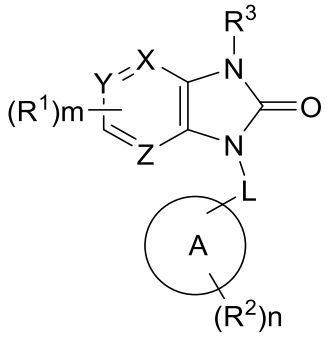
Currently there are no specific inhibitors are available against IL4I1. Some molecules have been shown to inhibit the related LAAOs found in snake venom, but they are generally non-selective and have little activity. Therefore there is a need for specific inhibitors of IL4I1. More specifically there is a need for compounds that specifically inhibit IL4I1 and can be useful for the treatment of indications where IL4I1 is most expressed and/or active, including endometrial, ovarian and triple negative breast cancers.

BRIEF SUMMARY ~~OF THE INVENTION~~

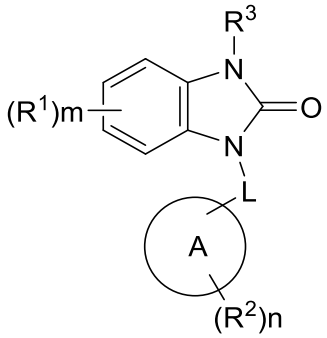
Described herein are compounds of Formula I:



I

and pharmaceutically acceptable salts thereof, wherein X, Y, Z, A, L, R^1, R^2 and R^3 are described below.

In one aspect, there is provided a compound, or a pharmaceutically acceptable salt thereof, having the Formula Ia



Ia,

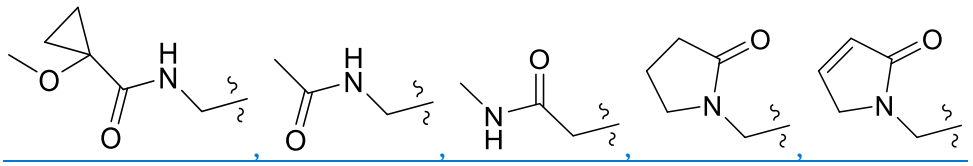
wherein,

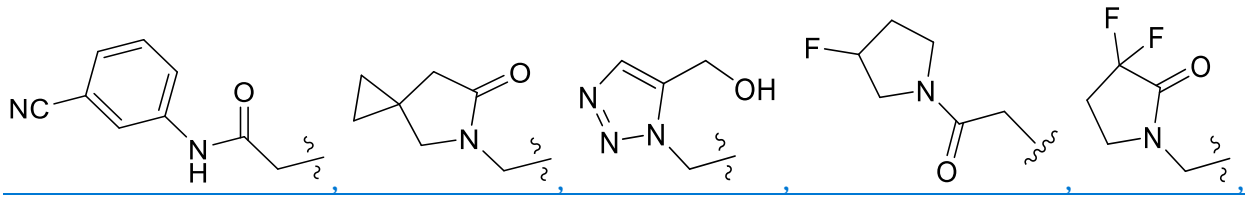
A is aryl;

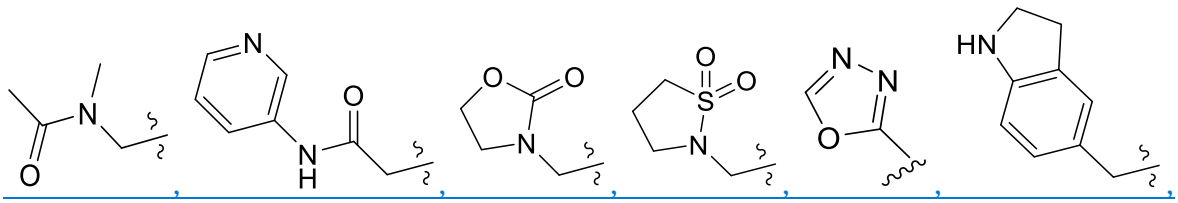
L is a straight or branched (C_1-C_5)alkylenyl, wherein one or more –CH_2- groups in L are optionally and independently replaced with a moiety selected from the group consisting of O, and NH;

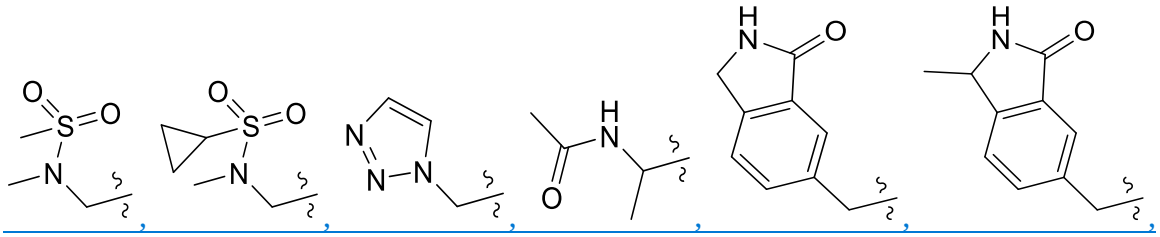
each occurrence of R^1 is independently halogen, C_1-C_6alkyl, or cycloheteroalkyl;

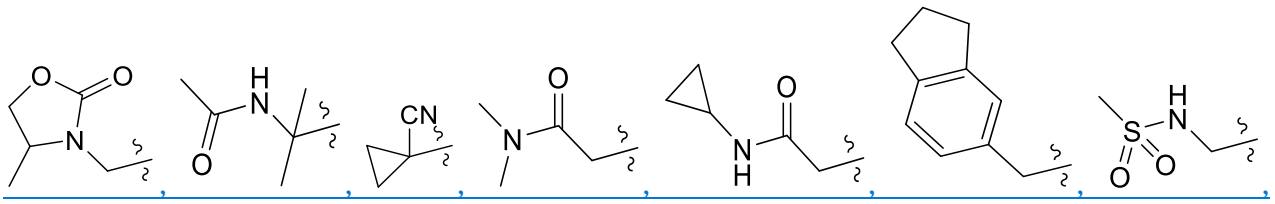
each occurrence of R^2 is independently chlorine, iodine, methoxy, isopropoxy, methyl, difluoromethyl,

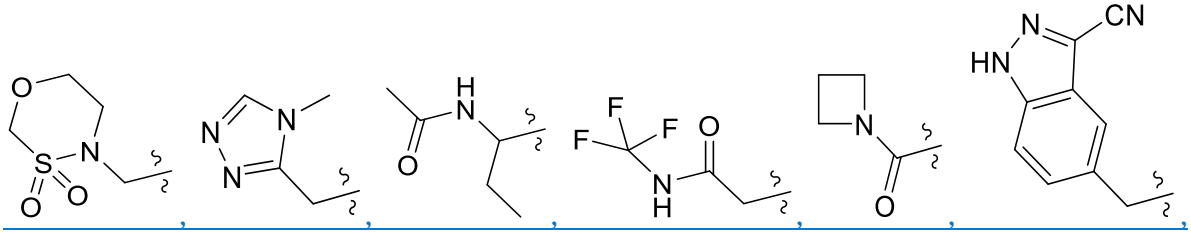




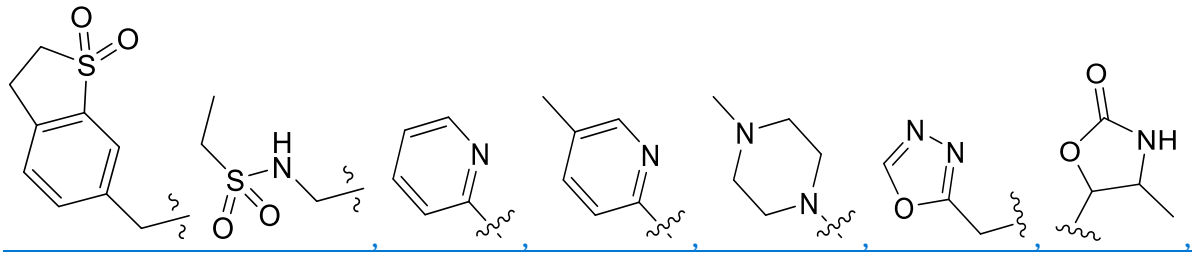


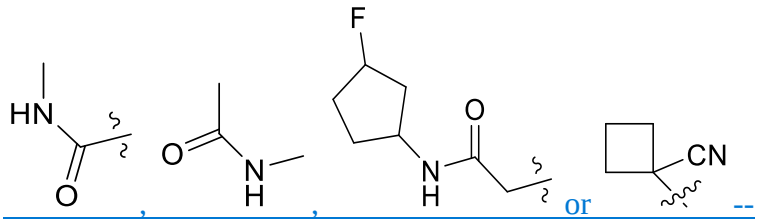






- 2a -





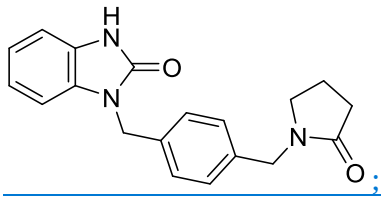
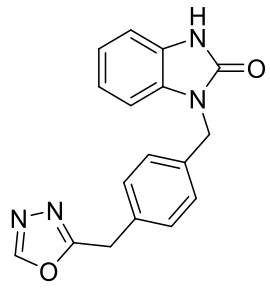
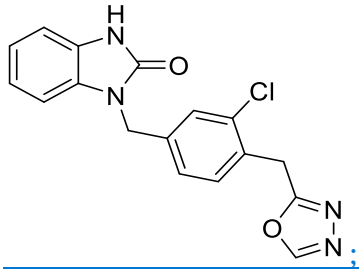
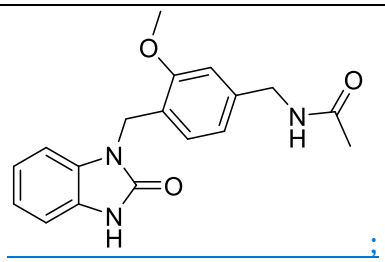
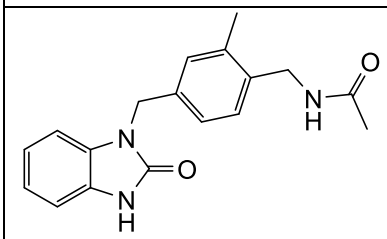
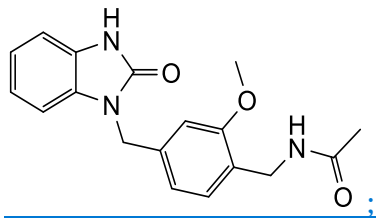
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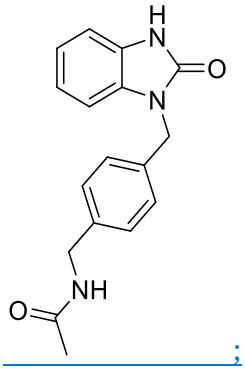
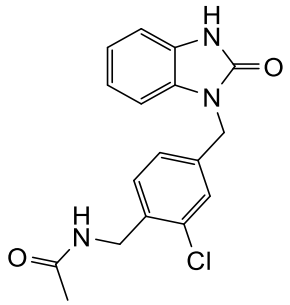
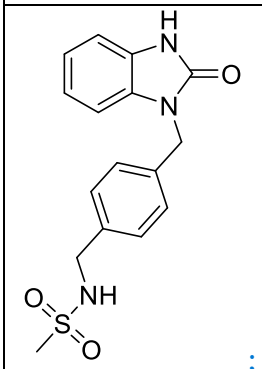
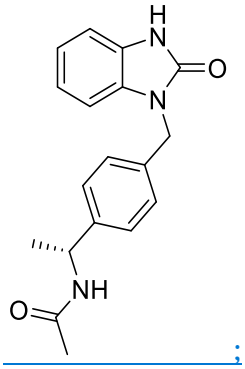
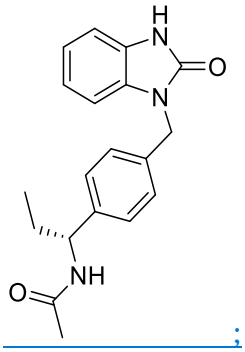
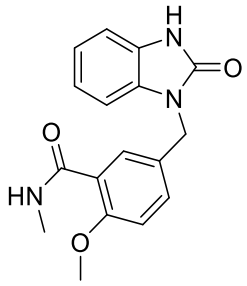
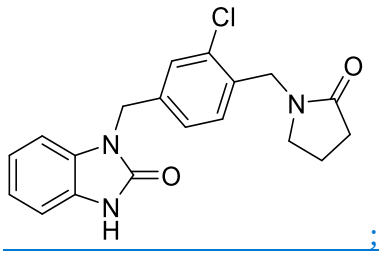
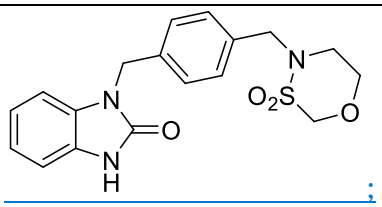
R^3 is hydrogen, C_1-C_6alkyl or haloC_1-C_6alkyl;

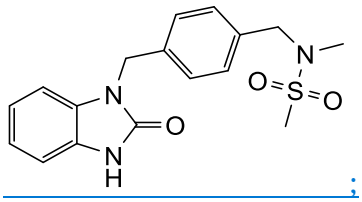
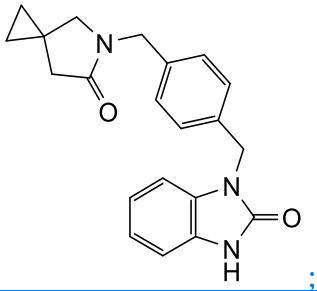
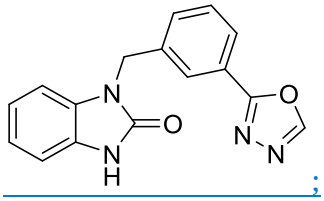
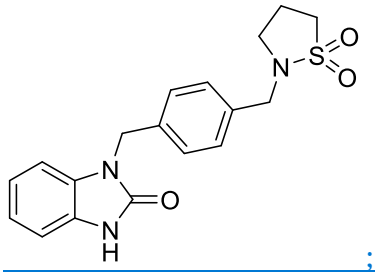
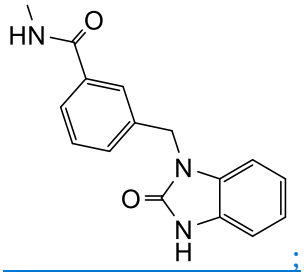
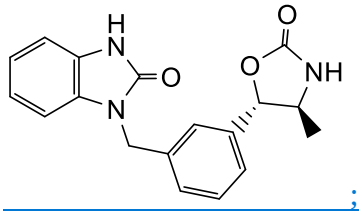
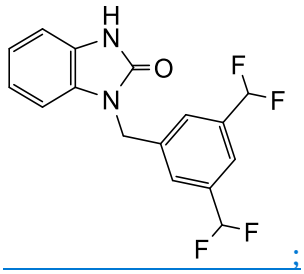
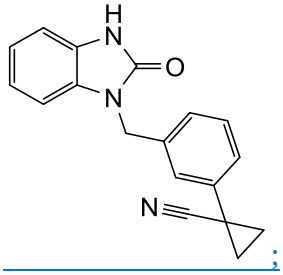
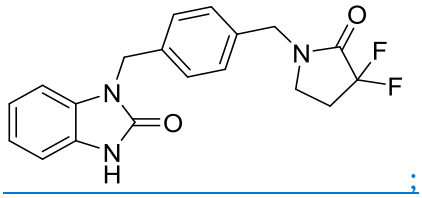
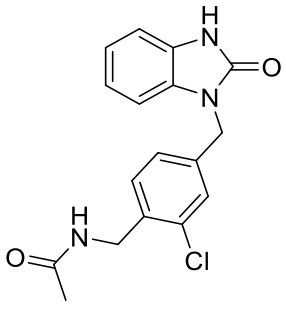
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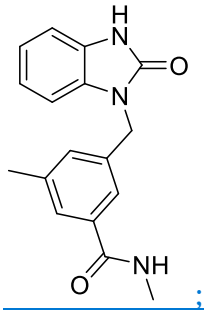
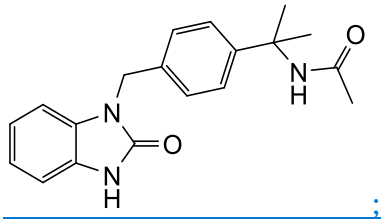
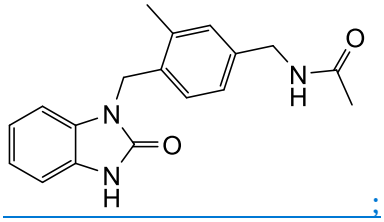
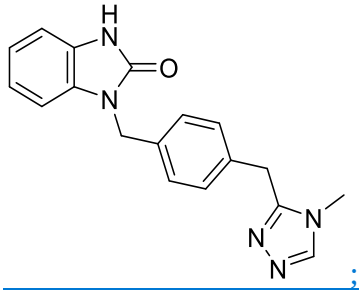
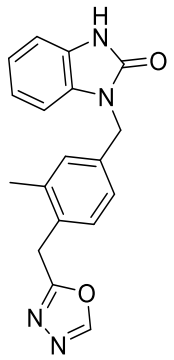
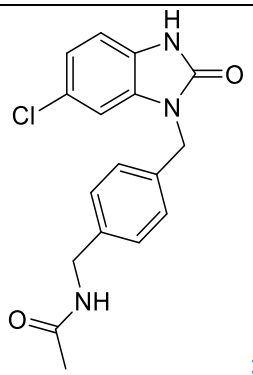
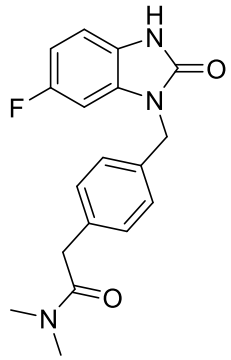
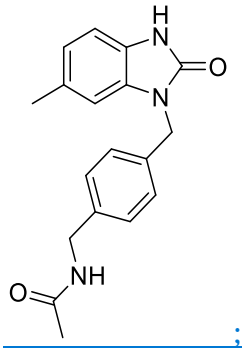
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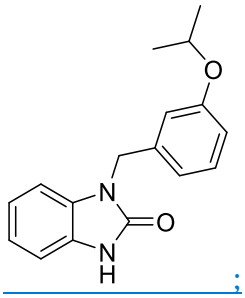
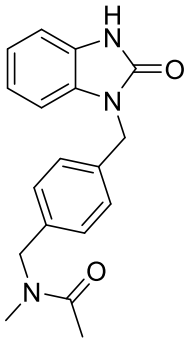
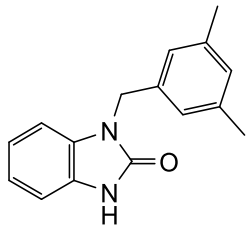
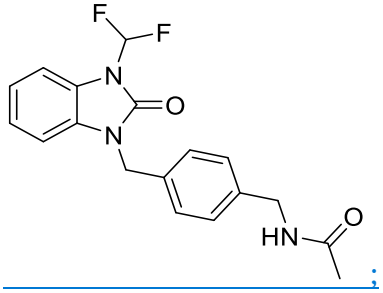
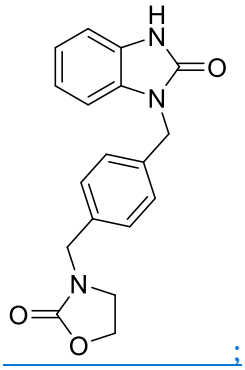
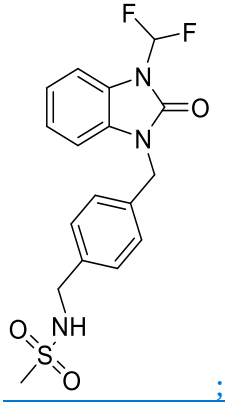
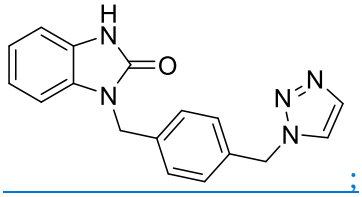
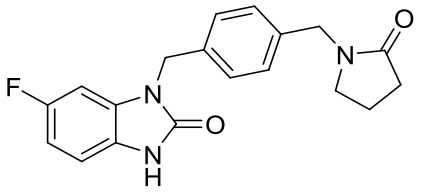
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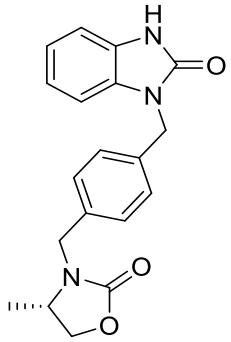
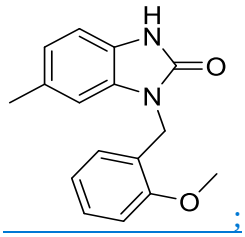
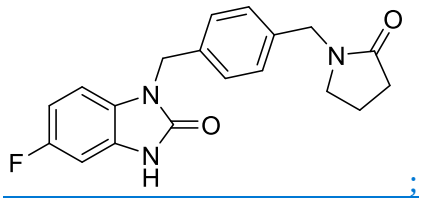
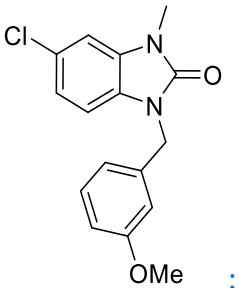
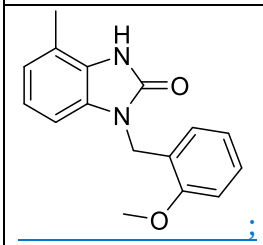
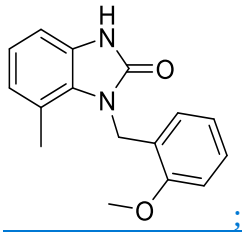
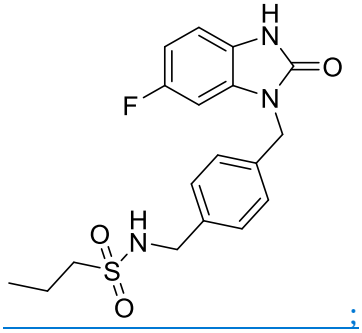
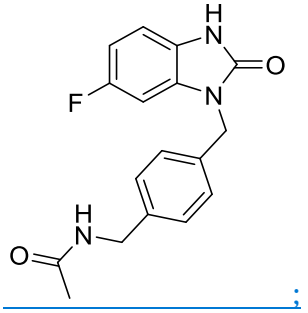
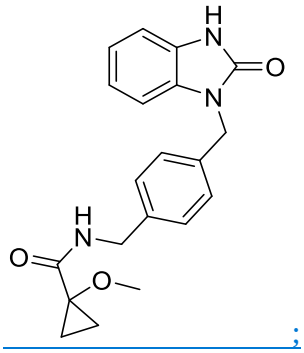
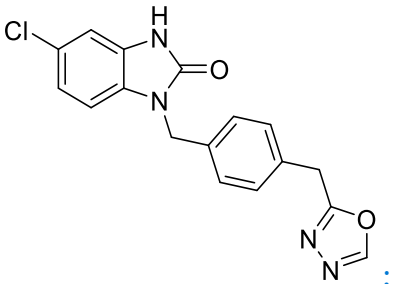
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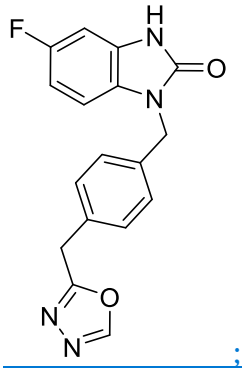
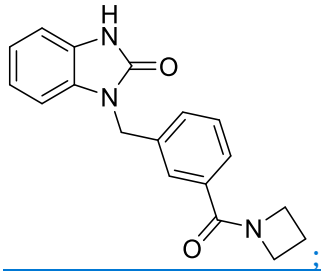
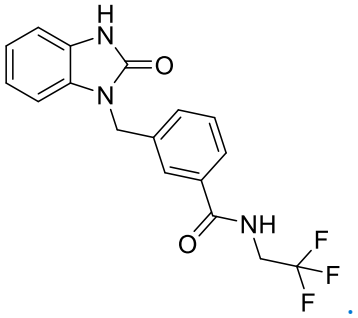
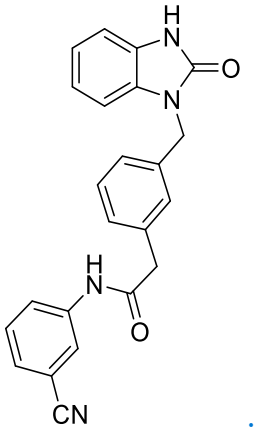
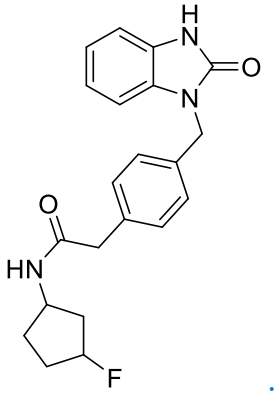
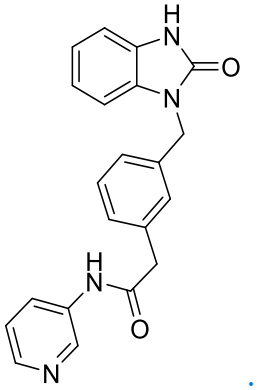
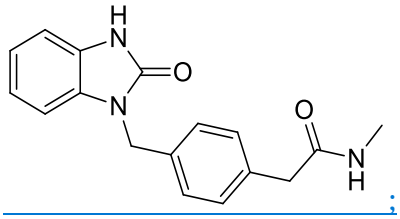
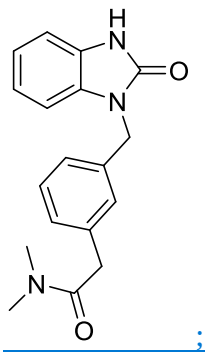
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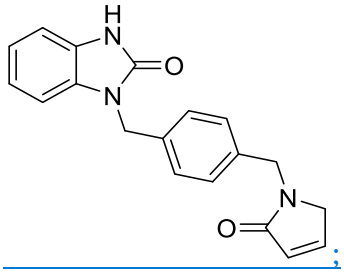
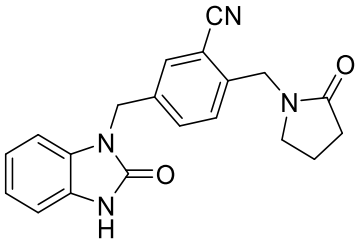
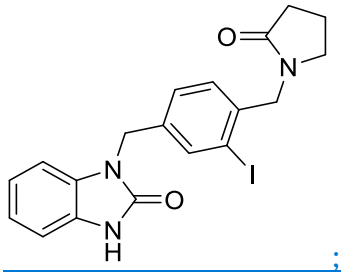
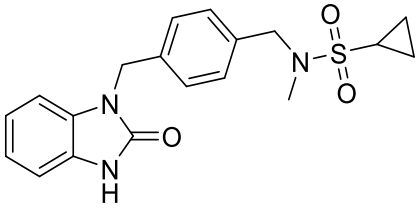
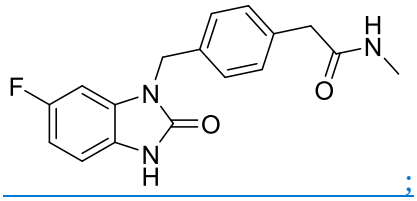
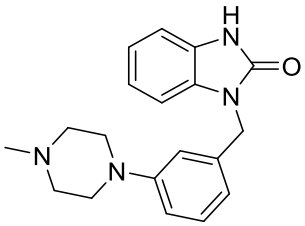
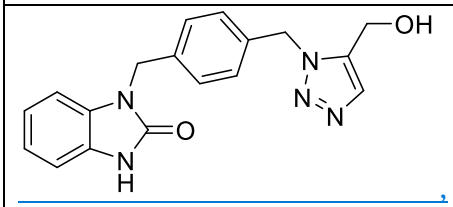
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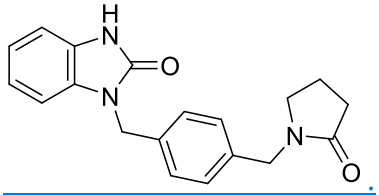
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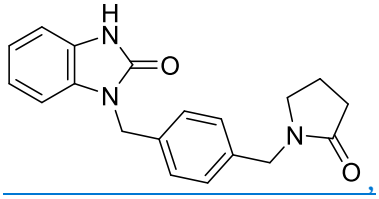
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or a pharmaceutically acceptable salt thereof.

In another aspect, there is provided a compound having the following structure

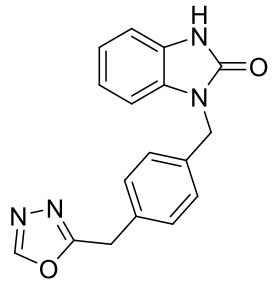
 .

In another aspect, there is provided a compound having the following structure

 ,

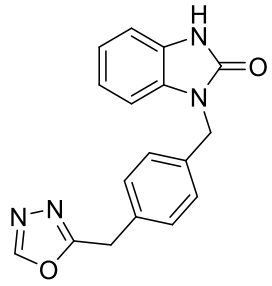
or a pharmaceutically acceptable salt thereof.

In another aspect, there is provided a compound having the following structure



.

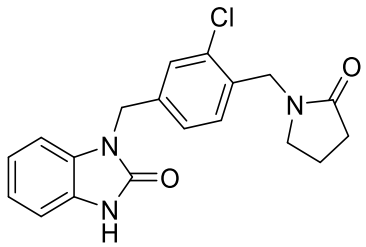
In another aspect, there is provided a compound having the following structure



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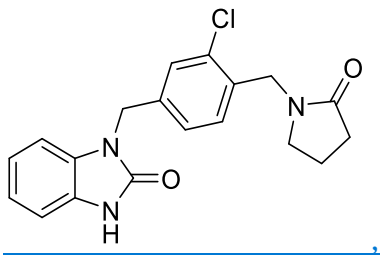
or a pharmaceutically acceptable salt thereof.

In another aspect, there is provided a compound having the following structure



.

In another aspect, there is provided a compound having the following structure



,

or a pharmaceutically acceptable salt thereof.

The compounds described herein are IL4I1 inhibitors, which can be useful in the prevention, treatment or amelioration of IL4I1- related diseases.

Also described herein are methods of preventing, treating or ameliorating the symptoms of cancer comprising administering to a patient in need thereof a compound described herein, or a pharmaceutically acceptable salt thereof.

In another aspect, there is provided a compound described herein, or pharmaceutically acceptable salt thereof for use in therapy.

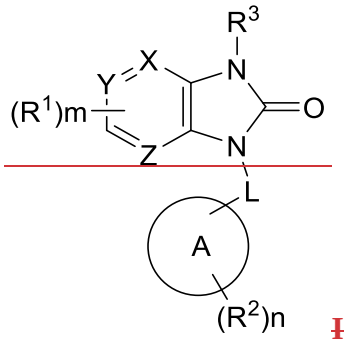
Also described herein are uses of a compound described herein, or a pharmaceutically acceptable salt thereof, to prevent, treat or ameliorate the conditions of cancer in a patient in need thereof. In another aspect, there is provided use of a compound described herein, or pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of cancer.

In another aspect, there is provided a ~~Also described herein are~~ pharmaceutical composition~~s~~ comprising a compound described herein, or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

In another aspect, there is provided a ~~Also described herein are~~ pharmaceutical composition~~s~~ comprising a compound described herein and a pharmaceutically acceptable carrier.

What is claimed is:

~~1. A compound of Formula I:~~



~~I~~

~~or a pharmaceutically acceptable salt thereof, wherein:~~

~~X is CH or S, wherein when X is S, Z is CH;~~

~~Y is CH or a bond;~~

~~Z is CH or S, wherein when Z is S, X is CH;~~

~~A is aryl, C_3-C_{10}cycloalkyl, heteroaryl or cycloheteroalkyl;~~

~~L is a straight or branched (C_1-C_5)alkylenyl, wherein one or more CH_2 groups in L are optionally and independently replaced with a moiety selected from the group consisting of O, and NH;~~

~~R^1 is halogen, C_1-C_6alkyl, or cycloheteroalkyl;~~

~~each occurrence of R^2 is independently selected from C_1-C_6alkylNR^{4}C(O)C_3-C_6cycloalkyl, C_1-C_6alkylNR^{4}C(O)C_1-C_6alkyl, C_1-C_6alkylCONR^4C_1-C_6alkyl, halogen, alkoxy, C_1-C_6alkylcycloheteroalkyl, C_1-C_6alkylCONR^{4}aryl, C_1-C_6alkyl, C_1-C_6alkylC(O)cycloheteroalkyl, C_1-C_6alkylCONR^{4}heteroaryl, C_1-C_6alkylNR^4$SO_2$$C_1$-$C_6$alkyl, C_1-C_6alkylNR^4$SO_2$$C_3$-$C_6$cycloalkyl, C_3-C_6cycloalkyl, C_1-C_6alkylCONR^4C_3-C_6cycloalkyl, cycloheteroalkyl, haloC_1-C_6alkyl, CONR^{4}haloalkyl, C(O)cycloheteroalkyl, CN, CONR^4C_1-C_6alkyl, CONR^4C_3-C_6cycloalkyl, heteroaryl, aryl, haloalkoxy, C_1-C_6alkylC_3-C_{10}cycloalkyl, oxo, C_1-C_6alkylheteroaryl, NR^{4}C(O)C_1-C_6alkyl, wherein the C_1-C_6alkylNR^{4}C(O)C_3-C_6cycloalkyl, C_1-C_6alkylCONR^4C_3-C_6cycloalkyl, C_1-C_6alkylCONR^{4}aryl, C_1-C_6alkylcycloheteroalkyl, C_1-C_6alkylC(O)cycloheteroalkyl, C_3-C_6cycloalkyl, cycloheteroalkyl, heteroaryl, C_1-C_6alkylC_3-C_{10}cycloalkyl, is unsubstituted or substituted with 1 to 3

~~substituents selected from the group consisting of alkoxy, CN, -C_1-C_6alkylOH, halogen, C_1-C_6alkyl, haloC_1-C_6alkyl, oxo, OH, CN, -C_1-C_6alkylCN, -COC_1-C_6alkyl and C_3-C_6cycloalkyl;~~

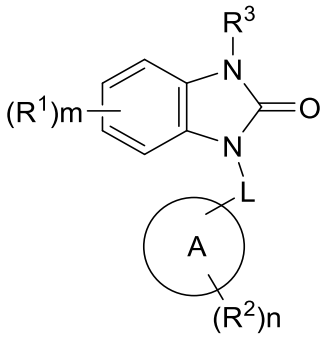
~~R^3 is hydrogen, C_1-C_6alkyl or haloC_1-C_6alkyl;~~

~~R^4 is C_1-C_6alkyl or hydrogen;~~

~~m is 0, 1 or 2; and~~

~~n is 0, 1, 2 or 3.~~

~~2.~~1. ~~The~~ A compound ~~of claim 1~~, or a pharmaceutically acceptable salt thereof, having the Formula Ia



Ia,

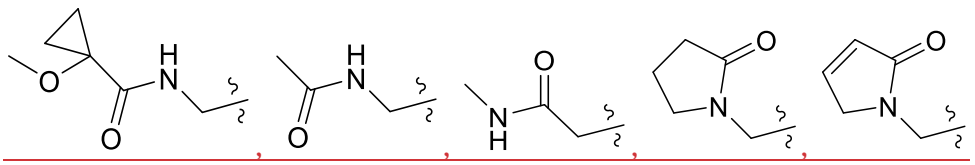
wherein,

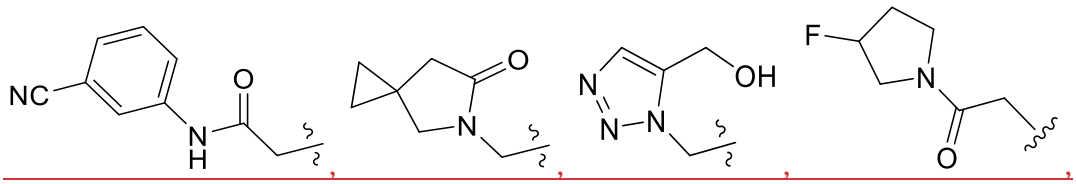
A is aryl~~, C_3-C_{10}cycloalkyl, heteroaryl or cycloheteroalkyl~~;

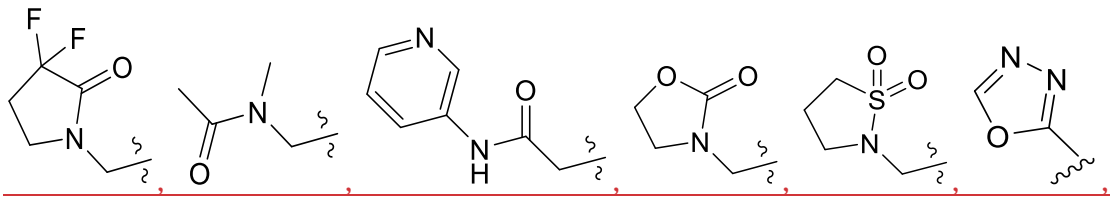
L is a straight or branched (C_1-C_5)alkylenyl, wherein one or more –CH_2- groups in L are optionally and independently replaced with a moiety selected from the group consisting of O, and NH;

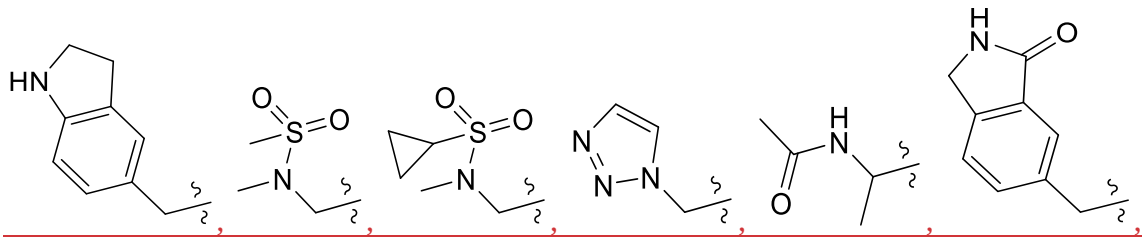
each occurrence of R^1 is independently ~~selected from~~ halogen, C_1-C_6alkyl, or cycloheteroalkyl;

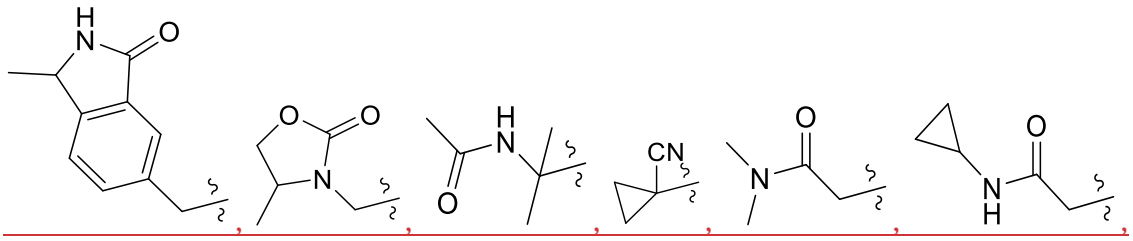
each occurrence of R^2 is independently ~~selected from~~ chlorine, iodine, methoxy, isopropoxy, methyl, difluoromethyl,

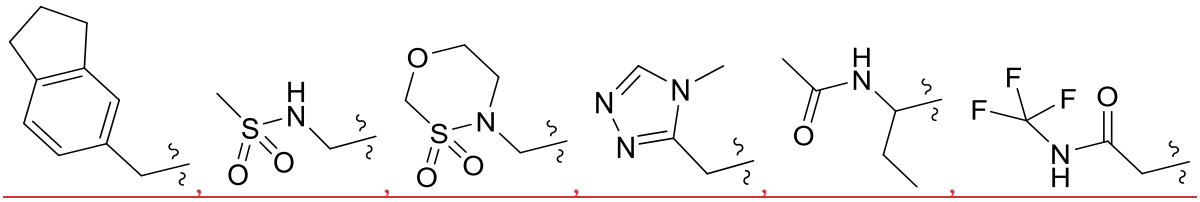


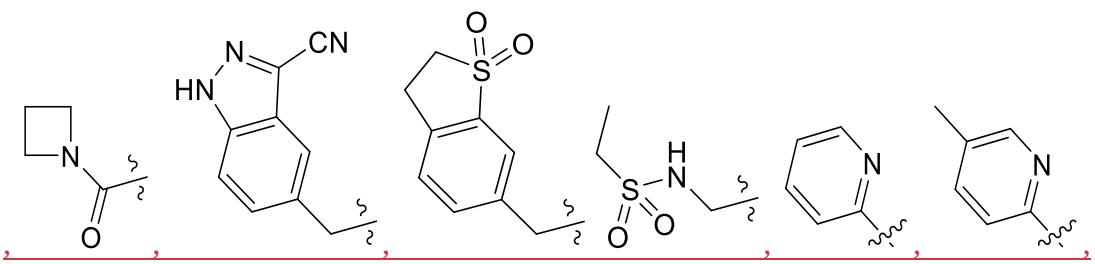




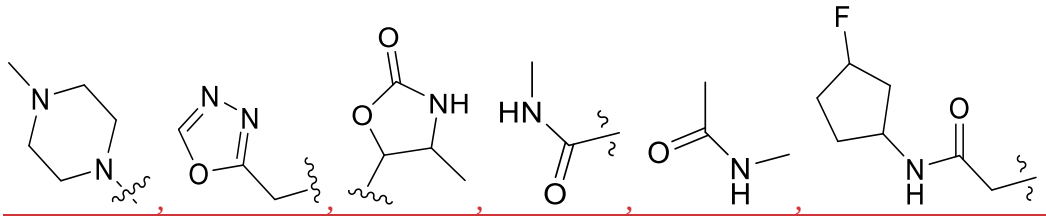




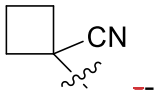




- 201 -



or



-- ~~C_1-C_6alkylNR^{4}COC_3-C_6cycloalkyl, -C_1-C_6alkylNR^{4}COC_1-C_6alkyl, -C_1-C_6alkylCONR^4C_1-C_6alkyl, halogen, alkoxy, -C_1-C_6alkylcycloheteroalkyl, -C_1-C_6alkylCONR^{4}aryl, C_1-C_6alkyl, -C_1-C_6alkylCOcycloheteroalkyl, -C_1-C_6alkylCONR^{4}heteroaryl, -C_1-C_6alkylNR^{4}SO$_2$$C_1$-$C_6$alkyl, -$C_1$-$C_6$alkylNR^{4}SO$_2$$C_3$-$C_6$cycloalkyl, C_3-C_6cycloalkyl, -C_1-C_6alkylCONR^4C_3-C_6cycloalkyl, cycloheteroalkyl, haloC$_1$-C_6alkyl, -CONR^{4}haloalkyl, -COcycloheteroalkyl, CN, -CONR^4C_1-C_6alkyl, -CONR^4C_3-C_6cycloalkyl, heteroaryl, aryl, haloalkoxy, -C_1-C_6alkylC_3-C_{10}cycloalkyl, oxo, -C_1-C_6alkylheteroaryl, -NR^{4}COC_1-C_6alkyl, wherein the -C_1-C_6alkylNR^{4}COC_3-C_6cycloalkyl, -C_1-C_6alkylCONR^4C_3-C_6cycloalkyl, -C_1-C_6alkylCONR^{4}aryl, -C_1-C_6alkylcycloheteroalkyl, -C_1-C_6alkylCOcycloheteroalkyl, C_3-C_6cycloalkyl, cycloheteroalkyl, heteroaryl, -C_1-C_6alkylC_3-C_{10}cycloalkyl, is unsubstituted or substituted with 1 to 3 substituents selected from the group consisting of alkoxy, CN, -C_1-C_6alkylOH, halogen, C_1-C_6alkyl, haloC$_1$-C_6alkyl, oxo, OH, CN, -C_1-C_6alkylCN, -COC_1-C_6alkyl and C_3-C_6cycloalkyl;~~

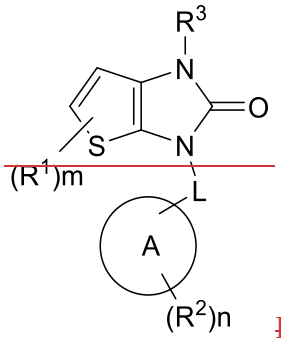
R^3 is hydrogen, C_1-C_6alkyl or haloC$_1$-C_6alkyl;

~~R^4 is C_1-C_6alkyl or hydrogen;~~

m is 0, 1 or 2; and

n is ~~0,~~ 1, 2 or 3.

~~3. The compound of claim 1, or a pharmaceutically acceptable salt thereof, having the Formula Ib~~



~~Ib,~~

~~A is aryl, C_3-C_{10}cycloalkyl, heteroaryl or cycloheteroalkyl;~~

~~L is a straight or branched (C_1-C_5)alkylenyl, wherein one or more $-CH_2-$ groups in L are optionally and independently replaced with a moiety selected from the group consisting of O, and NH;~~

~~each occurrence of R^1 is independently selected from halogen, C_1-C_6alkyl, or cycloheteroalkyl;~~

~~each occurrence of R^2 is independently selected from $-C_1$-C_6alkylNR^4COC_3-C_6cycloalkyl, $-C_1$-C_6alkylNR^4COC_1-C_6alkyl, $-C_1$-C_6alkyl$CONR^4C_1$-C_6alkyl, halogen, alkoxy, $-C_1$-C_6alkylcycloheteroalkyl, $-C_1$-C_6alkyl$CONR^4$aryl, C_1-C_6alkyl, $-C_1$-C_6alkylCOcycloheteroalkyl, $-C_1$-C_6alkyl$CONR^4$heteroaryl, $-C_1$-C_6alkyl$NR^4SO_2C_1$-C_6alkyl, $-C_1$-C_6alkyl$NR^4SO_2C_3$-C_6cycloalkyl, C_3-C_6cycloalkyl, $-C_1$-C_6alkyl$CONR^4C_3$-C_6cycloalkyl, cycloheteroalkyl, haloC_1-C_6alkyl, $-CONR^4$haloalkyl, $-$COcycloheteroalkyl, CN, $-CONR^4C_1$-C_6alkyl, $-CONR^4C_3$-C_6cycloalkyl, heteroaryl, aryl, haloalkoxy, $-C_1$-C_6alkylC_3-C_{10}cycloalkyl, oxo, $-C_1$-C_6alkylheteroaryl, $-NR^4COC_1$-C_6alkyl, wherein the $-C_1$-C_6alkylNR^4COC_3-C_6cycloalkyl, $-C_1$-C_6alkyl$CONR^4C_3$-C_6cycloalkyl, $-C_1$-C_6alkyl$CONR^4$aryl, $-C_1$-C_6alkylcycloheteroalkyl, $-C_1$-C_6alkylCOcycloheteroalkyl, C_3-C_6cycloalkyl, cycloheteroalkyl, heteroaryl, $-C_1$-C_6alkylC_3-C_{10}cycloalkyl, is unsubstituted or substituted with 1 to 3 substituents selected from the group consisting of alkoxy, CN, $-C_1$-C_6alkylOH, halogen, C_1-C_6alkyl, haloC_1-C_6alkyl, oxo, OH, CN, $-C_1$-C_6alkylCN, $-COC_1$-C_6alkyl and C_3-C_6cycloalkyl;~~

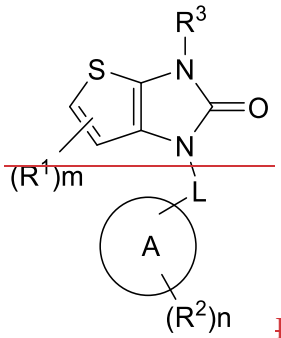
~~R^3 is C_1-C_6alkyl or haloC_1-C_6alkyl;~~

~~R^4 is C_1-C_6alkyl or hydrogen;~~

~~m is 0, 1 or 2; and~~

~~n is 0, 1, 2 or 3.~~

4. The compound of claim 1, or a pharmaceutically acceptable salt thereof, having the Formula Ic



Ic,

A is aryl, C_3-C_{10}cycloalkyl, heteroaryl or cycloheteroalkyl;

L is a straight or branched (C_1-C_5)alkylenyl, wherein one or more $-CH_2-$ groups in L are optionally and independently replaced with a moiety selected from the group consisting of O, and NH;

each occurrence of R^1 is independently selected from halogen, C_1-C_6alkyl, or cycloheteroalkyl;

each occurrence of R^2 is independently selected from $-C_1$-C_6alkylNR^4COC_3-C_6cycloalkyl, $-C_1$-C_6alkylNR^4COC_1-C_6alkyl, $-C_1$-C_6alkyl$CONR^4C_1$-C_6alkyl, halogen, alkoxy, $-C_1$-C_6alkylcycloheteroalkyl, $-C_1$-C_6alkyl$CONR^4$aryl, C_1-C_6alkyl, $-C_1$-C_6alkylCOcycloheteroalkyl, $-C_1$-C_6alkyl$CONR^4$heteroaryl, $-C_1$-C_6alkyl$NR^4SO_2C_1$-C_6alkyl, $-C_1$-C_6alkyl$NR^4SO_2C_3$-C_6cycloalkyl, C_3-C_6cycloalkyl, $-C_1$-C_6alkyl$CONR^4C_3$-C_6cycloalkyl, cycloheteroalkyl, haloC_1-C_6alkyl, $-CONR^4$haloalkyl, $-$COcycloheteroalkyl, CN, $-CONR^4C_1$-C_6alkyl, $-CONR^4C_3$-C_6cycloalkyl, heteroaryl, aryl, haloalkoxy, $-C_1$-C_6alkylC_3-C_{10}cycloalkyl, oxo, $-C_1$-C_6alkylheteroaryl, $-NR^4COC_1$-C_6alkyl, wherein the $-C_1$-C_6alkylNR^4COC_3-C_6cycloalkyl, $-C_1$-C_6alkyl$CONR^4C_3$-C_6cycloalkyl, $-C_1$-C_6alkyl$CONR^4$aryl, $-C_1$-C_6alkylcycloheteroalkyl, $-C_1$-C_6alkylCOcycloheteroalkyl, C_3-C_6cycloalkyl, cycloheteroalkyl, heteroaryl, $-C_1$-C_6alkylC_3-C_{10}cycloalkyl, is unsubstituted or substituted with 1 to 3 substituents selected from the group consisting of alkoxy, CN, $-C_1$-C_6alkylOH, halogen, C_1-C_6alkyl, haloC_1-C_6alkyl, oxo, OH, CN, $-C_1$-C_6alkylCN, COC_1-C_6alkyl and C_3-C_6cycloalkyl;

R^3 is C_1-C_6alkyl or haloC_1-C_6alkyl;

R^4 is C_1-C_6alkyl or hydrogen;

m is 0, 1 or 2; and

~~n is 0, 1, 2 or 3.~~

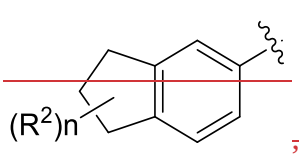
~~5.~~2. The compound of ~~any one of~~ claim~~s 1-4~~1, or pharmaceutically acceptable salt thereof, wherein L is -CH_2-, -CH_2CH_2-, -$CH_2CH_2CH_2CH_2$-, -$CH_2CH_2CH_2O$-, or -$CHCH_3$-.

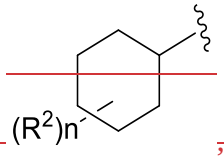
~~6. The compound of any one of claims 1-5, or a pharmaceutically acceptable salt thereof, wherein A is aryl.~~

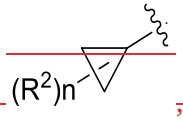
~~7.~~3. The compound of ~~any one of~~ claim~~s 1-6~~1 or 2, or a pharmaceutically acceptable salt thereof, wherein A is ~~aryl, wherein the aryl is~~ phenyl.

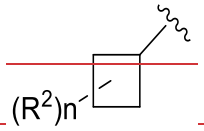
~~8. The compound of any one of claims 1-5, or a pharmaceutically acceptable salt thereof, wherein A is C_3-C_{10}cycloalkyl.~~

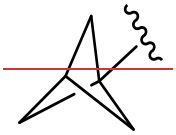
~~9. The compound of any one of claims 1-5 or 8, or a pharmaceutically acceptable salt thereof, wherein A is C_3-C_{10}cycloalkyl, wherein the C_3-C_{10}cycloalkyl is:~~



~~,~~ 

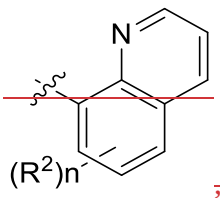
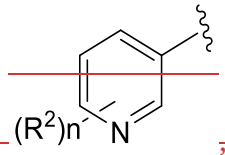
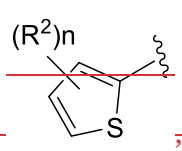
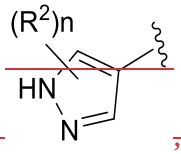
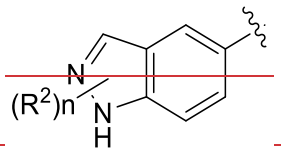
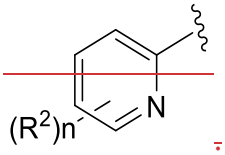
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~~or~~  .

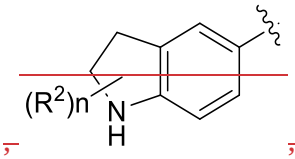
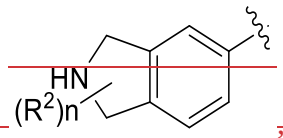
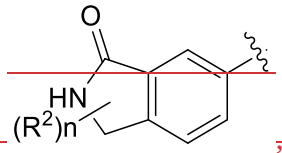
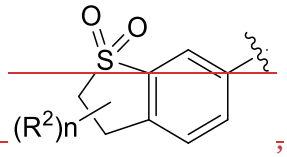
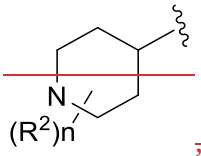
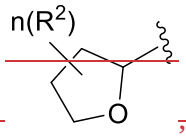
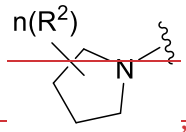
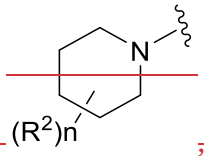
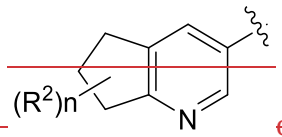
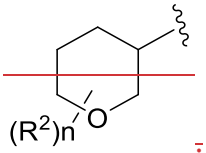
~~10. The compound of any one of claims 1-5, or a pharmaceutically acceptable salt thereof, wherein A is heteroaryl.~~

~~11. The compound of any one of claims 1-4 or 10, or a pharmaceutically acceptable salt thereof, wherein A is heteroaryl, wherein the heteroaryl is:~~

~~12. The compound of any one of claims 1-5, or a pharmaceutically acceptable salt thereof, wherein A is cycloheteroalkyl.~~

~~13. The compound of any one of claims 1-4 or 12, or a pharmaceutically acceptable salt thereof, wherein A is a cycloheteroalkyl, wherein the cycloheteroalkyl is:~~

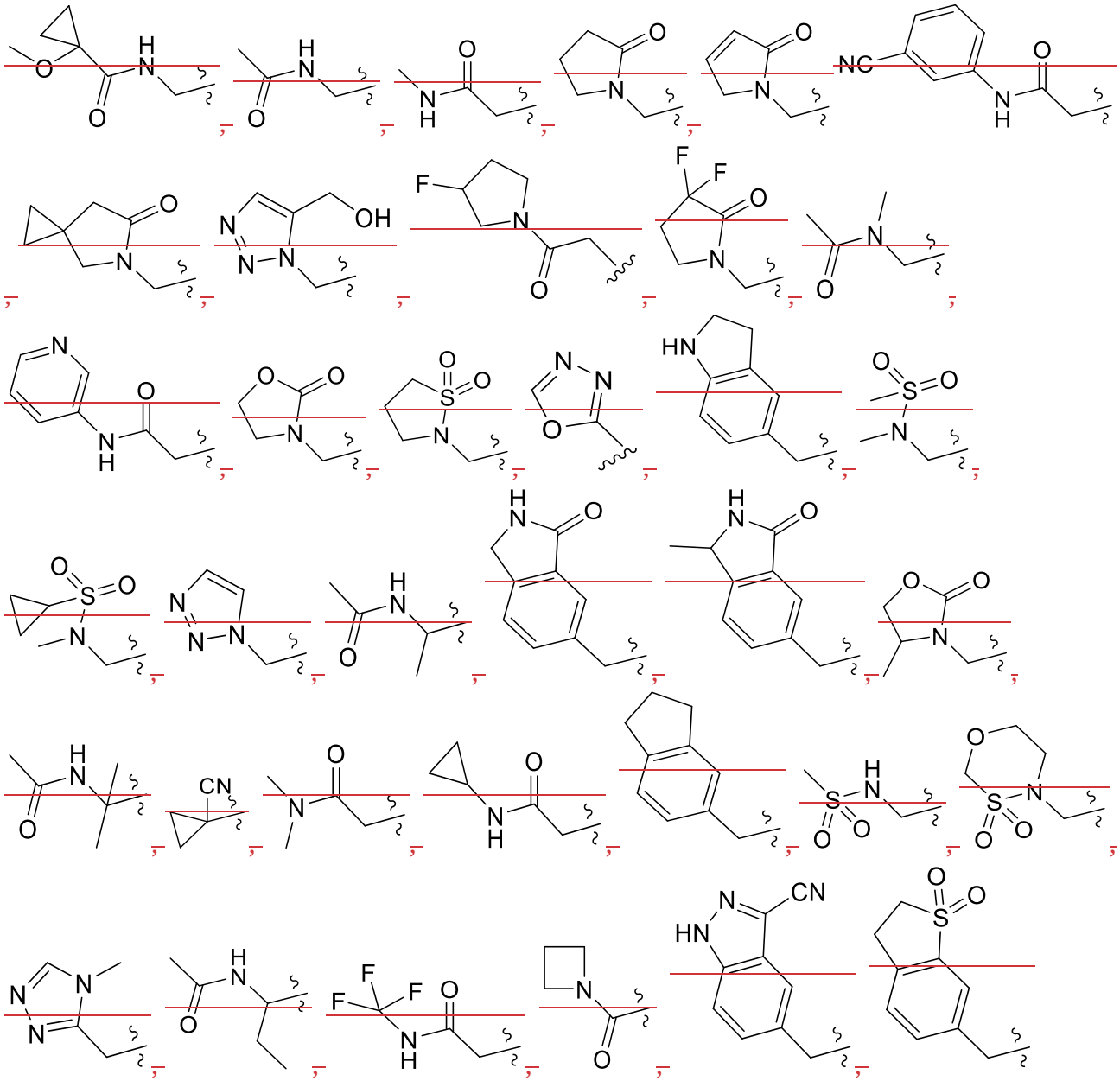











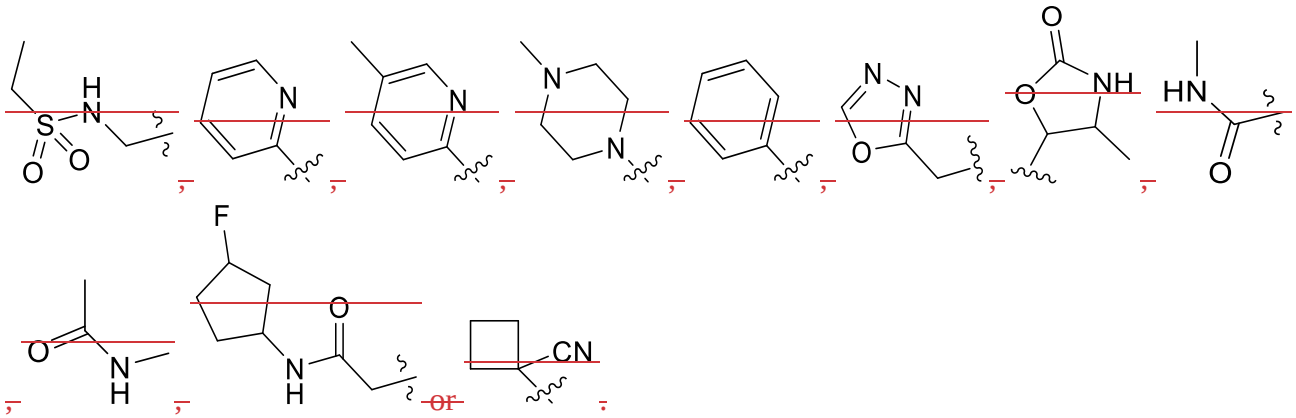
~~14.~~4. The compound of any one of claims ~~1-13~~1 to 3, or a pharmaceutically acceptable salt thereof, wherein m is 0.

~~15.~~5. The compound of any one of claims ~~1-13~~1 to 3, or a pharmaceutically acceptable salt thereof, wherein m is 1 or 2 and R^1 is fluorine, chlorine, pyrrolidine, methyl or ethyl.

16. The compound of any one of claims 1-15, or a pharmaceutically acceptable salt thereof, wherein n is 0.

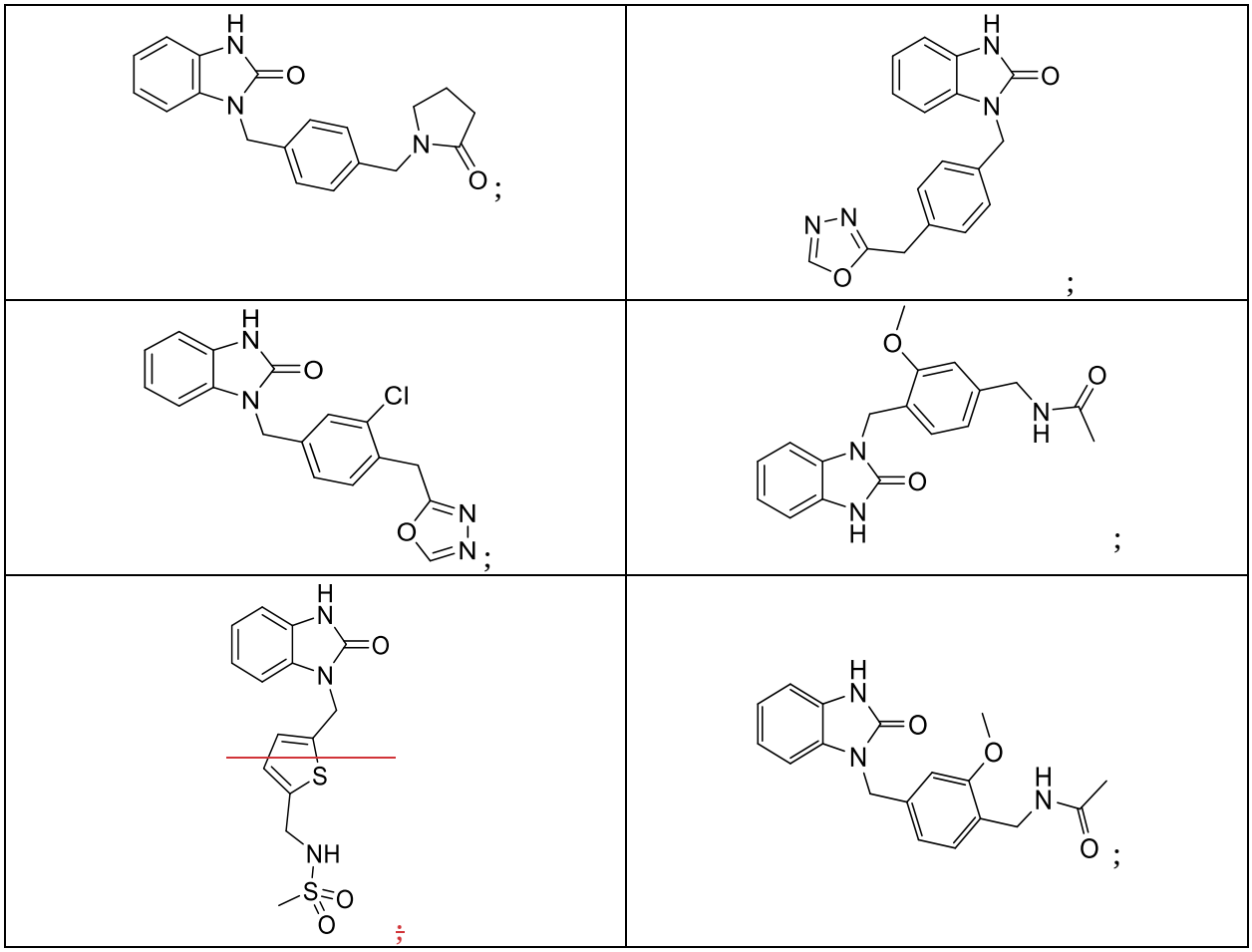
17. The compound of any one of claims 1-15, or a pharmaceutically acceptable salt thereof, wherein n is 1, 2 or 3 and R^2 is chlorine, fluorine, iodine, methoxy, isopropoxy, methyl, difluoromethyl, trifluoromethoxy, isobutyl,

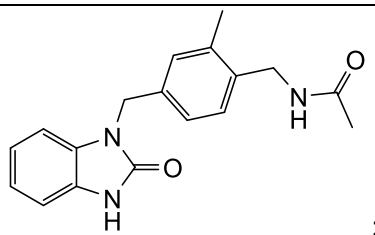
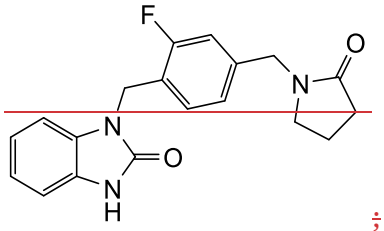
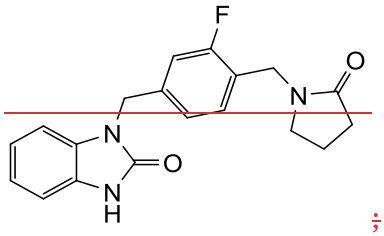
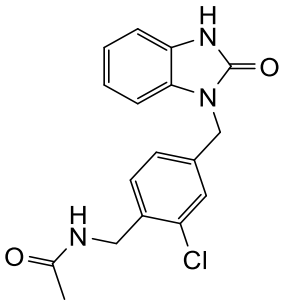
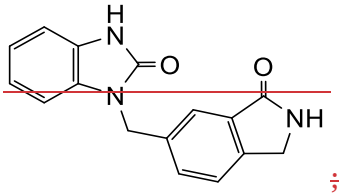
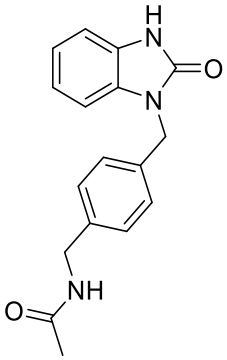
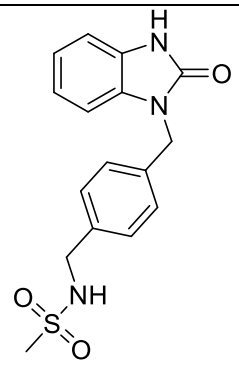
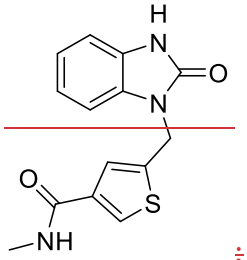
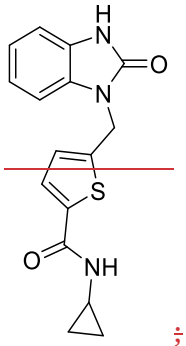
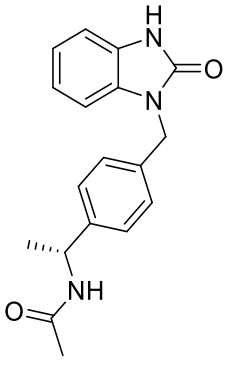


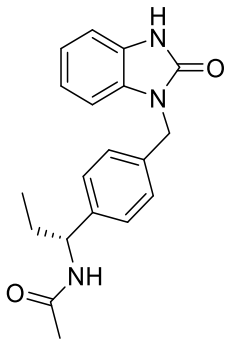
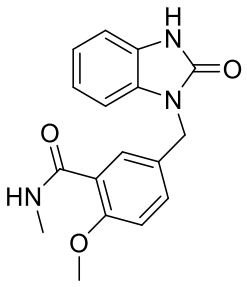
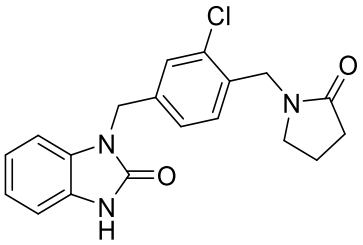
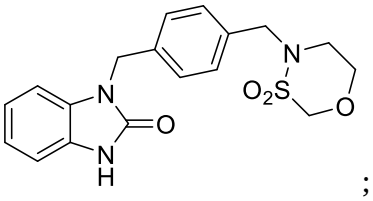
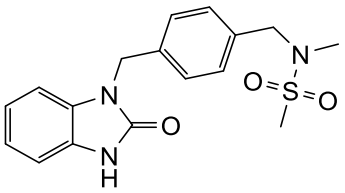
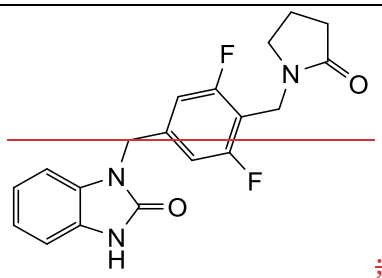
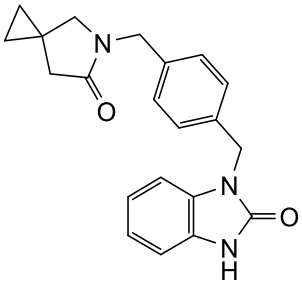
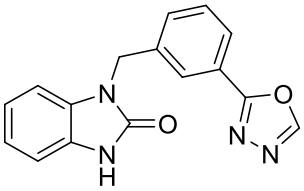
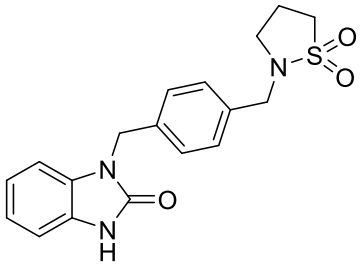
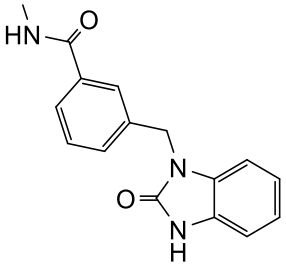
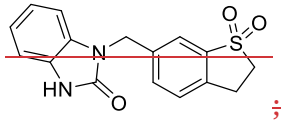
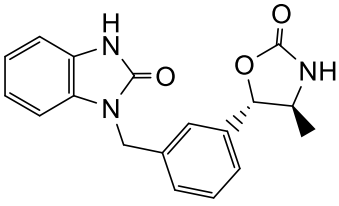


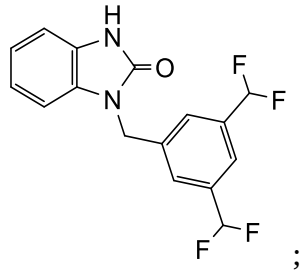
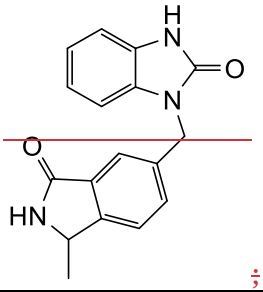
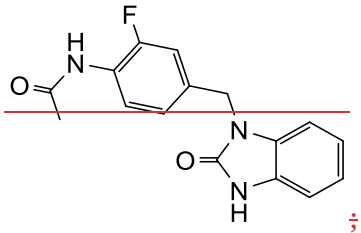
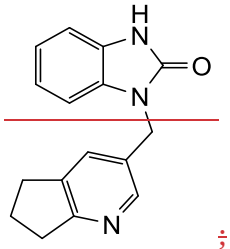
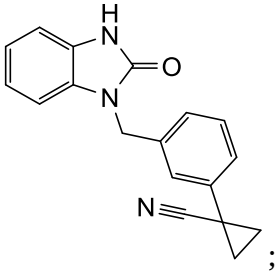
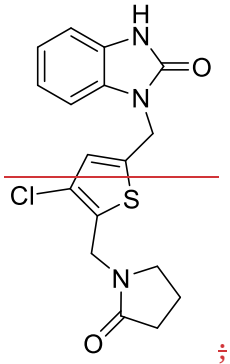
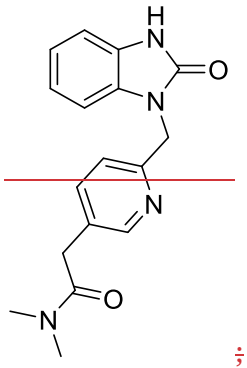
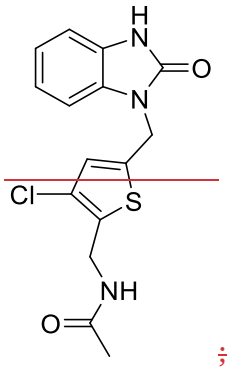
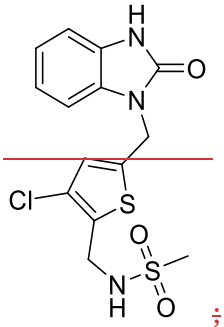
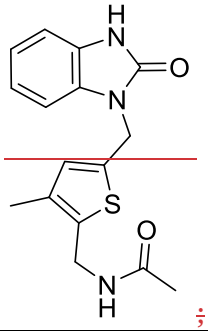
~~18.~~6. The compound of any one of claims ~~1-17~~1 to 5, or a pharmaceutically acceptable salt thereof, wherein ~~and~~ R^3 is hydrogen, methyl or difluoromethyl.

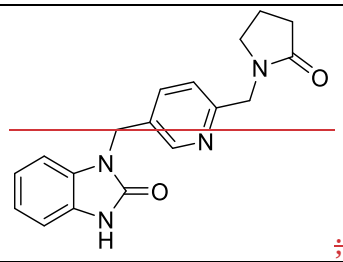
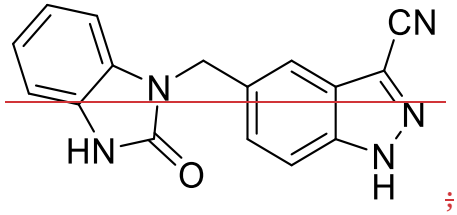
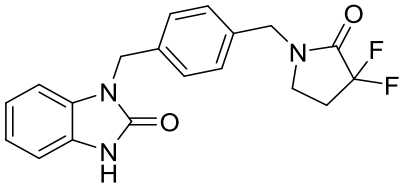
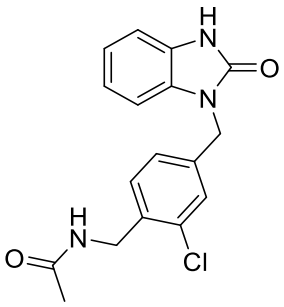
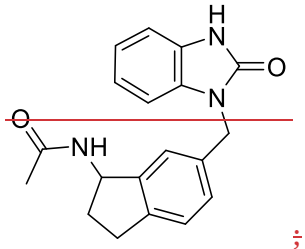
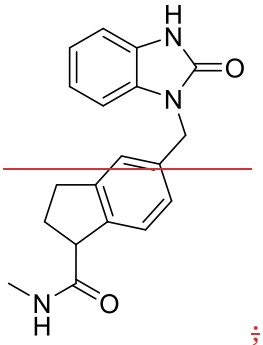
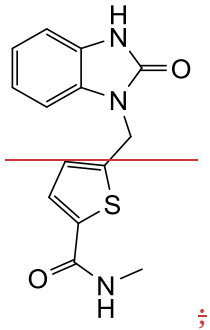
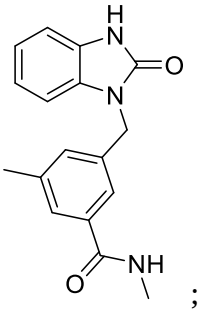
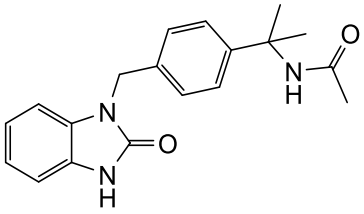
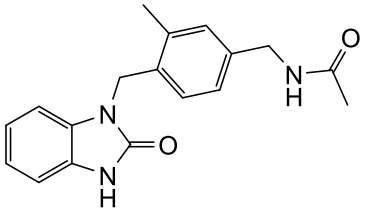
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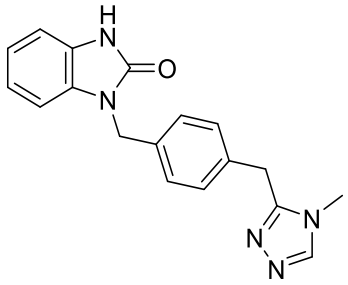
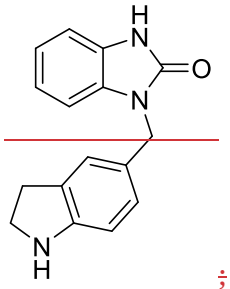
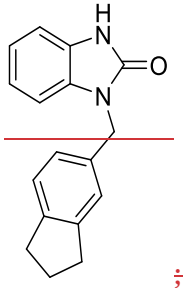
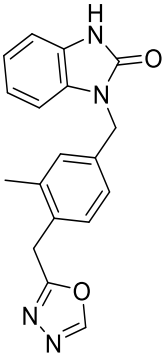
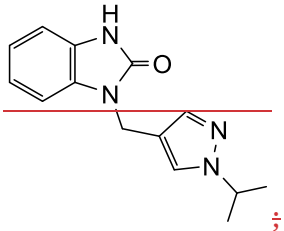
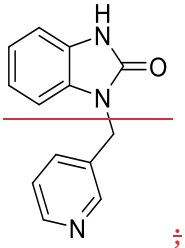
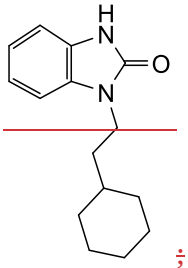
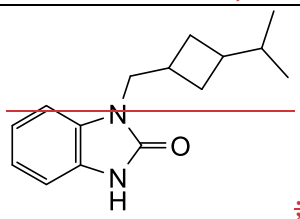
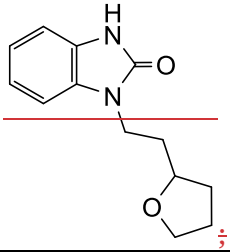
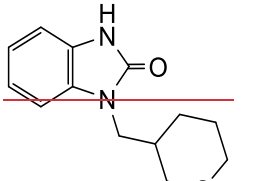


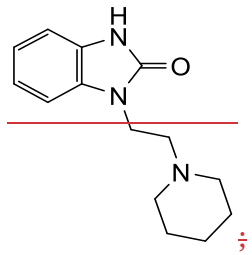
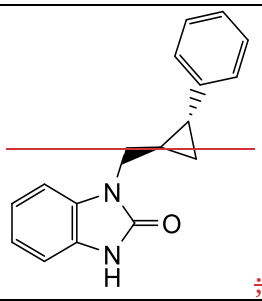
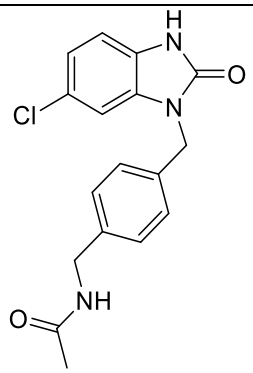
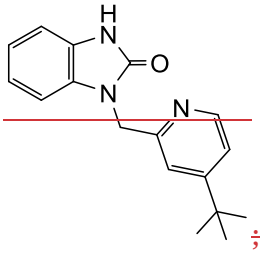
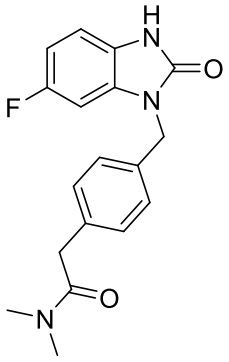
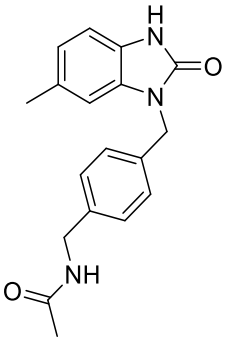
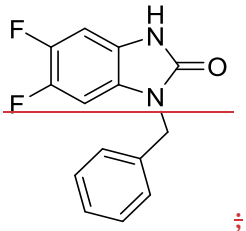
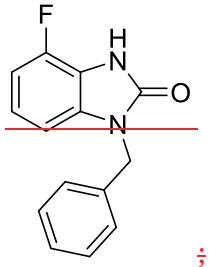
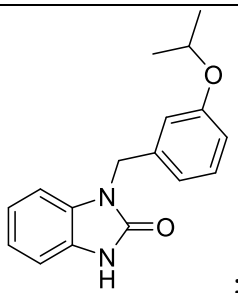
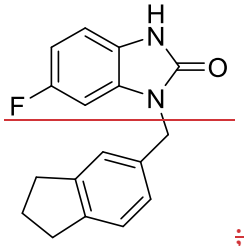
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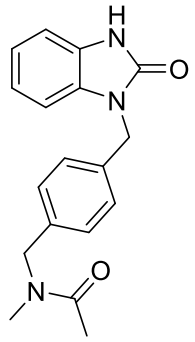
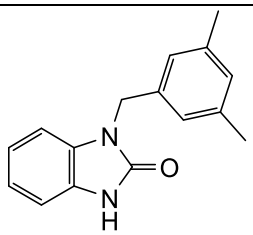
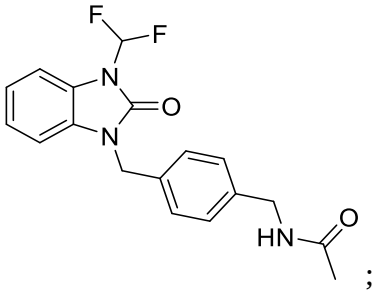
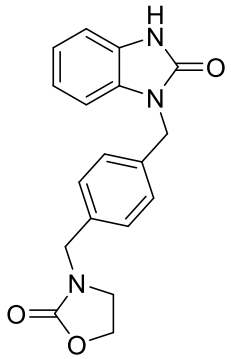
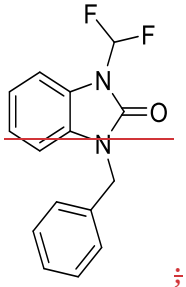
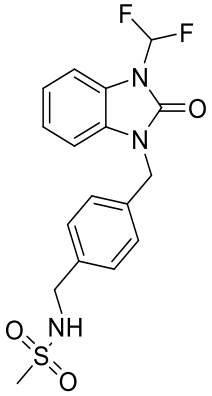
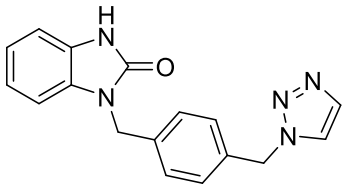
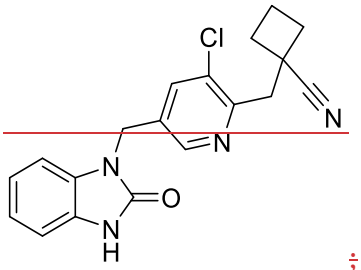
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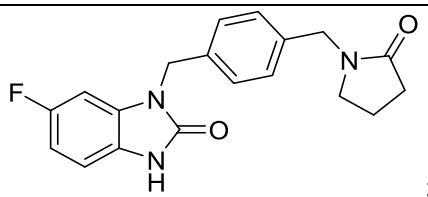
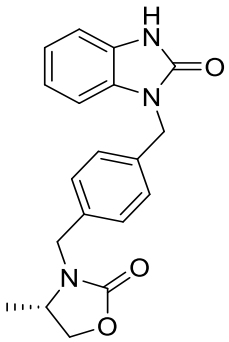
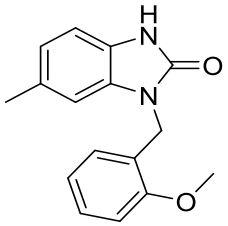
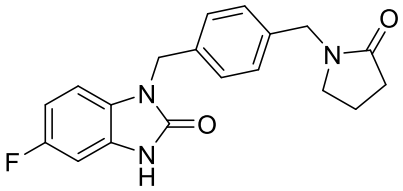
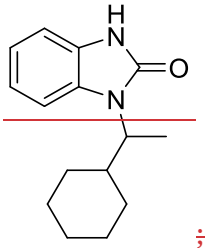
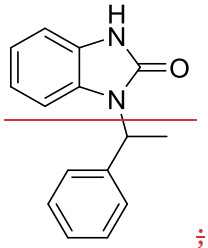
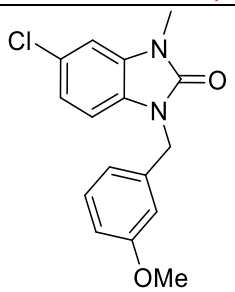
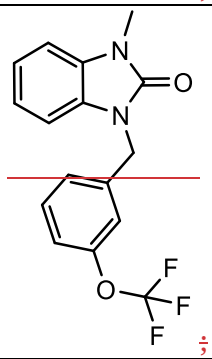
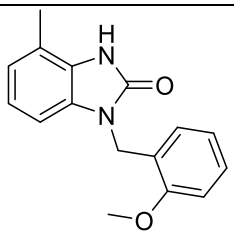
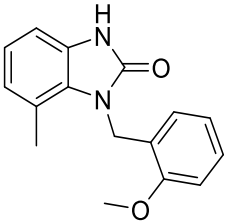
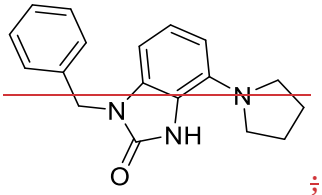
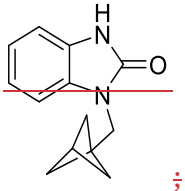
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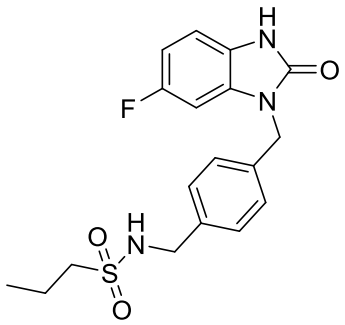
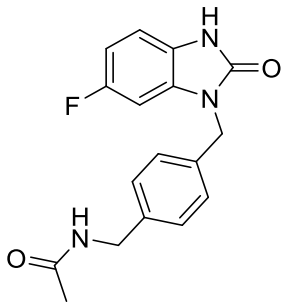
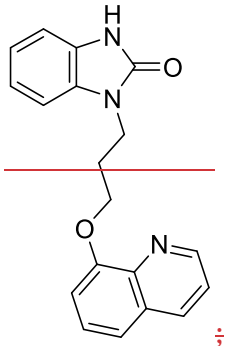
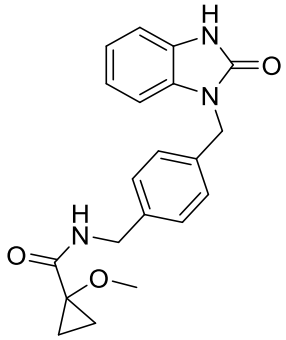
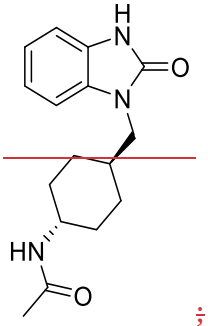
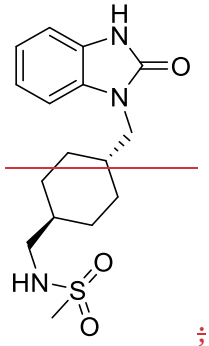
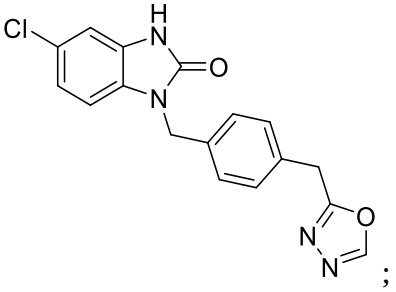
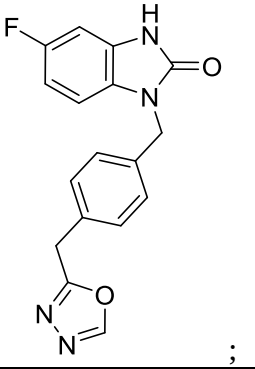
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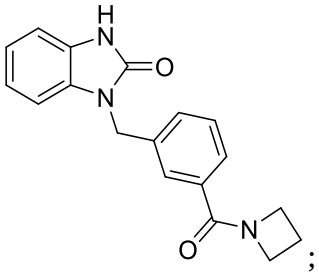
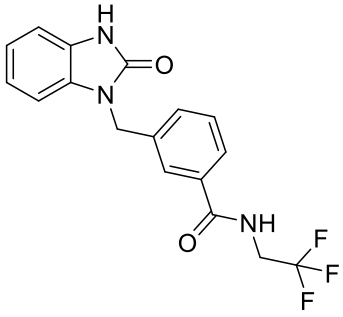
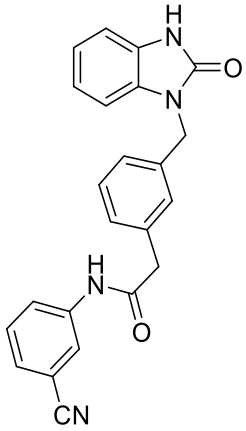
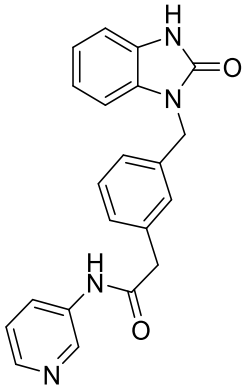
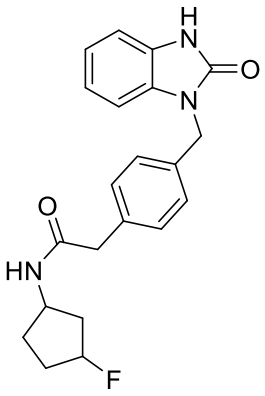
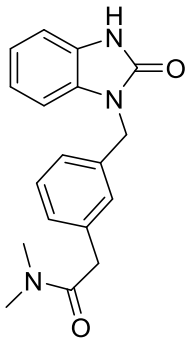
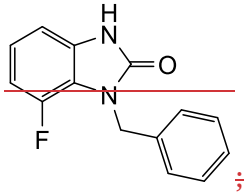
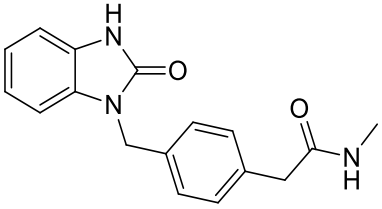
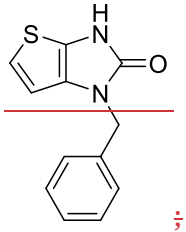
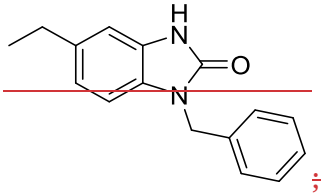
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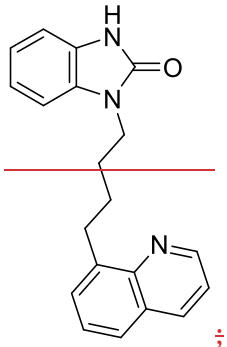
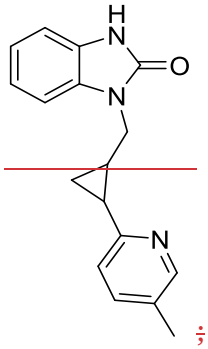
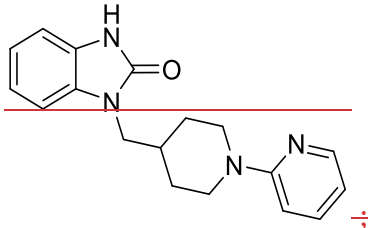
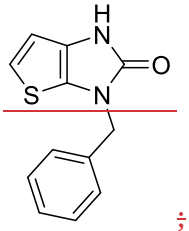
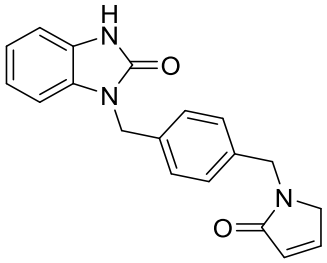
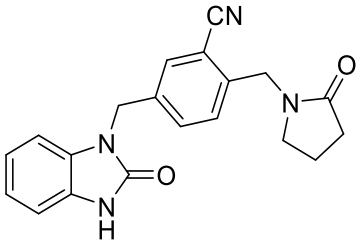
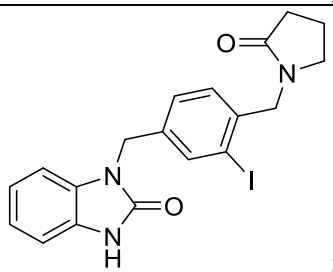
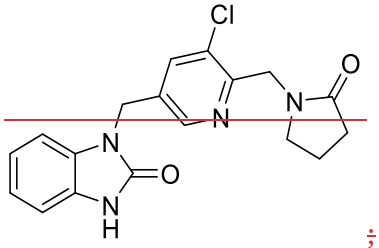
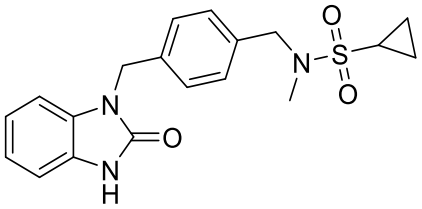
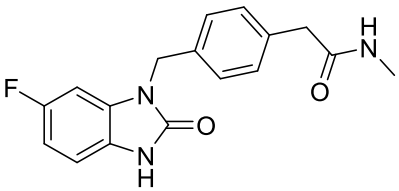
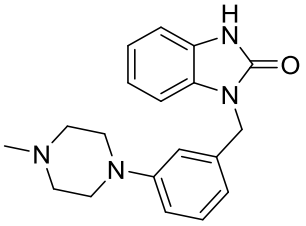
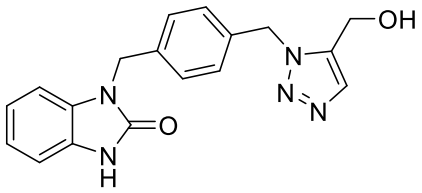
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or a pharmaceutically acceptable salt thereof.

~~20.~~8. Use of a compound of any one of claims 1 to 7 or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of ~~A method of treating~~ cancer ~~comprising administering to a patient in need thereof a compound, or pharmaceutically acceptable salt thereof, of any one of claims 1-19~~.

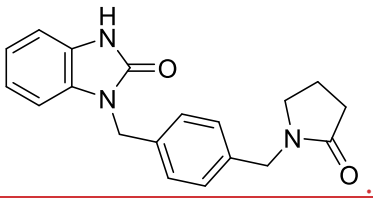
~~21. The use of a compound, or pharmaceutically acceptable salt thereof, of any one of claims 1-19 to treat cancer in a patient in need thereof.~~

9. A compound of any one of claims 1 to 7 or a pharmaceutically acceptable salt thereof for use in therapy.

~~22.~~10. A pharmaceutical composition comprising a compound of any one of claims ~~1-19~~1 to 7, or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

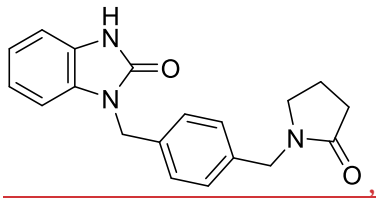
~~23~~11. A pharmaceutical composition comprising a compound of any one of claims ~~1-19~~1 to 7 and a pharmaceutically acceptable carrier.

12. A compound having the following structure



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13. A compound having the following structure



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or a pharmaceutically acceptable salt thereof.

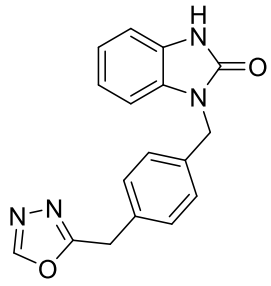
14. Use of a compound of claim 13, or pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of cancer.

15. A compound of claim 13, or pharmaceutically acceptable salt thereof for use in therapy.

16. A pharmaceutical composition comprising a compound of claim 13, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

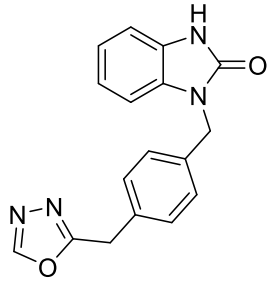
17. A pharmaceutical composition comprising a compound of claim 12 and a pharmaceutically acceptable carrier.

18. A compound having the following structure



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19. A compound having the following structure



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or a pharmaceutically acceptable salt thereof.

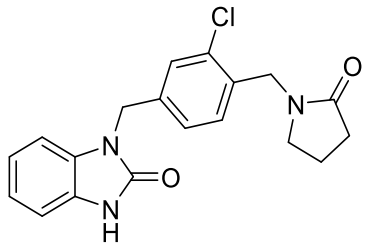
20. Use of a compound of claim 19, or pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of cancer.

21. A compound of claim 19, or pharmaceutically acceptable salt thereof for use in therapy.

22. A pharmaceutical composition comprising a compound of claim 19, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

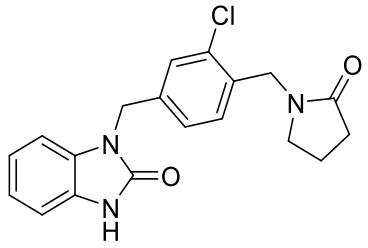
23. A pharmaceutical composition comprising a compound of claim 18 and a pharmaceutically acceptable carrier.

24. A compound having the following structure



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25. A compound having the following structure



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or a pharmaceutically acceptable salt thereof.

26. Use of a compound of claim 25, or pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of cancer.

27. A compound of claim 25, or pharmaceutically acceptable salt thereof for use in therapy.

28. A pharmaceutical composition comprising a compound of claim 25, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

29. A pharmaceutical composition comprising a compound of claim 24 and a pharmaceutically acceptable carrier.