composition according to claim 19 in preparing a medicament for treating a disease related to CRBN protein.

21. The compound or the pharmaceutically acceptable salt thereof according to any one of claims 1-18 and the pharmaceutical composition according to claim 19 for treating a disease related to CRBN protein.

22. The use according to Claim 20, wherein the disease related to CRBN protein is multiple myeloma.