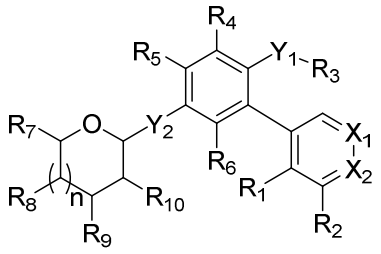
Summary

The present disclosure describes biaryl Hsp90 inhibitors with modified ether groups with therapeutic properties, pharmaceutical compositions thereof, methods for their manufacture, and methods for their use. The present disclosure refers to subject matter as defined in the attached set of claims.

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



(I),

wherein:

n is 0, 1, or 2;

Y_1 is −alkanediyl$_{(C\leq 6)}$− or substituted −alkanediyl$_{(C\leq 6)}$−;

Y_2 is O;

R_1 is hydrogen, halo, hydroxy, or alkyl$_{(C\leq 6)}$, alkoxy$_{(C\leq 6)}$, or a substituted version of any of either group;

R_2 is hydrogen, halo, hydroxy, or alkyl$_{(C\leq 6)}$, alkoxy$_{(C\leq 6)}$, or a substituted version of any of either group;

R_3 is –$NR_{11}R_{11}'$ or –$C(O)NR_{12}R_{12}'$, wherein:

R_{11} and R_{11}' are each independently hydrogen, alkyl$_{(C\leq 6)}$, substituted alkyl$_{(C\leq 6)}$, acyl$_{(C\leq 6)}$, or substituted acyl$_{(C\leq 6)}$;

R_{12} and R_{12}' are each independently hydrogen, alkyl$_{(C\leq 6)}$, or substituted alkyl$_{(C\leq 6)}$;

R_4, R_5, and R_6 are each hydrogen;

R_7 is carboxy or alkyl$_{(C\leq 6)}$, alkenyl$_{(C\leq 8)}$, alkynyl$_{(C\leq 8)}$, cycloalkyl$_{(C\leq 8)}$, aryl$_{(C\leq 12)}$, aralkyl$_{(C\leq 12)}$, −alkanediyl$_{(C\leq 6)}$−OR_{13}, or a substituted version of any of these groups wherein:

R_{13} is alkyl$_{(C\leq 12)}$, substituted alkyl$_{(C\leq 12)}$, aralkyl$_{(C\leq 12)}$, or substituted aralkyl$_{(C\leq 12)}$;

R_8 is hydroxy, or alkoxy$_{(C\leq 6)}$, aralkoxy$_{(C\leq 12)}$, or a substituted version of any of either group;

R_9 and R_{10} are each independently hydroxy, alkoxy$_{(C\leq 6)}$, or substituted alkoxy$_{(C\leq 6)}$;

X_1 is CR_{14} or N, wherein:

R_{14} is hydrogen, halo, hydroxy, or $alkyl_{(C\leq 6)}$, $alkoxy_{(C\leq 6)}$, or a substituted version of any of either group; and

X_2 is CR_{15} or N, wherein:

R_{15} is hydrogen, halo, hydroxy, or $alkyl_{(C\leq 6)}$, $alkoxy_{(C\leq 6)}$, or a substituted version of any of either group;

wherein when any of the terms is used with the "substituted" modifier, one or more hydrogen atom has been independently replaced by –OH, –F, –Cl, –Br, –I, $-NH_2$, $-NO_2$, $-CO_2H$, $-CO_2CH_3$, –CN, –SH, $-OCH_3$, $-OCH_2CH_3$, $-C(O)CH_3$, $-NHCH_3$, $-NHCH_2CH_3$, $-N(CH_3)_2$, $-C(O)NH_2$, $-C(O)NHCH_3$, $-C(O)N(CH_3)_2$, $-OC(O)CH_3$, $-NHC(O)CH_3$, $-S(O)_2OH$, or $-S(O)_2NH_2$;

or a pharmaceutically acceptable salt of the formula.

In another aspect, there is provided a pharmaceutical composition comprising:

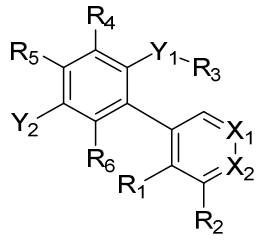
(A) a compound as defined above; and

(B) an excipient.

In another aspect, there is provided a therapeutically effective amount of a compound or composition as defined above for use in therapy.

In another aspect, there is provided a method of making a compound as defined above, comprising reacting (a) with (b) in the presence of a coupling agent:

(a) a compound of the formula:



(XXXIII),

wherein:

n is 0, 1, or 2;

Y_1 is $-alkanediyl_{(C\leq 6)}-$, or substituted $-alkanediyl_{(C\leq 6)}-$;

Y_2 is hydroxy;

R_1 is hydrogen, halo, hydroxy, or alkyl$_{(C\leq6)}$, alkoxy$_{(C\leq6)}$, or a substituted version of any of either group;

R_2 is hydrogen, halo, hydroxy, or alkyl$_{(C\leq6)}$, alkoxy$_{(C\leq6)}$, or a substituted version of any of either group;

R_3 is carboxy, $-NR_{11}R_{11}'$, or $-C(O)NR_{12}R_{12}'$, wherein:

R_{11} and R_{11}' are each independently hydrogen, alkyl$_{(C\leq6)}$, substituted alkyl$_{(C\leq6)}$, acyl$_{(C\leq6)}$, or substituted acyl$_{(C\leq6)}$;

R_{12} and R_{12}' are each independently hydrogen, alkyl$_{(C\leq6)}$, or substituted alkyl$_{(C\leq6)}$;

R_4, R_5, and R_6 are each hydrogen;

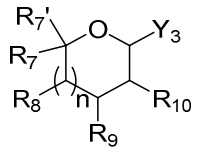
X_1 is CR_{14} or N, wherein:

R_{14} is hydrogen, halo, hydroxy, or alkyl$_{(C\leq6)}$, alkoxy$_{(C\leq6)}$, or a substituted version of any of either group; or

X_2 is CR_{15} or N, wherein:

R_{15} is hydrogen, halo, hydroxy, or alkyl$_{(C\leq6)}$, alkoxy$_{(C\leq6)}$, or a substituted version of any of either group;

(b) a compound of the formula:



(XXXIV),

wherein:

n is 0, 1, or 2;

Y_3 is hydroxy, halo, acyloxy$_{(C\leq8)}$, iminooxy$_{(C\leq8)}$,or a substituted version of either of these groups;

R_7 is carboxy, or alkyl$_{(C\leq8)}$, alkenyl$_{(C\leq8)}$, alkynyl$_{(C\leq8)}$, cycloalkyl$_{(C\leq8)}$, aryl$_{(C\leq12)}$, aralkyl$_{(C\leq12)}$, −alkanediyl$_{(C\leq6)}$−OR_{13}, or a substituted version of any of these groups wherein:

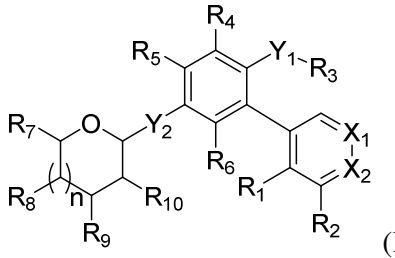
R_{13} is aralkyl$_{(C\leq12)}$ or substituted aralkyl$_{(C\leq12)}$;

R_7' is hydrogen;

R_8 is hydroxy, or alkoxy$_{(C\leq6)}$, aralkoxy$_{(C\leq12)}$, or a substituted version of either of these groups; and

R_9 and R_{10} are each independently hydroxy, alkoxy$_{(C\leq6)}$, or substituted alkoxy$_{(C\leq6)}$.

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



(I)

wherein:

n is 0, 1, or 2;

Y_1 is −alkanediyl$_{(C\leq 6)}$−, −C(O)−alkanediyl$_{(C\leq 6)}$−, or a substituted version of any of these groups;

Y_2 is CH_2, O, or S;

R_1 is hydrogen, amino, halo, hydroxy, carboxy, or alkyl$_{(C\leq 6)}$, alkenyl$_{(C\leq 6)}$, alkynyl$_{(C\leq 6)}$, cycloalkyl$_{(C\leq 8)}$, heterocycloalkyl$_{(C\leq 8)}$, amido$_{(C\leq 6)}$, alkoxy$_{(C\leq 6)}$, alkylsulfonyl$_{(C\leq 6)}$, or a substituted version of any of these groups;

R_2 is hydrogen, amino, halo, hydroxy, carboxy, or alkyl$_{(C\leq 6)}$, alkenyl$_{(C\leq 6)}$, alkynyl$_{(C\leq 6)}$, cycloalkyl$_{(C\leq 8)}$, heterocycloalkyl$_{(C\leq 8)}$, aryl$_{(C\leq 12)}$, aralkyl$_{(C\leq 12)}$, amido$_{(C\leq 6)}$, alkoxy$_{(C\leq 6)}$, alkylthio$_{(C\leq 6)}$, alkylsulfonyl$_{(C\leq 6)}$, or a substituted version of any of these groups;

R_2 and R_{15} are taken together and are alkanediyl$_{(C\leq 6)}$, alkoxydiyl$_{(C\leq 6)}$, alkylaminodiyl$_{(C\leq 6)}$, or a substituted version of any of these groups;

R_3 is $–NR_{11}R_{11}'$ or $–C(O)NR_{12}R_{12}'$, wherein:

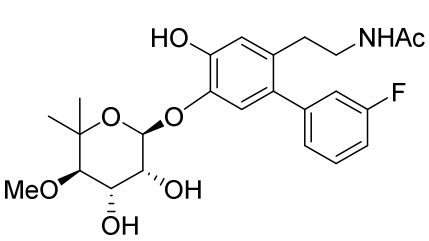
R_{11} and R_{11}' are each independently hydrogen, alkyl$_{(C\leq 6)}$, substituted alkyl$_{(C\leq 6)}$, acyl$_{(C\leq 6)}$, or substituted acyl$_{(C\leq 6)}$;

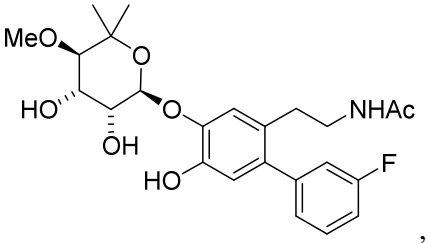
R_{12} and R_{12}' are each independently hydrogen, alkyl$_{(C\leq 6)}$, or substituted alkyl$_{(C\leq 6)}$;

R_4, R_5, and R_6 are each independently hydrogen, halo, alkyl$_{(C\leq 6)}$, substituted alkyl$_{(C\leq 6)}$, alkoxy$_{(C\leq 6)}$, substituted alkoxy$_{(C\leq 6)}$, acyloxy$_{(C\leq 6)}$, or substituted acyloxy$_{(C\leq 6)}$;

R_7 is carboxy or alkyl$_{(C\leq 6)}$, alkenyl$_{(C\leq 8)}$, alkynyl$_{(C\leq 8)}$, cycloalkyl$_{(C\leq 8)}$, heterocycloalkyl$_{(C\leq 8)}$, aryl$_{(C\leq 12)}$, heteroaryl$_{(C\leq 12)}$, aralkyl$_{(C\leq 12)}$, heteroaralkyl$_{(C\leq 12)}$, −alkanediyl$_{(C\leq 6)}$−OR_{13}, or a substituted version of any of these groups wherein:

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

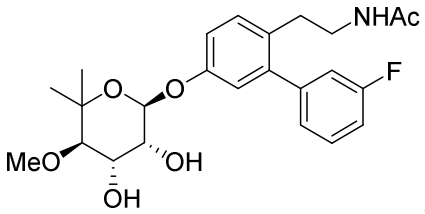


,


,

or a pharmaceutically acceptable salt of either of these formulas.

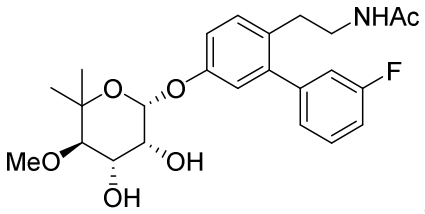
In yet another example, the present disclosure refers to a compound of the formula:



,

wherein the compound is essentially free of any other stereoisomers;
or a pharmaceutically acceptable salt of the formula.

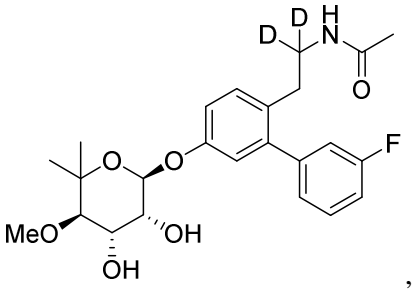
In yet another example, the present disclosure refers to a compound of the formula:



,

wherein the compound is essentially free of any other stereoisomers;
or a pharmaceutically acceptable salt of the formula.

In yet another example, the present disclosure refers to a compound of the formula, or a pharmaceutically acceptable salt of the formula:



,

wherein the compound is greater than 90% deuterated at the positions indicated in the formula.

In yet another example, the present disclosure refers to a pharmaceutical composition comprising:

(A) a compound as described herein; and

(B) an excipient.

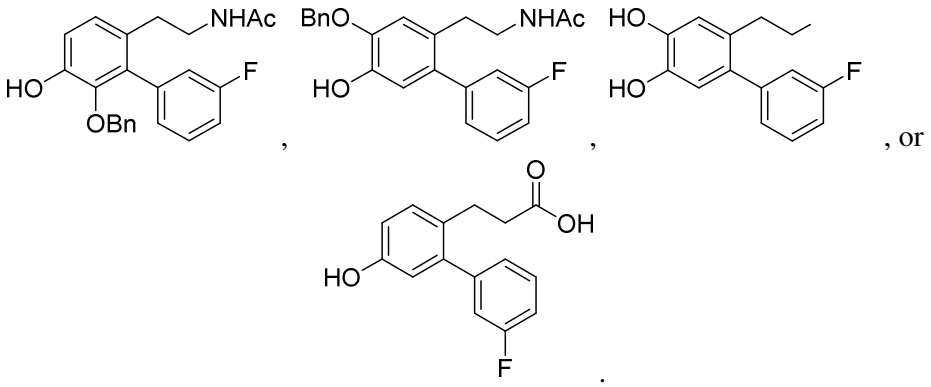
In some examples, the pharmaceutical compositions are formulated for administration: orally, intraadiposally, intraarterially, intraarticularly, intracranially, intradermally, intralesionally, intramuscularly, intranasally, intraocularly, intrapericardially, intraperitoneally, intrapleurally, intraprostatically, 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 yet another example, the present disclosure refers to a therapeutically effective amount of a compound or composition as described herein for use in therapy. In still yet another 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 described herein. 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 such as neuropathy, nephropathy, retinopathy, or vasculopathy. In some examples, the complication from diabetes is neuropathy such as diabetic peripheral neuropathy. 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 such as 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 yet another 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 described herein 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 such as 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 such as a neurodegenerative disease is associated with misfolded proteins, demyelination, inflammation, and neuropathy. In some examples, the neurodegenerative disease is diabetic peripheral neuropathy. In other examples, the disease or disorder is cancer. In other examples, the induction of Hsp70 protein expression results in a modulation in expression of one or more downstream products. In some examples, the induction of Hsp70 protein expression results in a modulation in activity of one or more downstream products.

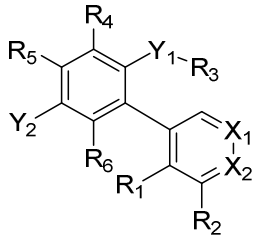
In still yet another example, the present disclosure provides methods of inhibiting of a Hsp90 protein comprising contacting the protein with an effective amount of a compound or composition described herein sufficient to inhibit the activity of the Hsp90 protein. In some examples, the protein is contacted *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% such as when 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 disorder. In some examples, the disease or disorder is associated with a highly proliferating cell. In some embodiemnts, the inhibition of Hsp90 protein expression results in a modulation in expression of one or more downstream products. In other examples, the inhibition of Hsp90 protein expression results in a modulation in activity of one or more downstream products.

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



In yet another example, the present disclosure refers to a method of making a compound as described herein, comprising reacting (a) with (b) in the presence of a coupling agent:

(a) a compound of the formula:



(XXXIII),

wherein:

n is 0, 1, or 2;

Y_1 is $-\text{alkanediyl}_{(C\leq 6)}-$, $-C(O)-\text{alkanediyl}_{(C\leq 6)}-$, $-\text{alkanediyl}_{(C\leq 6)}-C(O)R_{17}$, or a substituted version of any of these groups, wherein:

R_{17} is $\text{alkyl}_{(C\leq 6)}$ or substituted $\text{alkyl}_{(C\leq 6)}$;

Y_2 is hydroxy or mercapto;

R_1 is hydrogen, amino, halo, hydroxy, carboxy, or $\text{alkyl}_{(C\leq 6)}$, $\text{alkenyl}_{(C\leq 6)}$, $\text{alkynyl}_{(C\leq 6)}$, $\text{cycloalkyl}_{(C\leq 8)}$, $\text{heterocycloalkyl}_{(C\leq 8)}$, $\text{amido}_{(C\leq 6)}$, $\text{alkoxy}_{(C\leq 6)}$, $\text{alkylsulfonyl}_{(C\leq 6)}$, or a substituted version of any of these groups;

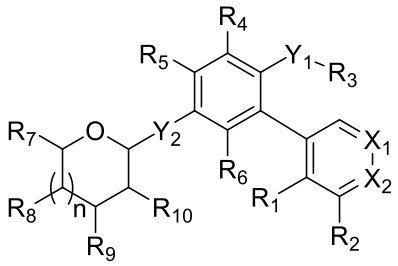
R_2 is hydrogen, amino, halo, hydroxy, carboxy, or $\text{alkyl}_{(C\leq 6)}$, $\text{alkenyl}_{(C\leq 6)}$, $\text{alkynyl}_{(C\leq 6)}$, $\text{cycloalkyl}_{(C\leq 8)}$, $\text{heterocycloalkyl}_{(C\leq 8)}$, $\text{aryl}_{(C\leq 12)}$, $\text{aralkyl}_{(C\leq 12)}$, $\text{amido}_{(C\leq 6)}$, $\text{alkoxy}_{(C\leq 6)}$, $\text{alkylthio}_{(C\leq 6)}$, $\text{alkylsulfonyl}_{(C\leq 6)}$, or a substituted version of any of these groups;

R_2 and R_{15} are taken together and are $\text{alkanediyl}_{(C\leq 6)}$, $\text{alkoxydiyl}_{(C\leq 6)}$, $\text{alkylaminodiyl}_{(C\leq 6)}$, or a substituted version of any of these groups;

R_3 is carboxy, $-NR_{11}R_{11}'$, or $-C(O)NR_{12}R_{12}'$, wherein:

CLAIMS

What is Claimed is:

1. A compound of the formula  (I), wherein:

n is 0, 1, or 2;

Y_1 is −alkanediyl$_{(C\leq 6)}$− or substituted −alkanediyl$_{(C\leq 6)}$−;

Y_2 is O;

R_1 is hydrogen, halo, hydroxy, or alkyl$_{(C\leq 6)}$, alkoxy$_{(C\leq 6)}$, or a substituted version of any of either group;

R_2 is hydrogen, halo, hydroxy, or alkyl$_{(C\leq 6)}$, alkoxy$_{(C\leq 6)}$, or a substituted version of any of either group;

R_3 is $–NR_{11}R_{11}'$ or $–C(O)NR_{12}R_{12}'$, wherein:

R_{11} and R_{11}' are each independently hydrogen, alkyl$_{(C\leq 6)}$, substituted alkyl$_{(C\leq 6)}$, acyl$_{(C\leq 6)}$, or substituted acyl$_{(C\leq 6)}$;

R_{12} and R_{12}' are each independently hydrogen, alkyl$_{(C\leq 6)}$, or substituted alkyl$_{(C\leq 6)}$;

R_4, R_5, and R_6 are each hydrogen;

R_7 is carboxy or alkyl$_{(C\leq 6)}$, alkenyl$_{(C\leq 8)}$, alkynyl$_{(C\leq 8)}$, cycloalkyl$_{(C\leq 8)}$, aryl$_{(C\leq 12)}$, aralkyl$_{(C\leq 12)}$, −alkanediyl$_{(C\leq 6)}$−OR_{13}, or a substituted version of any of these groups wherein:

R_{13} is alkyl$_{(C\leq 12)}$, substituted alkyl$_{(C\leq 12)}$, aralkyl$_{(C\leq 12)}$, or substituted aralkyl$_{(C\leq 12)}$;

R_8 is hydroxy, or alkoxy$_{(C\leq 6)}$, aralkoxy$_{(C\leq 12)}$, or a substituted version of any of either group;

R_9 and R_{10} are each independently hydroxy, alkoxy$_{(C\leq 6)}$, or substituted alkoxy$_{(C\leq 6)}$;

X_1 is CR_{14} or N, wherein:

R_{14} is hydrogen, halo, hydroxy, or alkyl$_{(C\leq6)}$, alkoxy$_{(C\leq6)}$, or a substituted version of any of either group; and

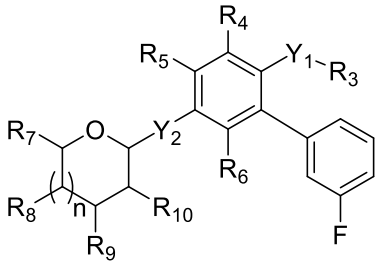
X_2 is CR_{15} or N, wherein:

R_{15} is hydrogen, halo, hydroxy, or alkyl$_{(C\leq6)}$, alkoxy$_{(C\leq6)}$, or a substituted version of any of either group;

wherein when any of the terms is used with the "substituted" modifier, one or more hydrogen atom has been independently replaced by −OH, −F, −Cl, −Br, −I, $-NH_2$, $-NO_2$, $-CO_2H$, $-CO_2CH_3$, −CN, −SH, $-OCH_3$, $-OCH_2CH_3$, $-C(O)CH_3$, $-NHCH_3$, $-NHCH_2CH_3$, $-N(CH_3)_2$, $-C(O)NH_2$, $-C(O)NHCH_3$, $-C(O)N(CH_3)_2$, $-OC(O)CH_3$, $-NHC(O)CH_3$, $-S(O)_2OH$, or $-S(O)_2NH_2$;

or a pharmaceutically acceptable salt of the formula.

2. The compound of claim 1 further defined as:



(VI),

wherein:

n is 0, 1, or 2;

Y_1 is −alkanediyl$_{(C\leq6)}$− or substituted −alkanediyl$_{(C\leq6)}$−;

Y_2 is O;

R_3 is $-NR_{11}R_{11}'$ or $-C(O)NR_{12}R_{12}'$, wherein:

R_{11} and R_{11}' are each independently hydrogen, alkyl$_{(C\leq6)}$, substituted alkyl$_{(C\leq6)}$, acyl$_{(C\leq6)}$, or substituted acyl$_{(C\leq6)}$;

R_{12} and R_{12}' are each independently hydrogen, alkyl$_{(C\leq6)}$, or substituted alkyl$_{(C\leq6)}$;

R_4, R_5, and R_6 are each independently hydrogen;

R_7 is carboxy or alkyl$_{(C\leq6)}$, alkenyl$_{(C\leq8)}$, alkynyl$_{(C\leq8)}$, cycloalkyl$_{(C\leq8)}$, aryl$_{(C\leq12)}$, aralkyl$_{(C\leq12)}$, −alkanediyl$_{(C\leq6)}$−OR_{13}, or a substituted version of any of these groups wherein:

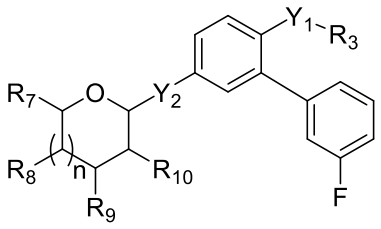
R_{13} is $alkyl_{(C\leq12)}$, substituted $alkyl_{(C\leq12)}$, $aralkyl_{(C\leq12)}$, or substituted $aralkyl_{(C\leq12)}$;

R_8 is hydroxy, or $alkoxy_{(C\leq6)}$, $aralkoxy_{(C\leq12)}$, or a substituted version of any of either group; and

R_9 and R_{10} are each independently hydroxy, $alkoxy_{(C\leq6)}$, or substituted $alkoxy_{(C\leq6)}$;

or a pharmaceutically acceptable salt of the formula.

3. The compound of either claim 1 or claim 2 further defined as:



(VII),

wherein:

n is 0, 1, or 2;

Y_1 is −$alkanediyl_{(C\leq6)}$− or substituted −$alkanediyl_{(C\leq6)}$−;

Y_2 is O;

R_3 is –$NR_{11}R_{11}'$ or –$C(O)NR_{12}R_{12}'$, wherein:

R_{11} and R_{11}' are each independently hydrogen, $alkyl_{(C\leq6)}$, substituted $alkyl_{(C\leq6)}$, $acyl_{(C\leq6)}$, or substituted $acyl_{(C\leq6)}$;

R_{12} and R_{12}' are each independently hydrogen, $alkyl_{(C\leq6)}$, or substituted $alkyl_{(C\leq6)}$;

R_7 is carboxy or $alkyl_{(C\leq6)}$, $alkenyl_{(C\leq8)}$, $alkynyl_{(C\leq8)}$, $cycloalkyl_{(C\leq8)}$, $aryl_{(C\leq12)}$, $aralkyl_{(C\leq12)}$, −$alkanediyl_{(C\leq6)}$−OR_{13}, or a substituted version of any of these groups wherein:

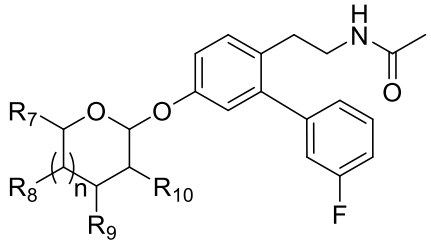
R_{13} is $alkyl_{(C\leq12)}$, substituted $alkyl_{(C\leq12)}$, $aralkyl_{(C\leq12)}$, or substituted $aralkyl_{(C\leq12)}$;

R_8 is hydroxy, $alkoxy_{(C\leq6)}$, or substituted $alkoxy_{(C\leq6)}$; and

R_9 and R_{10} are each independently hydroxy, $alkoxy_{(C\leq6)}$, or substituted $alkoxy_{(C\leq6)}$;

or a pharmaceutically acceptable salt of the formula.

4. The compound according to any one of claims 1-3 further defined as:



(VIII),

wherein:

n is 0, 1, or 2;

R_7 is carboxy or $alkyl_{(C\leq6)}$, $alkenyl_{(C\leq8)}$, $alkynyl_{(C\leq8)}$, $cycloalkyl_{(C\leq8)}$, $aryl_{(C\leq12)}$, $aralkyl_{(C\leq12)}$, $-alkanediyl_{(C\leq6)}-OR_{13}$, or a substituted version of any of these groups wherein:

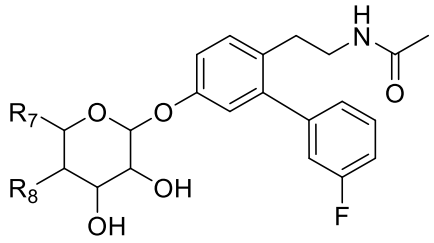
R_{13} is $alkyl_{(C\leq12)}$, substituted $alkyl_{(C\leq12)}$, $aralkyl_{(C\leq12)}$, or substituted $aralkyl_{(C\leq12)}$;

R_8 is hydroxy, $alkoxy_{(C\leq6)}$, or substituted $alkoxy_{(C\leq6)}$; and

R_9 and R_{10} are hydroxy;

or a pharmaceutically acceptable salt of the formula.

5. The compound according to any one of claims 1-4, wherein the compound is further defined as:



(IX)

wherein:

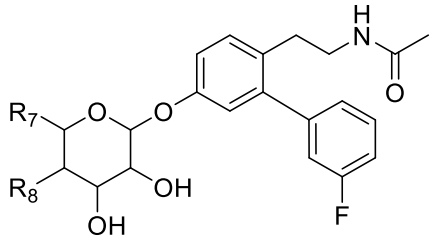
R_7 is carboxy or $alkyl_{(C\leq6)}$, $alkenyl_{(C\leq8)}$, $alkynyl_{(C\leq8)}$, $cycloalkyl_{(C\leq8)}$, $aryl_{(C\leq12)}$, $aralkyl_{(C\leq12)}$, $-alkanediyl_{(C\leq6)}-OR_{13}$, or a substituted version of any of these groups wherein:

R_{13} is $alkyl_{(C\leq12)}$, substituted $alkyl_{(C\leq12)}$, $aralkyl_{(C\leq12)}$, or substituted $aralkyl_{(C\leq12)}$; and

R_8 is hydroxy, $alkoxy_{(C\leq6)}$, or substituted $alkoxy_{(C\leq6)}$;

or a pharmaceutically acceptable salt of the formula.

6. The compound of claim 5 further defined as:



(IX)

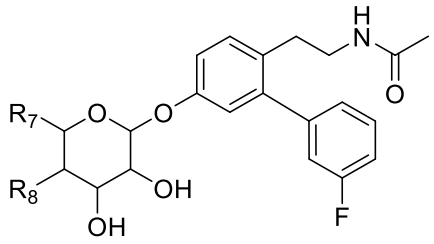
wherein:

R_7 is $alkyl_{(C\leq6)}$, $alkenyl_{(C\leq8)}$, $alkynyl_{(C\leq8)}$, or a substituted version of any of these groups; and

R_8 is hydroxy, $alkoxy_{(C\leq6)}$, or substituted $alkoxy_{(C\leq6)}$;

or a pharmaceutically acceptable salt of the formula.

7. The compound of claim 6 further defined as:



(IX)

wherein:

R_7 is $alkyl_{(C\leq6)}$ or substituted $alkyl_{(C\leq6)}$; and

R_8 is hydroxy, $alkoxy_{(C\leq6)}$, or substituted $alkoxy_{(C\leq6)}$;

or a pharmaceutically acceptable salt of the formula.

8. The compound of claim 1, wherein R_1 is hydrogen and R_2 is halo such as fluoro.

9. The compound of either claim 1 or claim 8, wherein X_1 is CR_{14}, wherein R_{14} is hydrogen or X_2 is CR_{15}, wherein R_{15} is hydrogen.

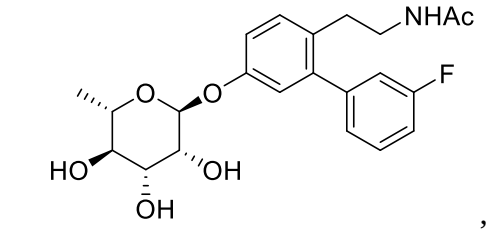
10. The compound according to any one of claims 1, 2, 8, and 9, wherein Y_1 is $-alkanediyl_{(C\leq6)}-$ and R_3 is $-NR_{11}R_{11}'$, wherein R_{11} is $acyl_{(C\leq6)}$ or substituted $acyl_{(C\leq6)}$, and R_{11}' is hydrogen.

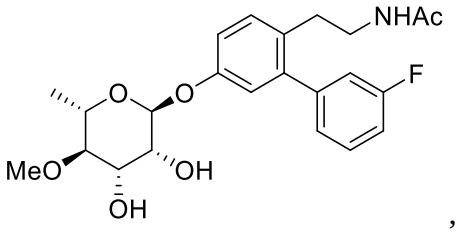
11. The compound according to any one of claims 1-3 and 8-10, wherein n is 1.

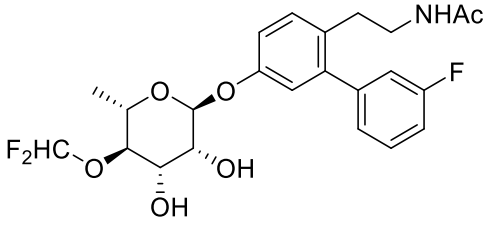
12. The compound according to any one of claims 1, 2, and 8-11, wherein R_9 is hydroxy, R_{10} is hydroxy, or R_8 is hydroxy, $alkoxy_{(C\leq6)}$, or substituted $alkoxy_{(C\leq6)}$.

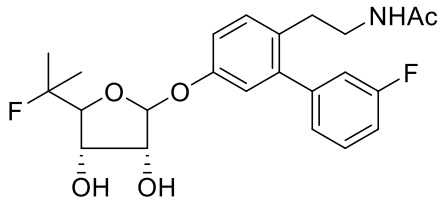
13. The compound according to any one of claims 1-12, wherein R_7 is $alkyl_{(C\leq6)}$ or substituted $alkyl_{(C\leq6)}$.

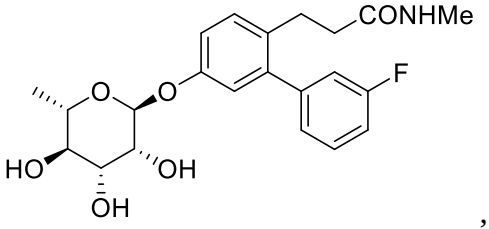
14. The compound of claim 1, wherein the compound is further defined as:

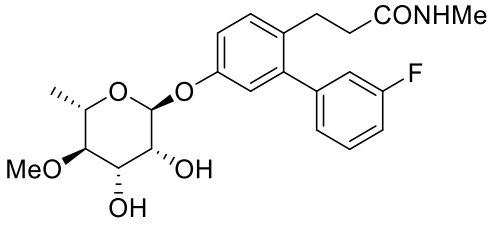


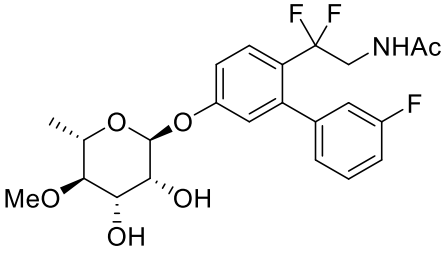
,


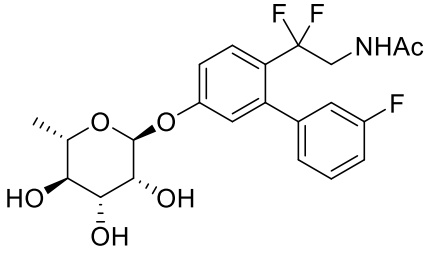
,


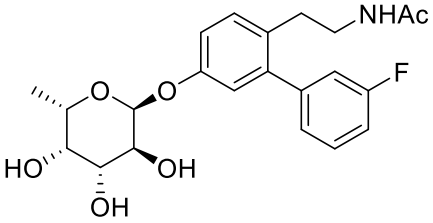
,


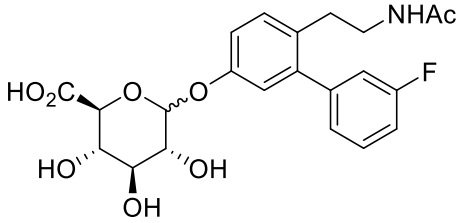
,


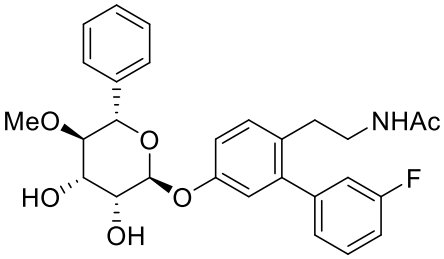
,


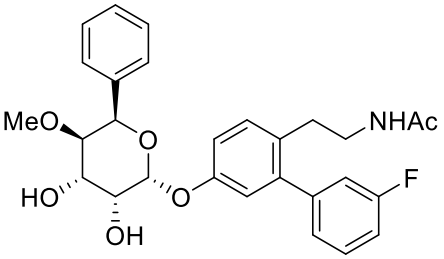
,


,


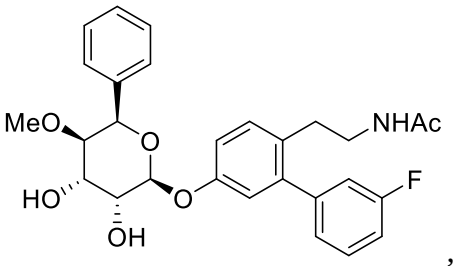
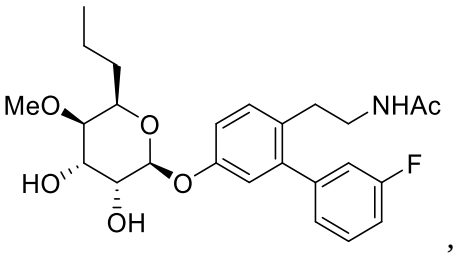
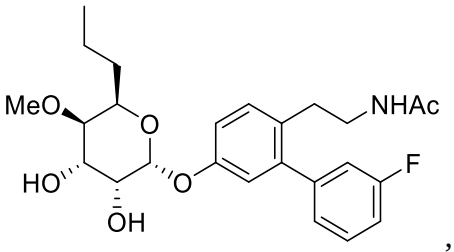
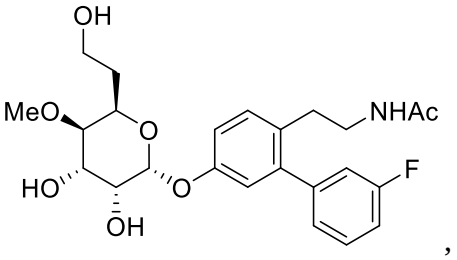
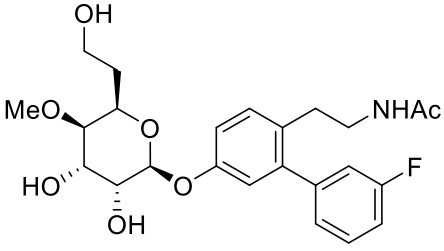
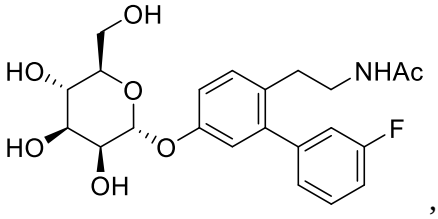
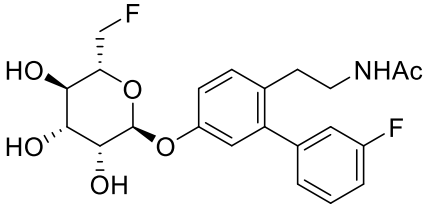
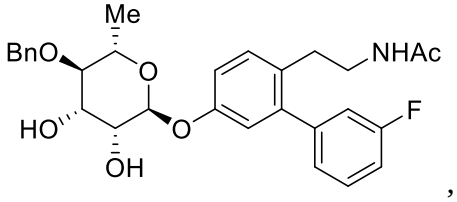
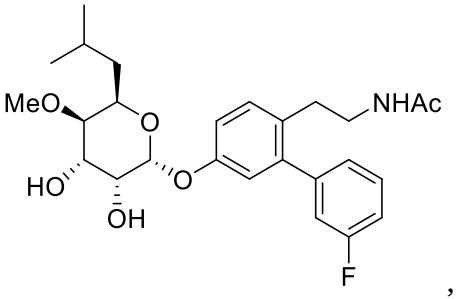
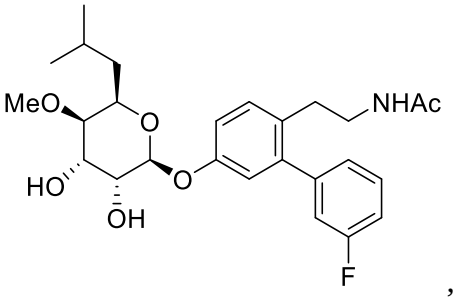
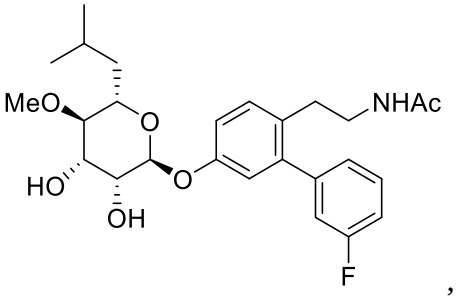
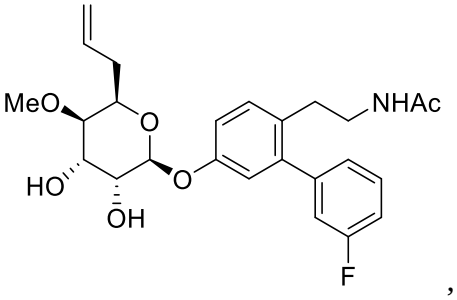
,


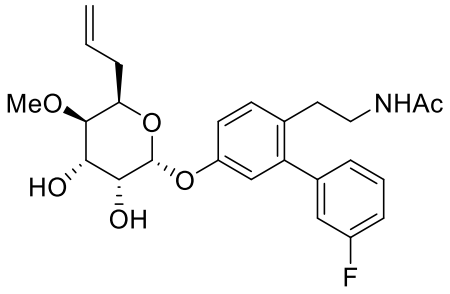
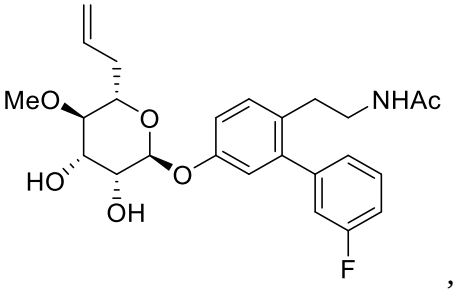
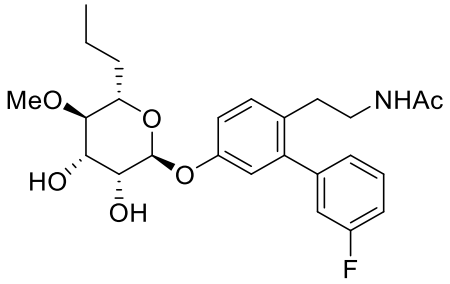
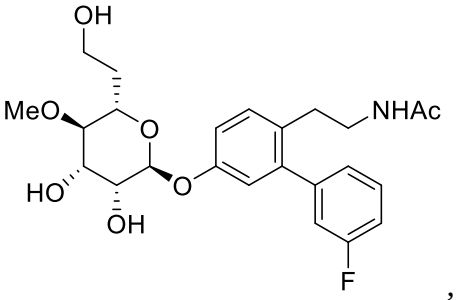
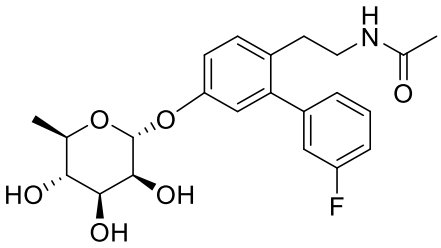
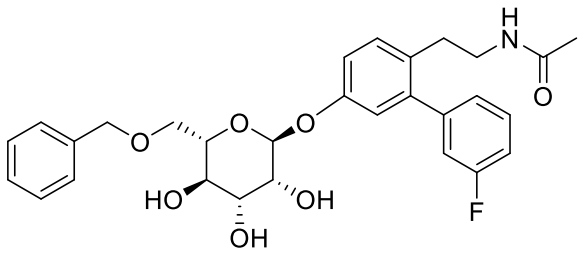
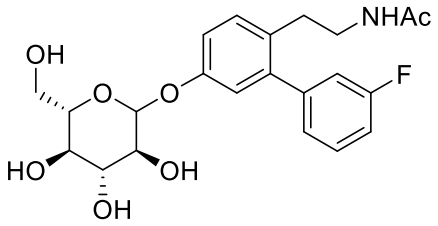
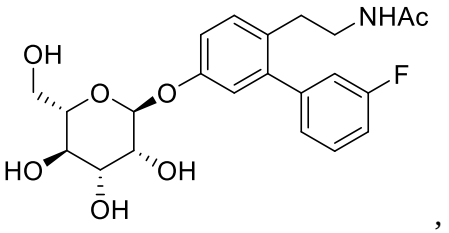
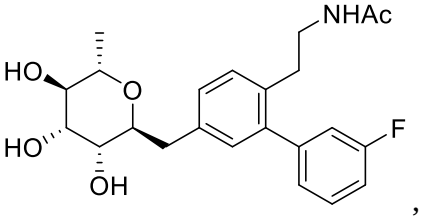
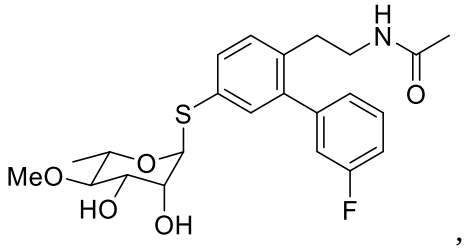
,


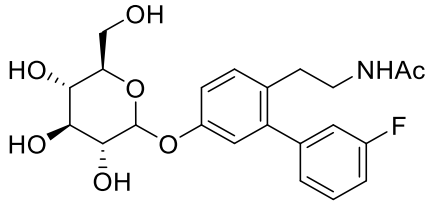
,


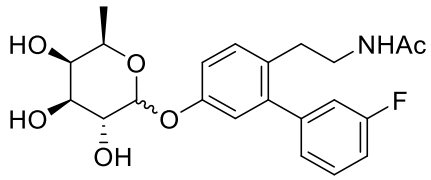
,


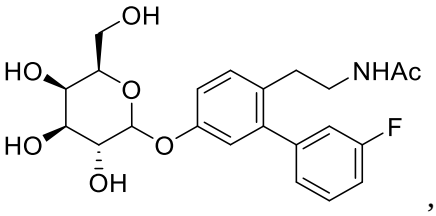
,

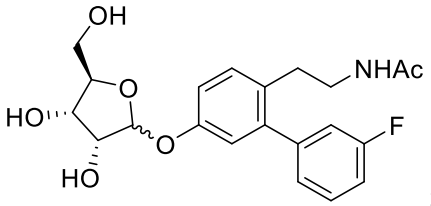

MeO
O
NHAc
HO
O
F
OH
,

MeO
O
NHAc
HO
O
F
OH
,

MeO
O
NHAc
HO
O
F
OH
,

OH
MeO
O
NHAc
HO
O
F
OH
,

OH
MeO
O
NHAc
HO
O
F
OH
,

OH
HO
O
NHAc
HO
O
F
OH
,

F
HO
O
NHAc
HO
O
F
OH
,

Me
BnO
O
NHAc
HO
O
F
OH
,

MeO
O
NHAc
HO
O
F
OH
,

MeO
O
NHAc
HO
O
F
OH
,

MeO
O
NHAc
HO
O
F
OH
,

MeO
O
NHAc
HO
O
F
OH
,


MeO
O
HO
OH
O
NHAc
F
,

MeO
O
HO
OH
O
NHAc
F
,

MeO
O
HO
OH
O
NHAc
F
,

OH
MeO
O
HO
OH
O
NHAc
F
,

H
N
O
O
O
HO
OH
OH
F
,

H
N
O
O
O
O
HO
OH
OH
F
,

OH
O
O
NHAc
F
HO
OH
OH
,

OH
O
O
NHAc
F
HO
OH
OH
,

HO
O
HO
OH
NHAc
F
,

H
N
O
S
O
MeO
HO
OH
F
,



,


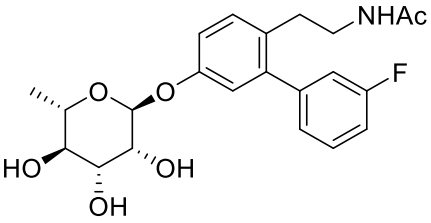
, ,


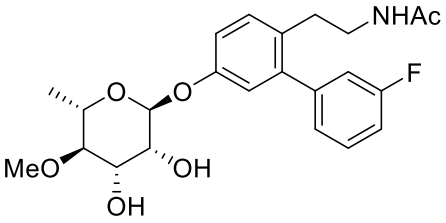
, or


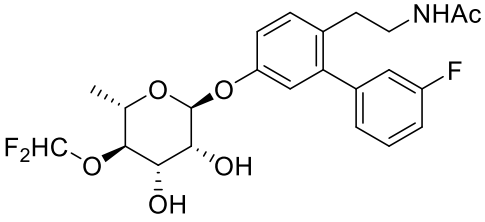
;

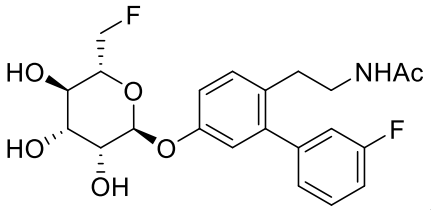
or a pharmaceutically acceptable salt of any of these formulas.

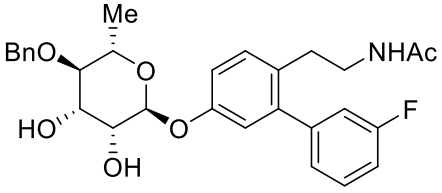
15. The compound of claim 14, wherein the compound is further defined as:

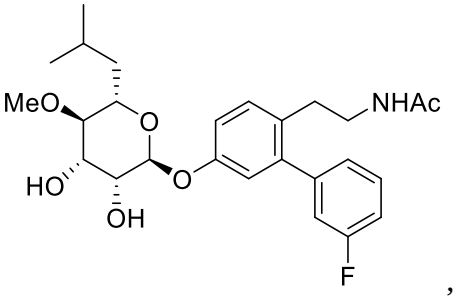


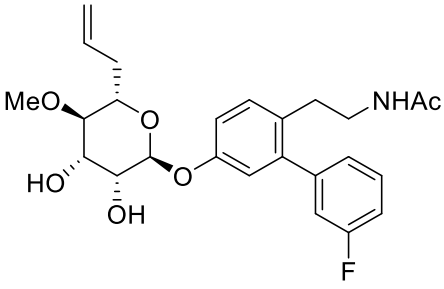
,


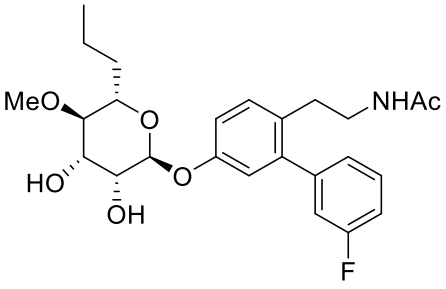
,


,


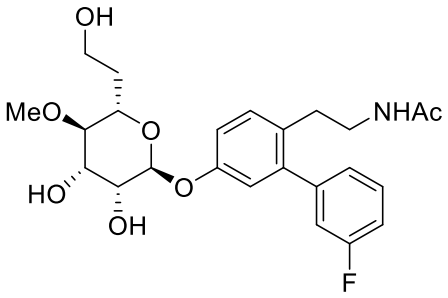
,


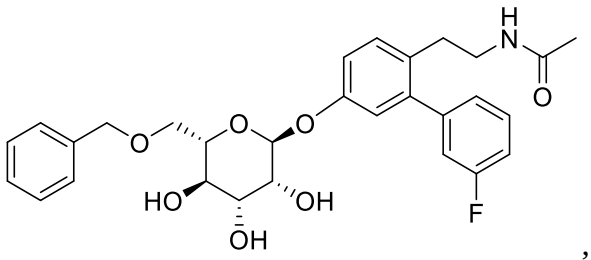
,


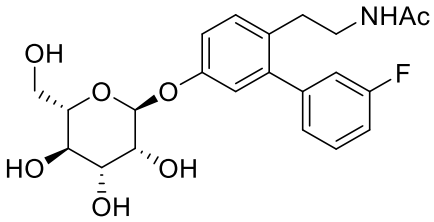
,


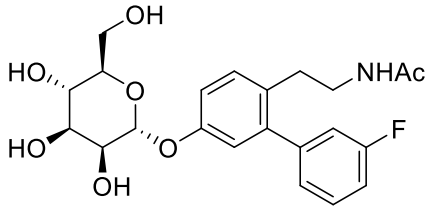
,


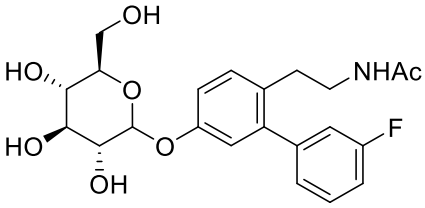
,

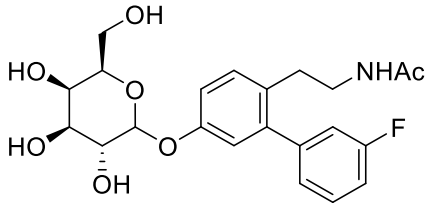


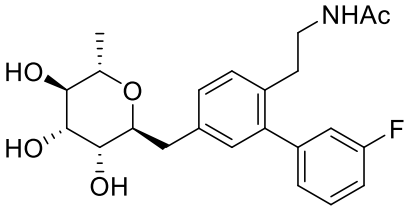
,


,


,


,


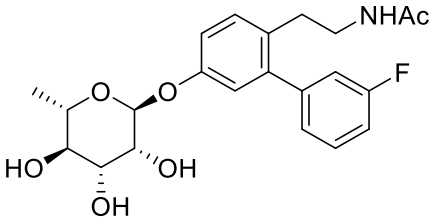
,


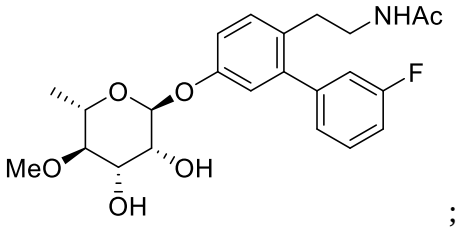
, or


;

or a pharmaceutically acceptable salt of any of these formulas.

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

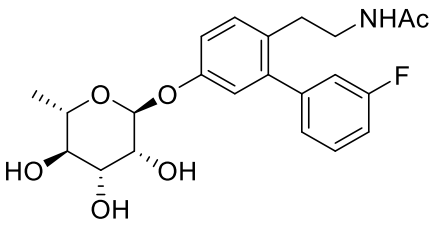


or


;

or a pharmaceutically acceptable salt of any of these formulas.

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



;

or a pharmaceutically acceptable salt of this formula.

18. A pharmaceutical composition comprising:

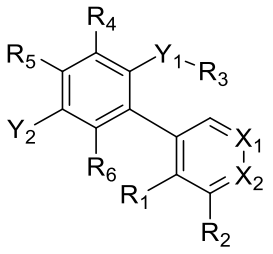
(A) a compound according to any one of claims 1-17; and

(B) an excipient.

19. A therapeutically effective amount of a compound or composition according to any one of claims 1-18 for use in therapy.

20. A method of making a compound according to any one of claims 1-17, comprising reacting (a) with (b) in the presence of a coupling agent:

(a) a compound of the formula:



(XXXIII),

wherein:

n is 0, 1, or 2;

Y_1 is −alkanediyl$_{(C\leq 6)}$−, or substituted −alkanediyl$_{(C\leq 6)}$−;

Y_2 is hydroxy;

R_1 is hydrogen, halo, hydroxy, or alkyl$_{(C\leq 6)}$, alkoxy$_{(C\leq 6)}$, or a substituted version of any of either group;

R_2 is hydrogen, halo, hydroxy, or alkyl$_{(C\leq 6)}$, alkoxy$_{(C\leq 6)}$, or a substituted version of any of either group;

R_3 is carboxy, –$NR_{11}R_{11}'$, or –$C(O)NR_{12}R_{12}'$, wherein:

R_{11} and R_{11}' are each independently hydrogen, $alkyl_{(C\leq6)}$, substituted $alkyl_{(C\leq6)}$, $acyl_{(C\leq6)}$, or substituted $acyl_{(C\leq6)}$;

R_{12} and R_{12}' are each independently hydrogen, $alkyl_{(C\leq6)}$, or substituted $alkyl_{(C\leq6)}$;

R_4, R_5, and R_6 are each hydrogen;

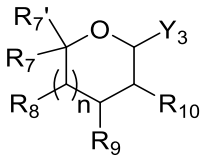
X_1 is CR_{14} or N, wherein:

R_{14} is hydrogen, halo, hydroxy, or $alkyl_{(C\leq6)}$, $alkoxy_{(C\leq6)}$, or a substituted version of any of either group; or

X_2 is CR_{15} or N, wherein:

R_{15} is hydrogen, halo, hydroxy, or $alkyl_{(C\leq6)}$, $alkoxy_{(C\leq6)}$, or a substituted version of any of either group;

(b) a compound of the formula:



(XXXIV),

wherein:

n is 0, 1, or 2;

Y_3 is hydroxy, halo, $acyloxy_{(C\leq8)}$, $iminooxy_{(C\leq8)}$,or a substituted version of either of these groups;

R_7 is carboxy, or $alkyl_{(C\leq8)}$, $alkenyl_{(C\leq8)}$, $alkynyl_{(C\leq8)}$, $cycloalkyl_{(C\leq8)}$, $aryl_{(C\leq12)}$, $aralkyl_{(C\leq12)}$, $-alkanediyl_{(C\leq6)}-OR_{13}$, or a substituted version of any of these groups wherein:

R_{13} is $aralkyl_{(C\leq12)}$ or substituted $aralkyl_{(C\leq12)}$;

R_7' is hydrogen;

R_8 is hydroxy, or $alkoxy_{(C\leq6)}$, $aralkoxy_{(C\leq12)}$, or a substituted version of either of these groups; and

R_9 and R_{10} are each independently hydroxy, $alkoxy_{(C\leq6)}$, or substituted $alkoxy_{(C\leq6)}$.