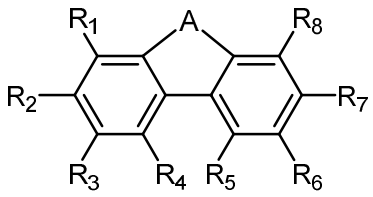
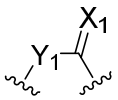
CLAIMS:

1. Use of a compound of Formula (Ia),



(Ia)

wherein

A is 

;

X_1 is selected from O and S;

Y_1 is O;

R_1, R_4, R_5 and R_8 are independently selected from H and halogen;

R_3 and R_6 are independently selected from H, CN, OH, CF_3, halogen, and alkyl;

one of R_2 and R_7 is H, OH, or OAc and the other of R_2 and R_7 is halogen, CN, CF_3, CO_2H, NO_2, NHAc, alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, alkylamino, alkyl-R_9, alkenyl-R_9, alkynyl-R_9, OR_{10}, NHR_{10}, $NR_{11}C(O)R_{12}$, $C(O)NR_{11}R_{12}$, and $NR_{11}SO_2R_{12}$;

each occurrence of R_9 is independently selected from OH, NH_2, O-alkyl, O-alkyl-O-alkyl, alkylamino, NHC(O)-alkyl, $N(CH_3)C(O)$-alkyl, $NHSO_2$-alkyl, $N(CH_3)SO_2$-alkyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl;

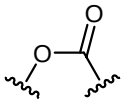
R_{10} is selected from C_2-C_{12} alkyl, C(O)-alkyl, hydroxyalkyl, aminoalkyl, alkyl-O-alkyl, alkyl-O-alkyl-OH, alkyl-O-alkyl-O-alkyl, alkenyl, alkynyl, arylalkyl, heteroarylalkyl, alkyl-cycloalkyl, alkyl-heterocycloalkyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, SO_3H, SO_2-alkyl, and SO_2-haloalkyl;

each occurrence of R_{11} is selected from H and alkyl; and

each occurrence of R_{12} is selected from alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, O-alkyl, aminoalkyl, arylalkyl, heteroarylalkyl, alkyl-cycloalkyl, and alkyl-heterocycloalkyl;

or a pharmaceutically acceptable salt thereof,

in the manufacture of a medicament for treating amyotrophic lateral sclerosis (ALS).

2. The use of claim 1, wherein A is  .

3. The use of claim 1 or 2, wherein R_2 is OH.

4. The use of any one of claims 1-3, wherein
R_7 is selected from haloalkyl, substituted cycloalkyl, alkynyl-R_9, OR_{10}, and $C(O)NR_{11}R_{12}$;
R_9 is selected from OH, substituted cycloalkyl and heterocycloalkyl;
R_{10} is selected from alkyl, substituted cycloalkyl, heterocycloalkyl and alkyl heterocycloalkyl; and
R_{11} is H and R_{12} is alkyl-heterocycloalkyl.

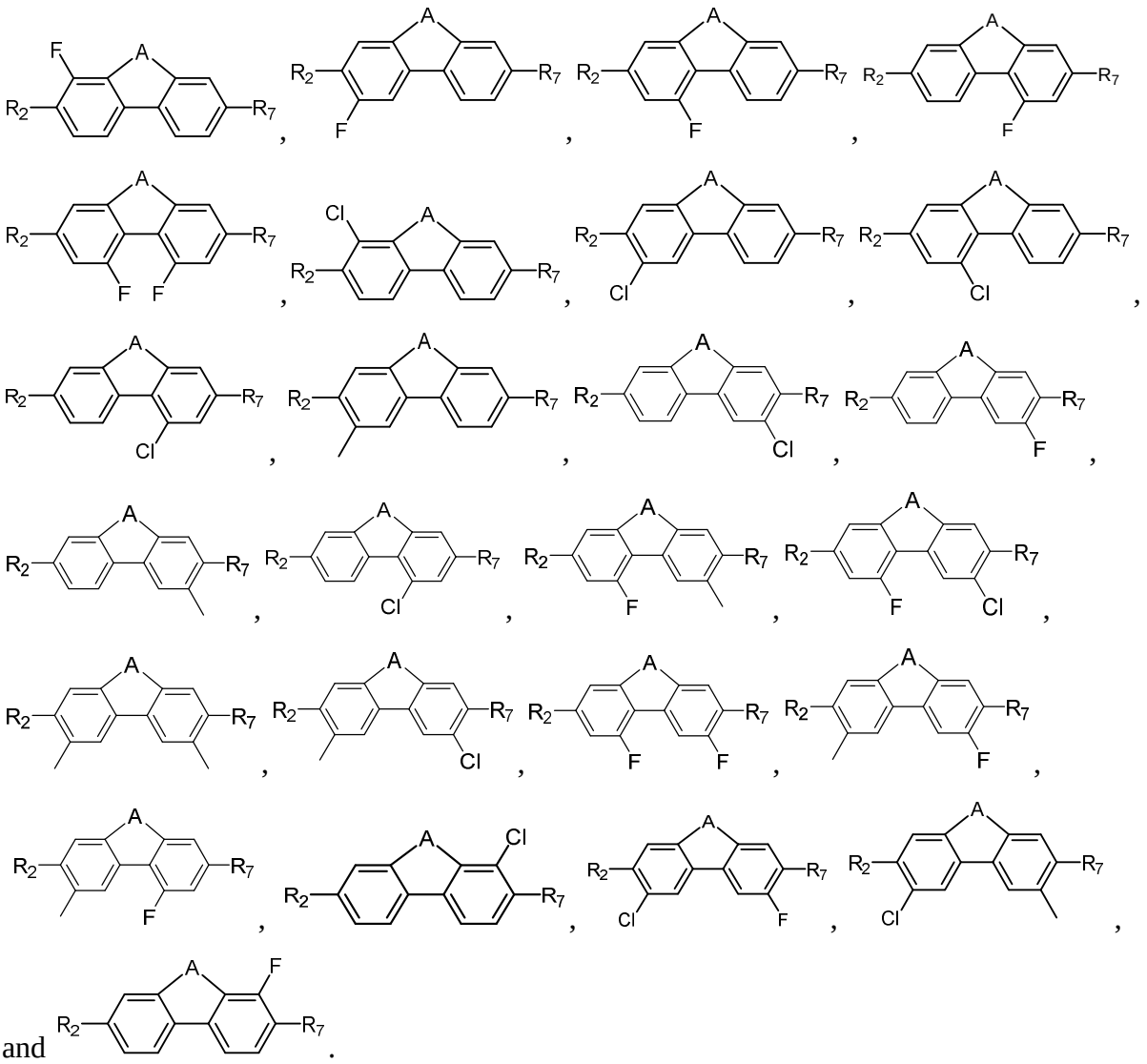
5. The use of claim 4, wherein each occurrence of substituted cycloalkyl is independently substituted with OH, halogen, or hydroxyalkyl.

6. The use of any one of claims 1-5, wherein R_1, R_3, R_4, R_5, R_6, and R_8 are each H.

7. The use of any one of claims 1-5, wherein one of R_1, R_3, R_4, R_5, R_6, and R_8 is not H or two of R_1, R_3, R_4, R_5, R_6, and R_8 are not H.

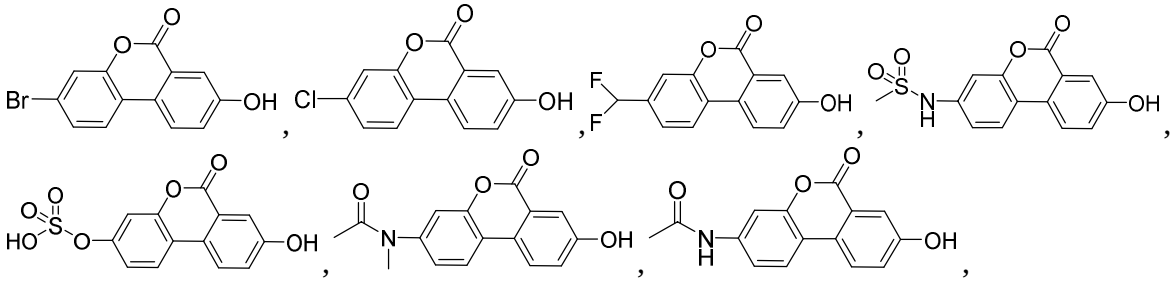
8. The use of claim 7, wherein one of R_1, R_3, R_4, R_5, R_6, and R_8 is alkyl or halogen or two of R_1, R_3, R_4, R_5, R_6, and R_8 are independently alkyl or halogen.

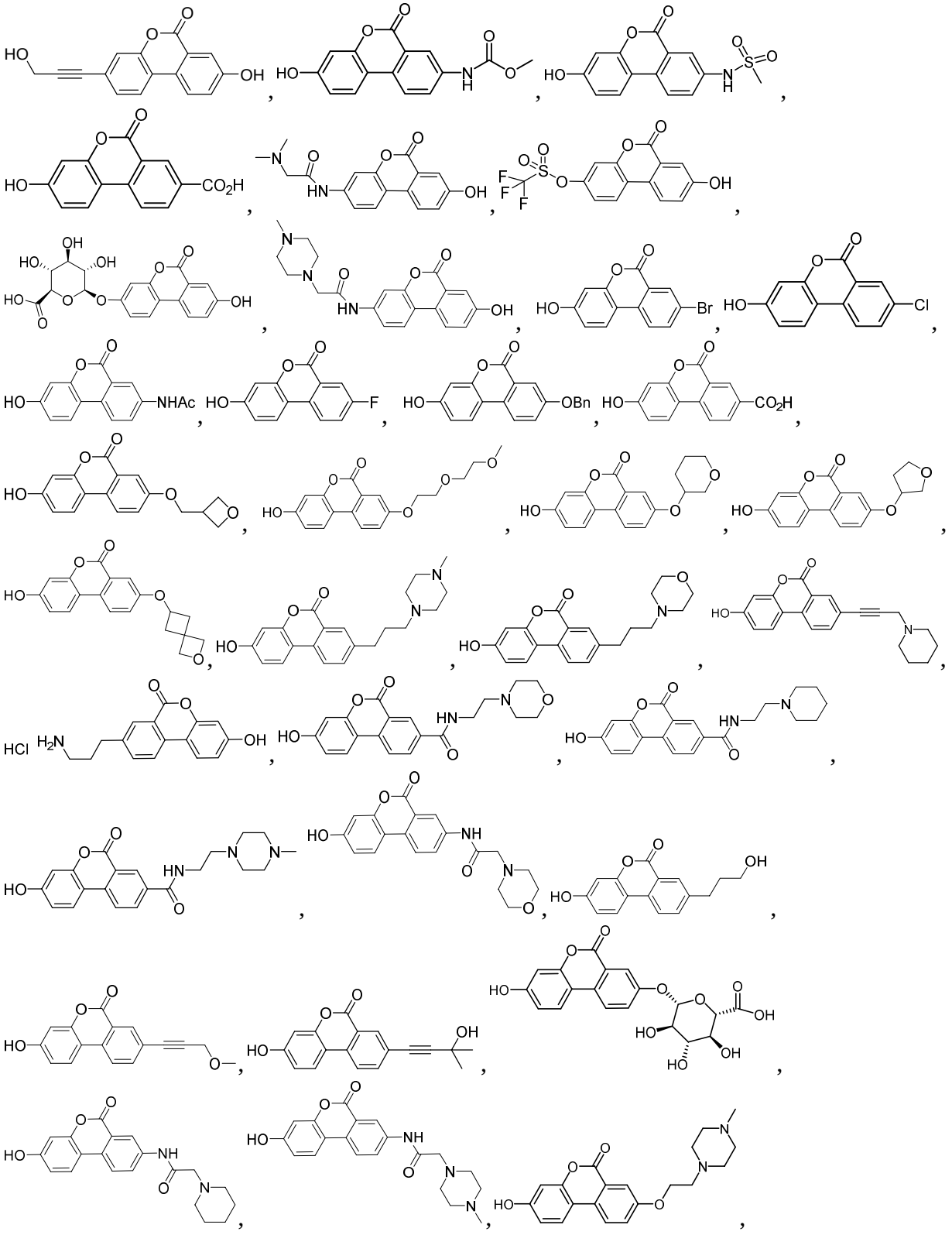
9. The use of claim 8, wherein the compound is selected from:

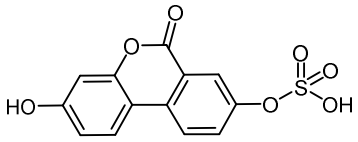


and .

10. The use of claim 1, wherein the compound is selected from:



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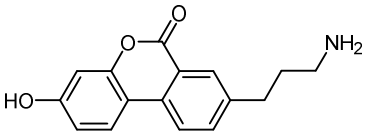
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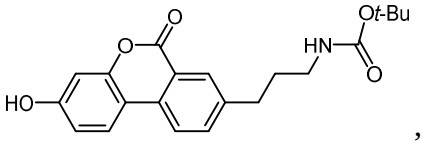
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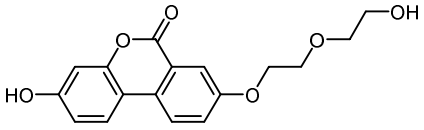
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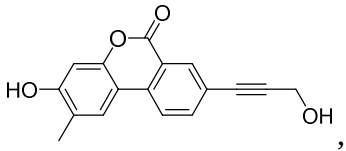
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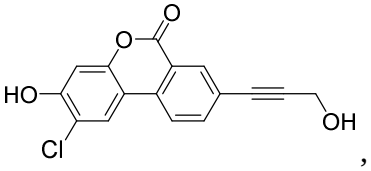
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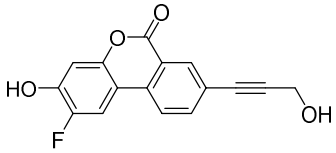
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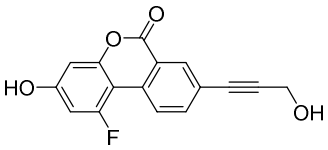
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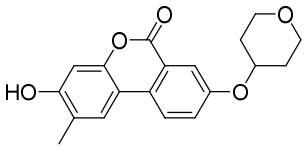
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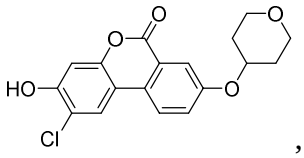
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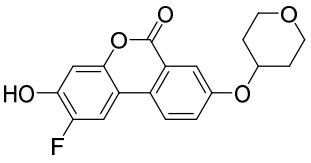
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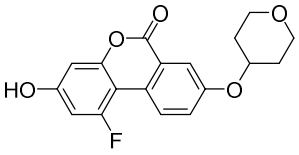
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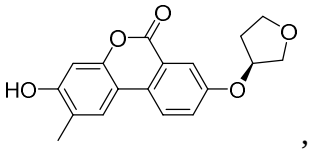
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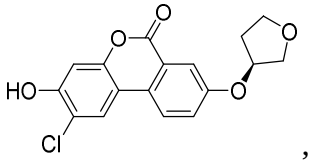
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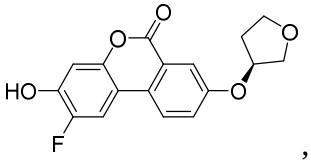
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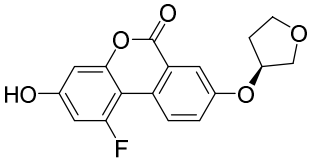
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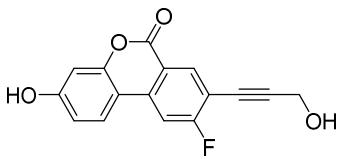
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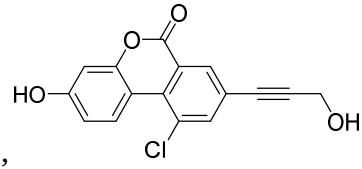
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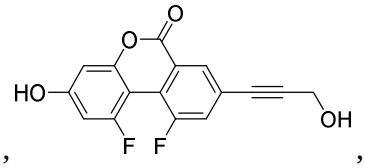
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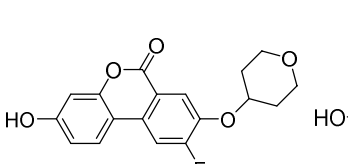
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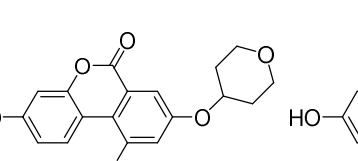
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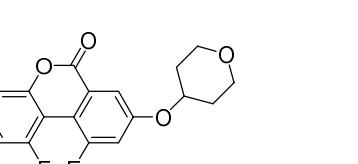
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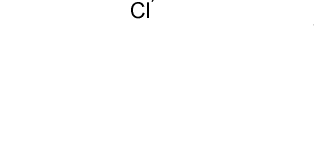
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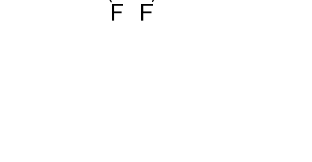
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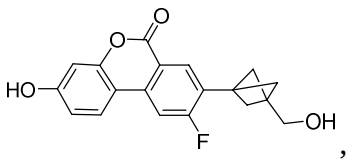
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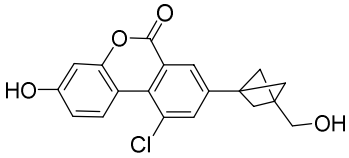
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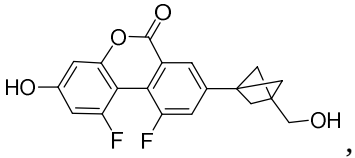
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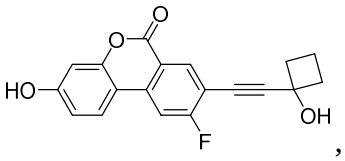
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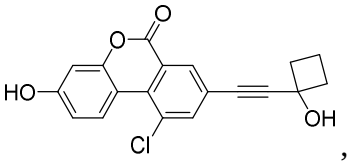
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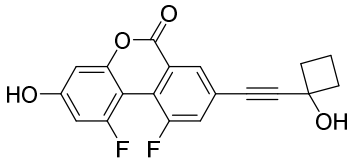
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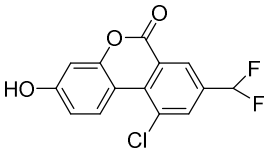
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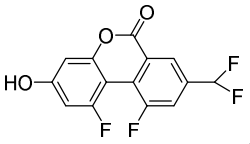
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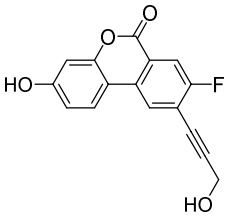
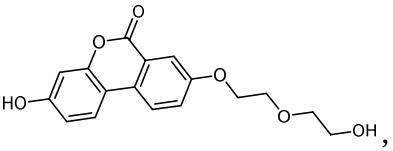
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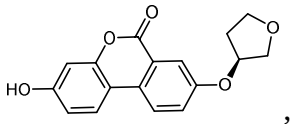
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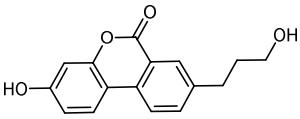
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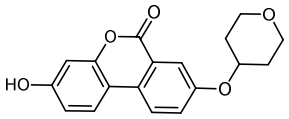
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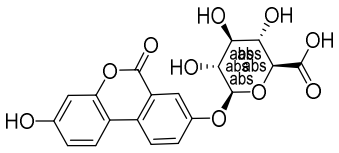
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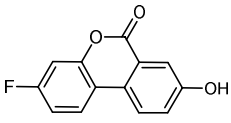
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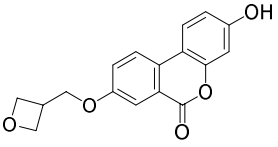
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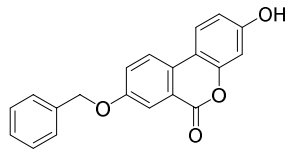
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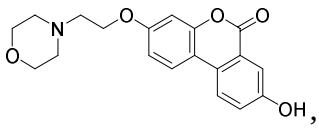
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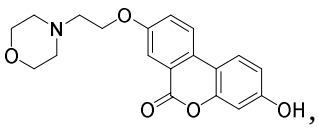
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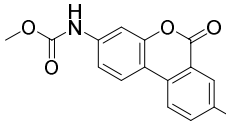
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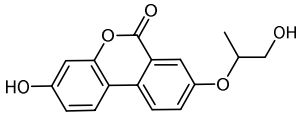
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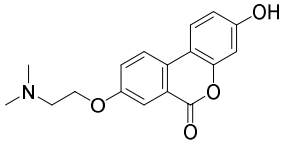
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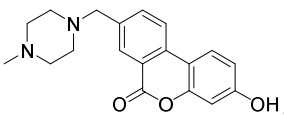
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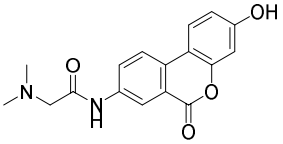
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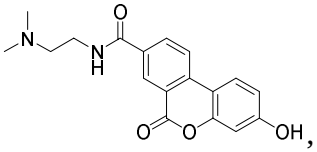
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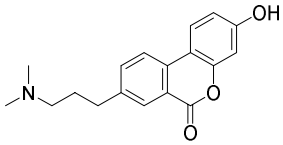
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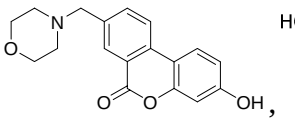
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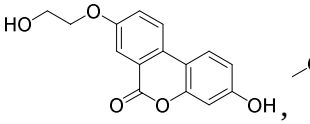
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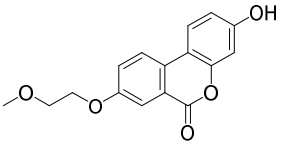
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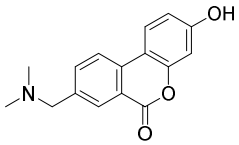
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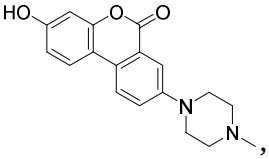
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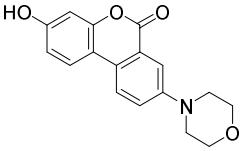
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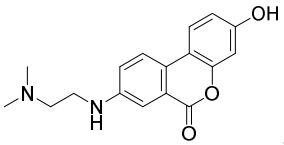
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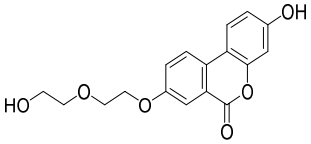
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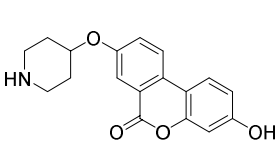
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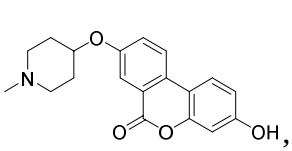
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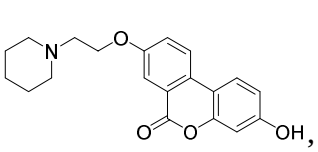
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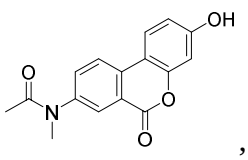
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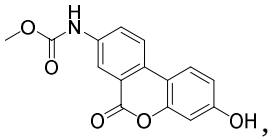
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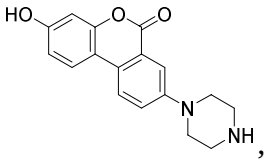
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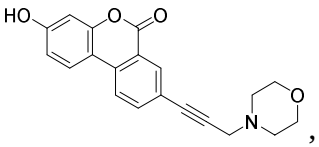
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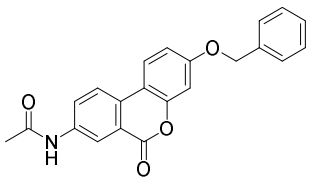
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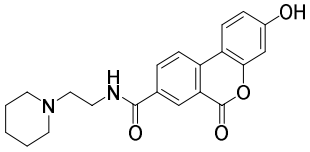
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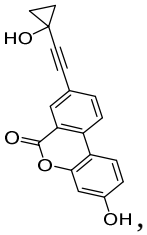
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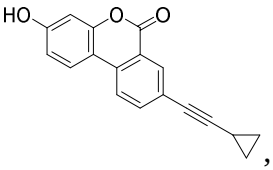
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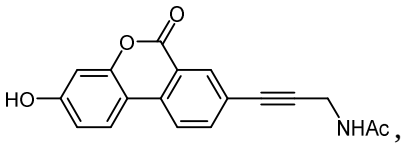
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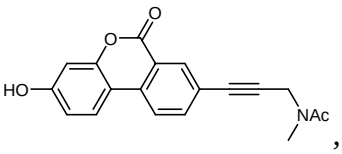
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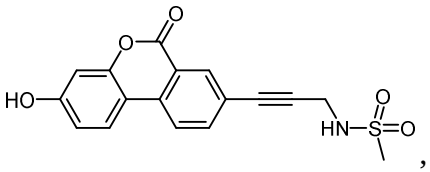
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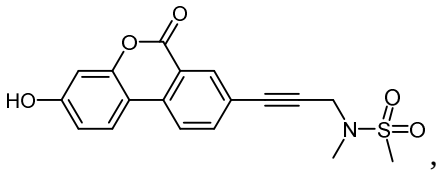
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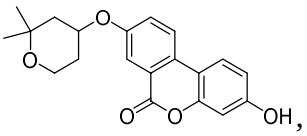
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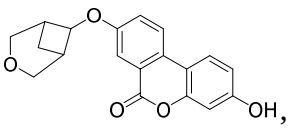
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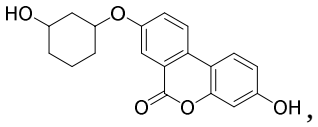
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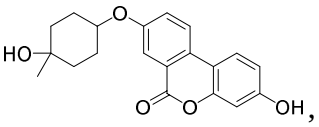
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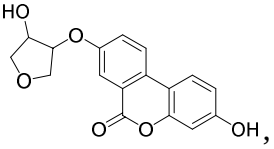
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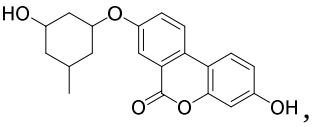
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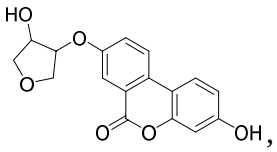
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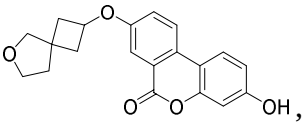
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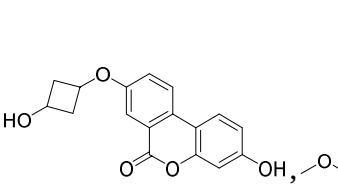
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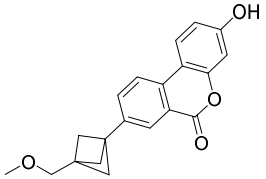
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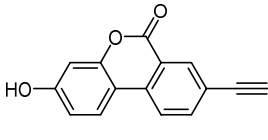
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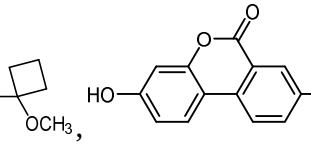
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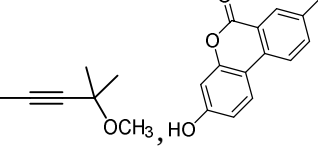
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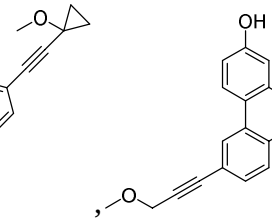
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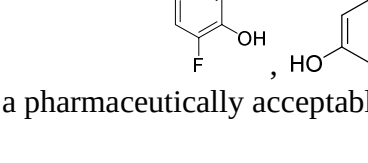
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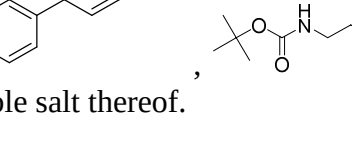
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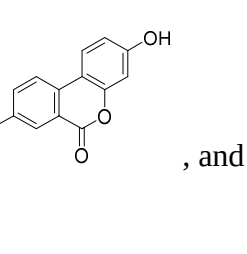
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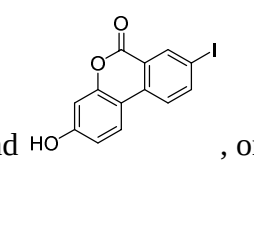
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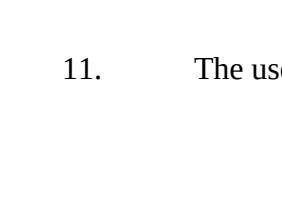
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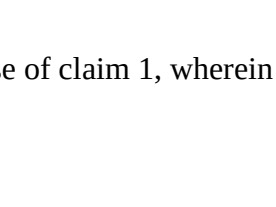
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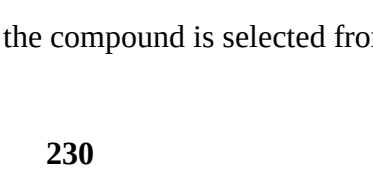
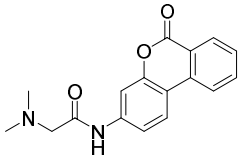
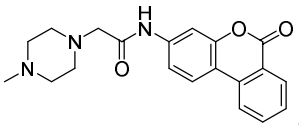
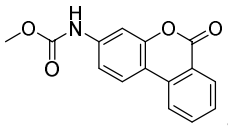
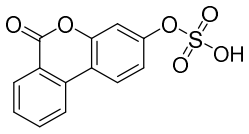
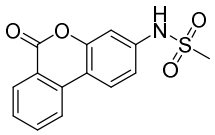
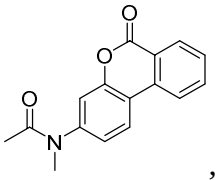
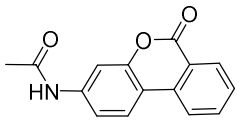
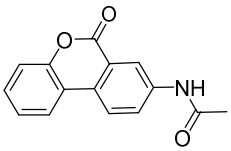
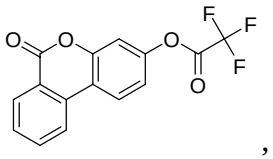
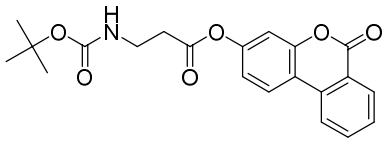
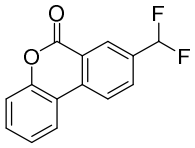
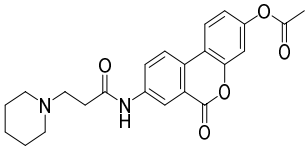
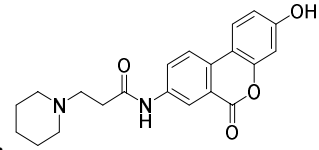
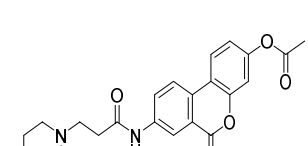
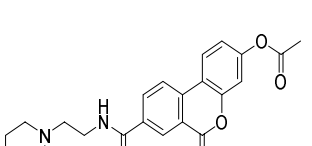
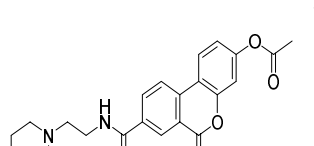
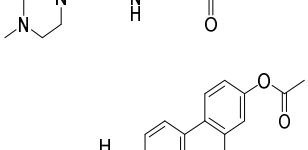
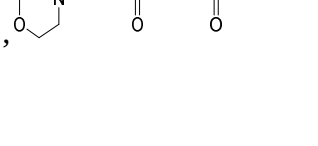
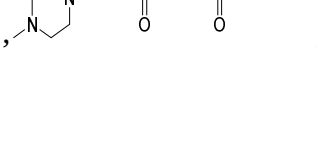
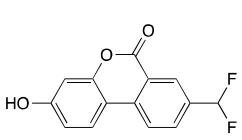
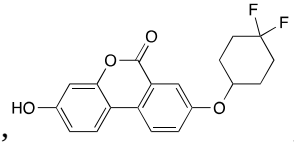
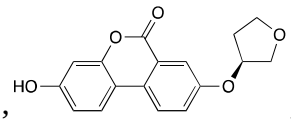
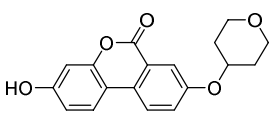
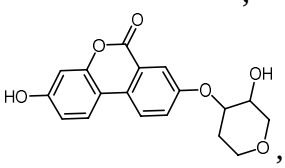
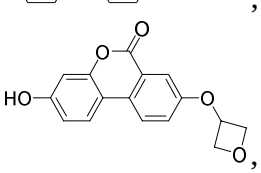
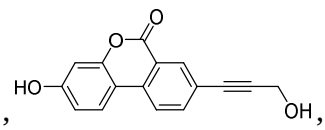
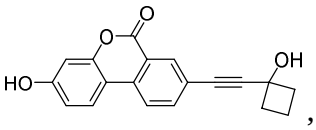

, and

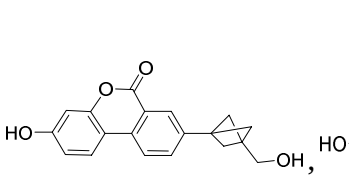
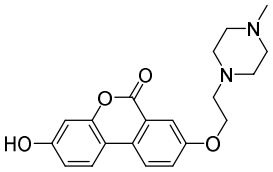
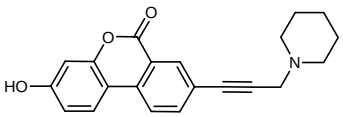
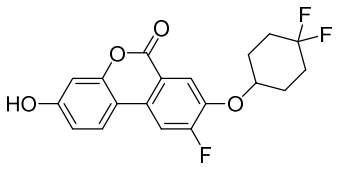
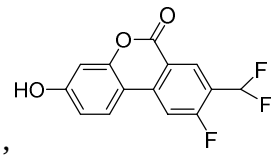
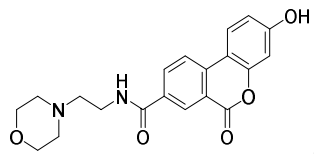
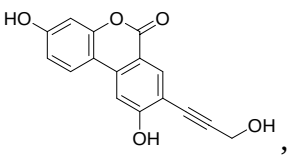
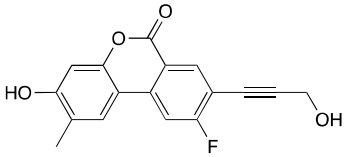
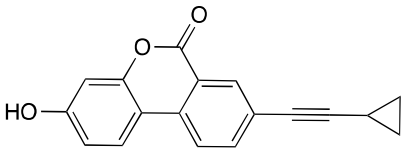
, or a pharmaceutically acceptable salt thereof.

11. The use of claim 1, wherein the compound is selected from:

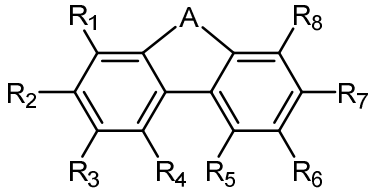
 ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , and , or a pharmaceutically acceptable salt thereof.

12. The use of claim 1, wherein the compound is selected from:

 ,  ,  ,  ,  ,  ,  ,  ,

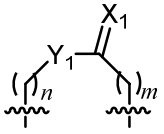
 ,  ,  ,  ,  ,  ,  ,  , and  , or a pharmaceutically acceptable salt thereof.

13. Use of a compound of Formula (Ic),



(Ic)

wherein

A is  ;

one of *n* and *m* is 0; and the other of *n* and *m* is 1;

X_1 and Y_1 are each O;

R_1, R_2, R_3, R_6, R_7, and R_8 are independently selected from H, OH, OCH_3, OAc, NH_2, halogen, CN, CF_3, CO_2H, NO_2, NHAc, alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, alkylamino, alkyl-R_9, alkenyl-R_9, alkynyl-R_9, OR_{10}, NHR_{10}, $NR_{11}C(O)R_{12}$, $C(O)NR_{11}R_{12}$, and $NR_{11}SO_2R_{12}$;

R_4 and R_5 are independently selected from H, halogen and alkyl;

each occurrence of R_9 is independently selected from OH, NH_2, O-alkyl, O-alkyl-O-alkyl, alkylamino, NHC(O)-alkyl, $N(CH_3)C(O)$-alkyl, $NHSO_2$-alkyl, $N(CH_3)SO_2$-alkyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl;

R_{10} is selected from C_2-C_{12} alkyl, hydroxyalkyl, aminoalkyl, alkyl-O-alkyl, alkyl-O-alkyl-OH, alkyl-O-alkyl-O-alkyl, alkenyl, alkynyl, arylalkyl, heteroarylalkyl, alkyl-cycloalkyl, alkyl-heterocycloalkyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, SO_3H, SO_2-alkyl, and SO_2-haloalkyl;

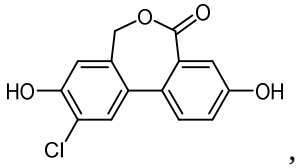
each occurrence of R_{11} is selected from H and alkyl; and

each occurrence of R_{12} is selected from alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, O-alkyl, aminoalkyl, arylalkyl, heteroarylalkyl, alkyl-cycloalkyl, and alkyl-heterocycloalkyl,

or a pharmaceutically acceptable salt thereof,

in the manufacture of a medicament for treating amyotrophic lateral sclerosis (ALS).

14. The use of claim 13, wherein the compound is selected from: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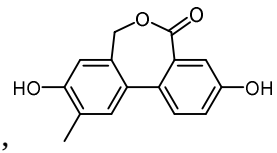
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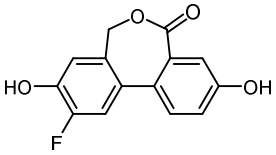
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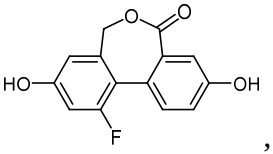
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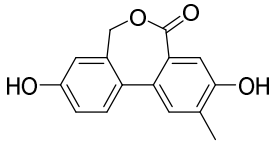
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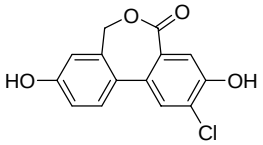
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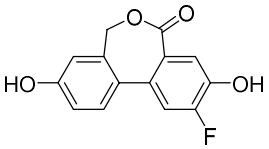
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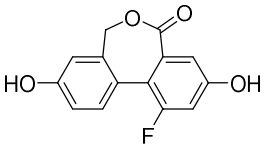
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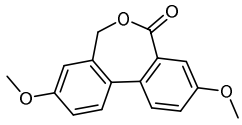
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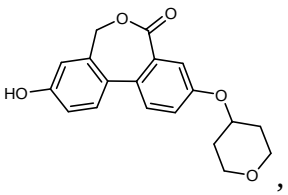
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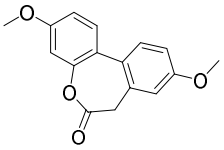
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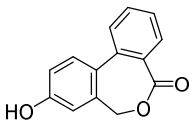
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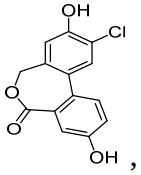
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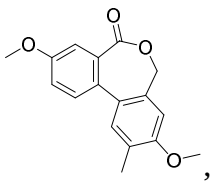
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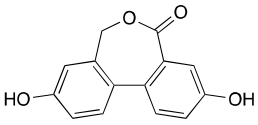
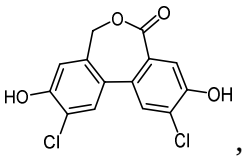
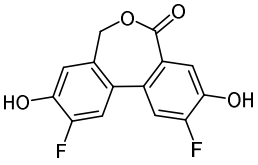
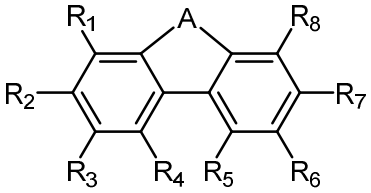
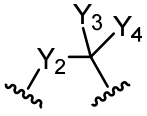
  , and  , or a pharmaceutically acceptable salt thereof.

15. Use of a compound of Formula (Id),



(Id)

wherein

A is  ;

Y_2 is O;

Y_3 and Y_4 are independently selected from H, halogen and alkyl; or together with the carbon to which they are bonded combine to form a cycloalkyl or heterocycloalkyl;

R_1, R_4, R_5, and R_8 are independently selected from H and halogen;

R_2, R_3, R_6, and R_7 are independently selected from H, OH, OCH_3, OAc, NH_2, halogen, CN, CF_3, CO_2H, NO_2, NHAc, alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, alkylamino, alkyl-R_9, alkenyl-R_9, alkynyl-R_9, OR_{10}, NHR_{10}, $NR_{11}C(O)R_{12}$, $C(O)NR_{11}R_{12}$, and $NR_{11}SO_2R_{12}$;

each occurrence of R_9 is independently selected from OH, NH_2, O-alkyl, O-alkyl-O-alkyl, alkylamino, NHC(O)-alkyl, $N(CH_3)C(O)$-alkyl, $NHSO_2$-alkyl, $N(CH_3)SO_2$-alkyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl;

R_{10} is selected from C_2-C_{12} alkyl, hydroxyalkyl, aminoalkyl, alkyl-O-alkyl, alkyl-O-alkyl-OH, alkyl-O-alkyl-O-alkyl, alkenyl, alkynyl, arylalkyl, heteroarylalkyl, alkyl-cycloalkyl, alkyl-heterocycloalkyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, SO_3H, SO_2-alkyl, and SO_2-haloalkyl;

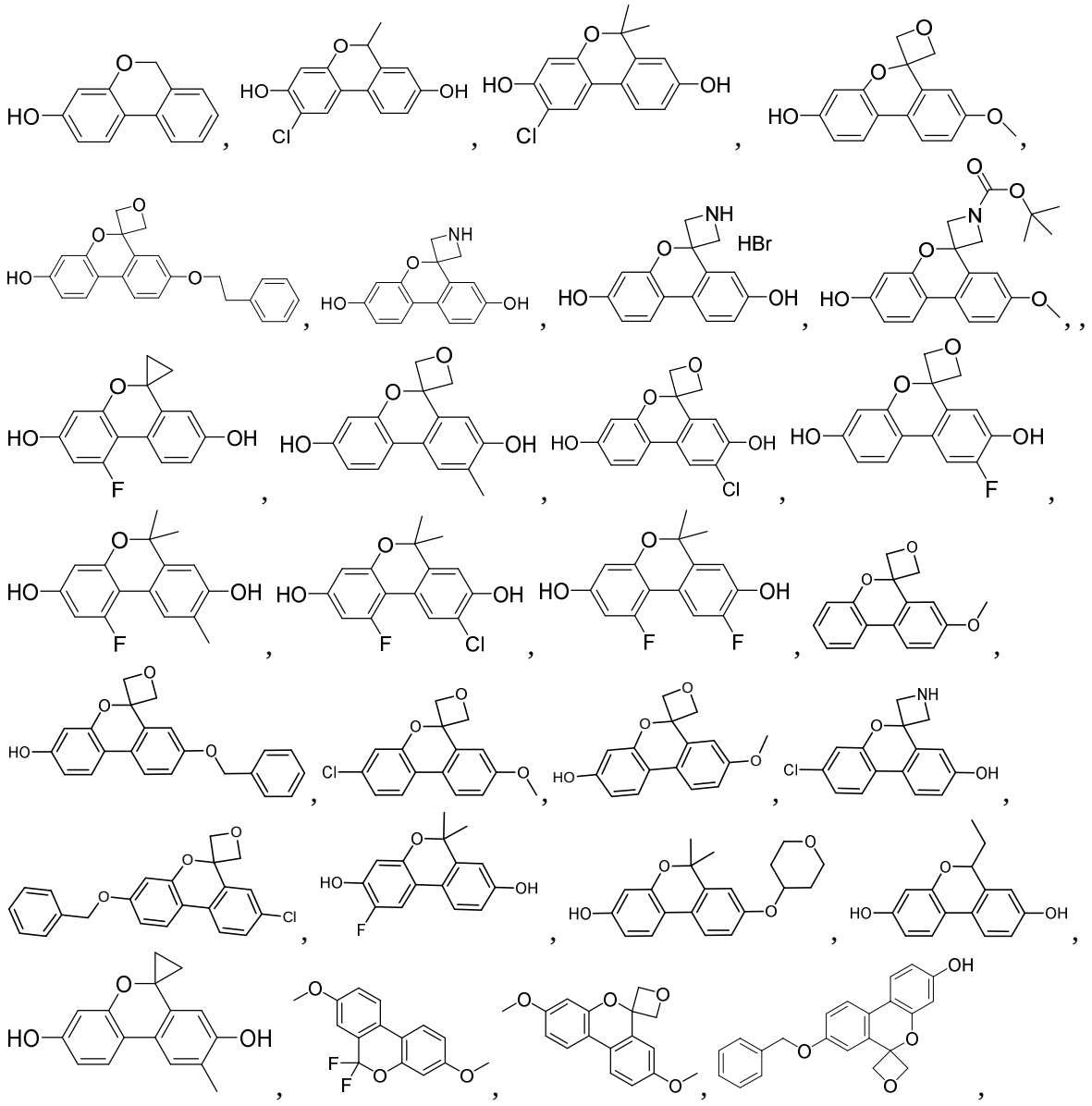
each occurrence of R_{11} is selected from H and alkyl; and

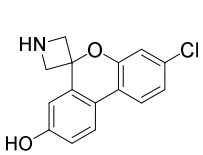
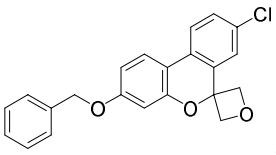
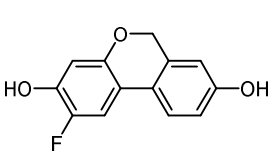
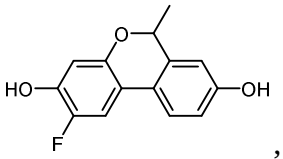
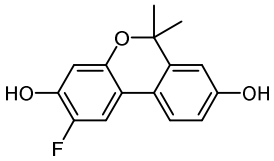
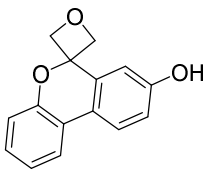
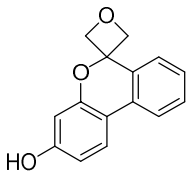
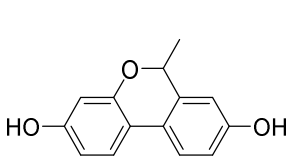
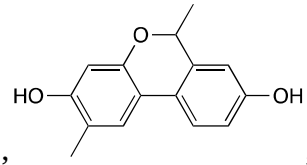
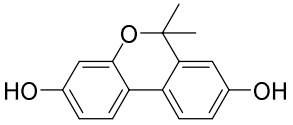
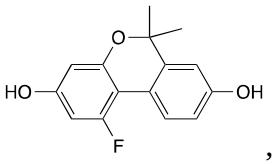
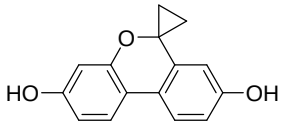
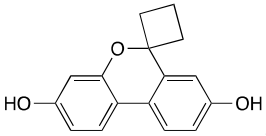
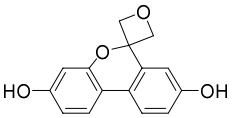
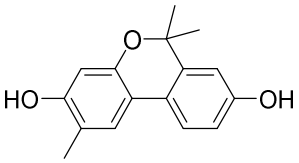
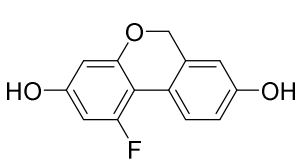
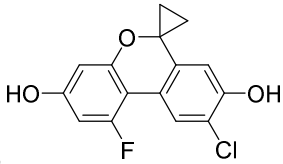
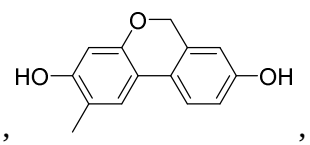
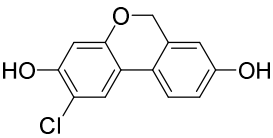
each occurrence of R_{12} is selected from alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, O-alkyl, aminoalkyl, arylalkyl, heteroarylalkyl, alkyl-cycloalkyl, and alkyl-heterocycloalkyl;

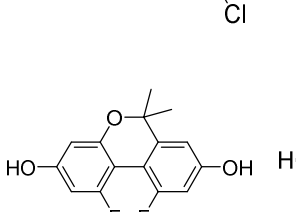
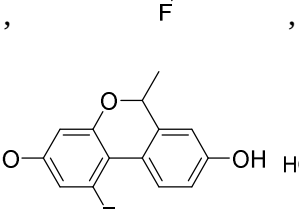
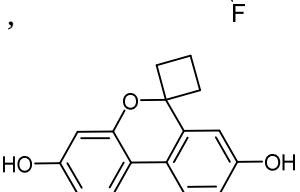
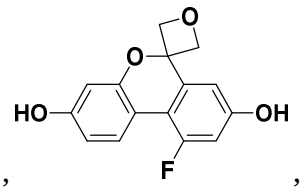
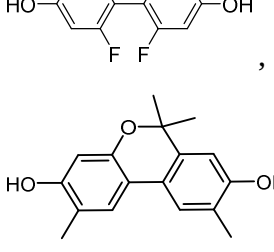
or a pharmaceutically acceptable salt thereof,

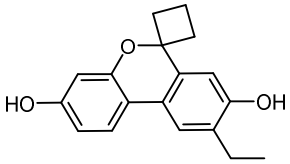
in the manufacture of a medicament for treating amyotrophic lateral sclerosis (ALS).

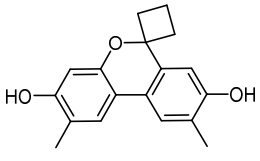
16. The use of claim 15, wherein the compound is selected from:



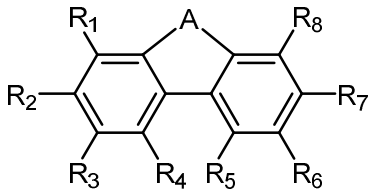






















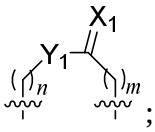

, and , or a pharmaceutically acceptable salt thereof.

17. Use of a compound of Formula (Ie),



(Ie)

wherein

A is  ;

n and *m* are both 0; or one of *n* and *m* is 0, and the other of *n* and *m* is 1;

X_1 is O;

Y_1 is selected from NH, N-CH_3, N-*t*-Bu, N-cycloalkyl, and N-heterocycloalkyl;

R_1, R_2, R_3, R_6, R_7, and R_8 are independently selected from H, OH, OCH_3, OAc, NH_2, halogen, CN, CF_3, CO_2H, NO_2, NHAc, alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, alkylamino, alkyl-R_9, alkenyl-R_9, alkynyl-R_9, OR_{10}, NHR_{10}, $NR_{11}C(O)R_{12}$, $C(O)NR_{11}R_{12}$, and $NR_{11}SO_2R_{12}$;

R_4 and R_5 are independently selected from H, alkyl, and halogen;

each occurrence of R_9 is independently selected from OH, NH_2, O-alkyl, O-alkyl-O-alkyl, alkylamino, NHC(O)-alkyl, N(CH_3)C(O)-alkyl, $NHSO_2$-alkyl, N(CH_3)SO_2-alkyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl;

R_{10} is selected from C_2-C_{12} alkyl, hydroxyalkyl, aminoalkyl, alkyl-O-alkyl, alkyl-O-alkyl-OH, alkyl-O-alkyl-O-alkyl, alkenyl, alkynyl, arylalkyl, heteroarylalkyl, alkyl-cycloalkyl, alkyl-heterocycloalkyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, SO_3H, SO_2-alkyl, and SO_2-haloalkyl;

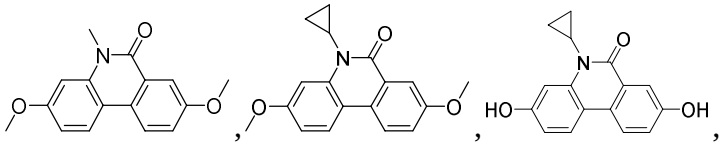
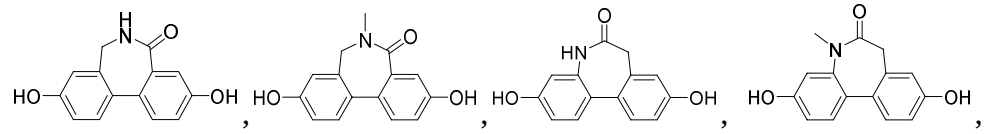
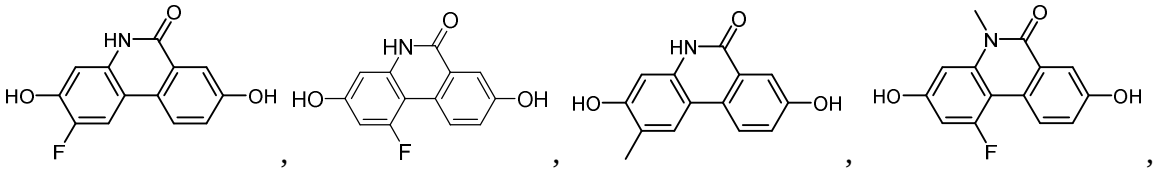
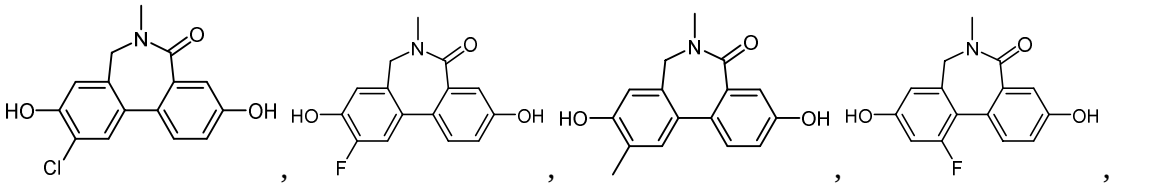
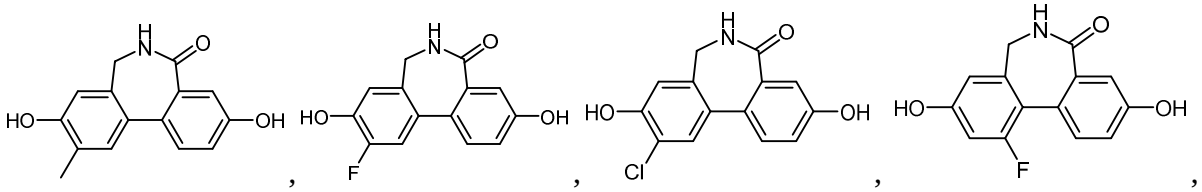
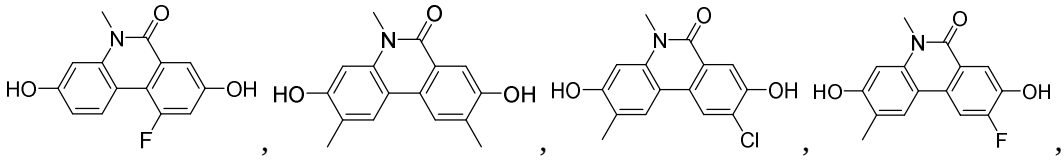
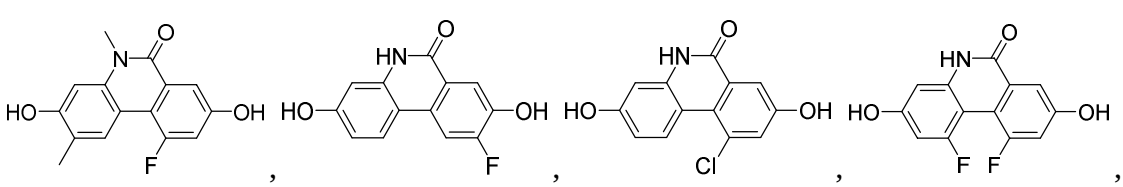
each occurrence of R_{11} is selected from H and alkyl; and

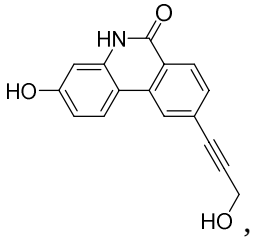
each occurrence of R_{12} is selected from alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, O-alkyl, aminoalkyl, arylalkyl, heteroarylalkyl, alkyl-cycloalkyl, and alkyl-heterocycloalkyl;

or a pharmaceutically acceptable salt thereof,

in the manufacture of a medicament for treating amyotrophic lateral sclerosis (ALS).

18. The use of claim 17, wherein the compound is selected from: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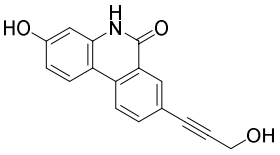
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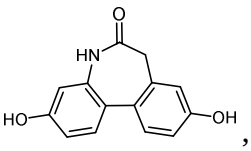
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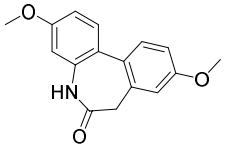
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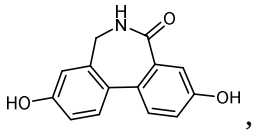
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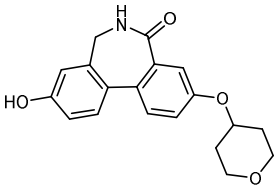
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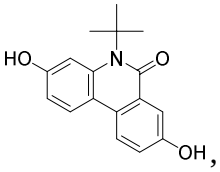
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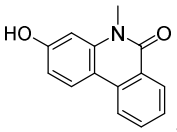
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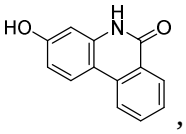
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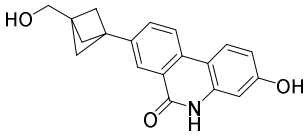
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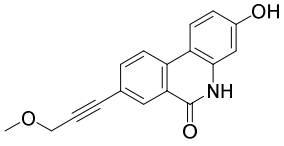
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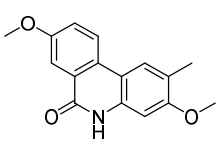
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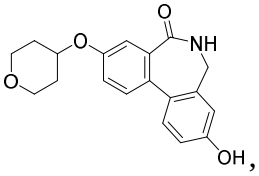
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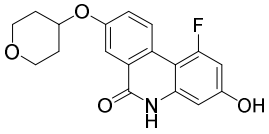
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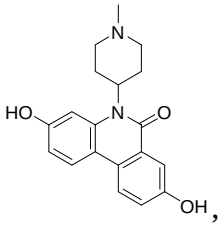
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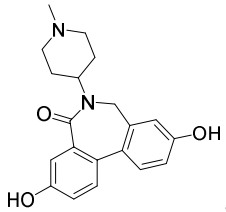
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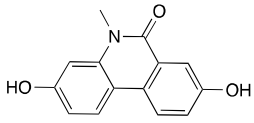
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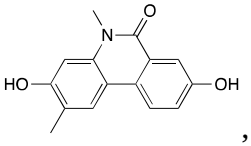
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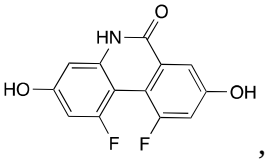
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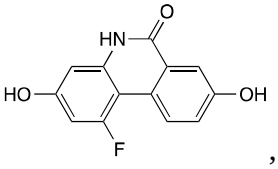
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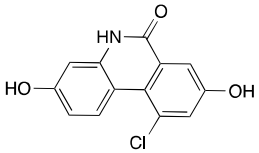
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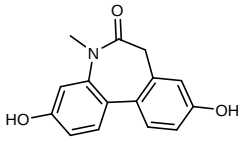
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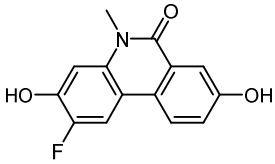
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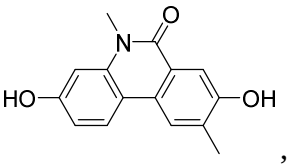
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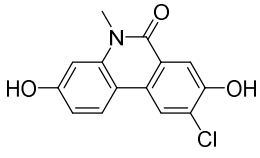
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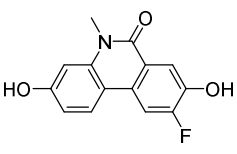
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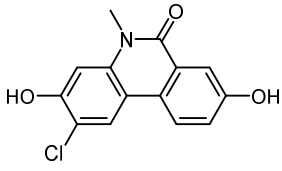
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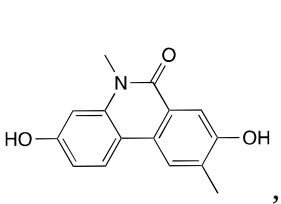
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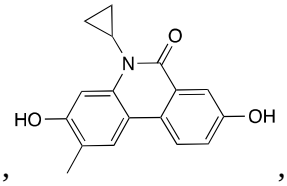
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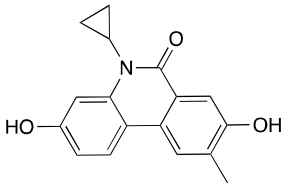
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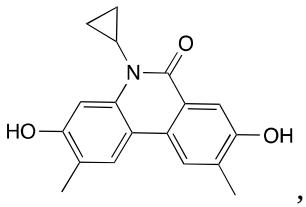
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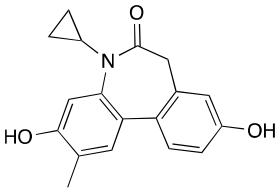
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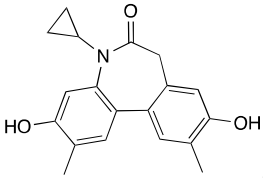
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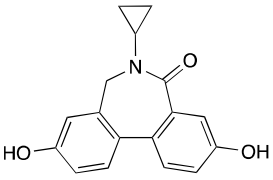
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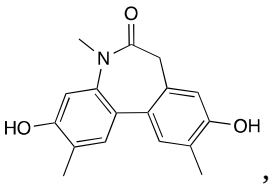
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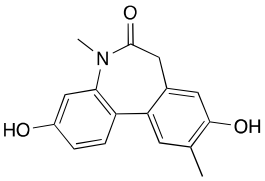
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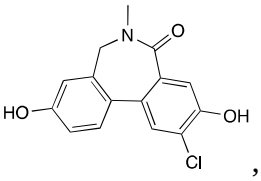
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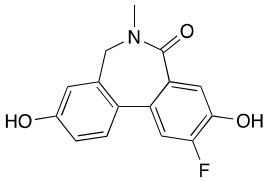
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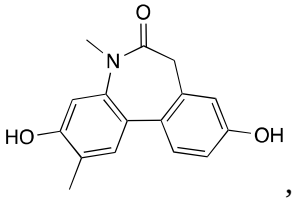
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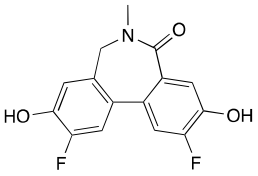
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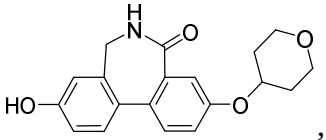
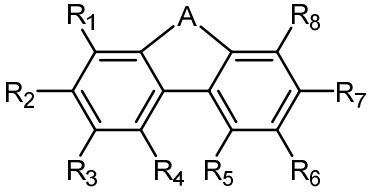
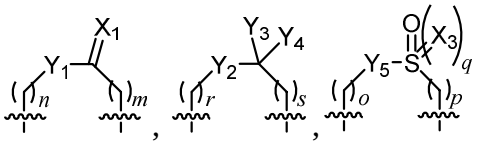

, or a pharmaceutically acceptable salt thereof.

19. Use of a compound of Formula (If),



(If)

wherein

A is selected from

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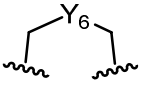
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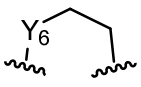
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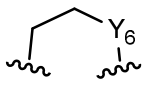
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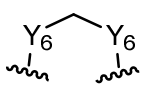
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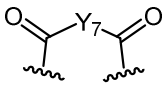
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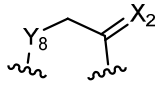
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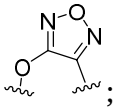

;

n and *m* are both 0; or one of *n* and *m* is 0 and the other of *n* and *m* is 1;

o and *p* are both 0; or one of *o* and *p* is 0 and the other of *o* and *p* is 1;

q is 0 or 1;

r and *s* are both 0; or one of *r* and *s* is 0 and the other of *r* and *s* is 1;

X_1 and X_2 are each O;

X_3 is O or N(alkyl);

Y_1 is S;

Y_2 is selected from O, CH_2, NH, N-alkyl, S, S(O), and SO_2;

Y_3 and Y_4 are independently selected from H, halogen, OH, and alkyl, or together with the carbon to which they are bonded combine to form a cycloalkyl or cycloheteroalkyl;

Y_5 is selected from CH_2, NH, N-alkyl, N-arylalkyl, N-cycloalkyl, and N-heterocycloalkyl;

Each occurrence of Y_6 is independently selected from O, S, S(O), SO_2, NH, N-alkyl, N-alkylaryl, and N-cycloalkyl;

Y_7 is selected from O, NH and N-alkyl;

Y_8 is selected from O and S;

R_1, R_2, R_3, R_6, R_7, and R_8 are independently selected from H, OH, OCH_3, OAc, NH_2, halogen, CN, CF_3, CO_2H, NO_2, NHAc, alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, alkylamino, alkyl-R_9, alkenyl-R_9, alkynyl-R_9, OR_{10}, NHR_{10}, $NR_{11}C(O)R_{12}$, $C(O)NR_{11}R_{12}$, and $NR_{11}SO_2R_{12}$,

R_4 and R_5 are independently selected from H, alkyl, and halogen;

each occurrence of R_9 is independently selected from OH, NH_2, O-alkyl, O-alkyl-O-alkyl, alkylamino, NHC(O)-alkyl, $N(CH_3)C(O)$-alkyl, $NHSO_2$-alkyl, $N(CH_3)SO_2$-alkyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl;

R_{10} is selected from C_2-C_{12} alkyl, hydroxyalkyl, aminoalkyl, alkyl-O-alkyl, alkyl-O-alkyl-OH, alkyl-O-alkyl-O-alkyl, alkenyl, alkynyl, arylalkyl, heteroarylalkyl, alkyl-cycloalkyl, alkyl-heterocycloalkyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, SO_3H, SO_2-alkyl, and SO_2-haloalkyl;

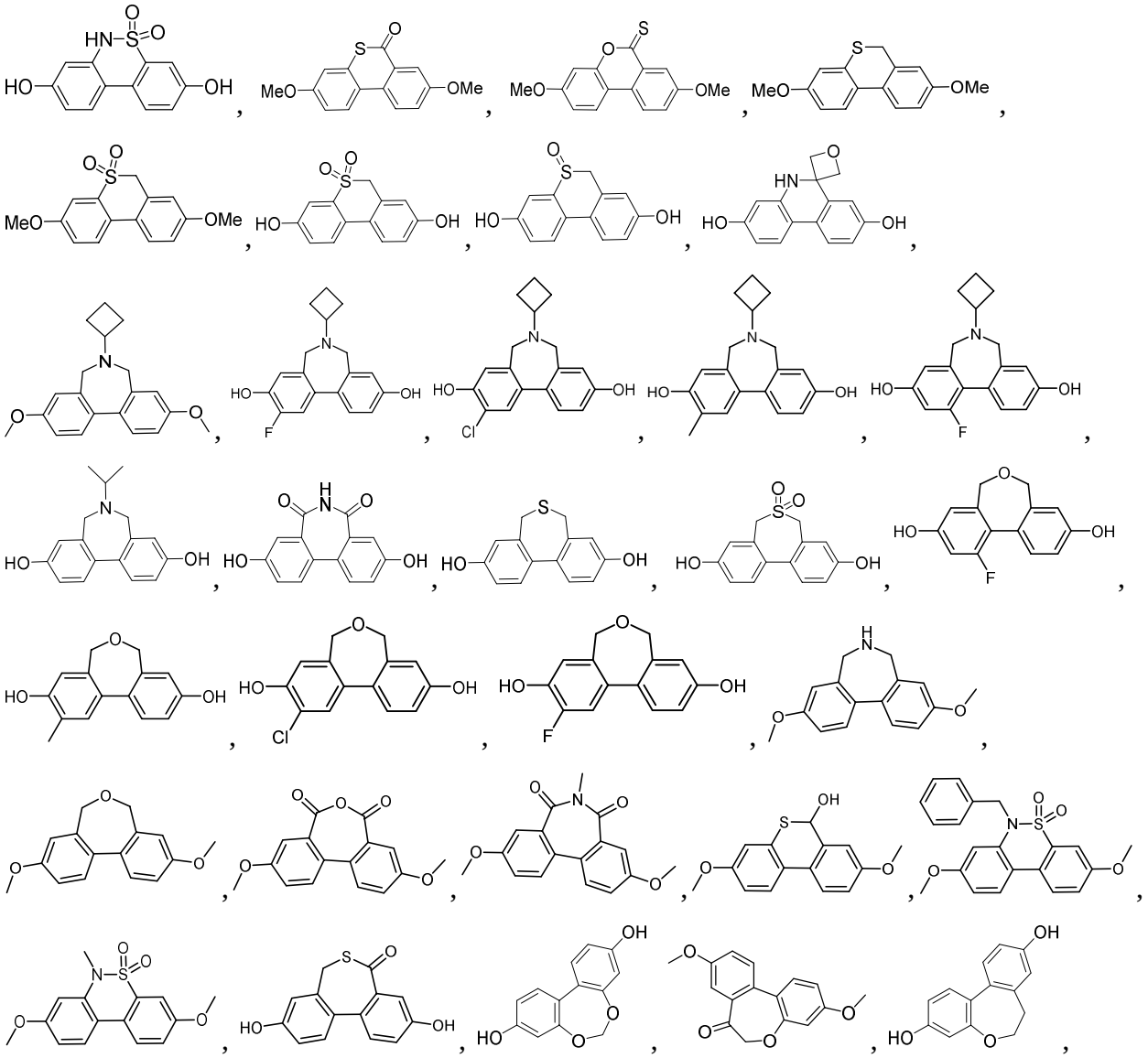
each occurrence of R_{11} is selected from H and alkyl; and

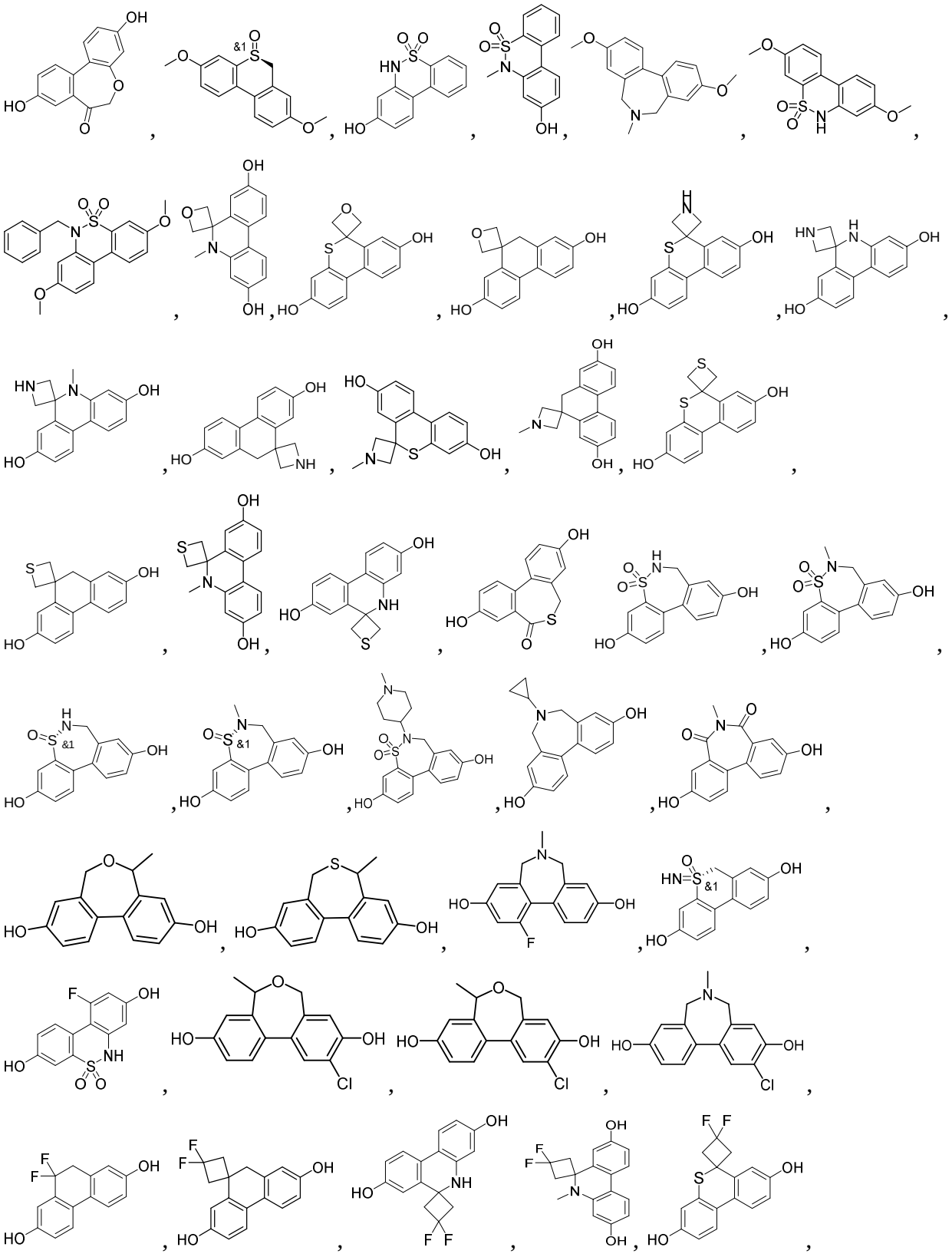
each occurrence of R_{12} is selected from alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, O-alkyl, aminoalkyl, arylalkyl, heteroarylalkyl, alkyl-cycloalkyl, and alkyl-heterocycloalkyl;

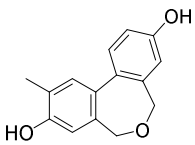
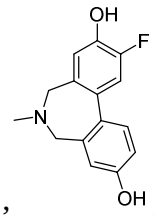
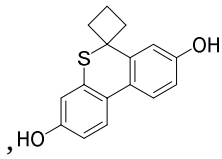
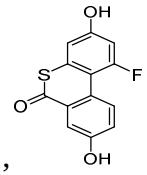
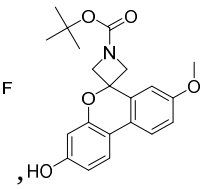
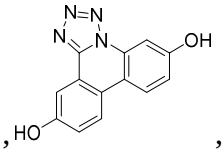
or a pharmaceutically acceptable salt thereof,

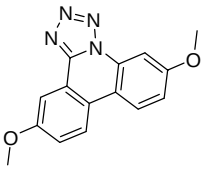
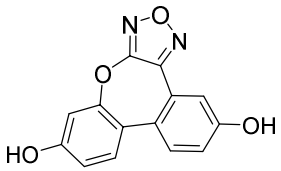
in the manufacture of a medicament for treating amyotrophic lateral sclerosis (ALS).

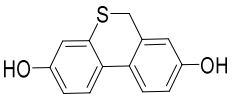
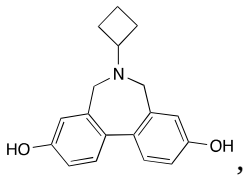
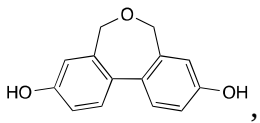
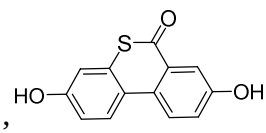
20. The use of claim 19, wherein the compound is selected from:

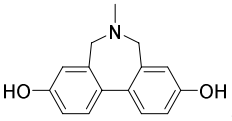
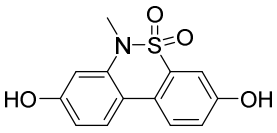




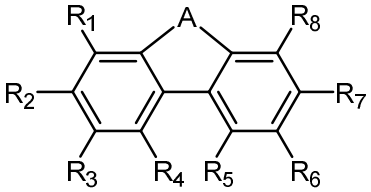
 ,  ,  ,  ,  ,  ,

 ,  ,

 ,  ,  ,  ,

 , and  , or a pharmaceutically acceptable salt thereof.

21. Use of a compound of Formula (Ih),



(Ih)

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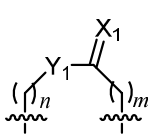
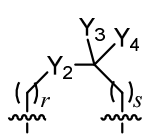
A is selected from  or  ;

n and *m* are both 0; or one of *n* and *m* is 0 and the other of *n* and *m* is 1;

r and *s* are both 0; or one of *r* and *s* is 0 and the other of *r* and *s* is 1;

X_1 is O;

Y_1 is selected from O, NH, N-alkyl, and N-cycloalkyl;

Y_2 is O;

Y_3 and Y_4 are independently selected from H, halogen, and alkyl, or together with the carbon to which they are bonded combine to form a cycloalkyl or cycloheteroalkyl;

R_1, R_4, R_5 and R_8 are independently selected from H and halogen;

R_3 and R_6 are independently selected from H, CN, OH, CF_3, halogen, and alkyl;

one of R_2 and R_7 is selected NH_2, $NHCH_3$, and $N(CH_3)_2$ and the other of R_2 and R_7 is selected from H, halogen, OCH_3, CN, CF_3, CO_2H, NO_2, NHAc, alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, alkylamino, alkyl-R_9, alkenyl-R_9, alkynyl-R_9, OR_{10}, NHR_{10}, $NR_{11}C(O)R_{12}$, $C(O)NR_{11}R_{12}$, and $NR_{11}SO_2R_{12}$;

each occurrence of R_9 is independently selected from OH, NH_2, O-alkyl, O-alkyl-O-alkyl, alkylamino, NHC(O)-alkyl, $N(CH_3)C(O)$-alkyl, $NHSO_2$-alkyl, $N(CH_3)SO_2$-alkyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl;

R_{10} is selected from H, C_2-C_{12} alkyl, hydroxyalkyl, aminoalkyl, alkyl-O-alkyl, alkyl-O-alkyl-OH, alkyl-O-alkyl-O-alkyl, alkenyl, alkynyl, arylalkyl, heteroarylalkyl, alkyl-cycloalkyl, alkyl-heterocycloalkyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, SO_3H, SO_2-alkyl, and SO_2-haloalkyl;

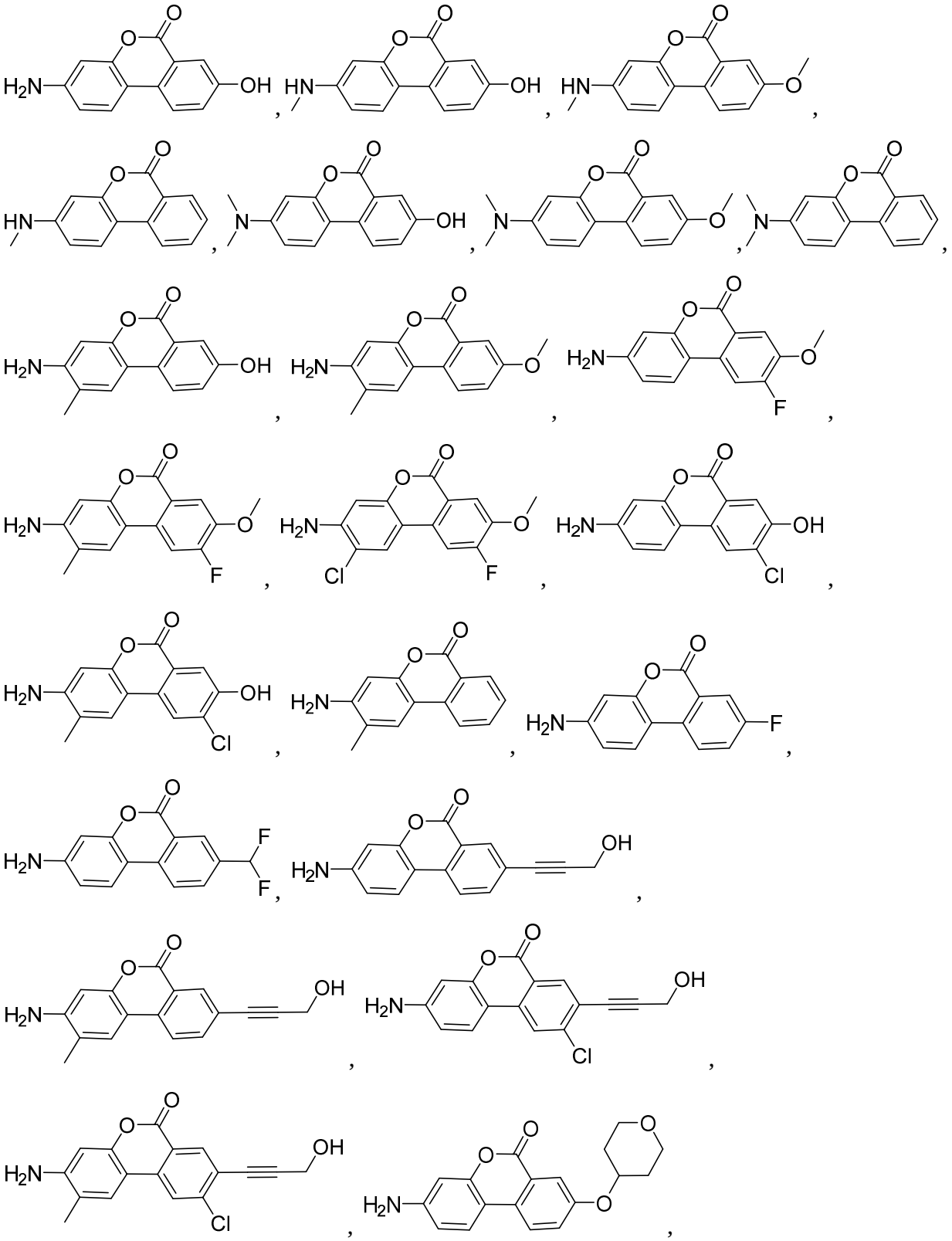
each occurrence of R_{11} is selected from H and alkyl; and

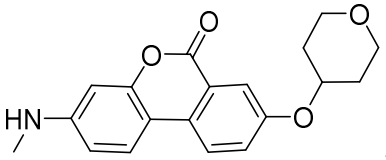
each occurrence of R_{12} is selected from alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, O-alkyl, aminoalkyl, arylalkyl, heteroarylalkyl, alkyl-cycloalkyl, and alkyl-heterocycloalkyl;

or a pharmaceutically acceptable salt thereof,

in the manufacture of a medicament for treating amyotrophic lateral sclerosis (ALS).

22. The use of claim 21, wherein the compound is selected from:

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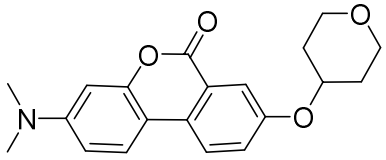
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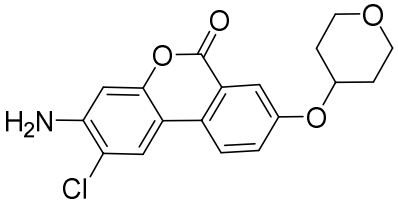
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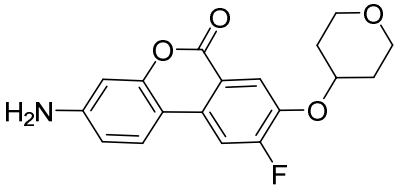
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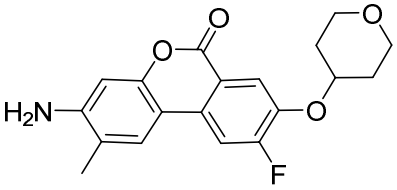
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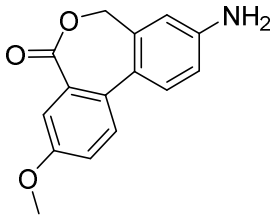
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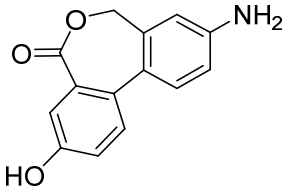
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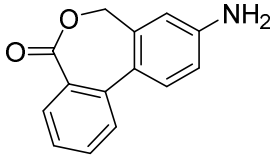
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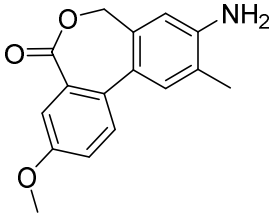
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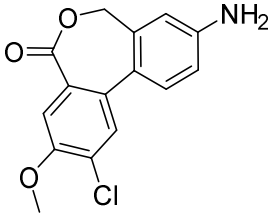
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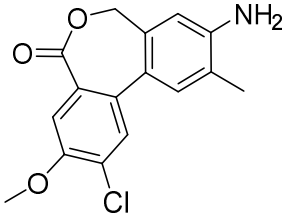
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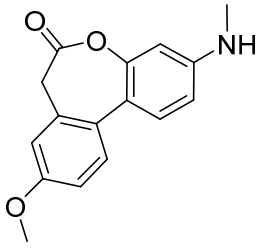
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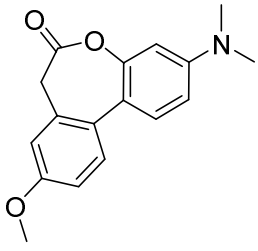
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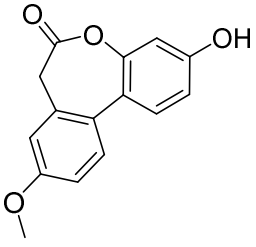
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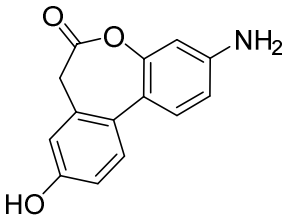
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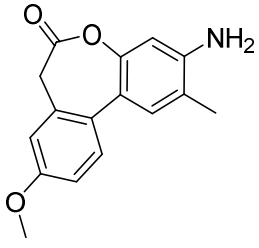
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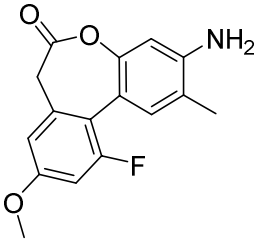
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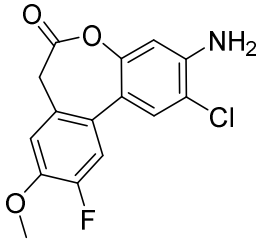
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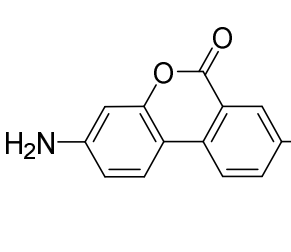
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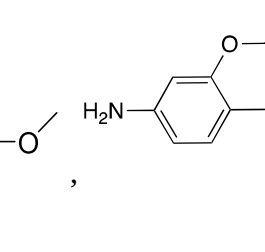
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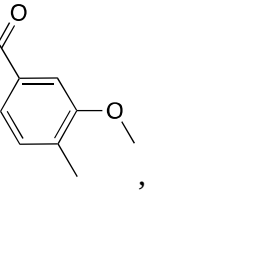
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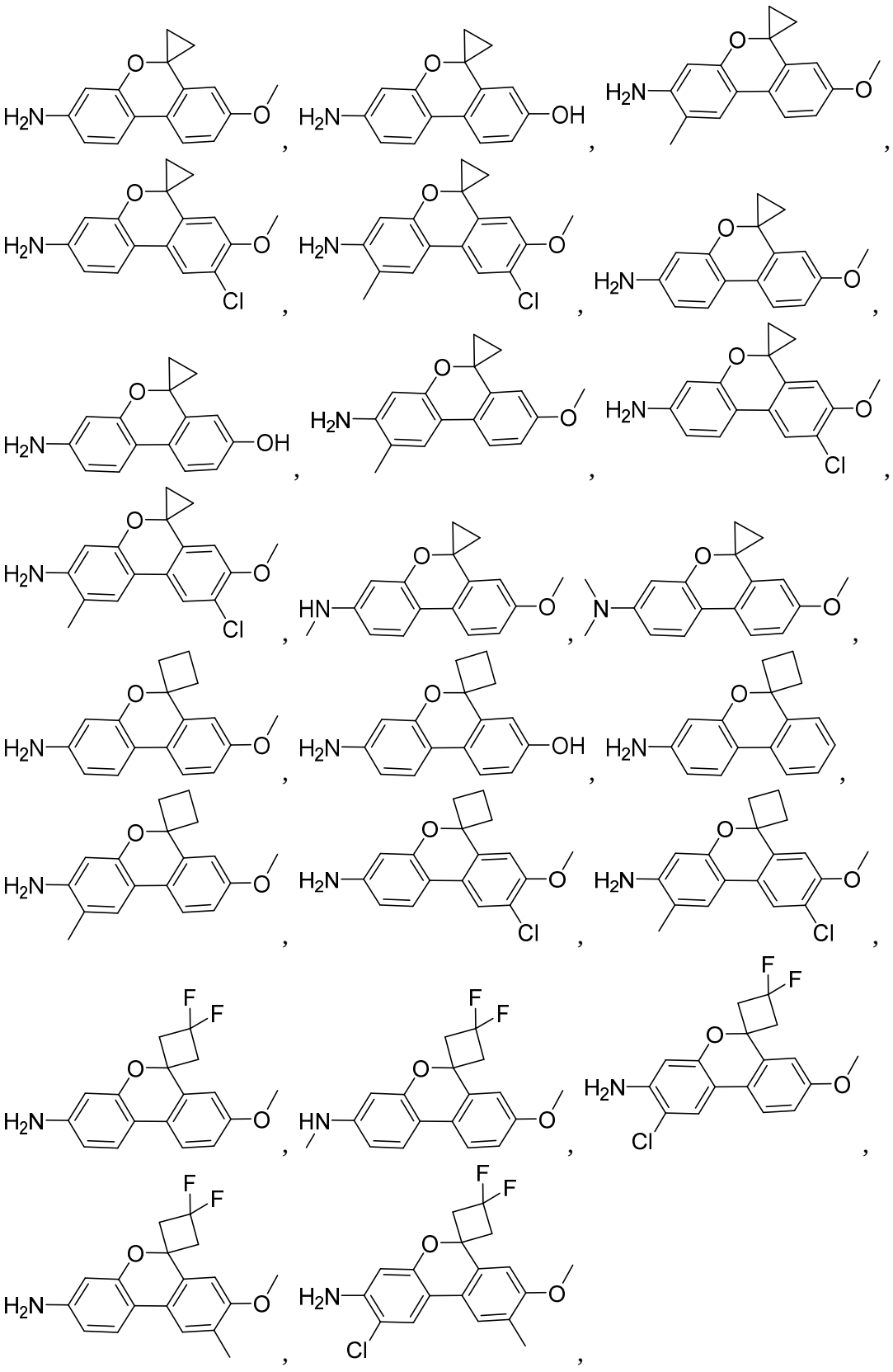

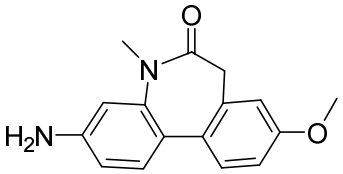
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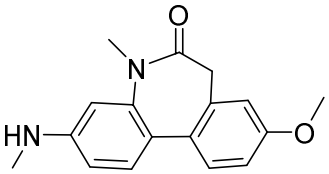
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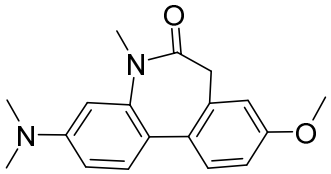
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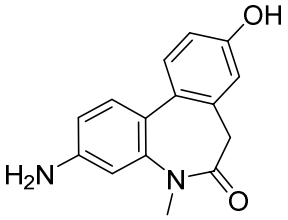
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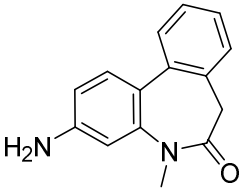
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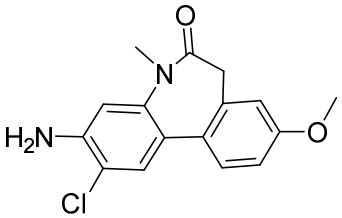
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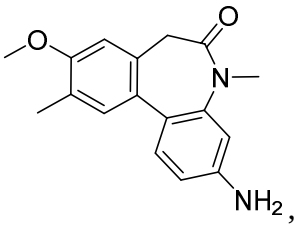
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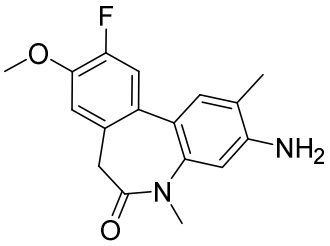
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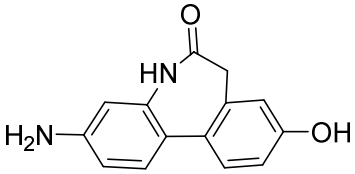
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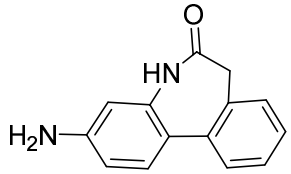
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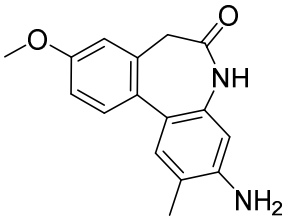
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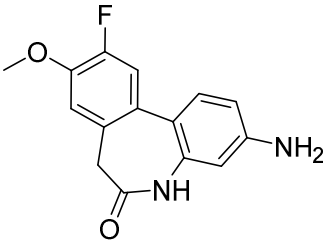
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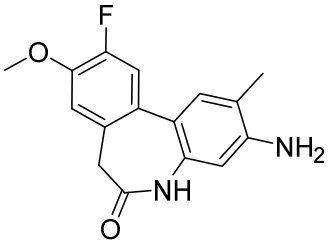
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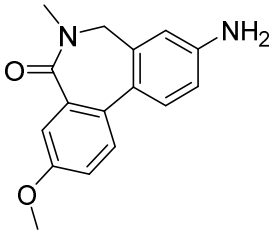
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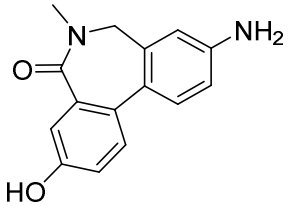
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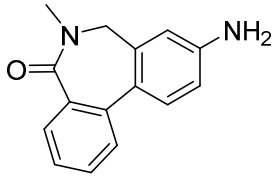
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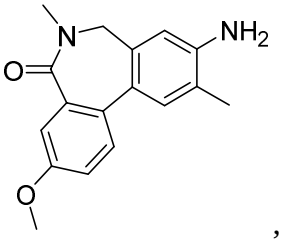
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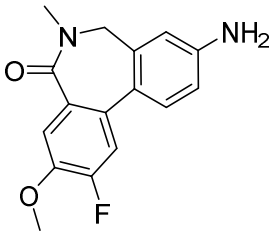
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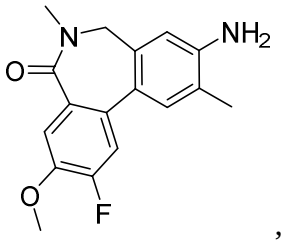
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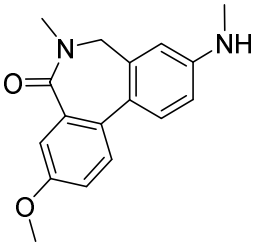
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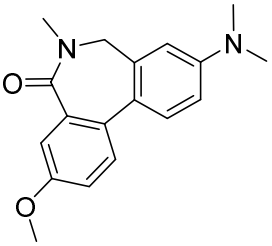
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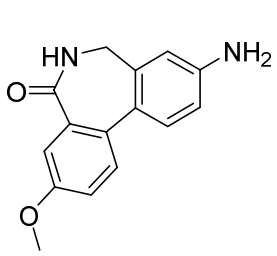

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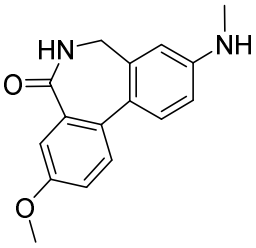

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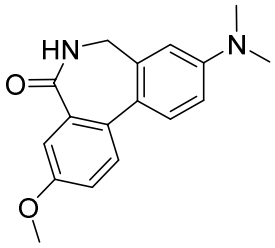

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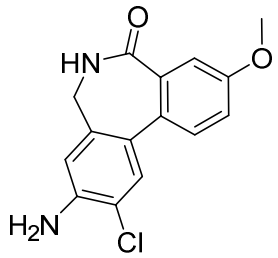

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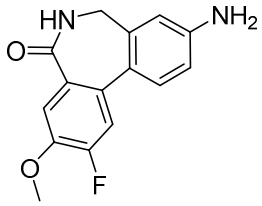

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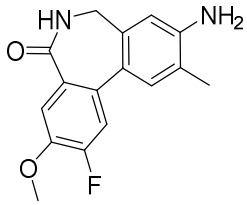
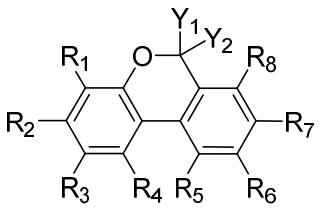


,

or a pharmaceutically acceptable salt thereof.

23. Use of a compound of Formula (IIa),



(IIa)

wherein

Y_1 and Y_2 are each alkyl; or taken together with the carbon to which they are bonded combine to form an unsubstituted or substituted spiro cycloalkyl;

R_1, R_4, R_5, and R_8 are independently selected from –H and halogen;

R_2 and R_7 are independently selected from –H, –OH, –OAc, $–NH_2$, halogen, –CN, $–CF_3$, $–CO_2H$, $–NO_2$, –NHAc, alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, alkylamino, alkyl–R_9, alkenyl–R_9, alkynyl–R_9, $–OR_{10}$, $–NHR_{10}$, $–NR_{11}C(O)R_{12}$, $–C(O)NR_{11}R_{12}$, and $–NR_{11}SO_2R_{12}$;

R_3 and R_6 are alkyl;

each occurrence of R_9 is independently selected from OH, NH_2, O–alkyl, O–alkyl–O–alkyl, alkylamino, NHC(O)–alkyl, $N(CH_3)C(O)$–alkyl, $NHSO_2$–alkyl, $N(CH_3)SO_2$–alkyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl;

R_{10} is selected from alkyl, hydroxyalkyl, aminoalkyl, alkyl–O–alkyl, alkyl–O–alkyl–OH, alkyl–O–alkyl–O–alkyl, alkenyl, alkynyl, arylalkyl, heteroarylalkyl, alkyl–cycloalkyl, alkyl–heterocycloalkyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, SO_3H, SO_2–alkyl, and SO_2–haloalkyl;

each occurrence of R_{11} is selected from H and alkyl; and

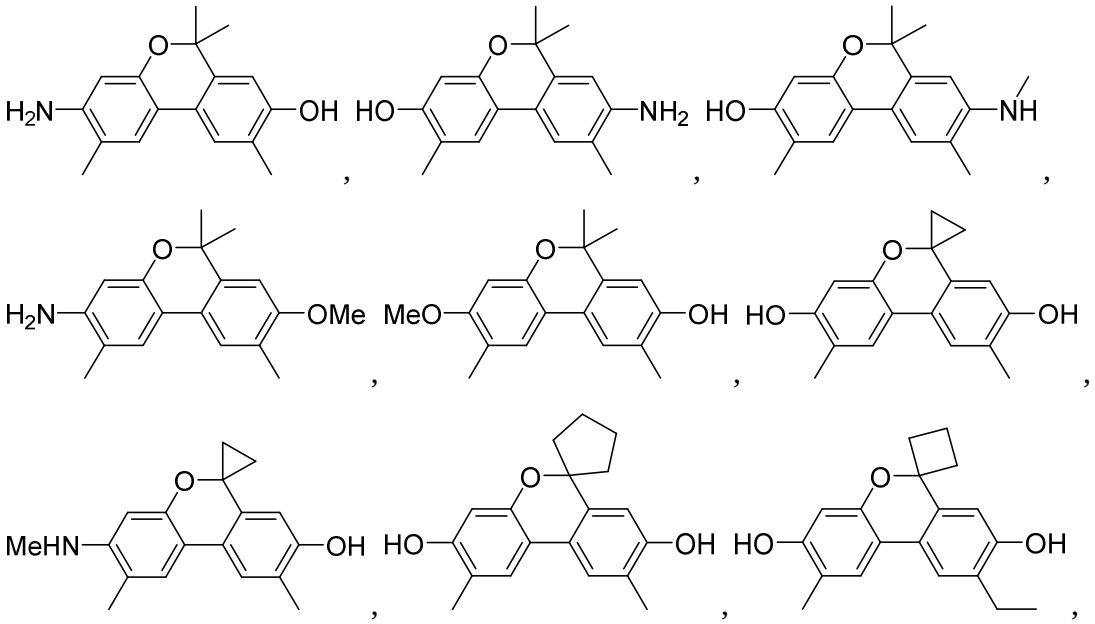
each occurrence of R_{12} is selected from alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, O–alkyl, aminoalkyl, arylalkyl, heteroarylalkyl, alkyl–cycloalkyl, and alkyl–heterocycloalkyl;

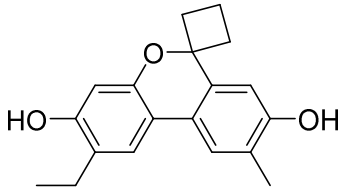
provided that when R_1, R_4, R_5, and R_8 are each –H, R_2 and R_7 are each –OH, and R_3 and R_6 are each CH_3, then Y_1 and Y_2 are not each –Me or are not taken together with the carbon to which they are bonded to form an unsubstituted spiro cyclobutyl;

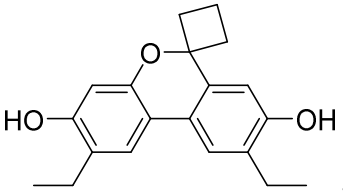
or a pharmaceutically acceptable salt thereof,

in the manufacture of a medicament for treating amyotrophic lateral sclerosis (ALS).

24. The use of claim 23, wherein the compound is selected from:



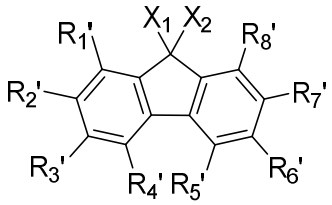


, and 

,

or a pharmaceutically acceptable salt thereof.

25. Use of a compound of Formula (IIb),



(IIb)

wherein

X_1 and X_2 are each alkyl; or taken together with the carbon to which they are bonded combine to form an unsubstituted or substituted spiro cycloalkyl;

R_1', R_4', R_5', and R_8' are independently selected from –H, –OH, $–NH_2$, alkyl, and halogen;

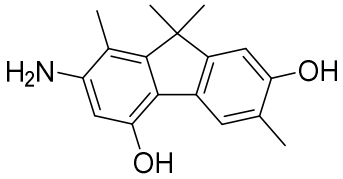
R_2', R_3', R_6', and R_7' are independently selected from –H, –OH, –OAc, $–NH_2$, halogen, –CN, $–CF_3$, $–CO_2H$, $–NO_2$, –NHAc, alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, alkylamino, and $–OR_8'$; and

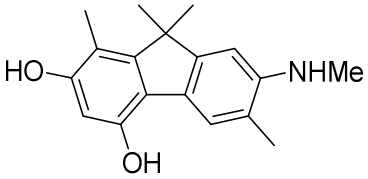
R_8' is selected from alkyl, hydroxyalkyl, aminoalkyl, aryl, heteroaryl, cycloalkyl, andheterocycloalkyl;

or a pharmaceutically acceptable salt thereof,

in the manufacture of a medicament for treating amyotrophic lateral sclerosis (ALS).

26. The use of claim 25, wherein the compound is selected from:



,


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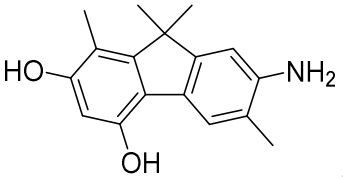

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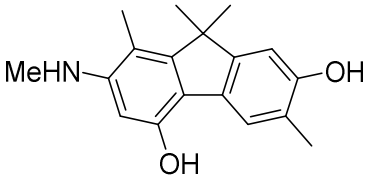
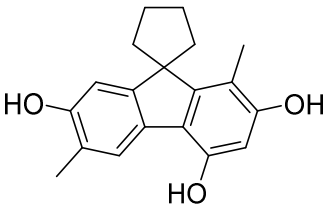


, and


,

or a pharmaceutically acceptable salt thereof.

27. The use of any one of claims 1, 13, 15, 17, 19, and 21, wherein the compound is a compound selected from Table 1.

28. The use of any one of claims 1-27, wherein amyotrophic lateral sclerosis (ALS) is C9orf72 amyotrophic lateral sclerosis (C9-ALS).