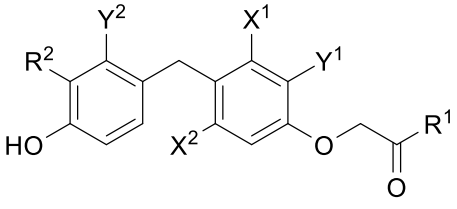
BRIEF SUMMARY

In a first aspect of the present disclosure, there is provided a compound having the structure of Formula (I):



(I)

or a pharmaceutically acceptable hydrate, solvate, or salt thereof, wherein:

X^1 is lower alkyl, lower alkenyl, lower haloalkyl, or halo;

X^2 is lower alkyl, lower alkenyl, lower haloalkyl, or halo;

Y^1 and Y^2 are each, independently, H, cyano, halogen, lower alkyl, or lower alkoxy, wherein at least one of Y^1 and Y^2 is not H;

R^1 is $-NR^{1a}R^{1b}$ or $-OR^{1c}$;

R^{1a} and R^{1b} are each, independently, H, lower alkyl, lower alkenyl, lower alkynyl, carbocycle, carbocyclealkyl, heterocycle, or heterocyclealkyl, or R^{1a} and R^{1b} taken together with the nitrogen atom to which they are attached form heterocycle;

R^{1c} is H, lower alkyl, carbocycle, heterocycle, carbocyclealkyl, or heterocyclealkyl; and

R^2 is lower alkyl, lower alkenyl, carbocycle, heterocycle, carbocyclealkyl, or heterocyclealkyl;

wherein R^{1a}, R^{1b}, R^{1c}, and R^2 are each, independently, optionally substituted with one or more halo, lower alkyl, lower haloalkyl, cyano, $-OR'$, $-NR'R''$, =O, =S, $-S(O)_2R'$ or $-S(O)_2OR'$, wherein R' and R'' are each, independently, H, lower alkyl, or lower haloalkyl.

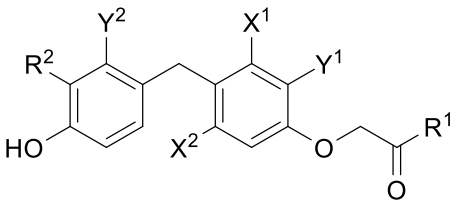
In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising a compound as disclosed herein, or a pharmaceutically acceptable hydrate, solvate, or salt thereof, and a pharmaceutically acceptable excipient.

In yet another aspect of the present disclosure, there is provided a use of a compound as disclosed herein, or a pharmaceutically acceptable hydrate, solvate, or salt thereof, in the manufacture of a medicament for treating a neurodegenerative disease;

wherein the neurodegenerative disease is adult Refsum disease, Alexander disease, Alzheimer's disease, Balo concentric sclerosis, Canavan disease, central pontine myelinolysis, cerebral palsy, cerebrotendineous xanthomatosis, chronic inflammatory demyelinating polyneuropathy, Devic's syndrome, diffuse myelinoclastic sclerosis, idiopathic inflammatory demyelinating disease, infantile Refsum disease, Krabbe disease, Leber hereditary optic neuropathy, Marburg multiple sclerosis, Marchiafava-Bignami disease, metachromatic leukodystrophy, multifocal motor neuropathy, paraproteinemic demyelinating polyneuropathy, Pelizaeus-Merzbacher disease, peroneal muscular atrophy, progressive multifocal leukoencephalopathy, transverse myelitis, tropical spastic paraparesis, van der Knaap disease, X-linked adrenoleukodystrophy, or Zellweger syndrome.

In a further aspect of the present disclosure, there is provided a compound as disclosed herein, or a pharmaceutically acceptable hydrate, solvate, or salt thereof, for use in therapy.

Disclosed herein are compounds according to Formula I:



(I)

or a pharmaceutically acceptable isomer, racemate, hydrate, solvate, isotope, or salt thereof, wherein R^1, R^2, X^1, X^2, Y^1, and Y^2 are as defined below.

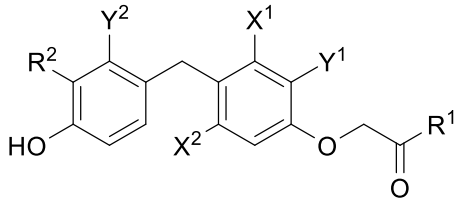
In an example, a pharmaceutical composition is provided comprising a compound having the structure of Formula (I), or a pharmaceutically acceptable isomer, racemate, hydrate, solvate, isotope, or salt thereof, in combination with a pharmaceutically acceptable carrier, diluent, or excipient. In an example, the pharmaceutical composition is for use in treating a neurodegenerative disorder including neurodegenerative disorders classified as a demyelinating disease such as X-linked adrenoleukodystrophy or multiple sclerosis. In another example, the pharmaceutical composition is for use in treating a medical condition associated increased activity of TGF-β, such as a fibrotic disease.

In an example, a method is provided for treating a neurodegenerative disorder in a subject in need thereof, comprising administering a compound having the structure of Formula (I), or a pharmaceutically acceptable salt or composition comprising the same. In some examples, the neurodegenerative disorder can be classified as a demyelinating disease such as X-linked adrenoleukodystrophy or multiple sclerosis.

In another example, a method is provided for treating a medical condition associated with over-expression of TGF-β in a subject in need thereof, comprising administering a compound having the structure of Formula (I), or a pharmaceutically acceptable salt or composition comprising the same. In some examples, the medical condition associated with over-expression of TGF-β is a fibrotic disease.

CLAIMS

1. A compound having the structure of Formula (I):



(I)

or a pharmaceutically acceptable hydrate, solvate, or salt thereof, wherein:

X^1 is lower alkyl, lower alkenyl, lower haloalkyl, or halo;

X^2 is lower alkyl, lower alkenyl, lower haloalkyl, or halo;

Y^1 and Y^2 are each, independently, H, cyano, halogen, lower alkyl, or lower alkoxy, wherein at least one of Y^1 and Y^2 is not H;

R^1 is $-NR^{1a}R^{1b}$ or $-OR^{1c}$;

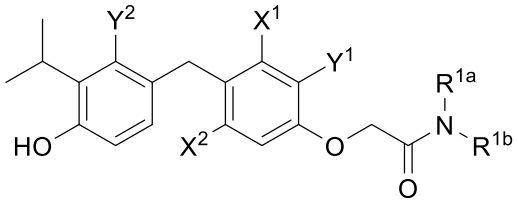
R^{1a} and R^{1b} are each, independently, H, lower alkyl, lower alkenyl, lower alkynyl, carbocycle, carbocyclealkyl, heterocycle, or heterocyclealkyl, or R^{1a} and R^{1b} taken together with the nitrogen atom to which they are attached form heterocycle;

R^{1c} is H, lower alkyl, carbocycle, heterocycle, carbocyclealkyl, or heterocyclealkyl; and

R^2 is lower alkyl, lower alkenyl, carbocycle, heterocycle, carbocyclealkyl, or heterocyclealkyl;

wherein R^{1a}, R^{1b}, R^{1c}, and R^2 are each, independently, optionally substituted with one or more halo, lower alkyl, lower haloalkyl, cyano, $-OR'$, $-NR'R''$, =O, =S, $-S(O)_2R'$ or $-S(O)_2OR'$, wherein R' and R'' are each, independently, H, lower alkyl, or lower haloalkyl.

2. The compound of claim 1, having the structure of Formula (II-A):



(II-A)

or a pharmaceutically acceptable hydrate, solvate, or salt thereof, wherein:

X^1 is lower alkyl, lower alkenyl, lower haloalkyl, or halo;

X^2 is lower alkyl, lower alkenyl, lower haloalkyl, or halo;

Y^1 and Y^2 are each, independently, H, cyano, halogen, lower alkyl, or lower alkoxy, wherein at least one of Y^1 and Y^2 is not H; and

R^{1a} and R^{1b} are each, independently, H, lower alkyl, lower alkenyl, lower alkynyl, carbocycle, carbocyclealkyl, heterocycle, or heterocyclealkyl, or R^{1a} and R^{1b} taken together with the nitrogen atom to which they are attached form heterocycle;

wherein R^{1a} and R^{1b} are each, independently, optionally substituted with one or more halo, cyano, $-OR'$, $-NR'R''$, =O, =S, $-S(O)_2R'$ or $-S(O)_2OR'$, wherein R' and R'' are each, independently, H, lower alkyl, or lower haloalkyl.

3. The compound of claim 1 or 2, or a pharmaceutically acceptable hydrate, solvate, or salt thereof, wherein:

R^{1a} is lower alkyl; and

R^{1b} is H.

4. The compound of any one of claims 1–3, or a pharmaceutically acceptable hydrate, solvate, or salt thereof, wherein:

X^1 is lower alkyl.

5. The compound of any one of claims 1–3, or a pharmaceutically acceptable hydrate, solvate, or salt thereof, wherein:

X^1 is halo.

6. The compound of any one of claims 1–5, or a pharmaceutically acceptable hydrate, solvate, or salt thereof, wherein:

X^2 is lower alkyl.

7. The compound of any one of claims 1–5, or a pharmaceutically acceptable hydrate, solvate, or salt thereof, wherein:

X^2 is halo.

8. The compound of any one of claims 1–3, or a pharmaceutically acceptable hydrate, solvate, or salt thereof, wherein:

X^1 is Cl; and

X^2 is Cl.

9. The compound of any one of claims 1-8, or a pharmaceutically acceptable hydrate, solvate, or salt thereof, wherein:

Y^1 is halogen.

10. The compound of any one of claims 1–8, or a pharmaceutically acceptable hydrate, solvate, or salt thereof, wherein:

Y^1 is H.

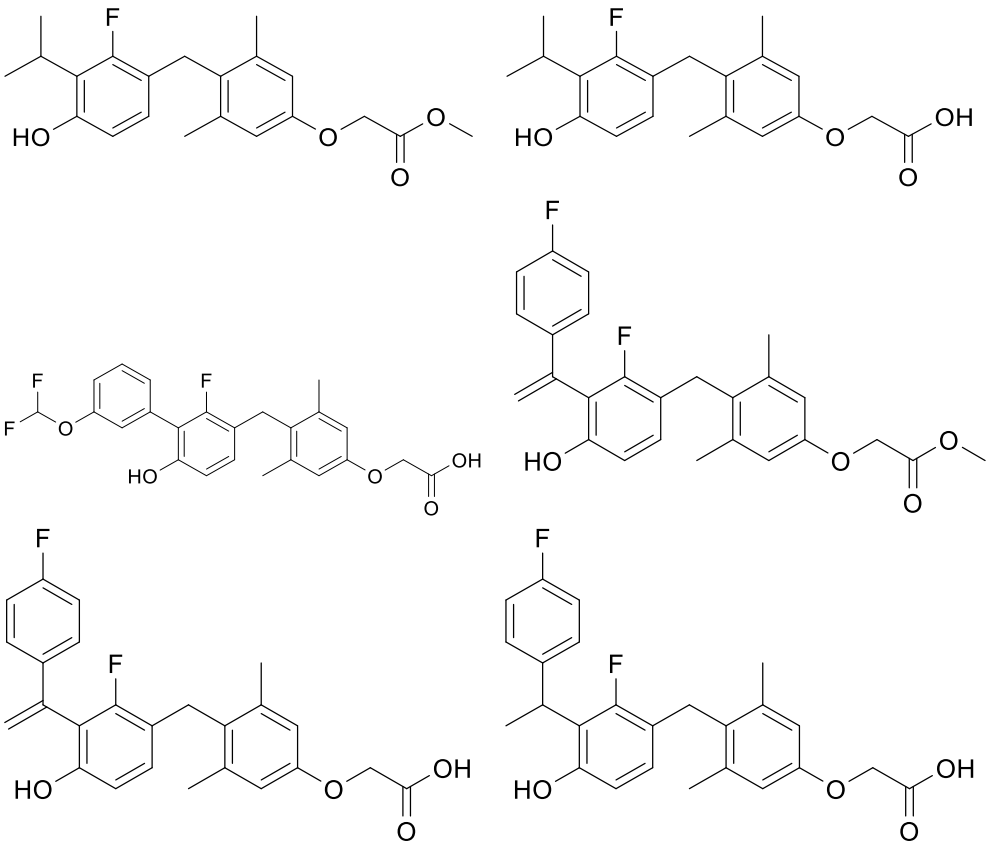
11. The compound of any one of claims 1–10, or a pharmaceutically acceptable hydrate, solvate, or salt thereof, wherein:

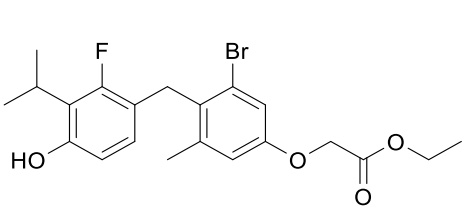
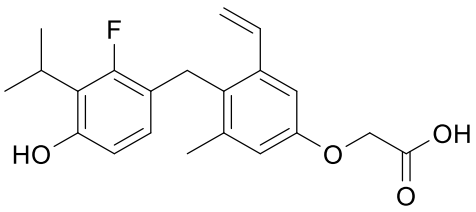
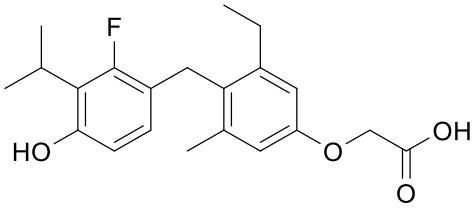
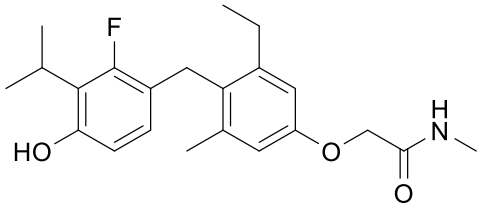
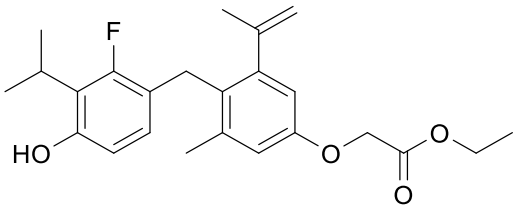
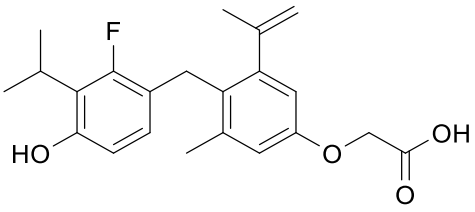
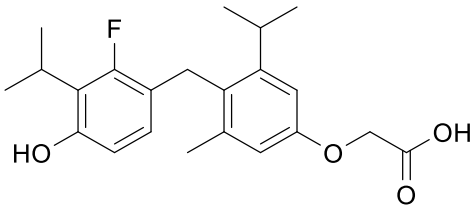
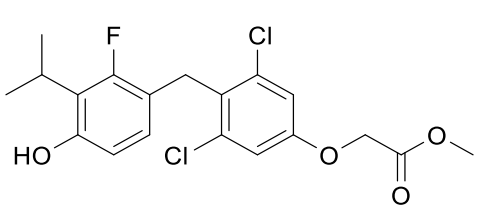
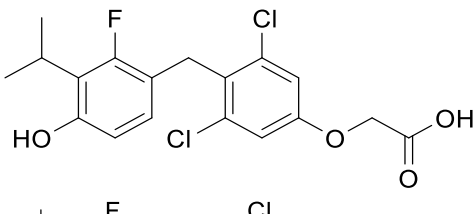
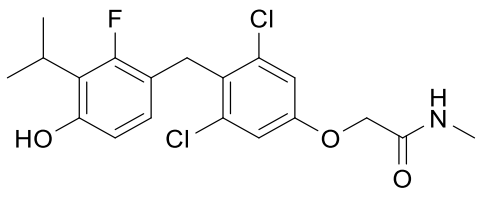
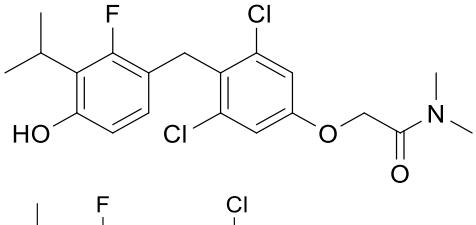
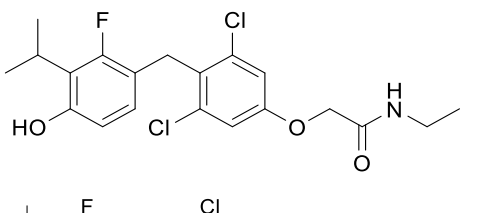
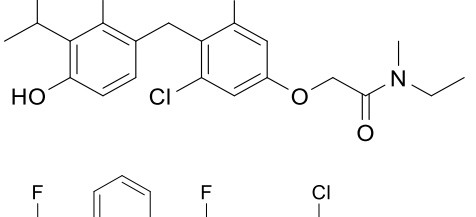
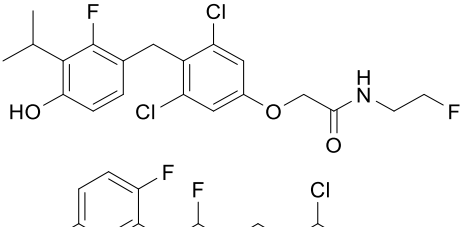
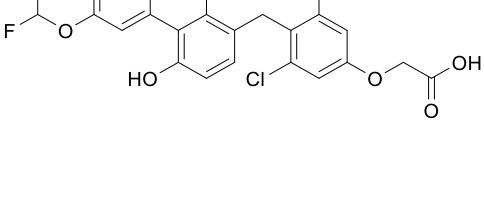
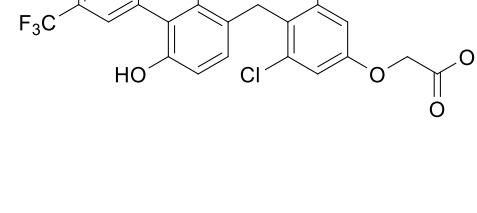
Y^2 is halogen.

12. The compound of any one of claims 1–10, or a pharmaceutically acceptable hydrate, solvate, or salt thereof, wherein:

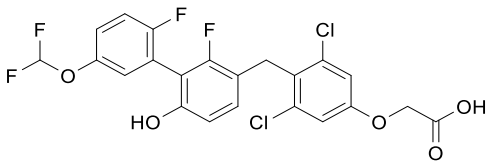
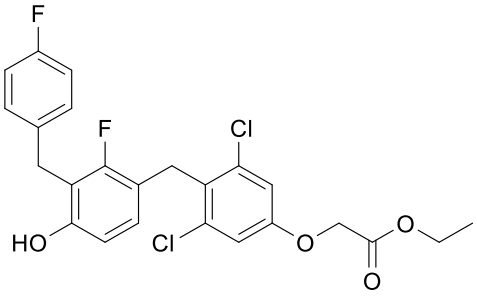
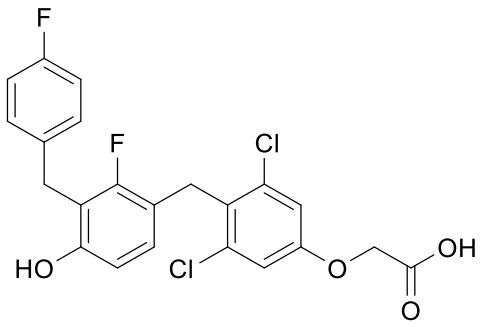
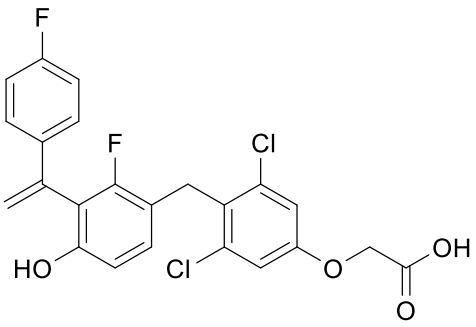
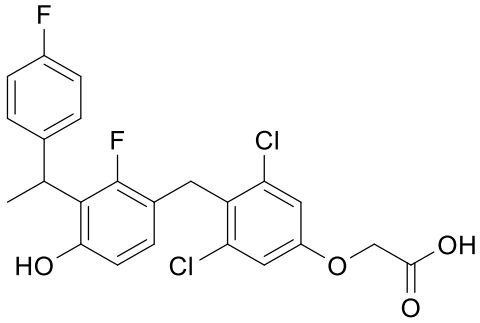
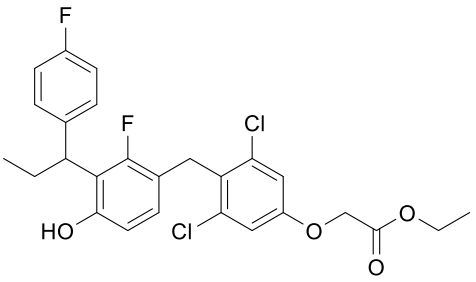
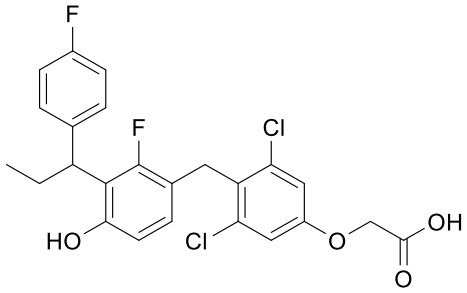
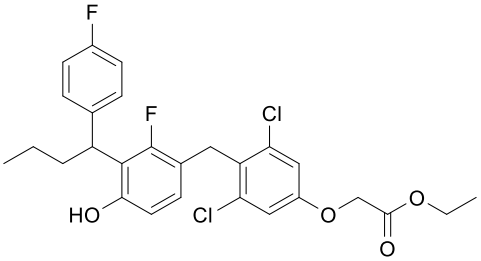
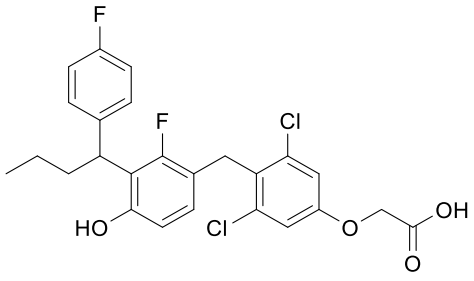
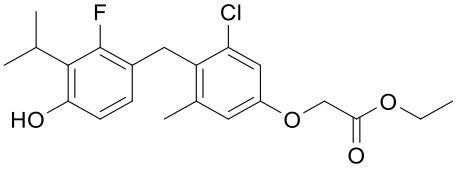
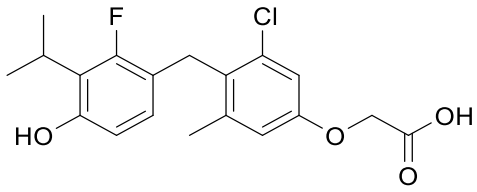
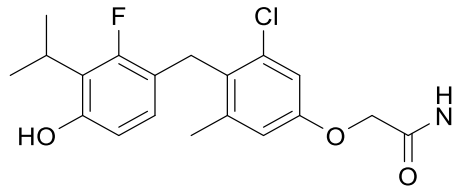
Y^2 is H.

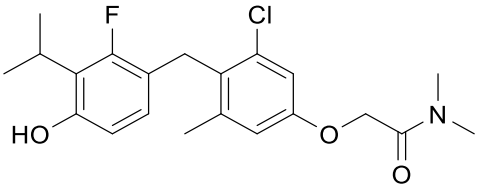
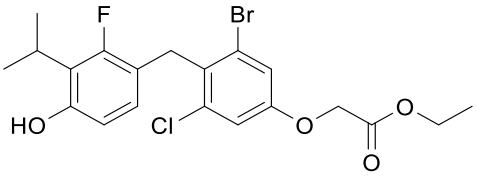
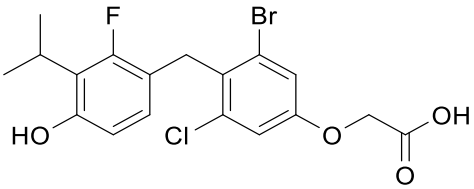
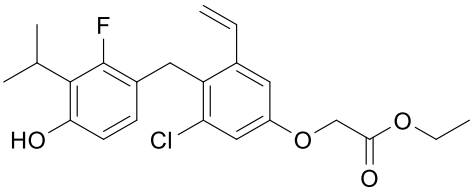
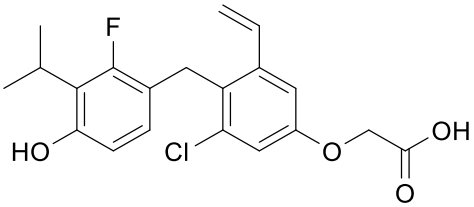
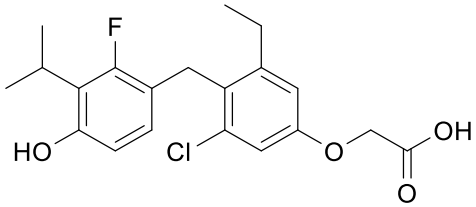
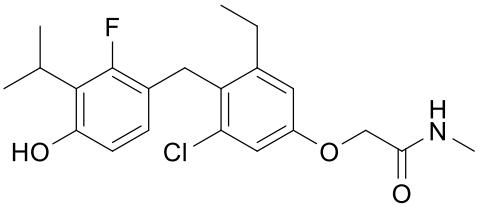
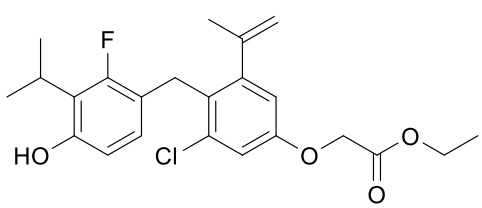
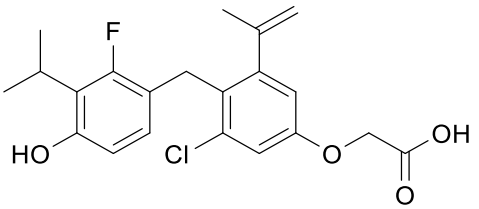
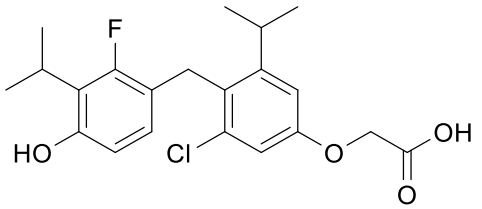
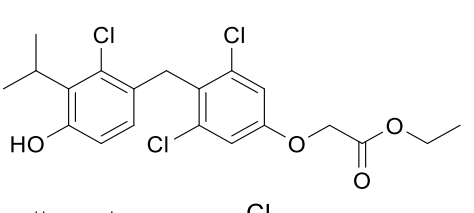
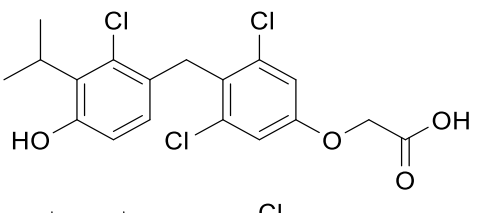
13. The compound of claim 1, or a pharmaceutically acceptable hydrate, solvate, or salt thereof, having the structure of any one of the following compounds:

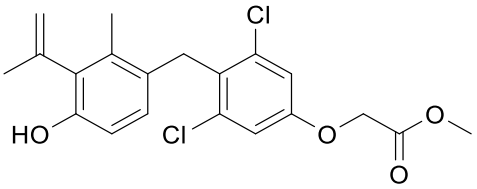
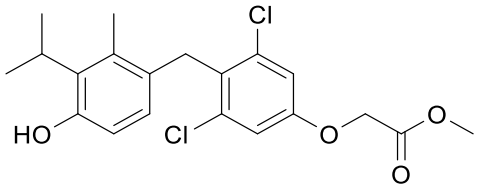
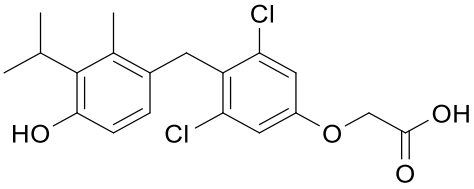
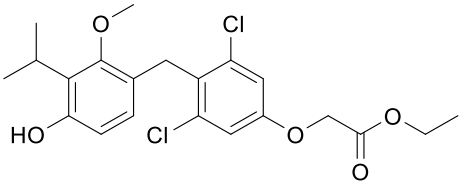
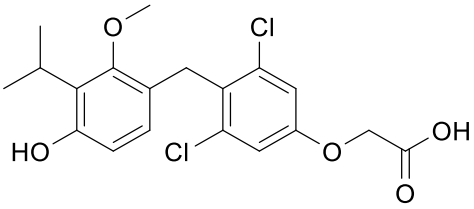
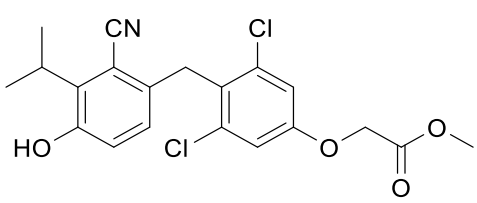


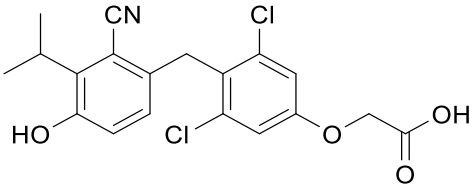
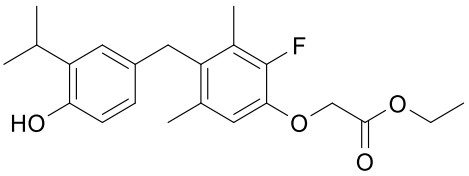
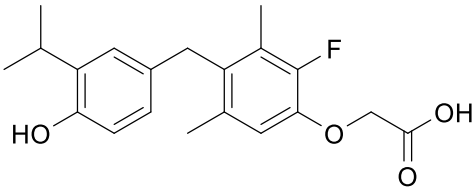
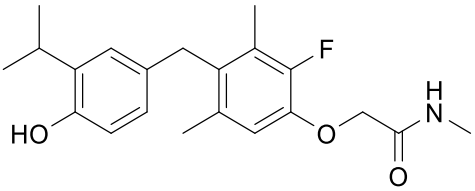
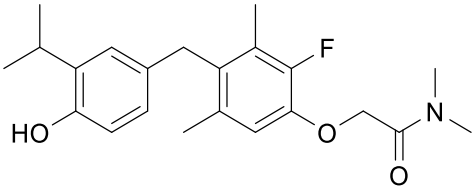
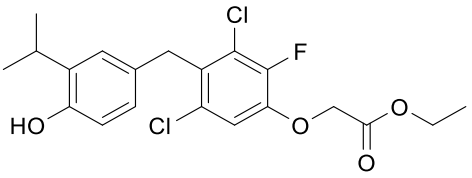
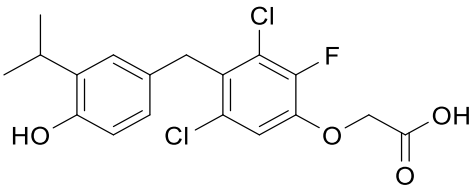
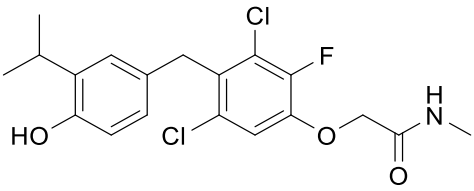
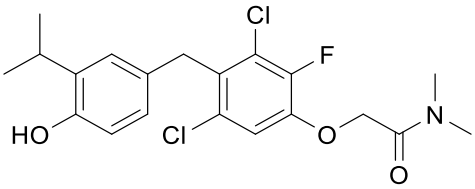
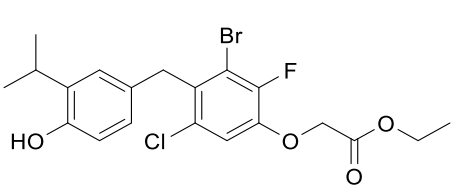

















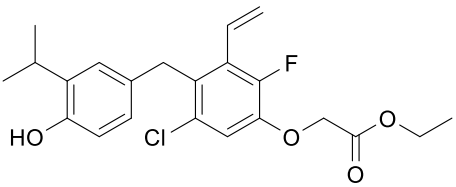
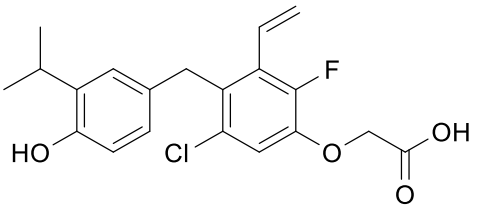
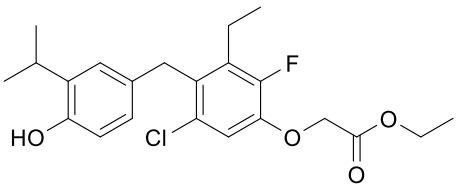
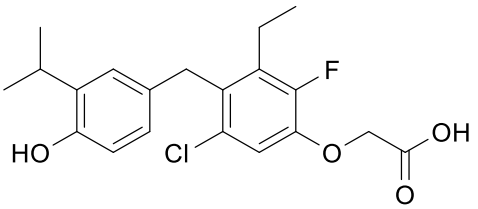
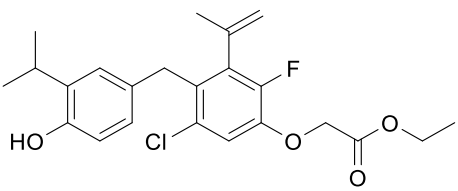
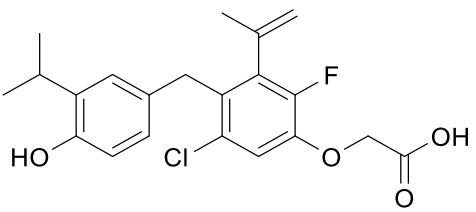
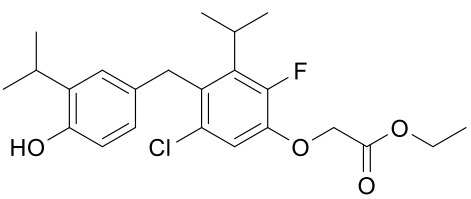
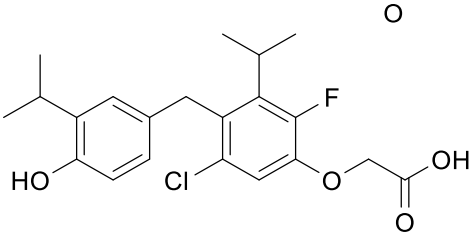


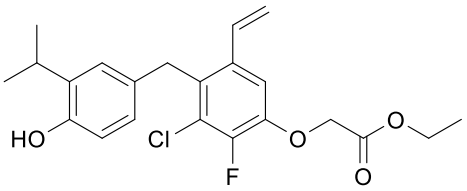
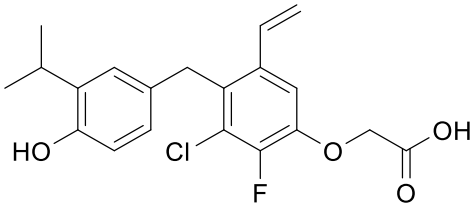
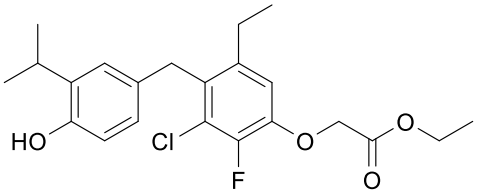
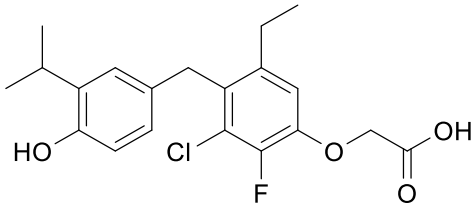
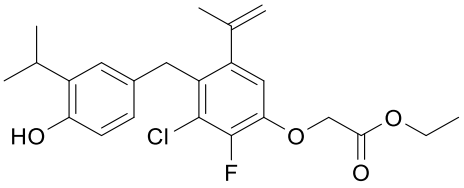
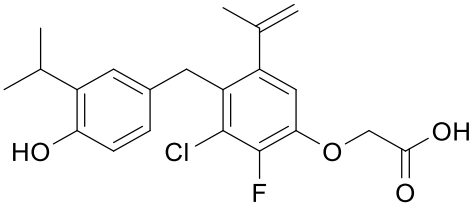
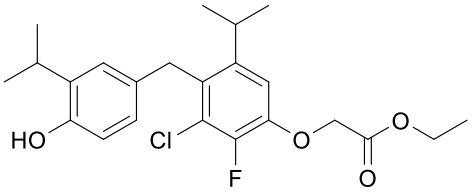
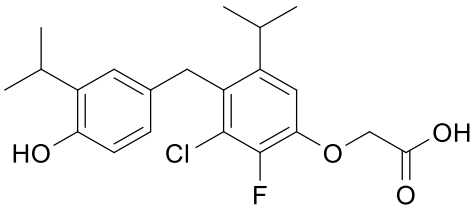
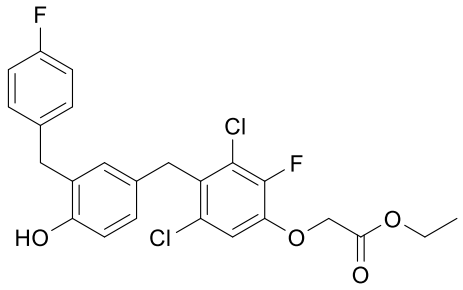
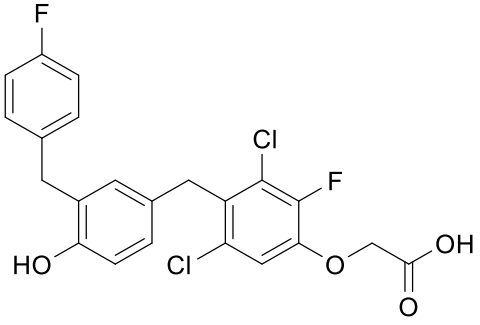
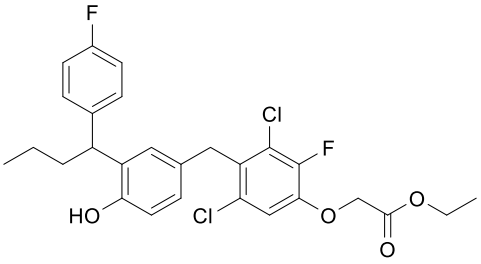
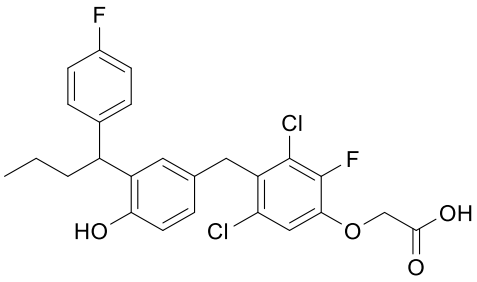
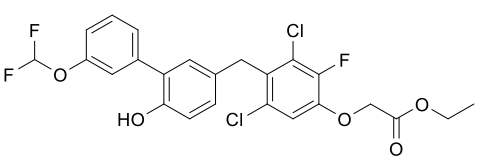
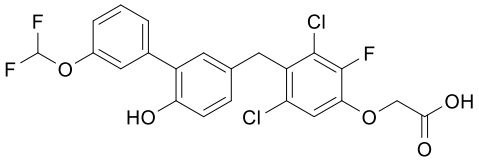
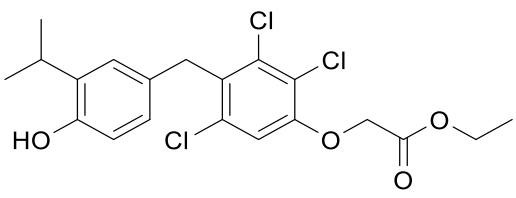
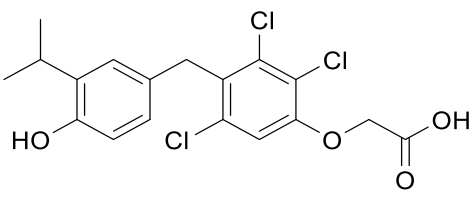













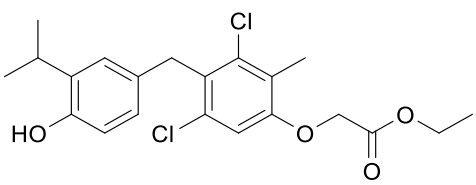
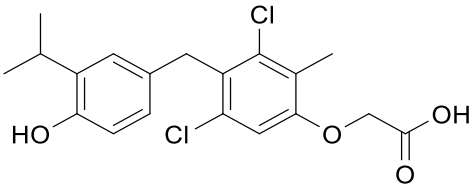
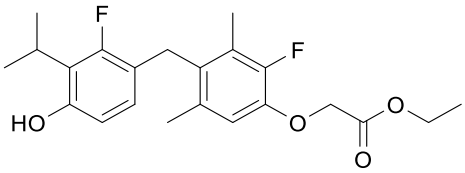
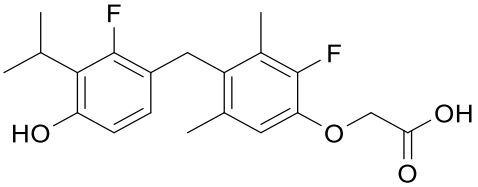
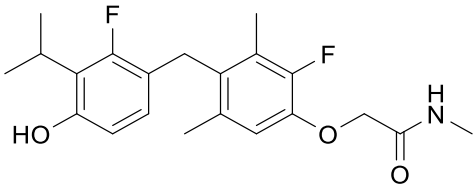
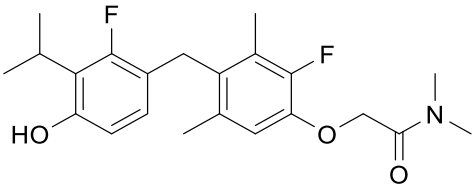
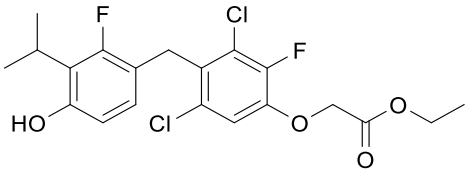
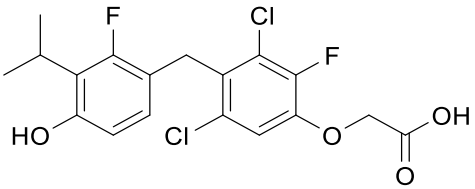
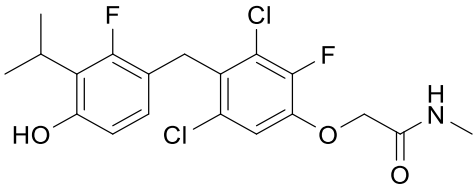
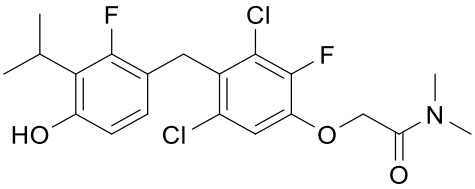
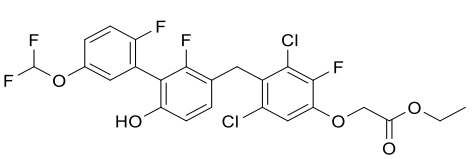
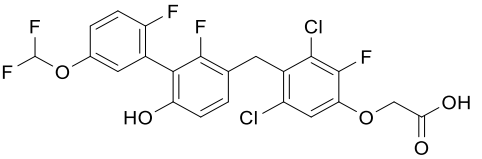













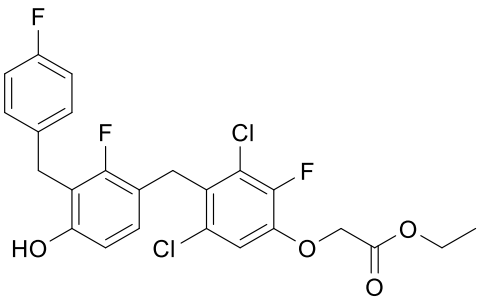
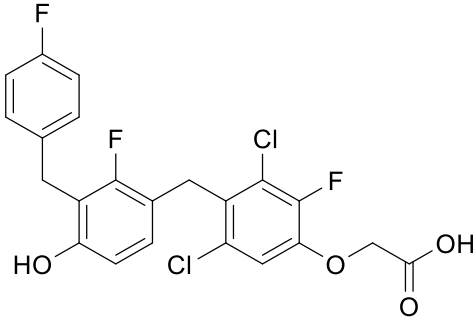
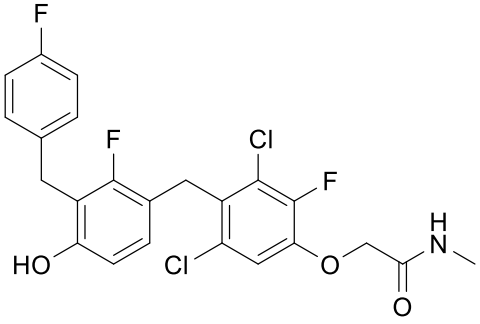
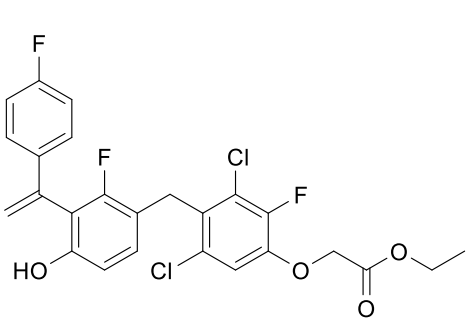







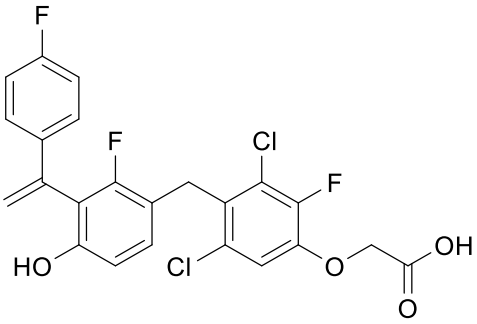
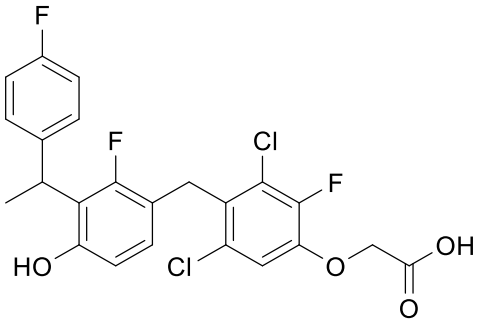
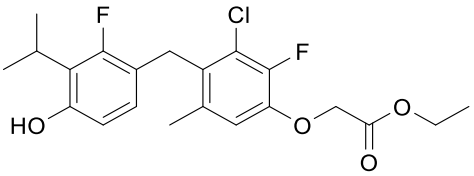
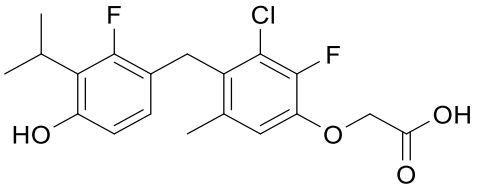
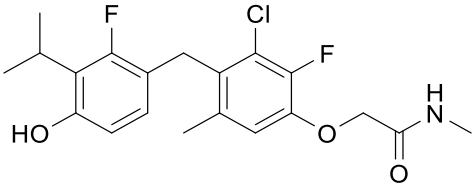
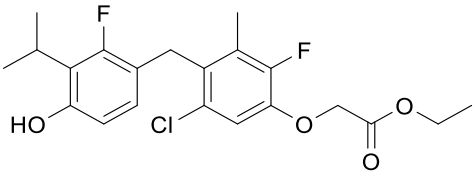
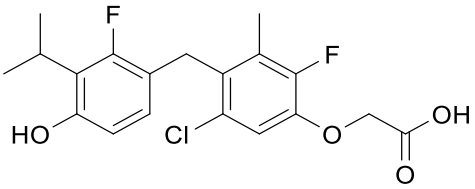
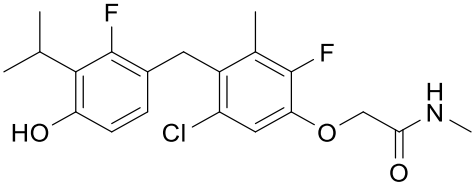
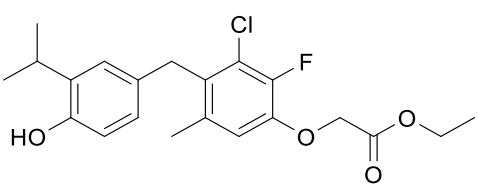
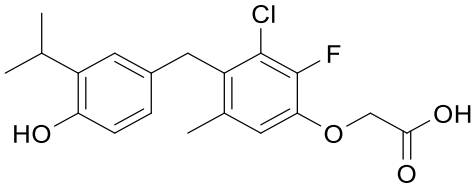
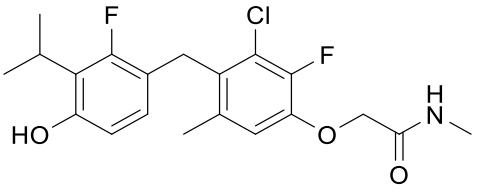
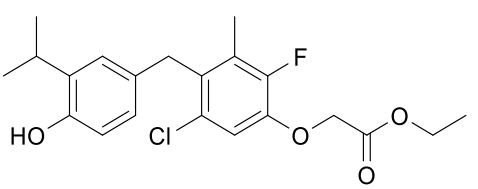
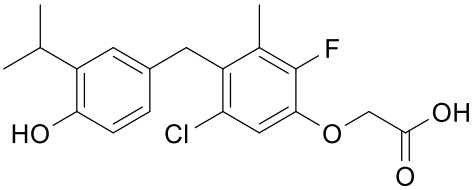
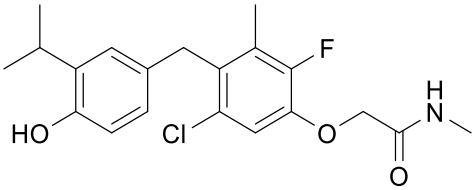
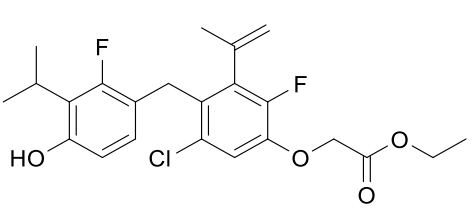
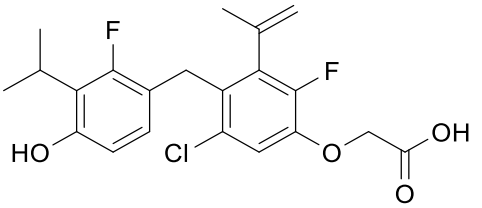











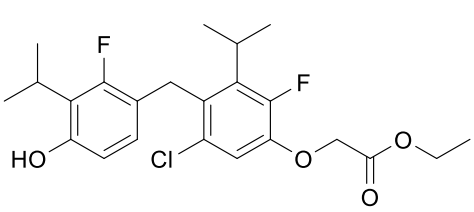
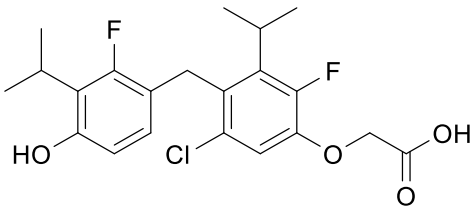
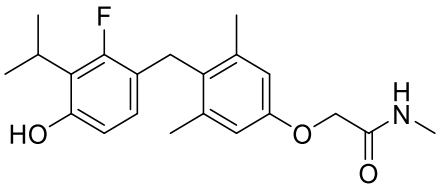
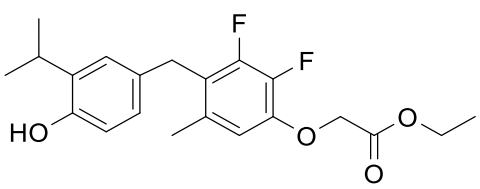
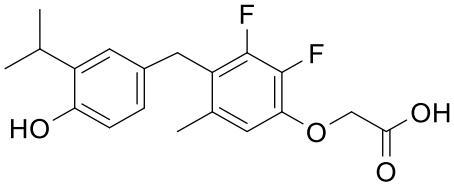
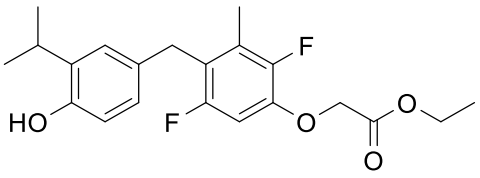
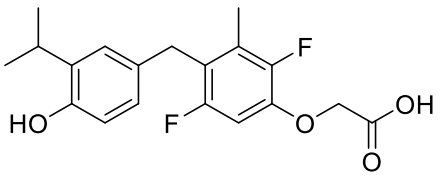
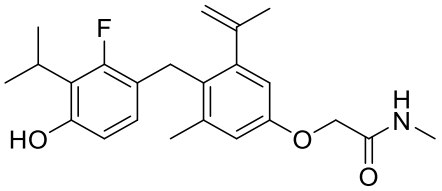

















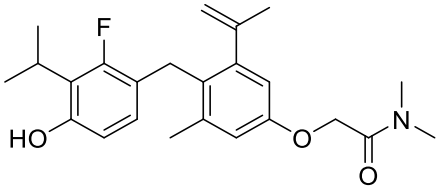
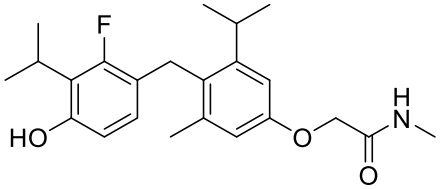
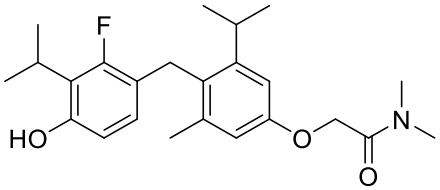
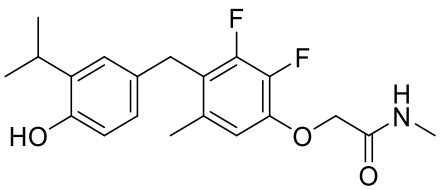
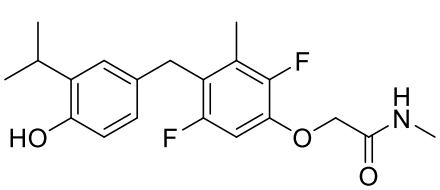
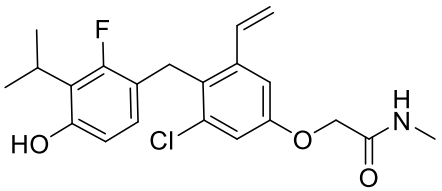
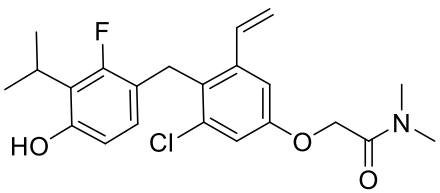
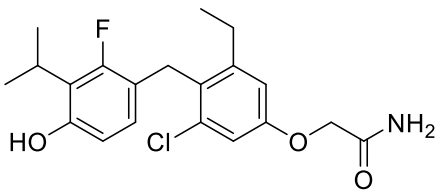
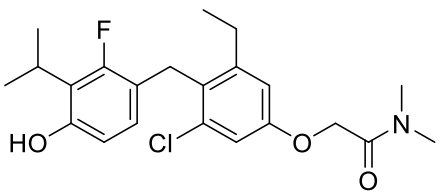
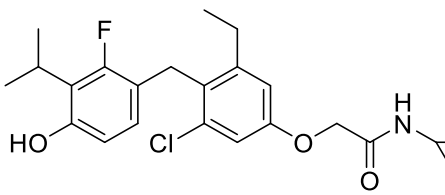













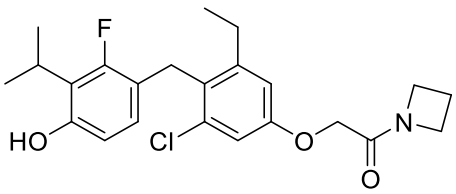

















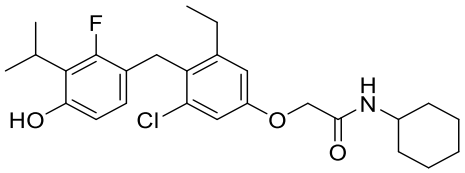


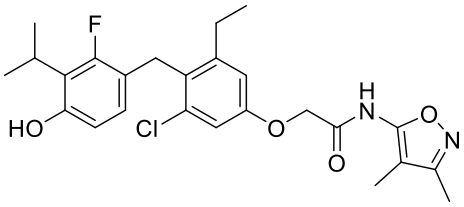









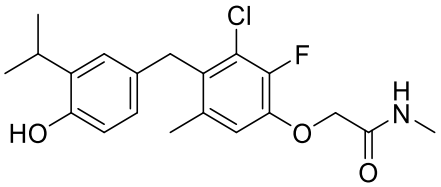











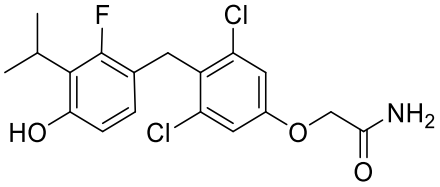


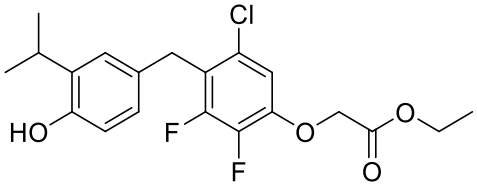


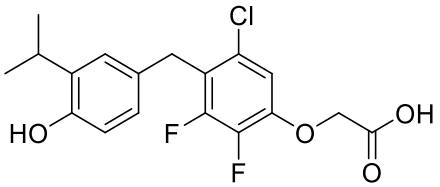


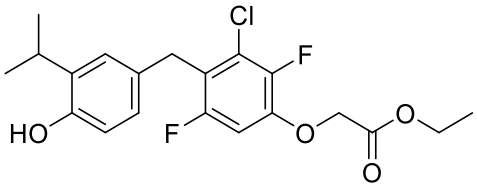


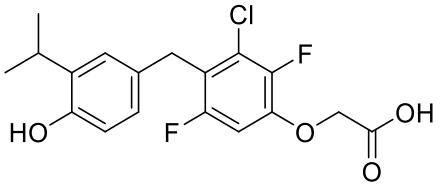


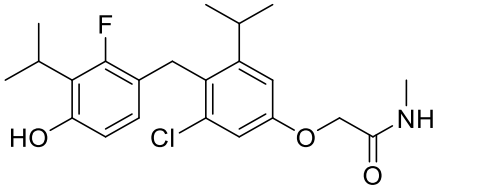


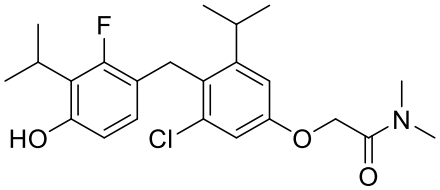


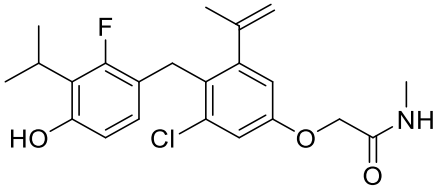


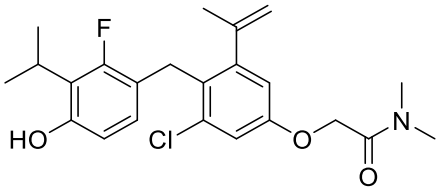


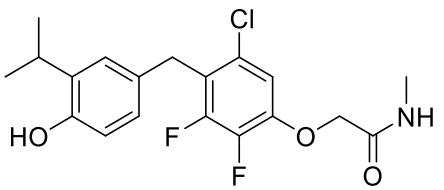


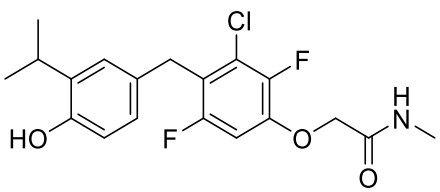


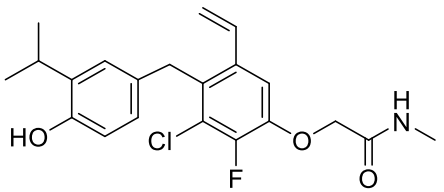


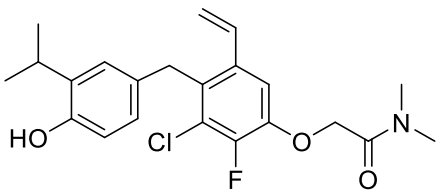


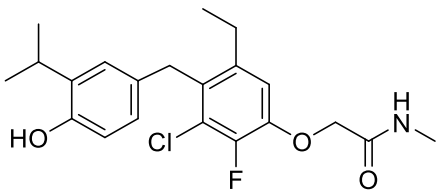




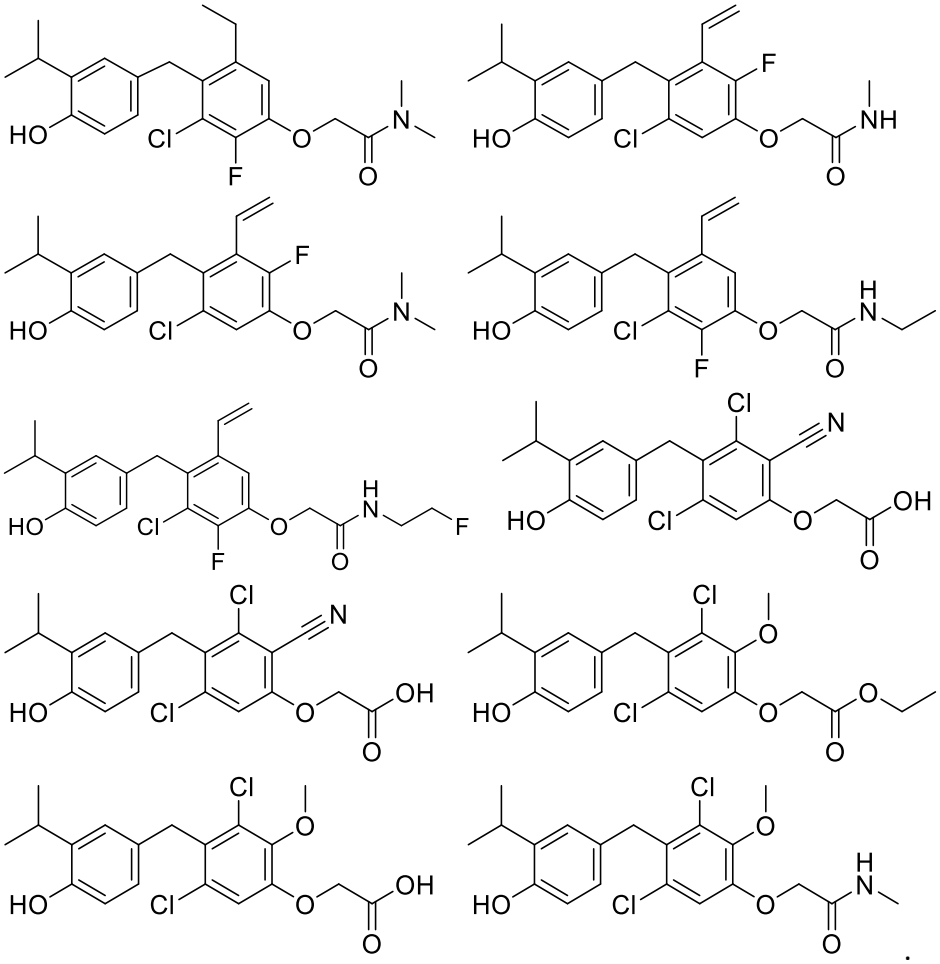












14. A pharmaceutical composition comprising a compound of any one of claims 1–13, or a pharmaceutically acceptable hydrate, solvate, or salt thereof, and a pharmaceutically acceptable excipient.

15. Use of a compound of any one of claims 1–13, or a pharmaceutically acceptable hydrate, solvate, or salt thereof, in the manufacture of a medicament for treating a neurodegenerative disease;

wherein the neurodegenerative disease is adult Refsum disease, Alexander disease, Alzheimer’s disease, Balo concentric sclerosis, Canavan disease, central pontine myelinolysis, cerebral palsy, cerebrotendineous xanthomatosis, chronic inflammatory demyelinating polyneuropathy, Devic's syndrome, diffuse myelinoclastic sclerosis, idiopathic inflammatory demyelinating disease, infantile Refsum disease, Krabbe disease, Leber hereditary optic neuropathy, Marburg multiple sclerosis, Marchiafava-Bignami disease,

metachromatic leukodystrophy, multifocal motor neuropathy, paraproteinemic demyelinating polyneuropathy, Pelizaeus-Merzbacher disease, peroneal muscular atrophy, progressive multifocal leukoencephalopathy, transverse myelitis, tropical spastic paraparesis, van der Knaap disease, X-linked adrenoleukodystrophy, or Zellweger syndrome.

16. A compound of any one of claims 1–13, or a pharmaceutically acceptable hydrate, solvate, or salt thereof, for use in therapy.