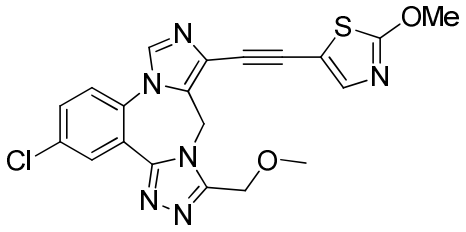
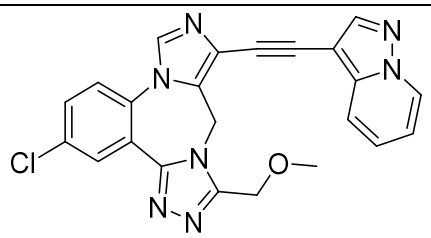
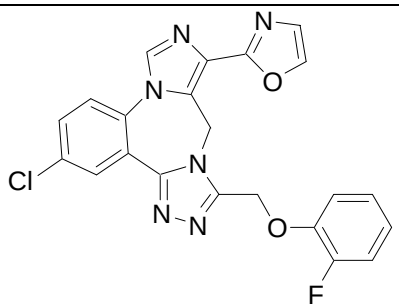
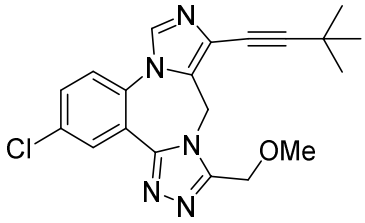
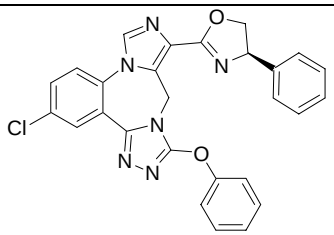
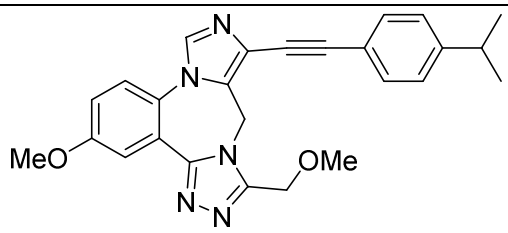
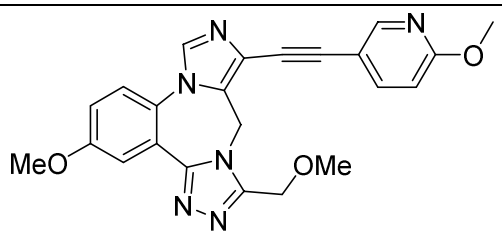
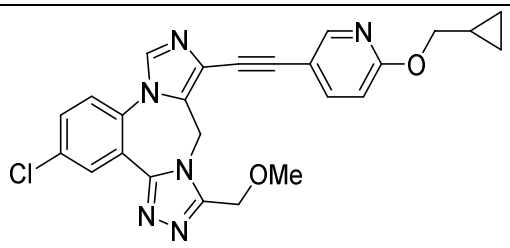
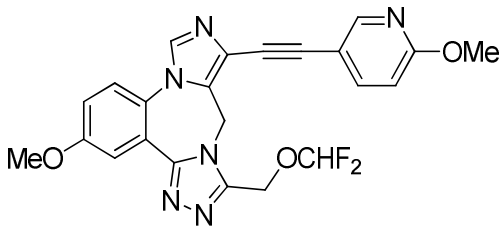
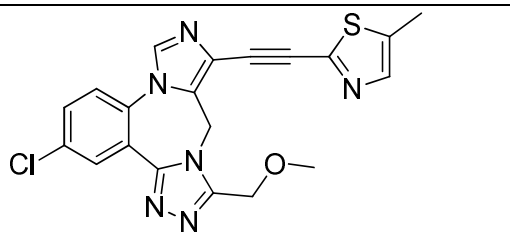
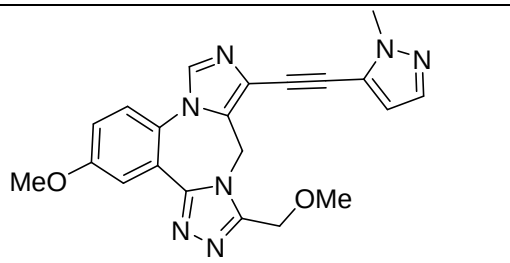
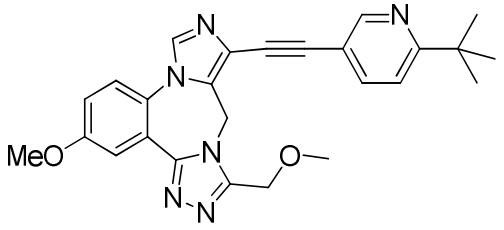
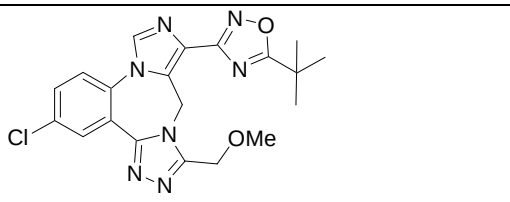
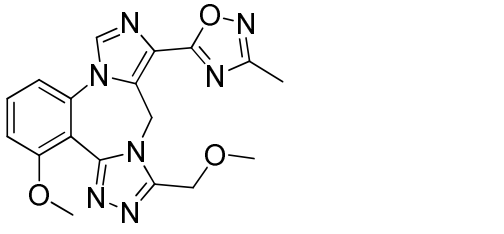
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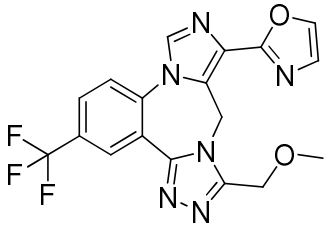
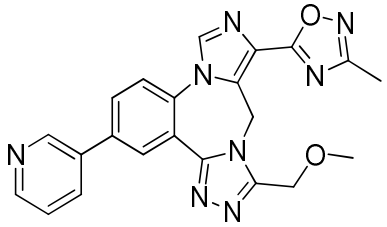
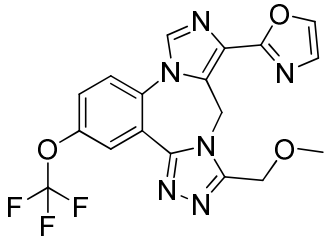
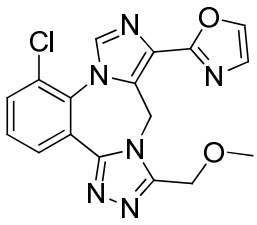
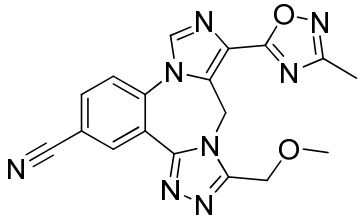
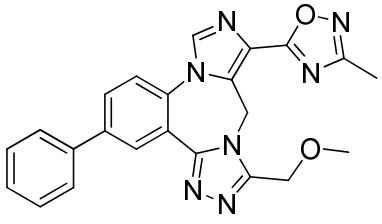
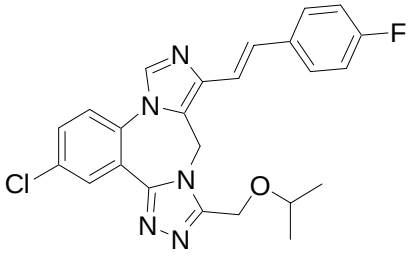
1. A pharmaceutical composition comprising:

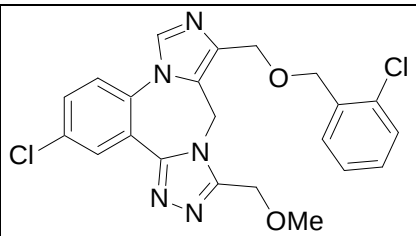
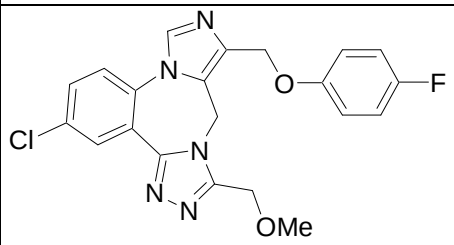
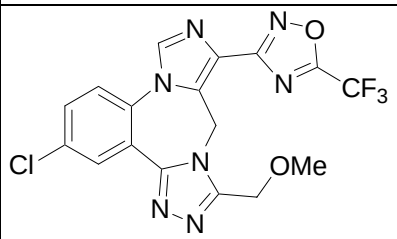
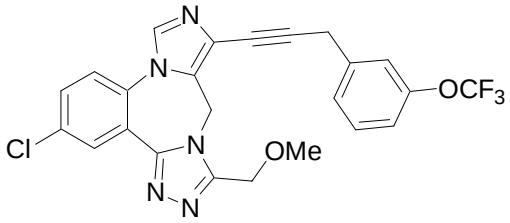
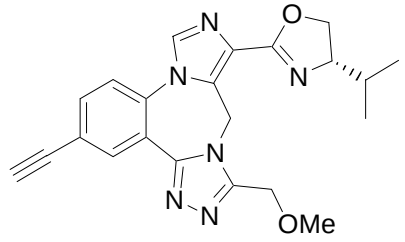
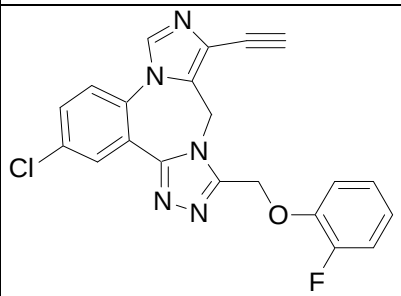
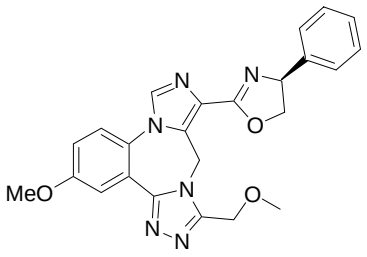
A) Levetiracetam, or a pharmaceutically acceptable salt, hydrate, solvate, isomer, or polymorph thereof; and

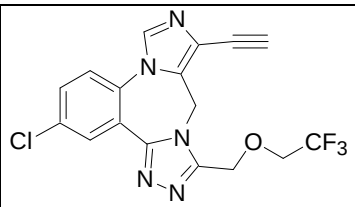
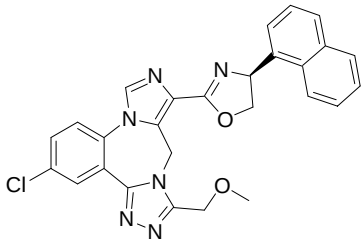
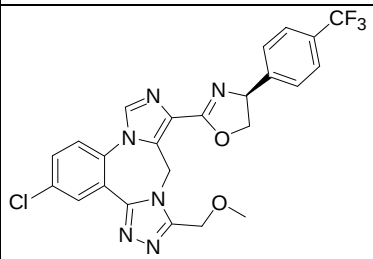
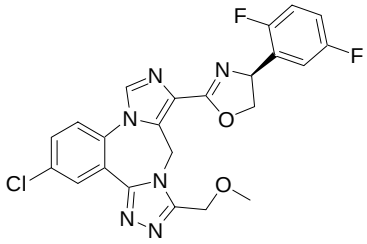
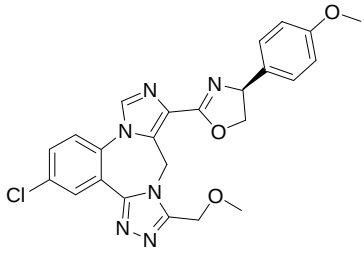
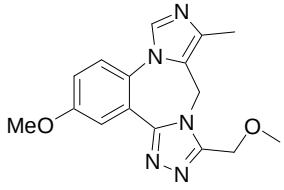
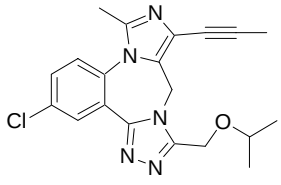
B) a $GABA_A$ α5 receptor agonist, or a pharmaceutically acceptable salt, hydrate, solvate, isomer, or polymorph thereof, wherein the $GABA_A$ α5 receptor agonist, or the pharmaceutically acceptable salt, hydrate, solvate, isomer, or polymorph thereof, is selected from the group consisting of:

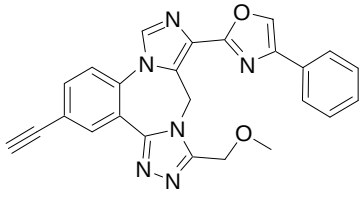
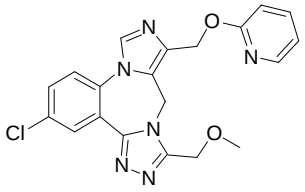
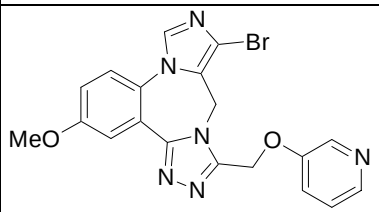
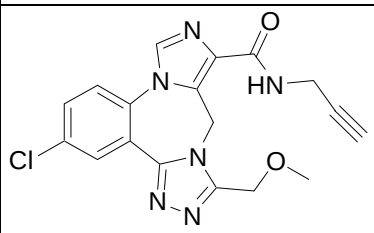
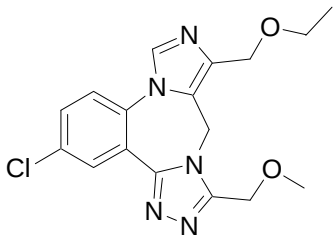
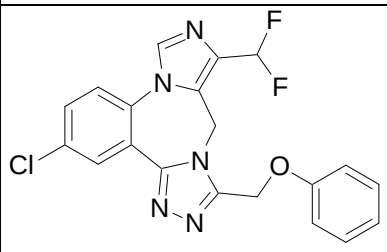
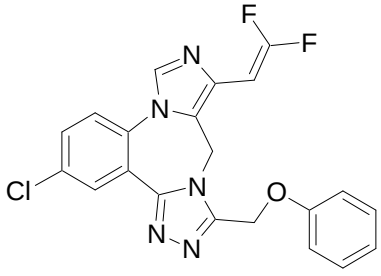
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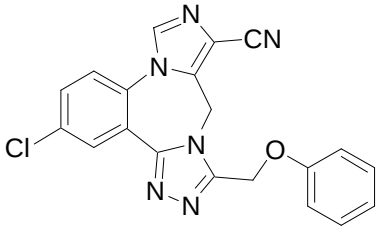
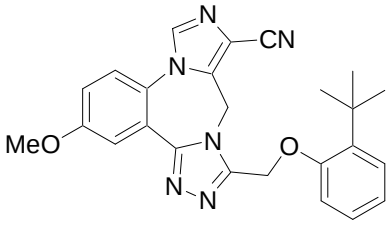
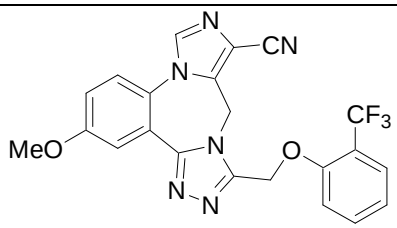
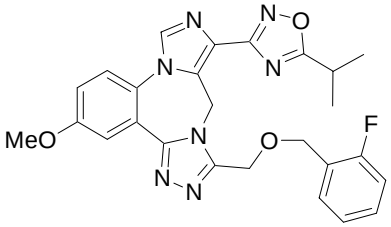
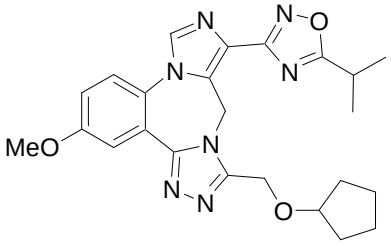
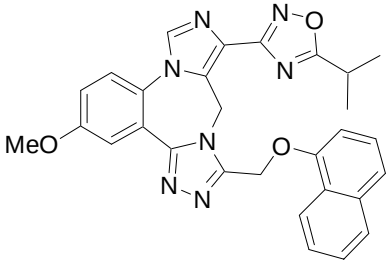
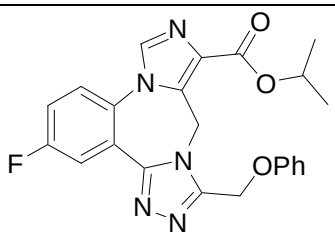
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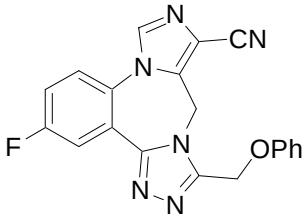
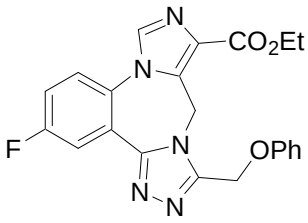
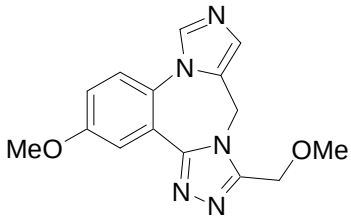
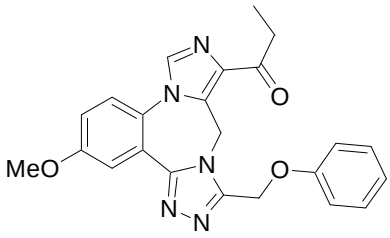
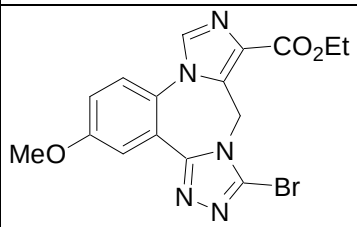
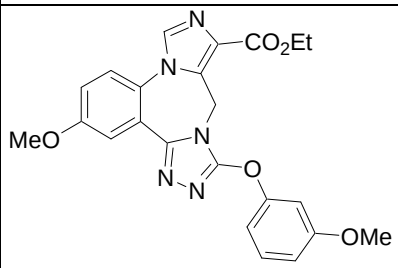
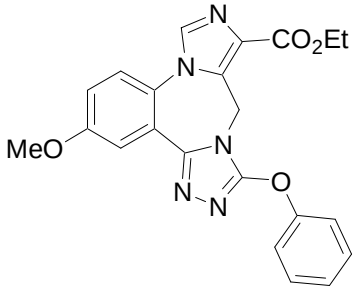
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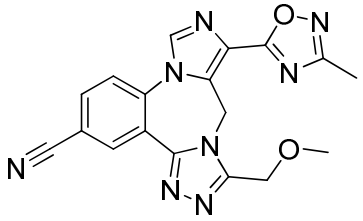
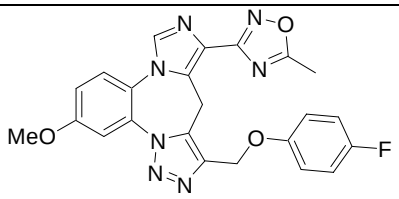
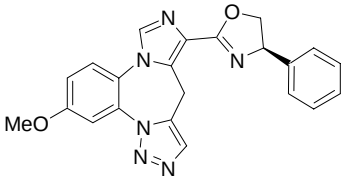
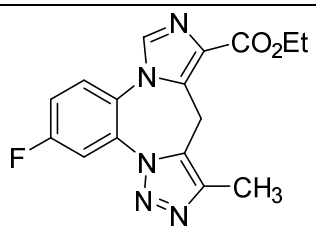
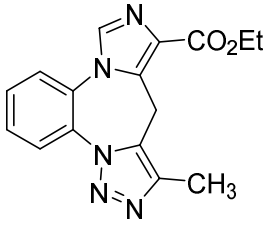
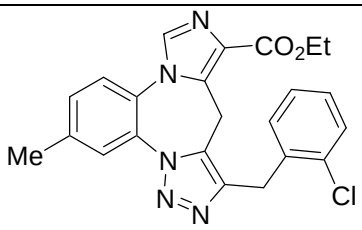
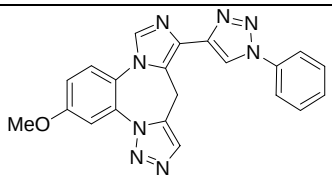
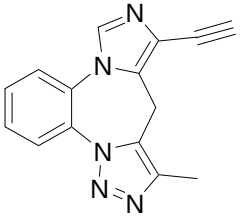
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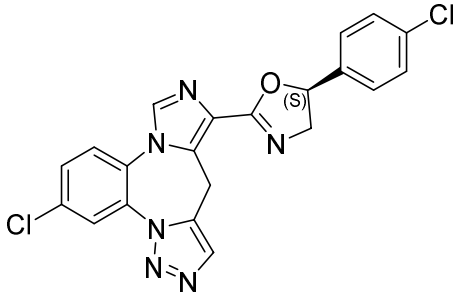
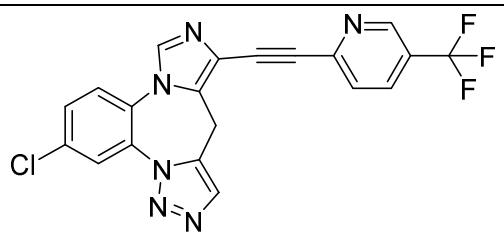
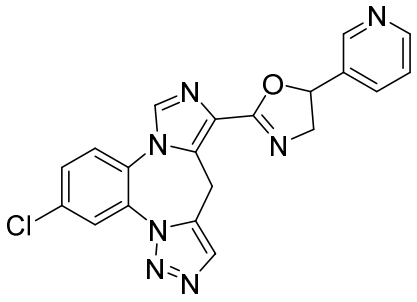
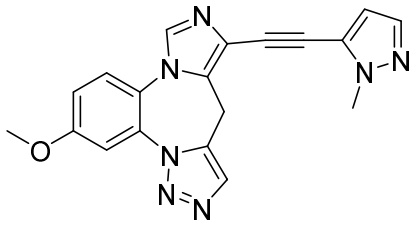
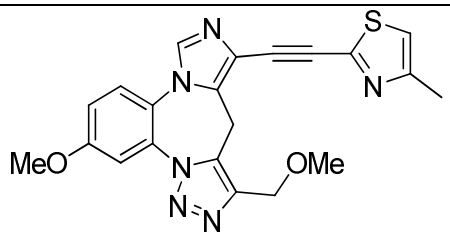
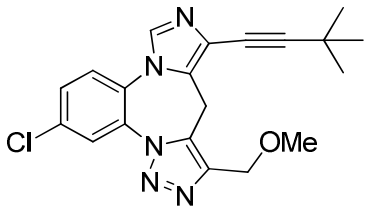
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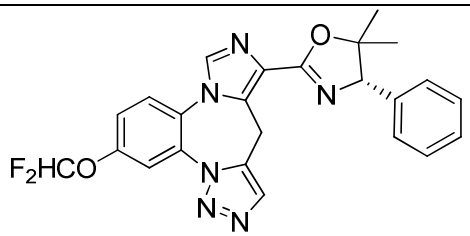
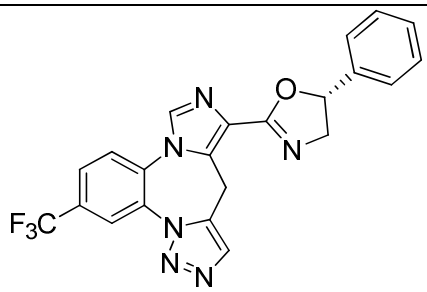
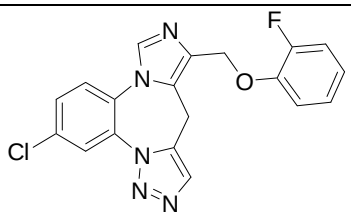
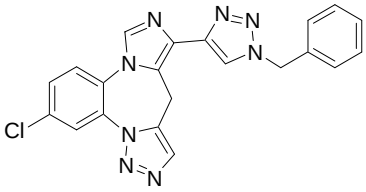
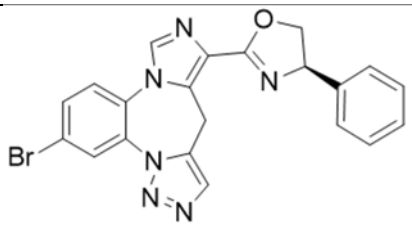
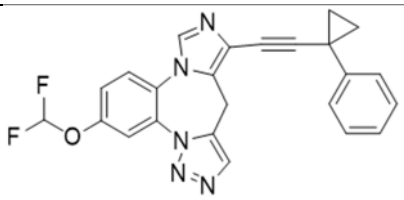
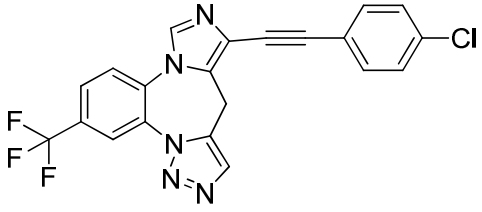
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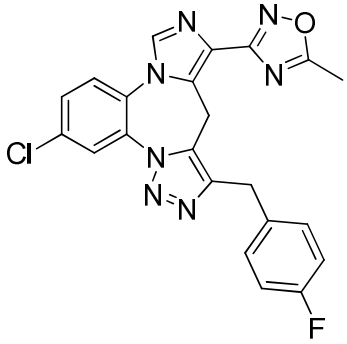
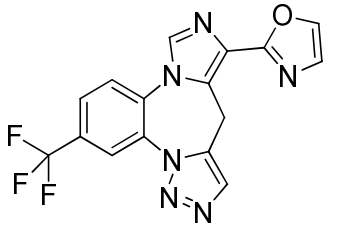
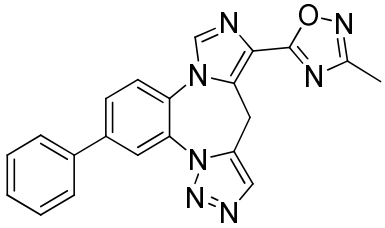
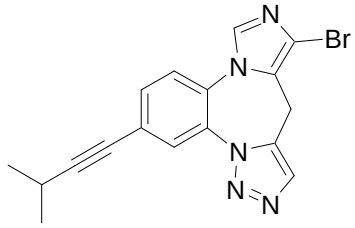
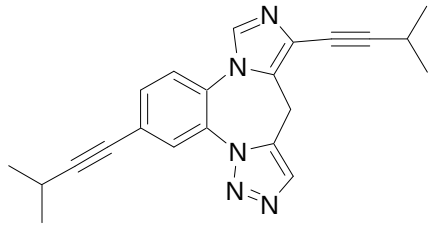
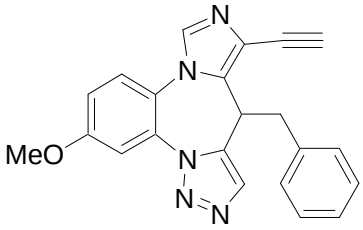
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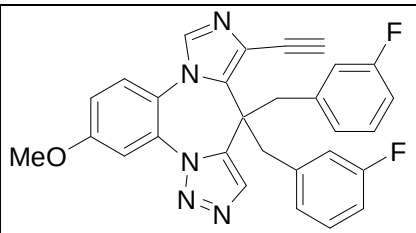
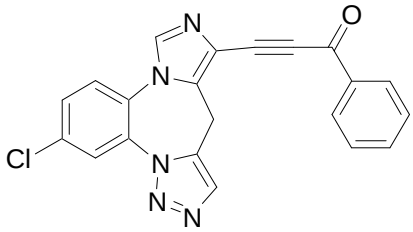
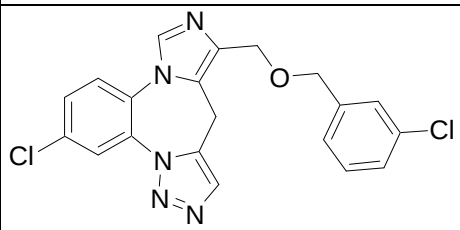
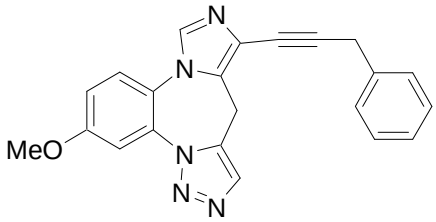
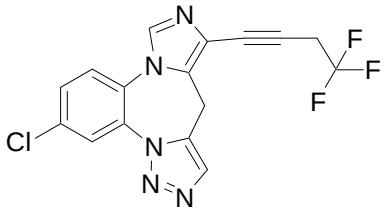
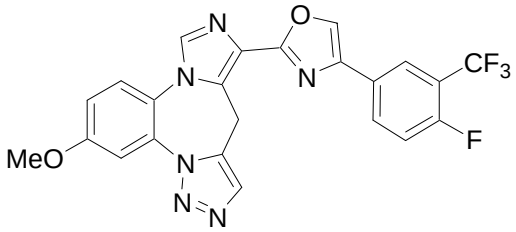
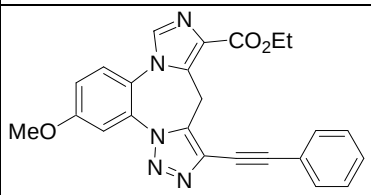
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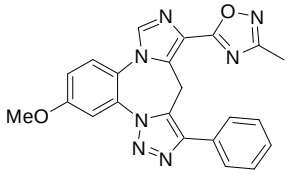
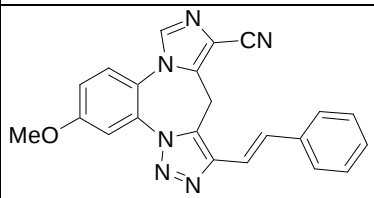
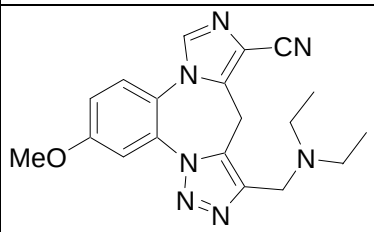
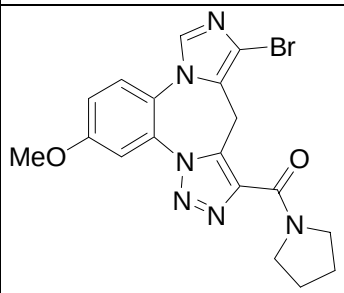
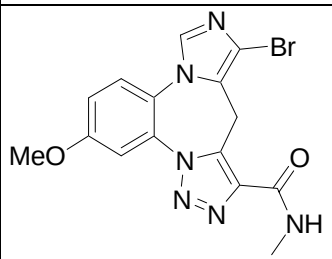
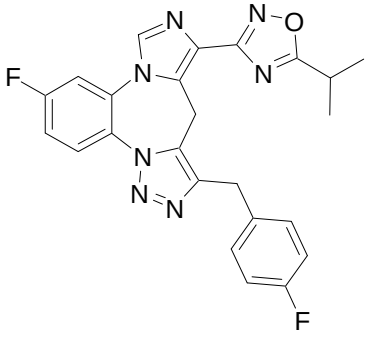
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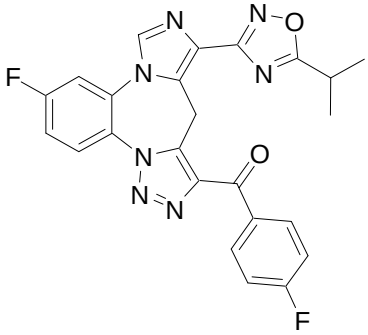
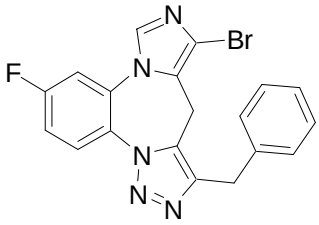
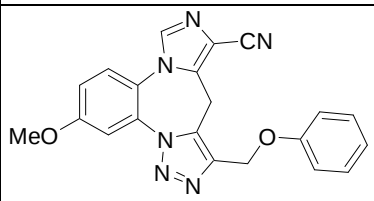
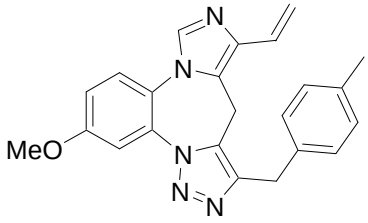
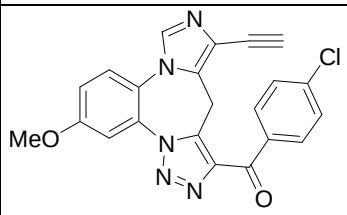
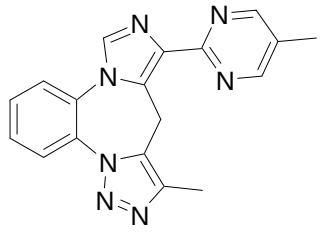
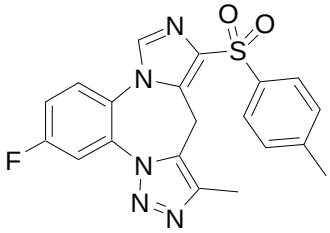
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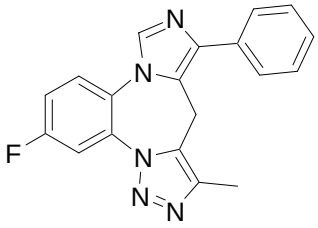
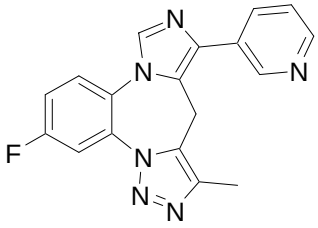
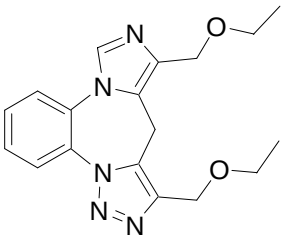
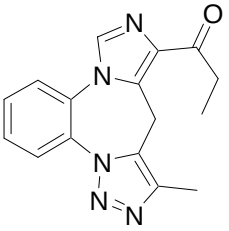
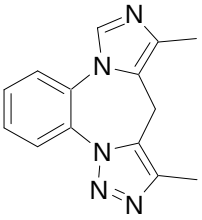
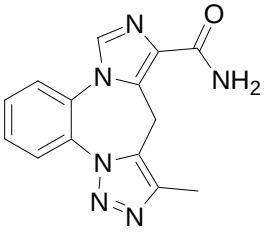
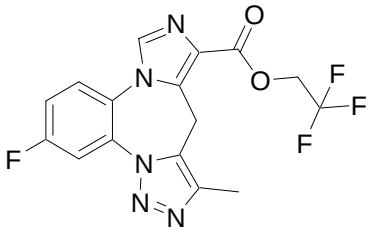
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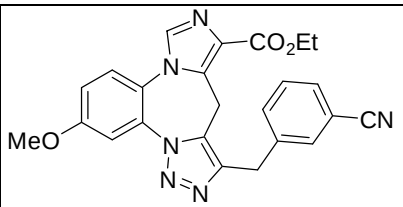
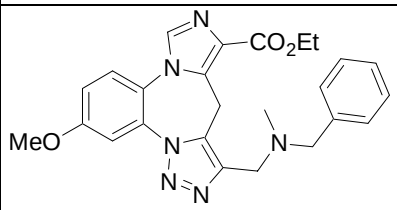
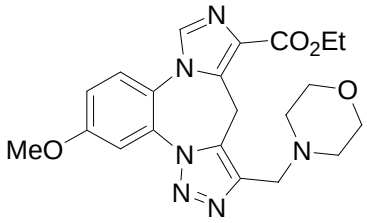
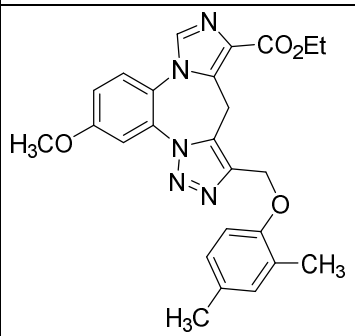
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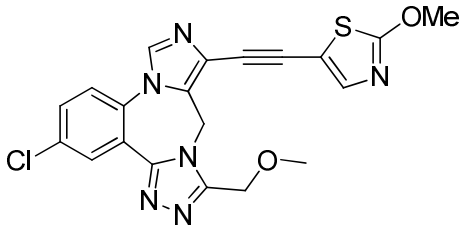
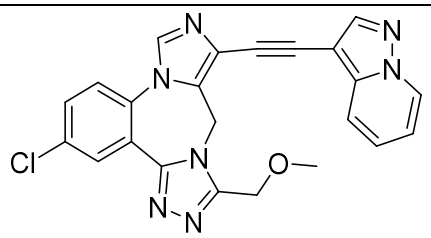
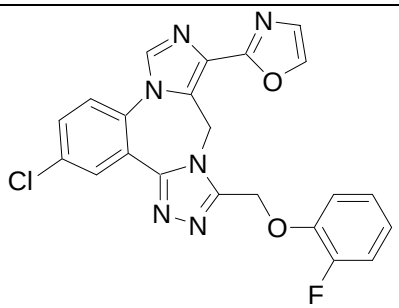
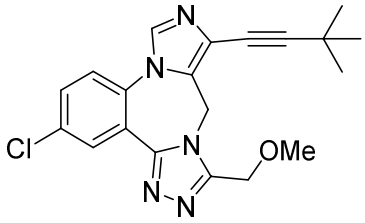
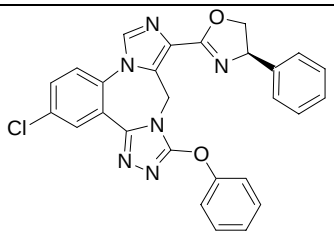
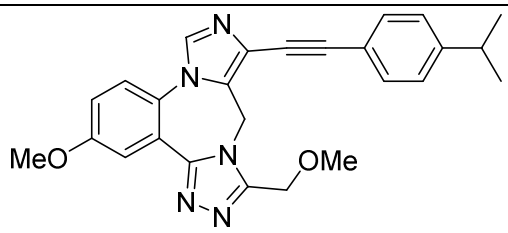
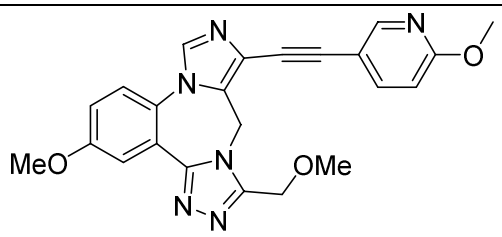
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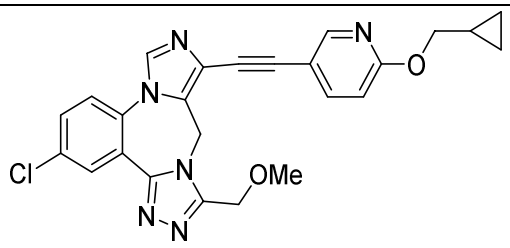
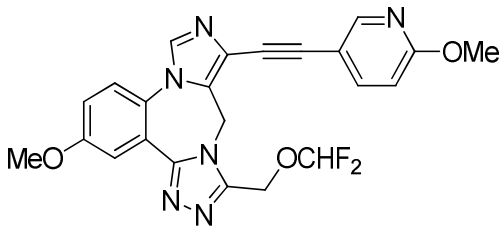
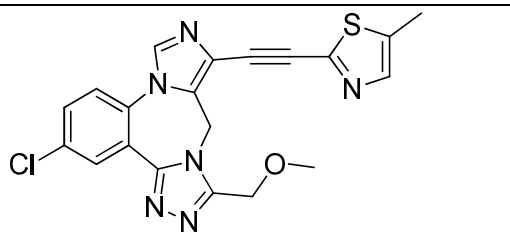
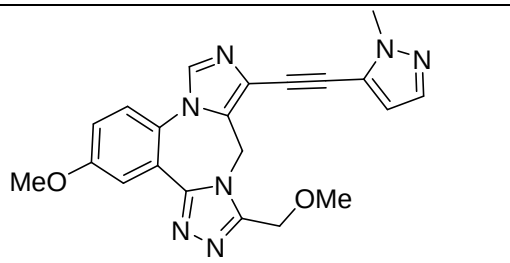
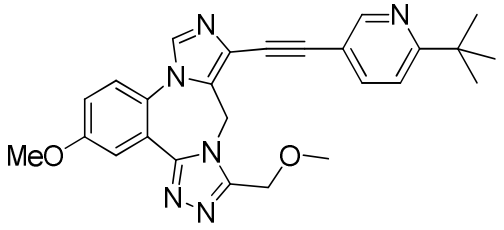
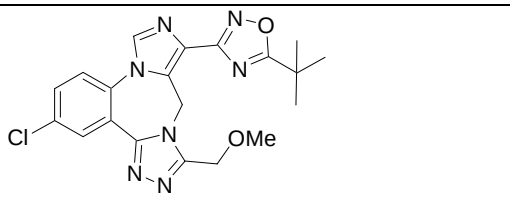
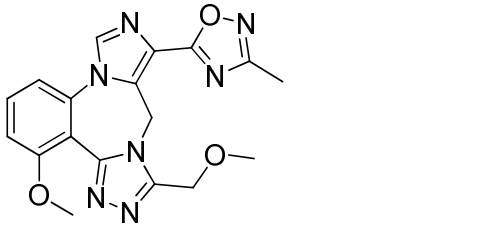
or a pharmaceutically acceptable salt, hydrate, solvate, polymorph, or isomer of any of the foregoing.

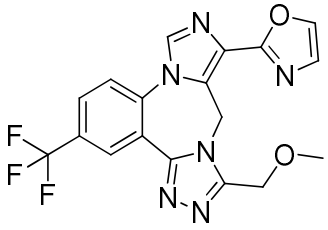
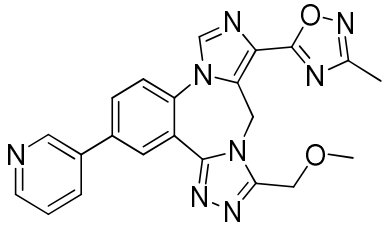
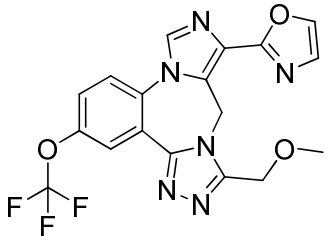
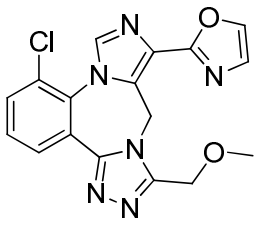
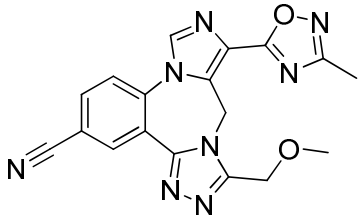
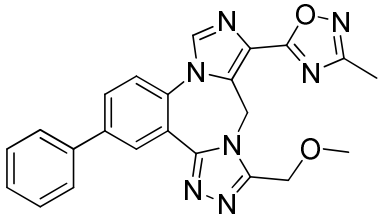
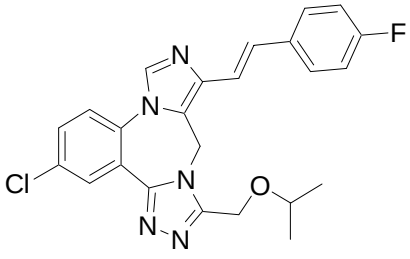
2. A combination comprising:

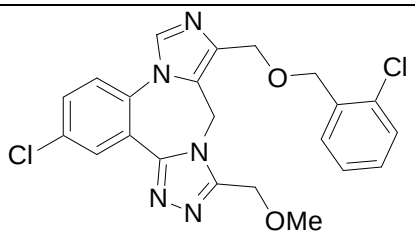
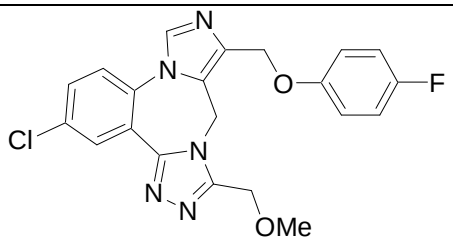
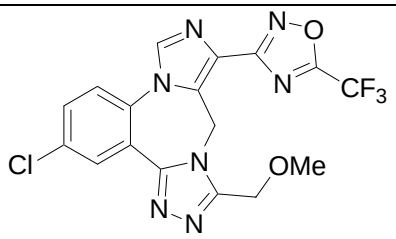
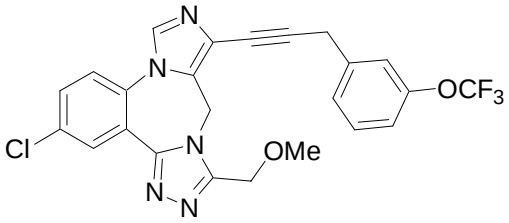
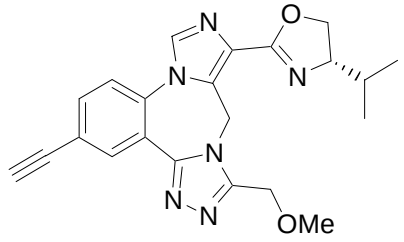
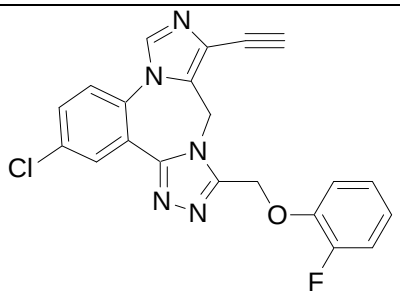
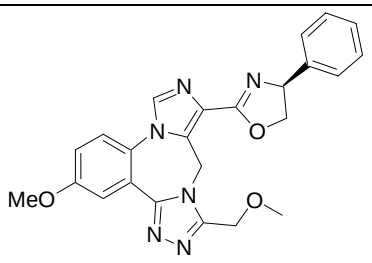
Component A: Levetiracetam, or a pharmaceutically acceptable salt, hydrate, solvate, isomer, or polymorph thereof; or a first pharmaceutical composition comprising levetiracetam, or a pharmaceutically acceptable salt, hydrate, solvate, polymorph or isomer thereof; and

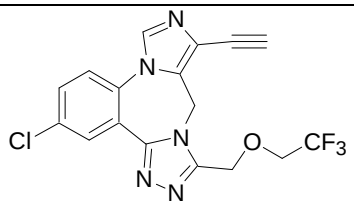
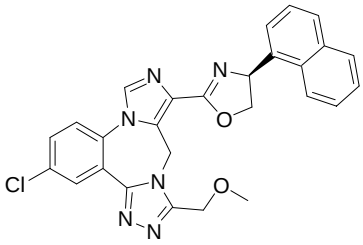
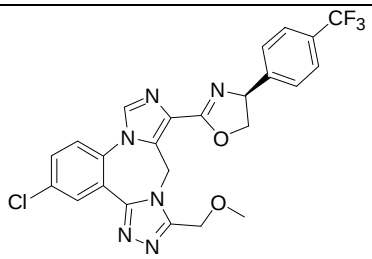
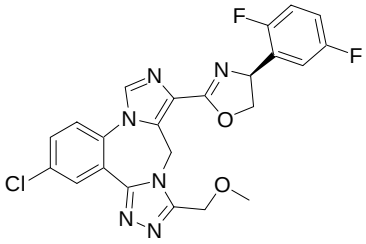
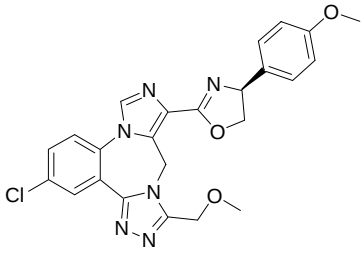
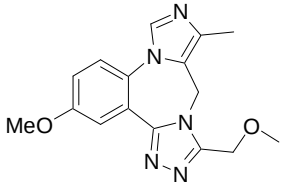
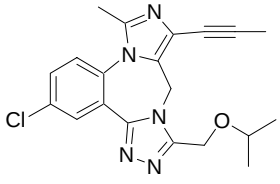
Component B: a $GABA_A$ α5 receptor agonist, or a pharmaceutically acceptable salt, hydrate, solvate, isomer, or polymorph thereof; or a second pharmaceutical composition comprising a $GABA_A$ α5 receptor agonist, or a pharmaceutically acceptable salt, hydrate, solvate, polymorph or isomer thereof, and wherein the $GABA_A$ α5 receptor agonist, or the pharmaceutically acceptable salt, hydrate, solvate, isomer, or polymorph thereof, is selected from the group consisting of:

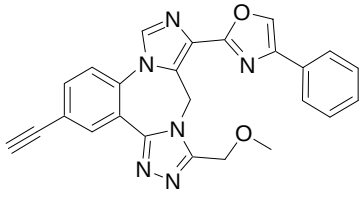
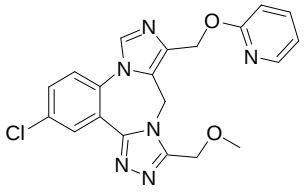
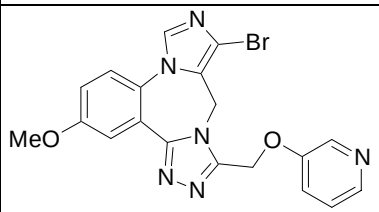
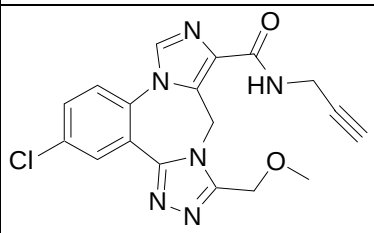
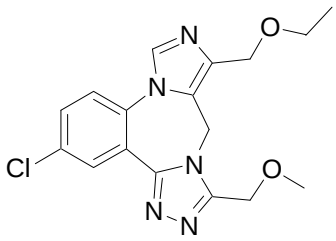
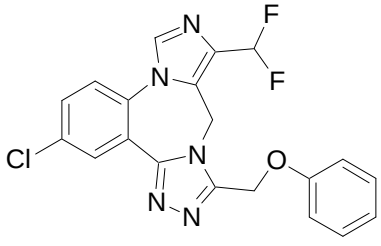
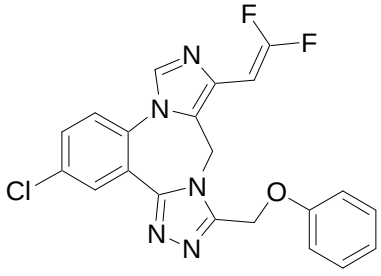
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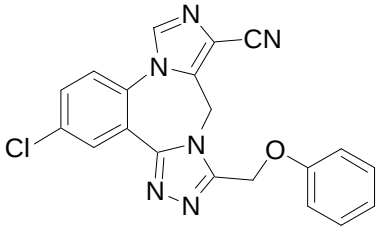
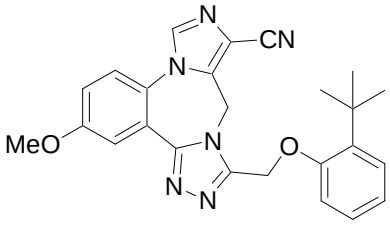
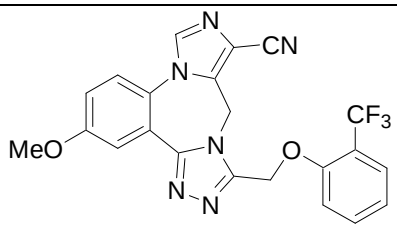
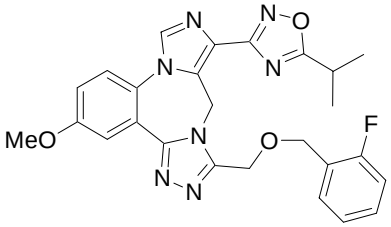
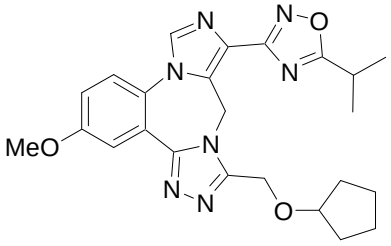
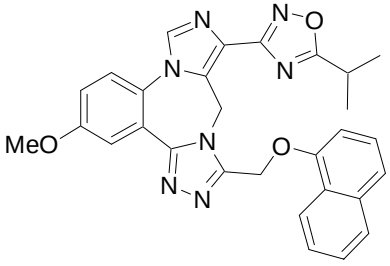
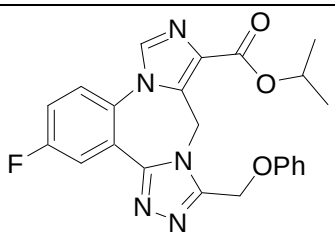
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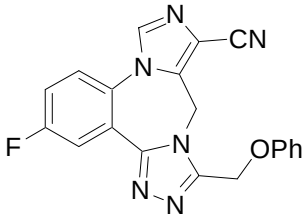
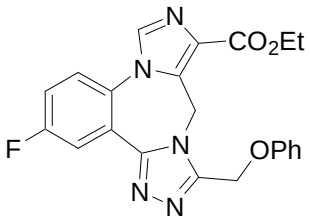
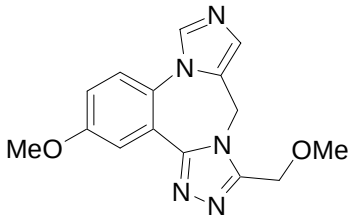
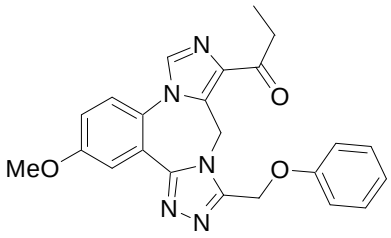
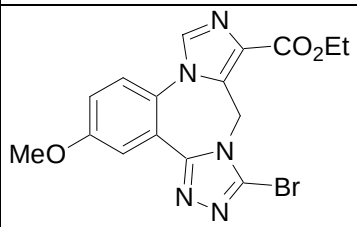
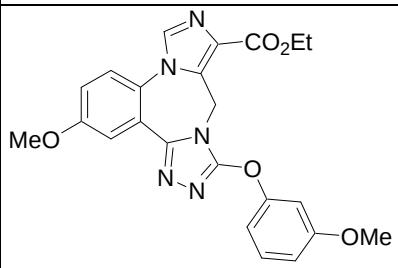
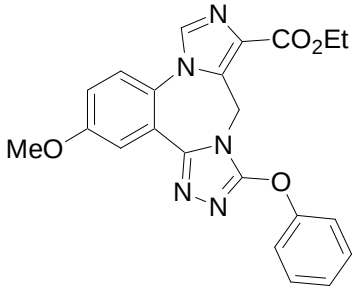
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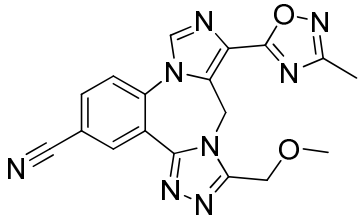
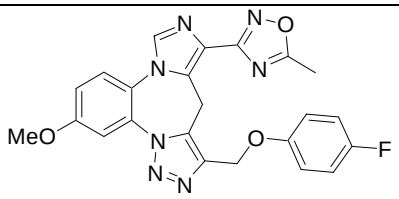
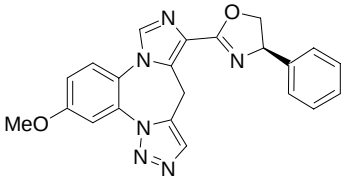
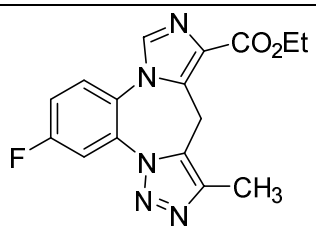
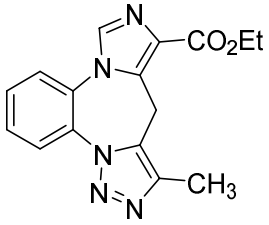
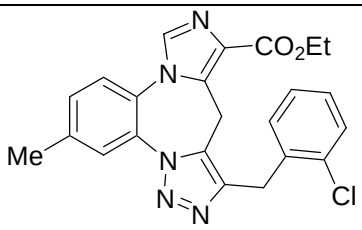
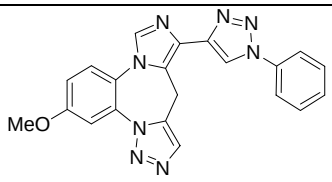
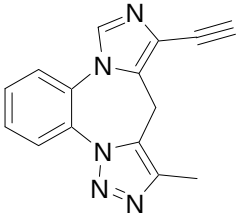
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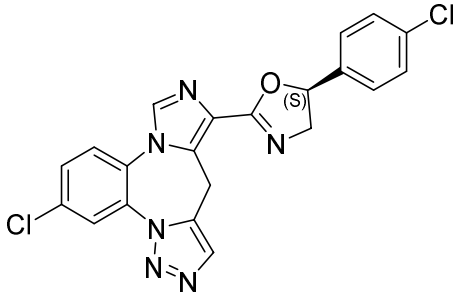
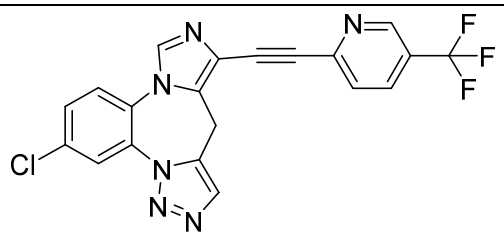
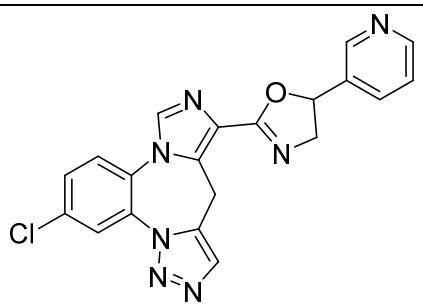
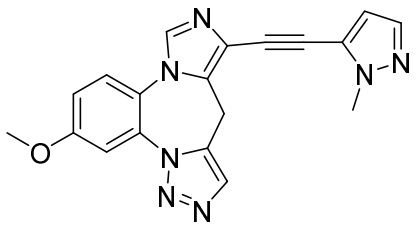
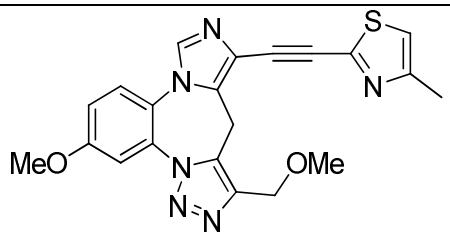
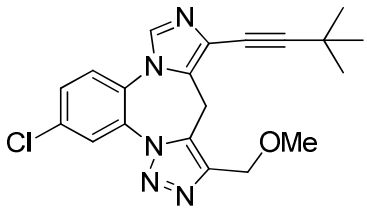
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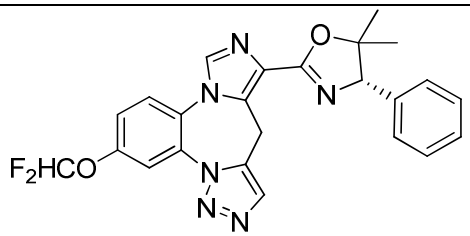
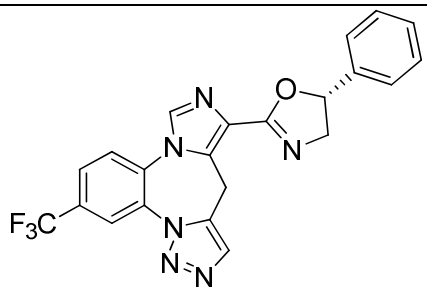
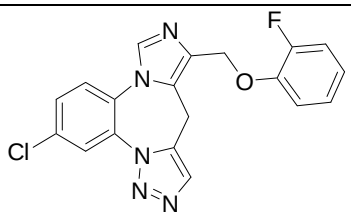
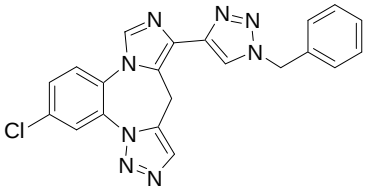
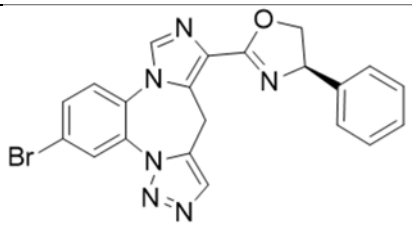
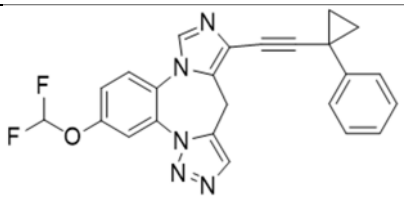
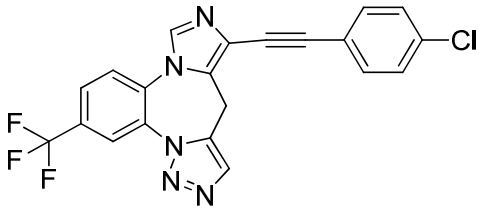
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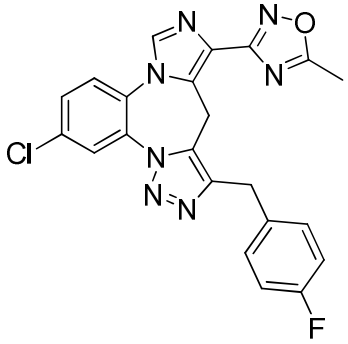
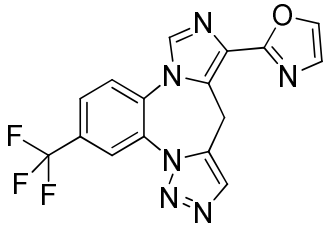
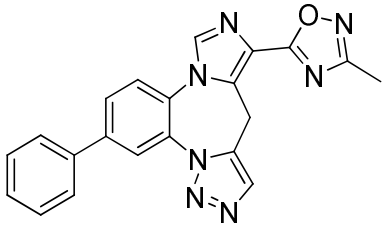
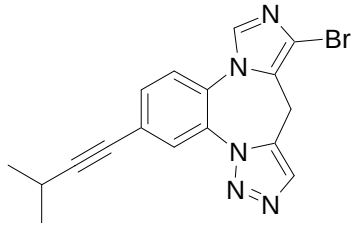
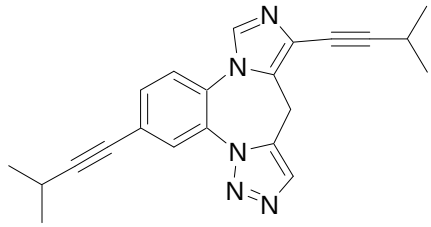
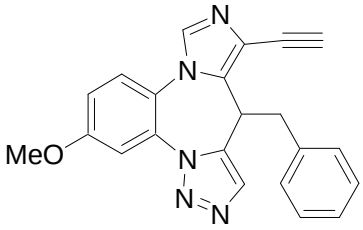
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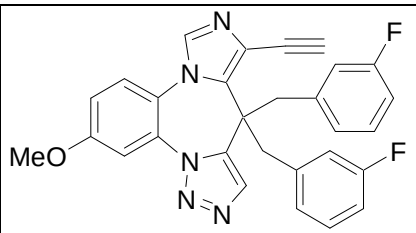
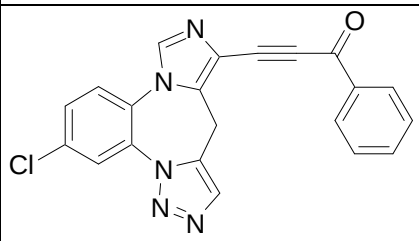
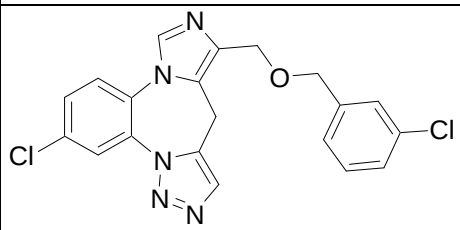
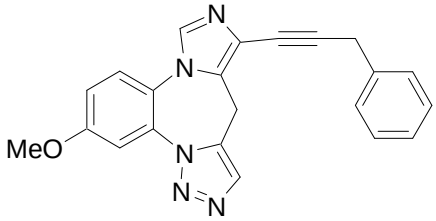
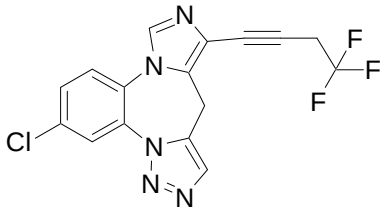
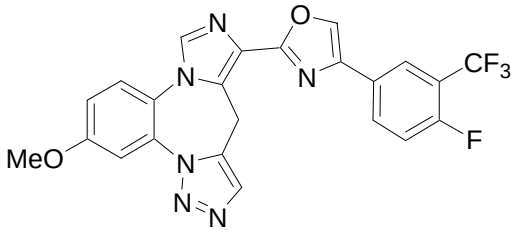
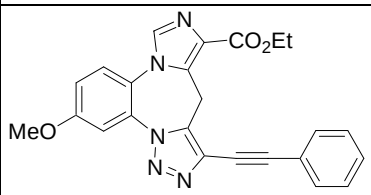
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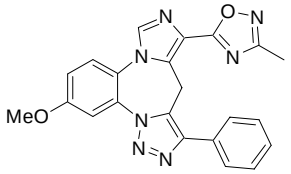
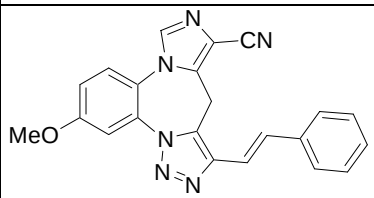
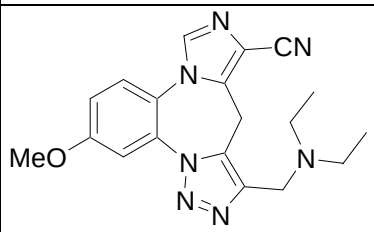
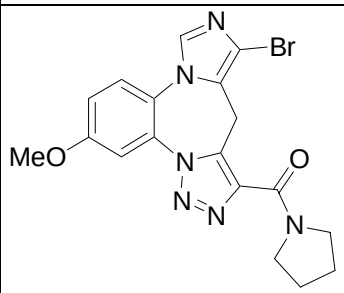
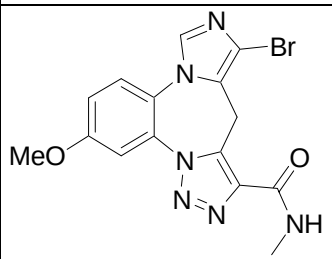
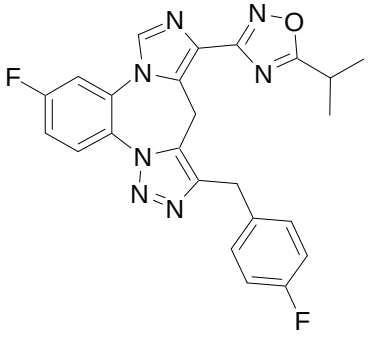
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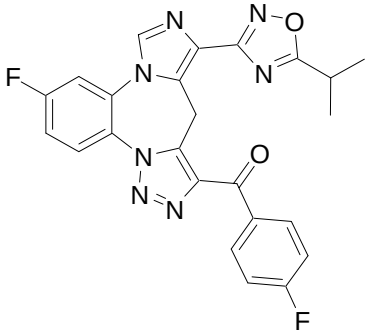
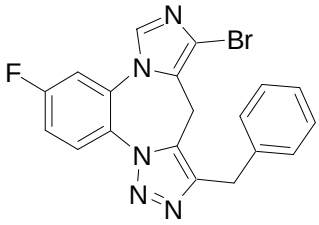
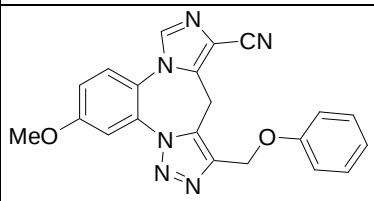
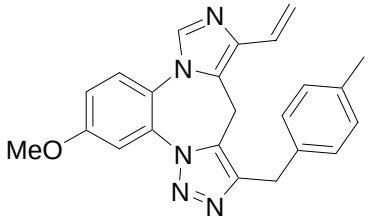
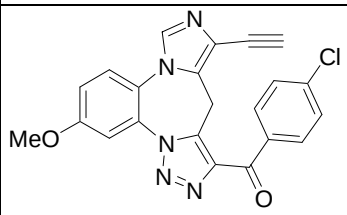
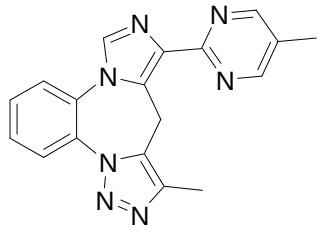
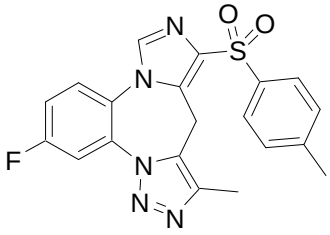
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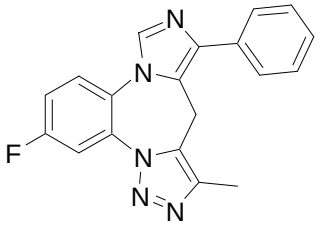
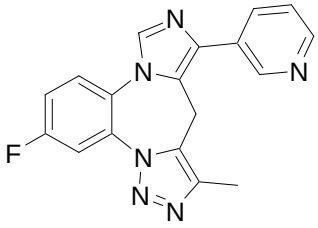
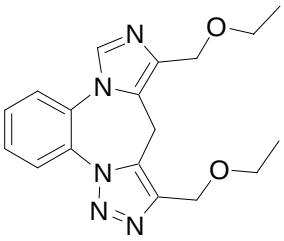
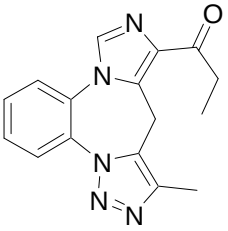
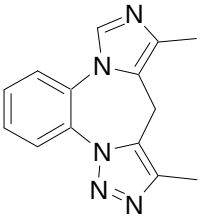
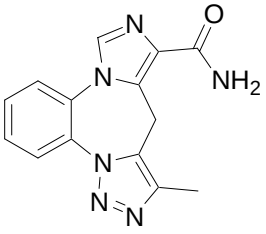
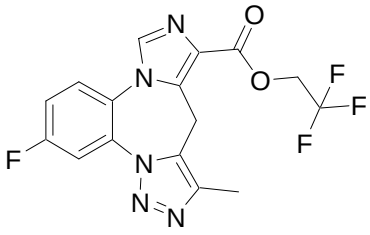
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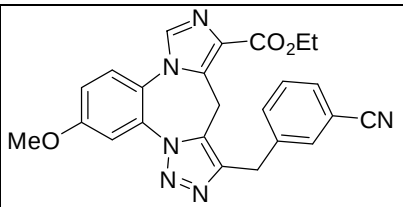
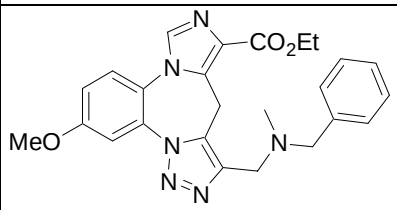
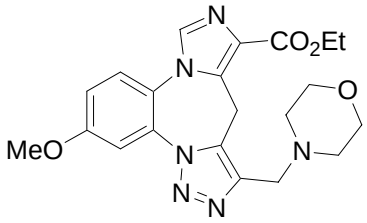
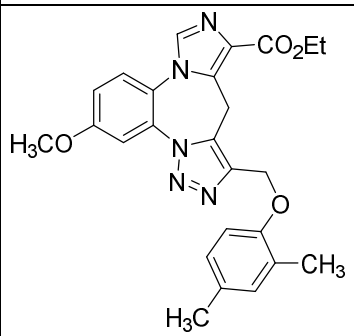
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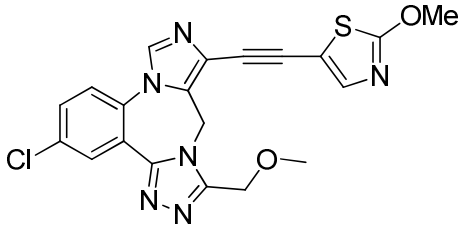
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or a pharmaceutically acceptable salt, hydrate, solvate, polymorph, or isomer of any of the foregoing.

3. The pharmaceutical composition or the combination of claim 1 or 2, wherein the GABA$_A$ α5 receptor agonist is  , or a pharmaceutically acceptable salt, hydrate, solvate, polymorph, or isomer thereof.

4. The pharmaceutical composition or the combination of claim 3, wherein the GABA$_A$ α5 receptor agonist is polymorph crystalline Form A exhibiting an XRPD comprising:

a. at least one peak selected from 3.0 and 21.0 degrees 2θ ± 0.2 degrees 2θ; and

b. at least one additional peak selected from the group consisting of 9.1, 10.7, 13.8, 22.0, 23.1, 23.9, 24.4, and 27.1 degrees 2θ ± 0.2 degrees 2θ.

5. The pharmaceutical composition or the combination of claim 3, wherein the $GABA_A$ α5 receptor agonist is polymorph crystalline Form B exhibiting an XRPD comprising:

a. at least one peak selected from 13.0 and 15.3 degrees 2θ ± 0.2 degrees 2θ; and

b. at least one additional peak selected from the group consisting of 7.0, 9.3, 10.2, 10.4, 12.5, 13.6, 14.0, 22.0, 23.0, 23.6, and 27.3 degrees 2θ ± 0.2 degrees 2θ.

6. The pharmaceutical composition or the combination of claim 3, wherein the $GABA_A$ α5 receptor agonist is solvate crystalline Form C exhibiting an XRPD comprising:

a. at least one peak selected from 8.5 and 18.9 degrees 2θ ± 0.2 degrees 2θ; and

b. at least one additional peak selected from the group consisting of 7.1, 9.4, 10.3, 12.3, 12.5, 14.2, 20.7, 22.1, 23.2, 23.7, 24.0, and 26.4 degrees 2θ ± 0.2 degrees 2θ.

7. The pharmaceutical composition or the combination of claim 3, wherein the $GABA_A$ α5 receptor agonist is polymorph crystalline Form E exhibiting an XRPD comprising:

a. at least one peak selected from the group consisting of 11.4, 18.1, and 21.6 degrees 2θ ± 0.2 degrees 2θ; and

b. at least one additional peak selected from the group consisting of 7.2, 22.0, 23.0, 24.2, 25.0, and 26.6 degrees 2θ ± 0.2 degrees 2θ.

8. The pharmaceutical composition or the combination of claim 3, wherein the $GABA_A$ α5 receptor agonist is hydrate crystalline Form F exhibiting an XRPD comprising:

a. at least one peak selected from the group consisting of 9.9, 11.9, 17.3, 19.4, and 25.7 degrees 2θ ± 0.2 degrees 2θ; and

b. at least one additional peak selected from the group consisting of 9.7, 12.1, 20.8, 23.2, 23.7, 24.2, 25.0, and 26.4 degrees 2θ ± 0.2 degrees 2θ.

9. The pharmaceutical composition of any one of claim 1 or claims 3-8 or the combination of any one of claims 2-8, wherein the $GABA_A$ α5 receptor agonist, or the pharmaceutically

acceptable salt, hydrate, solvate, isomer, or polymorph thereof, is present in an amount between 5 mg and 1000 mg.

10. The pharmaceutical composition of any one of claim 1 or claims 3-9 or the combination of any one of claims 2-9, wherein the levetiracetam, or the pharmaceutically acceptable salt, hydrate, solvate, isomer, or polymorph thereof, is present in an amount between 0.07 mg to 350 mg.

11. The pharmaceutical composition of any one of claim 1 or claims 3-10 or the combination of any one of claims 2-10, wherein the $GABA_A$ α5 receptor agonist, or a pharmaceutically acceptable salt, hydrate, solvate, isomer, or polymorph thereof, and levetiracetam, or a pharmaceutically acceptable salt, hydrate, solvate, isomer, or polymorph thereof, are formulated as a tablet, capsule, pill, lozenge, powder, granule, solution, or suspension, are in an extended release form, a non-extended release form, or an immediate release form.

12. The combination of claim 11, wherein the $GABA_A$ α5 receptor agonist, or a pharmaceutically acceptable salt, hydrate, solvate, isomer, or polymorph thereof, and the levetiracetam, or a pharmaceutically acceptable salt, hydrate, solvate, isomer, or polymorph thereof, are in a unit dosage form, or in separate packages for simultaneous or sequential administration.

13. Use of a pharmaceutical composition according to any one of claims 1 and 3-12 or of a combination according to any one of claims 2-12 in the manufacture of a medicament for treating cognitive impairment associated with a central nervous system (CNS) disorder in a subject in need thereof or at risk thereof.

14. Use of a pharmaceutical composition according to any one of claims 1 and 3-12 or of a combination according to any one of claims 2-12 in the manufacture of a medicament for treating cognitive impairment associated with a brain cancer in a subject in need thereof.

15. Use of a pharmaceutical composition according to any one of claims 1 and 3-12 or of a combination according to any one of claims 2-12 in the manufacture of a medicament for treating a brain cancer in a subject in need thereof.

16. Use of a pharmaceutical composition according to any one of claims 1 and 3-12 or of a combination according to any one of claims 2-12 in the manufacture of a medicament for treating Parkinson’s disease psychosis in a subject in need thereof.

17. The use according to claim 13, wherein the CNS disorder is age-related cognitive impairment, mild cognitive impairment (MCI), amnestic mild cognitive impairment (aMCI), dementia, Alzheimer's disease, schizophrenia, amyotrophic lateral sclerosis (ALS), post-traumatic stress disorder (PTSD), mental retardation, Parkinson's disease (PD), autism, compulsive behavior, substance addiction, bipolar disorder, or cancer-therapy-related cognitive impairment.

18. The use of any one of claims 13-17, wherein the pharmaceutical composition or the combination is administered subcutaneously, intravenously, orally, sublingually, buccally, transdermally, arterially, intradermally, intramuscularly, intraperitoneally, ocularly, intranasally, intraspinally or intracerebrally.

19. The use of any one of claims 13-18, wherein the pharmaceutical composition or the combination is administered once or twice daily.