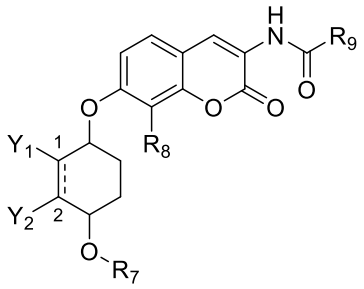
In one ~~aspect~~example, the present disclosure refers to a compound of the formula:



(II)

wherein:

R_7 is $aryl_{(C\leq12)}$, $aralkyl_{(C\leq12)}$, or a substituted version of either of these groups;

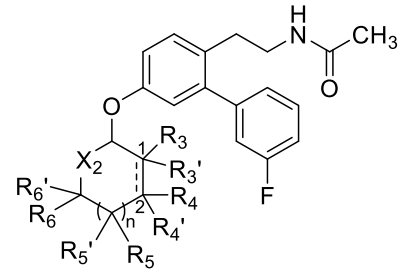
R_8 is hydrogen, $alkyl_{(C\leq12)}$, $cycloalkyl_{(C\leq12)}$, substituted $alkyl_{(C\leq12)}$, or substituted $cycloalkyl_{(C\leq12)}$;

R_9 is $alkyl_{(C\leq12)}$, $cycloalkyl_{(C\leq12)}$, $aryl_{(C\leq12)}$, $heteroaryl_{(C\leq12)}$, or a substituted version of any of these groups; and

Y_1 and Y_2 are each independently hydrogen or hydroxy;

or a pharmaceutically acceptable salt thereof.

In an aspect, there is provided a compound of the formula:



(I)

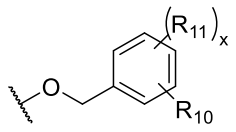
wherein:

the bond between atom 1 and atom 2 is either a single bond or a double bond;

X_2 is $-CH_2-$;

R_3, R_4, R_3', R_4' are each independently hydrogen or hydroxy;

R_5 is



wherein:

R_{10} is halo, or $alkyl_{(C\leq 8)}$ optionally substituted with one or more halogen;

R_{11} are halo; and

x is 0 or 1;

R_5' is hydrogen;

R_6 and R_6' are each independently hydrogen, or $alkyl_{(C\leq 12)}$; and

n is 1;

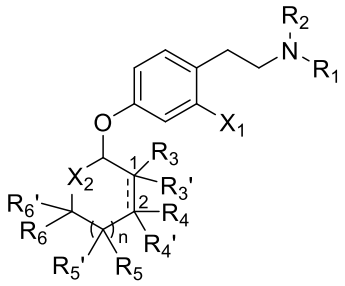
or a pharmaceutically acceptable salt thereof.

In some examples, the bond between atom 1 and atom 2 in formula I is a single bond. In other examples, the bond between atom 1 and atom 2 in formula I is a double bond. In some examples, X_2 is $-CH_2-$. In other examples, X_2 is $-O-$.

In some examples, R_3 is hydrogen. In other examples, R_3 is hydroxy. In some examples, R_3' is hydrogen. In other examples, R_3' is hydroxy. In some examples, R_4 is hydrogen. In other examples, R_4 is hydroxy. In other examples, R_4 is $aralkoxy_{(C\leq 12)}$ or substituted $aralkoxy_{(C\leq 12)}$. In some examples, R_4 is benzyloxy. In some examples, R_4' is hydrogen. In other examples, R_4' is hydroxy. In other examples, R_4' is $aralkoxy_{(C\leq 12)}$ or substituted $aralkoxy_{(C\leq 12)}$. In some examples, R_4' is benzyloxy.

In some examples, R_5 is hydrogen. In other examples, R_5 is hydroxy. In other examples, R_5 is $aralkoxy_{(C\leq 12)}$ or substituted $aralkoxy_{(C\leq 12)}$. In some examples, R_5 is $aralkoxy_{(C\leq 12)}$. In some examples, R_5 is benzyloxy, 1-(2-napthyl)methoxy, 2-methylphenylmethoxy, 4-methylphenylmethoxy, or 4-*t*-butylphenylmethoxy. In other examples, R_5 is substituted $aralkoxy_{(C\leq 12)}$. In some examples, R_5 is 2-fluorophenylmethoxy, 2-bromophenylmethoxy, 2-chlorophenylmethoxy, 2-methoxy-

In one ~~aspect~~example, the present disclosure refers to a compound of the formula:



(III)

wherein:

the bond between atom 1 and atom 2 is either a single bond or a double bond;

X_1 is $aryl_{(C\leq12)}$, $heteroaryl_{(C\leq12)}$, or a substituted version of either of these groups;

X_2 is $-CH_2-$ or $-O-$;

R_1 is $acyl_{(C\leq12)}$ or substituted $acyl_{(C\leq12)}$;

R_2 is hydrogen, $alkyl_{(C\leq12)}$, or substituted $alkyl_{(C\leq12)}$;

R_3, R_4, R_3', R_4' are each independently hydrogen, hydroxy, $aryloxy_{(C\leq12)}$, $aralkoxy_{(C\leq12)}$, substituted $aryloxy_{(C\leq12)}$, or substituted $aralkoxy_{(C\leq12)}$;

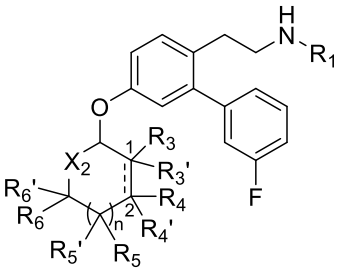
each R_5 and R_5' are each independently hydrogen, hydroxy, $heteroaryloxy_{(C\leq12)}$, $heteroaralkoxy_{(C\leq12)}$, substituted $aryloxy_{(C\leq12)}$, substituted $aralkoxy_{(C\leq12)}$, substituted $heteroaryloxy_{(C\leq12)}$, or substituted $heteroaralkoxy_{(C\leq12)}$;

R_6 and R_6' are each independently hydrogen, $alkyl_{(C\leq12)}$, $cycloalkyl_{(C\leq12)}$, substituted $alkyl_{(C\leq12)}$, or substituted $cycloalkyl_{(C\leq12)}$; and

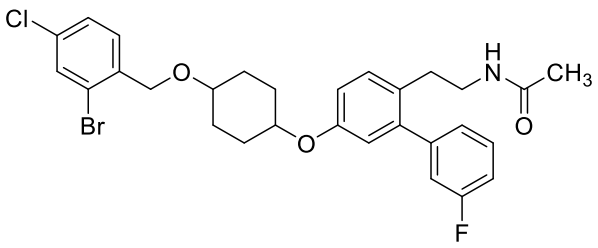
n is 0, 1, or 2; provided that if n is 2 then the R_5 and R_5' on each methylene are independently selected;

or a pharmaceutically acceptable salt thereof.

In some examples, the compounds are further defined as:



(IV)



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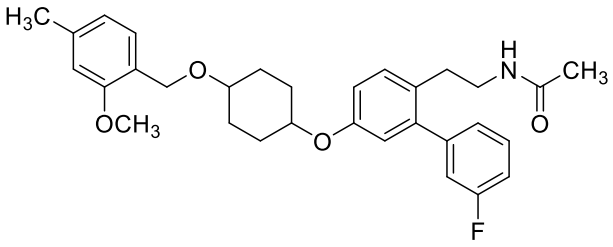
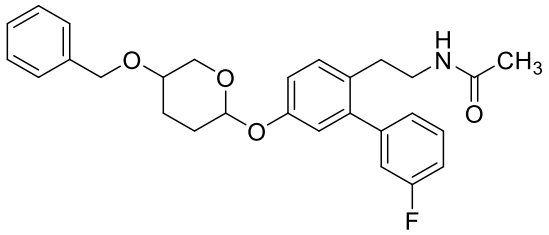


;

or a pharmaceutically acceptable salt thereof.

In an ~~aspect~~example, the present disclosure refers to a compound of the formula:



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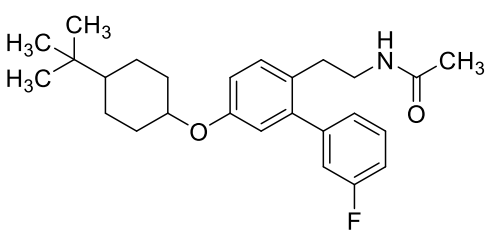

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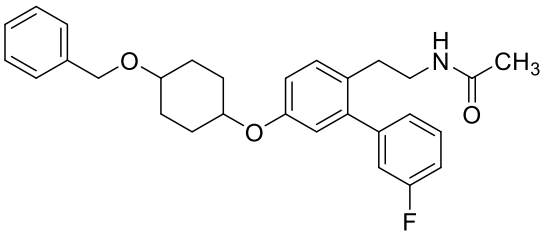

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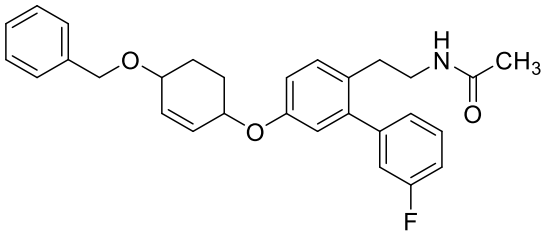

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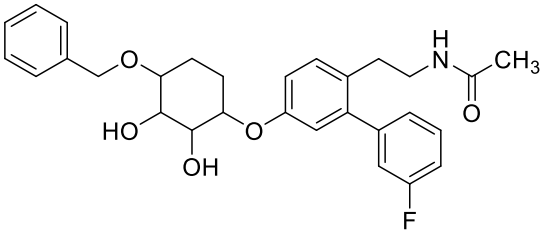

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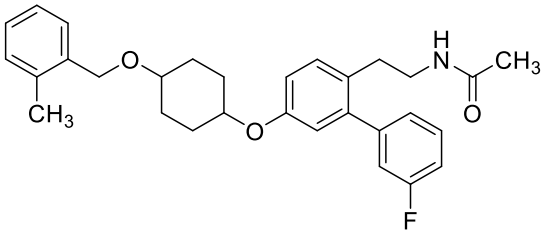

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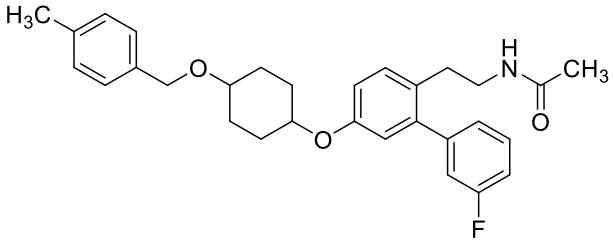

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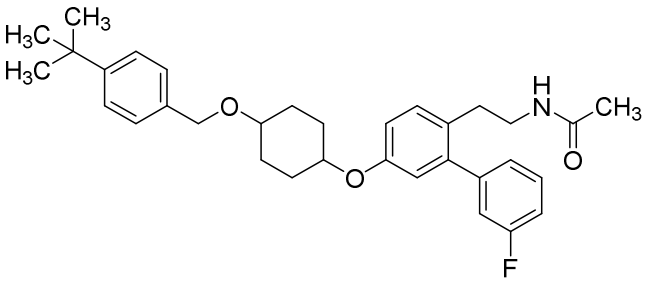

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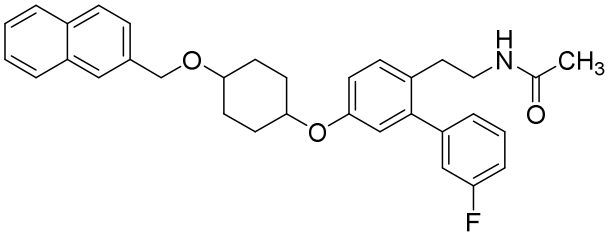
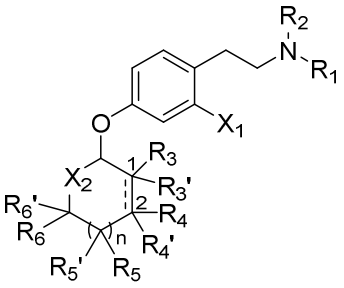


;

or a pharmaceutically acceptable salt thereof.

In another ~~aspect~~example, the present disclosure refers to a compound of the formula:



(III)

wherein:

the bond between atom 1 and atom 2 is either a single bond or a double bond;

X_1 is $aryl_{(C\leq12)}$, $heteroaryl_{(C\leq12)}$, or a substituted version of either of these groups;

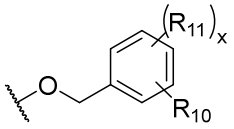
X_2 is $-CH_2-$ or $-O-$;

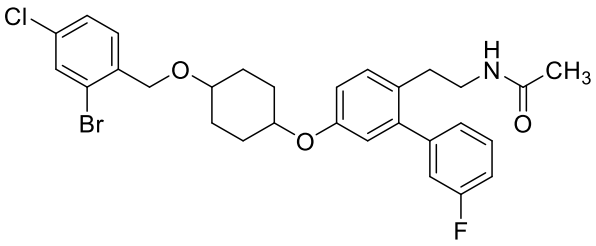
R_1 is $acyl_{(C\leq12)}$ or substituted $acyl_{(C\leq12)}$;

R_2 is hydrogen, $alkyl_{(C\leq12)}$, or substituted $alkyl_{(C\leq12)}$;

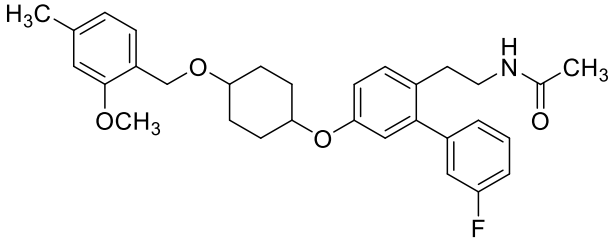
R_3, R_4, R_3', R_4' are each independently hydrogen, hydroxy, $aryloxy_{(C\leq12)}$, $aralkoxy_{(C\leq12)}$, substituted $aryloxy_{(C\leq12)}$, or substituted $aralkoxy_{(C\leq12)}$;

each R_5 and R_5' are each independently hydrogen, hydroxy; or a group of the formula:





, or



;

or a pharmaceutically acceptable salt thereof.

In one aspect, the present disclosure refers to a pharmaceutical compositions comprising:

(A) a compound of the present disclosure; and

(B) a pharmaceutically acceptable carrier.

In some examples, the pharmaceutical compositions are formulated for administration: orally, intraadiposally, intraarterially, intraarticularly, intracranially, intradermally, intralesionally, intramuscularly, intranasally, intraocularly, intrapericardially, intraperitoneally, intrapleurally, intraprostatically, intrarectally, intrathecally, intratracheally, intratumorally, intraumbilically, intravaginally, intravenously, intravesicularlly, intravitreally, liposomally, locally, mucosally, parenterally, rectally, subconjunctival, subcutaneously, sublingually, topically, transbuccally, transdermally, vaginally, in crèmes, in lipid compositions, via a catheter, via a lavage, via continuous infusion, via infusion, via inhalation, via injection, via local delivery, or via localized perfusion. In some examples, the pharmaceutical compositions are formulated for oral, intraarterial, or intravenous administration. In some examples, the pharmaceutical compositions are formulated as a unit dose.

In an aspect, the present disclosure refers to a use of a compound or pharmaceutical composition as disclosed herein in the manufacture of a medicament for treating a disease or disorder, wherein the disease or disorder is selected from the group consisting of neurological disorder, diabetes, neuropathy, nephropathy, retinopathy, vasculopathy and cancer, in a patient. In an example, the present disclosure provides methods of treating a disease or disorder in a patient comprising administering to the patient in need thereof a therapeutically effective amount of a compound or composition of the present disclosure. In some examples, the disease or disorder is a neurological disorder. In other examples, the disease or disorder is diabetes or a complication thereof. In some examples, the disease

or disorder is a complication from diabetes. In some examples, the complication from diabetes is neuropathy, nephropathy, retinopathy, or vasculopathy. In some examples, the complication from diabetes is neuropathy. In some examples, the disease or disorder is diabetic peripheral neuropathy. In other examples, the disease or disorder is cancer.

In some examples, the disease or disorder is associated with misregulation of the Hsp70 protein. In some examples, the disease or disorder is associated with misregulation of the Hsp90 protein. In some examples, the patient is a mammal. In some examples, the patient is human. In some examples, the compound is administered once to the patient. In other examples, the compound is administered two or more times to the patient.

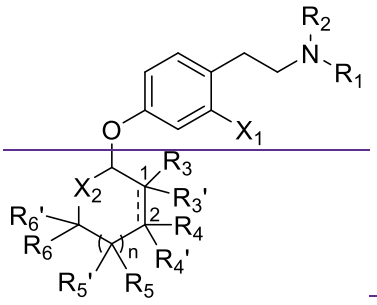
In another aspect, there is provided a compound or pharmaceutical composition as defined above for use in therapy.

In yet another ~~aspect~~example, the present disclosure provides methods of inducing expression of a Hsp70 protein comprising contacting the protein with an effective amount of a compound or composition of the present disclosure sufficient to induce the expression of the Hsp70 protein. In some examples, the protein is contacted *in vitro*. In other examples, the protein is contacted *in vivo*. In some examples, the effective amount of a compound or composition is effective enough to induce expression by at least 50% of the Hsp70 protein. In some examples, the Hsp70 protein expression is induced by more than 100%. In some examples, the induction of Hsp70 protein expression is sufficient to treat a disease or disorder. In some examples, the disease or disorder is a neurodegenerative disease. In some examples, the neurodegenerative disease is associated with misfolded proteins, demyelination, inflammation, and neuropathy. In some examples, the neurodegenerative disease is diabetic peripheral neuropathy. In some examples, the induction of Hsp70 protein expression results in a modulation in expression of one or more downstream products. In other examples, the induction of Hsp70 protein expression results in a modulation in activity of one or more downstream products.

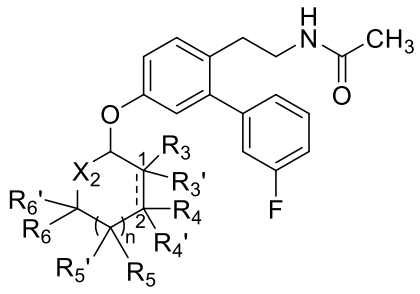
In still yet another ~~aspect~~example, the present disclosure provides methods of inhibiting of a Hsp90 protein comprising contacting the protein with an effective amount of a compound or composition of the present disclosure sufficient to inhibit the activity of the Hsp90 protein. In some examples, the protein is contacted *in vitro*. In other examples, the protein is contacted *in vivo*. In some examples, the effective amount of a compound or composition is effective enough to inhibit the expression of the Hsp90 protein by at least 50%. In some examples, the Hsp90 protein expression is inhibited by more than 75%. In some examples, the inhibition of Hsp90 protein expression is sufficient to treat a disease or disorder. In some examples, the disease or disorder is cancer or a hyperproliferative

What is claimed is:

1. A compound of the formula:



~~(III)~~



(I)

wherein:

the bond between atom 1 and atom 2 is either a single bond or a double bond;

~~X_1 is aryl$_{(C\leq12)}$, heteroaryl$_{(C\leq12)}$, or a substituted version of either of these groups;~~

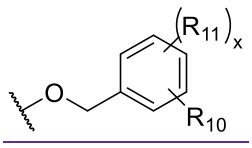
X_2 is $-CH_2-$ ~~or $-O-$~~;

~~R_1 is acyl$_{(C\leq12)}$ or substituted acyl$_{(C\leq12)}$;~~

~~R_2 is hydrogen, alkyl$_{(C\leq12)}$, or substituted alkyl$_{(C\leq12)}$;~~

R_3, R_4, R_3', R_4' are each independently hydrogen~~,~~ or hydroxy~~, aryloxy$_{(C\leq12)}$, aralkoxy$_{(C\leq12)}$, substituted aryloxy$_{(C\leq12)}$, or substituted aralkoxy$_{(C\leq12)}$~~;

~~each~~ R_5 is



wherein:

R_{10} is halo, or alkyl$_{(C\leq8)}$ optionally substituted with one or more halogen;

R_{11} are halo; and

x is 0 or 1;

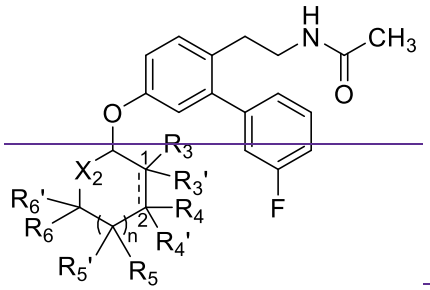
and R_5' are each independentlyis hydrogen, hydroxy, heteroaryloxy$_{(C\leq12)}$, heteroaralkoxy$_{(C\leq12)}$, substituted aryloxy$_{(C\leq12)}$, substituted aralkoxy$_{(C\leq12)}$, substituted heteroaryloxy$_{(C\leq12)}$, or substituted heteroaralkoxy$_{(C\leq12)}$;

R_6 and R_6' are each independently hydrogen, or alkyl$_{(C\leq12)}$, cycloalkyl$_{(C\leq12)}$, substituted alkyl$_{(C\leq12)}$, or substituted cycloalkyl$_{(C\leq12)}$; and

n is 0, 1, or 2; provided that if n is 2 then the R_5 and R_5' on each methylene are independently selected;

or a pharmaceutically acceptable salt thereof.

2. The compound of claim 1, wherein the compound is further defined as:



(I)

wherein:

the bond between atom 1 and atom 2 is either a single bond or a double bond;

X_2 is $-CH_2-$ or $-O-$;

R_3, R_4, R_3', R_4' are each independently hydrogen, hydroxy, aryloxy$_{(C\leq12)}$, aralkoxy$_{(C\leq12)}$, substituted aryloxy$_{(C\leq12)}$, or substituted aralkoxy$_{(C\leq12)}$;

each R_5 and R_5' are each independently hydrogen, hydroxy, heteroaryloxy$_{(C\leq12)}$, heteroaralkoxy$_{(C\leq12)}$, substituted aryloxy$_{(C\leq12)}$, substituted aralkoxy$_{(C\leq12)}$, substituted heteroaryloxy$_{(C\leq12)}$, or substituted heteroaralkoxy$_{(C\leq12)}$;

R_6 and R_6' are each independently hydrogen, alkyl$_{(C\leq12)}$, cycloalkyl$_{(C\leq12)}$, substituted alkyl$_{(C\leq12)}$, or substituted cycloalkyl$_{(C\leq12)}$; and

~~n is 0, 1, or 2; provided that if n is 2 then the R_5 and R_5' on each methylene are independently selected;~~

~~or a pharmaceutically acceptable salt thereof.~~

~~3. The compound of either claim 1 or claim 2, wherein X_2 is $-CH_2-$.~~

~~4~~2. The compound ~~according to any one~~ of claim~~s~~ 1~~-3~~, wherein ~~R_3 is hydrogen or hydroxy, R_3' is hydrogen or hydroxy, R_4 is hydrogen or hydroxy, R_4' is hydrogen or hydroxy,~~ R_6 is hydrogen~~, alkyl$_{(C\leq12)}$ or substituted alkyl$_{(C\leq12)}$, R_6' is hydrogen alkyl$_{(C\leq12)}$ or substituted alkyl$_{(C\leq12)}$, or n is 0 or 1~~.

3. The compound of either claim 1 or claim 2, wherein R_6' is hydrogen.

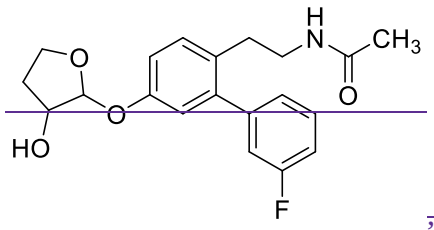
~~5. The compound according to any one of claims 1-4, wherein R_5 is hydrogen, hydroxy, or substituted aralkoxy$_{(C\leq12)}$ and R_5' is hydrogen, hydroxy, or substituted aralkoxy$_{(C\leq12)}$.~~

4. The compound according to any one of claims 1-3, wherein R_{10} is chloro.

5. The compound according to any one of claims 1-4, wherein R_{11} is chloro.

6. The compound according to any one of claims 1-5, wherein x is 1.

7~~6~~. The compound according to any one of claims 1-6~~5~~, wherein the compound is further defined as:



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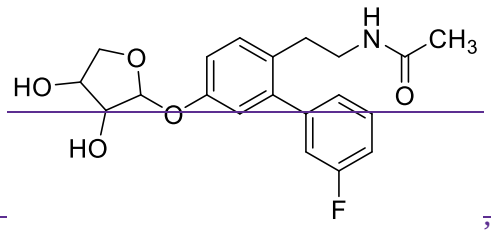

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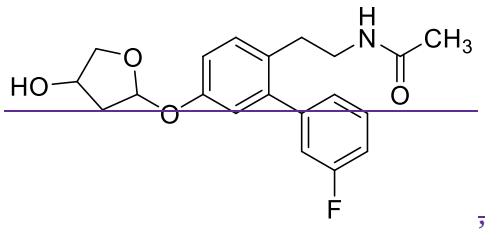

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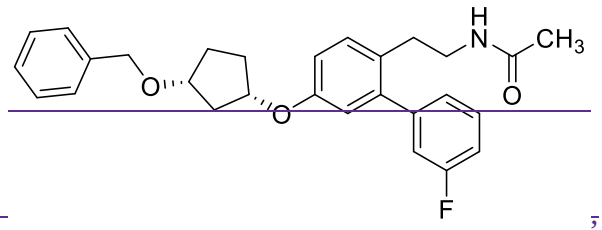

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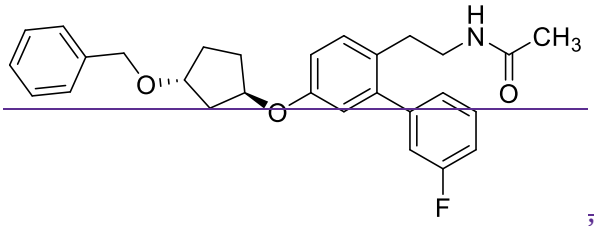
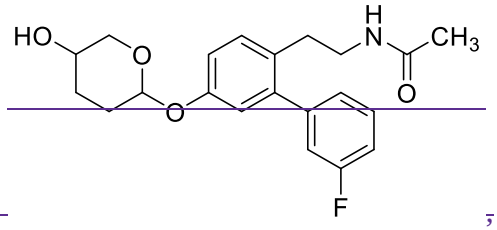
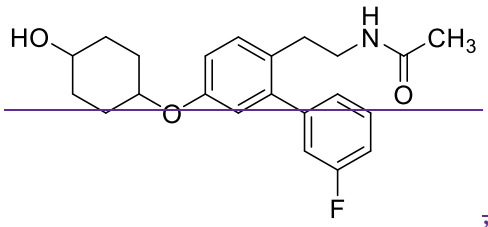
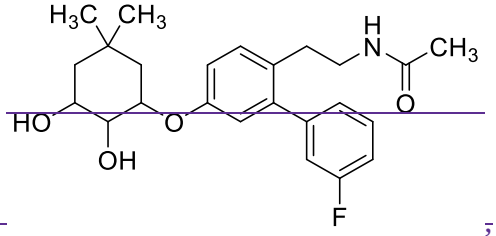
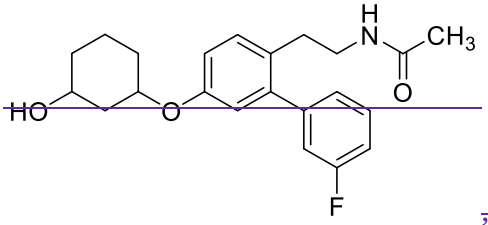
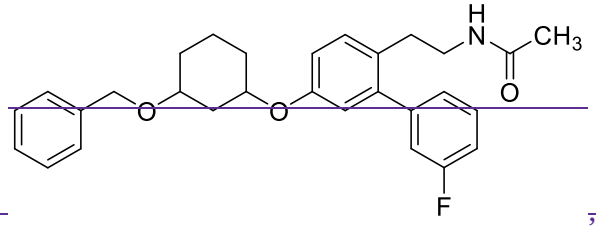
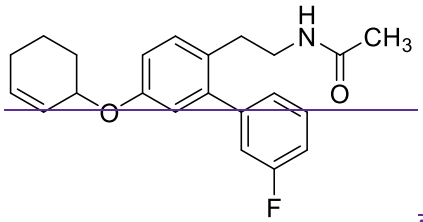
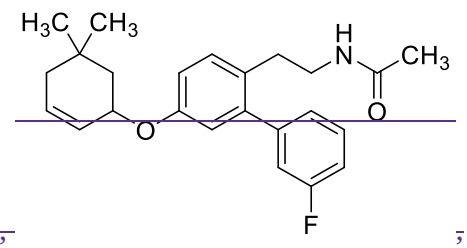
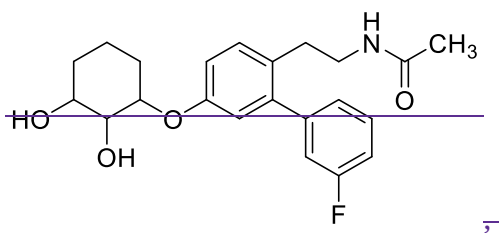
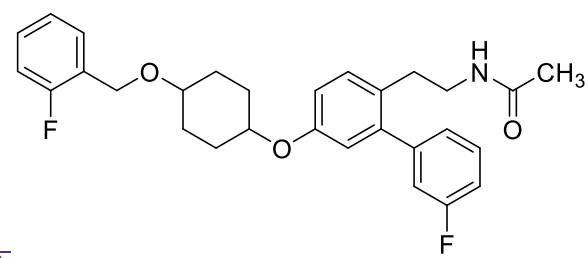
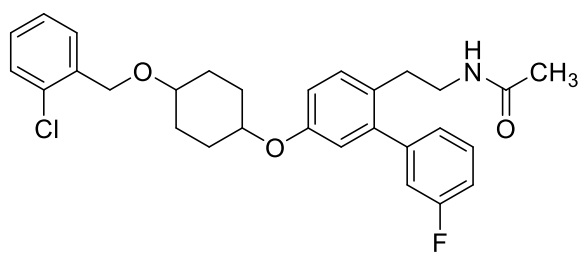

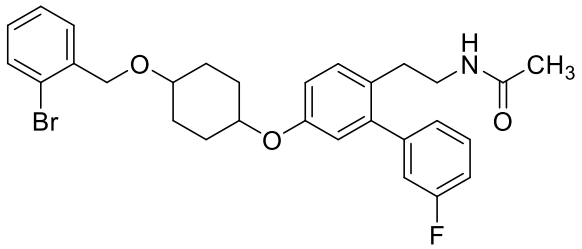
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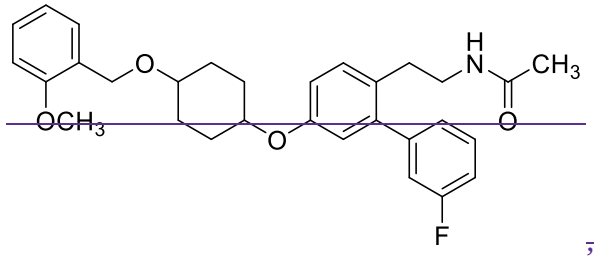
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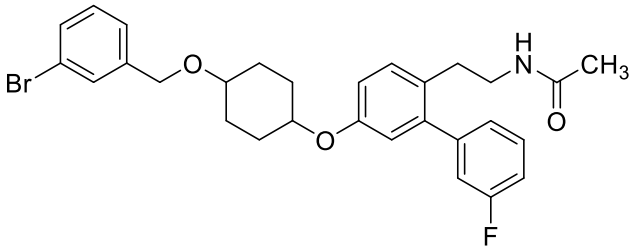
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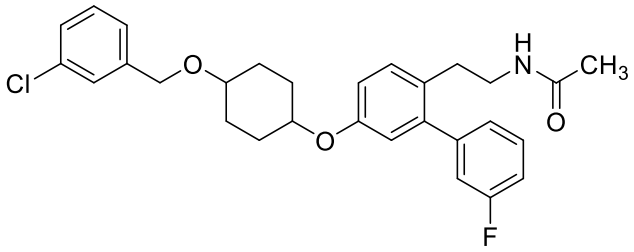
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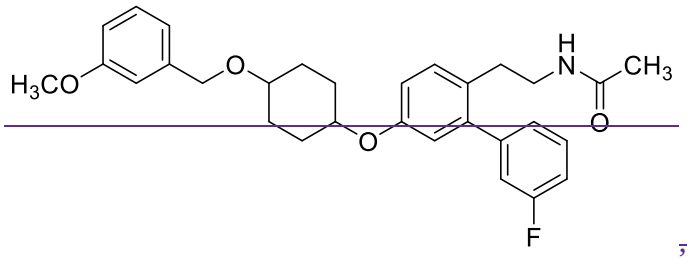
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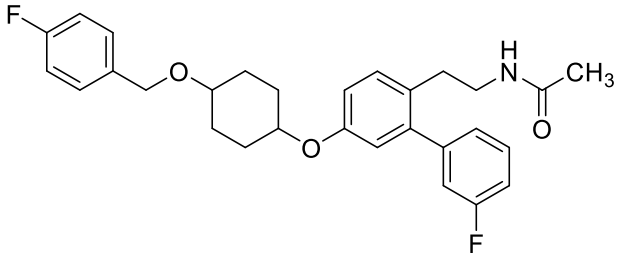
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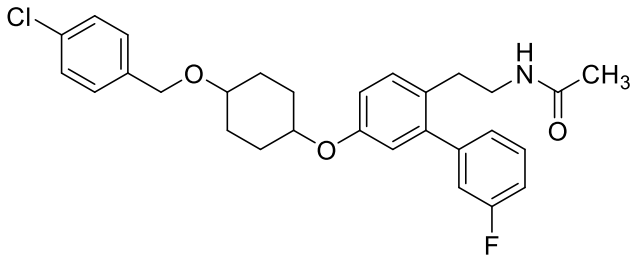
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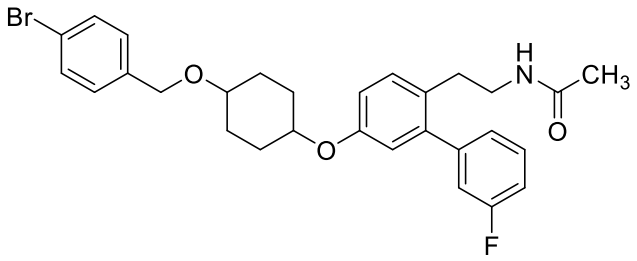
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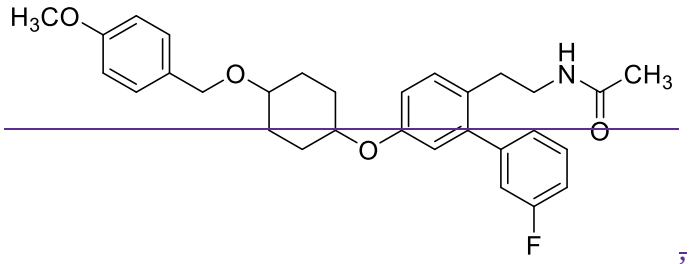
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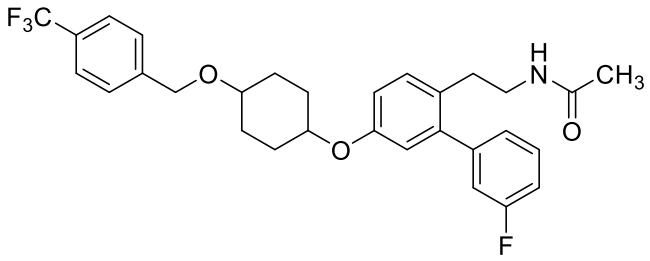
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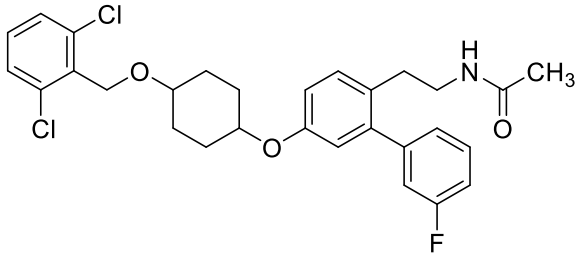
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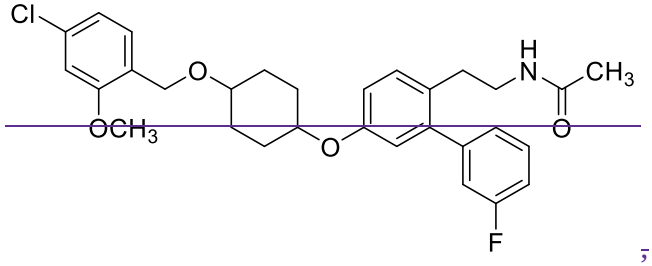
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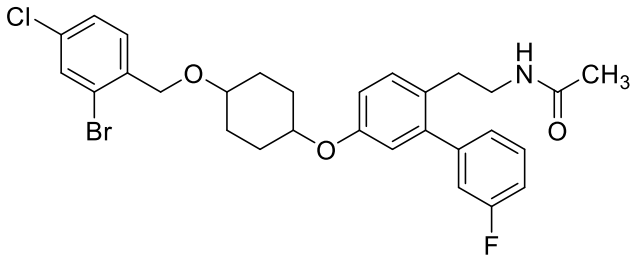

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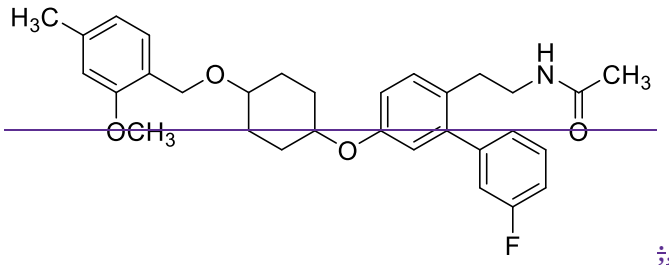

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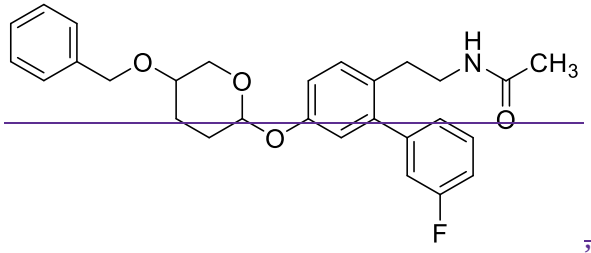
or a pharmaceutically acceptable salt thereof.

7. A compound of the formula:



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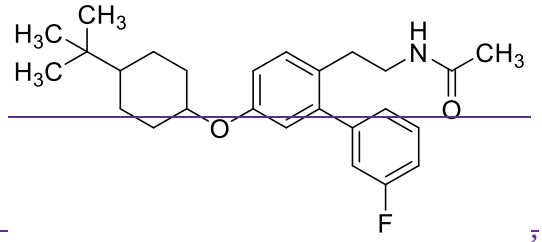

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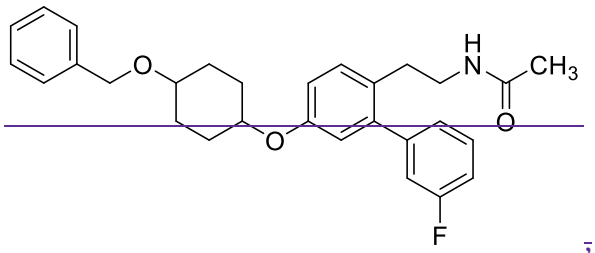

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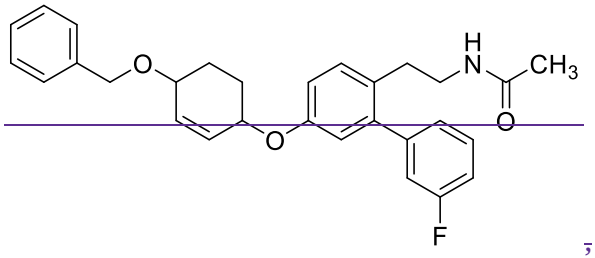

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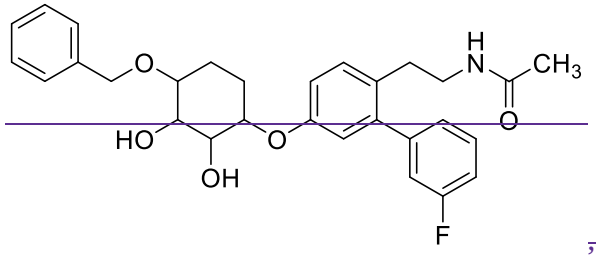

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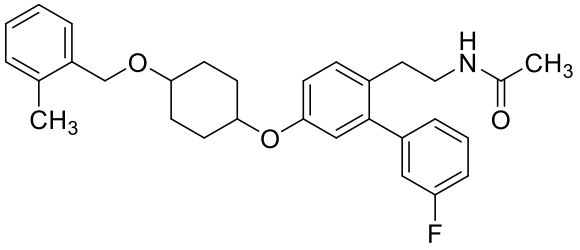

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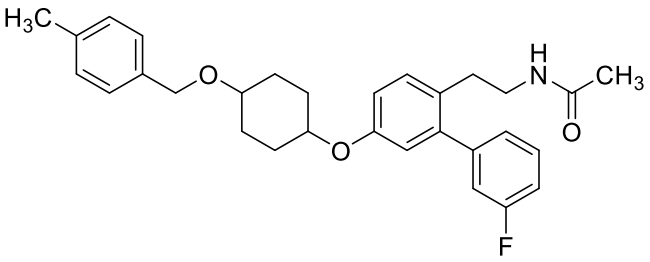

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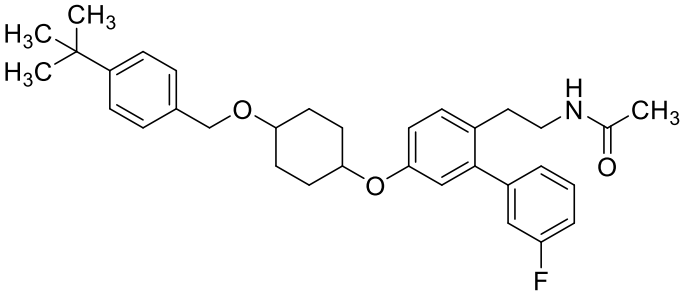

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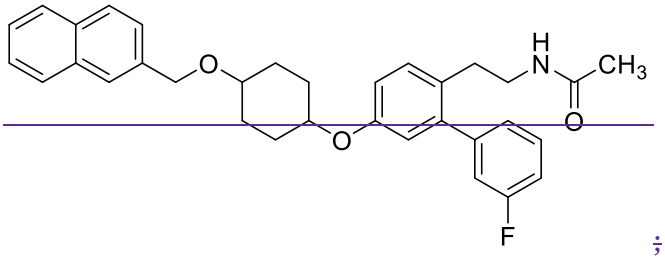

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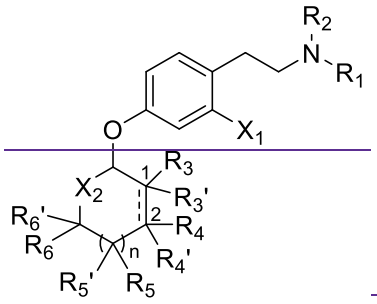
or a pharmaceutically acceptable salt thereof.

8. A compound of the formula:



(III)

wherein:

the bond between atom 1 and atom 2 is either a single bond or a double bond;

X_1 is aryl$_{(C\leq 12)}$, heteroaryl$_{(C\leq 12)}$, or a substituted version of either of these groups;

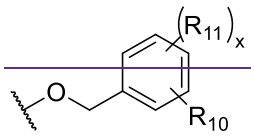
X_2 is $-CH_2-$ or $-O-$;

R_1 is acyl$_{(C\leq 12)}$ or substituted acyl$_{(C\leq 12)}$;

R_2 is hydrogen, alkyl$_{(C\leq 12)}$, or substituted alkyl$_{(C\leq 12)}$;

R_3, R_4, R_3', R_4' are each independently hydrogen, hydroxy, aryloxy$_{(C\leq 12)}$, aralkoxy$_{(C\leq 12)}$, substituted aryloxy$_{(C\leq 12)}$, or substituted aralkoxy$_{(C\leq 12)}$;

each R_5 and R_5' are each independently hydrogen, hydroxy; or a group of the formula:



wherein:

R_{10} and R_{11} are amino, carboxy, cyano, halo, hydroxy, hydroxysulfonyl, or sulfonamide; or

alkyl$_{(C\leq 8)}$, aryl$_{(C\leq 8)}$, acyl$_{(C\leq 8)}$, alkoxy$_{(C\leq 8)}$, acyloxy$_{(C\leq 8)}$, amido$_{(C\leq 8)}$, alkylamino$_{(C\leq 8)}$, dialkylamino$_{(C\leq 8)}$, or a substituted version of any of these groups; and

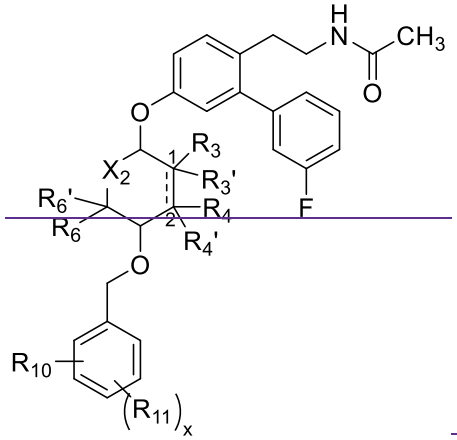
x is 0, 1, 2, 3, or 4;

R_6 and R_6' are each independently hydrogen, $alkyl_{(C\leq12)}$, $cycloalkyl_{(C\leq12)}$, $substituted\ alkyl_{(C\leq12)}$, or $substituted\ cycloalkyl_{(C\leq12)}$; and

n is 0, 1, or 2; provided that if n is 2 then the R_5 and R_5' on each methylene are independently selected;

or a pharmaceutically acceptable salt thereof.

9. The compound of claim 8, wherein the compound is further defined as:



(V)

wherein:

the bond between atom 1 and atom 2 is either a single bond or a double bond;

X_2 is $-CH_2-$ or $-O-$;

R_3, R_4, R_3', R_4' are each independently hydrogen, hydroxy, $aryloxy_{(C\leq12)}$, $aralkoxy_{(C\leq12)}$, $substituted\ aryloxy_{(C\leq12)}$, or $substituted\ aralkoxy_{(C\leq12)}$;

R_6 and R_6' are each independently hydrogen, $alkyl_{(C\leq12)}$, $cycloalkyl_{(C\leq12)}$, $substituted\ alkyl_{(C\leq12)}$, or $substituted\ cycloalkyl_{(C\leq12)}$; and

R_{10} and R_{11} are amino, carboxy, cyano, halo, hydroxy, hydroxysulfonyl, or sulfonamide; or

$alkyl_{(C\leq8)}$, $aryl_{(C\leq8)}$, $acyl_{(C\leq8)}$, $alkoxy_{(C\leq8)}$, $acyloxy_{(C\leq8)}$, $amido_{(C\leq8)}$, $alkylamino_{(C\leq8)}$, $dialkylamino_{(C\leq8)}$, or a substituted version of any of these groups; and

x is 0, 1, 2, 3, or 4;

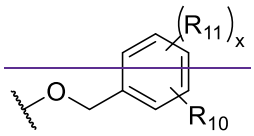
or a pharmaceutically acceptable salt thereof.

10. The compound of either claim 8 or claim 9, wherein R_2 is hydrogen, R_1 is $acyl_{(C\leq12)}$, or X_2 is $=CH_2=$.

11. The compound according to any one of claims 8-10, wherein R_3 is hydrogen or hydroxy, R_3' is hydrogen or hydroxy, R_4 is hydrogen or hydroxy, or R_4' is hydrogen or hydroxy, R_5' is hydrogen or hydroxy, R_6 is hydrogen $alkyl_{(C\leq12)}$, or substituted $alkyl_{(C\leq12)}$, or R_6' is hydrogen, $alkyl_{(C\leq12)}$, or substituted $alkyl_{(C\leq12)}$.

12. The compound according to any one of claims 8-11, wherein n is 0 or 1.

13. The compound according to any one of claims 8-12, wherein R_5 is:



wherein:

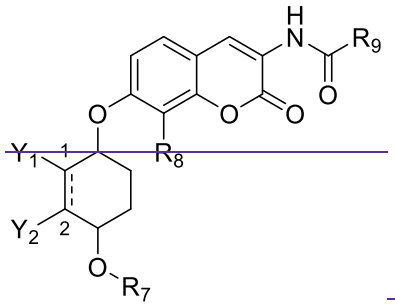
R_{10} and R_{11} are amino, carboxy, cyano, halo, hydroxy, hydroxysulfonyl, or sulfonamide; or

$alkyl_{(C\leq8)}$, $aryl_{(C\leq8)}$, $acyl_{(C\leq8)}$, $alkoxy_{(C\leq8)}$, $acyloxy_{(C\leq8)}$, $amido_{(C\leq8)}$, $alkylamino_{(C\leq8)}$, $dialkylamino_{(C\leq8)}$, or a substituted version of any of these groups; and

x is 0, 1, 2, 3, or 4.

14. The compound of claim 13, wherein R_{10} is halo, $alkyl_{(C\leq8)}$ or substituted $alkyl_{(C\leq8)}$, $alkoxy_{(C\leq8)}$ or substituted $alkoxy_{(C\leq8)}$, or x is 0, 1, or 2.

15. A compound of the formula:



(II)

wherein:

R_7 is $aryl_{(C\leq12)}$, $aralkyl_{(C\leq12)}$, or a substituted version of either of these groups;

R_8 is hydrogen, $alkyl_{(C\leq12)}$, $cycloalkyl_{(C\leq12)}$, substituted $alkyl_{(C\leq12)}$, or substituted $cycloalkyl_{(C\leq12)}$;

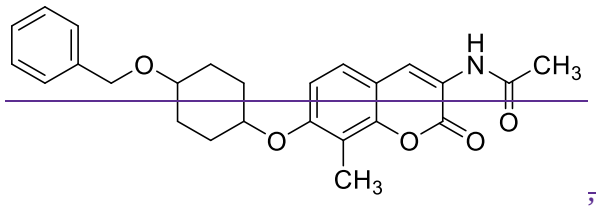
R_9 is $alkyl_{(C\leq12)}$, $cycloalkyl_{(C\leq12)}$, $aryl_{(C\leq12)}$, $heteroaryl_{(C\leq12)}$, or a substituted version of any of these groups; and

Y_1 and Y_2 are each independently hydrogen or hydroxy;

or a pharmaceutically acceptable salt thereof.

16. The compound of claim 15, wherein Y_1 is hydrogen, Y_2 is hydrogen, R_8 is $alkyl_{(C\leq12)}$, R_9 is $alkyl_{(C\leq12)}$, or R_7 is $aralkyl_{(C\leq12)}$ or substituted $aralkyl_{(C\leq12)}$.

17. The compound of either claim 15 or claim 16, wherein the compound is further defined as:



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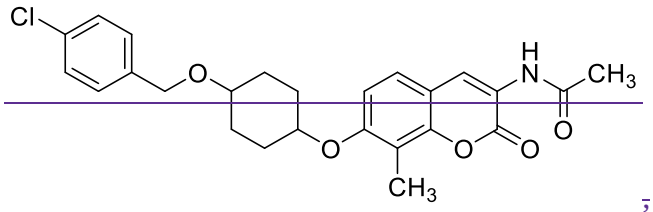

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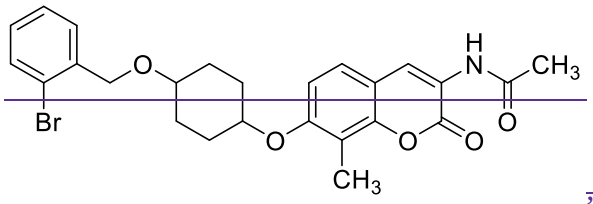

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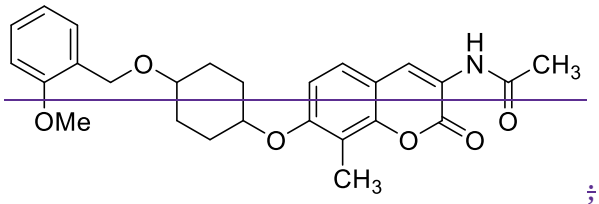

~~;~~

~~or a pharmaceutically acceptable salt thereof.~~

~~1~~8. A pharmaceutical composition comprising:

(A) a compound according to any one of claims 1-~~1~~7; and

(B) a pharmaceutically acceptable carrier.

~~1~~9. Use of a compound or pharmaceutical composition according to any one of claims 1-~~1~~8 in the manufacture of a medicament for treating a disease or disorder, wherein the disease or disorder is selected from the group consisting of neurological disorder, diabetes, neuropathy, nephropathy, retinopathy, vasculopathy and cancer, in a patient.

10. A compound or pharmaceutical composition according to any one of claims 1-8 for use in therapy.