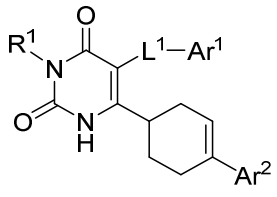
aldosterone and cortisol have similar affinity for MR. However, glucocorticoids circulate at roughly 100 times the level of mineralocorticoids. An enzyme (11-β hydroxsteroid dehydrogenase 1) exists in mineralocorticoid target tissues to prevent overstimulation by glucocorticoids.

[0005] When administered to subjects in need thereof, steroids can provide both intended therapeutic effects. as well as negative side effects. What is needed in the art are new compositions and methods for selectively modulating GR Surprisingly, the present invention meets these and other needs.

BRIEF SUMMARY

[0006] In one example, the present disclosure provides a compound of formula I:



(I)

or a pharmaceutically acceptable salt thereof,

wherein

R^1 is H or C_{1-6} alkyl;

L^1 is C_{1-4} alkylene;

Ar^1 is a C_{6-12} aryl or 5-10 membered heteroaryl having 1-4 heteroatoms selected from N, O, and S, each of which is optionally substituted with 1-3 R^a groups;

each R^a is independently H, halogen, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, $-SO_2R^{a1}$, or $-NR^{a1}R^{a2}$;

R^{a1} and R^{a2} are each independently H or C_{1-4} alkyl; or R^{a1} and R^{a2} when attached to a nitrogen atom are combined to form a 3-6 membered heterocycle having 1-2 heteroatoms selected from N, O, and S, which is optionally substituted with 1-2 R^{a3};

each R^{a3} is independently H, halogen, C_{1-4} alkyl, or C_{1-4} alkoxy;

Ar^2 is a C_{6-12} aryl or 5-10 membered heteroaryl having 1-4 heteroatoms selected from N, O, and S, each of which is optionally substituted with 1-4 R^b groups;

each R^b is independently H, halogen, CN, hydroxy, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} alkoxy, C_{1-4} alkoxy-C_{1-4} alkyl, C_{1-4} hydroxyalkyl, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, $-OR^{b4}$, $-NR^{b1}R^{b2}$, $-C(O)R^{b1}$, $-C(O)OR^{b1}$, $-OC(O)R^{b1}$, $-C(O)NR^{b1}R^{b2}$, $-NR^{b1}C(O)R^{b2}$, $-SO_2R^{b1}$, $-SO_2NR^{b1}R^{b2}$, or C_{3-6} cycloalkyl;

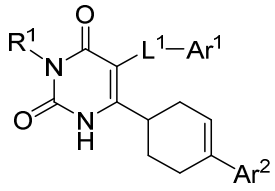
alternatively, two R^b groups on adjacent ring atoms can be combined to form a C_{5-8} cycloalkyl or a 5-8 membered heterocycle having 1-2 heteroatoms selected from N, O, and S;

R^{b1} and R^{b2} are each independently H or C_{1-4} alkyl; or R^{b1} and R^{b2} when attached to a nitrogen atom are combined to form a 3-6 membered heterocycle having 1-2 heteroatoms selected from N, O, and S, which is optionally substituted with 1-2 R^{b3};

each R^{b3} is independently H, halogen, C_{1-4} alkyl, or C_{1-4} alkoxy; and

each R^{b4} is independently C_{1-4} hydroxyalkyl, C_{1-4} alkoxy-C_{1-4} alkyl, C_{3-6} cycloalkyl or C_{3-6} cycloalkyl-C_{1-4} alkyl.

In one example, the present disclosure provides a compound of formula I:



(I)

or a pharmaceutically acceptable salt thereof, or an isomer thereof,
wherein

R^1 is H or C_{1-6} alkyl;

L^1 is C_{1-4} alkylene;

Ar^1 is a C_{6-12} aryl or 5-10 membered heteroaryl having 1-4 heteroatoms selected from N, O, and S, each of which is optionally substituted with 1-3 R^a groups;

each R^a is independently H, halogen, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, $-SO_2R^{a1}$, or $-NR^{a1}R^{a2}$;

R^{a1} and R^{a2} are each independently H or C_{1-4} alkyl; or R^{a1} and R^{a2} when attached to a nitrogen atom are combined to form a 3-6 membered heterocycle having 1-2 heteroatoms selected from N, O, and S, which is optionally substituted with 1-2 R^{a3};

each R^{a3} is independently H, halogen, C_{1-4} alkyl, or C_{1-4} alkoxy;

Ar^2 is a C_{6-12} aryl or 5-10 membered heteroaryl having 1-4 heteroatoms selected from N, O, and S, each of which is optionally substituted with 1-4 R^b groups;

each R^b is independently H, halogen, CN, hydroxy, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} alkoxy, C_{1-4} alkoxy-C_{1-4} alkyl, C_{1-4} hydroxyalkyl, C_{1-4} haloalkyl,

C_{1-4} haloalkoxy, $-OR^{b4}$, $-NR^{b1}R^{b2}$, $-C(O)R^{b1}$, $-C(O)OR^{b1}$, $-OC(O)R^{b1}$, $-C(O)NR^{b1}R^{b2}$, $-NR^{b1}C(O)R^{b2}$, $-SO_2R^{b1}$, $-SO_2NR^{b1}R^{b2}$, or C_{3-6} cycloalkyl;

alternatively, two R^b groups on adjacent ring atoms can be combined to form a C_{5-8} cycloalkyl or a 5-8 membered heterocycle having 1-2 heteroatoms selected from N, O, and S;

R^{b1} and R^{b2} are each independently H or C_{1-4} alkyl; or R^{b1} and R^{b2} when attached to a nitrogen atom are combined to form a 3-6 membered heterocycle having 1-2 heteroatoms selected from N, O, and S, which is optionally substituted with 1-2 R^{b3};

each R^{b3} is independently H, halogen, C_{1-4} alkyl, or C_{1-4} alkoxy; and

each R^{b4} is independently C_{1-4} hydroxyalkyl, C_{1-4} alkoxy-C_{1-4} alkyl, C_{3-6} cycloalkyl or C_{3-6} cycloalkyl-C_{1-4} alkyl.

[0007] In a second aspect, the present disclosure provides a pharmaceutical composition comprising one or more pharmaceutically acceptable excipients and a compound of the disclosure. In a second example, the present disclosure provides a pharmaceutical composition including one or more pharmaceutically acceptable excipients and the compound of formula I.

[0008] In a third aspect, the present disclosure provides a use of a therapeutically effective amount of a compound of the disclosure or a pharmaceutical composition of the disclosure in the manufacture of a medicament for treating a disorder or condition through modulating a glucocorticoid receptor. In a third example, the present disclosure provides a method of treating a disorder or condition through modulating a glucocorticoid receptor, the method including administering to a subject in need of such treatment, a therapeutically effective amount of the compound of formula I or a pharmaceutical composition of the compound of formula I, thereby treating the disorder or condition.

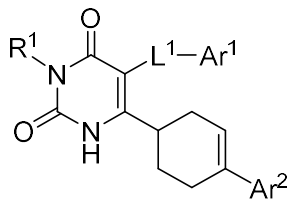
[0009] In a fourth aspect, the present disclosure provides a use of an effective amount of the compound of the disclosure or a pharmaceutical composition of the disclosure in the manufacture of a medicament for treating a disorder or condition through antagonizing a glucocorticoid receptor. In a fourth example, the present disclosure provides a method of treating a disorder or condition through antagonizing a glucocorticoid receptor, the method including administering to a subject in need of such treatment, an effective amount of the compound of formula I or a pharmaceutical composition of the compound of formula I.

BRIEF DESCRIPTION OF THE DRAWINGS

[0010] FIG. 1 shows a method of preparing the compounds of the present invention.

WHAT IS CLAIMED IS:

1. A compound of formula I:



(I)

or a pharmaceutically acceptable salt thereof,

wherein

R^1 is H or C_{1-6} alkyl;

L^1 is C_{1-4} alkylene;

Ar^1 is a C_{6-12} aryl or 5-10 membered heteroaryl having 1-4 heteroatoms selected from N, O, and S, each of which is optionally substituted with 1-3 R^a groups;

each R^a is independently H, halogen, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, $-SO_2R^{a1}$, or $-NR^{a1}R^{a2}$;

R^{a1} and R^{a2} are each independently H or C_{1-4} alkyl; or R^{a1} and R^{a2} when attached to a nitrogen atom are combined to form a 3-6 membered heterocycle having 1-2 heteroatoms selected from N, O, and S, which is optionally substituted with 1-2 R^{a3};

each R^{a3} is independently H, halogen, C_{1-4} alkyl, or C_{1-4} alkoxy;

Ar^2 is a C_{6-12} aryl or 5-10 membered heteroaryl having 1-4 heteroatoms selected from N, O, and S, each of which is optionally substituted with 1-4 R^b groups;

each R^b is independently H, halogen, CN, hydroxy, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} alkoxy, C_{1-4} alkoxy-C_{1-4} alkyl, C_{1-4} hydroxyalkyl, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, $-OR^{b4}$, $-NR^{b1}R^{b2}$, $-C(O)R^{b1}$, $-C(O)OR^{b1}$, $-OC(O)R^{b1}$, $-C(O)NR^{b1}R^{b2}$, $-NR^{b1}C(O)R^{b2}$, $-SO_2R^{b1}$, $-SO_2NR^{b1}R^{b2}$, or C_{3-6} cycloalkyl;

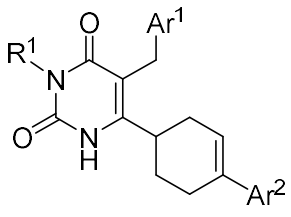
alternatively, two R^b groups on adjacent ring atoms can be combined to form a C_{5-8} cycloalkyl or a 5-8 membered heterocycle having 1-2 heteroatoms selected from N, O, and S;

R^{b1} and R^{b2} are each independently H or C_{1-4} alkyl; or R^{b1} and R^{b2} when attached to a nitrogen atom are combined to form a 3-6 membered heterocycle having 1-2 heteroatoms selected from N, O, and S, which is optionally substituted with 1-2 R^{b3};

each R^{b3} is independently H, halogen, C_{1-4} alkyl, or C_{1-4} alkoxy; and

each R^{b4} is independently C_{1-4} hydroxyalkyl, C_{1-4} alkoxy-C_{1-4} alkyl, C_{3-6} cycloalkyl or C_{3-6} cycloalkyl-C_{1-4} alkyl.

2. The compound of claim 1, having formula Ia:



(Ia).

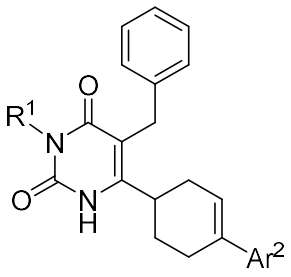
3. The compound of claim 1 or 2, wherein Ar^1 is phenyl, pyridinyl, or thiazolyl, each of which is optionally substituted with 1-2 R^a groups.

4. The compound of any one of claims 1 to 3, wherein Ar^1 is phenyl, which is optionally substituted with 1-2 R^a groups.

5. The compound of any one of claims 1 to 4, wherein each R^a is independently H, F, Cl, CN, Me, Et, OMe, CF_3, NH_2, or $N(Me)_2$.

6. The compound of any one of claims 1 to 4, wherein each R^a is independently H, F, CF_3, or 1-pyrrolidinyl.

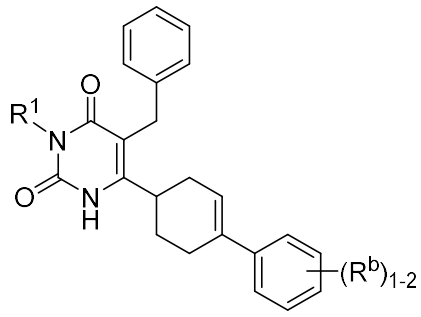
7. The compound of any one of claims 1 to 6, having formula Ib:



(Ib).

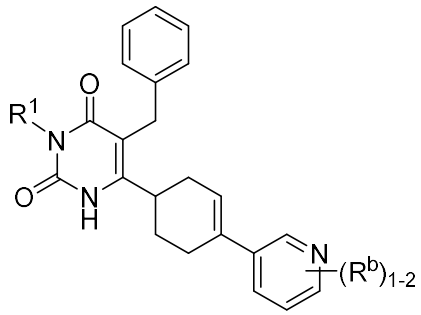
8. The compound of any one of claims 1 to 7, wherein Ar^2 is phenyl, pyridinyl, pyrimidiniyl, thiazolyl, pyrazolyl, indazolyl, benzothiazolyl, benzopyrazolyl, or [1,2,4]triazolo[4,3-a]pyridinyl each of which is optionally substituted with 1-2 R^b groups.

9. The compound of any one of claims 1 to 8, having formula Ic:



(Ic).

10. The compound of any one of claims 1 to 8, having formula Id:



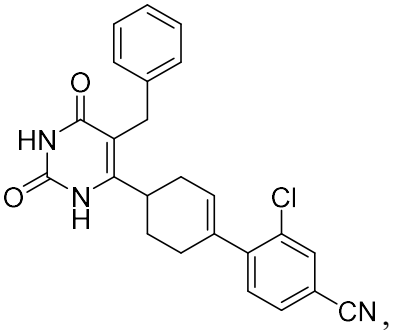
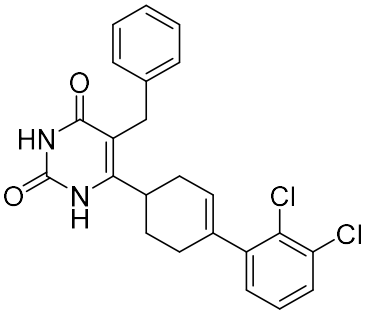
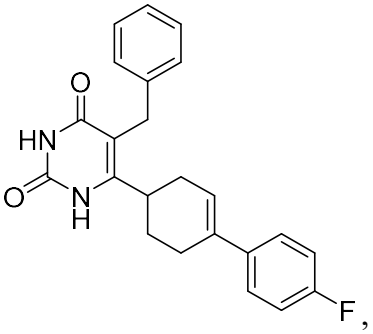
(Id).

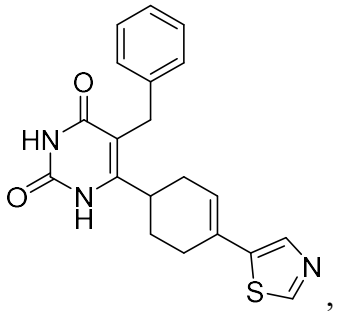
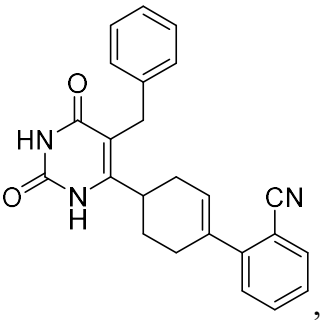
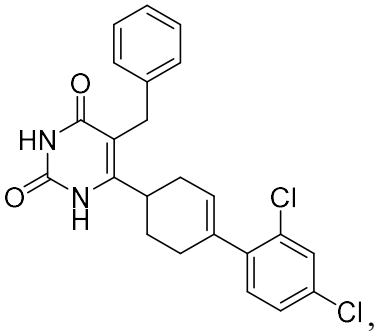
11. The compound of any one of claims 1 to 10, wherein each R^b is independently H, F, Cl, CN, Me, Et, iBu, OMe, OEt, OiPr, CF_3, $OCHF_2$, OCF_3, OCH_2CF_3, $-CH_2OH$, $-OCH_2CH_2OH$, -O-cyclopropyl, -O-cyclopropylmethyl, $-NMe_2$, $-S(O)_2Me$, $-S(O)_2Et$, $-S(O)_2iPr$, $-S(O)_2NHMe$, $-S(O)_2NMe_2$, 1-pyrrolidinyl, 1-piperidinyl, 4,4-diflouro-1-piperidinyl, 3,3-dimethyl-1-piperidinyl, 3-methyl-1-piperidinyl, 3-methoxy-1-piperidinyl, -C(O)-1-pyrrolidinyl, -C(O)-4-methyl-1-piperazinyl, or cyclopropyl.

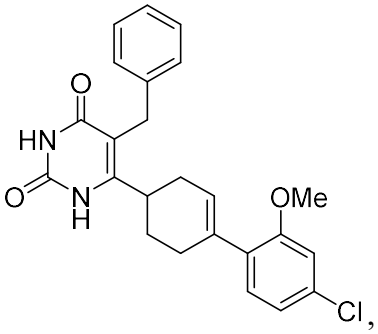
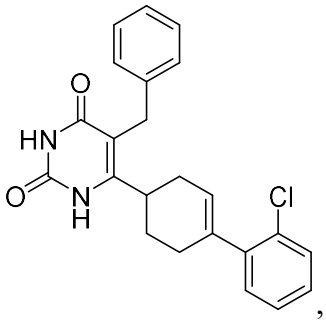
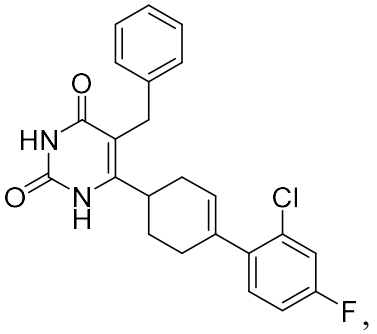
12. The compound of any one of claims 1 to 11, wherein each R^b is independently H, F, Cl, CN, Me, CF_3, OCF_3, or $–CH_2OH$.

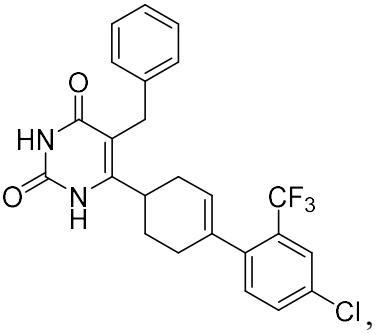
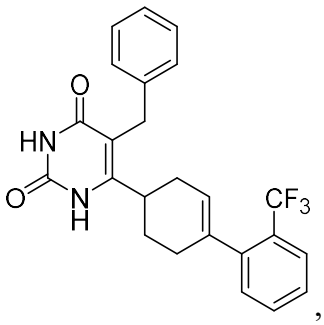
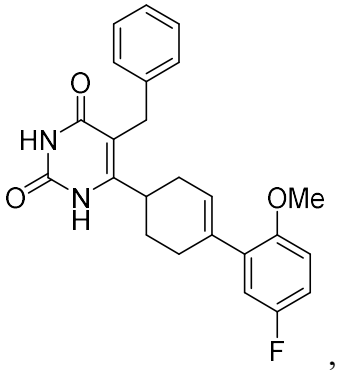
13. The compound of any one of claims 1 to 12, wherein R^1 is H.

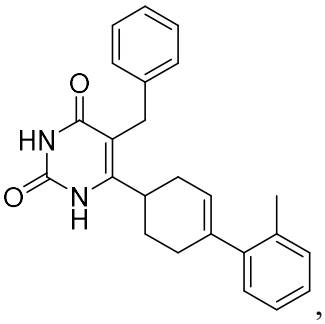
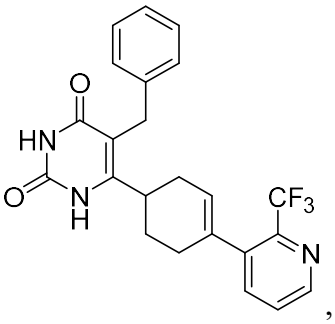
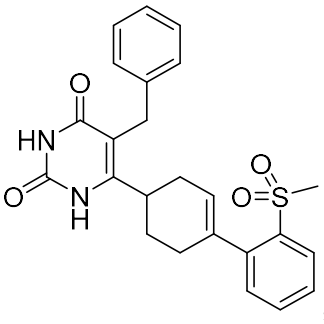
14. The compound of claim 1, selected from the group consisting of:

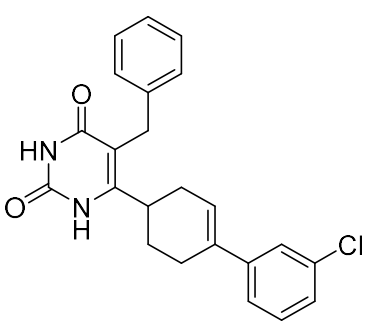
 ,  ,  ,

 ,  ,  ,

 ,  ,  ,

 ,  ,  ,

 ,  ,  ,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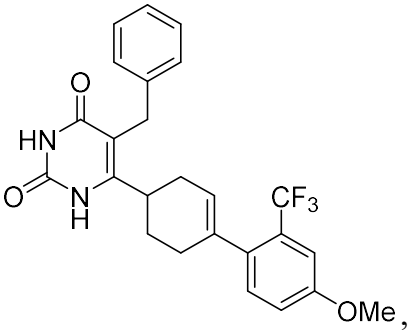
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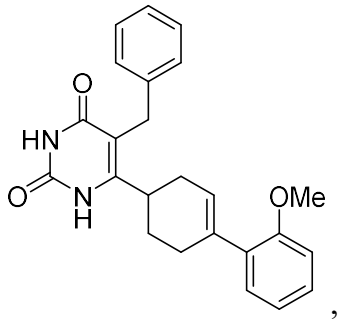
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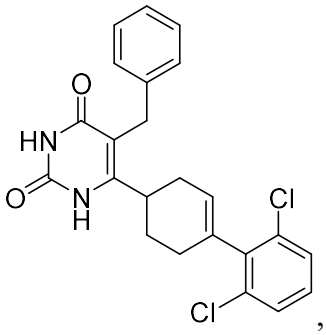
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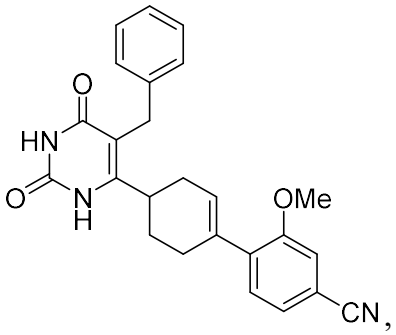
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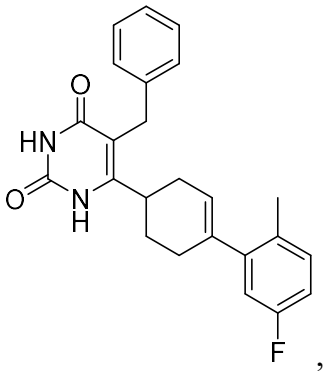
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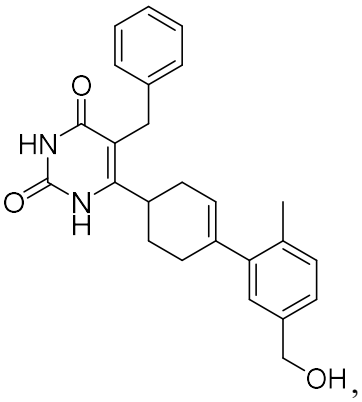
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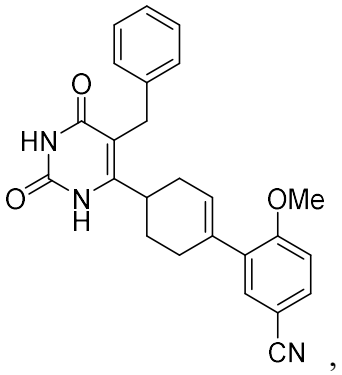
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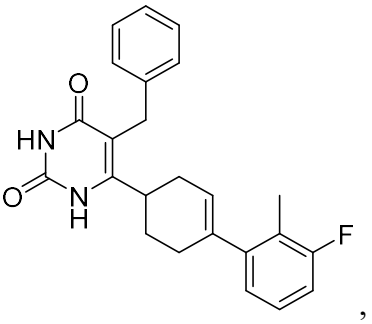
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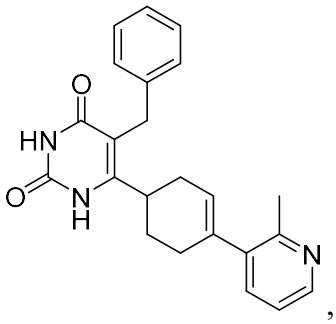
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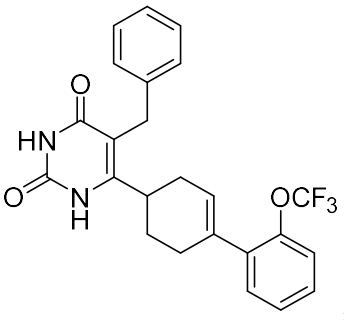
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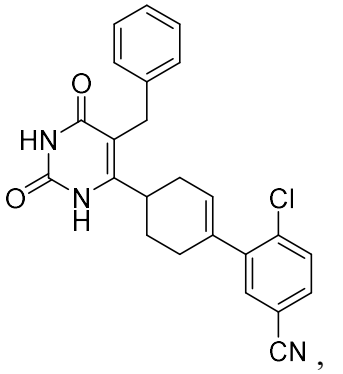

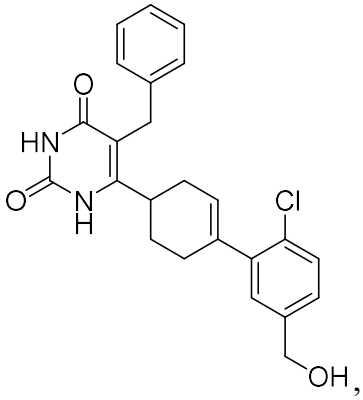
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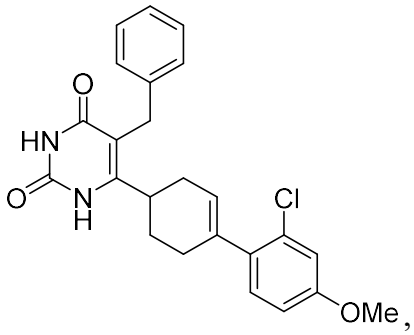
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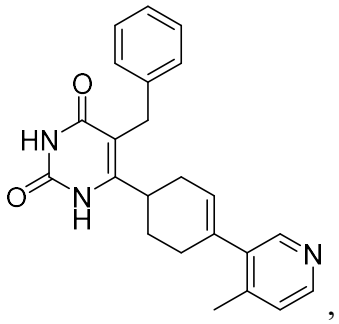
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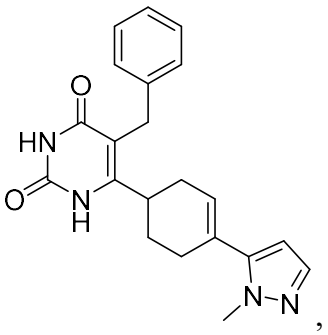
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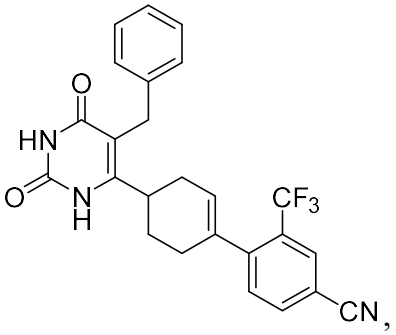
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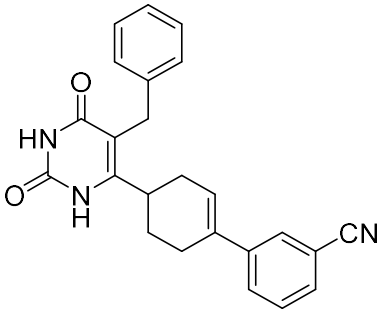
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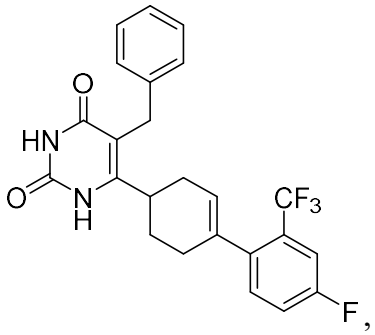
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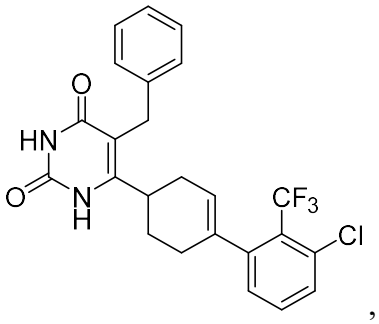
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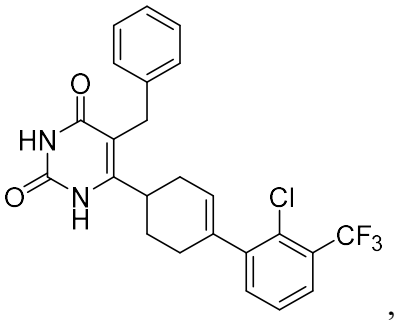
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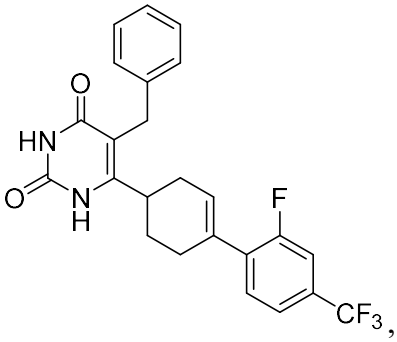
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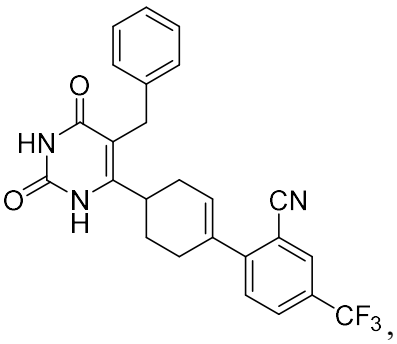
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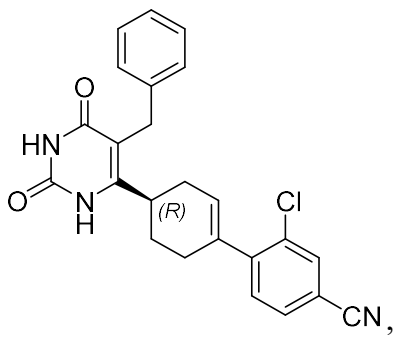
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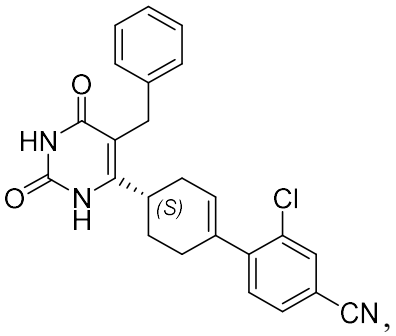
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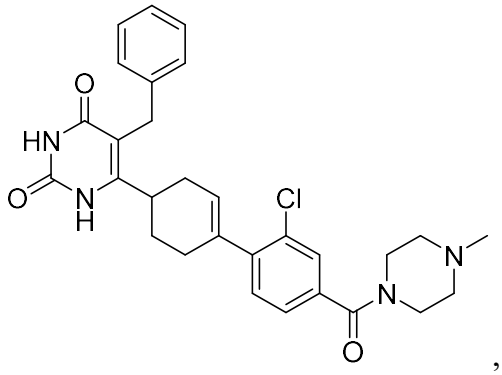
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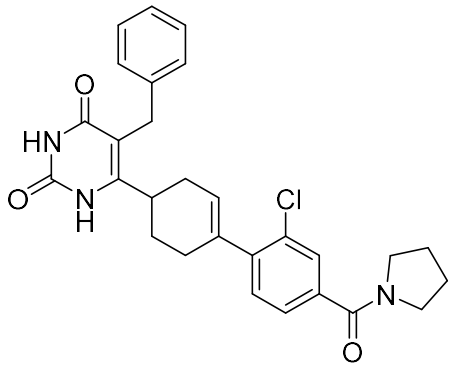
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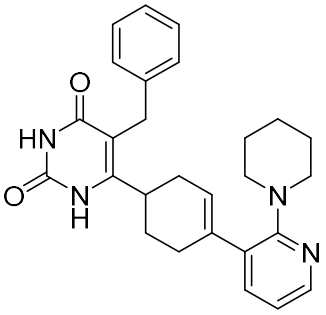
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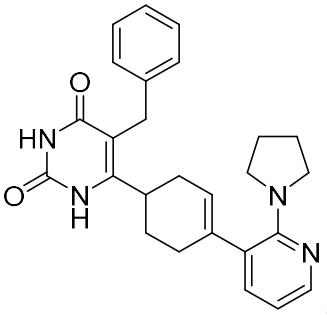
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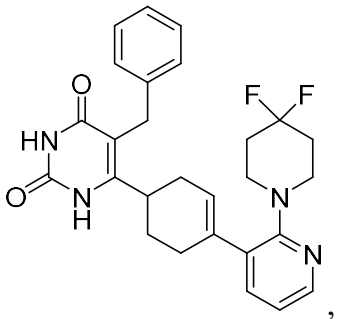
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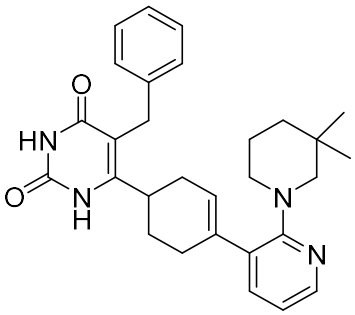
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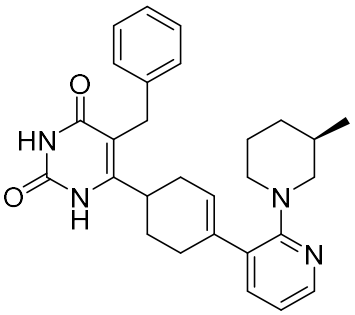
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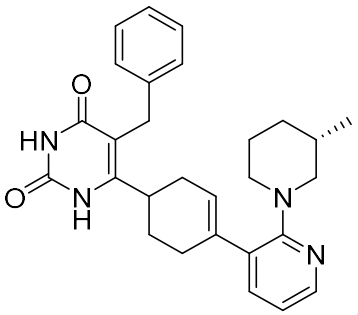
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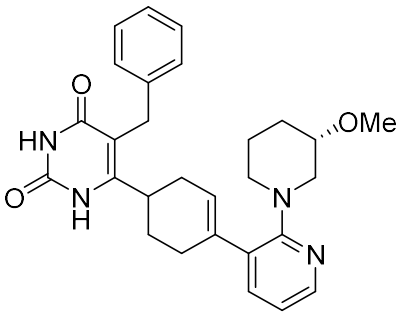
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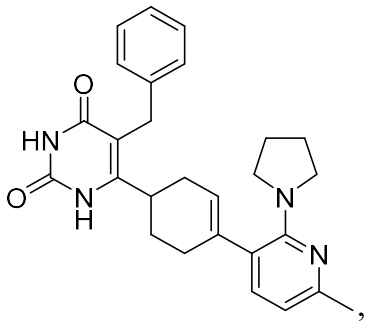
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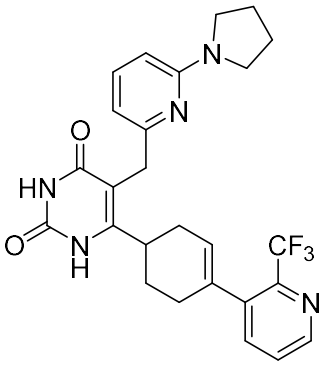
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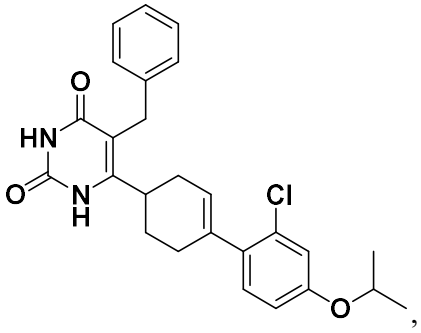
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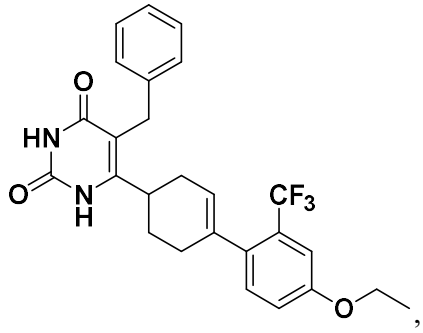
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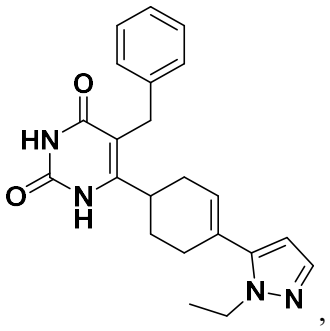
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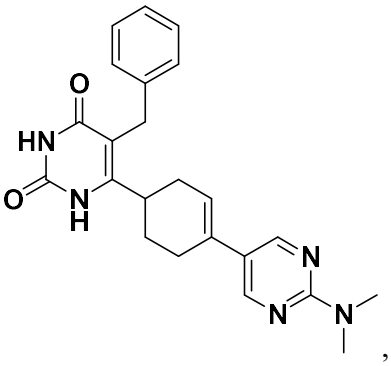
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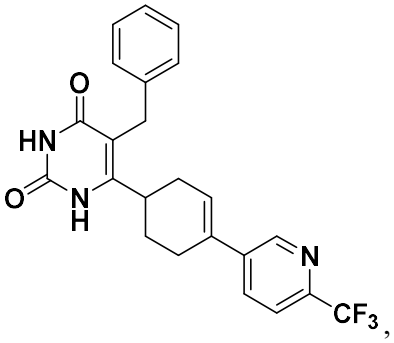
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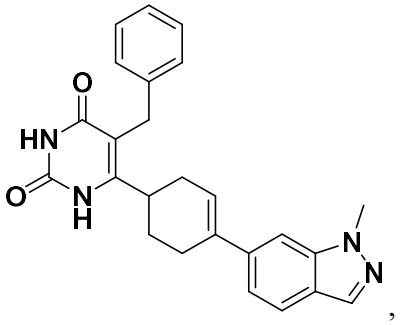
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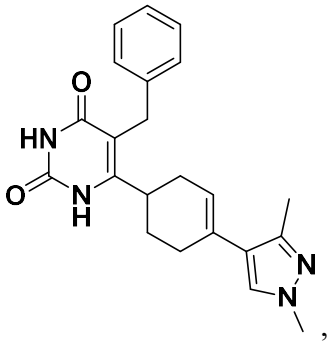
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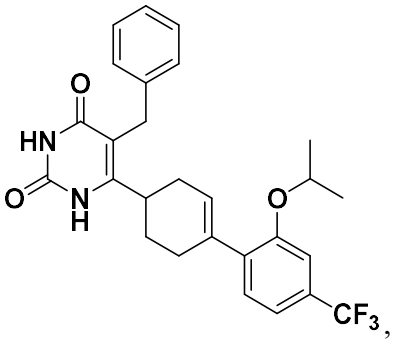
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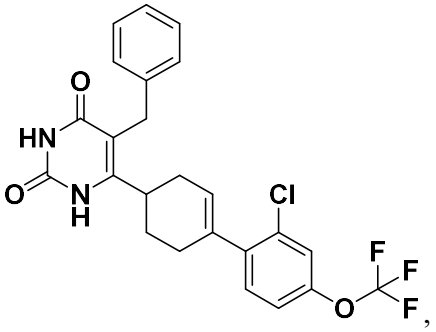
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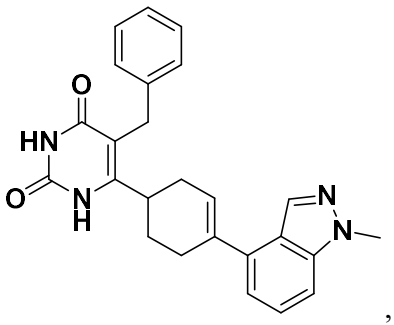
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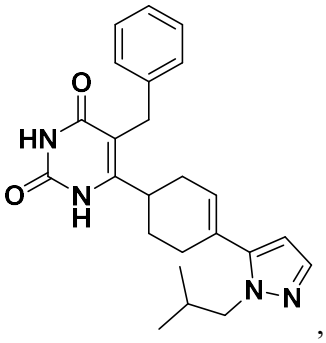
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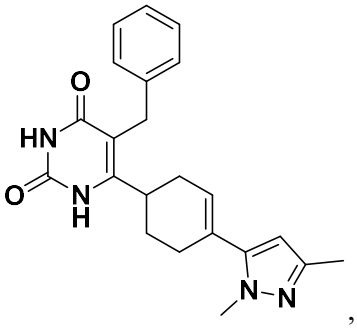
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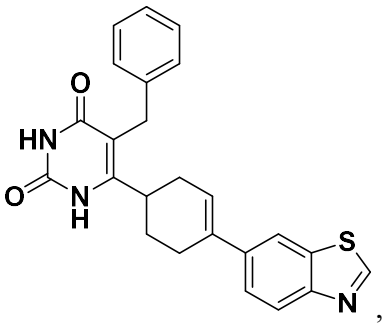
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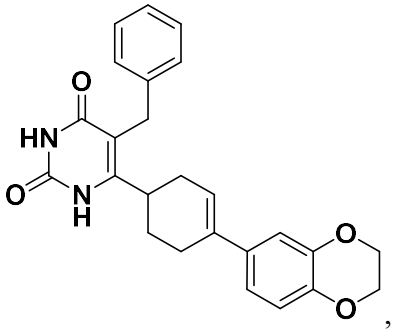
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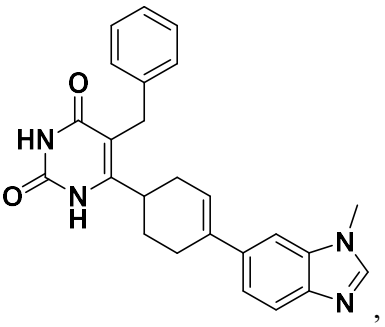
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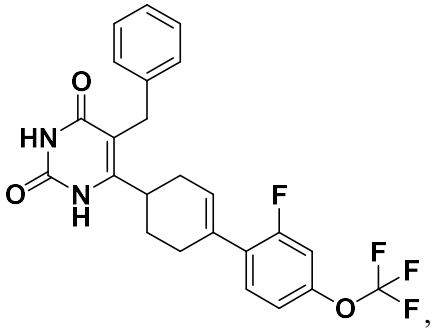
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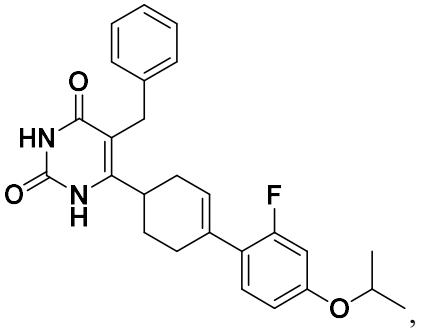
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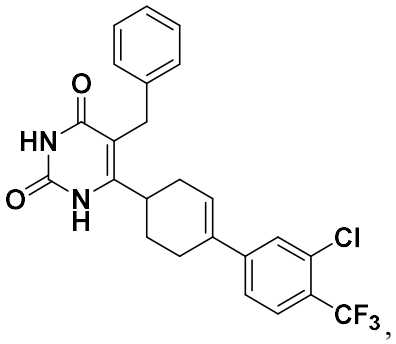
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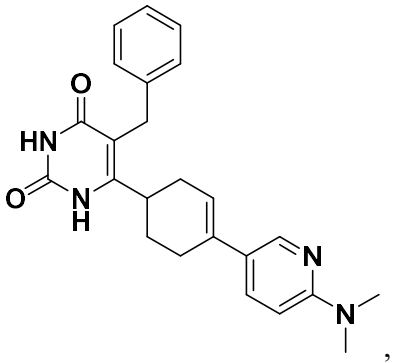
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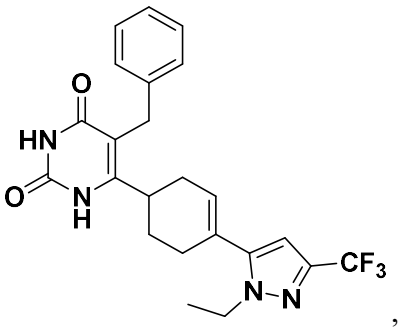
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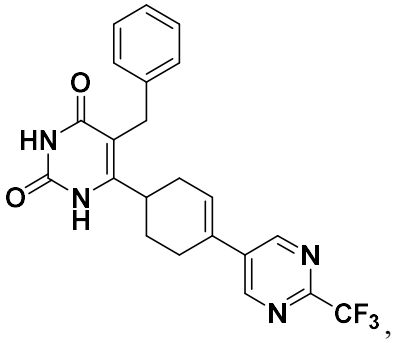
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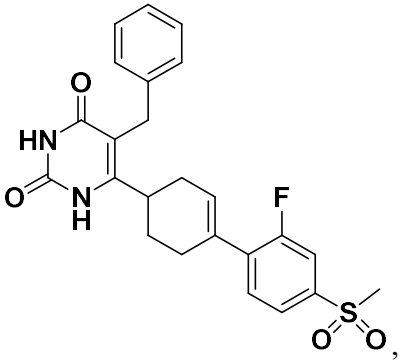
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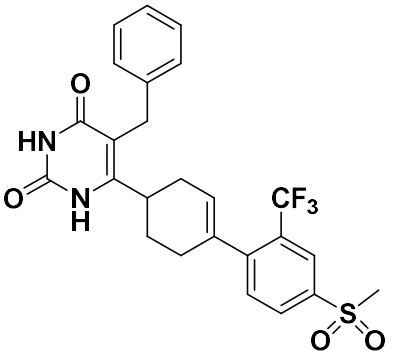
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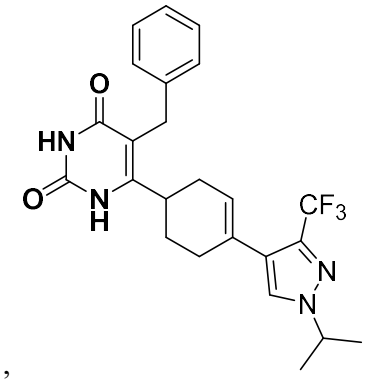
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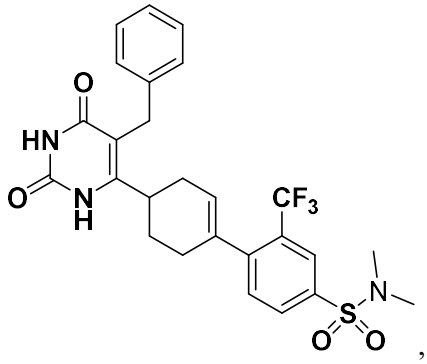
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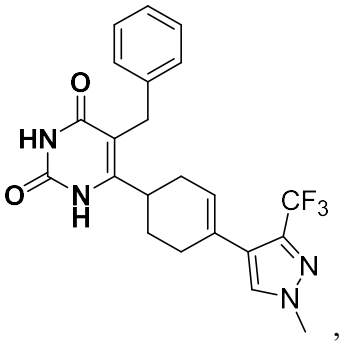
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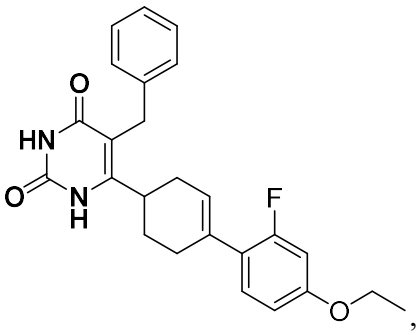
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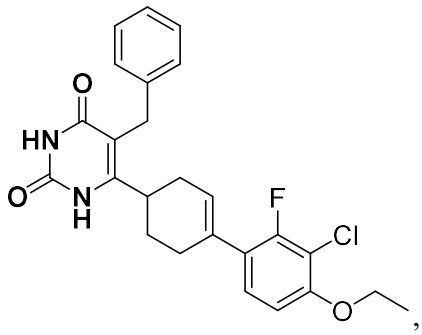
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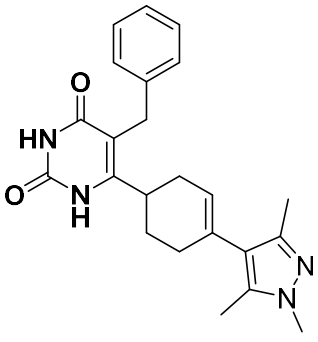
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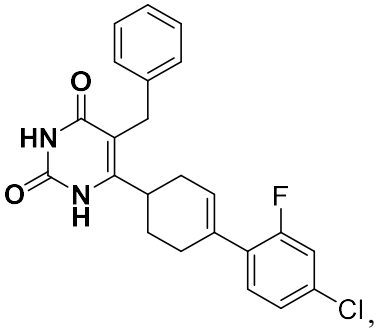
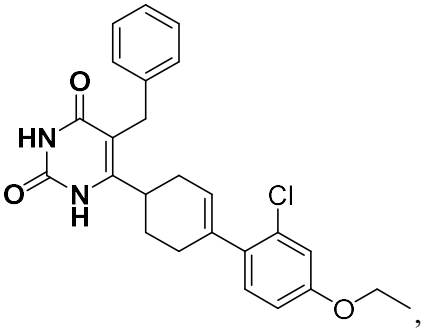
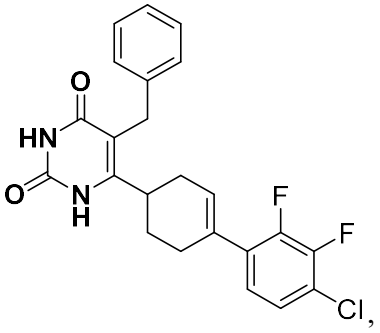
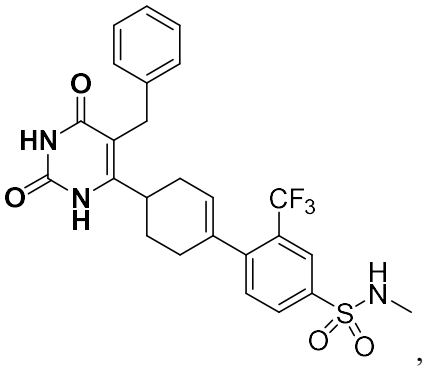
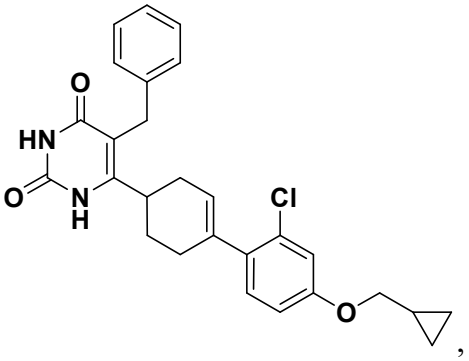
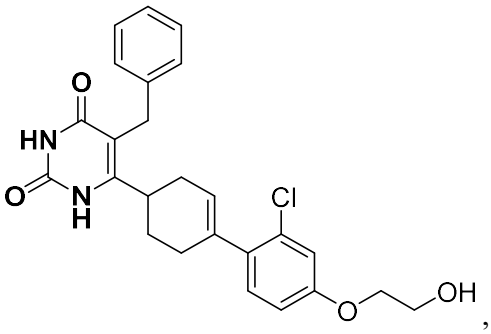
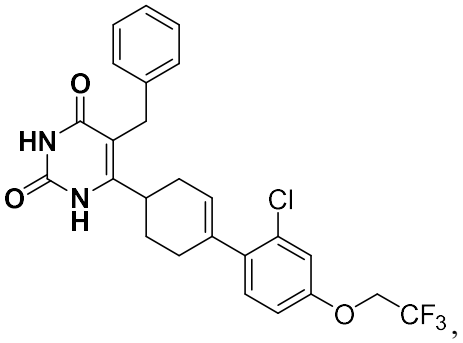
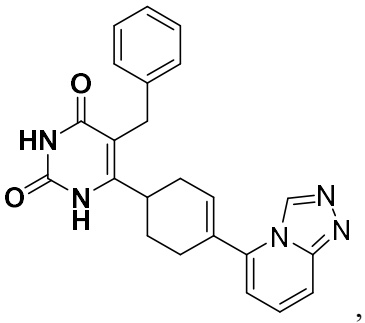
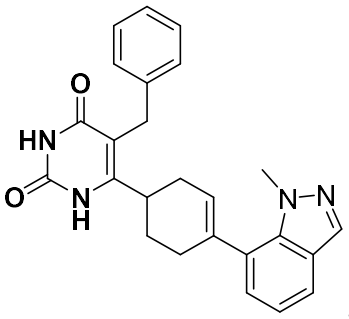
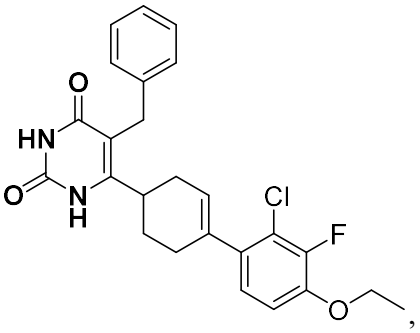
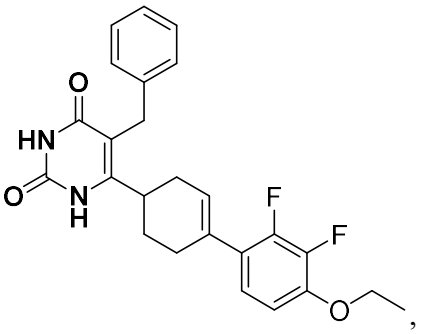
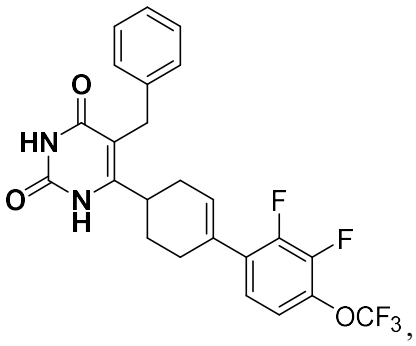

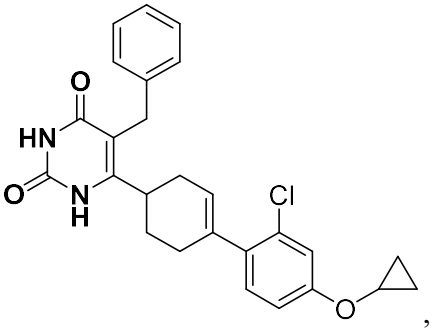
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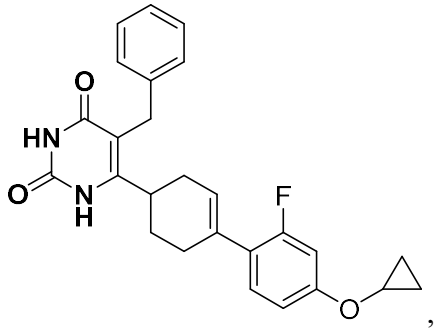
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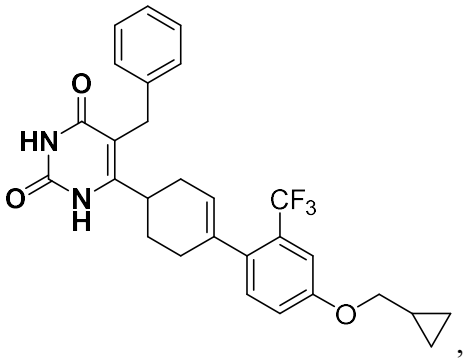
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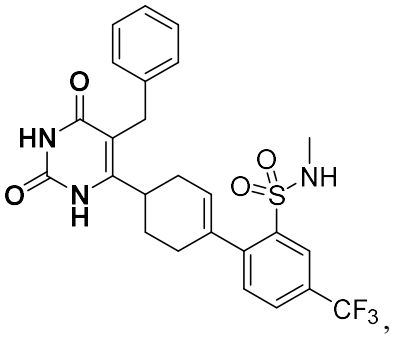
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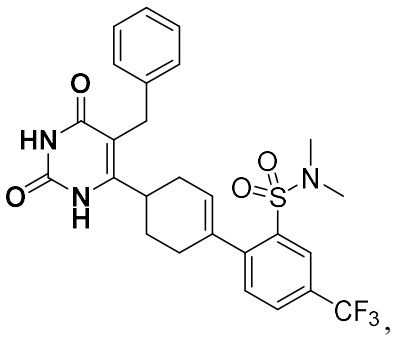
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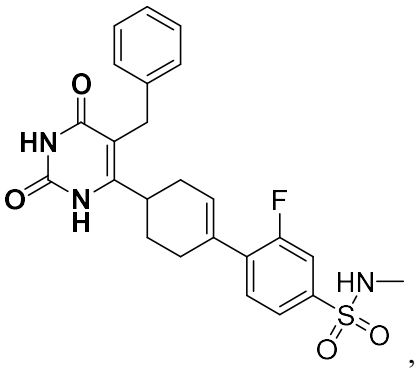
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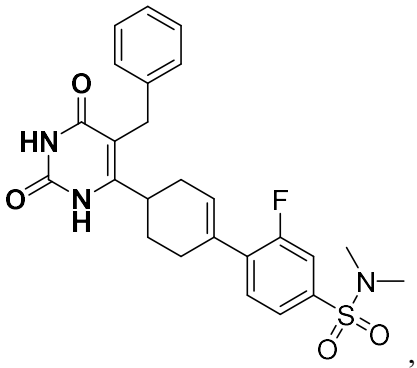
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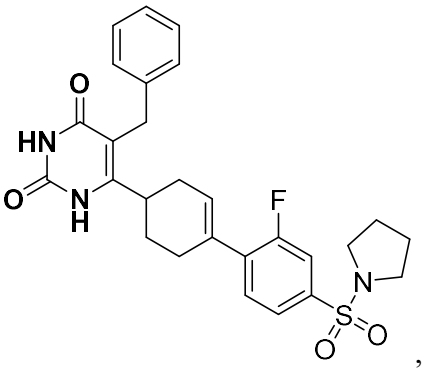
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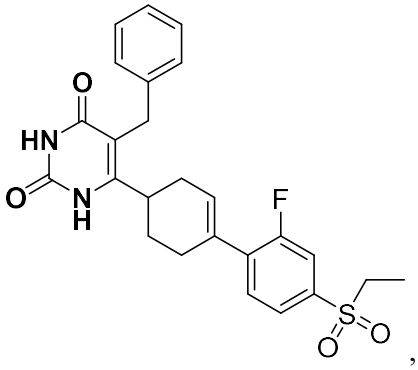
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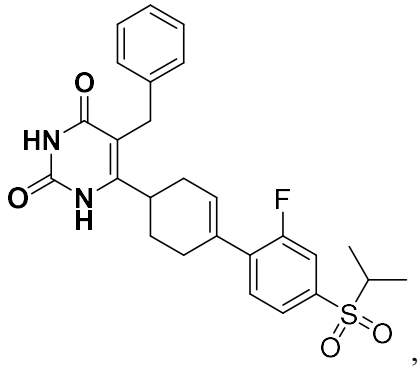
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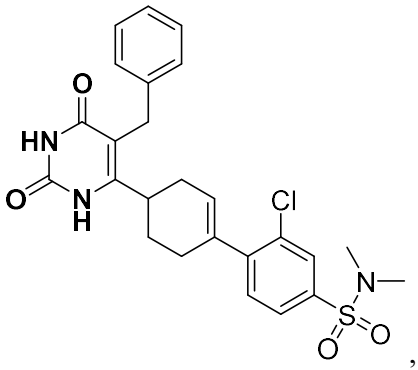
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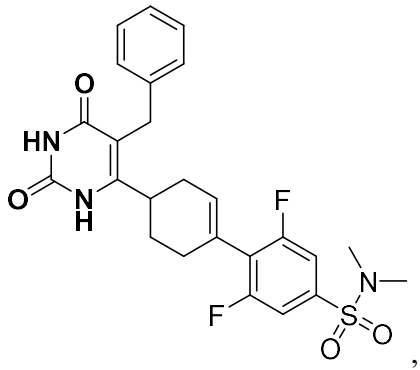
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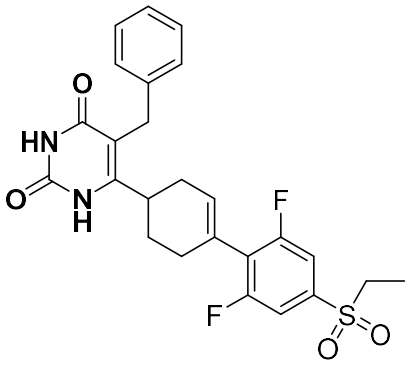
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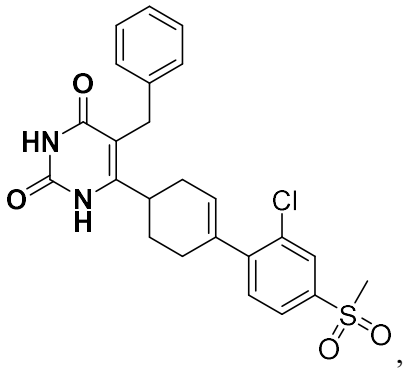
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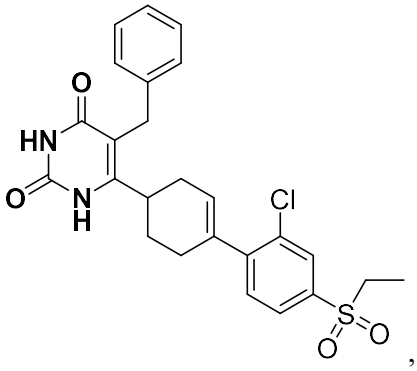
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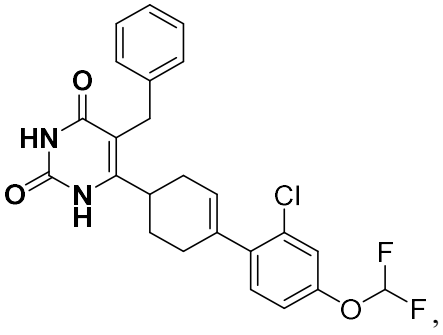
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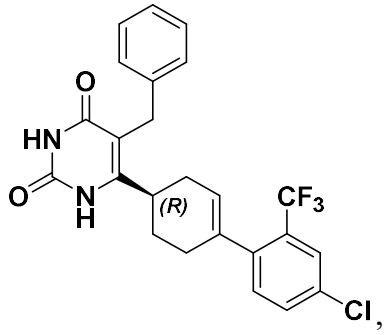
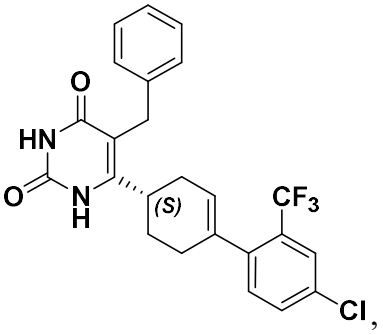
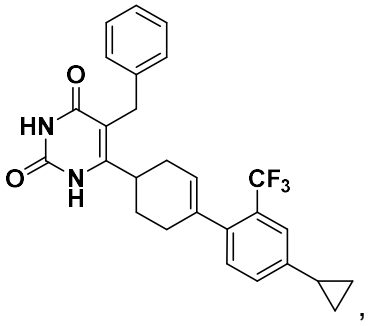
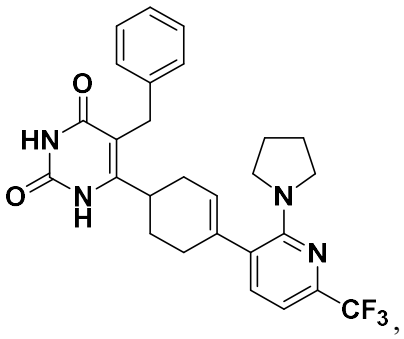
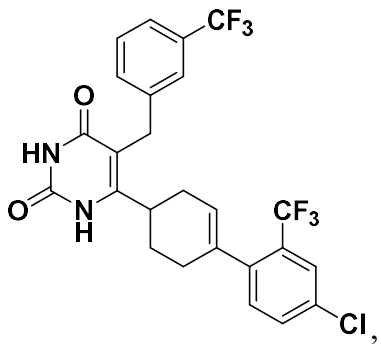
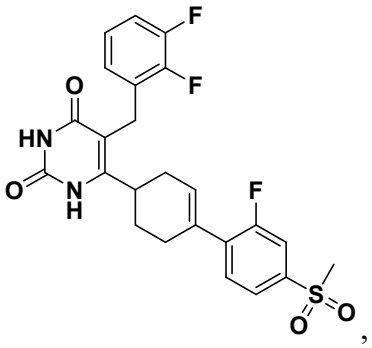
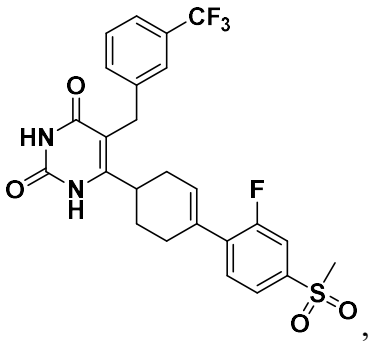
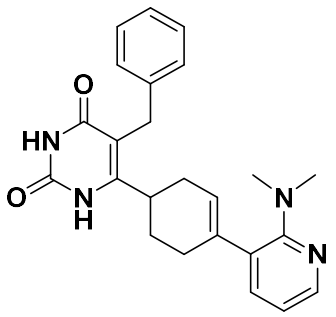
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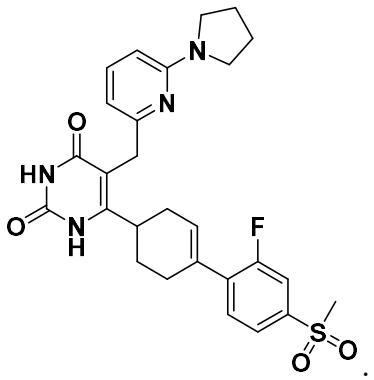

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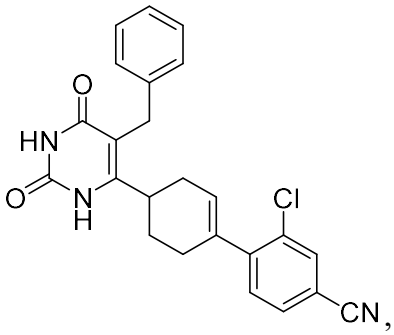
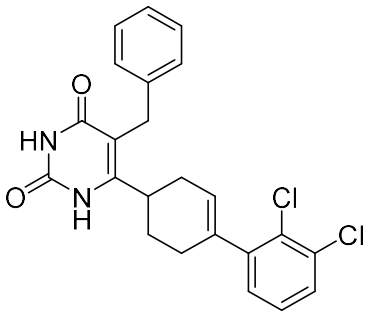
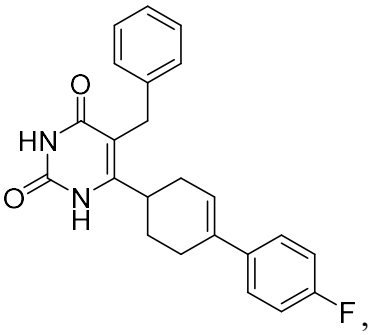

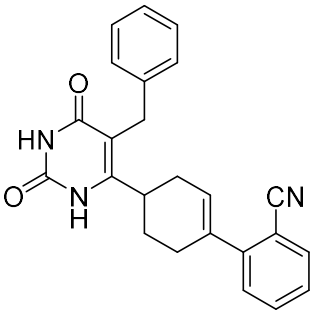
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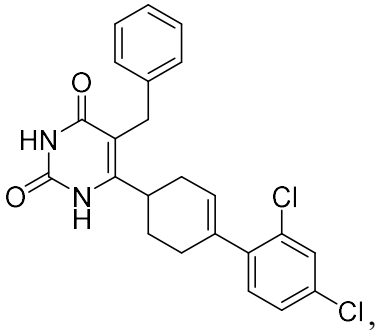
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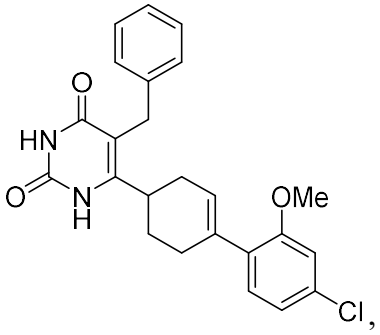
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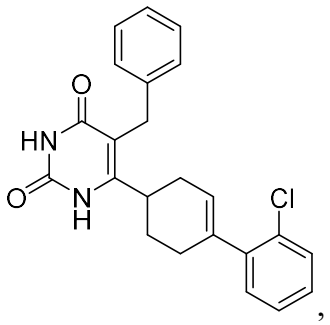
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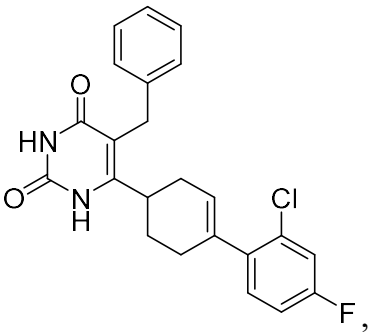
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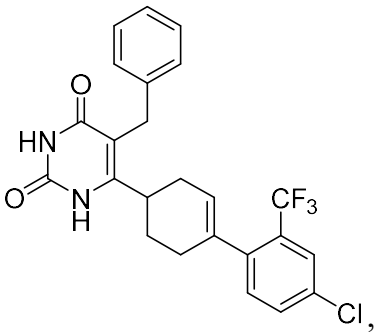
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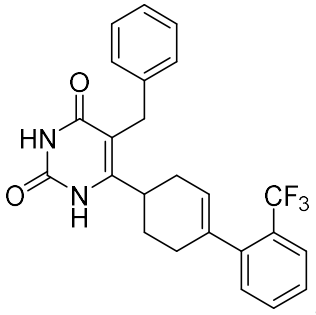
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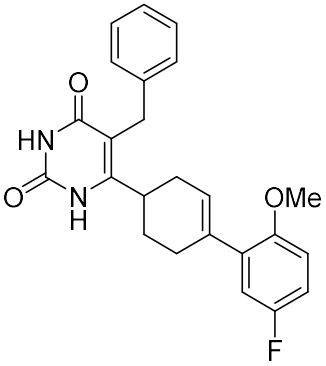
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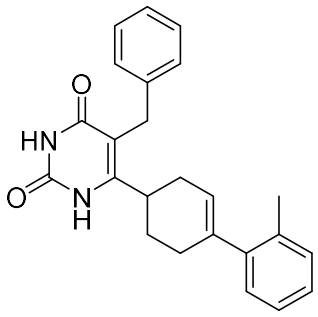
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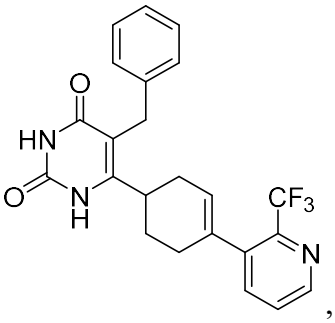
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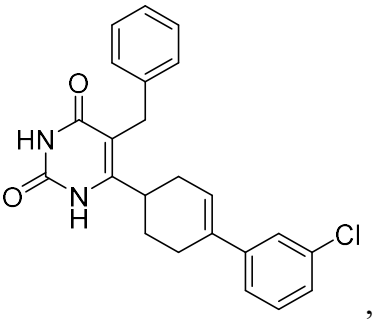
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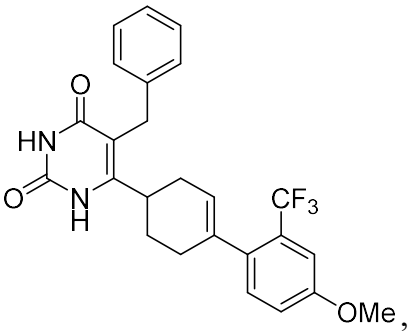
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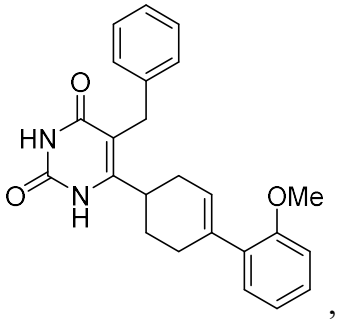
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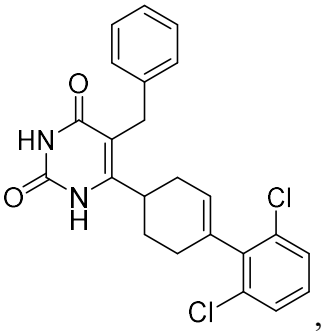
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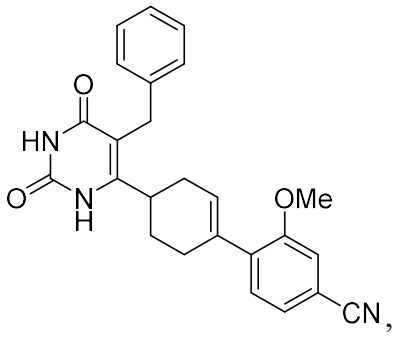
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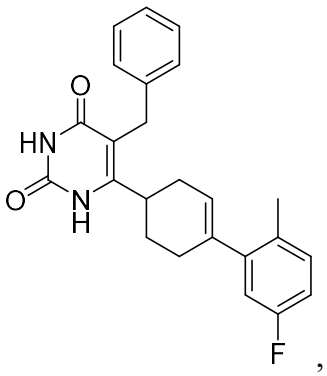
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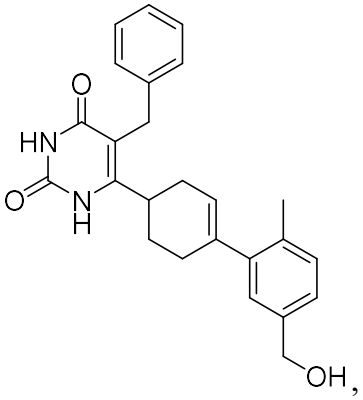
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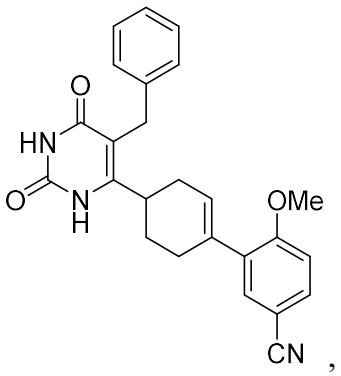
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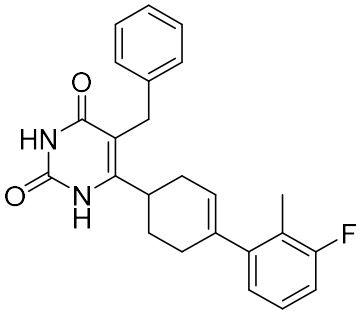
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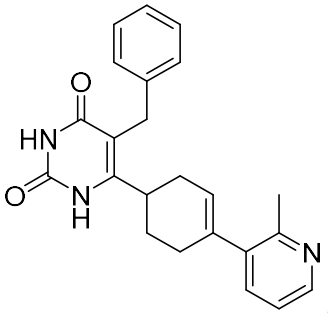
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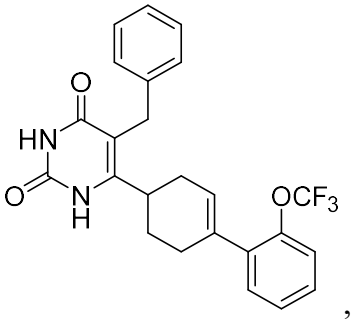
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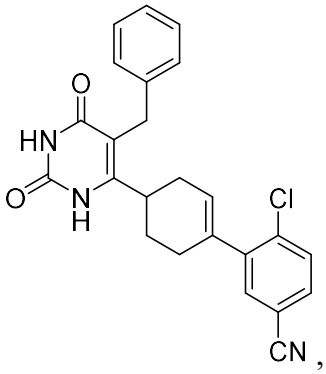
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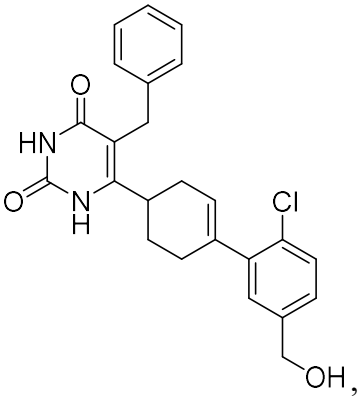
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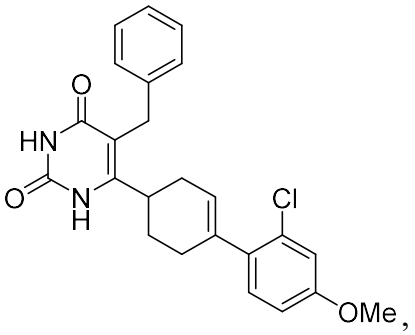
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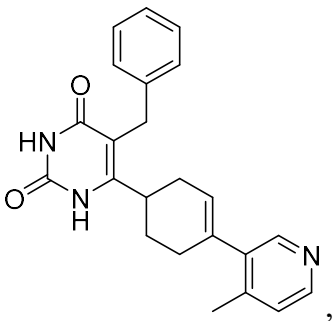
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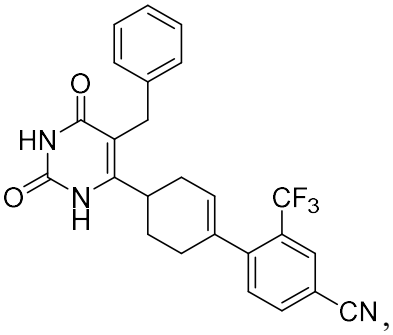
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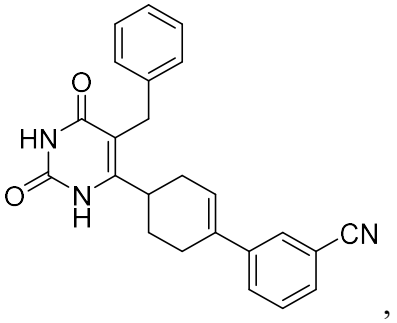
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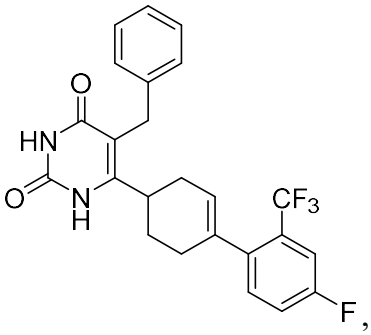
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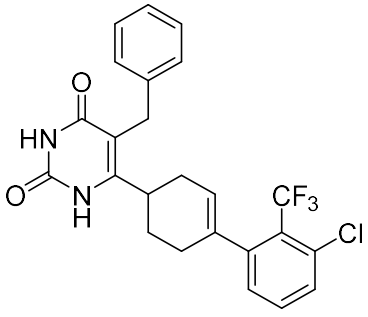
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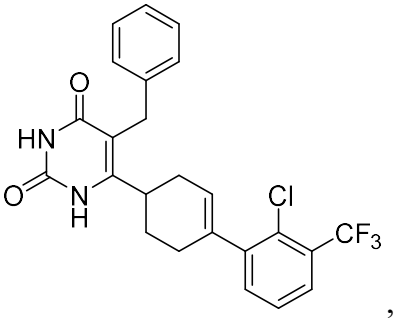
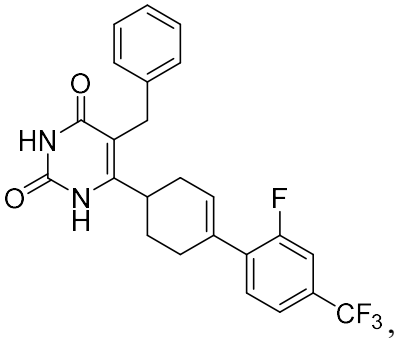

,



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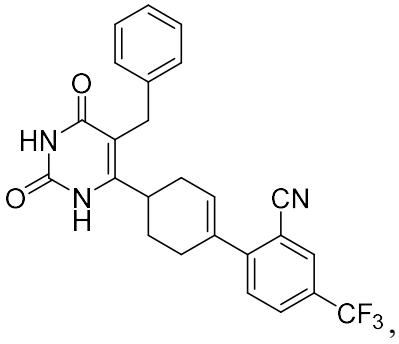

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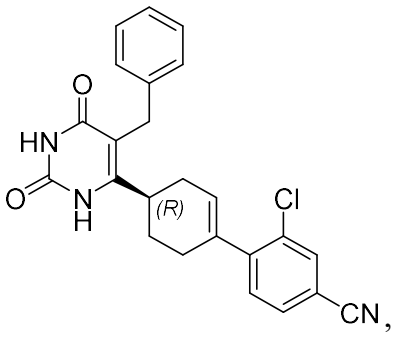

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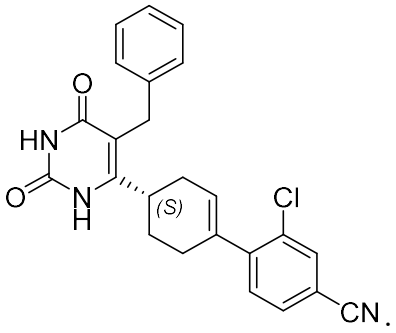
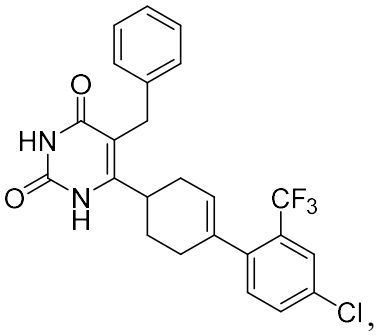


.

and

17. The compound of claim 14, selected from the group consisting of:



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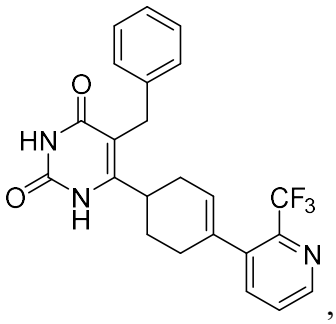

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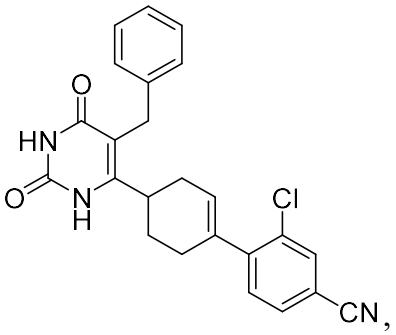
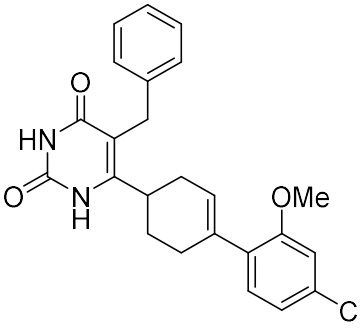
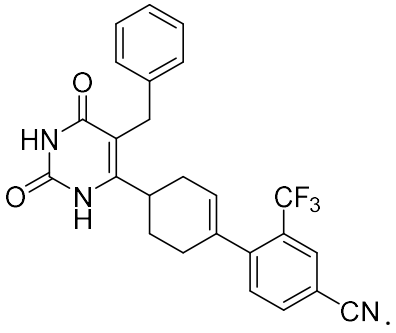


,



, and



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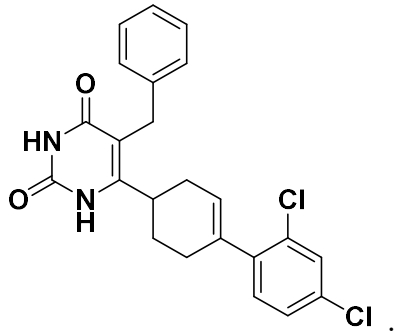
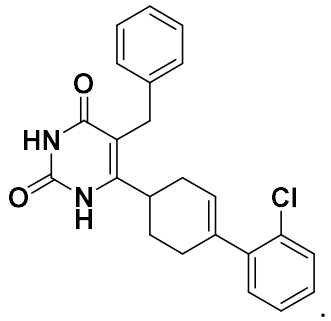
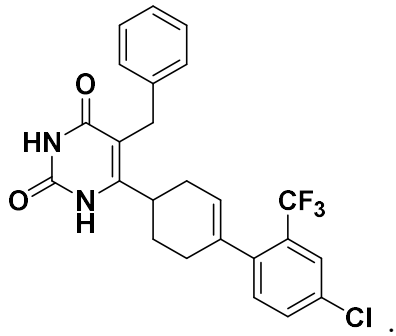
18. The compound of claim 14, having the structure



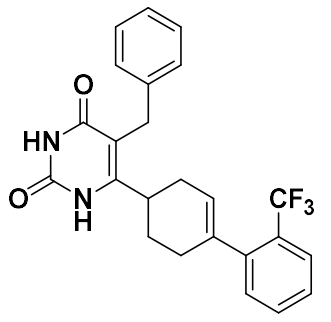
19. The compound of claim 14, having the structure



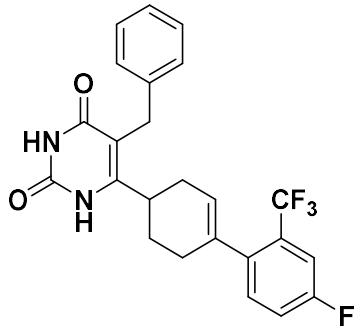
20. The compound of claim 14, having the structure



21. The compound of claim 14, having the structure



22. The compound of claim 14, having the structure



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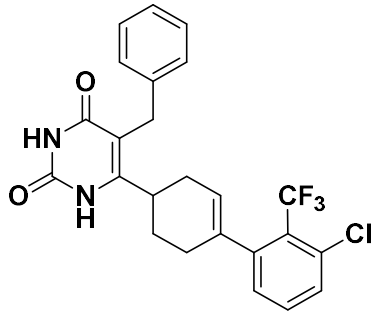
23. The compound of claim 14, having the structure



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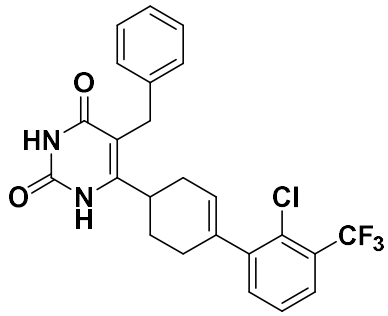
24. The compound of claim 14, having the structure



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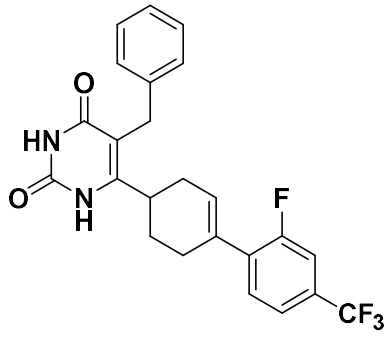
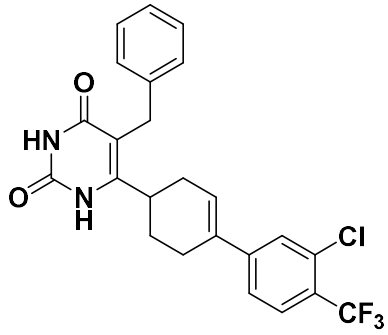
25. The compound of claim 14, having the structure



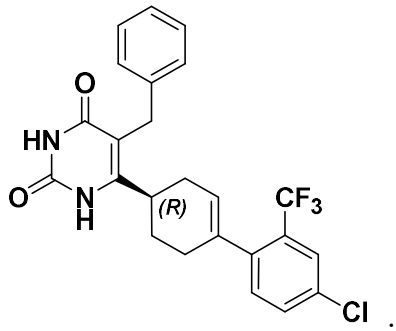
.

26. The compound of claim 15, having the structure



.

27. The compound of claim 15, having the structure



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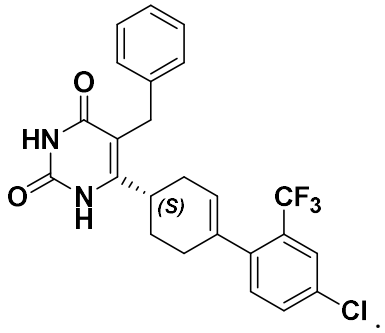
28. The compound of claim 15, having the structure



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29. A pharmaceutical composition comprising one or more pharmaceutically acceptable excipients and a compound of any one of claims 1 to 28.

30. Use of a therapeutically effective amount of a compound of any one of claims 1 to 28 or a pharmaceutical composition of claim 29 in the manufacture of a medicament for treating a disorder or condition through modulating a glucocorticoid receptor.

31. Use of an effective amount of the compound of any of claims 1 to 28 or a pharmaceutical composition of claim 29 in the manufacture of a medicament for treating a disorder or condition through antagonizing a glucocorticoid receptor.

32. The use of claim 31, wherein the disorder or condition is selected from the group consisting of obesity, diabetes, cardiovascular disease, hypertension, Syndrome X, depression, anxiety, glaucoma, human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS), neurodegeneration, Alzheimer's disease, Parkinson's disease, cognition enhancement, Cushing's Syndrome, Addison's Disease, osteoporosis, frailty, muscle frailty, inflammatory diseases, osteoarthritis, rheumatoid arthritis, asthma and rhinitis, adrenal function-related ailments, viral infection, immunodeficiency, immunomodulation, autoimmune diseases, allergies, wound healing, compulsive behavior, multi-drug resistance, addiction, psychosis, anorexia, cachexia, post-traumatic stress syndrome, post-surgical bone fracture, medical catabolism, major psychotic depression, mild cognitive impairment, psychosis, dementia, hyperglycemia, stress disorders, antipsychotic induced weight gain, delirium, cognitive impairment in depressed patients, cognitive deterioration in individuals with Down's syndrome, psychosis associated with interferon-alpha therapy, chronic pain, pain associated with gastroesophageal reflux disease, postpartum psychosis, postpartum depression, neurological disorders in premature infants, and migraine headaches.

33. The use of claim 31, wherein the disorder or condition is nonalcoholic fatty liver disease and/or nonalcoholic steatohepatitis.

34. The use of claim 31, wherein the disorder or condition is an addiction disorder.

35. The use of claim 31, wherein the disorder or condition is cancer.