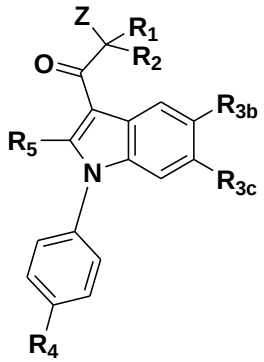
deubiquitinating enzyme is Usp14 which has been shown to act as an inhibitor of the proteasome [Lee et al. (2010)].

Both proteasome dysfunction and dysfunction in proteostasis have been implicated in a diverse range of diseases including, for example, neurodegenerative disease, metabolic diseases, inflammatory diseases, and cancer. In many such diseases and conditions, the proteasome has decreased ability to degrade misfolded or abnormal proteins, leading to the presence of toxic protein aggregates. In addition, the enhancement of proteasome activity can be therapeutic for any disease characterized by deficient proteasome activity, or deficient activity of other components of the ubiquitin-proteasome pathway including, but not limited to, von Hippel-Lindau disease, spinocerebellar ataxia 1, Angelman syndrome, giant axon neuropathy, inclusion body myopathy with Paget disease of bone and frontotemporal dementia (IBMPFD), and others [Lehman, N. L., (2009), Acta Neuropathologica, *118(3)*, 329-347; Weihl et al., (2007), Neuromuscular Disorders, *17*, 87-87]. Enhancing proteasome activity is also therapeutic for diseases in which proteasome substrates are involved and contribute to pathology, but which do not satisfy a strict definition of proteinopathies. For example, numerous oncoproteins are proteasome substrates and their ability to promote cancer can potentially be attenuated by enhancing proteasome activity.

Therefore, there is a need for compounds and pharmaceutical compositions to treat conditions associated with proteostasis dysfunction and/or that provide therapies based on enhancing proteasome activity.

SUMMARY

In one aspect of the present disclosure, there is provided a compound having the Formula (Ib):



(Ib);

or a pharmaceutically acceptable salt, solvate, or clathrate thereof; wherein:

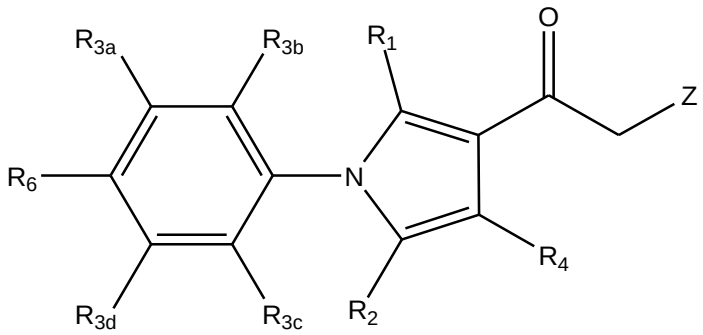
Z is an optionally substituted, 6- to 12-membered bridged N-heterocyclic;

optionally substituted heterocyclic, optionally substituted aryl, and optionally substituted heteroaryl;

each R_d is independently selected from the group consisting of hydrogen, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_1-C_{10} alkoxy, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, and optionally substituted heteroaryl; or two geminal R_d groups are taken together with the nitrogen atom to which they are attached to form an optionally substituted heterocyclic or an optionally substituted heteroaryl;

each n is independently 0, 1 or 2.

In another aspect of the present disclosure, there is provided a compound of formula (III):



(III);

or a pharmaceutically acceptable salt, solvate, or clathrate thereof; wherein:

R_1 is selected from the group consisting of hydrogen, optionally substituted C_1-C_4 alkyl, and halo;

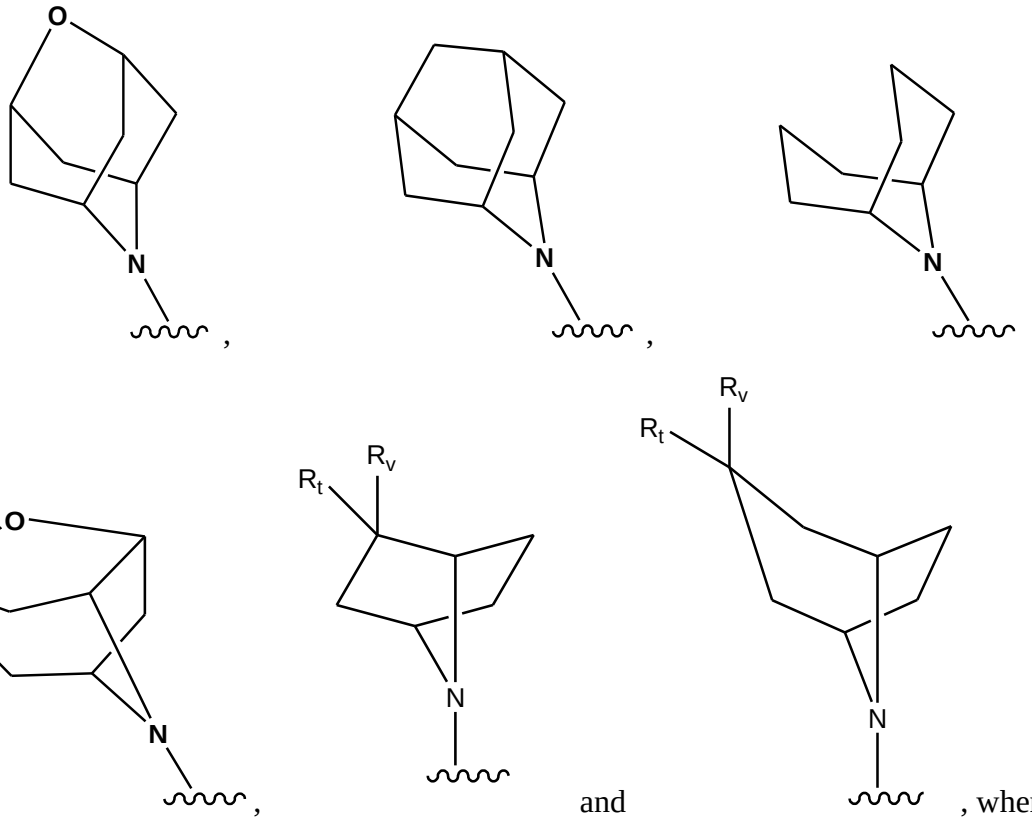
R_2 is selected from the group consisting of optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted 4- to 12-membered heterocyclic, optionally substituted aryl, optionally substituted 4- to 12-membered heteroaryl, halo, and CN;

R_{3a}, R_{3b}, R_{3c} and R_{3d} are each independently selected from the group consisting of hydrogen, optionally substituted C_1-C_6 alkyl, CN, and halo;

R_4 is selected from the group consisting of hydrogen, optionally substituted C_1-C_{10} alkyl, halo, and CN;

R_6 is selected from the group consisting of hydrogen, optionally substituted C_1-C_6 alkyl, CN, and halo; and

Z is selected from the group consisting of



, wherein

R_t is selected from the group consisting of hydrogen, optionally substituted C_1-C_4 alkyl, optionally substituted C_2-C_4 alkenyl, OR_{c2}, and $C(O)OR_{e2}$, wherein

each R_{c2} and R_{e2} is independently selected from the group consisting of hydrogen, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted 4- to 12-membered heterocyclic, optionally substituted aryl, and optionally substituted 4- to 12-membered heteroaryl; and

R_v is hydrogen or optionally substituted C_1-C_{10} alkyl;

wherein substituents of optionally substituted Z, R_1, R_2, R_{3a}, R_{3b}, R_{3c}, R_{3d}, R_4, and R_6 are each independently selected from the group consisting of C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_{12} cycloalkyl, C_3-C_{12} cycloalkenyl, aryl, halo, N_3, OR_c, NR_dR_d, $C(O)OR_c$, NO_2, CN, $C(O)R_c$, $C(O)C(O)R_c$, $C(O)NR_dR_d$, $NR_dC(O)R_c$, $NR_dS(O)_nR_c$, $N(R_d)(COOR_c)$, $NR_dC(O)C(O)R_c$, $NR_dC(O)NR_dR_d$, $NR_dS(O)_nNR_dR_d$, $NR_dS(O)_nR_c$, $S(O)_nR_c$, $S(O)_nNR_dR_d$, $OC(O)OR_c$, $(C{=}NR_d)R_c$, $OC(O)R_c$, $Si(R_c)_3$, heterocyclic, and heteroaryl;

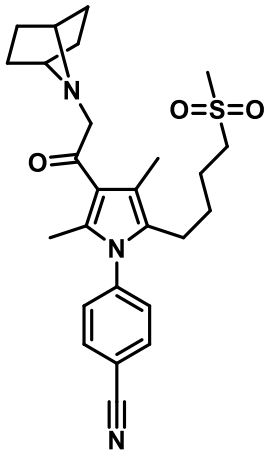
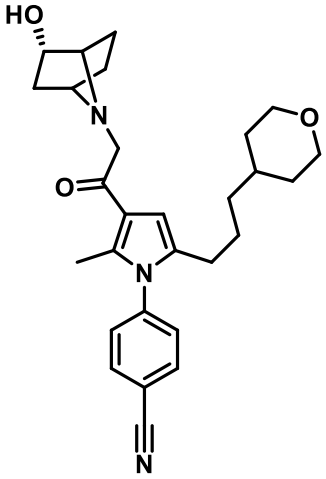
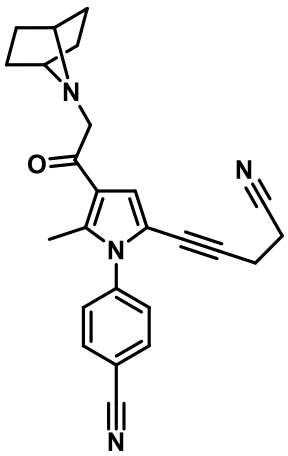
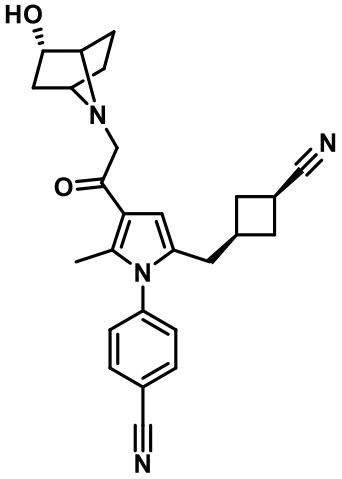
each R_c is independently selected from the group consisting of hydrogen, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl,

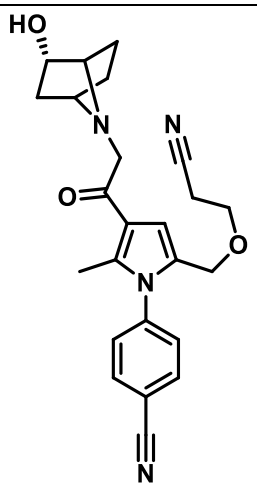
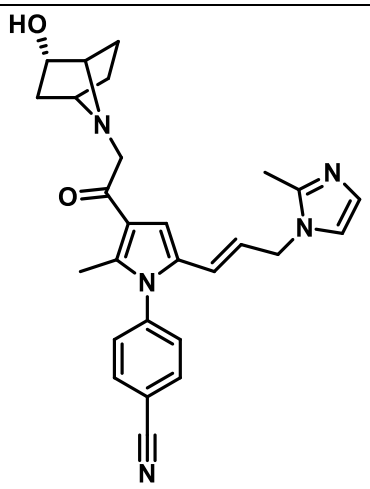
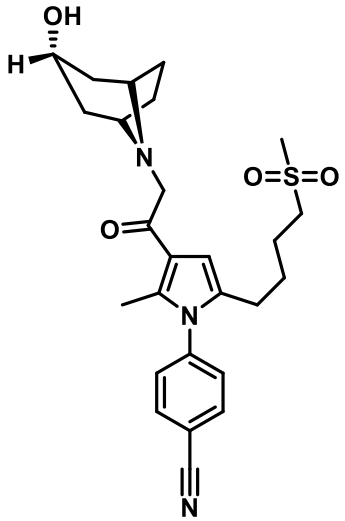
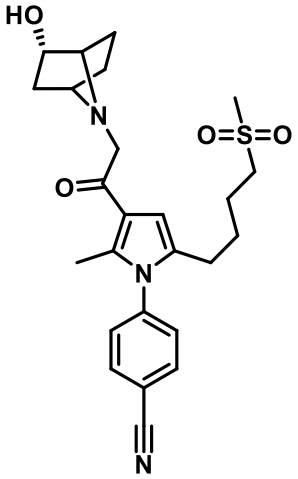
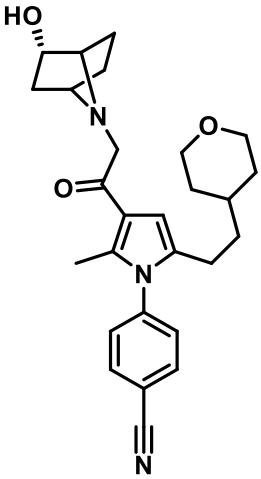
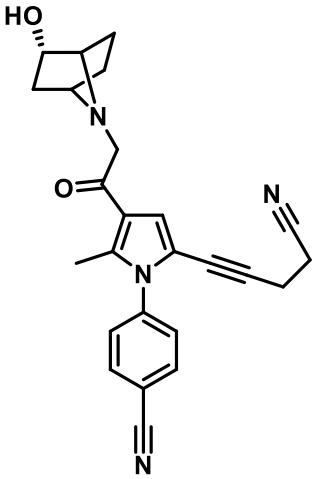
optionally substituted heterocyclic, optionally substituted aryl, and optionally substituted heteroaryl;

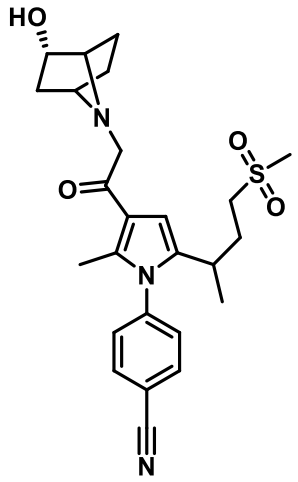
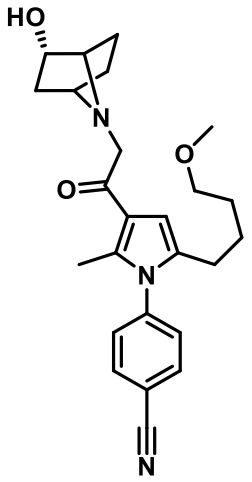
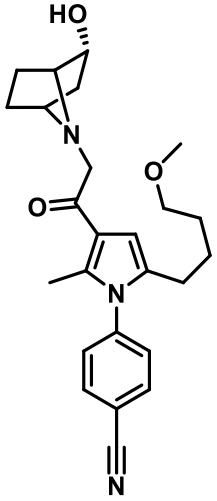
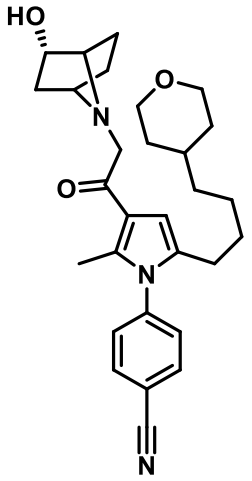
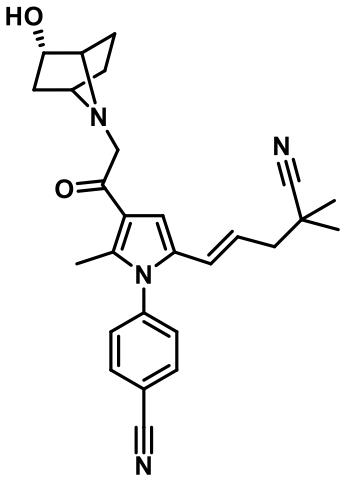
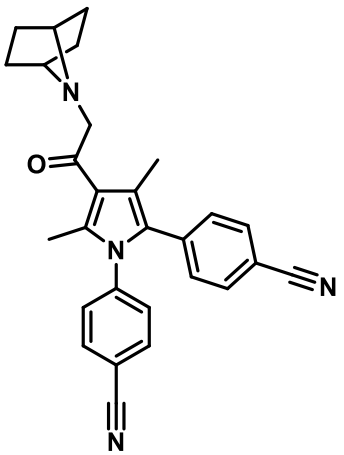
each R_d is independently selected from the group consisting of hydrogen, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_1-C_{10} alkoxy, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, and optionally substituted heteroaryl; or two geminal R_d groups are taken together with the nitrogen atom to which they are attached to form an optionally substituted heterocyclic or an optionally substituted heteroaryl; and

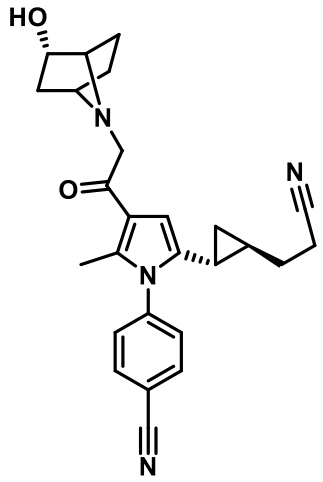
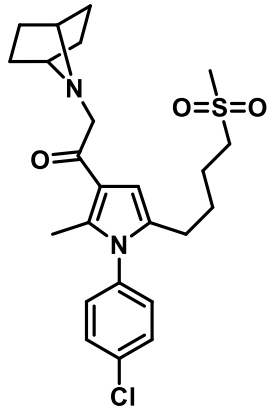
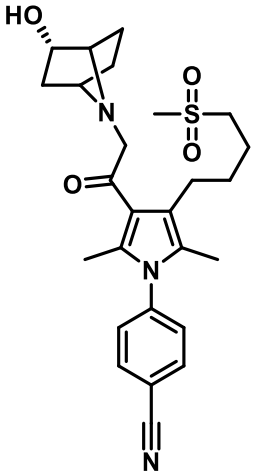
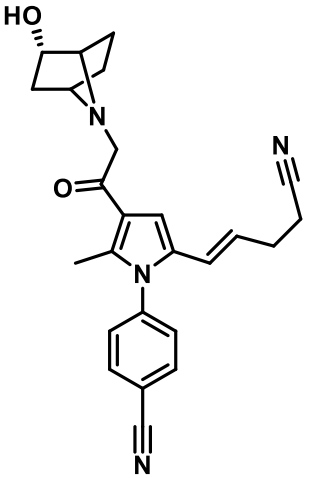
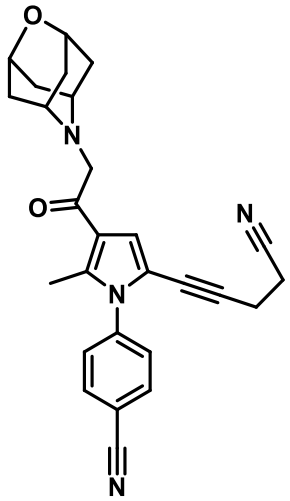
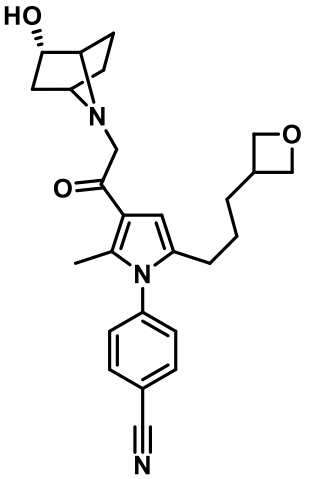
each n is independently 0, 1 or 2.

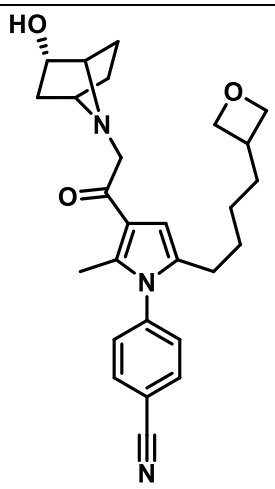
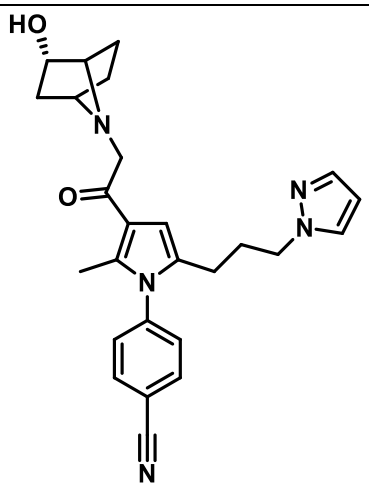
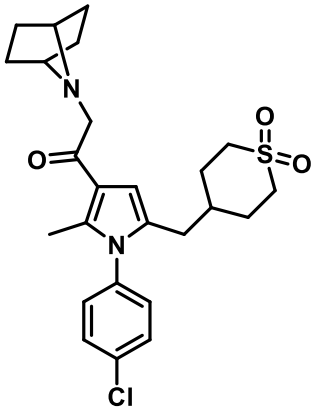
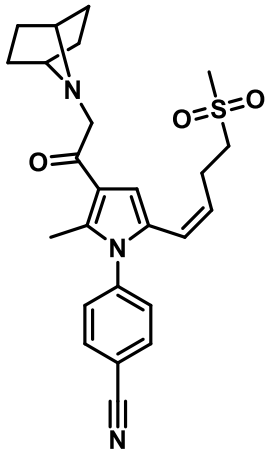
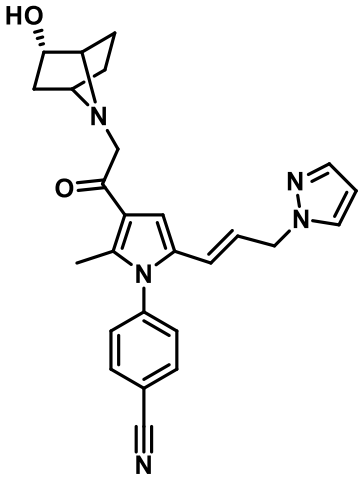
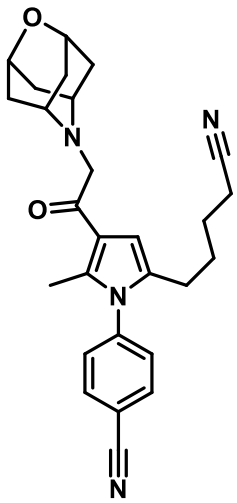
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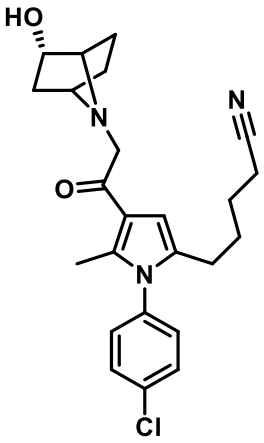
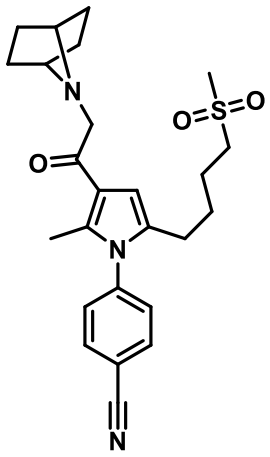
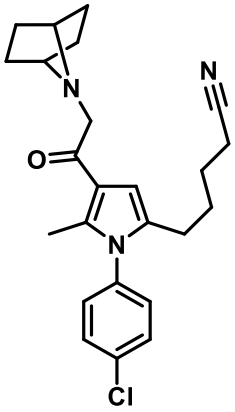
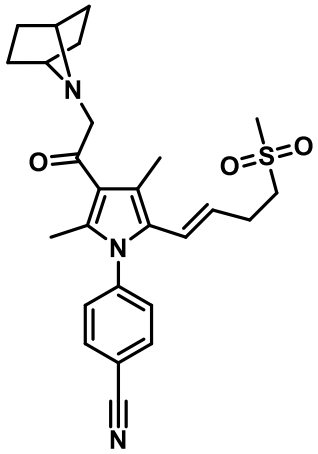
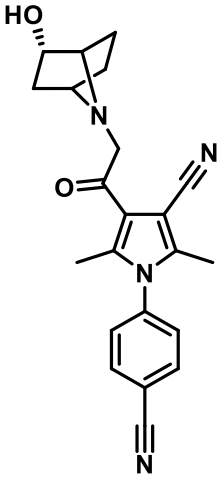
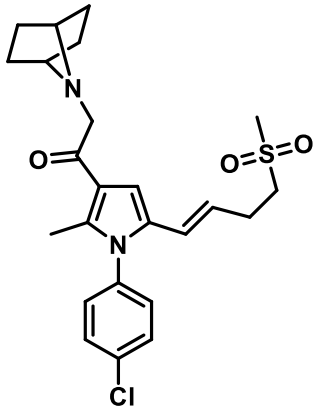
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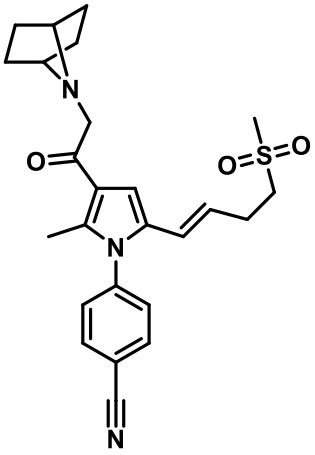
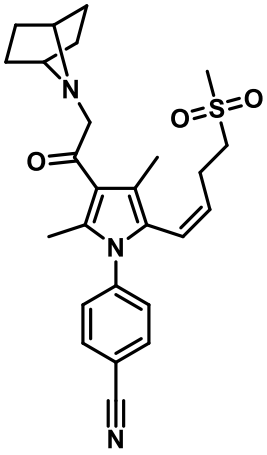
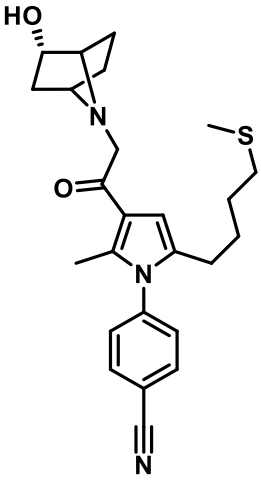
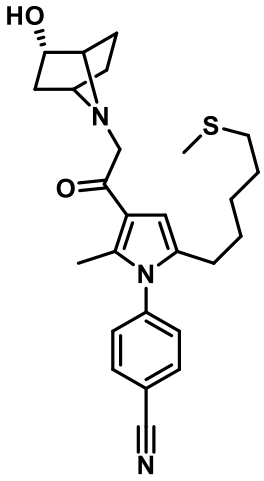
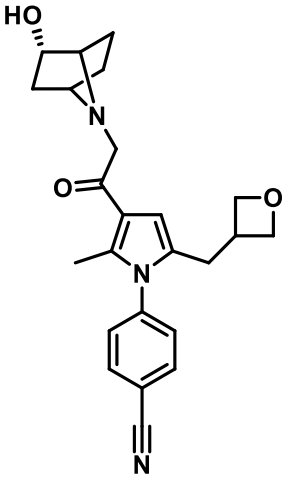
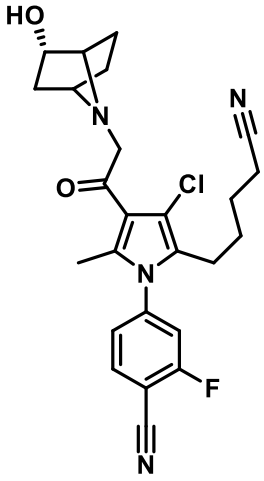
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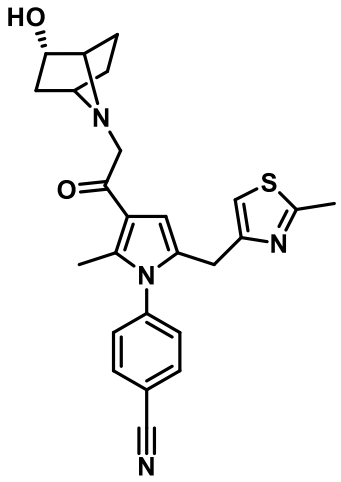
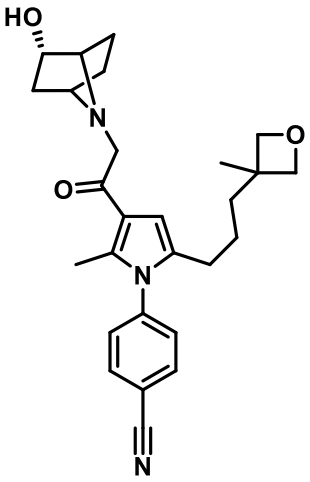
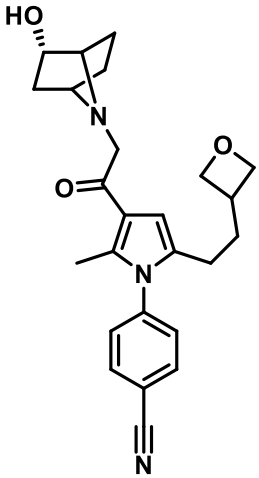
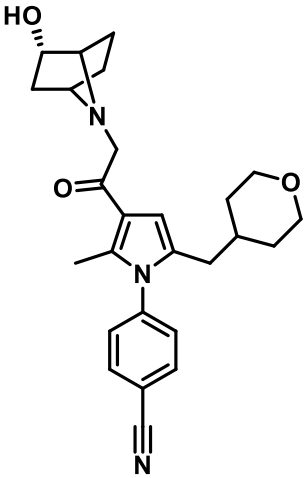
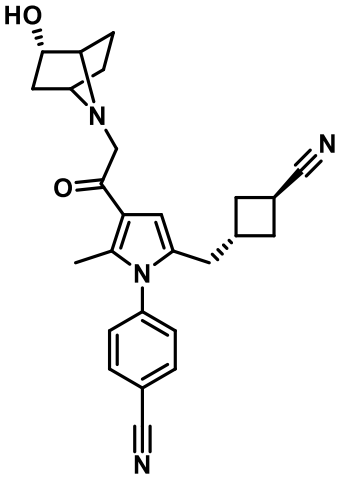
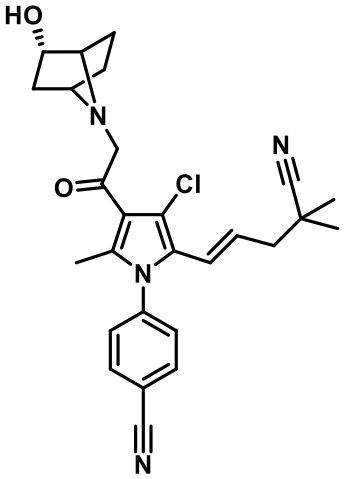
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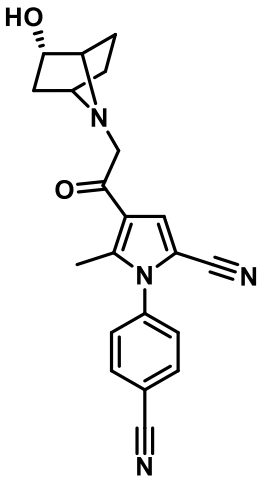
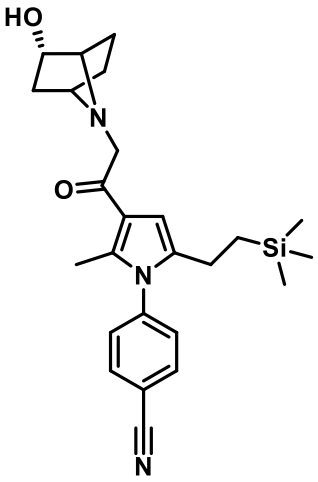
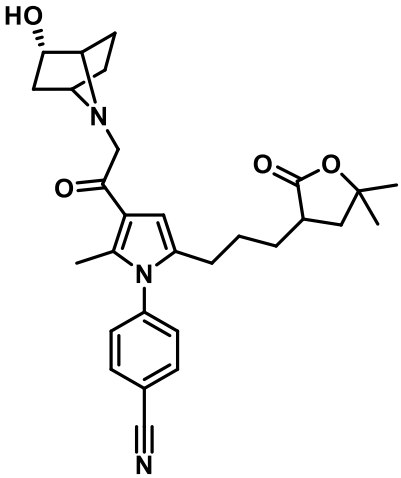
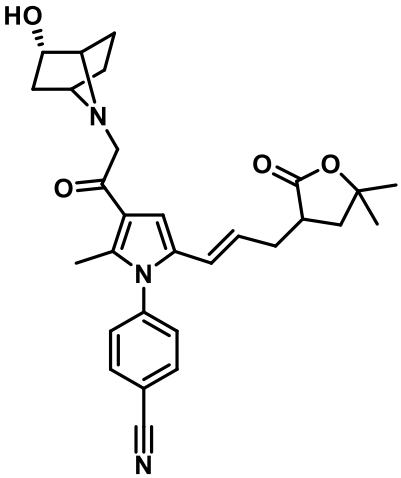
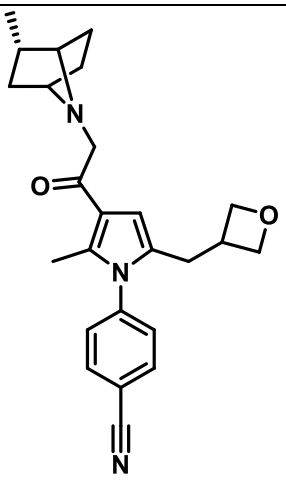
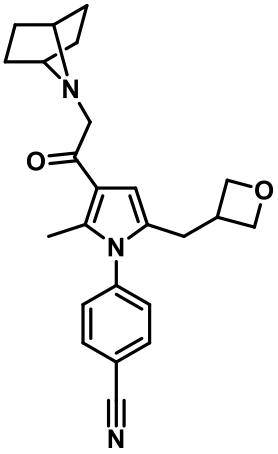
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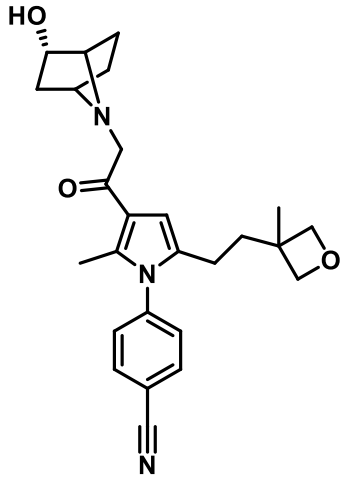
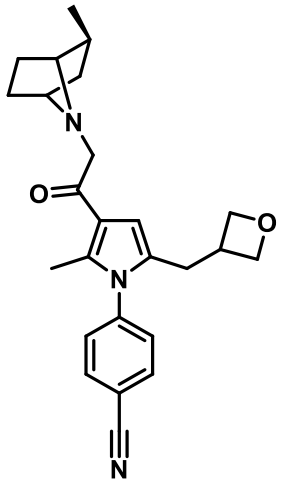
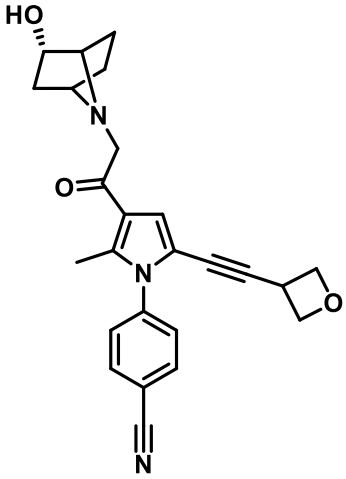
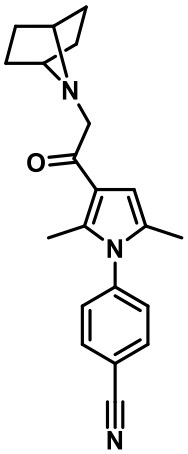
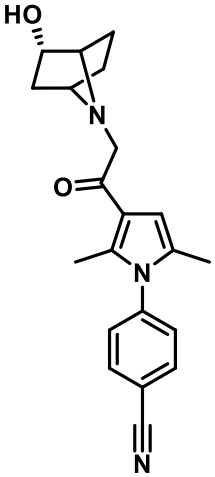
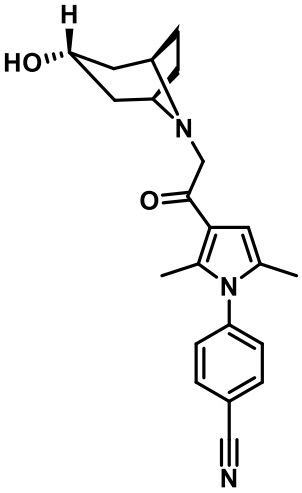
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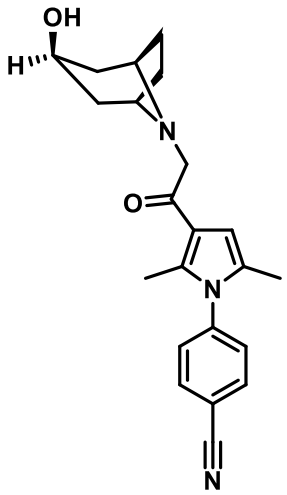
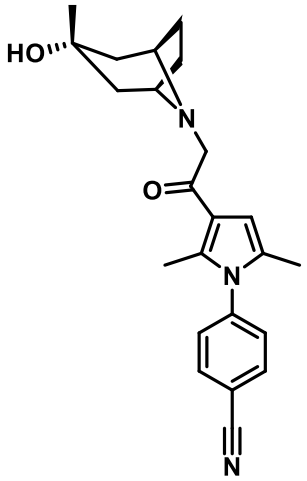
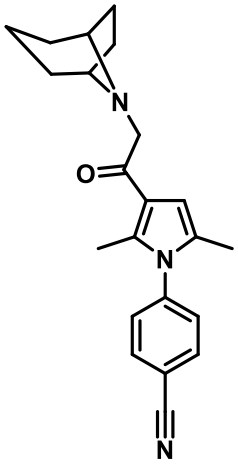
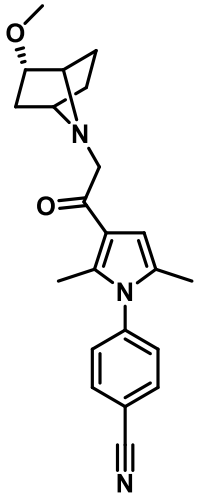
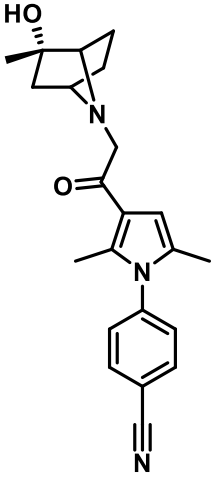
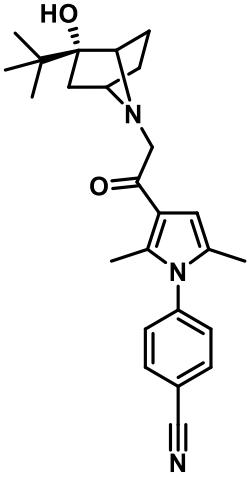
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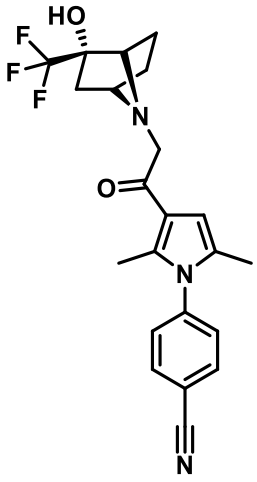
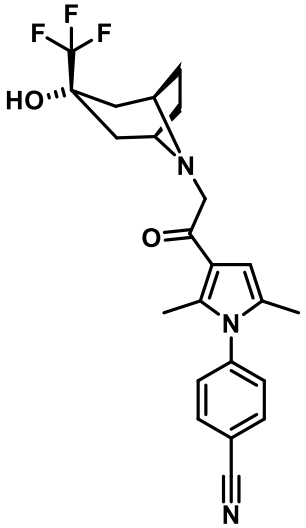
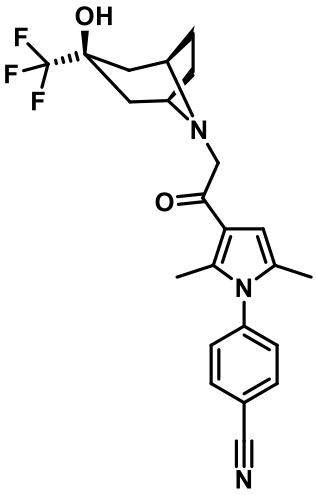
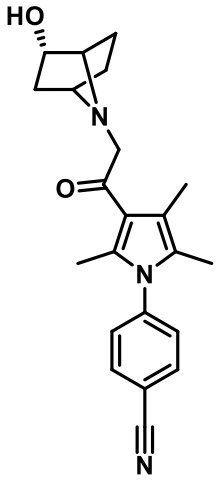
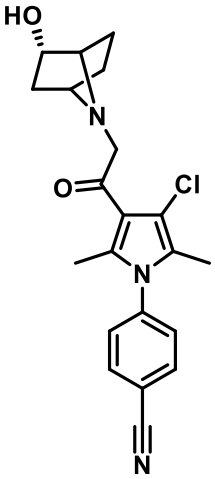
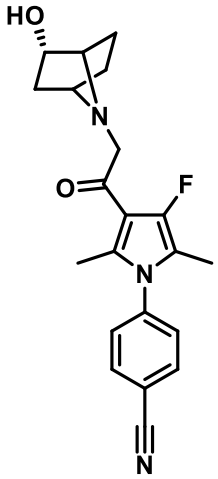
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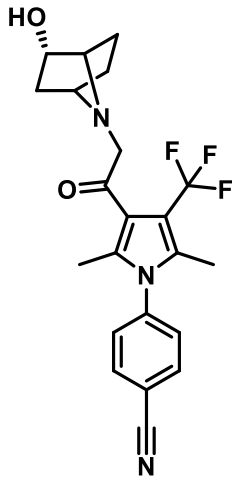
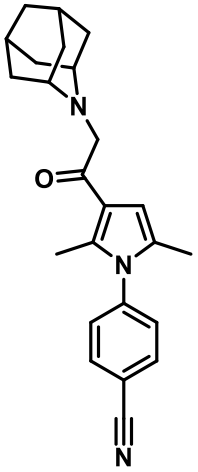
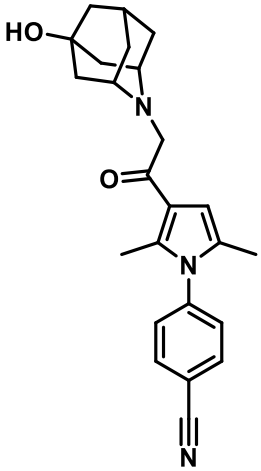
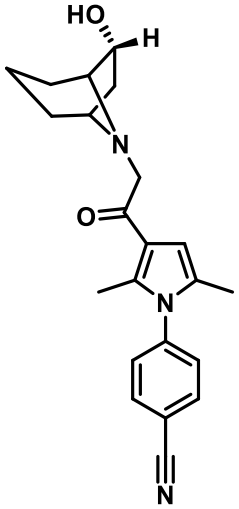
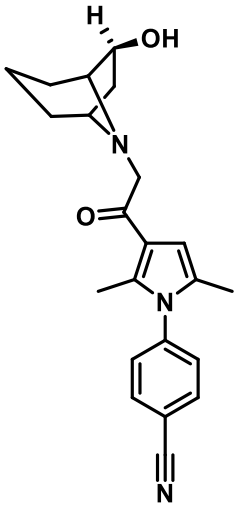
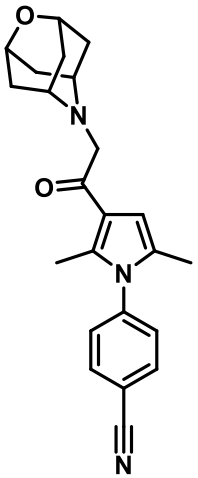
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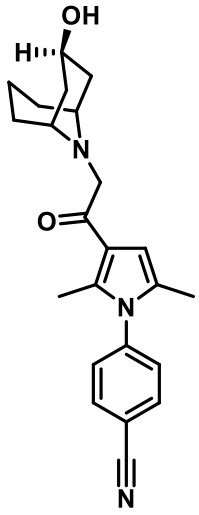
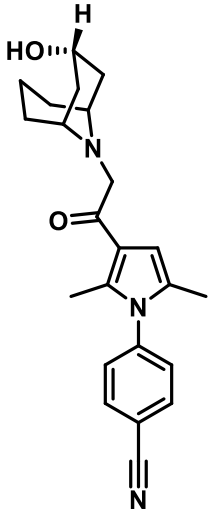
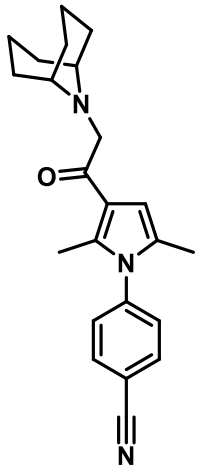
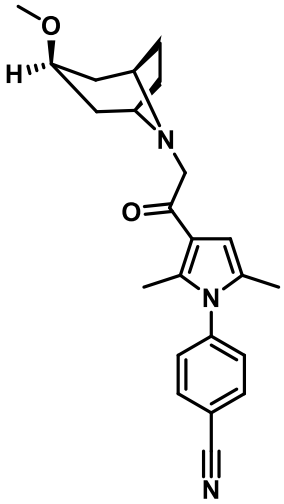
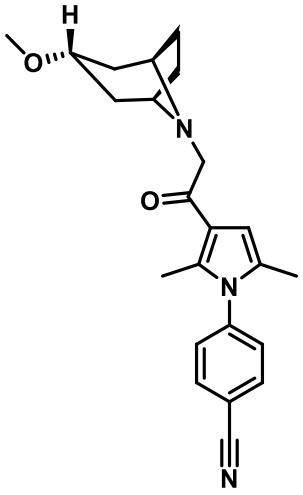
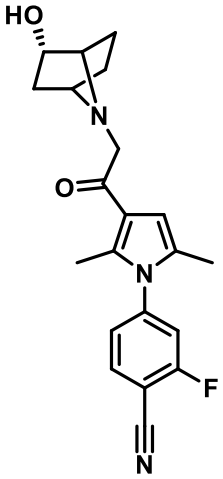
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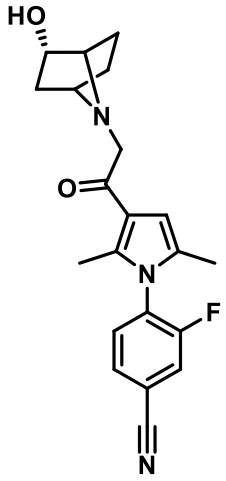
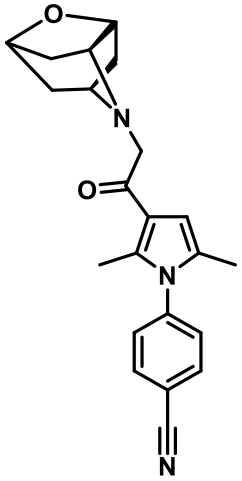
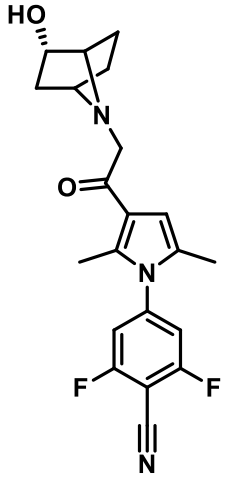
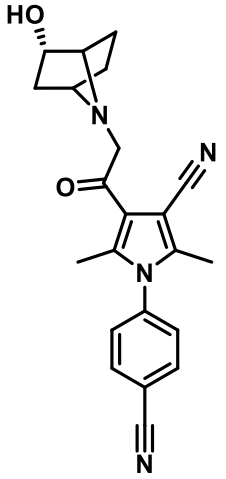
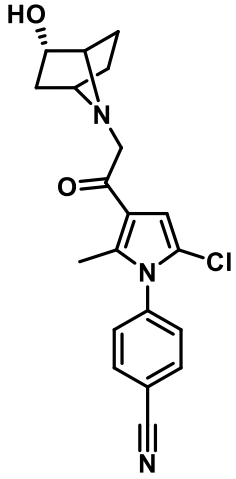
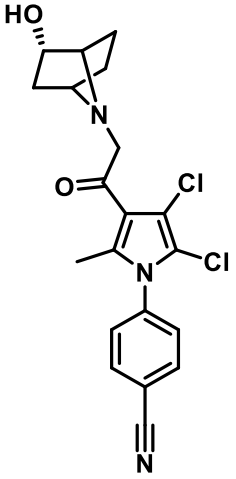
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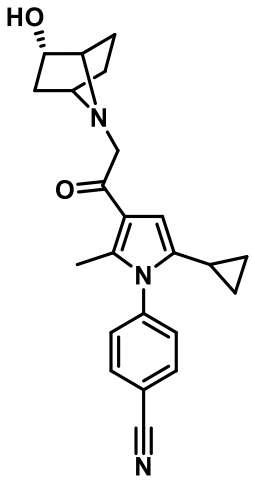
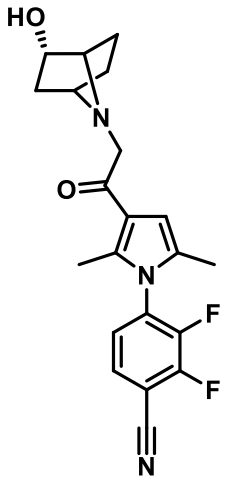
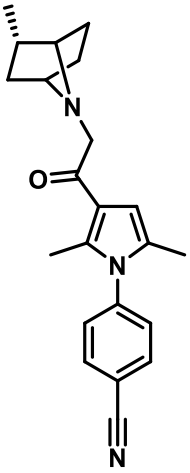
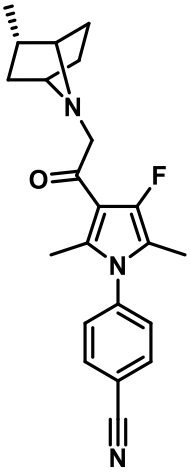
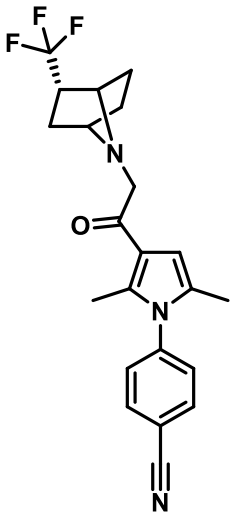
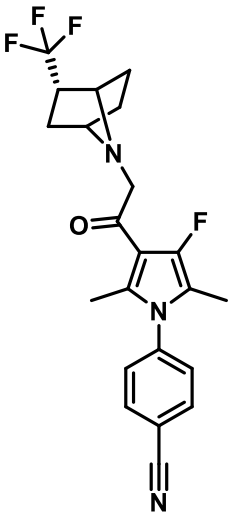
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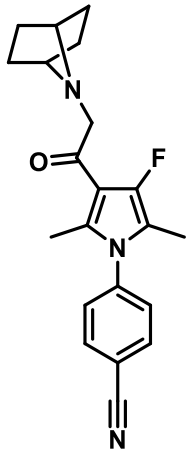
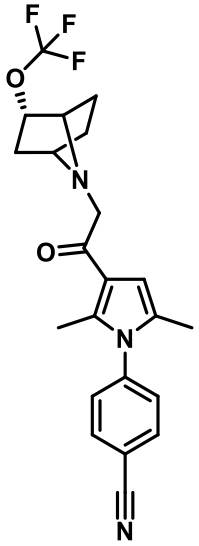
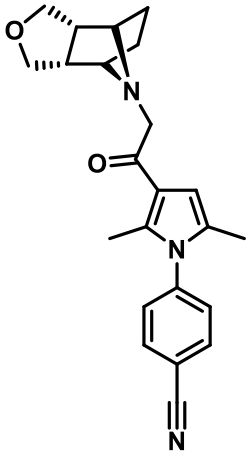
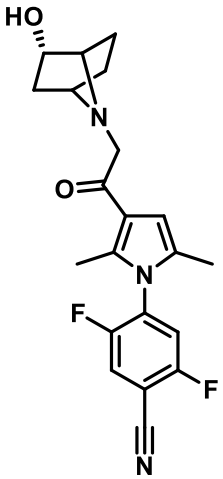
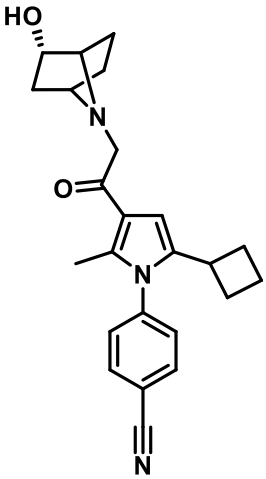
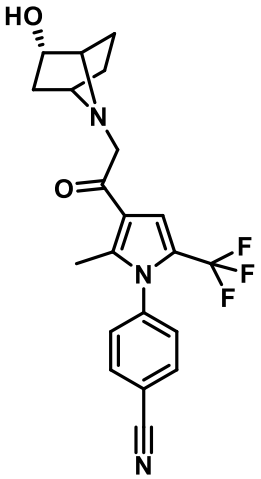
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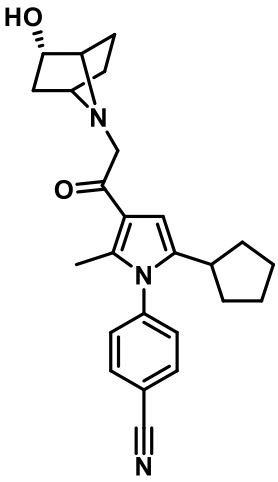
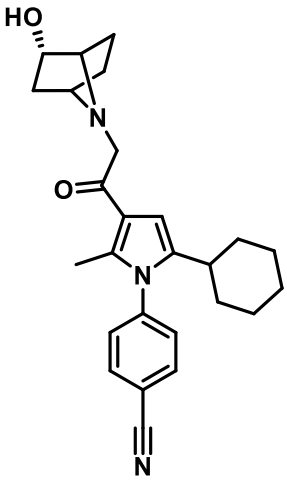
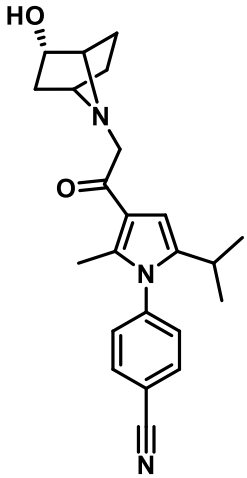
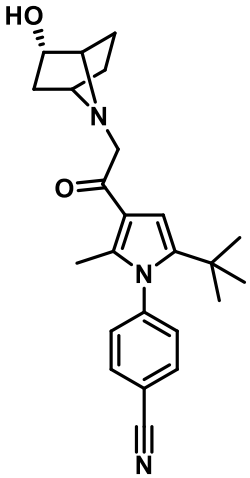
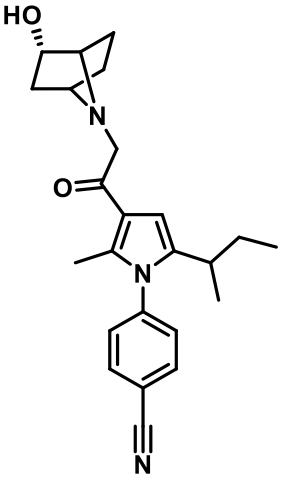
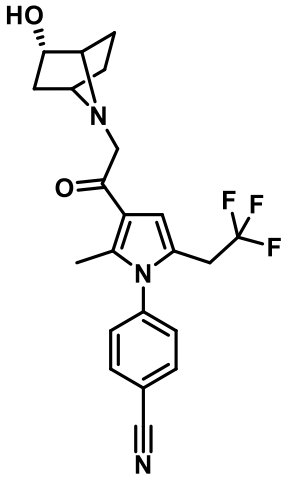
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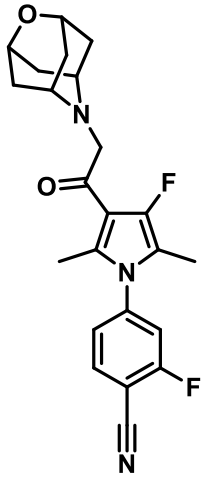
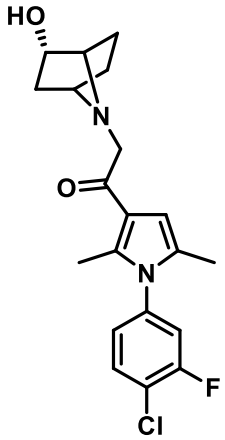
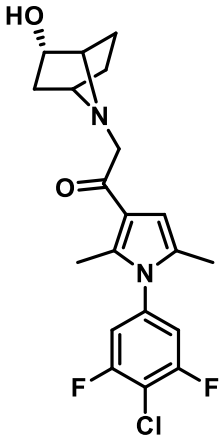
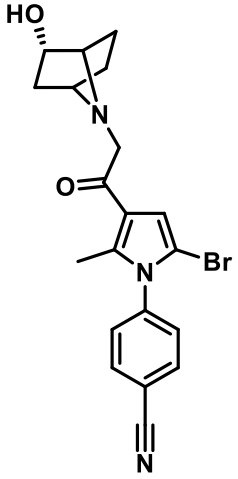
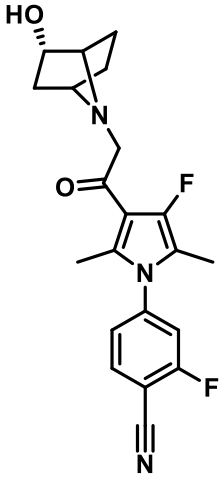
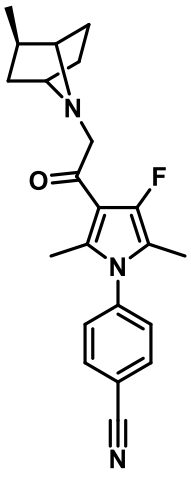
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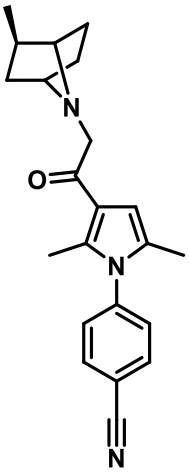
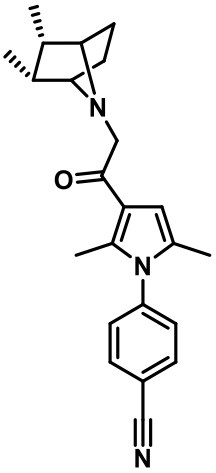
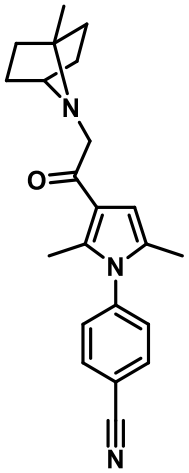
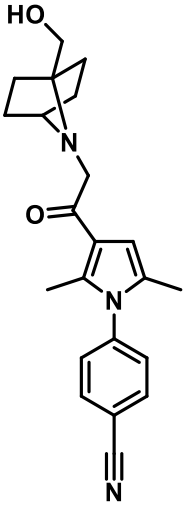
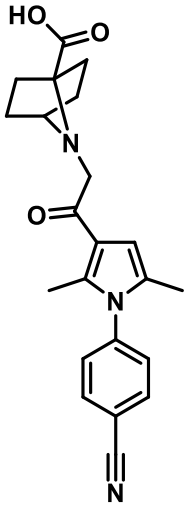
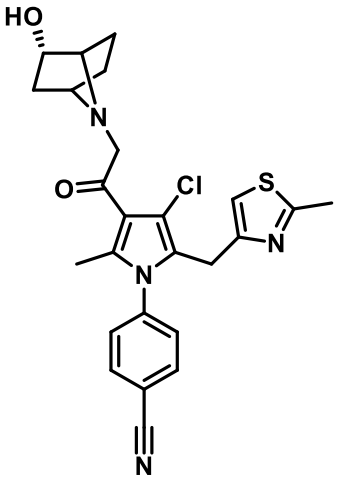
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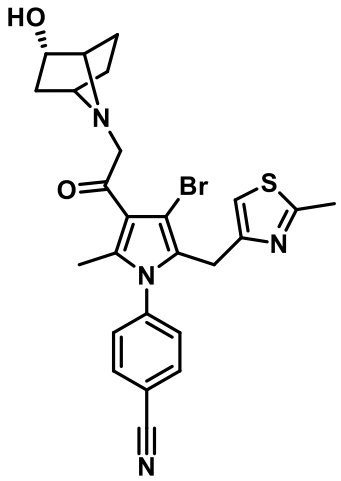
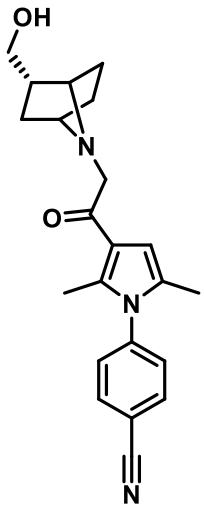
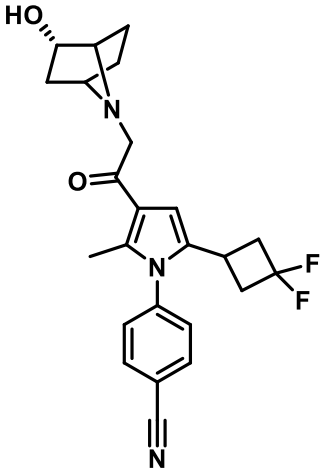
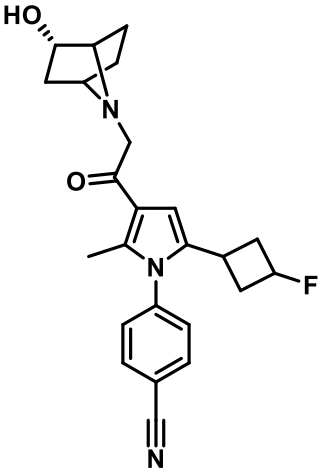
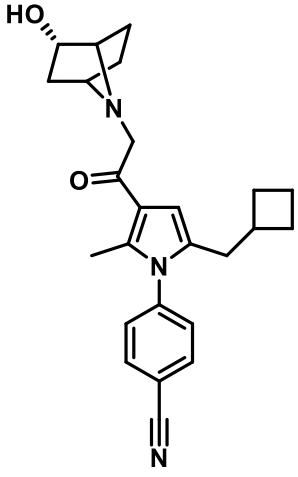
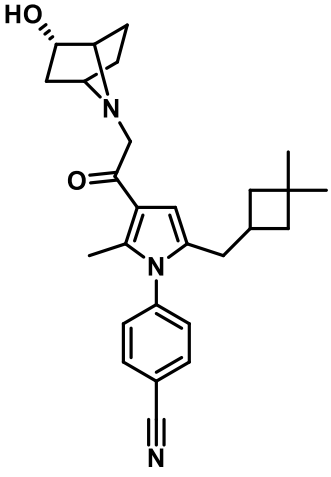
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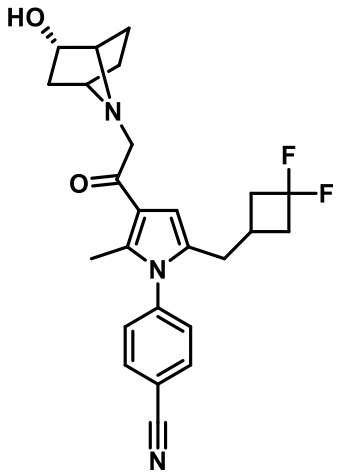
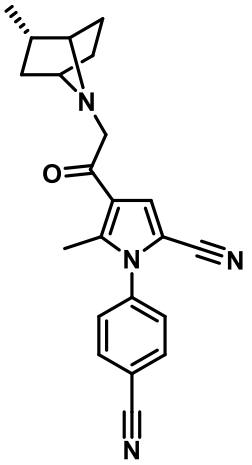
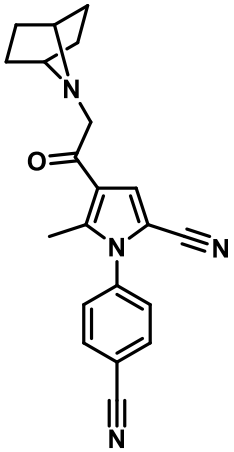
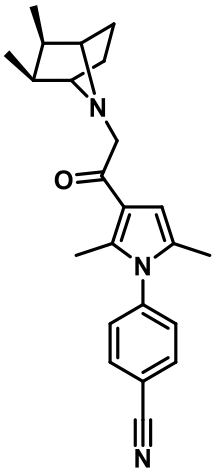
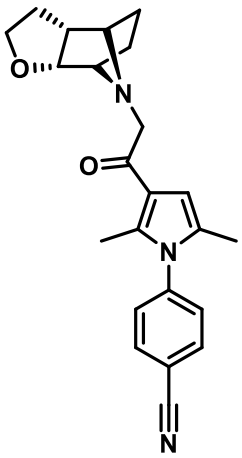
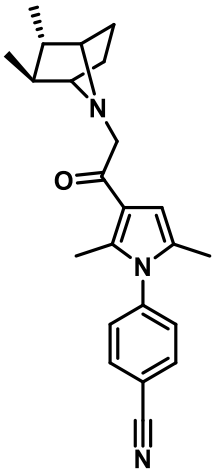
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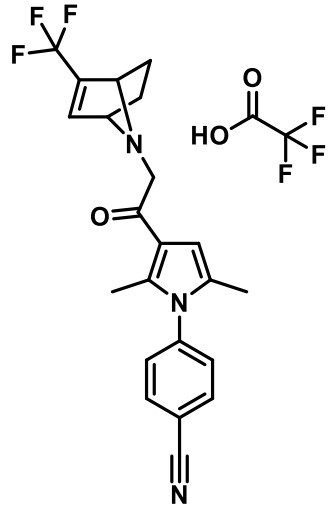
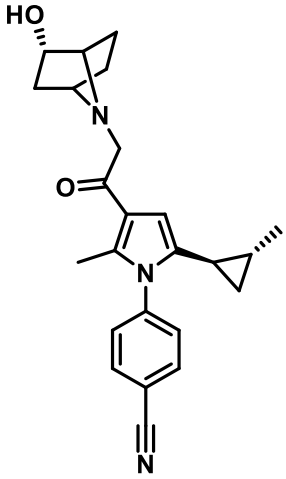
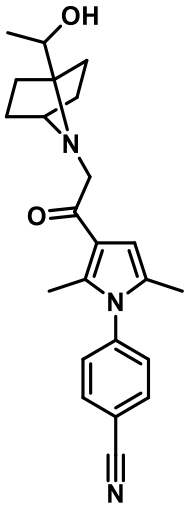
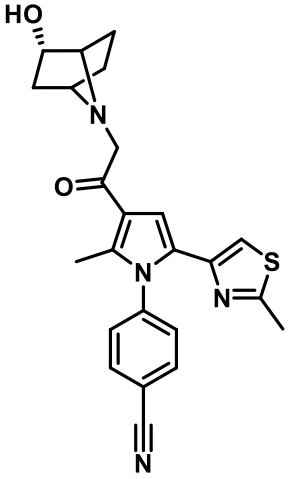
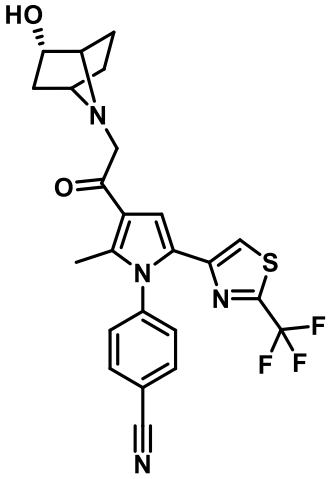
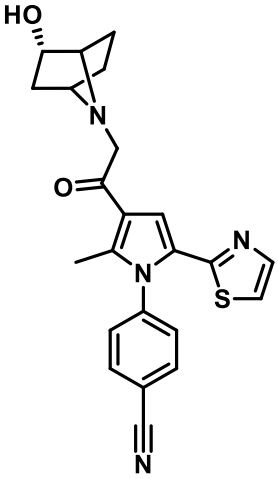
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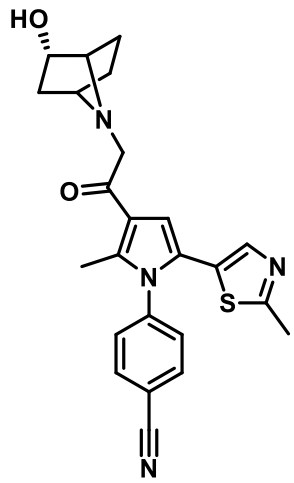
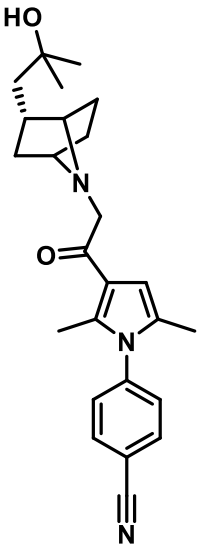
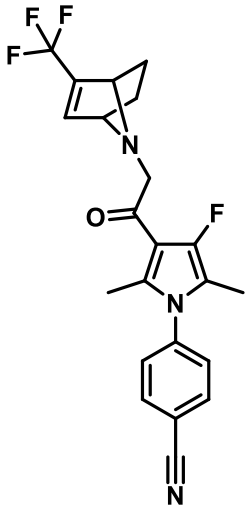
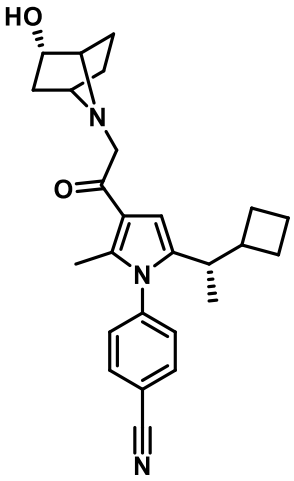
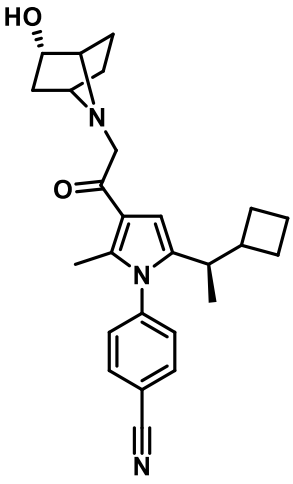
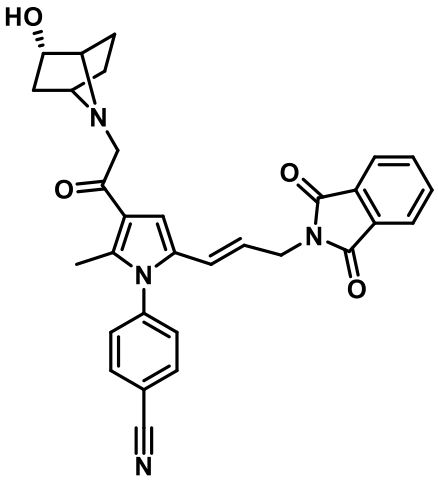
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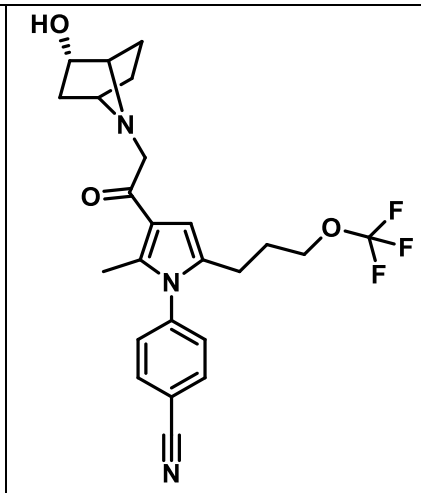
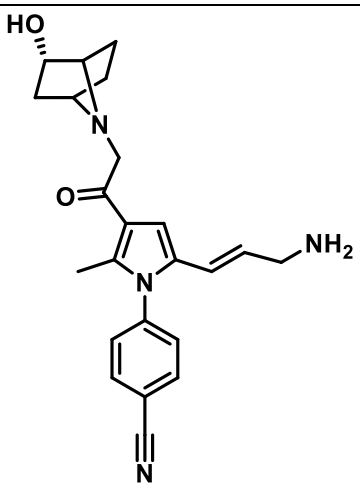
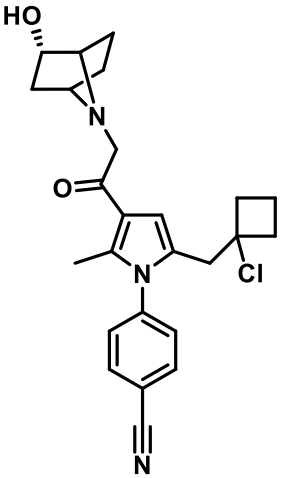
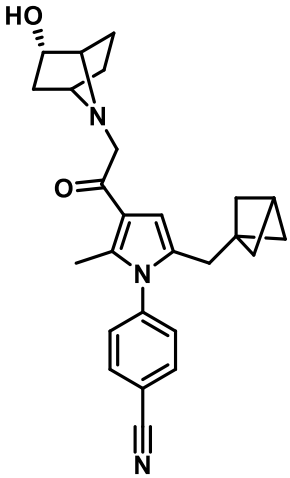
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137B		138B	
139B		140B	

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143B		144B	
145B		146B	

147B		148B	
149B		150B	
151B		153B	

155B		156B	
157B		158B	

or a pharmaceutically acceptable salt, solvate, or clathrate thereof.

In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising the compound disclosed herein, and a pharmaceutically acceptable excipient.

In a further aspect of the present disclosure, there is provided a use of a compound disclosed herein, in the manufacture of a medicament for treating a patient suffering from alysosomal storage disease, a myopathy, a cardiovascular disease, diabetes and/or complications of diabetes, an ocular disease, Huntington's disease, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, a cancer, a tumor, a hemoglobinopathy, inflammatory disease, intermediate filament disease, drug-induced lung damage, hearing loss, Hippel-Lindau disease, spinocerebellar ataxia, Angelman syndrome, giant axon neuropathy, inclusion body myopathy with Paget disease, frontotemporal dementia, frontotemporal lobar dementia, progressive supranuclear palsy, prion disease or autism.

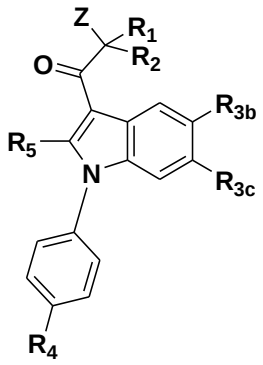
In a further aspect of the present disclosure, there is provided a compound disclosed herein, for use in the treatment of a patient suffering from a lysosomal storage disease, a myopathy, a cardiovascular disease, diabetes and/or complications of diabetes, an ocular disease, Huntington's disease, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, a cancer, a tumor, a hemoglobinopathy, inflammatory disease, intermediate filament disease, drug-induced lung damage, hearing loss, Hippel-Lindau disease, spinocerebellar ataxia, Angelman syndrome, giant axon neuropathy, inclusion body myopathy with Paget disease, frontotemporal dementia, frontotemporal lobar dementia, progressive supranuclear palsy, prion disease or autism.

The present disclosure is based, in part, on the discovery that compounds of the present disclosure inhibit Usp14. The present disclosure is directed to compounds encompassed by any of the Formulae (Ia), (Ib), (Ic), (Id), (II), (IIa), (IIb), (IIc), (III), (IIIa), (IIIb), (IIIc), (IIId), and (IIIe), and pharmaceutically acceptable salts, solvates, clathrates and prodrugs of any of thereof, compositions thereof, methods for the treatment of a condition associated with a dysfunction in proteostasis, methods for enhancing proteasome activity and methods for treating cancer or tumor.

CLAIMS

What is claimed is:

1. A compound having the Formula (Ib):



(Ib);

or a pharmaceutically acceptable salt, solvate, or clathrate thereof; wherein:

Z is an optionally substituted, 6- to 12-membered bridged N-heterocyclic;

each of R_1 and R_2 is independently selected from the group consisting of hydrogen, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl;

each of R_{3b} and R_{3c} is independently selected from the group consisting of hydrogen, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted aryl, halo, N_3, OR_c, NR_dR_d, $C(O)OR_c$, NO_2, CN, $C(O)R_c$, $C(O)C(O)R_c$, $C(O)NR_dR_d$, $NR_dC(O)R_c$, $NR_dS(O)_nR_c$, $N(R_d)(COOR_c)$, $NR_dC(O)C(O)R_c$, $NR_dC(O)NR_dR_d$, $NR_dS(O)_nNR_dR_d$, $NR_dS(O)_nR_c$, $S(O)_nR_c$, $S(O)_nNR_dR_d$, $OC(O)OR_c$, $(C=NR_d)R_c$, $OC(O)R_c$, optionally substituted heterocyclic and optionally substituted heteroaryl;

R_4 is selected from the group consisting of hydrogen, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted aryl, halo, N_3, OR_c, NR_dR_d, $C(O)OR_c$, NO_2, CN, $C(O)R_c$, $C(O)C(O)R_c$, $C(O)NR_dR_d$, $NR_dC(O)R_c$, $NR_dS(O)_nR_c$, $N(R_d)(COOR_c)$, $NR_dC(O)C(O)R_c$, $NR_dC(O)NR_dR_d$, $NR_dS(O)_nNR_dR_d$, $NR_dS(O)_nR_c$, $S(O)_nR_c$, $S(O)_nNR_dR_d$, $OC(O)OR_c$, $(C=NR_d)R_c$, $OC(O)R_c$, optionally substituted heterocyclic and optionally substituted heteroaryl;

R_5 is independently selected from the group consisting of hydrogen, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl,

optionally substituted aryl, halo, N_3, OR_c, NR_dR_d, $C(O)OR_c$, NO_2, CN, $C(O)R_c$, $C(O)C(O)R_c$, $C(O)NR_dR_d$, $NR_dC(O)R_c$, $NR_dS(O)_nR_c$, $N(R_d)(COOR_c)$, $NR_dC(O)C(O)R_c$, $NR_dC(O)NR_dR_d$, $NR_dS(O)_nNR_dR_d$, $NR_dS(O)_nR_c$, $S(O)_nR_c$, $S(O)_nNR_dR_d$, $OC(O)OR_c$, $(C=NR_d)R_c$, $OC(O)R_c$, optionally substituted heterocyclic, and optionally substituted heteroaryl;

wherein substituents of optionally substituted Z, R_1, R_2, R_{3b}, R_{3c}, R_4, and R_5 are each independently selected from the group consisting of C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_{12} cycloalkyl, C_3-C_{12} cycloalkenyl, aryl, halo, N_3, OR_c, NR_dR_d, $C(O)OR_c$, NO_2, CN, $C(O)R_c$, $C(O)C(O)R_c$, $C(O)NR_dR_d$, $NR_dC(O)R_c$, $NR_dS(O)_nR_c$, $N(R_d)(COOR_c)$, $NR_dC(O)C(O)R_c$, $NR_dC(O)NR_dR_d$, $NR_dS(O)_nNR_dR_d$, $NR_dS(O)_nR_c$, $S(O)_nR_c$, $S(O)_nNR_dR_d$, $OC(O)OR_c$, $(C=NR_d)R_c$, $OC(O)R_c$, heterocyclic, and heteroaryl;

each R_c is independently selected from the group consisting of hydrogen, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, and optionally substituted heteroaryl;

each R_d is independently selected from the group consisting of hydrogen, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_1-C_{10} alkoxy, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, and optionally substituted heteroaryl; or two geminal R_d groups are taken together with the nitrogen atom to which they are attached to form an optionally substituted heterocyclic or an optionally substituted heteroaryl;

each n is independently 0, 1 or 2.

2. The compound of claim 1, wherein substituents of optionally substituted Z, R_1, R_2, R_{3b}, R_{3c}, R_4 and R_5 are each independently selected from the group consisting of C_1-C_4 alkyl, halo, OR_c, CN, $S(O)_nR_c$, heterocyclyl, and heteroaryl.

3. The compound of claim 1, wherein each of R_1 and R_2 is hydrogen.

4. The compound of claim 1, wherein R_4 is halo.

5. The compound of claim 4, wherein R_4 is Cl.

6. The compound of claim 1, wherein R_5 is hydrogen or C_1-C_{10} alkyl.

7. The compound of claim 6, wherein R_5 is methyl.

8. The compound of claim 1, wherein R_{3b} is hydrogen.

9. The compound of claim 1, wherein

each of R_1 and R_2 is hydrogen;

R_4 is Cl;

R_5 is methyl; and

R_{3b} is hydrogen.

10. The compound of claim 1, wherein R_{3c} is independently selected from the group consisting of optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted aryl, halo, N_3, OR_c, NR_dR_d, $C(O)OR_c$, NO_2, CN, $C(O)R_c$, $C(O)C(O)R_c$, $C(O)NR_dR_d$, $NR_dC(O)R_c$, $NR_dS(O)_nR_c$, $N(R_d)(COOR_c)$, $NR_dC(O)C(O)R_c$, $NR_dC(O)NR_dR_d$, $NR_dS(O)_nNR_dR_d$, $NR_dS(O)_nR_c$, $S(O)_nR_c$, $S(O)_nNR_dR_d$, $OC(O)OR_c$, $(C{=}NR_d)R_c$, $OC(O)R_c$, optionally substituted heterocyclic and optionally substituted heteroaryl, wherein

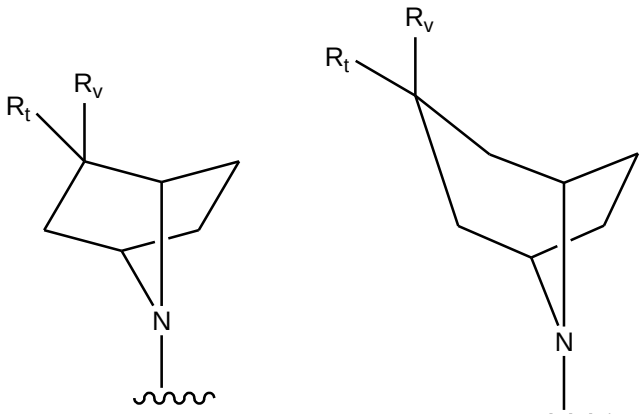
each R_c is independently selected from the group consisting of hydrogen, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, and optionally substituted heteroaryl;

each R_d is independently selected from the group consisting of hydrogen, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_1-C_{10} alkoxy, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, and optionally substituted heteroaryl; or two geminal R_d groups are taken together with the nitrogen atom to which they are attached to form an optionally substituted heterocyclic or an optionally substituted heteroaryl; and

each n is independently 0, 1 or 2.

11. The compound of claim 1, wherein R_{3c} is independently selected from the group consisting of C_1-C_{10} alkyl substituted with CN; $S(O)_nR_c$, wherein R_c is C_1-C_{10} alkyl or C_3-C_{12} cycloalkyl, and n is 2; optionally substituted heterocyclic; or and optionally substituted heteroaryl.

12. The compound of claim 1, wherein Z is:



or ; wherein

wherein R_t is selected from the group consisting of hydrogen, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted aryl, halo, N_3, OR_c, NR_dR_d, $C(O)OR_c$, NO_2, CN, $C(O)R_c$, $C(O)C(O)R_c$, $C(O)NR_dR_d$, $NR_dC(O)R_c$, $NR_dS(O)_nR_c$, $N(R_d)(COOR_c)$, $NR_dC(O)C(O)R_c$, $NR_dC(O)NR_dR_d$, $NR_dS(O)_nNR_dR_d$, $NR_dS(O)_nR_c$, $S(O)_nR_c$, $S(O)_nNR_dR_d$, $OC(O)OR_c$, $(C=NR_d)R_c$, $OC(O)R_c$, optionally substituted heterocyclic and optionally substituted heteroaryl; wherein

each R_c is independently selected from the group consisting of hydrogen, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, and optionally substituted heteroaryl;

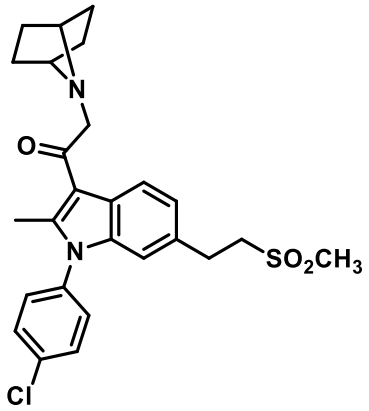
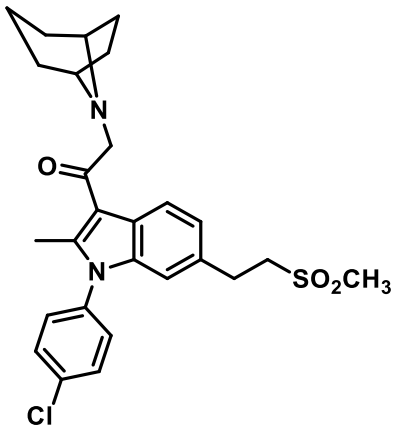
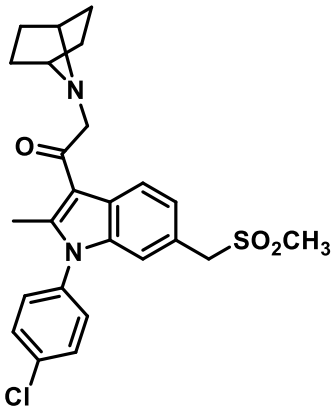
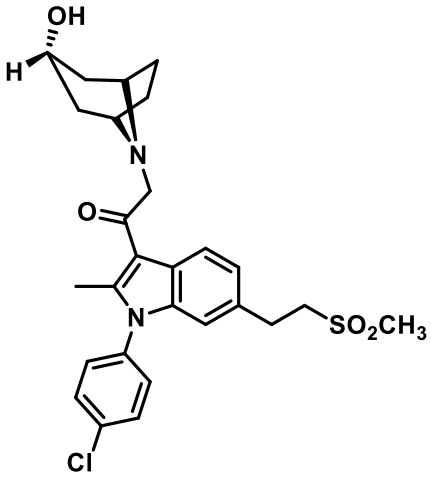
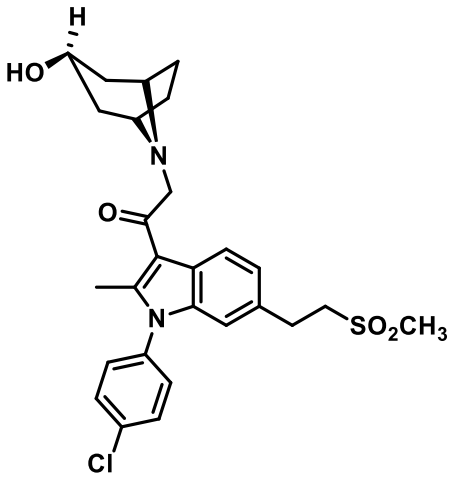
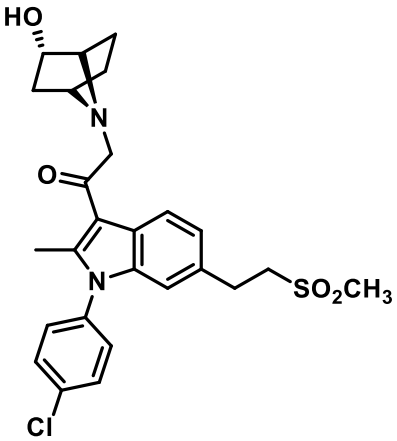
each R_d is independently selected from the group consisting of hydrogen, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_1-C_{10} alkoxy, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, and optionally substituted heteroaryl; or two geminal R_d groups are taken together with the nitrogen atom to which they are attached to form an optionally substituted heterocyclic or an optionally substituted heteroaryl; and

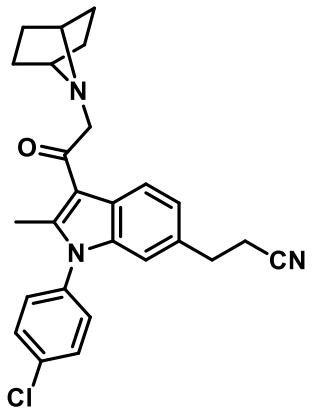
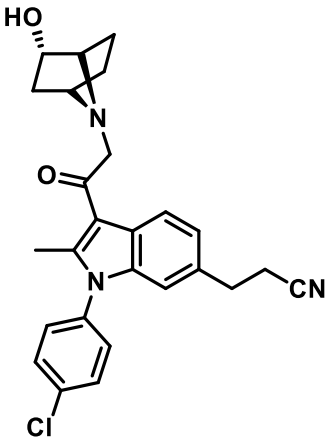
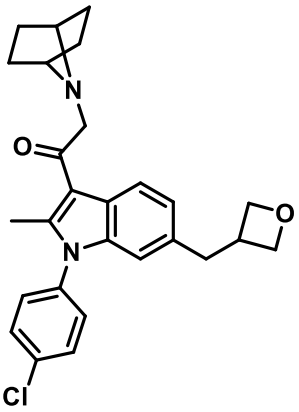
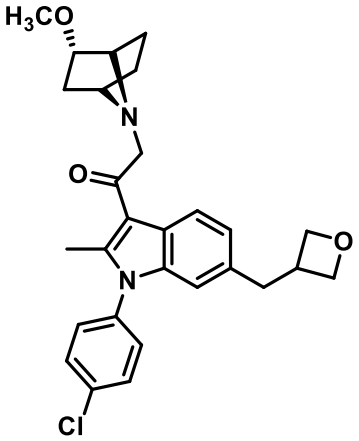
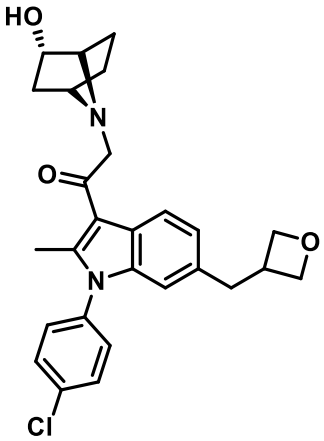
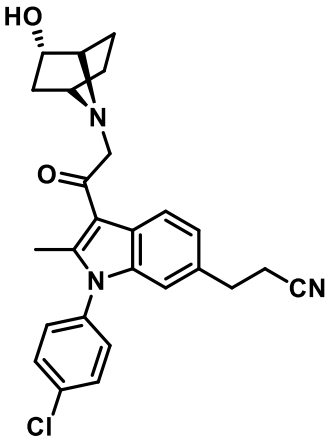
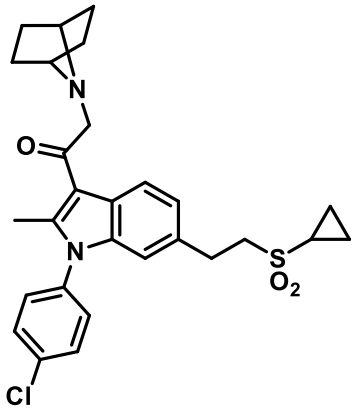
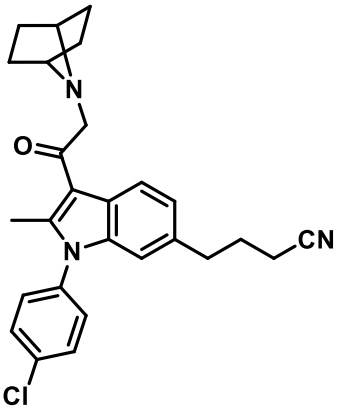
each n is independently 0, 1 or 2; and

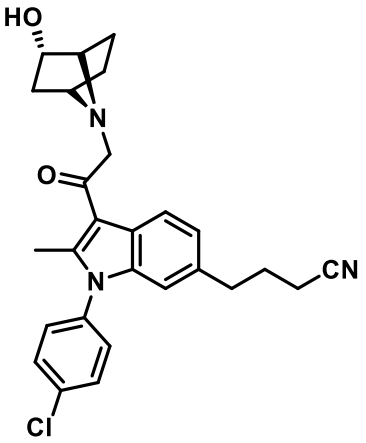
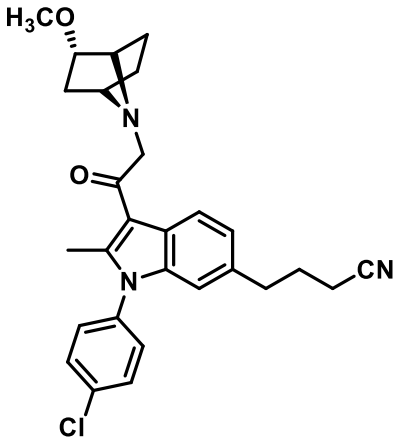
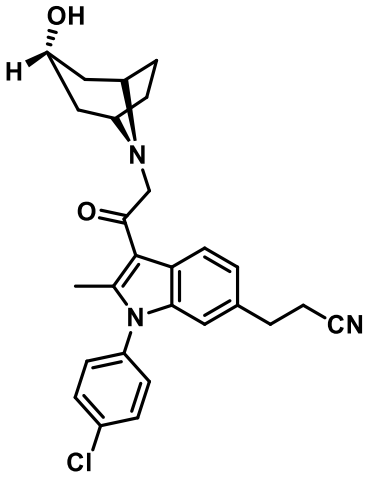
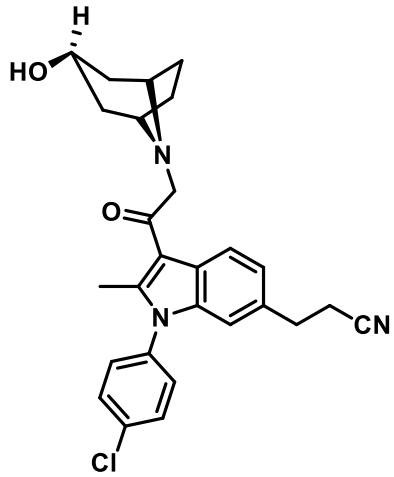
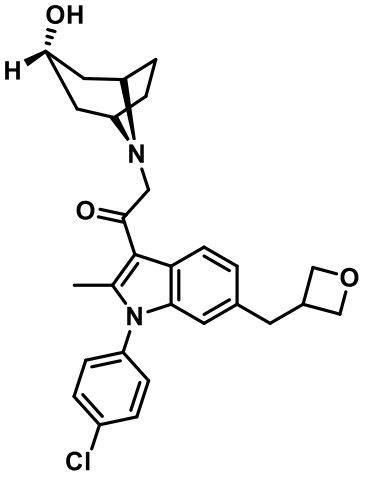
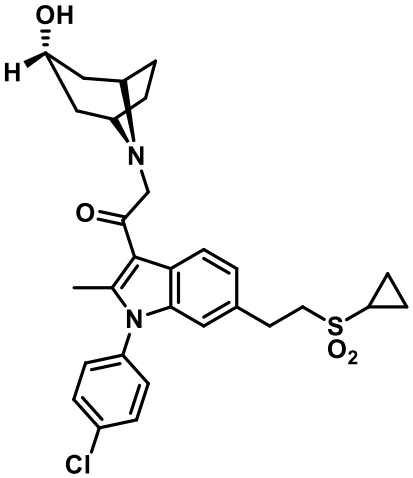
R_v is selected from the group consisting of hydrogen and optionally substituted C_1-C_{10} alkyl.

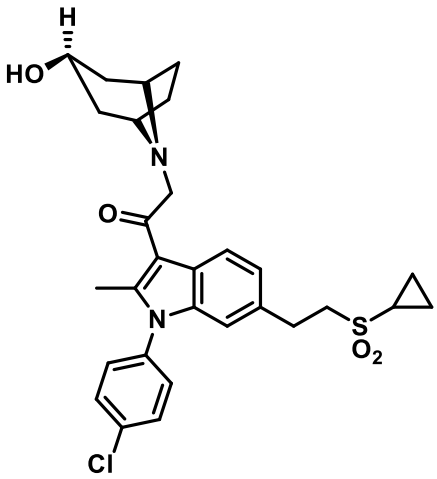
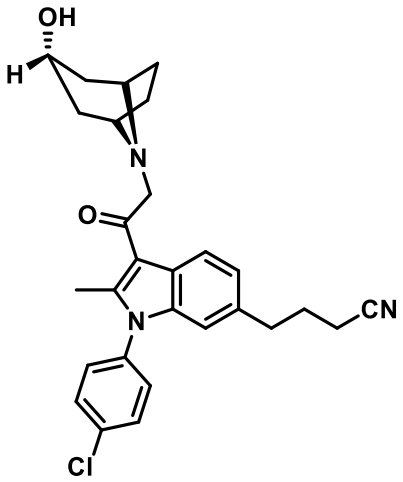
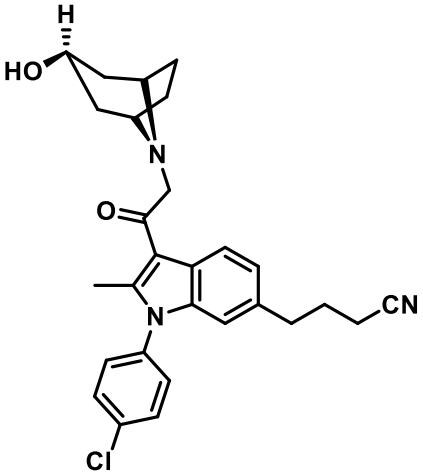
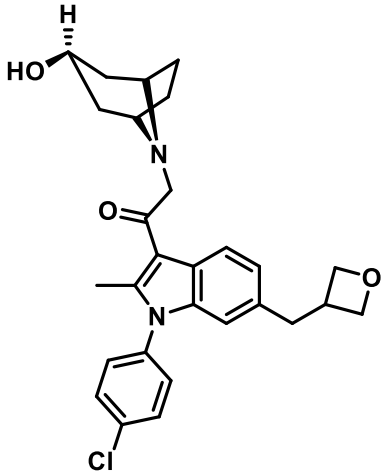
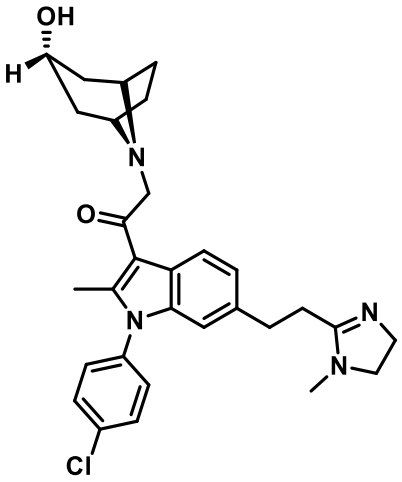
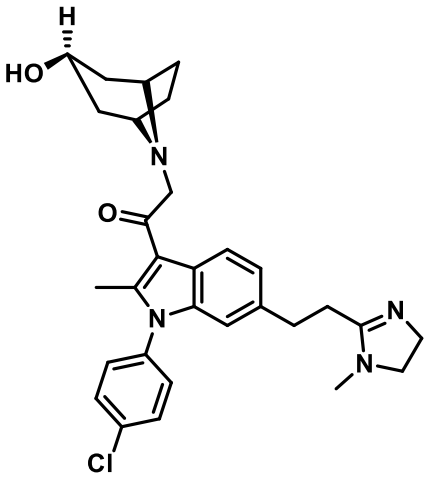
13. The compound of claim 12, wherein R_t is selected from the group consisting of hydrogen, C_1-C_{10} alkyl, and OR_c, wherein R_c is hydrogen or C_1-C_{10} alkyl; and R_v is hydrogen or C_1-C_4 alkyl.

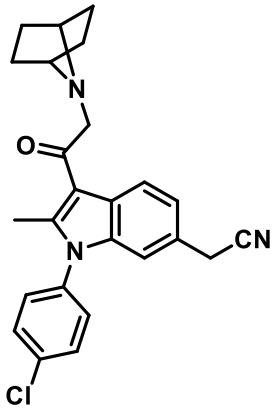
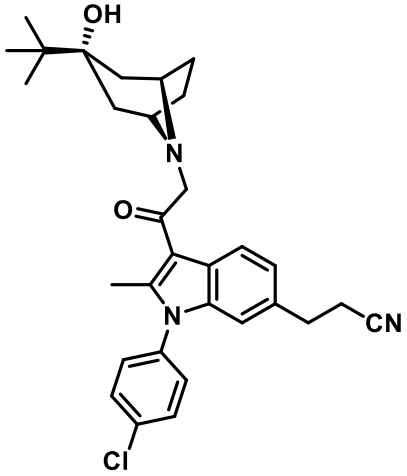
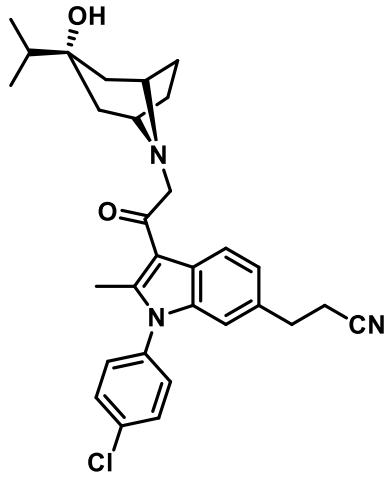
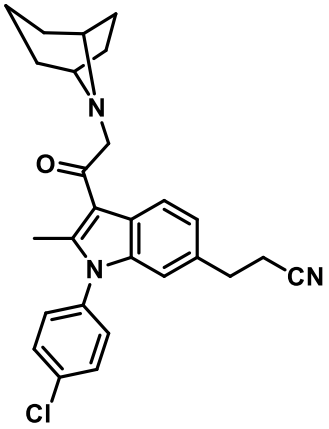
14. The compound of claim 1, said compound selected from the group consisting of:

1A		2A	
3A		4A	
5A		6A	

8A		10A	
11A		12A	
13A		15A	
16A		17A	

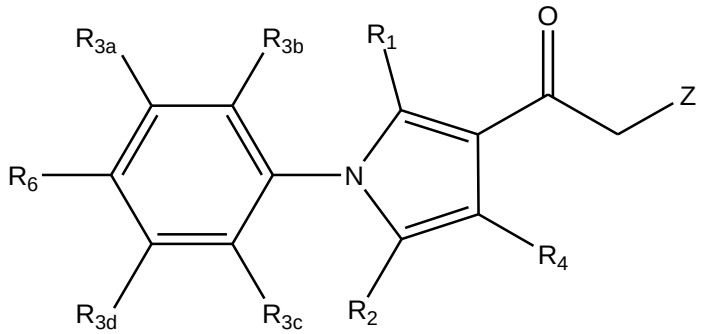
18A		19A	
20A		21A	
22A		23A	

24A		25A	
26A		27A	
28A		29A	

30A		31A	
32A		33A	

or a pharmaceutically acceptable salt, solvate, or clathrate thereof.

15. A compound of formula (III):



(III);

or a pharmaceutically acceptable salt, solvate, or clathrate thereof; wherein:

R_1 is selected from the group consisting of hydrogen, optionally substituted C_1-C_4 alkyl, and halo;

R_2 is selected from the group consisting of optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12}

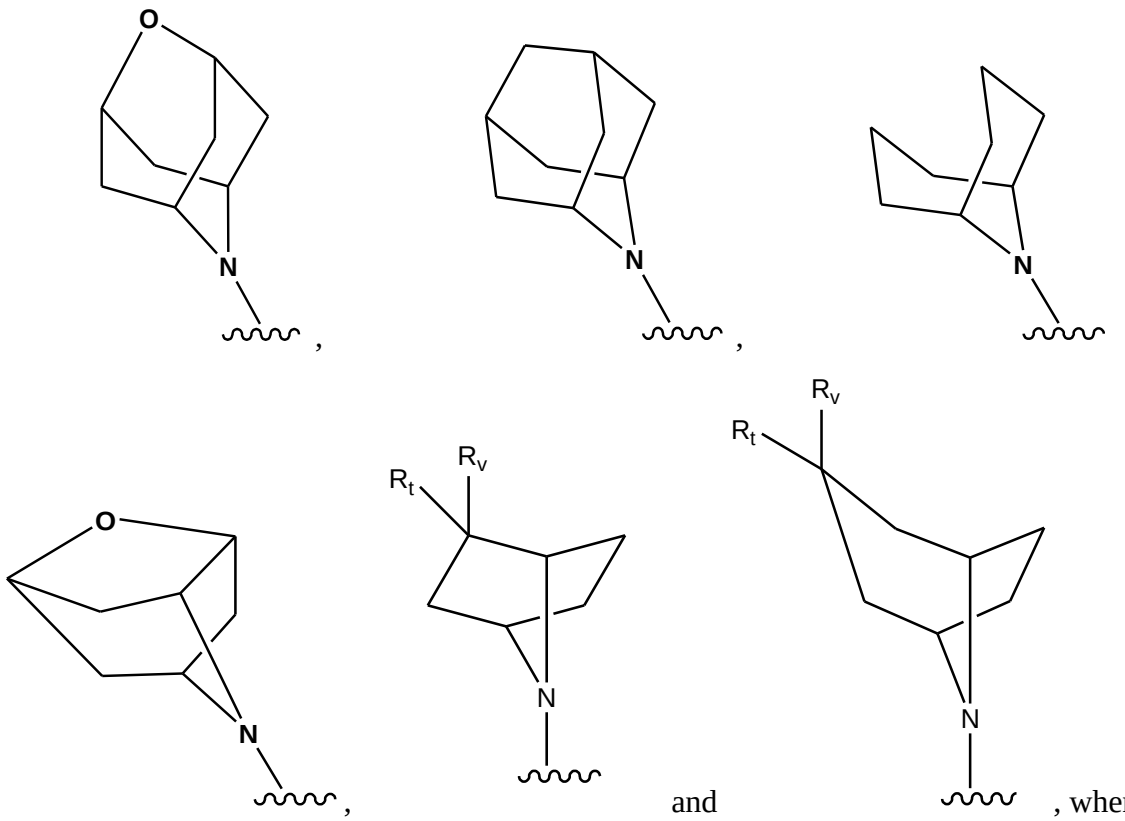
cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted 4- to 12-membered heterocyclic, optionally substituted aryl, optionally substituted 4- to 12-membered heteroaryl, halo, and CN;

R_{3a}, R_{3b}, R_{3c} and R_{3d} are each independently selected from the group consisting of hydrogen, optionally substituted C_1-C_6 alkyl, CN, and halo;

R_4 is selected from the group consisting of hydrogen, optionally substituted C_1-C_{10} alkyl, halo, and CN;

R_6 is selected from the group consisting of hydrogen, optionally substituted C_1-C_6 alkyl, CN, and halo; and

Z is selected from the group consisting of



, wherein

R_t is selected from the group consisting of hydrogen, optionally substituted C_1-C_4 alkyl, optionally substituted C_2-C_4 alkenyl, OR_{c2}, and $C(O)OR_{e2}$, wherein

each R_{c2} and R_{e2} is independently selected from the group consisting of hydrogen, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted 4- to 12-membered heterocyclic, optionally substituted aryl, and optionally substituted 4- to 12-membered heteroaryl; and

R_v is hydrogen or optionally substituted C_1-C_{10} alkyl;

wherein substituents of optionally substituted Z, R_1, R_2, R_{3a}, R_{3b}, R_{3c}, R_{3d}, R_4, and R_6 are each independently selected from the group consisting of C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_{12} cycloalkyl, C_3-C_{12} cycloalkenyl, aryl, halo, N_3, OR_c, NR_dR_d, $C(O)OR_c$, NO_2, CN, $C(O)R_c$, $C(O)C(O)R_c$, $C(O)NR_dR_d$, $NR_dC(O)R_c$, $NR_dS(O)_nR_c$, $N(R_d)(COOR_c)$, $NR_dC(O)C(O)R_c$, $NR_dC(O)NR_dR_d$, $NR_dS(O)_nNR_dR_d$, $NR_dS(O)_nR_c$, $S(O)_nR_c$, $S(O)_nNR_dR_d$, $OC(O)OR_c$, $(C=NR_d)R_c$, $OC(O)R_c$, $Si(R_c)_3$, heterocyclic, and heteroaryl;

each R_c is independently selected from the group consisting of hydrogen, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, and optionally substituted heteroaryl;

each R_d is independently selected from the group consisting of hydrogen, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_1-C_{10} alkoxy, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, and optionally substituted heteroaryl; or two geminal R_d groups are taken together with the nitrogen atom to which they are attached to form an optionally substituted heterocyclic or an optionally substituted heteroaryl; and

each n is independently 0, 1 or 2.

16. The compound of claim 15, wherein substituents of optionally substituted R_1, R_2, R_{3a}, R_{3b}, R_{3c},R_{3d} , R_4, and R_6 are each independently selected from the group consisting of C_1-C_4 alkyl, halo, OR_c, CN, $S(O)_nR_c$, $Si(R_c)_3$, heterocyclyl, and heteroaryl.

17. The compound of claim 15, wherein R_1 is hydrogen or C_1-C_{10} alkyl.

18. The compound of claim 15, wherein R_1 is methyl.

19. The compound of claim 15, wherein R_{3a}, R_{3b}, R_{3c} and R_{3d} are each hydrogen.

20. The compound of claim 15, wherein R_4 is selected from the group consisting of hydrogen, methyl, chloro, and CN.

21. The compound of claim 15, wherein R_6 is CN or halo.

22. The compound of claim 15, wherein R_6 is Cl.

23. The compound of claim 15, wherein

R_1 is methyl;

R_{3a}, R_{3b}, R_{3c} and R_{3d} are each hydrogen;

R_4 is selected from the group consisting of hydrogen, methyl, chloro, and CN; and

R_6 is CN or chloro.

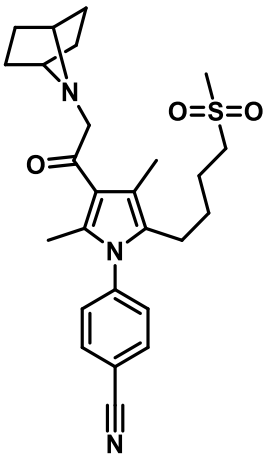
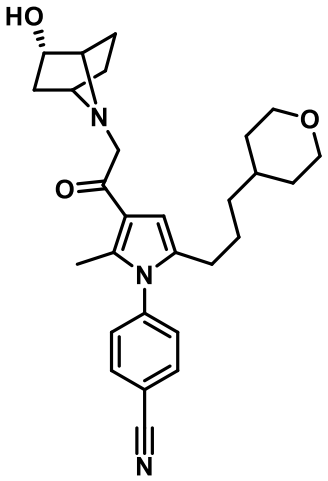
24. The compound of claim 15, wherein R_t is hydroxyl, and R_v is selected hydrogen.

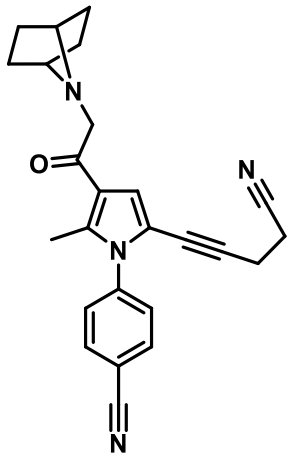
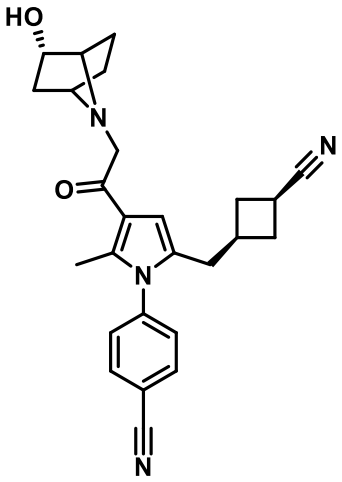
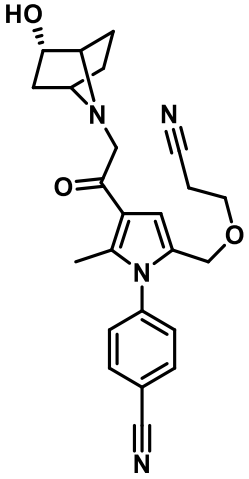
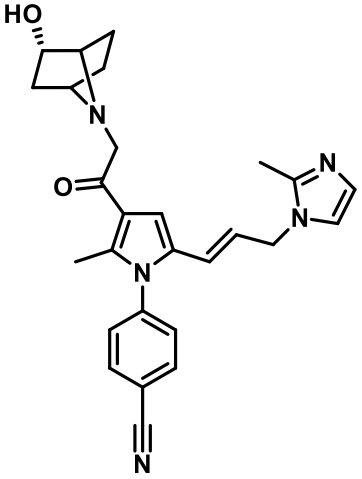
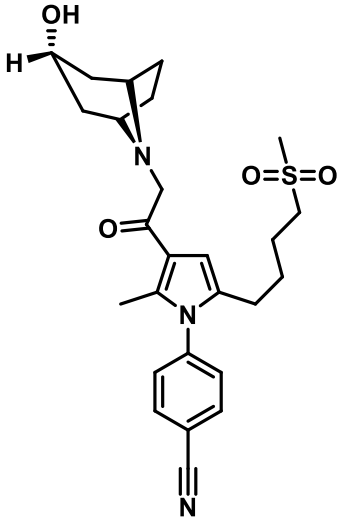
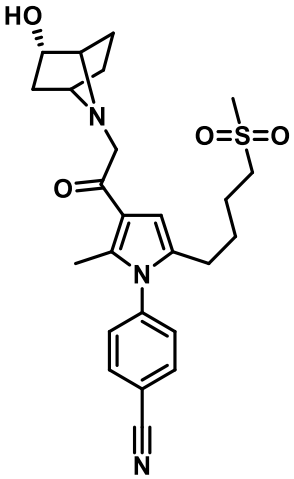
25. The compound of claim 15, wherein R_t is selected from the group consisting of hydrogen, hydroxyl, methanol, methyl, trifluoromethyl, O-CF_3, and methoxy.

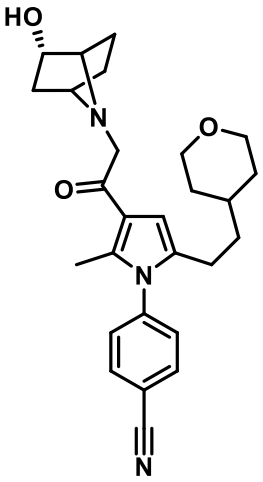
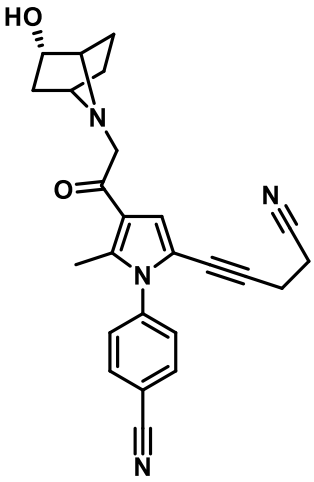
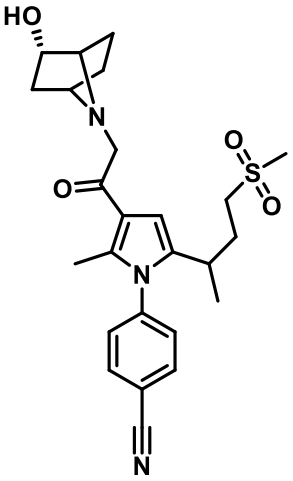
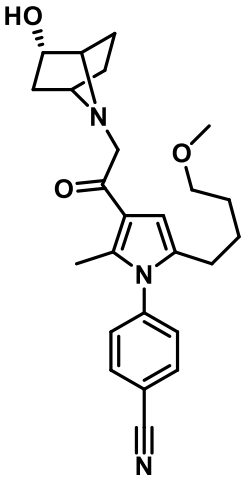
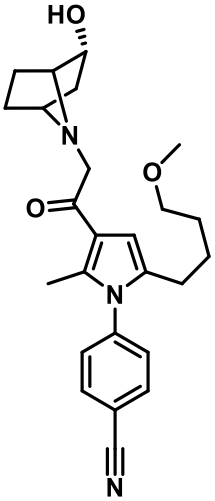
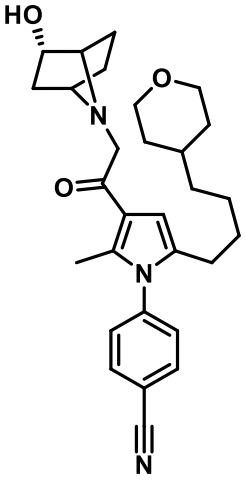
26. The compound of claim 15, wherein R_2 is selected from the group consisting of optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted 4- to 12-membered heterocyclic, optionally substituted aryl, optionally substituted 4- to 12-membered heteroaryl, halo, and CN.

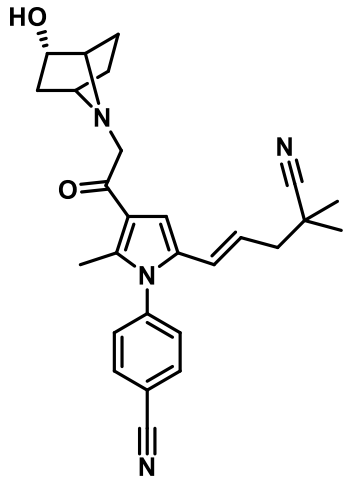
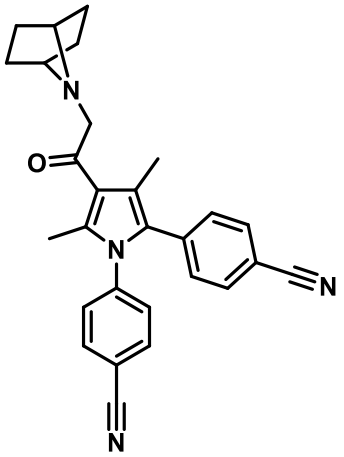
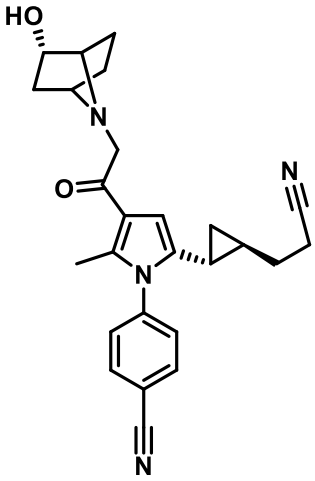
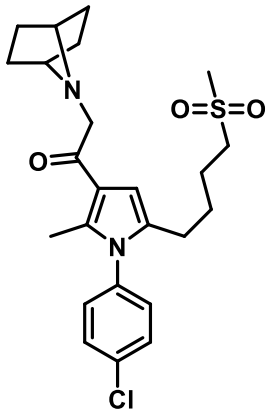
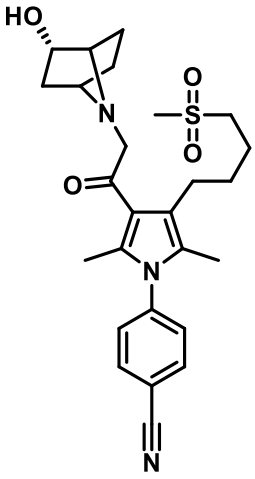
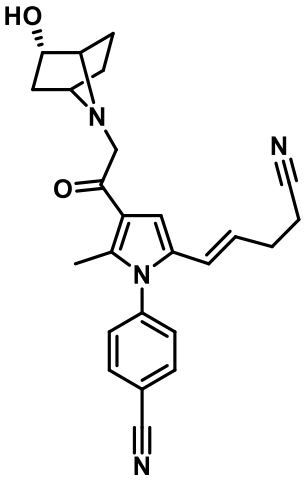
27. The compound of claim 26, wherein substituents of optionally substituted R_2 are each independently selected from the group consisting of C_1-C_4 alkyl, halo, OR_c, CN, $S(O)_nR_c$, $Si(R_c)_3$, heterocyclyl, and heteroaryl.

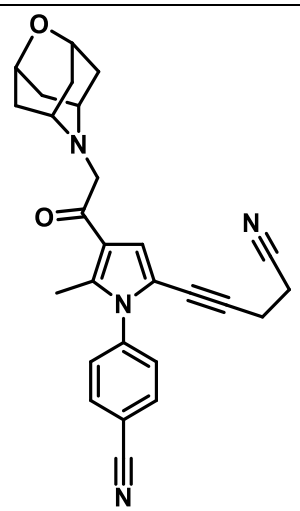
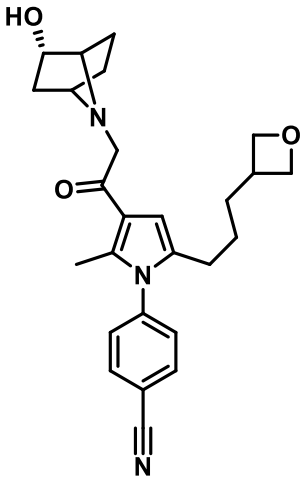
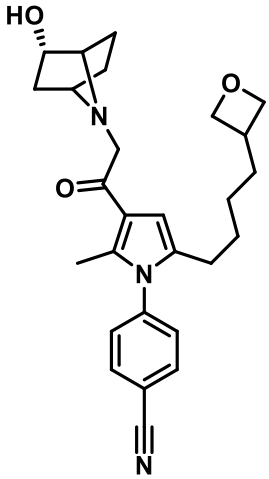
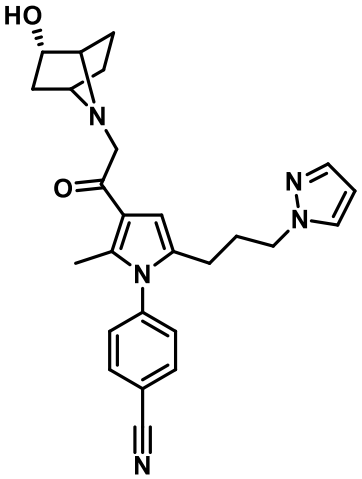
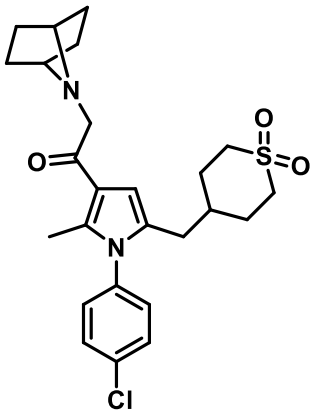
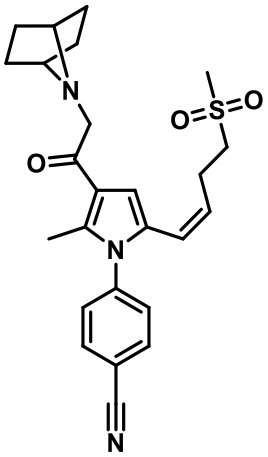
28. A compound selected from the group consisting of:

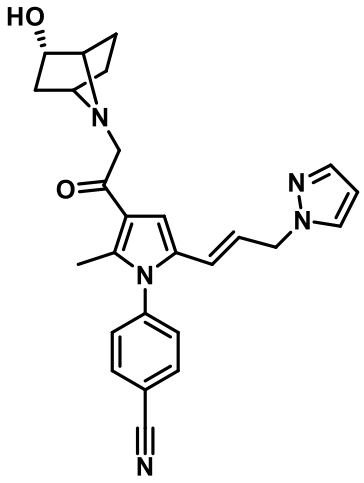
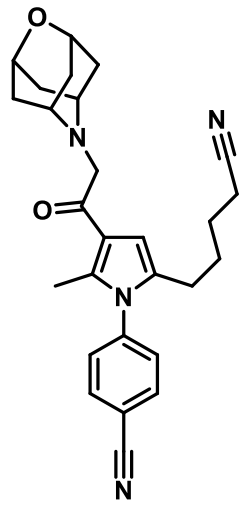
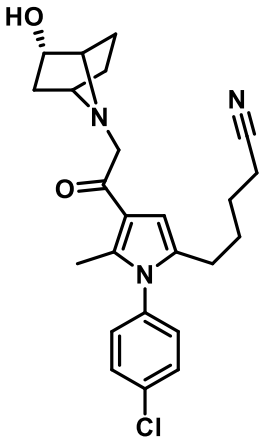
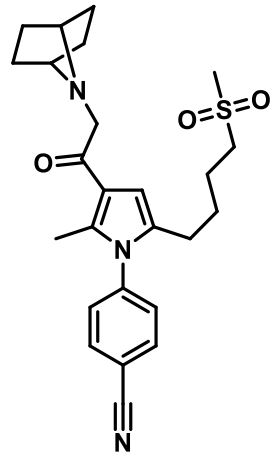
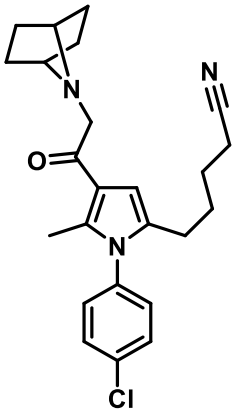
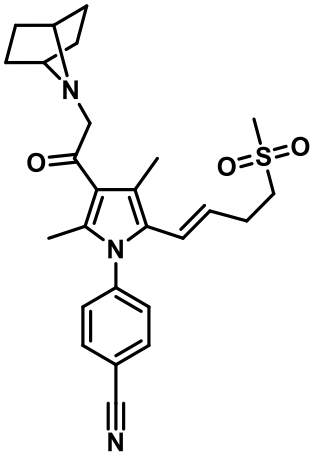
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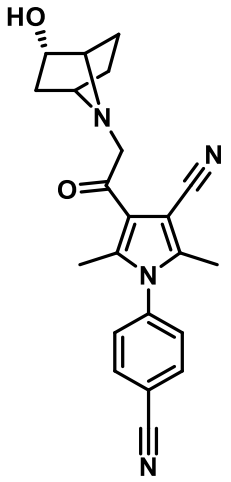
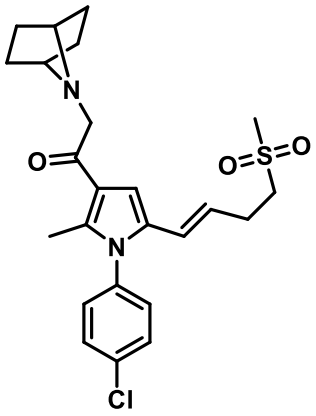
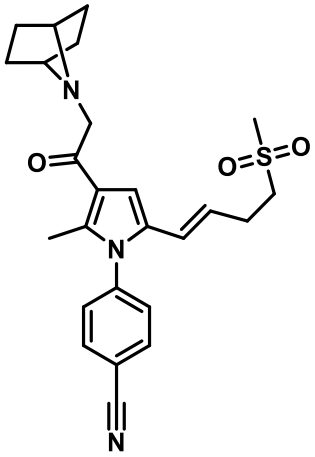
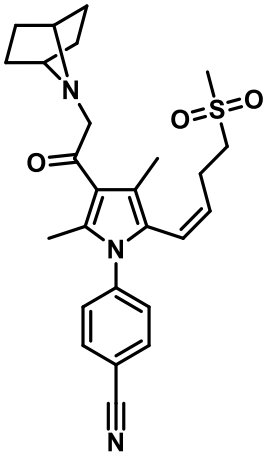
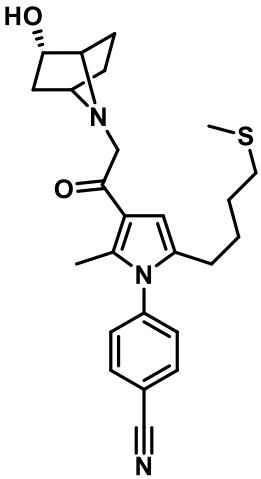
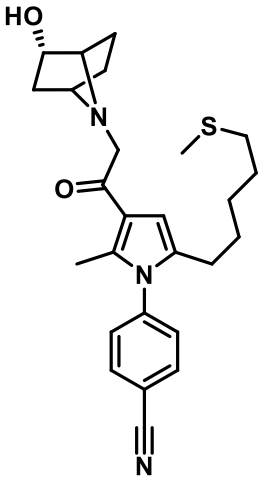
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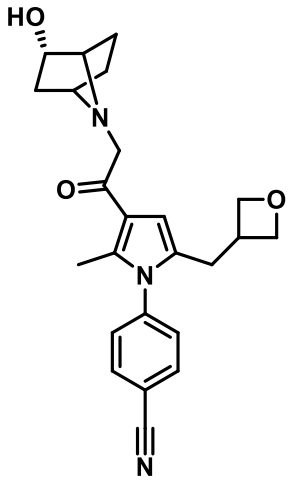
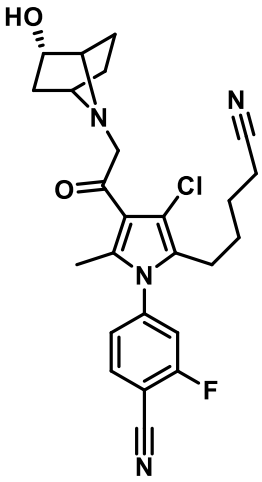
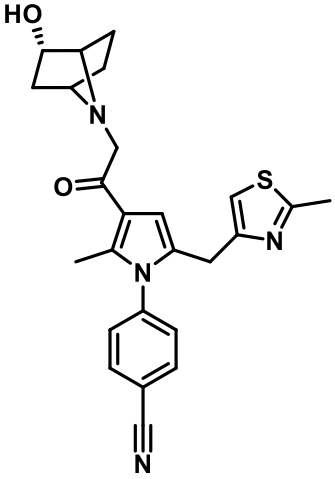
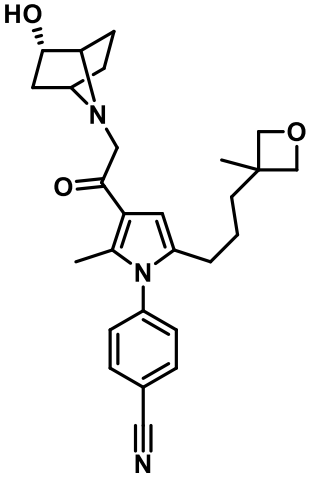
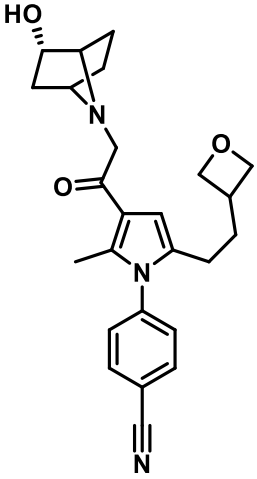
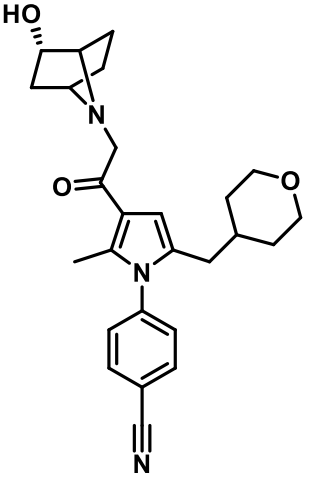
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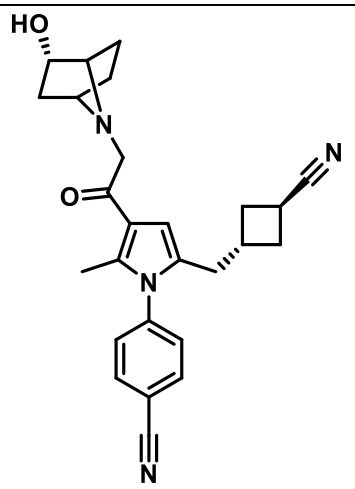
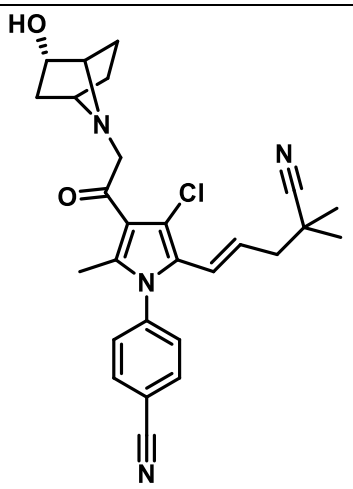
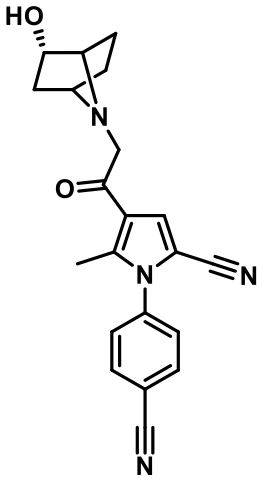
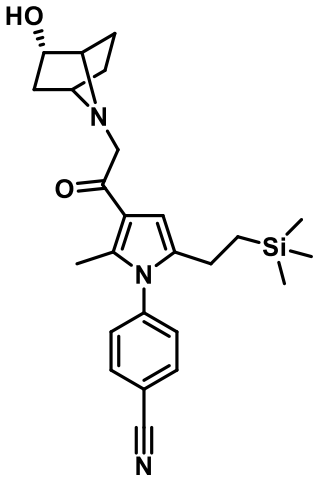
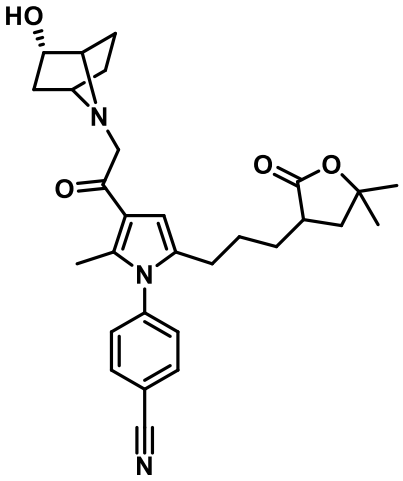
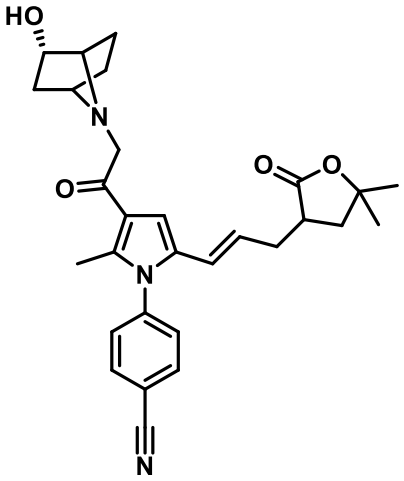
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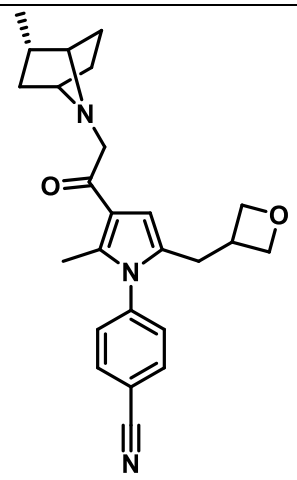
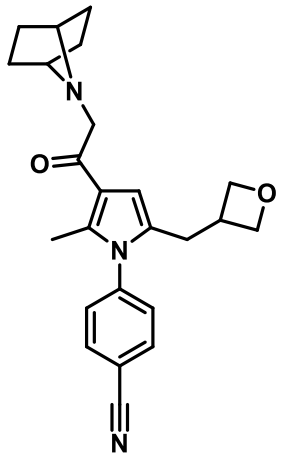
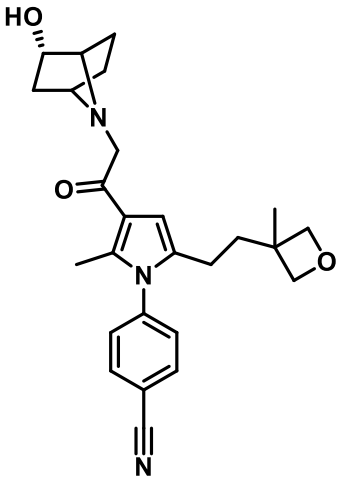
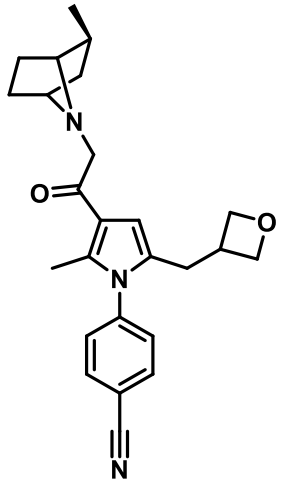
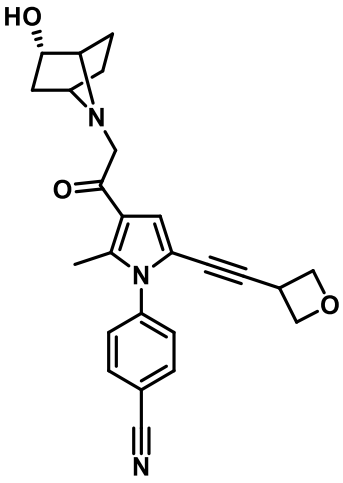
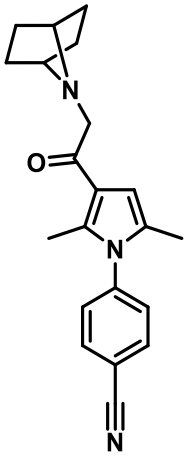
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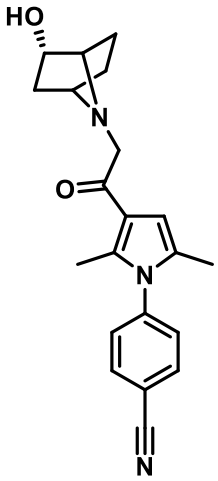
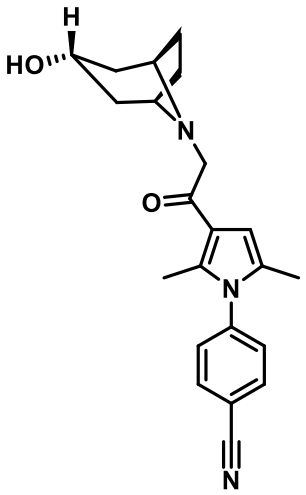
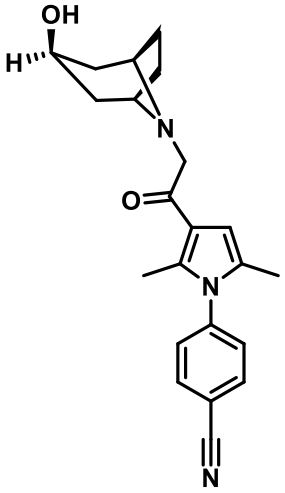
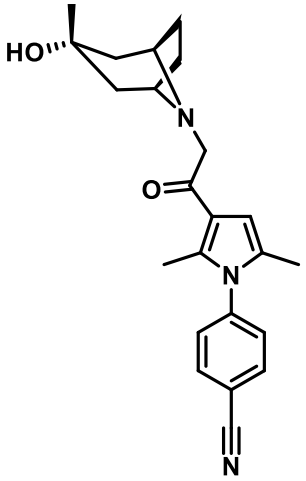
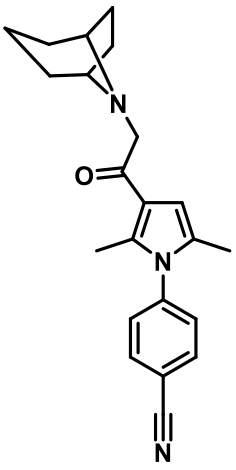
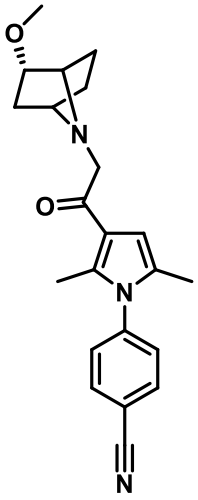
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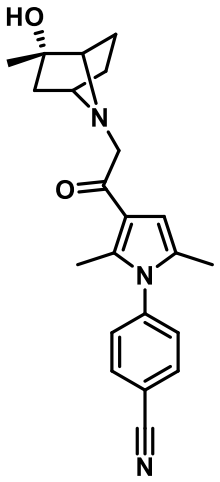
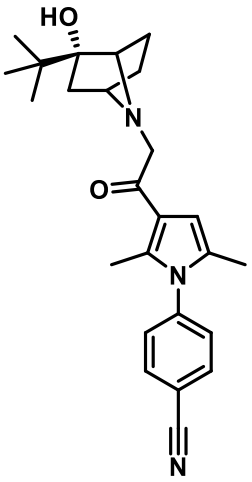
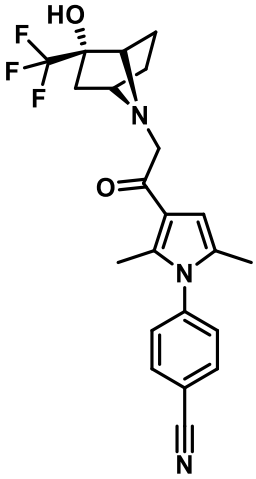
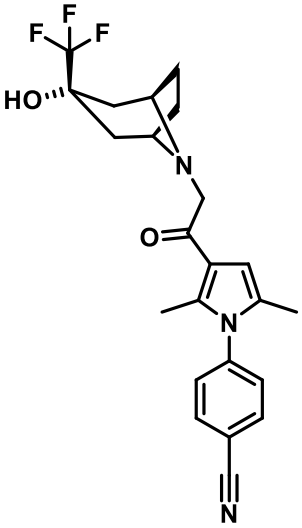
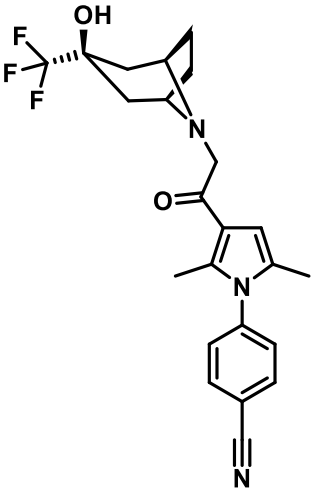
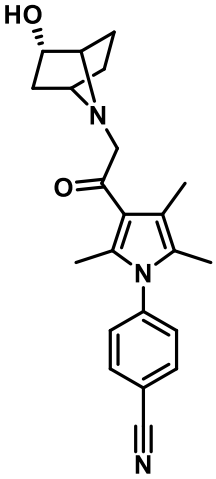
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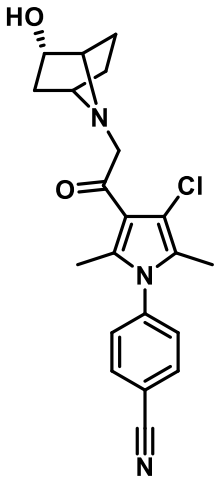
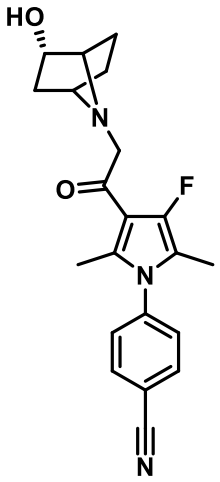
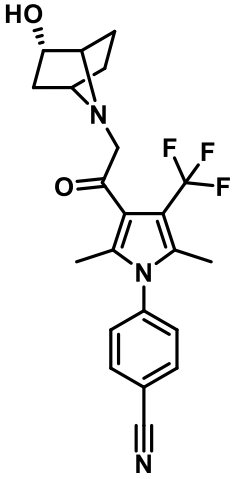
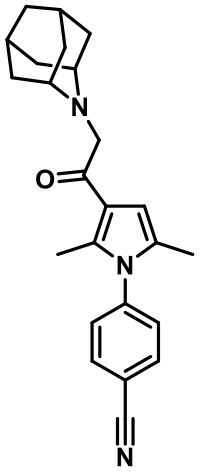
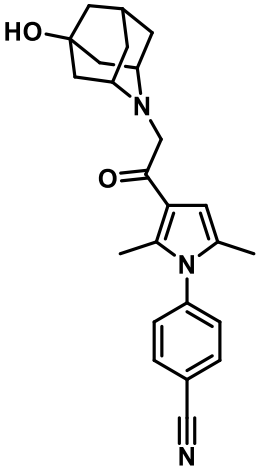
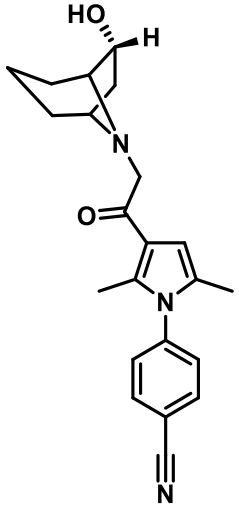
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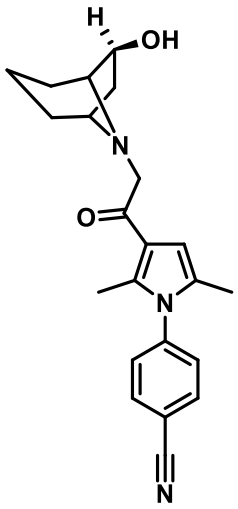
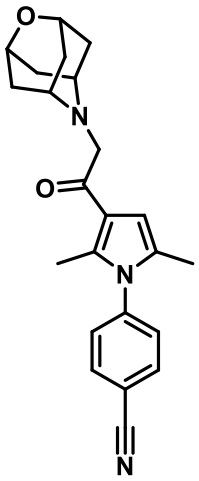
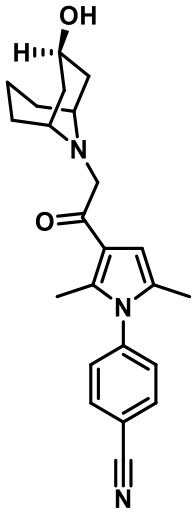
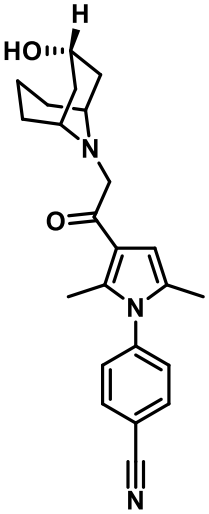
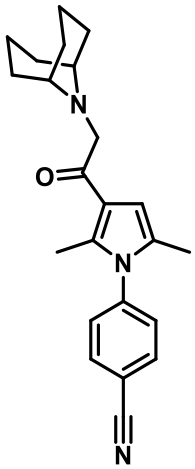
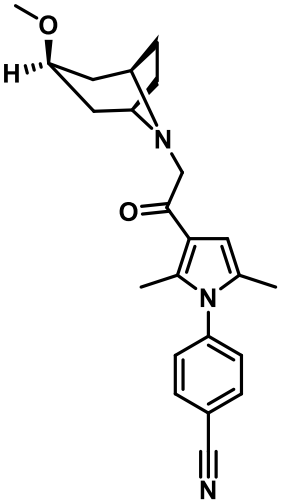
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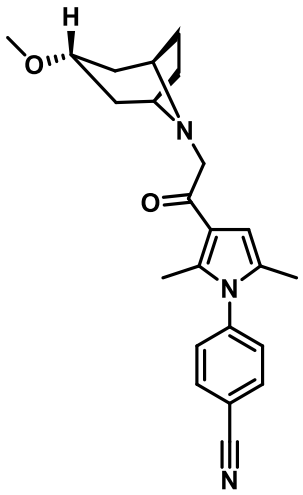
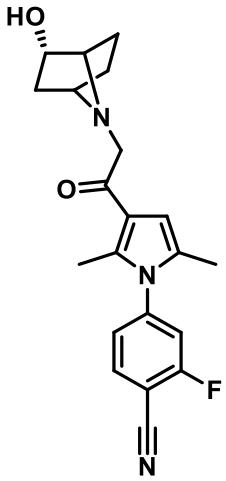
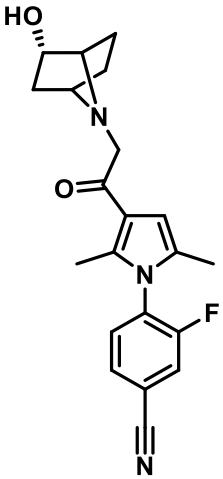
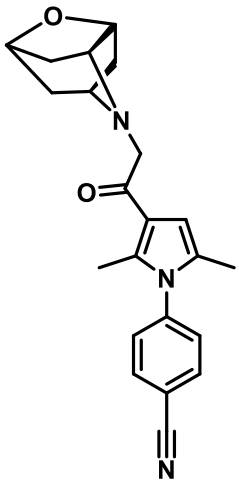
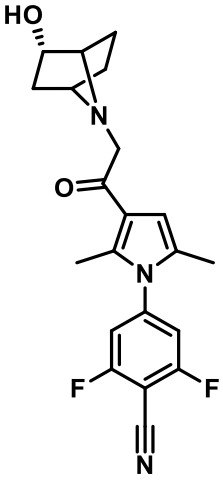
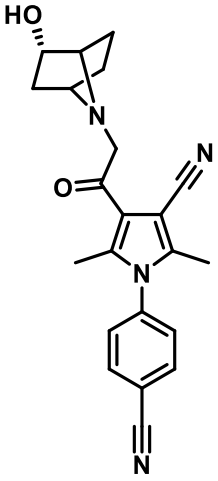
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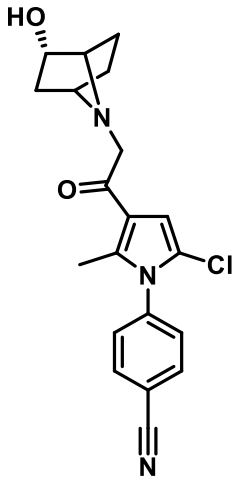
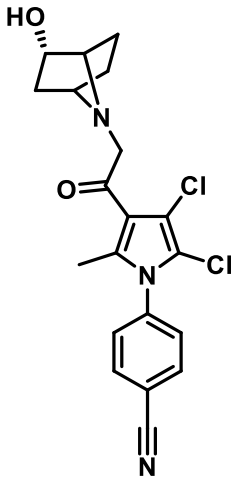
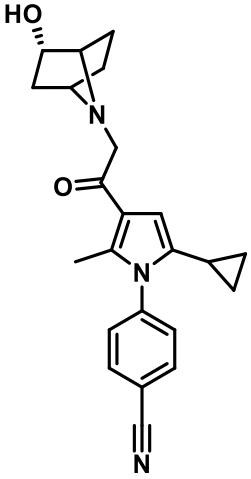
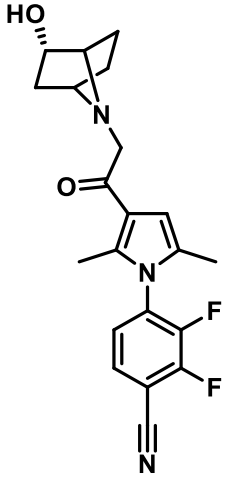
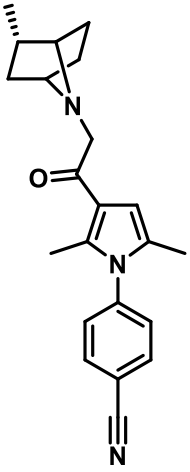
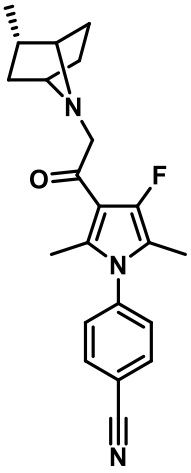
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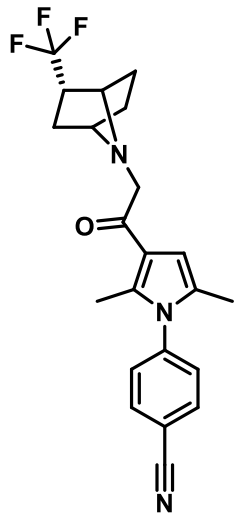
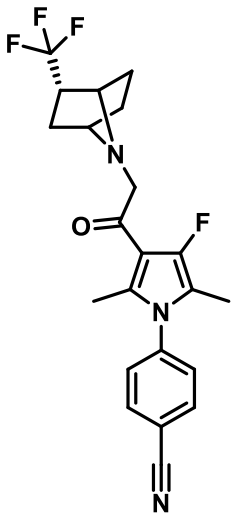
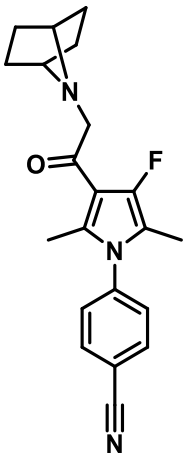
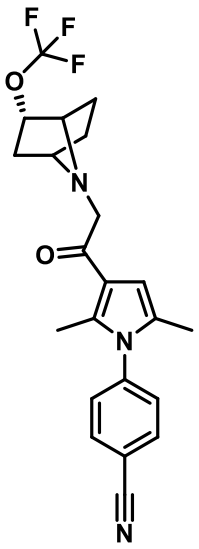
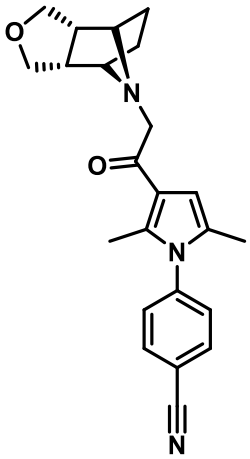
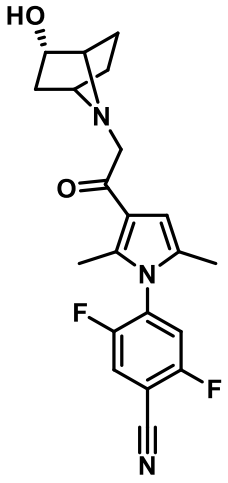
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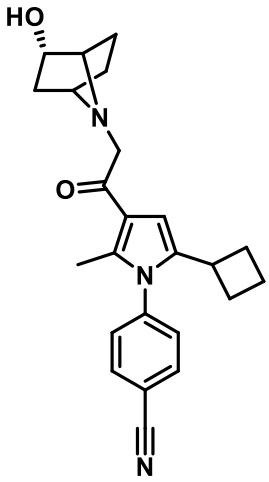
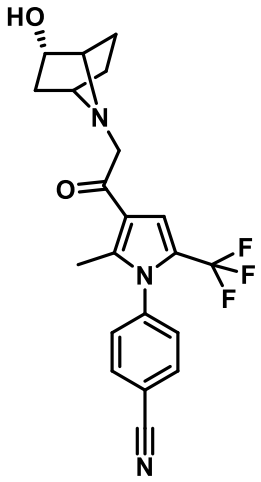
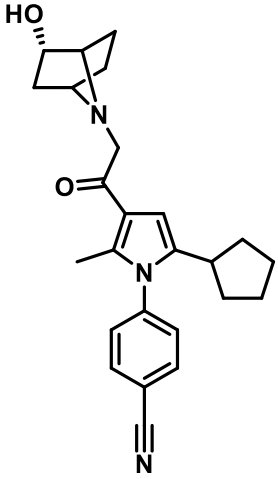
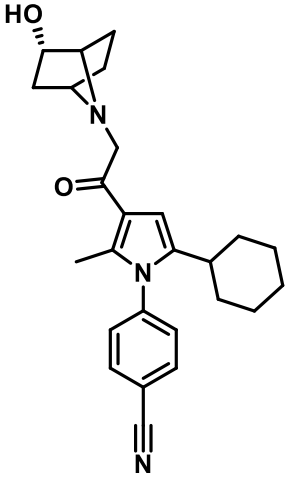
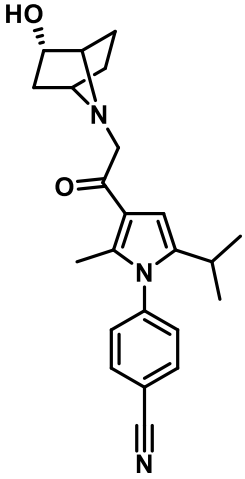
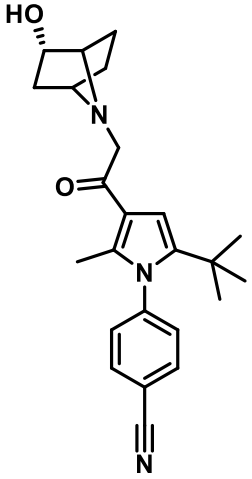
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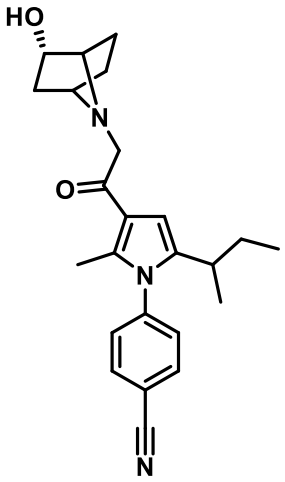
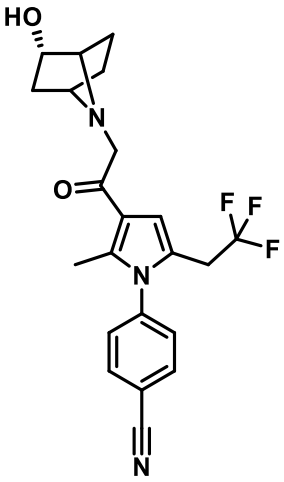
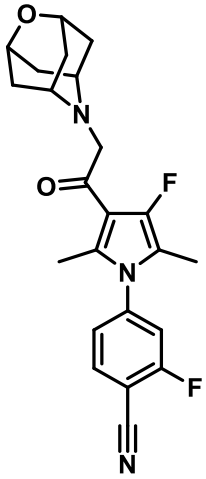
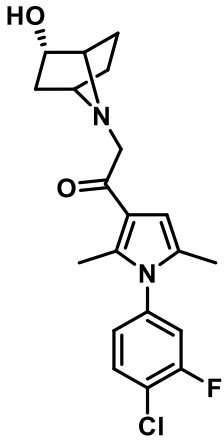
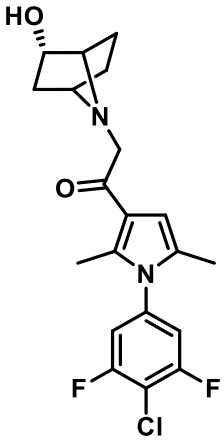
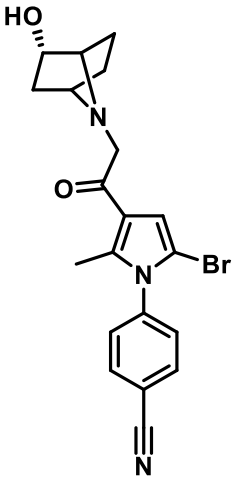
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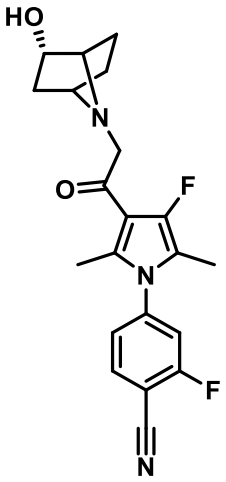
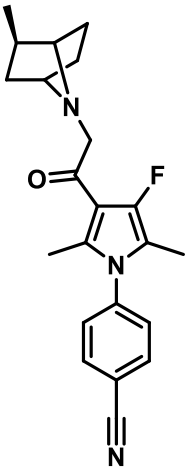
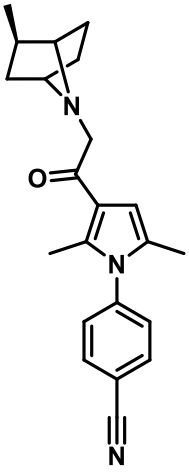
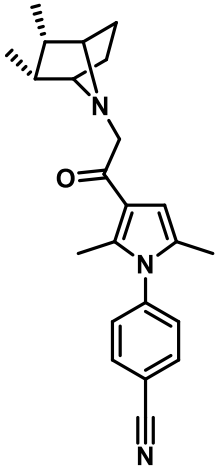
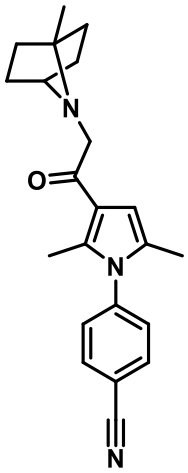
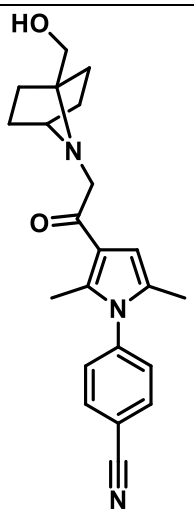
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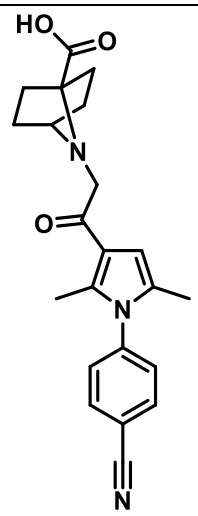
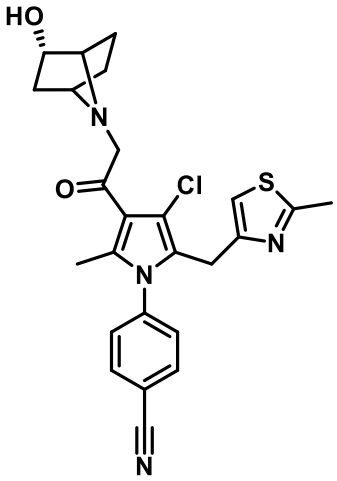
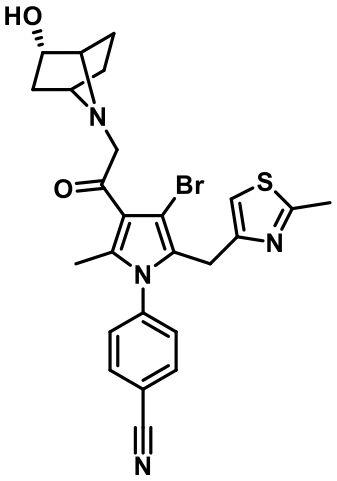
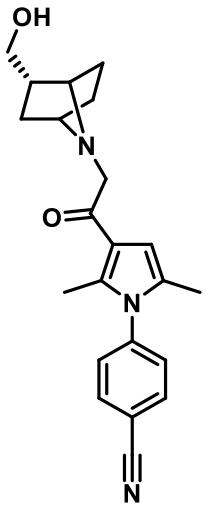
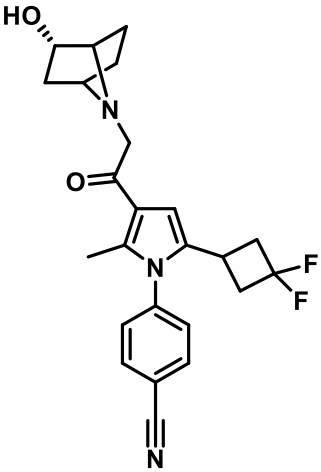
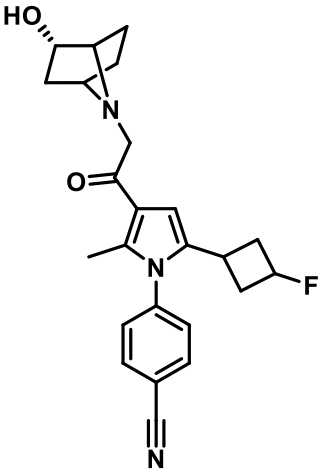
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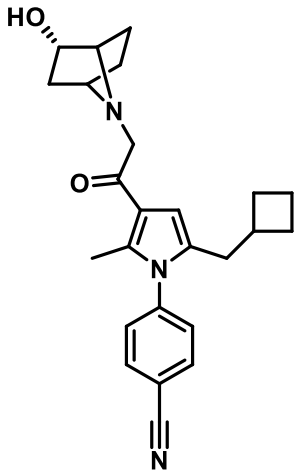
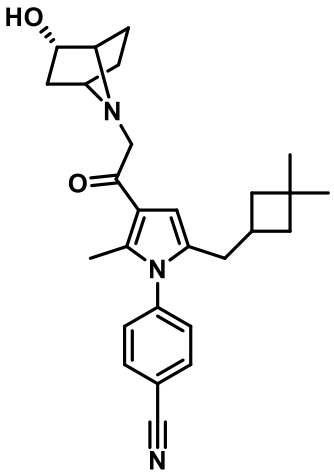
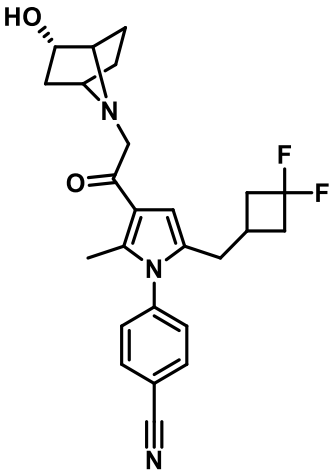
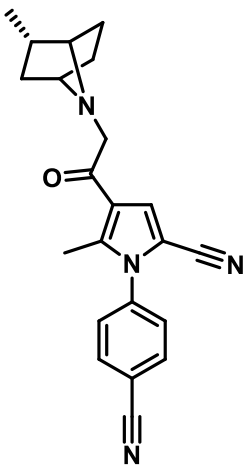
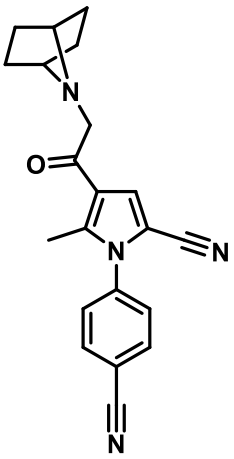
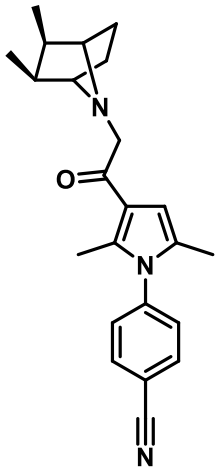
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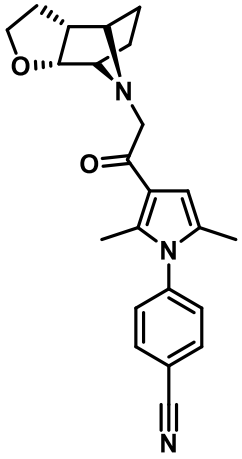
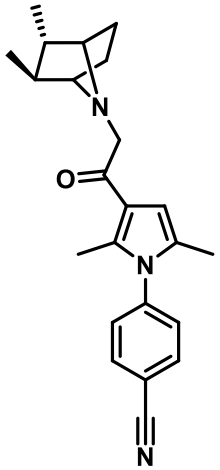
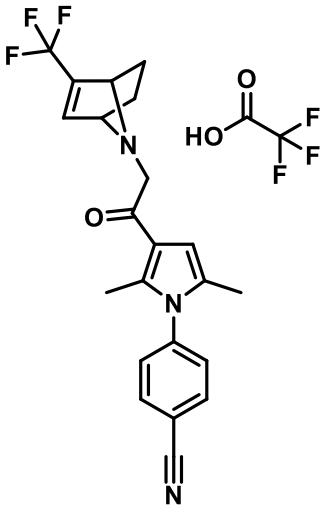
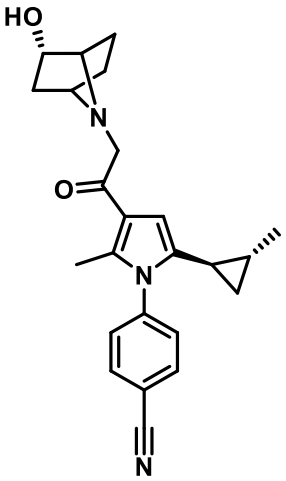
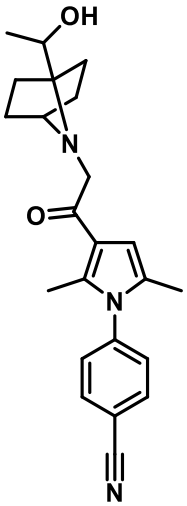
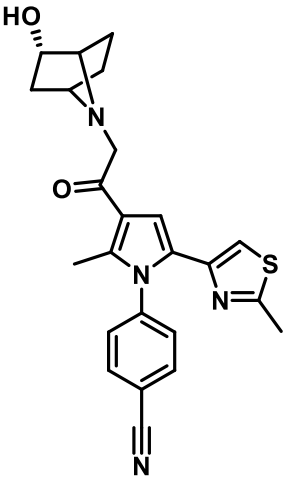
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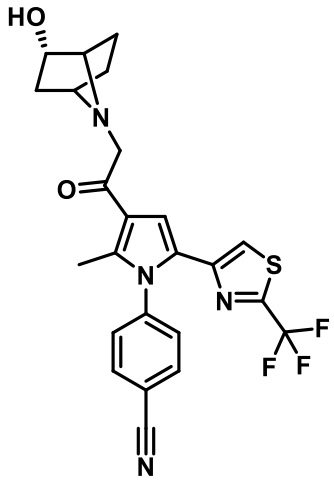
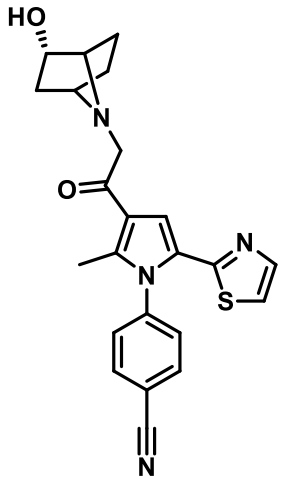
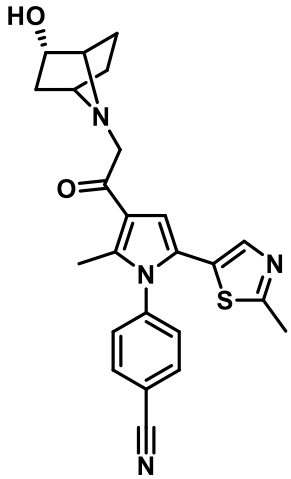
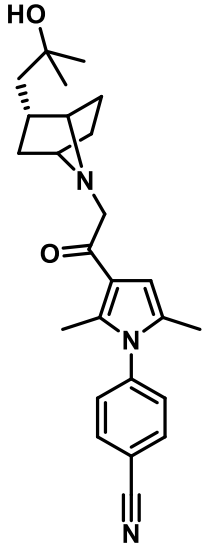
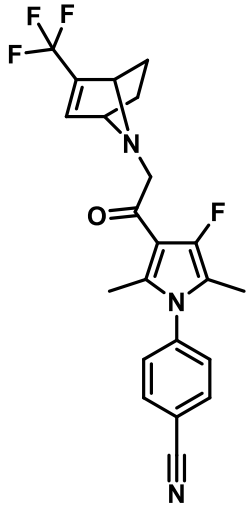
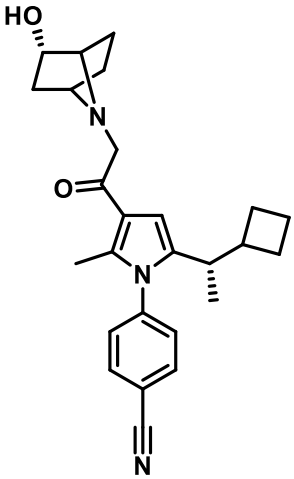
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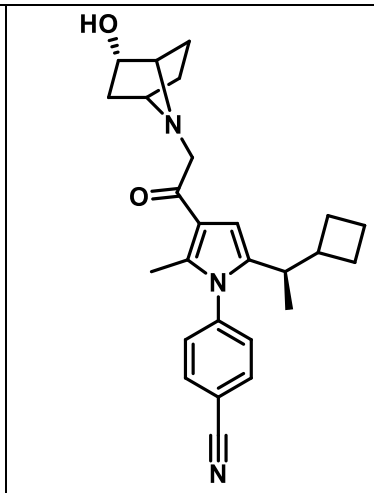
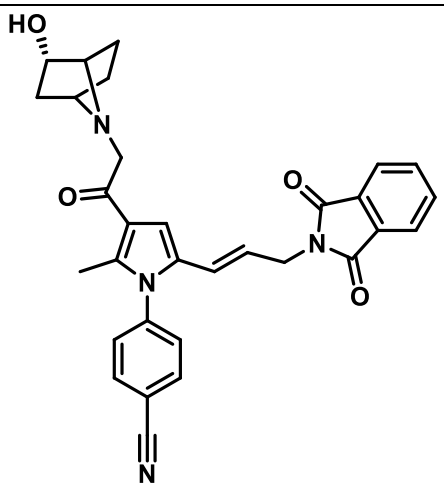
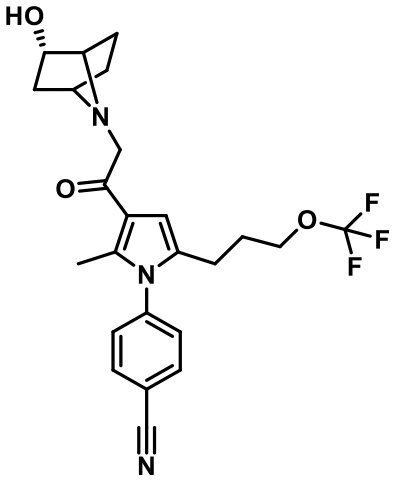
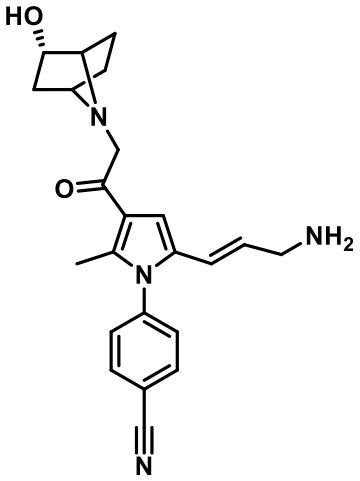
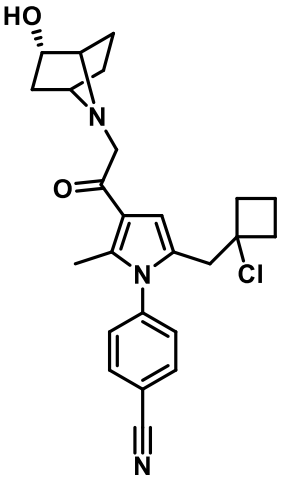
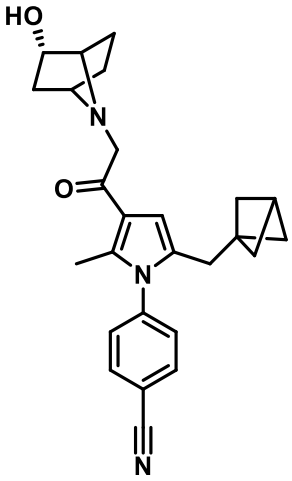
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137B		138B	

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141B		142B	
143B		144B	

145B		146B	
147B		148B	
149B		150B	

151B		153B	
155B		156B	
157B		158B	

or a pharmaceutically acceptable salt, solvate, or clathrate thereof.

29. A pharmaceutical composition comprising the compound of any one of claims 1-28, and a pharmaceutically acceptable excipient.

30. Use of a compound of any one of claims 1 to 28, in the manufacture of a medicament for treating a patient suffering from a lysosomal storage disease, a myopathy, a

cardiovascular disease, diabetes and/or complications of diabetes, an ocular disease, Huntington's disease, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, a cancer, a tumor, a hemoglobinopathy, inflammatory disease, intermediate filament disease, drug-induced lung damage, hearing loss, Hippel-Lindau disease, spinocerebellar ataxia, Angelman syndrome, giant axon neuropathy, inclusion body myopathy with Paget disease, frontotemporal dementia, frontotemporal lobar dementia, progressive supranuclear palsy, prion disease or autism.

31. A compound of any claims 1 to 28, for use in the treatment of a patient suffering from a lysosomal storage disease, a myopathy, a cardiovascular disease, diabetes and/or complications of diabetes, an ocular disease, Huntington's disease, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, a cancer, a tumor, a hemoglobinopathy, inflammatory disease, intermediate filament disease, drug-induced lung damage, hearing loss, Hippel-Lindau disease, spinocerebellar ataxia, Angelman syndrome, giant axon neuropathy, inclusion body myopathy with Paget disease, frontotemporal dementia, frontotemporal lobar dementia, progressive supranuclear palsy, prion disease or autism.