Ecteinascidin compound and use thereof

This application claims priority to Chinese Patent Application No. 2024101788699 filed on February 8, 2024; Chinese Patent Application No. 2024110452422 filed on July 31, 2024; Chinese Patent Application No. 2024113891578 filed on September 30, 2024; and Chinese Patent Application No. 2025101161329 filed on January 24, 2025. This application incorporates by reference the entire contents of the aforementioned Chinese patent applications.

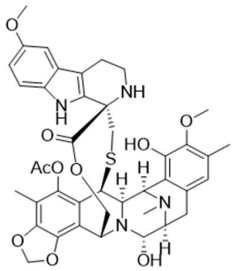
Technical Field

The present application relates to the field of pharmaceutical technology, and in particular to ecteinascidin compound and use thereof.

Background Of The Invention

Cancer is one of the malignant diseases that seriously endanger human health. More than 5 million people die of cancer worldwide each year, and in recent years, the incidence of tumors has been increasing annually, with cancer having the highest mortality rate among all diseases. Chemotherapy is currently a commonly used and effective clinical treatment for cancer. However, due to multidrug resistance of cancer cells and severe toxic side effects of existing anticancer drugs, there is an urgent clinical need for new anticancer agents with better efficacy and milder side effects.

Et-743 (Trabectedin) is a highly effective antitumor agent isolated from the marine tunicate Ecteinascidia turbinata and has been approved by the European Union and the United States for the treatment of advanced soft tissue sarcoma. Lurbinectedin (PM01183) is a structural analog of trabectedin and was approved in the United States in 2020 for the treatment of small cell lung cancer. Lurbinectedin exerts its anticancer effect through covalent modification of guanine in the DNA minor groove, ultimately leading to double-strand DNA breaks, S-phase arrest, and apoptosis in cancer cells.



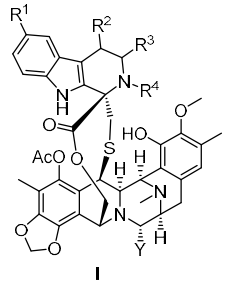
(Lurbinectedin, PM01183)

There remains a need to continue developing ecteinascidin compounds with improved efficacy and reduced toxicity to meet broader clinical demands.

Summary

The technical problem addressed by the present application is to overcome the deficiencies of existing drugs and thereby provide an ecteinascidin compound and use thereof. The ecteinascidin compound of the present application exhibits one or more of the following effects: (1) inhibitory activity on in vitro proliferation of tumor cells; (2) in vivo antitumor effect; (3) in vivo tumor-targeting ability; and (4) favorable in vivo safety.

The present application provides a compound of formula (I), or a pharmaceutically acceptable salt, ester, stereoisomer, tautomer, polymorph, solvate, isotope-labeled compound, metabolite, or prodrug thereof:



I

wherein,

R^1 is hydrogen, deuterium, halogen, -OH, -CN, $-NH_2$, C_{1-6} alkyl, $-OC_{1-6}$ alkyl, $-NHC_{1-6}$ alkyl, $-NH\text{-}S(O)_2\text{-}R^{1-2}$, $-C(O)R^{1-2}$, $C(O)\text{-}N(R^{1-1})R^{1-2}$, $-C_{1-6}$ alkylene-$N(R^{1-1})$-$C(O)R^{1-2}$, -O-C_{3-12} cycloalkyl, -O-(4 to 12-membered heterocycloalkylene)-$C(O)R^{1-2}$, -O-C_{3-12} cycloalkylene-$N(R^{1-1})$-$C(O)R^{1-2}$, -O-C(O)-$N(R^{1-1})R^{1-2}$, $-N(R^{1-1})$-$C(O)R^{1-2}$, $-N(R^{1-1})$-C(O)-OR^{1-2}, $-N(R^{1-1})$-(4 to 12-membered heterocycloalkylene)-$C(O)R^{1-2}$, $-N(R^{1-1})$-C_{3-12} cycloalkylene-$N(R^{1-3})$-$C(O)R^{1-2}$, -(4 to 12-membered heterocycloalkylene)-$C(O)R^{1-2}$, -(4 to 12-membered heterocycloalkylene)-$N(R^{1-1})$-$C(O)R^{1-2}$, $-N(R^{1-1})C(O)C_{3-12}$ cycloalkyl, (4 to 12-membered heterocycloalkylene), or $-N(R^{1-1})C(O)$(4 to 12-membered heterocycloalkyl); wherein said C_{1-6} alkyl, C_{1-6} alkylene, C_{3-12} cycloalkyl, C_{3-12} cycloalkylene, 4 to 12-membered heterocycloalkylene, and 4 to 12-membered heterocycloalkyl are each optionally substituted with one or more substituents selected from halogen, -OH, -SH, $-NH_2$, $-NHC_{1-6}$ alkyl, $-SC_{1-6}$ alkyl, $-C_{1-6}$ alkylene-OH, $-C_{1-6}$ alkylene-SH, $-C_{1-6}$ alkylene-S(C_{1-6} alkyl), and $-C_{1-6}$ alkylene-NH_2;

R^2 is hydrogen, deuterium, halogen, $-C_{1-6}$ alkyl, -OH, -O-C(O)-$N(R^{2-1})R^{2-2}$, $-C(O)R^{2-2}$, $C(O)\text{-}N(R^{2-1})R^{2-2}$, $-NH_2$, $-NHC_{1-6}$ alkyl, $-NHC(O)C_{1-6}$ alkyl, $-N(R^{2-1})$-C(O)-OR^{2-2}, $-N(R^{2-1})$-C(O)-$N(R^{2-1})R^{2-2}$, $-NHC(O)C_{3-12}$ cycloalkyl, -NHC(O)(4 to 12-membered heterocycloalkyl), $-N(C_{1-6}$ alkyl)$C(O)C_{1-6}$ alkyl, $-N(C_{1-6}$ alkyl)$C(O)C_{3-12}$ cycloalkyl, C(O)(4 to 12-membered heterocycloalkyl), $-N(C_{1-6}$ alkyl)C(O)(4 to 12-membered heterocycloalkyl), or $-NH\text{-}S(O)_2\text{-}R^{2-2}$; wherein said C_{1-6} alkyl, C_{3-12} cycloalkyl, and 4 to 12-

membered heterocycloalkyl are each optionally substituted with one or more substituents selected from halogen, -OH, -O-NHCH$_3$, -SH, -NH$_2$, -NHC$_{1-6}$ alkyl, and -SC$_{1-6}$ alkyl;

R^3 is hydrogen, deuterium, -C$_{1-6}$ alkyl, -CH$_2$-NHC$_{1-6}$ alkyl, -CH$_2$-NHC(O)C$_{1-6}$ alkyl, -CH$_2$-OC(O)-NR$^{3-1}$R$^{3-2}$, -CH$_2$-NR$^{3-1}$C(O)NR$^{3-1}$-R$^{3-2}$, -CH$_2$-NR$^{3-1}$C(O)O-R$^{3-2}$, -CH$_2$-NHC(O)C$_{3-12}$ cycloalkyl, -CH$_2$-NHC(O)(4 to 12-membered heterocycloalkyl), -CH$_2$-N(C$_{1-6}$ alkyl)C(O)C$_{1-6}$ alkyl, -CH$_2$-N(C$_{1-6}$ alkyl)C(O)C$_{3-12}$ cycloalkyl, -CH$_2$-N(C$_{1-6}$ alkyl)C(O)(4 to 12-membered heterocycloalkyl), -CH$_2$NH-S(O)$_2$-R$^{3-2}$, -CH$_2$-S(O)$_2$-R$^{3-2}$, or -C(O)R$^{3-2}$; wherein said C$_{1-6}$ alkyl, C$_{3-12}$ cycloalkyl, and 4 to 12-membered heterocycloalkyl are each optionally substituted with one or more substituents selected from halogen, cyclopropyl, -OH, -O-NHCH$_3$, -SH, -NH$_2$, -NHC$_{1-6}$ alkyl, and -SC$_{1-6}$ alkyl;

R^4 is hydrogen, deuterium, -C$_{1-6}$ alkyl, -C(O)C$_{1-6}$ alkyl, -C(O)C$_{3-12}$ cycloalkyl, or -C(O)(4 to 12-membered heterocycloalkyl); wherein said C$_{1-6}$ alkyl, C$_{3-12}$ cycloalkyl, and 4 to 12-membered heterocycloalkyl are each optionally substituted with one or more substituents selected from halogen, -OH, -SH, -NH$_2$, -NHC$_{1-6}$ alkyl, and -SC$_{1-6}$ alkyl;

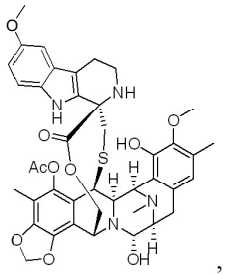
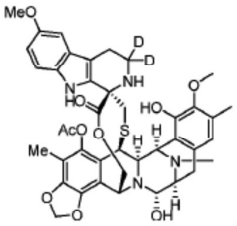
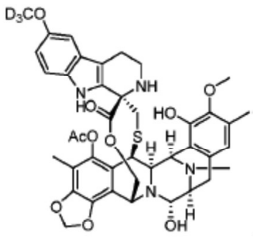
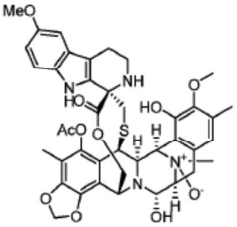
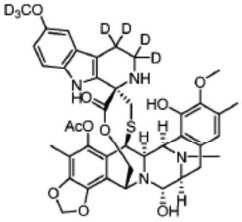
or R^3 and R^4, together with the atom to which they are attached, form a 5- to 12-membered heterocycloalkyl; wherein said 5- to 12-membered heterocycloalkyl is optionally substituted with one or more substituents selected from halogen, oxo group, -OH, -CN, -NH$_2$, -NHC$_{1-6}$ alkyl, -N(C$_{1-6}$ alkyl)$_2$, -C$_{1-6}$ alkyl, -C$_{1-6}$ alkylene-OH, -C(O)C$_{1-6}$ alkylene-OH, -C(O)-C$_{3-12}$ cycloalkylene-OH, and -C(O)-(4 to 12-membered heterocycloalkylene)-OH;

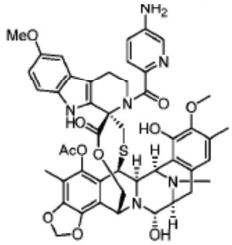
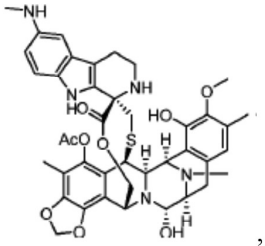
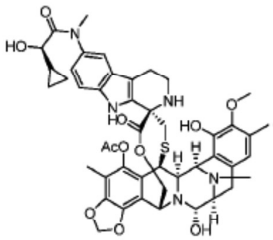
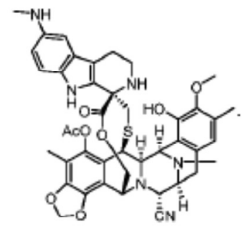
R^{1-1}, R^{2-1}, and R^{3-1} are each independently hydrogen, deuterium, C$_{1-6}$ alkyl, or halo-C$_{1-6}$ alkyl;

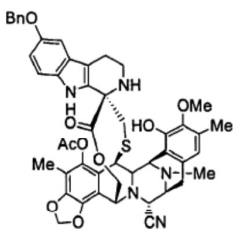
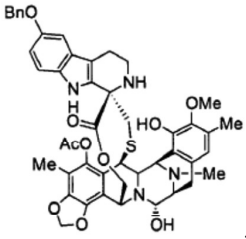
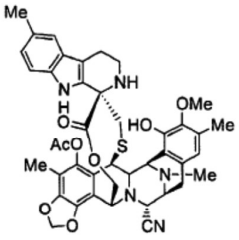
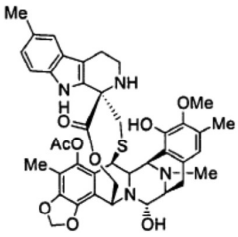
R^{1-2}, R^{2-2}, and R^{3-2} are each independently C$_{1-6}$ alkyl, C$_{3-12}$ cycloalkyl, or 4 to 12-membered heterocycloalkyl; wherein said C$_{1-6}$ alkyl, C$_{3-12}$ cycloalkyl, and 4 to 12-membered heterocycloalkyl are each optionally substituted with one or more substituents independently selected from halogen, -OH, -O-NHCH$_3$, -SH, -NH$_2$, -NHC$_{1-6}$ alkyl, and -SC$_{1-6}$ alkyl;

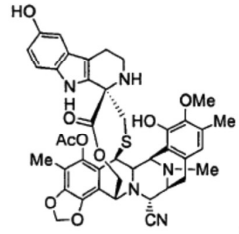
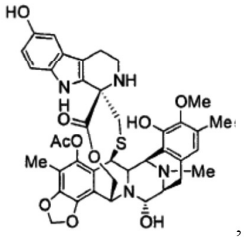
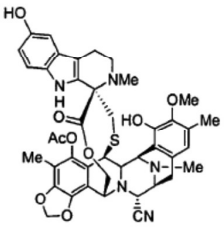
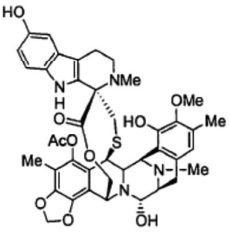
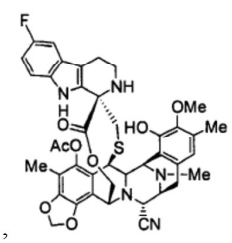
Y is -OH or -CN.

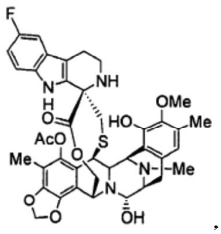
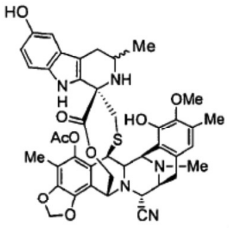
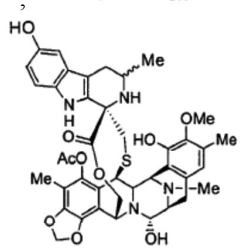
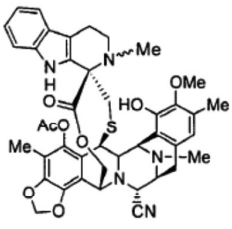
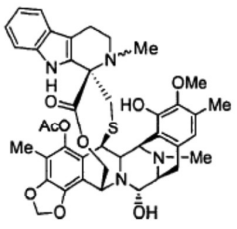
In some embodiments, the compound of formula (I) is not the following compound:

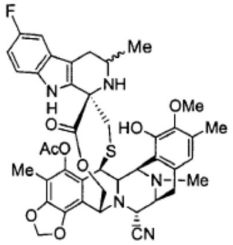
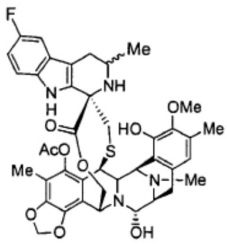
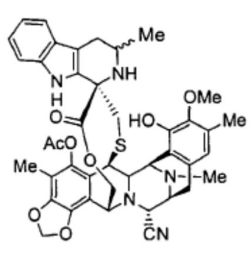
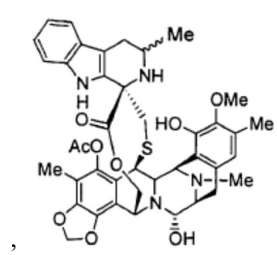
 ,  ,  ,  ,  ,

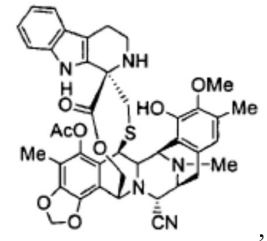
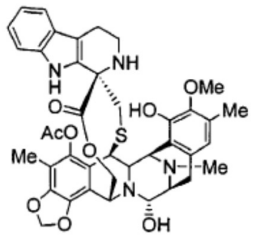
 ,  ,  ,  ,

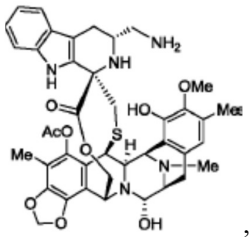
 ,  ,  ,  ,

 ,  ,  ,  ,  ,

 ,  ,  ,  ,  ,

 ,  ,  ,  ,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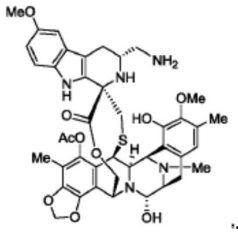
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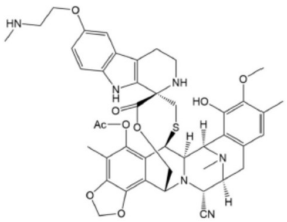
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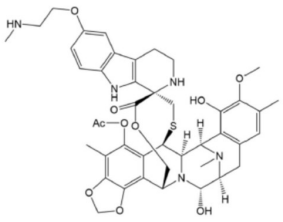
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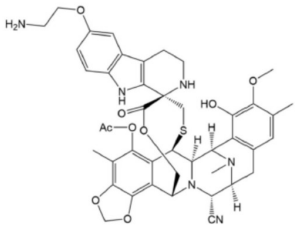
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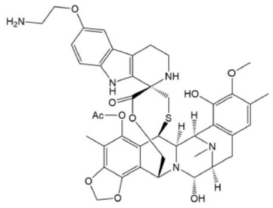
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In some embodiments, in the compound of formula (I),

R^1 is hydrogen, deuterium, halogen, -OH, -CN, $-NH_2$, C_{1-6} alkyl, $-OC_{1-6}$ alkyl, $-NHC_{1-6}$ alkyl, $-NH-S(O)_2-R^{1-2}$, $-C(O)R^{1-2}$, $C(O)-N(R^{1-1})R^{1-2}$, $-C_{1-6}$ alkylene-$N(R^{1-1})-C(O)R^{1-2}$, $-O-C_{3-12}$ cycloalkyl, -O-(4 to 12-membered heterocycloalkylene)-$C(O)R^{1-2}$, $-O-C_{3-12}$ cycloalkylene-$N(R^{1-1})-C(O)R^{1-2}$, $-O-C(O)-N(R^{1-1})R^{1-2}$, $-N(R^{1-1})-C(O)R^{1-2}$, $-N(R^{1-1})-C(O)-OR^{1-2}$, $-N(R^{1-1})$-(4 to 12-membered heterocycloalkylene)-$C(O)R^{1-2}$, $-N(R^{1-1})-C_{3-12}$ cycloalkylene-$N(R^{1-3})-C(O)R^{1-2}$, -(4 to 12-membered heterocycloalkylene)-$C(O)R^{1-2}$, -(4 to 12-membered heterocycloalkylene)-$N(R^{1-1})-C(O)R^{1-2}$, $-N(R^{1-1})C(O)C_{3-12}$ cycloalkyl, or $-N(R^{1-1})C(O)$(4 to 12-membered heterocycloalkyl); wherein said C_{1-6} alkyl, C_{1-6} alkylene, C_{3-12} cycloalkyl, C_{3-12} cycloalkylene, 4 to 12-membered heterocycloalkylene, and 4 to 12-membered heterocycloalkyl are each optionally substituted with one or more substituents selected from halogen, -OH, -SH, $-NH_2$, $-NHC_{1-6}$ alkyl, $-SC_{1-6}$ alkyl, $-C_{1-6}$ alkylene-OH, $-C_{1-6}$ alkylene-SH, $-C_{1-6}$ alkylene-S(C_{1-6} alkyl), and $-C_{1-6}$ alkylene-NH_2;

R^2 is hydrogen, deuterium, halogen, $-C_{1-6}$ alkyl, -OH, $-O-C(O)-N(R^{2-1})R^{2-2}$, $-C(O)R^{2-2}$, $C(O)-N(R^{2-1})R^{2-2}$, $-NH_2$, $-NHC_{1-6}$ alkyl, $-NHC(O)C_{1-6}$ alkyl, $-N(R^{2-1})-C(O)-OR^{2-2}$, $-N(R^{2-1})-C(O)-N(R^{2-1})R^{2-2}$, $-NHC(O)C_{3-12}$ cycloalkyl, -NHC(O)(4 to 12-membered heterocycloalkyl), $-N(C_{1-6}$ alkyl$)C(O)C_{1-6}$ alkyl, $-N(C_{1-6}$ alkyl$)C(O)C_{3-12}$ cycloalkyl, $-N(C_{1-6}$ alkyl$)C(O)$(4 to 12-membered heterocycloalkyl), or $-NH-S(O)_2-R^{2-2}$; wherein said C_{1-6} alkyl, C_{3-12} cycloalkyl, and 4 to 12-membered heterocycloalkyl are each optionally substituted with one or more substituents selected from halogen, -OH, $-O-NHCH_3$, -SH, $-NH_2$, $-NHC_{1-6}$ alkyl, and $-SC_{1-6}$ alkyl;

R^3 is hydrogen, deuterium, $-C_{1-6}$ alkyl, $-CH_2-NHC_{1-6}$ alkyl, $-CH_2-NHC(O)C_{1-6}$ alkyl, $-CH_2-OC(O)-NR^{3-1}R^{3-2}$, $-CH_2-NR^{3-1}C(O)NR^{3-1}-R^{3-2}$, $-CH_2-NR^{3-1}C(O)O-R^{3-2}$, $-CH_2-NHC(O)C_{3-12}$ cycloalkyl, $-CH_2-NHC(O)$(4 to 12-membered heterocycloalkyl), $-CH_2-N(C_{1-6}$ alkyl$)C(O)C_{1-6}$ alkyl, $-CH_2-N(C_{1-6}$ alkyl$)C(O)C_{3-12}$ cycloalkyl, $-CH_2-N(C_{1-6}$ alkyl$)C(O)$(4 to 12-membered heterocycloalkyl), $-CH_2-S(O)_2-R^{3-2}$, or $-C(O)R^{3-2}$; wherein said C_{1-6} alkyl, C_{3-12} cycloalkyl, and 4 to 12-membered heterocycloalkyl are each

optionally substituted with one or more substituents selected from halogen, -OH, -O-NHCH$_3$, -SH, -NH$_2$, -NHC$_{1-6}$ alkyl, and -SC$_{1-6}$ alkyl;

R^4 is hydrogen, deuterium, -C$_{1-6}$ alkyl, -C(O)C$_{1-6}$ alkyl, -C(O)C$_{3-12}$ cycloalkyl, or -C(O)(4 to 12-membered heterocycloalkyl); wherein said C$_{1-6}$ alkyl, C$_{3-12}$ cycloalkyl, and 4 to 12-membered heterocycloalkyl are each optionally substituted with one or more substituents selected from halogen, -OH, -SH, -NH$_2$, -NHC$_{1-6}$ alkyl, and -SC$_{1-6}$ alkyl;

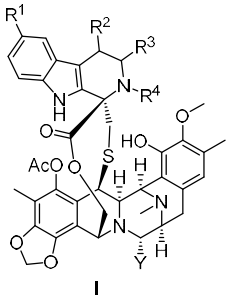
or R^3 and R^4, together with the atom to which they are attached, form a 5- to 12-membered heterocycloalkyl; wherein said 5- to 12-membered heterocycloalkyl is optionally substituted with one or more substituents selected from halogen, oxo group, -OH, -CN, -NH$_2$, -NHC$_{1-6}$ alkyl, -N(C$_{1-6}$ alkyl)$_2$, -C$_{1-6}$ alkyl, -C$_{1-6}$ alkylene-OH, -C(O)C$_{1-6}$ alkylene-OH, -C(O)-C$_{3-12}$ cycloalkylene-OH, and -C(O)-(4 to 12-membered heterocycloalkylene)-OH;

R^{1-1}, R^{2-1}, and R^{3-1} are each independently hydrogen, deuterium, C$_{1-6}$ alkyl, or halo-C$_{1-6}$ alkyl;

R^{1-2}, R^{2-2}, and R^{3-2} are each independently C$_{1-6}$ alkyl, C$_{3-12}$ cycloalkyl, or 4 to 12-membered heterocycloalkyl; wherein said C$_{1-6}$ alkyl, C$_{3-12}$ cycloalkyl, and 4 to 12-membered heterocycloalkyl are each optionally substituted with one or more substituents independently selected from halogen, -OH, -O-NHCH$_3$, -SH, -NH$_2$, -NHC$_{1-6}$ alkyl, and -SC$_{1-6}$ alkyl;

Y is -OH or -CN.

In some embodiments,



I

wherein,

R^1 is hydrogen, deuterium, halogen, -OH, -CN, -NH$_2$, C$_{1-6}$ alkyl, -OC$_{1-6}$ alkyl, -NHC$_{1-6}$ alkyl, -C$_{1-6}$ alkylene-N(R^{1-1})-C(O)R^{1-2}, -O-C$_{3-12}$ cycloalkyl, -O-(4 to 12-membered heterocycloalkylene)-C(O)R^{1-2}, -O-C$_{3-12}$ cycloalkylene-N(R^{1-1})-C(O)R^{1-2}, -N(R^{1-1})-C(O)R^{1-2}, -N(R^{1-1})-(4 to 12-membered heterocycloalkylene)-C(O)R^{1-2}, -N(R^{1-1})-C$_{3-12}$ cycloalkylene-N(R^{1-3})-C(O)R^{1-2}, -(4 to 12-membered heterocycloalkylene)-C(O)R^{1-2}, -(4 to 12-membered heterocycloalkylene)-N(R^{1-1})-C(O)R^{1-2}, -N(R^{1-1})C(O)C$_{3-12}$ cycloalkyl, or -N(R^{1-1})C(O)(4 to 12-membered heterocycloalkyl); wherein said C$_{1-6}$ alkyl, C$_{1-6}$ alkylene, C$_{3-12}$ cycloalkyl, C$_{3-12}$ cycloalkylene, 4 to 12-membered heterocycloalkylene, and 4 to 12-membered heterocycloalkyl are each optionally substituted with one or more substituents selected from

halogen, -OH, -SH, -NH_2, -NHC_{1-6} alkyl, -SC_{1-6} alkyl, -C_{1-6} alkylene-OH, -C_{1-6} alkylene-SH, -C_{1-6} alkylene-S(C_{1-6} alkyl), and -C_{1-6} alkylene-NH_2;

R^{1-1} is hydrogen, deuterium, C_{1-6} alkyl, or halo-C_{1-6} alkyl;

R^{1-2} is C_{1-6} alkyl, C_{3-12} cycloalkyl, or 4 to 12-membered heterocycloalkyl; wherein said C_{1-6} alkyl, C_{3-12} cycloalkyl, and 4 to 12-membered heterocycloalkyl are each optionally substituted with one or more substituents independently selected from halogen, -OH, -SH, -NH_2, -NHC_{1-6} alkyl, and -SC_{1-6} alkyl;

R^2 is hydrogen, deuterium, halogen, -C_{1-6} alkyl, -OH, -NH_2, -NHC_{1-6} alkyl, -$NHC(O)C_{1-6}$ alkyl, -$NHC(O)C_{3-12}$ cycloalkyl, -NHC(O)(4 to 12-membered heterocycloalkyl), -$N(C_{1-6}$ alkyl)$C(O)C_{1-6}$ alkyl, -$N(C_{1-6}$ alkyl)$C(O)C_{3-12}$ cycloalkyl, or -$N(C_{1-6}$ alkyl)C(O)(4 to 12-membered heterocycloalkyl); wherein said C_{1-6} alkyl, C_{3-12} cycloalkyl, and 4 to 12-membered heterocycloalkyl are each optionally substituted with one or more substituents selected from halogen, -OH, -SH, -NH_2, -NHC_{1-6} alkyl, and -SC_{1-6} alkyl;

R^3 is hydrogen, deuterium, -C_{1-6} alkyl, -CH_2-NHC_{1-6} alkyl, -CH_2-$NHC(O)C_{1-6}$ alkyl, -CH_2-$NHC(O)C_{3-12}$ cycloalkyl, -CH_2-NHC(O)(4 to 12-membered heterocycloalkyl), -CH_2-$N(C_{1-6}$ alkyl)$C(O)C_{1-6}$ alkyl, -CH_2-$N(C_{1-6}$ alkyl)$C(O)C_{3-12}$ cycloalkyl, or -CH_2-$N(C_{1-6}$ alkyl)C(O)(4 to 12-membered heterocycloalkyl); wherein said C_{1-6} alkyl, C_{3-12} cycloalkyl, and 4 to 12-membered heterocycloalkyl are each optionally substituted with one or more substituents selected from halogen, -OH, -SH, -NH_2, -NHC_{1-6} alkyl, and -SC_{1-6} alkyl;

R^4 is hydrogen, deuterium, -C_{1-6} alkyl, -$C(O)C_{1-6}$ alkyl, -$C(O)C_{3-12}$ cycloalkyl, or -C(O)(4 to 12-membered heterocycloalkyl); wherein said C_{1-6} alkyl, C_{3-12} cycloalkyl, and 4 to 12-membered heterocycloalkyl are each optionally substituted with one or more substituents selected from halogen, -OH, -SH, -NH_2, -NHC_{1-6} alkyl, and -SC_{1-6} alkyl;

or R^3 and R^4, together with the atom to which they are attached, form a 5- to 12-membered heterocycloalkyl; wherein said 5- to 12-membered heterocycloalkyl is optionally substituted with one or more substituents selected from halogen, oxo group, -OH, -CN, -NH_2, -NHC_{1-6} alkyl, -$N(C_{1-6}$ alkyl$)_2$, -C_{1-6} alkyl, -C_{1-6} alkylene-OH, -$C(O)C_{1-6}$ alkylene-OH, -$C(O)$-C_{3-12} cycloalkylene-OH, and -C(O)-(4 to 12-membered heterocycloalkylene)-OH;

Y is -OH or -CN.

In some embodiments, certain groups in the compound of formula (I), or a pharmaceutically acceptable salt, ester, stereoisomer, tautomer, polymorph, solvate, isotope-labeled compound, metabolite, or prodrug thereof, are defined as follows, and groups not mentioned are as defined in any embodiment of the present application (hereinafter referred to as “in some embodiments”), satisfying at least one of the following conditions:

(1) R^1 is deuterium, halogen, -OH, -CN, -NH_2, C_{1-6} alkyl, -NH-$S(O)_2$-R^{1-2}, -$C(O)R^{1-2}$, $C(O)$-$N(R^{1-1})R^{1-2}$, -C_{1-6} alkylene-$N(R^{1-1})$-$C(O)R^{1-2}$, -O-C_{3-12} cycloalkyl, -O-(4 to 12-membered heterocycloalkylene)-$C(O)R^{1-}$

^{2}, -O-C_{3-12} cycloalkylene-N(R^{1-1})-C(O)R^{1-2}, -O-C(O)-N(R^{1-1})R^{1-2}, -N(R^{1-1})-C(O)R^{1-2}, -N(R^{1-1})-C(O)-OR^{1-2}, -N(R^{1-1})-(4 to 12-membered heterocycloalkylene)-C(O)R^{1-2}, -N(R^{1-1})-C_{3-12} cycloalkylene-N(R^{1-3})-C(O)R^{1-2}, -(4 to 12-membered heterocycloalkylene)-C(O)R^{1-2}, -(4 to 12-membered heterocycloalkylene)-N(R^{1-1})-C(O)R^{1-2}, -N(R^{1-1})C(O)C_{3-12} cycloalkyl, (4 to 12-membered heterocycloalkylene), or -N(R^{1-1})C(O)(4 to 12-membered heterocycloalkyl); wherein said C_{1-6} alkyl, C_{1-6} alkylene, C_{3-12} cycloalkyl, C_{3-12} cycloalkylene, 4 to 12-membered heterocycloalkylene, and 4 to 12-membered heterocycloalkyl are each optionally substituted with one or more substituents selected from halogen, -OH, -SH, -NH_2, -O-$NHCH_3$, -NHC_{1-6} alkyl, -SC_{1-6} alkyl, -C_{1-6} alkylene-OH, -C_{1-6} alkylene-SH, -C_{1-6} alkylene-S(C_{1-6} alkyl), and -C_{1-6} alkylene-NH_2;

(2) R^2 is halogen, -C_{1-6} alkyl, -OH, -O-C(O)-N(R^{2-1})R^{2-2}, -C(O)R^{2-2}, C(O)-N(R^{2-1})R^{2-2}, -NH_2, -NHC_{1-6} alkyl, -NHC(O)C_{1-6} alkyl, -N(R^{2-1})-C(O)-OR^{2-2}, -N(R^{2-1})-C(O)-N(R^{2-1})R^{2-2}, -NHC(O)C_{3-12} cycloalkyl, -NHC(O)(4 to 12-membered heterocycloalkyl), -N(C_{1-6} alkyl)C(O)C_{1-6} alkyl, -N(C_{1-6} alkyl)C(O)C_{3-12} cycloalkyl, C(O)(4 to 12-membered heterocycloalkyl), -N(C_{1-6} alkyl)C(O)(4 to 12-membered heterocycloalkyl), or -NH-S(O)$_2$-R^{2-2}; wherein said C_{1-6} alkyl, C_{3-12} cycloalkyl, and 4 to 12-membered heterocycloalkyl are each optionally substituted with one or more substituents selected from halogen, -OH, -O-$NHCH_3$, -SH, -NH_2, -NHC_{1-6} alkyl, and -SC_{1-6} alkyl;

(3) R^3 is -CH_2-NHC_{1-6} alkyl, -CH_2-NHC(O)C_{1-6} alkyl, -CH_2-OC(O)-N$R^{3-1}R^{3-2}$, -CH_2-NR^{3-1}C(O)NR^{3-1}-R^{3-2}, -CH_2-NR^{3-1}C(O)O-R^{3-2}, -CH_2-NHC(O)C_{3-12} cycloalkyl, -CH_2-NHC(O)(4 to 12-membered heterocycloalkyl), -CH_2-NHC(O)C_{3-12} cycloalkyl, -CH_2-N(C_{1-6} alkyl)C(O)C_{1-6} alkyl, -CH_2-N(C_{1-6} alkyl)C(O)C_{3-12} cycloalkyl, -CH_2-N(C_{1-6} alkyl)C(O)(4 to 12-membered heterocycloalkyl), -CH_2NH-S(O)$_2$-R^{3-2}, -CH_2-S(O)$_2$-R^{3-2}, or -C(O)R^{3-2}; wherein said C_{1-6} alkyl, C_{3-12} cycloalkyl, and 4 to 12-membered heterocycloalkyl are each optionally substituted with one or more substituents selected from halogen, cyclopropyl, -OH, -O-$NHCH_3$, -SH, -NH_2, -NHC_{1-6} alkyl, and -SC_{1-6} alkyl;

(4) R^4 is -C(O)C_{1-6} alkyl, -C(O)C_{3-12} cycloalkyl, or -C(O)(4 to 12-membered heterocycloalkyl); wherein said C_{1-6} alkyl, C_{3-12} cycloalkyl, and 4 to 12-membered heterocycloalkyl are each optionally substituted with one or more substituents selected from halogen, -OH, -SH, -NH_2, -NHC_{1-6} alkyl, and -SC_{1-6} alkyl;

(5) R^3 and R^4, together with the atom to which they are attached, form a 5- to 12-membered heterocycloalkyl; wherein said 5- to 12-membered heterocycloalkyl is optionally substituted with one or more substituents selected from halogen, oxo group, -OH, -CN, -NH_2, -NHC_{1-6} alkyl, -N(C_{1-6} alkyl)$_2$, -C_{1-6} alkyl, -C_{1-6} alkylene-OH, -C(O)C_{1-6} alkylene-OH, -C(O)-C_{3-12} cycloalkylene-OH, and -C(O)-(4 to 12-membered heterocycloalkylene)-OH.

In some embodiments, the compound of formula (I) satisfies at least one of the following conditions:

(1) R^1 is deuterium, halogen, -OH, -CN, -NH_2, C_{1-6} alkyl, -C_{1-6} alkylene-N(R^{1-1})-C(O)R^{1-2}, -O-C_{3-12} cycloalkyl, -O-(4 to 12-membered heterocycloalkylene)-C(O)R^{1-2}, -O-C_{3-12} cycloalkylene-N(R^{1-1})-C(O)R^{1-2}, -N(R^{1-1})-C(O)R^{1-2}, -N(R^{1-1})-(4 to 12-membered heterocycloalkylene)-C(O)R^{1-2}, -N(R^{1-1})-C_{3-12} cycloalkylene-N(R^{1-3})-C(O)R^{1-2}, -(4 to 12-membered heterocycloalkylene)-C(O)R^{1-2}, -(4 to 12-membered

heterocycloalkylene)-N(R^{1-1})-C(O)R^{1-2}, -N(R^{1-1})C(O)C_{3-12} cycloalkyl, or -N(R^{1-1})C(O)(4 to 12-membered heterocycloalkyl); wherein said C_{1-6} alkyl, C_{1-6} alkylene, C_{3-12} cycloalkyl, C_{3-12} cycloalkylene, 4 to 12-membered heterocycloalkylene, and 4 to 12-membered heterocycloalkyl are each optionally substituted with one or more substituents selected from halogen, -OH, -SH, -NH_2, -NHC_{1-6} alkyl, -SC_{1-6} alkyl, -C_{1-6} alkylene-OH, -C_{1-6} alkylene-SH, -C_{1-6} alkylene-S(C_{1-6} alkyl), and -C_{1-6} alkylene-NH_2;

(2) R^2 is deuterium, halogen, C_{1-6} alkyl, -OH, -NH_2, -NHC_{1-6} alkyl, -NHC(O)C_{1-6} alkyl, -NHC(O)C_{3-12} cycloalkyl, -NHC(O)(4 to 12-membered heterocycloalkyl), -N(C_{1-6} alkyl)C(O)C_{1-6} alkyl, -N(C_{1-6} alkyl)C(O)C_{3-12} cycloalkyl, or -N(C_{1-6} alkyl)C(O)(4 to 12-membered heterocycloalkyl); wherein said C_{1-6} alkyl, C_{3-12} cycloalkyl, and 4 to 12-membered heterocycloalkyl are each optionally substituted with one or more substituents selected from halogen, -OH, -SH, -NH_2, -NHC_{1-6} alkyl, and -SC_{1-6} alkyl;

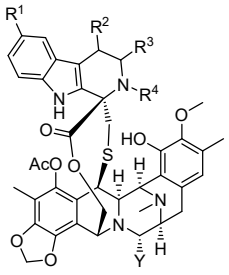
(3) R^3 is -CH_2-NHC_{1-6} alkyl, -CH_2-NHC(O)C_{1-6} alkyl, -CH_2-NHC(O)C_{3-12} cycloalkyl, -CH_2-NHC(O)(4 to 12-membered heterocycloalkyl), -CH_2-N(C_{1-6} alkyl)C(O)C_{1-6} alkyl, -CH_2-N(C_{1-6} alkyl)C(O)C_{3-12} cycloalkyl, or -CH_2-N(C_{1-6} alkyl)C(O)(4 to 12-membered heterocycloalkyl); wherein said C_{1-6} alkyl, C_{3-12} cycloalkyl, and 4 to 12-membered heterocycloalkyl are each optionally substituted with one or more substituents selected from halogen, -OH, -SH, -NH_2, -NHC_{1-6} alkyl, and -SC_{1-6} alkyl;

(4) R^4 is C_{1-6} alkyl, -C(O)C_{1-6} alkyl, -C(O)C_{3-12} cycloalkyl, or -C(O)(4 to 12-membered heterocycloalkyl); wherein said C_{1-6} alkyl, C_{3-12} cycloalkyl, and 4 to 12-membered heterocycloalkyl are each optionally substituted with one or more substituents selected from halogen, -OH, -SH, -NH_2, -NHC_{1-6} alkyl, and -SC_{1-6} alkyl;

(5) R^3 and R^4, together with the atom to which they are attached, form a 5- to 12-membered heterocycloalkyl; wherein said 5- to 12-membered heterocycloalkyl is optionally substituted with one or more substituents selected from halogen, oxo group, -OH, -CN, -NH_2, -NHC_{1-6} alkyl, -N(C_{1-6} alkyl)$_2$, C_{1-6} alkyl, -C_{1-6} alkylene-OH, -C(O)C_{1-6} alkylene-OH, -C(O)-C_{3-12} cycloalkylene-OH, and -C(O)-(4 to 12-membered heterocycloalkylene)-OH.

In some embodiments, the number of heteroatoms in the 4 to 12-membered heterocycloalkylene and 4 to 12-membered heterocycloalkyl is one or more, with each heteroatom independently selected from N, O, and S; preferably, the 4 to 12-membered heterocycloalkylene and 4 to 12-membered heterocycloalkyl are 4 to 6-membered heterocycloalkylene and 4 to 6-membered heterocycloalkyl, respectively, containing one or two heteroatoms independently selected from N; for example, azetidinyl ( , ), piperidinyl ( , ), piperazinyl ( , ), or their divalent groups.

In some embodiments, the compound of general formula (I) is a compound of formula (IA):



IA

wherein,

R^1 is hydrogen, halogen, -OH, or -OC_{1-6} alkyl;

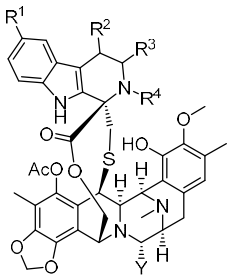
R^2 is hydrogen or deuterium; R^3 is -CH_2-NHC_{1-6} alkyl, -CH_2-$NHC(O)C_{1-6}$ alkyl, -CH_2-$OC(O)$-$NR^{3-1}R^{3-2}$, -CH_2-$NR^{3-1}C(O)NR^{3-1}$-R^{3-2}, -CH_2-$NR^{3-1}C(O)O$-R^{3-2}, -CH_2-$NHC(O)C_{3-12}$ cycloalkyl, -CH_2-NHC(O)(4 to 12-membered heterocycloalkyl), -CH_2-$NHC(O)C_{3-12}$ cycloalkyl, -CH_2-$N(C_{1-6}$ alkyl)$C(O)C_{1-6}$ alkyl, -CH_2-$N(C_{1-6}$ alkyl)$C(O)C_{3-12}$ cycloalkyl, -CH_2-$N(C_{1-6}$ alkyl)C(O)(4 to 12-membered heterocycloalkyl), -CH_2NH-$S(O)_2$-R^{3-2}, -CH_2-$S(O)_2$-R^{3-2}, or -$C(O)R^{3-2}$; wherein said C_{1-6} alkyl, C_{3-12} cycloalkyl, and 4 to 12-membered heterocycloalkyl are each optionally substituted with one or more substituents selected from halogen, cyclopropyl, -OH, -O-$NHCH_3$, -SH, -NH_2, -NHC_{1-6} alkyl, and -SC_{1-6} alkyl; R^4 is hydrogen or C_{1-6} alkyl;

or R^2 is hydrogen or deuterium; R^3 and R^4, together with the atom to which they are attached, form a 5- to 12-membered heterocycloalkyl; wherein said 5- to 12-membered heterocycloalkyl is optionally substituted with one or more substituents selected from -$C(O)C_{1-6}$ alkylene-OH;

or R^2 is halogen, -C_{1-6} alkyl, -OH, -O-$C(O)$-$N(R^{2-1})R^{2-2}$, -$C(O)R^{2-2}$, $C(O)$-$N(R^{2-1})R^{2-2}$, -NH_2, -NHC_{1-6} alkyl, -$NHC(O)C_{1-6}$ alkyl, -$N(R^{2-1})$-$C(O)$-OR^{2-2}, -$N(R^{2-1})$-$C(O)$-$N(R^{2-1})R^{2-2}$, -$NHC(O)C_{3-12}$ cycloalkyl, -NHC(O)(4 to 12-membered heterocycloalkyl), -$N(C_{1-6}$ alkyl)$C(O)C_{1-6}$ alkyl, -$N(C_{1-6}$ alkyl)$C(O)C_{3-12}$ cycloalkyl, C(O)(4 to 12-membered heterocycloalkyl), -$N(C_{1-6}$ alkyl)C(O)(4 to 12-membered heterocycloalkyl), or -NH-$S(O)_2$-R^{2-2}; wherein said C_{1-6} alkyl, C_{3-12} cycloalkyl, and 4 to 12-membered heterocycloalkyl are each optionally substituted with one or more substituents selected from halogen, -OH, -O-$NHCH_3$, -SH, -NH_2, -NHC_{1-6} alkyl, and -SC_{1-6} alkyl; R^3 is hydrogen or deuterium; R^4 is hydrogen or C_{1-6} alkyl;

Y is -OH or -CN.

In some embodiments, the compound of general formula (I) is a compound of formula (Ia):



Ia

wherein,

R^1 is hydrogen, deuterium, halogen, -OH, -CN, -NH_2, C_{1-6} alkyl, halo-C_{1-6} alkyl, -OC_{1-6} alkyl, -O-halo-C_{1-6} alkyl, -NHC$_{1-6}$ alkyl, -O-halo-C_{1-6} alkyl, or -NH-halo-C_{1-6} alkyl;

R^2 is hydrogen, deuterium, halogen, C_{1-6} alkyl, -OH, -NH_2, -NHC$_{1-6}$ alkyl, -NHC(O)C_{1-6} alkyl, -NHC(O)C_{3-12} cycloalkyl, -NHC(O)(4 to 12-membered heterocycloalkyl), -N(C_{1-6} alkyl)C(O)C_{1-6} alkyl, -N(C_{1-6} alkyl)C(O)C_{3-12} cycloalkyl, or -N(C_{1-6} alkyl)C(O)(4 to 12-membered heterocycloalkyl); wherein said C_{1-6} alkyl, C_{3-12} cycloalkyl, or 4 to 12-membered heterocycloalkyl is optionally substituted with one or more substituents selected from halogen, -OH, -SH, -NH_2, -NHC$_{1-6}$ alkyl, and -SC_{1-6} alkyl;

R^3 is H or -CH_2-$NR^{3a}R^{3b}$;

R^{3a} is hydrogen or C_{1-6} alkyl; wherein said C_{1-6} alkyl is optionally substituted with one or more substituents selected from halogen, -OH, -SH, -NH_2, -NHC$_{1-6}$ alkyl, and -SC_{1-6} alkyl;

R^{3b} is -C(O)C_{1-6} alkyl, -C(O)C_{3-12} cycloalkyl, or -C(O)(4 to 12-membered heterocycloalkyl); wherein said C_{1-6} alkyl, C_{3-12} cycloalkyl, or 4 to 12-membered heterocycloalkyl is optionally substituted with one or more substituents selected from halogen, -OH, -SH, -NH_2, -NHC$_{1-6}$ alkyl, and -SC_{1-6} alkyl;

R^4 is hydrogen, deuterium, C_{1-6} alkyl, -C(O)C_{1-6} alkyl, -C(O)C_{3-12} cycloalkyl, or -C(O)(4 to 12-membered heterocycloalkyl); wherein said C_{1-6} alkyl, C_{3-12} cycloalkyl, or 4 to 12-membered heterocycloalkyl is optionally substituted with one or more substituents selected from halogen, -OH, -SH, -NH_2, -NHC$_{1-6}$ alkyl, and -SC_{1-6} alkyl;

or R^3 and R^4, together with the atom to which they are attached, form a 5- to 12-membered heterocycloalkyl; wherein said 5- to 12-membered heterocycloalkyl is optionally substituted with one or more substituents selected from halogen, oxo group, -OH, -CN, -NH_2, -NHC$_{1-6}$ alkyl, -N(C_{1-6} alkyl)$_2$, -C_{1-6} alkyl, -C_{1-6} alkylene-OH, -C(O)C_{1-6} alkylene-OH, -C(O)-C_{3-12} cycloalkylene-OH, and -C(O)-(4 to 12-membered heterocycloalkylene)-OH;

Y is selected from -OH or -CN;

provided that R^2 and R^3 cannot both be H.

In some embodiments, one of R^2 and R^3 is H and the other is not H.

In some embodiments, the compound of formula (I) or formula (Ia), wherein  is  ,  or a combination thereof.

In some embodiments, the compound of formula (I) or formula (Ia), wherein  is  ,  or a combination thereof.

In some embodiments, the compound of formula (I) or formula (Ia), wherein R^1 is hydrogen, halogen, -OH, -CN, $-NH_2$, $-CH_3$, $-OCH_3$, or $-NHCH_3$.

In some embodiments, the compound of formula (I) or formula (Ia), wherein R^1 is hydrogen, deuterium, -F, -Cl, -OH, $-CH_3$, $-OCH_3$, $-NH_2$, or $-NHCH_3$.

In some embodiments, R^1 is hydrogen, deuterium, halogen, -OH, -CN, $-CH_3$, or $-NHCH_3$.

In some embodiments, the compound of formula (I) or formula (Ia), wherein R^1 is hydrogen.

In some embodiments, the compound of formula (I), wherein R^1 is -OH.

In some embodiments, the compound of formula (I), wherein R^1 is $-OC_{1-6}$ alkyl; preferably $-OCH_3$.

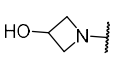
In some embodiments, the compound of formula (I), wherein R^1 is F.

In some embodiments, the compound of formula (I), wherein R^2 is H.

In some embodiments, the compound of formula (I) or formula (Ia), wherein R^{2-1} is hydrogen or C_{1-3} alkyl.

In some embodiments, the compound of formula (I) or formula (Ia), wherein R^{2-1} is H or CH_3.

In some embodiments, the compound of formula (I) or formula (Ia), wherein R^{2-2} is C_{1-6} alkyl, C_{3-12} cycloalkyl, or a 4- to 12-membered heterocycloalkyl; said C_{1-6} alkyl, C_{3-12} cycloalkyl, and 4- to 12-membered heterocycloalkyl are optionally substituted with one or more substituents independently selected from halogen and -OH, for example, -OH.

In some embodiments, the compound of formula (I) or formula (Ia), wherein R^{2-2} is $-CH_2OH$, $-CH_2CH_2OH$, $-CH(OH)CH_3$, $-CH_2ONH(CH_3)$,  or  .

In some embodiments, the compound of formula (I) or formula (Ia), wherein R^2 is -OH, $-NH_2$, C_{1-6} alkyl, $-NHC_{1-6}$ alkyl, $-NHC(O)C_{1-6}$ alkyl, $-N(C_{1-6}$ alkyl$)C(O)C_{1-6}$ alkyl, or $-N(C_{1-6}$ alkyl$)C(O)C_{3-12}$ cycloalkyl;

said C_{1-6} alkyl, C_{3-12} cycloalkyl, or 4- to 12-membered heterocycloalkyl is each optionally substituted with one or more substituents selected from -OH, -SH, $-NH_2$, $-NHCH_3$, and $-SCH_3$.

In some embodiments, the compound of formula (I) or formula (Ia), wherein R^2 is -OH, $-NH_2$, C_{1-6} alkyl, $-NHC(O)C_{1-6}$ alkyl, or $-N(C_{1-6}$ alkyl$)C(O)C_{1-6}$ alkyl; said C_{1-6} alkyl groups are each optionally substituted with one or more substituents selected from -OH, -SH, $-NH_2$, $-NHCH_3$, and $-SCH_3$.

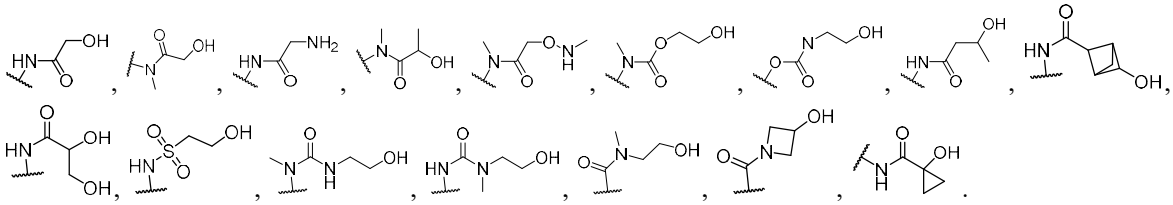
In some embodiments, the compound of formula (I) or formula (Ia), wherein R^2 is -OH, $-NH_2$, $-C_{1-6}$ alkylene-OH, $-NHC(O)C_{1-6}$ alkylene-OH, or $-N(C_{1-6}$ alkyl$)C(O)C_{1-6}$ alkylene-OH.

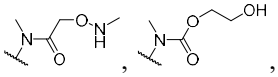
In some embodiments, the compound of formula (I) or formula (Ia), wherein R^2 is $-NHC(O)C_{1-6}$ alkylene-NH_2 or $-N(C_{1-6}$ alkyl$)C(O)C_{1-6}$ alkylene-NH_2.

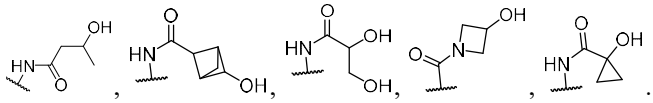
In some embodiments, the compound of formula (I) or formula (Ia), wherein R^2 is $-NHC(O)C_{1-3}$ alkylene-NH_2 or $-N(C_{1-6}$ alkyl$)C(O)C_{1-3}$ alkylene-NH_2. In some embodiments, the compound of formula (I) or formula (Ia), wherein R^2 is $-O-C(O)-N(R^{2-1})R^{2-2}$, $-C(O)R^{2-2}$, $-NHC(O)C_{3-12}$ cycloalkyl, C(O)(4- to 12-membered heterocycloalkyl), $C(O)-N(R^{2-1})R^{2-2}$, $-N(R^{2-1})-C(O)-OR^{2-2}$, $-N(R^{2-1})-C(O)-N(R^{2-1})R^{2-2}$, or $-NH-S(O)_2-R^{2-2}$.

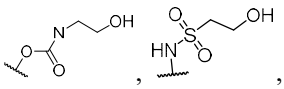
In some embodiments, the compound of formula (I) or formula (Ia), wherein R^2 is NH_2, OH, $-C_{1-6}$ alkyl, $-NHC(O)C_{1-6}$ alkyl, $-N(C_{1-6}$ alkyl$)C(O)C_{1-6}$ alkyl, $-N(R^{2-1})-C(O)-OR^{2-2}$, $-O-C(O)-N(R^{2-1})R^{2-2}$, $-N(R^{2-1})-C(O)-N(R^{2-1})R^{2-2}$, $-NHC(O)C_{3-12}$ cycloalkyl, C(O)(4- to 12-membered heterocycloalkyl), $C(O)-N(R^{2-1})R^{2-2}$, or $-NH-S(O)_2-R^{2-2}$.

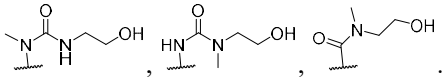
In some embodiments, the compound of formula (I) or formula (Ia), wherein R^2 is NH_2, OH, CH_2OH,

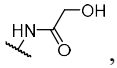
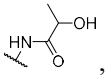
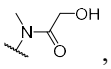
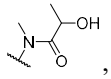
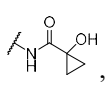
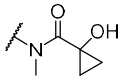
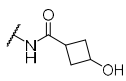
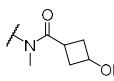


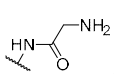
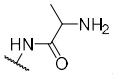
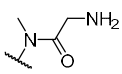
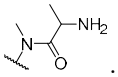
In some embodiments, the compound of formula (I) or formula (Ia), wherein R^2 is 

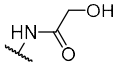
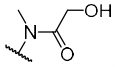


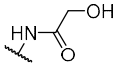
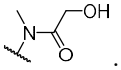
In some embodiments, the compound of formula (I) or formula (Ia), wherein R^2 is 

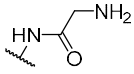
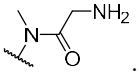


In some embodiments, the compound of formula (I) or formula (Ia), wherein R^2 is -OH, -NH_2, -$NHCH_3$, -CH_2OH,  ,  ,  ,  ,  ,  ,  or  .

In some embodiments, the compound of formula (I) or formula (Ia), wherein R^2 is  ,  ,  ,  .

In some embodiments, the compound of formula (I) or formula (Ia), wherein R^2 is -OH, -NH_2, -$NHCH_3$, -CH_2OH,  or  .

In some embodiments, the compound of formula (I) or formula (Ia), wherein R^2 is -OH, -NH_2, -CH_2OH,  or  .

In some embodiments, the compound of formula (I) or formula (Ia), wherein R^2 is  or  .

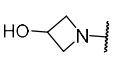
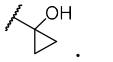
In some embodiments, the compound of formula (I) or formula (Ia), wherein R^3 is H.

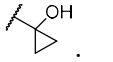
In some embodiments, the compound of formula (I) or formula (Ia), wherein R^{3-1} is hydrogen or C_{1-3} alkyl.

In some embodiments, the compound of formula (I) or formula (Ia), wherein R^{3-1} is hydrogen or -CH_3.

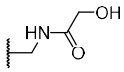
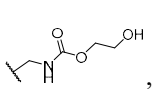
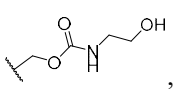
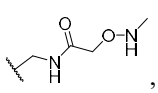
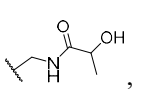
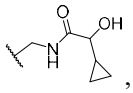
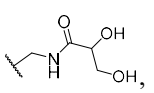
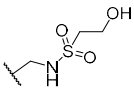
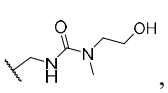
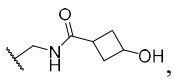
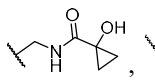
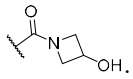
In some embodiments, the compound of formula (I) or formula (Ia), wherein R^{3-2} is C_{1-6} alkyl; said C_{1-6} alkyl is optionally substituted with one or more substituents independently selected from halogen and -OH; for example, substituted with -OH.

In some embodiments, the compound of formula (I) or formula (Ia), wherein R^{3-2} is  ,  .

In some embodiments, the compound of formula (I) or formula (Ib), wherein R^{3-2} is -CH_2OH, -CH_2CH_2OH, -$CH(OH)CH_3$, -CH_2O-$NHCH_3$, -$CH_2ONH(CH_3)$,  or  .

In some embodiments, the compound of formula (I) or formula (Ib), wherein R^{3-2} is -CH_2OH, -CH_2CH_2OH, -$CH(OH)CH_3$, -$CH_2ONH(CH_3)$, or  .

In some embodiments, the compound of formula (I) or formula (Ia), wherein R^3 is -C(O)R^{3-2}, -CH_2-NHC(O)C_{1-6} alkyl, -CH_2-N(C_{1-6} alkyl)C(O)C_{1-6} alkyl, -CH_2NH-S(O)$_2$-R^{3-2}, -CH_2-NR^{3-1}C(O)O-R^{3-2}, -CH_2-OC(O)-$NR^{3-1}R^{3-2}$, -CH_2-NR^{3-1}C(O)NR^{3-1}-R^{3-2}, or -CH_2-NHC(O)C_{3-12} cycloalkyl; said C_{1-6} alkyl, C_{3-12} cycloalkyl, and 4- to 12-membered heterocycloalkyl are each optionally substituted with one or more substituents selected from cyclopropyl, -OH, and -O-$NHCH_3$.

In some embodiments, the compound of formula (I) or formula (Ia), wherein R^3 is  , ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  .

In some embodiments, the compound of formula (I) or formula (Ia), wherein R^{3a} is hydrogen or C_{1-3} alkyl.

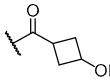
In some embodiments, the compound of formula (I) or formula (Ia), wherein R^{3a} is hydrogen or -CH_3.

In some embodiments, the compound of formula (I) or formula (Ia), wherein

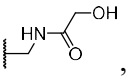
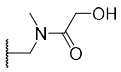
R^{3b} is -C(O)C_{1-6} alkyl or -C(O)C_{3-6} cycloalkyl; said C_{1-6} alkyl and C_{3-6} cycloalkyl are each optionally substituted with one or more substituents selected from -OH, -SH, -NH_2, -$NHCH_3$, and -SCH_3.

In some embodiments, the compound of formula (I) or formula (Ia), wherein

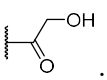
R^{3b} is -C(O)C_{1-6} alkylene-OH.

In some embodiments, the compound of formula (I) or formula (Ia), wherein R^{3b} is  ,  ,  or  .

In some embodiments, the compound of formula (I) or formula (Ia), wherein R^{3b} is  .

In some embodiments, the compound of formula (I) or formula (Ia), wherein -CH_2-$NR^{3a}R^{3b}$ is  ,  .

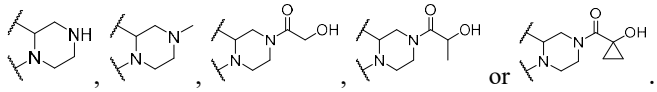
In some embodiments, the compound of formula (I) or formula (Ia), wherein R^4 is hydrogen, deuterium, -C_{1-6} alkyl, or -C(O)C_{1-6} alkylene-OH.

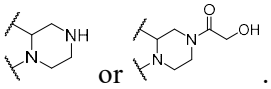
In some embodiments, the compound of formula (I) or formula (Ia), wherein R^4 is hydrogen or  .

In some embodiments, the compound of formula (I) or formula (Ia), wherein R^4 is hydrogen.

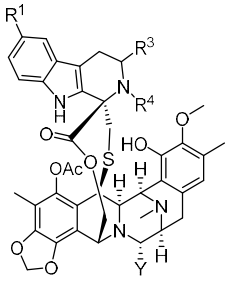
In some embodiments, the compound of formula (Ia), wherein R^3 and R^4, together with the atoms to which they are attached, form a 5- to 6-membered heterocycloalkyl, wherein said 5- to 6-membered heterocycloalkyl is optionally substituted with one or more substituents selected from halogen, oxo group, -OH, -CN, -NH_2, -NHC_{1-6} alkyl, -$N(C_{1-6}$ alkyl$)_2$, -C_{1-6} alkyl, -C_{1-6} alkyl-OH, -$C(O)C_{1-6}$ alkylene-OH, -$C(O)$-C_{3-12} cycloalkylene-OH, and -$C(O)$-(4- to 12-membered heterocycloalkylene)-OH.

In some embodiments, the compound of formula (I) or formula (Ia), wherein R^3 and R^4, together with the atoms to which they are attached, form a piperazinyl, wherein said piperazinyl is optionally substituted with one or more substituents selected from halogen, oxo group, -OH, -CN, -NH_2, -NHC_{1-6} alkyl, -$N(C_{1-6}$ alkyl$)_2$, -C_{1-6} alkyl, -C_{1-6} alkyl-OH, -$C(O)C_{1-6}$ alkylene-OH, -$C(O)$-C_{3-12} cycloalkylene-OH, and -$C(O)$-(4- to 12-membered heterocycloalkylene)-OH.

In some embodiments, the compound of formula (I) or formula (Ia), wherein R^3 and R^4, together with the atoms to which they are attached, form  or .

In some embodiments, the compound of formula (I) or formula (Ia), wherein R^3 and R^4, together with the atoms to which they are attached, form  or .

In some embodiments, the compound of formula (I) or formula (IA) is a compound of formula (IA-1),



IA-1

wherein

R^1 is hydrogen, halogen, -OH, or -OC_{1-6} alkyl;

R^3 is -CH_2-NHC_{1-6} alkyl, -CH_2-$NHC(O)C_{1-6}$ alkyl, -CH_2-$OC(O)$-$NR^{3-1}R^{3-2}$, -CH_2-$NR^{3-1}C(O)NR^{3-1}$-R^{3-2}, -CH_2-$NR^{3-1}C(O)O$-R^{3-2}, -CH_2-$NHC(O)C_{3-12}$ cycloalkyl, -CH_2-NHC(O)(4- to 12-membered heterocycloalkyl), -CH_2-$NHC(O)C_{3-12}$ cycloalkyl, -CH_2-$N(C_{1-6}$ alkyl$)C(O)C_{1-6}$ alkyl, -CH_2-$N(C_{1-6}$ alkyl$)C(O)C_{3-12}$ cycloalkyl, -CH_2-$N(C_{1-6}$ alkyl$)C(O)$(4- to 12-membered heterocycloalkyl), -CH_2NH-$S(O)_2$-R^{3-2}, -CH_2-$S(O)_2$-R^{3-2}, or -$C(O)R^{3-2}$, wherein said C_{1-6} alkyl, C_{3-12} cycloalkyl, and 4- to 12-

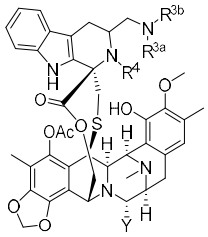
membered heterocycloalkyl are each optionally substituted with one or more substituents selected from halogen, cyclopropyl, -OH, -O-NHCH$_3$, -SH, -NH$_2$, -NHC$_{1-6}$ alkyl, and -SC$_{1-6}$ alkyl;

R^4 is hydrogen or C$_{1-6}$ alkyl;

or R^3 and R^4, together with the atoms to which they are attached, form a 5- to 12-membered heterocycloalkyl; said 5- to 12-membered heterocycloalkyl is optionally substituted with one or more substituents selected from -C(O)C$_{1-6}$ alkylene-OH;

Y is -OH or -CN.

In some embodiments, the compound of formula (I) or formula (Ia) is a compound of formula (Ia-1),



Ia-1

wherein

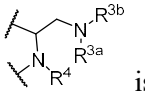
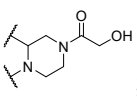
Y, R^{3a}, R^{3b}, and R^4 are as defined for any one of formulae (I) and (Ia) of the present application.

In some embodiments, the compound of formula (I), formula (Ia), or formula (Ia-1), wherein

R^{3a} is hydrogen or -CH$_3$;

R^{3b} is -C(O)C$_{1-6}$ alkylene-OH;

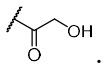
R^4 is hydrogen;

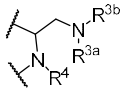
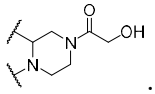
or  is  or  ;

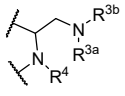
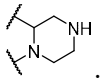
Y is -OH or -CN.

In some embodiments, the compound of formula (I), formula (Ia), or formula (Ia-1), wherein R^{3a} is -CH$_3$.

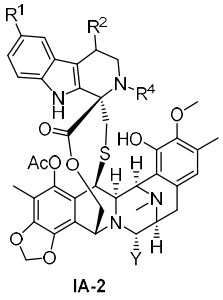
In some embodiments, the compound of formula (I), formula (Ia), or formula (Ia-1), wherein R^{3b} is -C(O)C$_{1-3}$ alkylene-OH.

In some embodiments, the compound of formula (I), formula (Ia), or formula (Ia-1), wherein R^{3b} is  .

In some embodiments, the compound of formula (I), formula (Ia), or formula (Ia-1), wherein  is  or  .

In some embodiments, the compound of formula (I), formula (Ia), or formula (Ia-1), wherein  is  .

In some embodiments, the compound of formula (I) is a compound of formula (IA-2):


IA-2

wherein

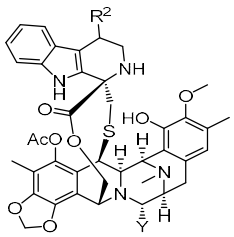
R^1 is hydrogen, halogen, -OH, or -OC_{1-6} alkyl;

R^2 is halogen, -C_{1-6} alkyl, -OH, -O-C(O)-N(R^{2-1})R^{2-2}, -C(O)R^{2-2}, C(O)-N(R^{2-1})R^{2-2}, -NH_2, -NHC_{1-6} alkyl, -$NHC(O)C_{1-6}$ alkyl, -N(R^{2-1})-C(O)-OR^{2-2}, -N(R^{2-1})-C(O)-N(R^{2-1})R^{2-2}, -$NHC(O)C_{3-12}$ cycloalkyl, -NHC(O)(4- to 12-membered heterocycloalkyl), -N(C_{1-6} alkyl)C(O)C_{1-6} alkyl, -N(C_{1-6} alkyl)C(O)C_{3-12} cycloalkyl, C(O)(4- to 12-membered heterocycloalkyl), -N(C_{1-6} alkyl)C(O)(4- to 12-membered heterocycloalkyl), or -NH-$S(O)_2$-R^{2-2}, wherein said C_{1-6} alkyl, C_{3-12} cycloalkyl, and 4- to 12-membered heterocycloalkyl are each optionally substituted with one or more substituents selected from halogen, -OH, -O-$NHCH_3$, -SH, -NH_2, -NHC_{1-6} alkyl, and -SC_{1-6} alkyl;

R^4 is hydrogen or C_{1-6} alkyl;

Y is -OH or -CN.

In some embodiments, the compound of formula (I) or formula (Ia) is a compound of formula (Ia-2):



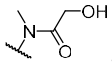
Ia-2

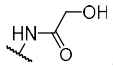
wherein Y and R^2 are as defined for any one of formula (Ia) of the present application.

In some embodiments, the compound of formula (I), formula (Ia), or formula (Ia-2), wherein R^2 is -OH, -NH_2, -C_{1-6} alkylene-OH, -NHC(O)C_{1-6} alkylene-OH, or -N(C_{1-6} alkyl)C(O)C_{1-6} alkylene-OH.

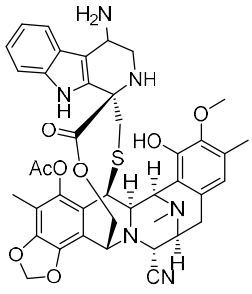
In some embodiments, the compound of formula (I), formula (Ia), or formula (Ia-2), wherein R^2 is -NHC(O)C_{1-6} alkylene-NH_2 or -N(C_{1-6} alkyl)C(O)C_{1-6} alkylene-NH_2; preferably, R^2 is -NHC(O)C_{1-3} alkylene-NH_2 or -N(C_{1-3} alkyl)C(O)C_{1-3} alkylene-NH_2.

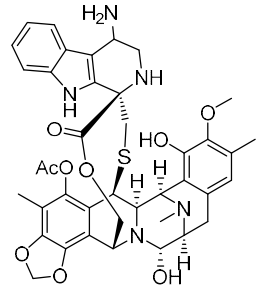
In some embodiments, the compound of formula (I), formula (Ia), or formula (Ia-2), wherein R^2 is -OH, -NH_2, -C_{1-3} alkylene-OH, -NHC(O)C_{1-3} alkylene-OH, or -N(C_{1-3} alkyl)C(O)C_{1-3} alkylene-OH.

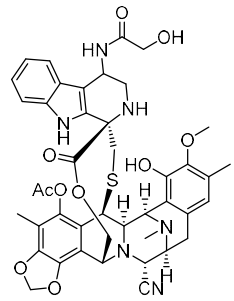
In some embodiments, the compound of formula (I), formula (Ia), or formula (Ia-2), wherein R^2 is -NH_2, -CH_2OH, or  .

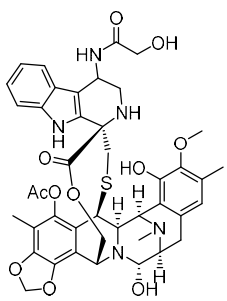
In some embodiments, the compound of formula (I), formula (Ia), or formula (Ia-2), wherein R^2 is  .

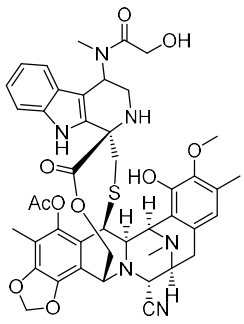
In some embodiments, the compound of formula (I) or formula (Ⅰa) of the present application is:



13, 

14, 

15, 

16, 

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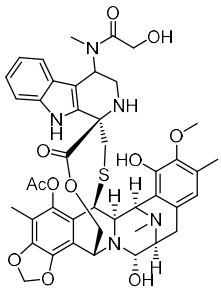
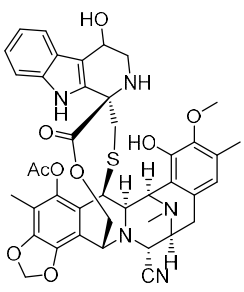
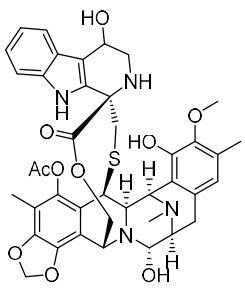
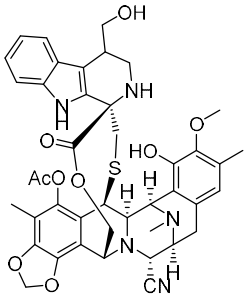
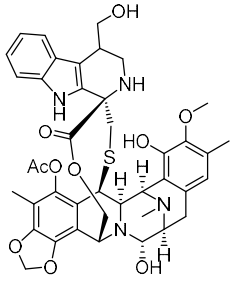


18, 

19, 

20, 

21, 

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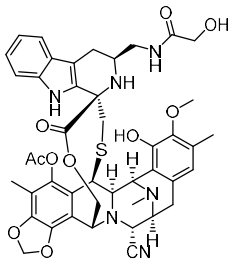
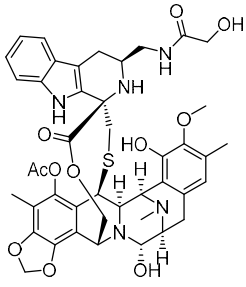
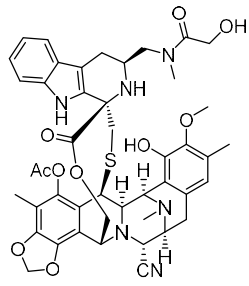
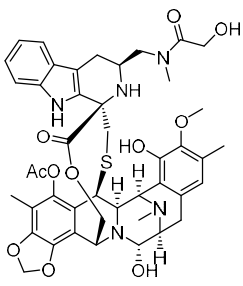
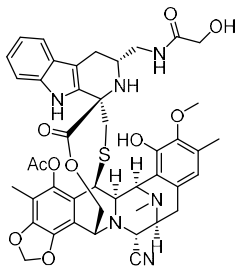


23, 

24, 

25, 

26, 

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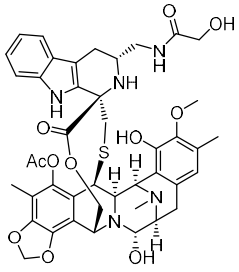
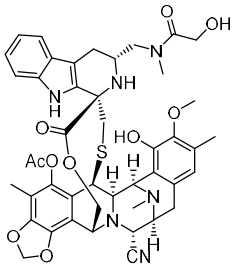
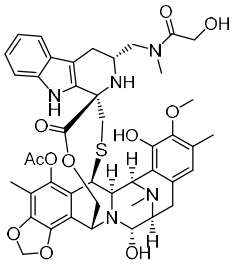
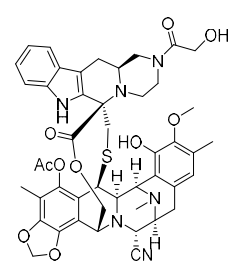
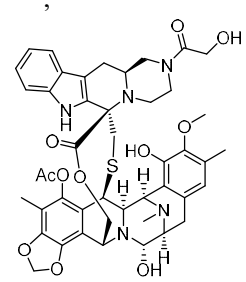


28, 

29, 

30, 

31, 

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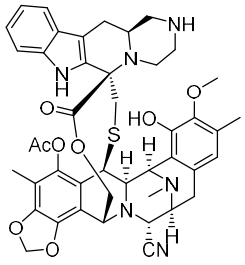

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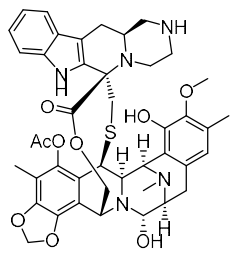

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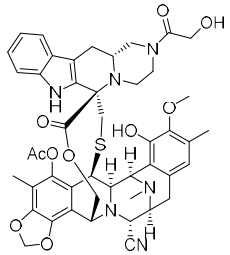

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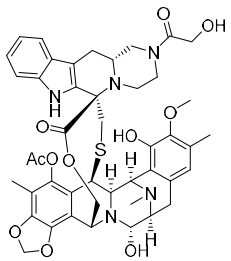

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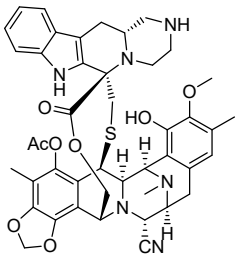

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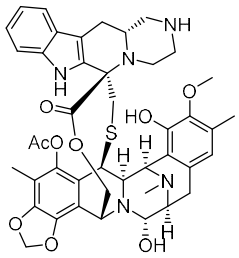

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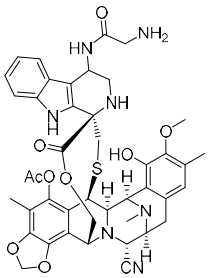

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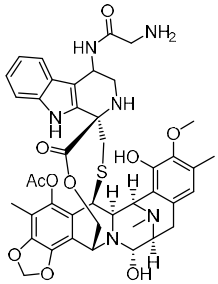

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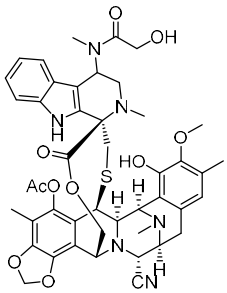

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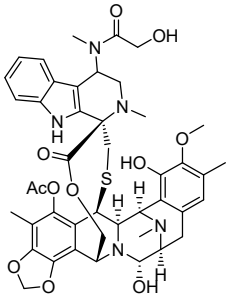

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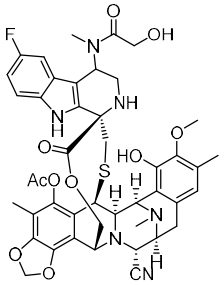

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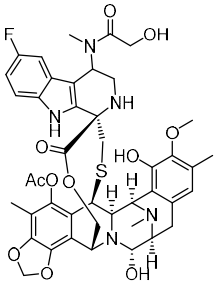

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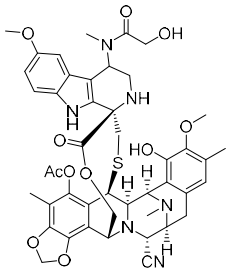

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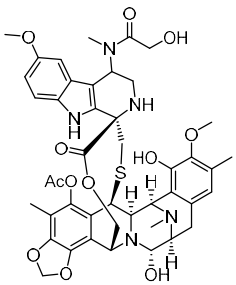

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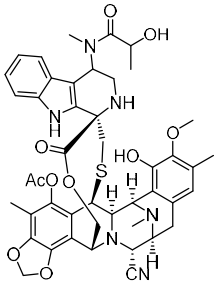

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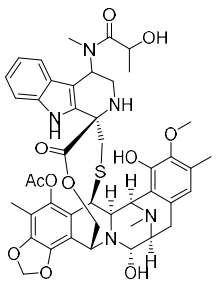

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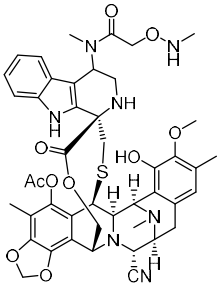

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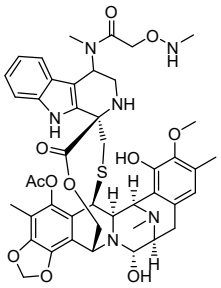

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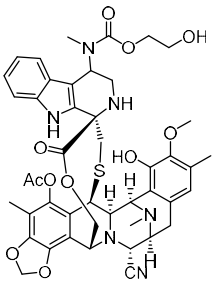

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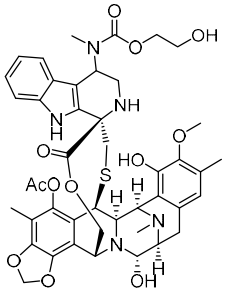

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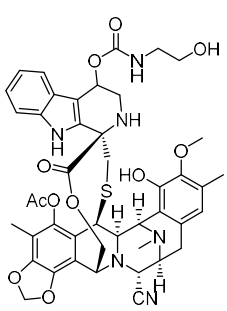

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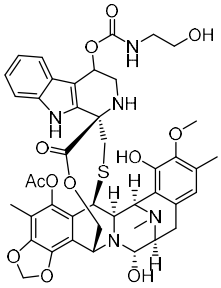

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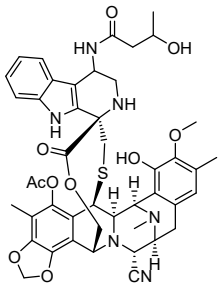

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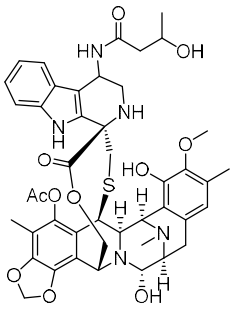

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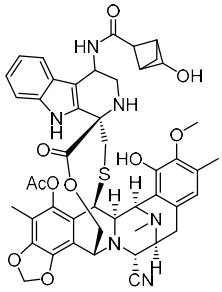

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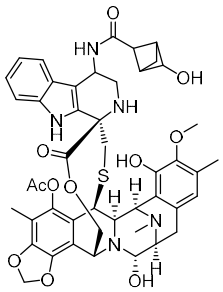

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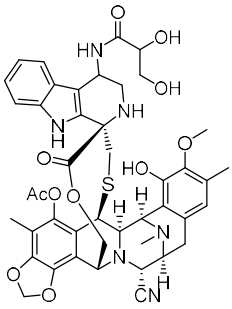

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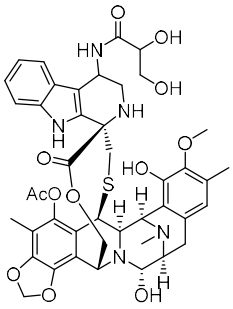

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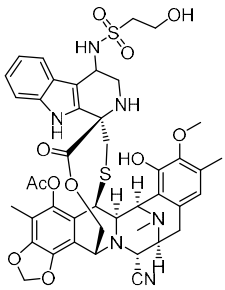

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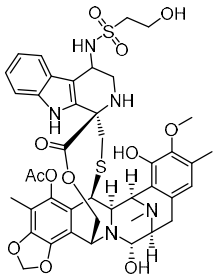

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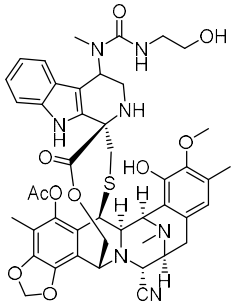

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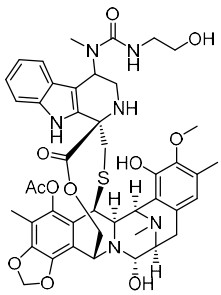

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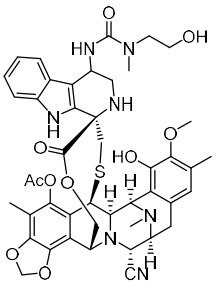

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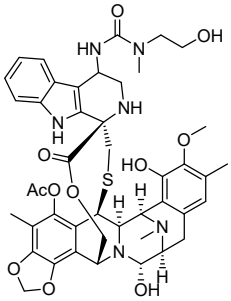

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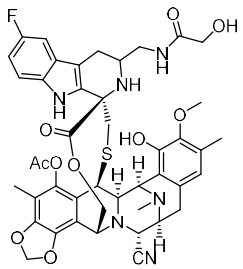

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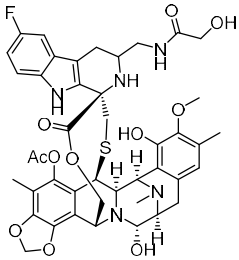

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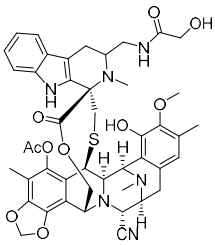

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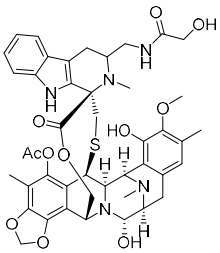

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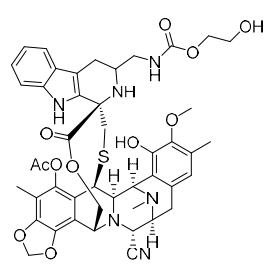

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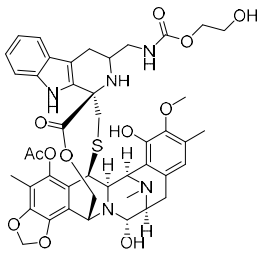

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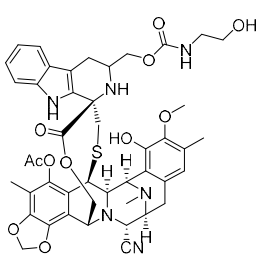

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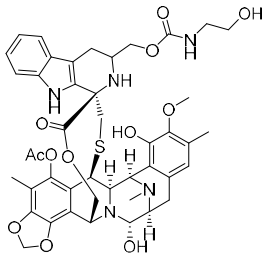

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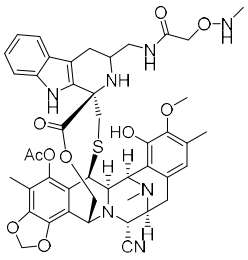

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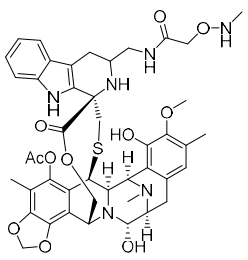

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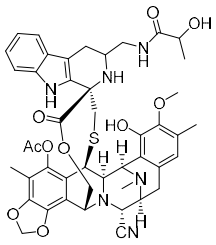

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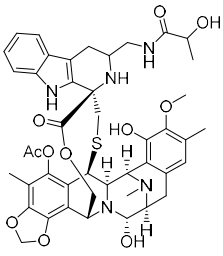

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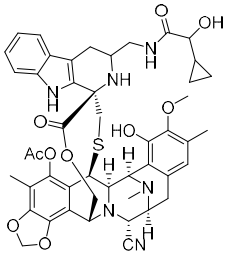

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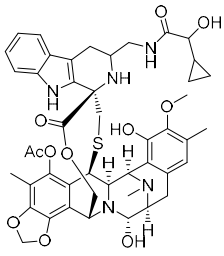

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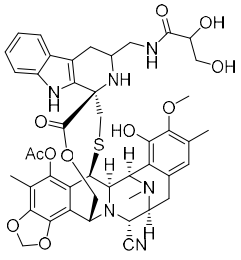

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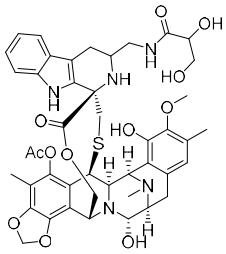

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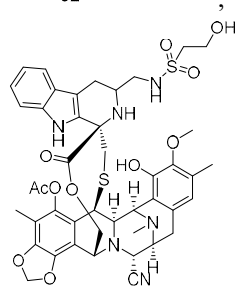

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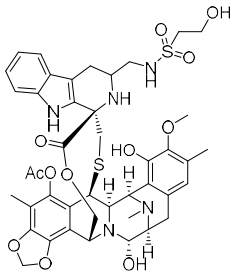

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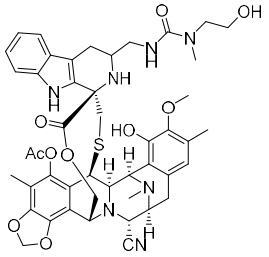

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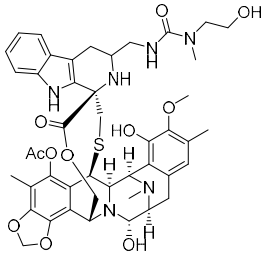

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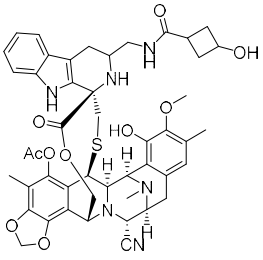

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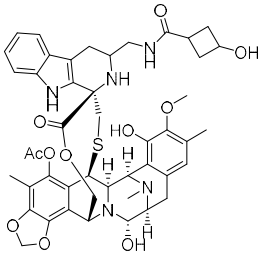

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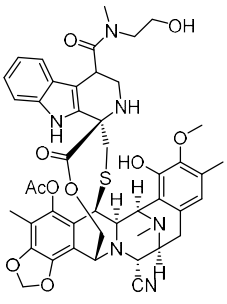

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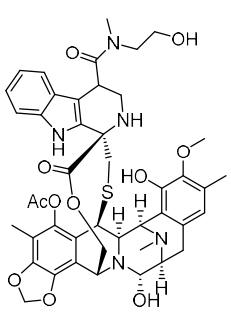
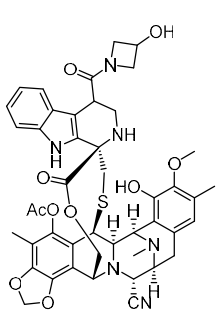
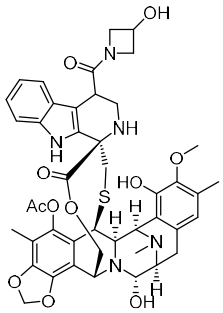
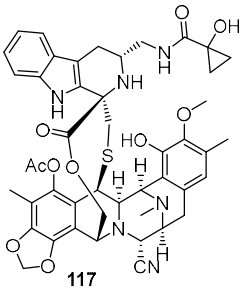
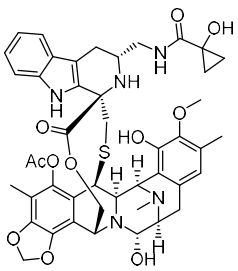
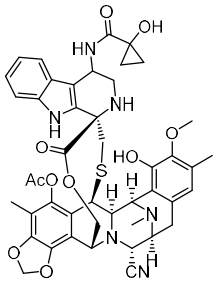


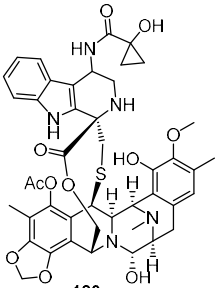
108, 

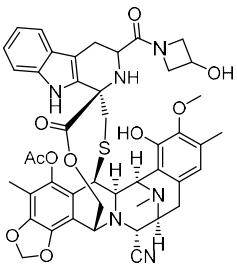
109, 

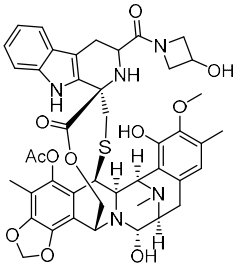
110, 

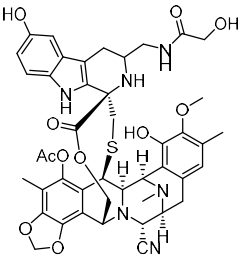
117, 

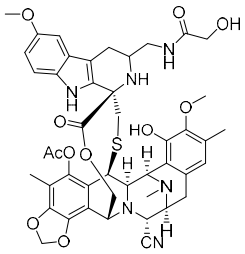
118, 

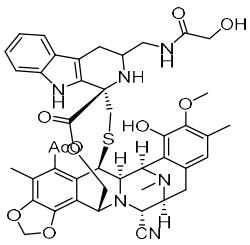
119, 

120, 

121, 

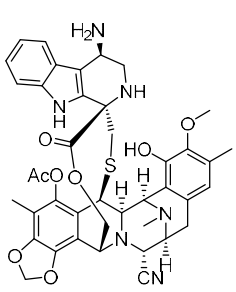
122, 

124, 

125 or 

126 .

In some embodiments, the compounds of formula (Ia) of the present application are:



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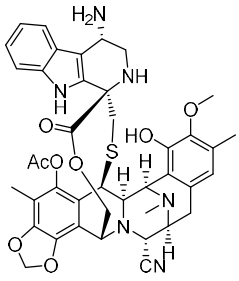

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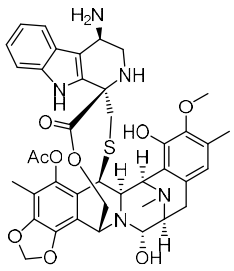

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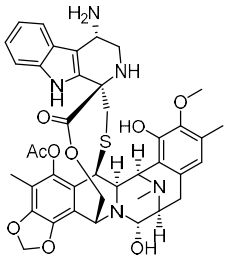

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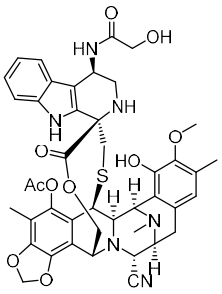

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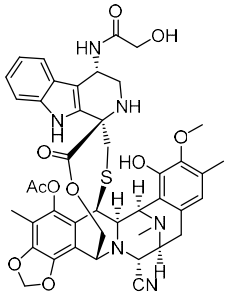

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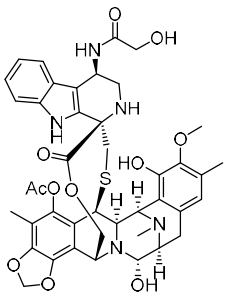

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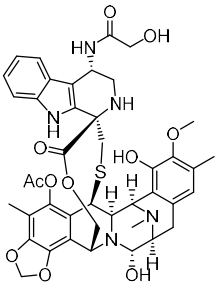

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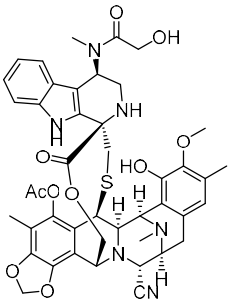

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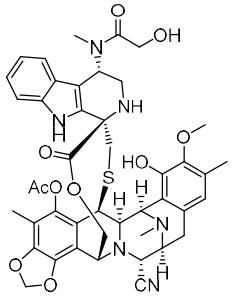

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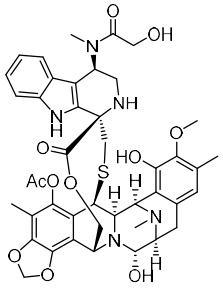

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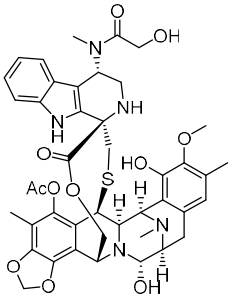

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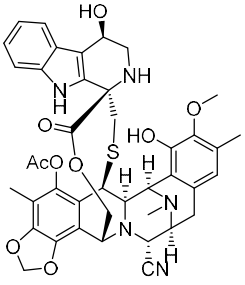

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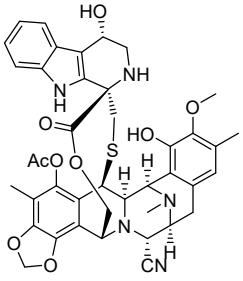

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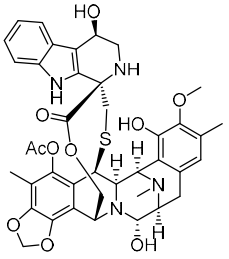

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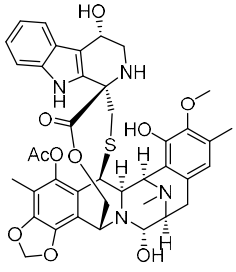

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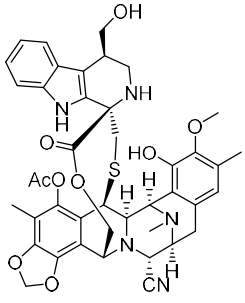

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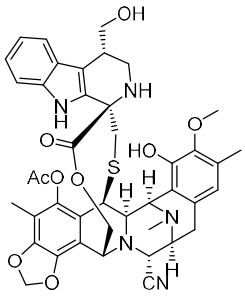

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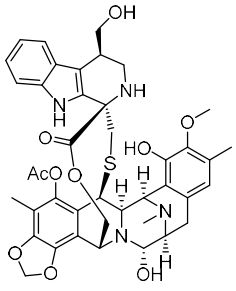

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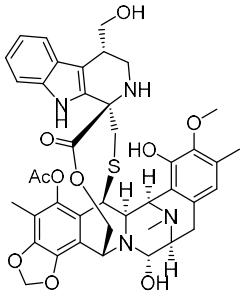

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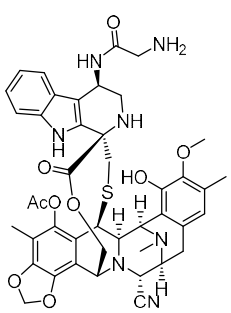

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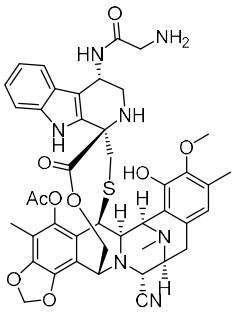

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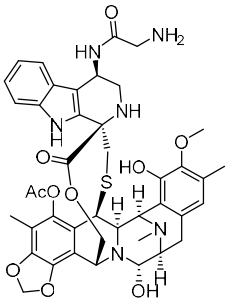

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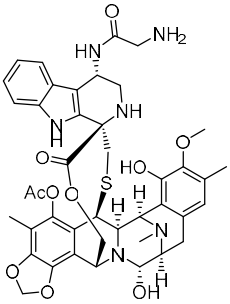

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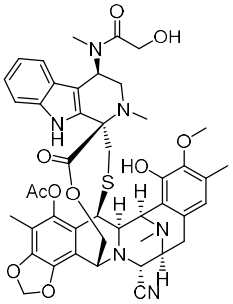

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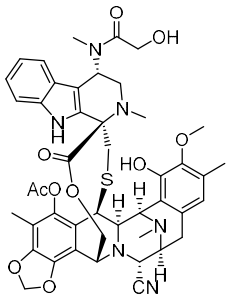

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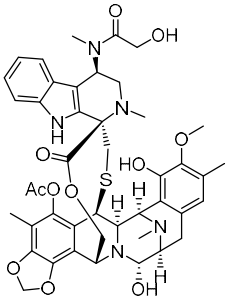

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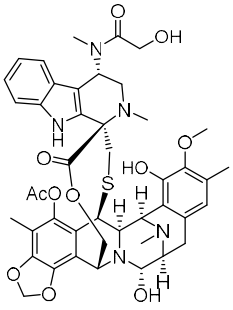

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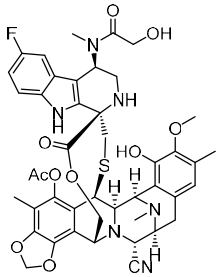

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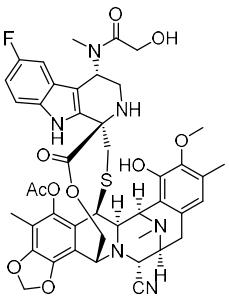

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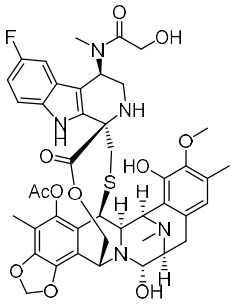

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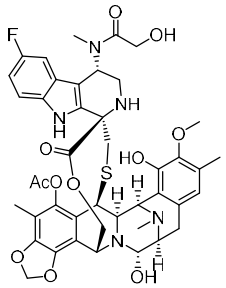

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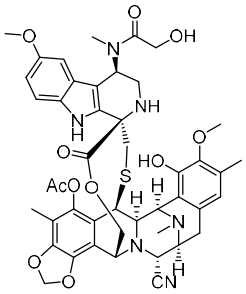

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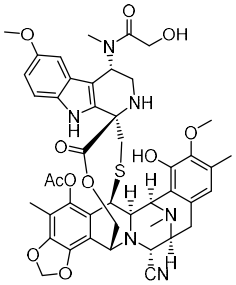

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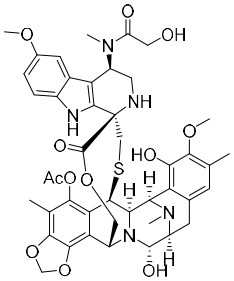

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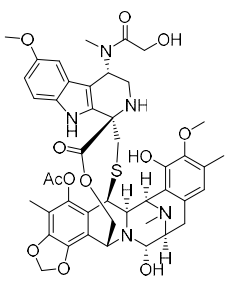

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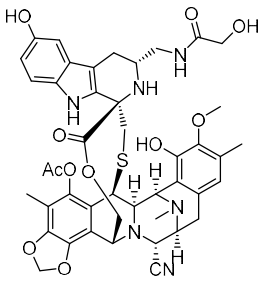

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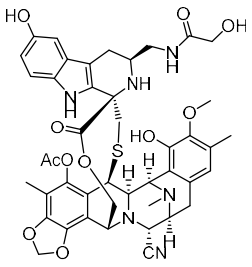

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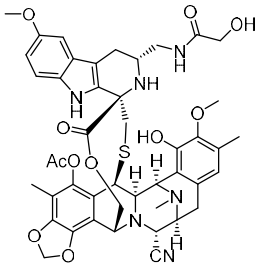
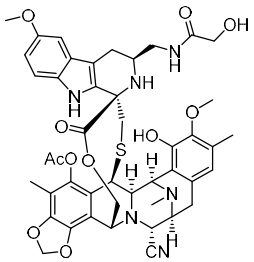


125S

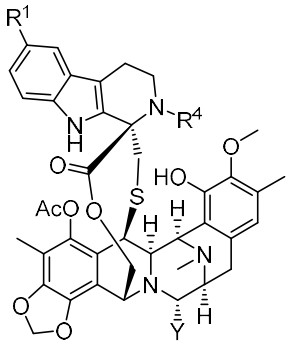
or



125R

.

In some embodiments, the compound of formula (I) is a compound having the structure of formula (IB):



IB

wherein,

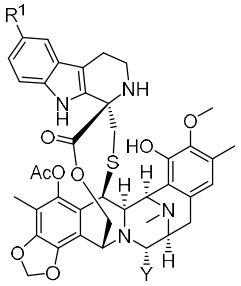
R^1 is -OH, -CN, $-NH_2$, C_{1-6} alkyl, $-NH-S(O)_2-R^{1-2}$, $-C(O)R^{1-2}$, $C(O)-N(R^{1-1})R^{1-2}$, $-C_{1-6}$ alkylene-$N(R^{1-1})$-$C(O)R^{1-2}$, $-O-C_{3-12}$ cycloalkyl, -O-(4- to 12-membered heterocycloalkylene)-$C(O)R^{1-2}$, $-O-C_{3-12}$ cycloalkylene-$N(R^{1-1})$-$C(O)R^{1-2}$, $-O-C(O)-N(R^{1-1})R^{1-2}$, $-N(R^{1-1})-C(O)R^{1-2}$, $-N(R^{1-1})-C(O)-OR^{1-2}$, $-N(R^{1-1})$-(4- to 12-membered heterocycloalkylene)-$C(O)R^{1-2}$, $-N(R^{1-1})-C_{3-12}$ cycloalkylene-$N(R^{1-3})-C(O)R^{1-2}$, -(4- to 12-membered heterocycloalkylene)-$C(O)R^{1-2}$, -(4- to 12-membered heterocycloalkylene)-$N(R^{1-1})-C(O)R^{1-2}$, $-N(R^{1-1})C(O)C_{3-12}$ cycloalkyl, (4- to 12-membered heterocycloalkylene), or $-N(R^{1-1})C(O)$(4- to 12-membered heterocycloalkyl), wherein said C_{1-6} alkyl, C_{1-6} alkylene, C_{3-12} cycloalkyl, C_{3-12} cycloalkylene, 4- to 12-membered heterocycloalkylene, and 4- to 12-membered heterocycloalkyl are each optionally substituted with one or more substituents selected from halogen, -OH, -SH, $-NH_2$, $-O-NHCH_3$, $-NHC_{1-6}$

alkyl, -SC$_{1-6}$ alkyl, -C$_{1-6}$ alkylene-OH, -C$_{1-6}$ alkylene-SH, -C$_{1-6}$ alkylene-S(C$_{1-6}$ alkyl), and -C$_{1-6}$ alkylene-NH$_2$;

R^4 is hydrogen or -C$_{1-6}$ alkyl;

Y is -OH or -CN.

In some embodiments, the compound of formula (I) is a compound having the structure of formula (Ib):



Ib

wherein,

R^1 is -NH$_2$, -C$_{1-6}$ alkylene-N(R$^{1-1}$)-C(O)R$^{1-2}$, -O-C$_{3-12}$ cycloalkyl, -O-(4- to 12-membered heterocycloalkylene)-C(O)R$^{1-2}$, -O-C$_{3-12}$ cycloalkylene-N(R$^{1-1}$)-C(O)R$^{1-2}$, -N(R$^{1-1}$)-(4- to 12-membered heterocycloalkylene)-C(O)R$^{1-2}$, -N(R$^{1-1}$)-C$_{3-12}$ cycloalkylene-N(R$^{1-3}$)-C(O)R$^{1-2}$, -(4- to 12-membered heterocycloalkylene)-C(O)R$^{1-2}$, -(4- to 12-membered heterocycloalkylene)-N(R$^{1-1}$)-C(O)R$^{1-2}$, -N(R$^{1-1}$)C(O)C$_{3-12}$ cycloalkyl, or -N(R$^{1-1}$)C(O)(4- to 12-membered heterocycloalkyl), wherein said C$_{1-6}$ alkyl, C$_{1-6}$ alkylene, C$_{3-12}$ cycloalkyl, C$_{3-12}$ cycloalkylene, 4- to 12-membered heterocycloalkylene, and 4- to 12-membered heterocycloalkyl is each optionally substituted with one or more substituents selected from halogen, -OH, -SH, -NH$_2$, -NHC$_{1-6}$ alkyl, -SC$_{1-6}$ alkyl, -C$_{1-6}$ alkylene-OH, -C$_{1-6}$ alkylene-SH, -C$_{1-6}$ alkylene-S(C$_{1-6}$ alkyl), and -C$_{1-6}$ alkylene-NH$_2$;

R$^{1-1}$ is hydrogen, deuterium, C$_{1-6}$ alkyl, or halo-C$_{1-6}$ alkyl;

R$^{1-2}$ is C$_{1-6}$ alkyl, C$_{3-12}$ cycloalkyl, or 4- to 12-membered heterocycloalkyl; said C$_{1-6}$ alkyl, C$_{3-12}$ cycloalkyl, or 4- to 12-membered heterocycloalkyl is each optionally substituted with one or more substituents selected from halogen, -OH, -SH, -NH$_2$, -NHC$_{1-6}$ alkyl, and -SC$_{1-6}$ alkyl;

Y is -OH or -CN.

In some embodiments, the compounds having the structure of formula (I) or formula (Ib), wherein,

R^1 is -C$_{1-6}$ alkylene-N(R$^{1-1}$)-C(O)R$^{1-2}$, -O-C$_{3-12}$ cycloalkyl, -O-(4- to 12-membered heterocycloalkylene)-C(O)R$^{1-2}$, -O-C$_{3-12}$ cycloalkylene-N(R$^{1-1}$)-C(O)R$^{1-2}$, -N(R$^{1-1}$)-(4- to 12-membered heterocycloalkylene)-C(O)R$^{1-2}$, -N(R$^{1-1}$)-C$_{3-12}$ cycloalkylene-N(R$^{1-3}$)-C(O)R$^{1-2}$, -(4- to 12-membered heterocycloalkylene)-C(O)R$^{1-2}$, -(4- to 12-membered heterocycloalkylene)-N(R$^{1-1}$)-C(O)R$^{1-2}$, -N(R$^{1-1}$)C(O)C$_{3-12}$ cycloalkyl, or -

$N(R^{1-1})C(O)$(4- to 12-membered heterocycloalkyl), wherein said C_{1-6} alkyl, C_{1-6} alkylene, C_{3-12} cycloalkyl, C_{3-12} cycloalkylene, 4- to 12-membered heterocycloalkylene, and 4- to 12-membered heterocycloalkyl are each optionally substituted with one or more substituents selected from halogen, -OH, -SH, $-NH_2$, $-NHC_{1-6}$ alkyl, $-SC_{1-6}$ alkyl, $-C_{1-6}$ alkylene-OH, $-C_{1-6}$ alkylene-SH, $-C_{1-6}$ alkylene-S(C_{1-6} alkyl), and $-C_{1-6}$ alkylene-NH_2;

R^{1-1} is hydrogen, deuterium, C_{1-6} alkyl, or halo-C_{1-6} alkyl;

R^{1-2} is C_{1-6} alkyl, C_{3-12} cycloalkyl, or 4- to 12-membered heterocycloalkyl; said C_{1-6} alkyl, C_{3-12} cycloalkyl, or 4- to 12-membered heterocycloalkyl is each optionally substituted with one or more substituents selected from halogen, -OH, -SH, $-NH_2$, $-NHC_{1-6}$ alkyl, and $-SC_{1-6}$ alkyl;

Y is -OH or -CN.

In some embodiments, the compound having the structure of formula (I) or formula (Ib), wherein R^{1-1} is hydrogen, deuterium, or $-C_{1-6}$ alkyl.

In some embodiments, the compound having the structure of formula (I) or formula (Ib), wherein R^{1-1} is hydrogen, deuterium, or $-CH_3$.

In some embodiments, the compound having the structure of formula (I) or formula (Ib), wherein R^{1-2} is C_{1-6} alkyl, C_{3-6} cycloalkyl, or 4- to 6-membered heterocycloalkyl; said C_{1-6} alkyl, C_{3-6} cycloalkyl, or 4- to 6-membered heterocycloalkyl is each optionally substituted with one or more substituents selected from halogen, -OH, -SH, $-NH_2$, $-NHC_{1-6}$ alkyl, and $-SC_{1-6}$ alkyl.

In some embodiments, the compound having the structure of formula (I) or formula (Ib), wherein R^{1-2} is -C_{1-6} alkylene-OH or -C_{3-6} cycloalkylene-OH.

In some embodiments, the compound having the structure of formula (I) or formula (Ib), wherein R^{1-2} is -CH_2OH, $-CH(CH_3)OH$,  , or .

In some embodiments, the compound having the structure of formula (I) or formula (Ib), wherein R^{1-2} is -CH_2OH, $-CH(CH_3)OH$, or  .

In some embodiments, the compound having the structure of formula (I) or formula (Ib), wherein R^{1-2} is -CH_2CH_2OH, $-CH_2ONH(CH_3)$.

In some embodiments, the compound having the structure of formula (I) or formula (Ib), wherein R^{1-2} is -CH_2OH, $-CH(CH_3)OH$, $-CH_2CH_2OH$, $-CH_2ONH(CH_3)$,  , or .

In some embodiments, the compound having the structure of formula (I) or formula (Ib), wherein R^1 is -NH_2, $-C_{1-6}$ alkylene-$N(R^{1-1})$-$C(O)R^{1-2}$, -O-(4- to 6-membered heterocycloalkylene)-$C(O)R^{1-2}$, -O-C_{3-6} cycloalkylene-$N(R^{1-1})$-$C(O)R^{1-2}$, -$N(R^{1-1})$-(4- to 6-membered heterocycloalkylene)-$C(O)R^{1-2}$, -(4- to 6-

membered heterocycloalkylene)-C(O)R^{1-2}, -(4- to 6-membered heterocycloalkylene)-N(R^{1-1})-C(O)R^{1-2}, -N(R^{1-1})C(O)C_{3-6} cycloalkyl, or -N(R^{1-1})C(O)(4- to 6-membered heterocycloalkyl), wherein said C_{1-6} alkylene, C_{3-6} cycloalkyl, C_{3-6} cycloalkylene, 4- to 6-membered heterocycloalkyl, or 4- to 6-membered heterocycloalkylene is each optionally substituted with one or more substituents selected from halogen, -OH, -SH, -NH_2, -NHC_{1-6} alkyl, -SC_{1-6} alkyl, -C_{1-6} alkylene-OH, -C_{1-6} alkylene-SH, -C_{1-6} alkylene-S(C_{1-6} alkyl), and -C_{1-6} alkylene-NH_2; R^{1-1} is as defined in any one of the preceding embodiments of formula (Ib) of the present application, and R^{1-2} is as defined in any one of the preceding embodiments of formula (Ib) of the present application.

In some embodiments, the compound having the structure of formula (I) or formula (Ib), wherein R^1 is -NH_2, -C_{1-6} alkylene-NH-C(O)R^{1-2}, -C_{1-6} alkylene-N(CH_3)-C(O)R^{1-2}, -O-(4- to 6-membered heterocycloalkylene)-C(O)R^{1-2}, -O-C_{3-6} cycloalkylene-NH-C(O)R^{1-2}, -O-C_{3-6} cycloalkylene-N(CH_3)-C(O)R^{1-2}, -NH-(4- to 6-membered heterocycloalkylene)-C(O)R^{1-2}, -N(CH_3)-(4- to 6-membered heterocycloalkylene)-C(O)R^{1-2}, -NHC(O)C_{3-6} cycloalkyl, -N(CH_3)C(O)C_{3-6} cycloalkyl, -NHC(O)(4- to 6-membered heterocycloalkyl), or -N(CH_3)C(O)(4- to 6-membered heterocycloalkyl), wherein said C_{1-6} alkylene, C_{3-6} cycloalkyl, C_{3-6} cycloalkylene, 4- to 6-membered heterocycloalkyl, or 4- to 6-membered heterocycloalkylene is each optionally substituted with one or more substituents selected from halogen, -OH, -NH_2, -NHCH_3, -C_{1-6} alkylene-OH; R^{1-1} is as defined in any one of the preceding embodiments of formula (Ib) of the present application, and R^{1-2} is as defined in any one of the preceding embodiments of formula (Ib) of the present application.

In some embodiments, the compound having the structure of formula (I) or formula (Ib), wherein R^1 is -C_{1-6} alkylene-N(R^{1-1})-C(O)R^{1-2}, -O-(4- to 6-membered heterocycloalkylene)-C(O)R^{1-2}, -O-C_{3-6} cycloalkylene-N(R^{1-1})-C(O)R^{1-2}, -N(R^{1-1})-(4- to 6-membered heterocycloalkylene)-C(O)R^{1-2}, -(4- to 6-membered heterocycloalkylene)-C(O)R^{1-2}, -(4- to 6-membered heterocycloalkylene)-N(R^{1-1})-C(O)R^{1-2}, -N(R^{1-1})C(O)C_{3-6} cycloalkyl, or -N(R^{1-1})C(O)(4- to 6-membered heterocycloalkyl), wherein said C_{1-6} alkylene, C_{3-6} cycloalkyl, C_{3-6} cycloalkylene, 4- to 6-membered heterocycloalkyl, or 4- to 6-membered heterocycloalkylene is each optionally substituted with one or more substituents selected from halogen, -OH, -SH, -NH_2, -NHC_{1-6} alkyl, -SC_{1-6} alkyl, -C_{1-6} alkylene-OH, -C_{1-6} alkylene-SH, -C_{1-6} alkylene-S(C_{1-6} alkyl), and -C_{1-6} alkylene-NH_2; R^{1-1} is as defined in any one of the preceding embodiments of formula (Ib) of the present application, and R^{1-2} is as defined in any one of the preceding embodiments of formula (Ib) of the present application.

In some embodiments, the compound having the structure of formula (I) or formula (Ib), wherein R^1 is -C_{1-6} alkylene-NH-C(O)R^{1-2}, -C_{1-6} alkylene-N(CH_3)-C(O)R^{1-2}, -O-(4- to 6-membered heterocycloalkylene)-C(O)R^{1-2}, -O-C_{3-6} cycloalkylene-NH-C(O)R^{1-2}, -O-C_{3-6} cycloalkylene-N(CH_3)-C(O)R^{1-2}, -NH-(4- to 6-membered heterocycloalkylene)-C(O)R^{1-2}, -N(CH_3)-(4- to 6-membered heterocycloalkylene)-C(O)R^{1-2}, -NHC(O)C_{3-6} cycloalkyl, -N(CH_3)C(O)C_{3-6} cycloalkyl, -NHC(O)(4- to 6-membered heterocycloalkyl), or -N(CH_3)C(O)(4- to 6-membered heterocycloalkyl), wherein said C_{1-6} alkylene, C_{3-6} cycloalkyl, C_{3-6} cycloalkylene, 4- to 6-membered heterocycloalkyl, or 4- to 6-membered heterocycloalkylene is each optionally substituted with one or more substituents selected from halogen, -OH, -NH_2, -NHCH_3, -C_{1-6}

alkylene-OH; R^{1-1} is as defined in any one of the preceding embodiments of formula (Ib) of the present application, and R^{1-2} is as defined in any one of the preceding embodiments of formula (Ib) of the present application.

In some embodiments, the compound having the structure of formula (I) or formula (Ib), wherein R^1 is -NH_2, -O-(4- to 6-membered heterocycloalkylene)-$C(O)R^{1-2}$, or -C_{1-6} alkylene-$N(CH_3)$-$C(O)R^{1-2}$; R^{1-2} is as defined in any one of the preceding embodiments of formula (Ib) of the present application.

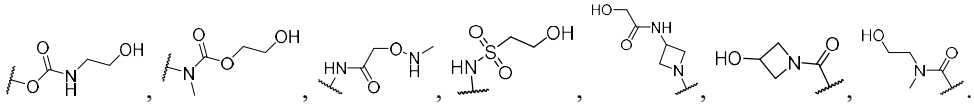
In some embodiments, the compound having the structure of formula (I) or formula (Ib), wherein R^1 is -O-(4- to 6-membered heterocycloalkylene)-$C(O)R^{1-2}$ or -C_{1-6} alkylene-$N(CH_3)$-$C(O)R^{1-2}$; R^{1-2} is as defined in any one of the preceding embodiments of formula (Ib) of the present application.

In some embodiments, the compound having the structure of formula (I) or formula (Ib), wherein R^1 is (4- to 12-membered heterocycloalkylene).

In some embodiments, the compound having the structure of formula (I) or formula (Ib), wherein R^1 is -NH-$S(O)_2$-R^{1-2}, -$C(O)R^{1-2}$, $C(O)$-$N(R^{1-1})R^{1-2}$, -O-$C(O)$-$N(R^{1-1})R^{1-2}$, -$N(R^{1-1})$-$C(O)$-OR^{1-2}.

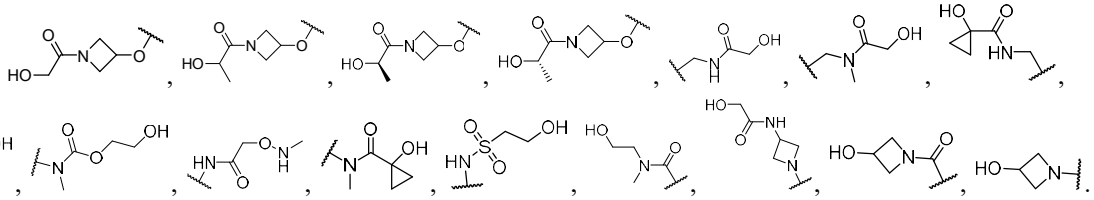
In some embodiments, the compound having the structure of formula (I) or formula (Ib), wherein R^1 is -OH.

In some embodiments, the compound having the structure of formula (I) or formula (Ib), wherein R^1 is

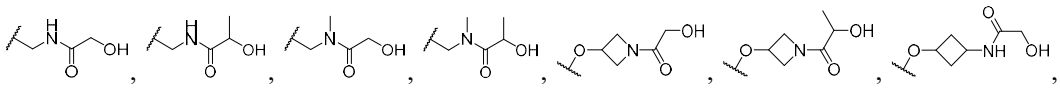


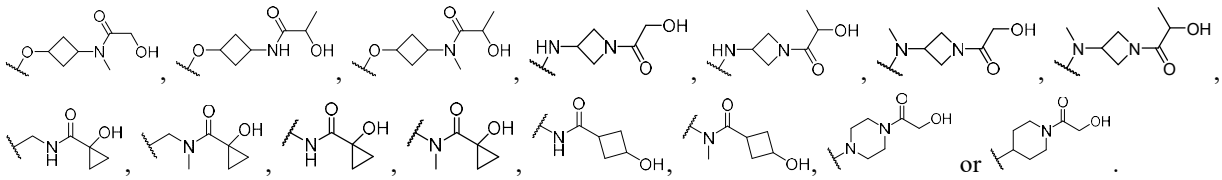
In some embodiments, the compound having the structure of formula (I) or formula (Ib), wherein R^1 is NH_2, -OH, -O-(4- to 12-membered heterocycloalkylene)-$C(O)R^{1-2}$, -C_{1-6} alkylene-$N(R^{1-1})$-$C(O)R^{1-2}$, -O-$C(O)$-$N(R^{1-1})R^{1-2}$, -$N(R^{1-1})$-$C(O)$-OR^{1-2}, -$N(R^{1-1})$-$C(O)R^{1-2}$, -NH-$S(O)_2$-R^{1-2}, $C(O)$-$N(R^{1-1})R^{1-2}$, -(4- to 12-membered heterocycloalkylene)-$N(R^{1-1})$-$C(O)R^{1-2}$, -$C(O)R^{1-2}$, or (4- to 12-membered heterocycloalkylene).

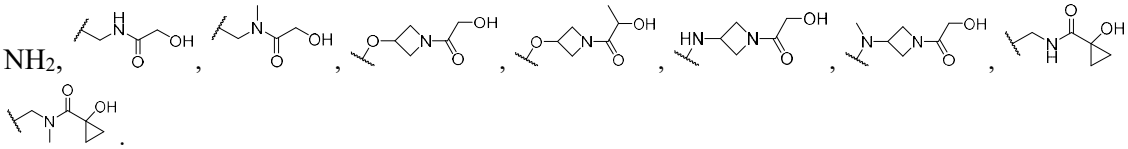
In some embodiments, the compound having the structure of formula (I) or formula (Ib), wherein R^1 is NH_2, -OH,

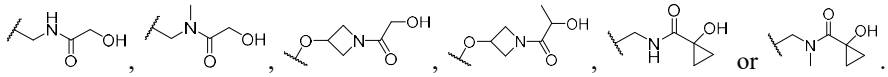


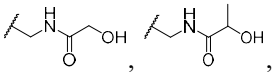
In some embodiments, the compound having the structure of formula (I) or formula (Ib), wherein R^1 is -NH_2,

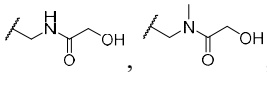


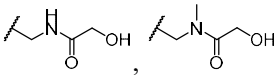


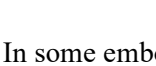
In some embodiments, the compound having the structure of formula (I) or formula (Ib), wherein R^1 is -NH_2, 

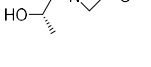
In some embodiments, the compound having the structure of formula (I) or formula (Ib), wherein R^1 is -NH_2, 

In some embodiments, the compound of formula (I) or formula (Ib), wherein R^1 is 

In some embodiments, the compound of formula (I) or formula (Ib), wherein R^1 is 

In some embodiments, the compound of formula (I) or formula (Ib), wherein R^1 is 

In some embodiments, the compound of formula (I) or formula (Ib), wherein R^1 is 

In some embodiments, the compound of formula (I) or formula (Ib), wherein R^1 is  .

In some embodiments, the compound of formula (I) or formula (Ib), wherein

R^1 is $-NH_2$, -O-(4- to 6-membered heterocycloalkylene)-$C(O)R^{1-2}$, or $-C_{1-6}$ alkylene-$N(CH_3)$-$C(O)R^{1-2}$;

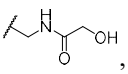
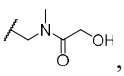
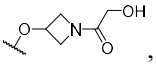
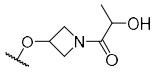
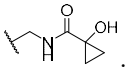
R^{1-2} is $-C_{1-6}$ alkylene-OH or $-C_{3-6}$ cycloalkylene-OH.

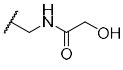
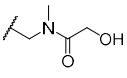
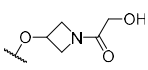
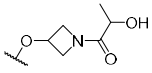
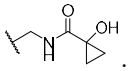
In some embodiments, the compound of formula (I) or formula (Ib), wherein

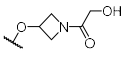
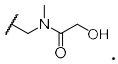
R^1 is -O-(4- to 6-membered heterocycloalkylene)-$C(O)R^{1-2}$ or $-C_{1-6}$ alkylene-$N(CH_3)$-$C(O)R^{1-2}$;

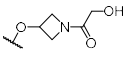
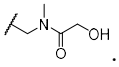
R^{1-2} is $-C_{1-6}$ alkylene-OH or $-C_{3-6}$ cycloalkylene-OH.

In some embodiments, the compound of formula (I) or formula (Ib), wherein R^{1-2} is $-NH_2$, $-C_{1-3}$ alkylene-OH, or $-C_{3-4}$ cycloalkylene-OH.

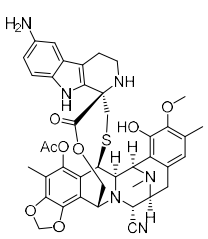
In some embodiments, the compound of formula (I) or formula (Ib), wherein R^1 is $-NH_2$,  ,
 ,  ,  or  .

In some embodiments, the compound of formula (I) or formula (Ib), wherein R^1 is  ,  ,
 ,  or  .

In some embodiments, the compound of formula (I) or formula (Ib), wherein R^1 is $-NH_2$,  or
 .

In some embodiments, the compound of formula (I) or formula (Ib), wherein R^1 is  or  .

In some embodiments, the compounds of formula (I) or formula (Ib) of the present application are: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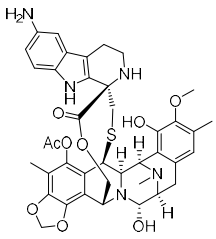
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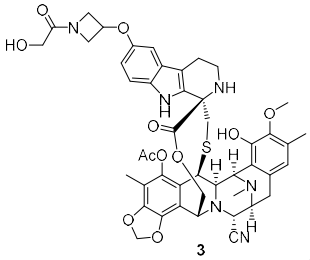
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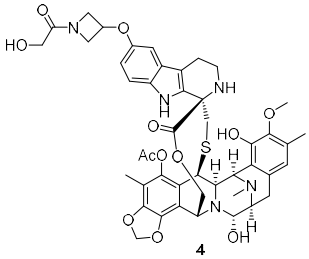
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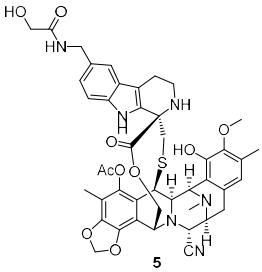
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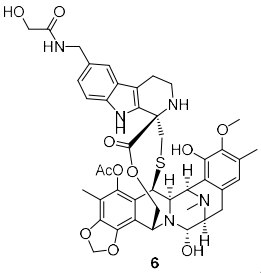
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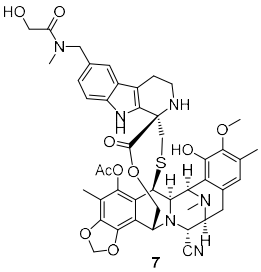
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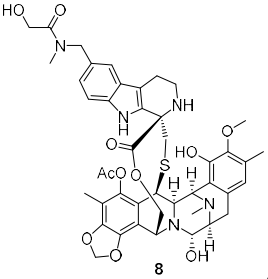
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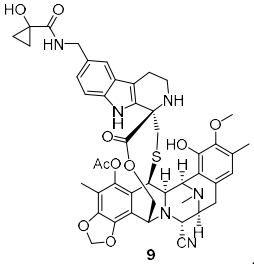
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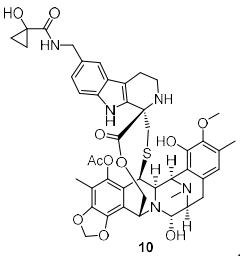
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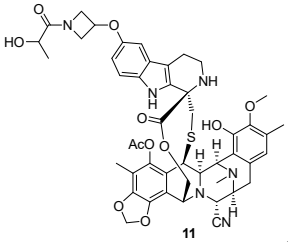
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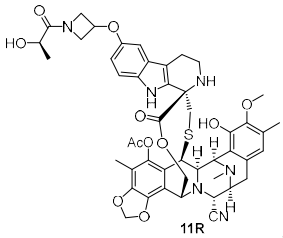
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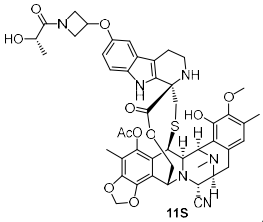
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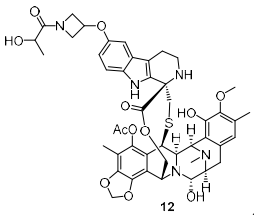
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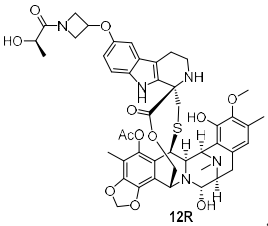
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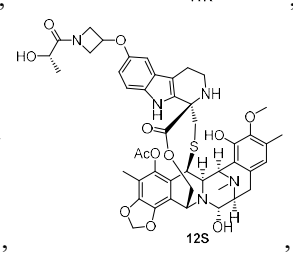
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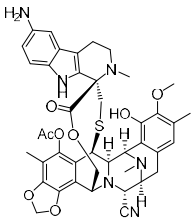
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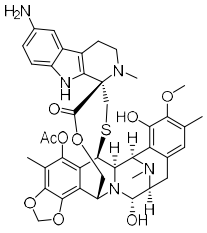
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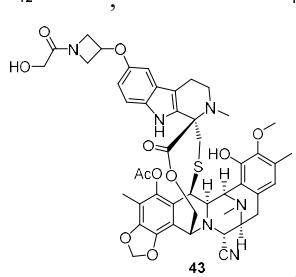
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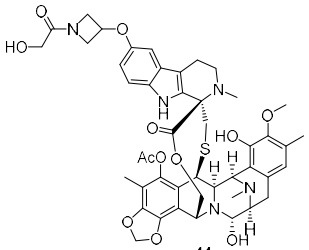
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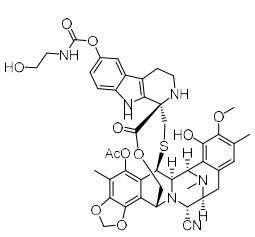

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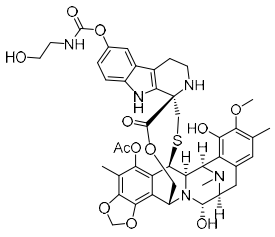

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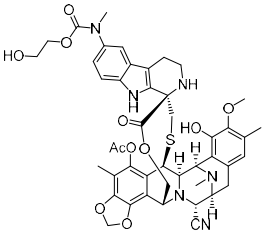

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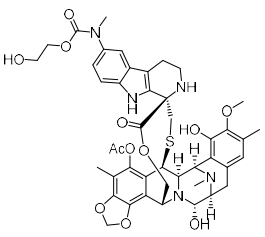

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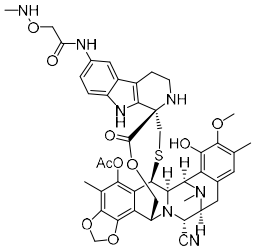

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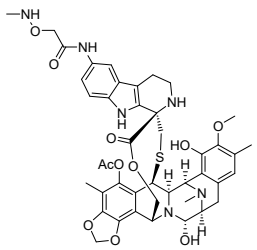

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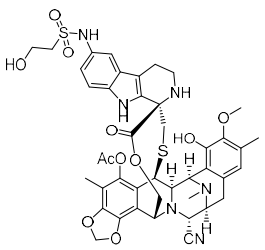

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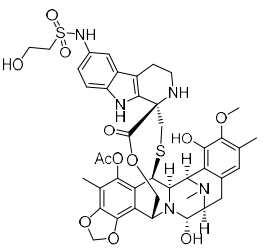

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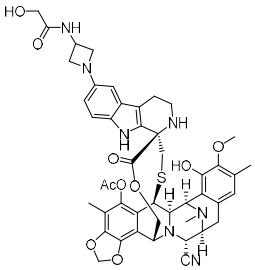

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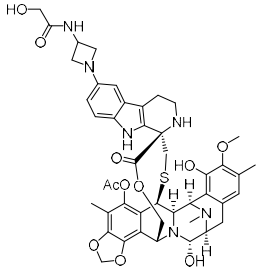

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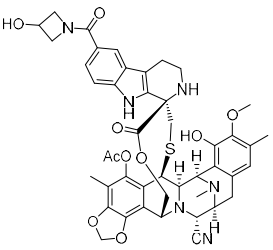

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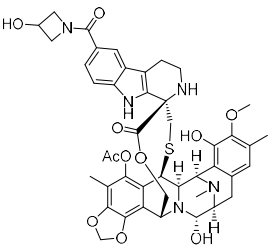

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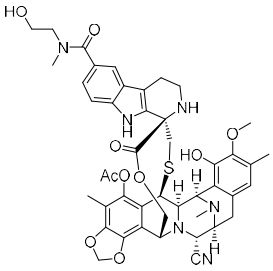

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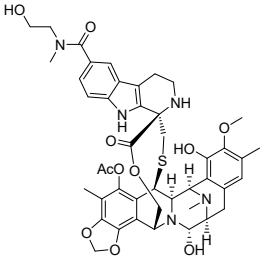

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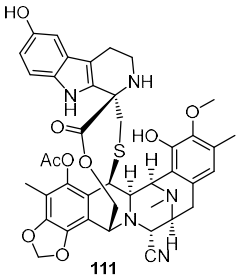

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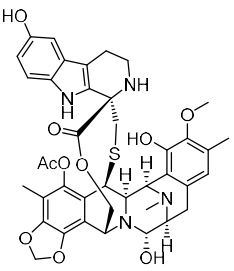

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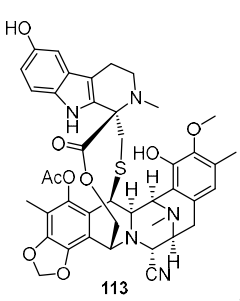
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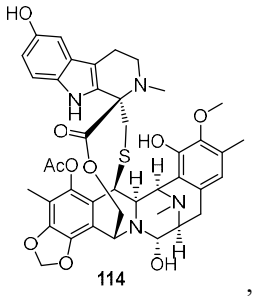
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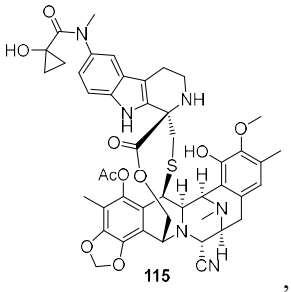
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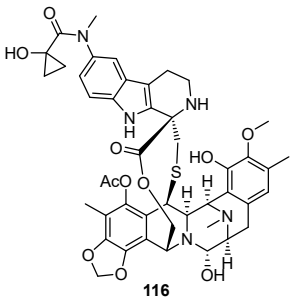
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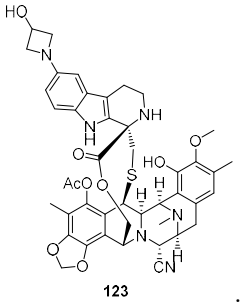
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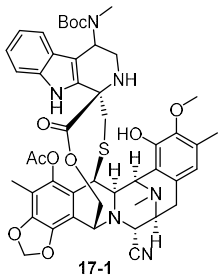
Those skilled in the art will appreciate that the present application encompasses compounds obtained by any combination of the various embodiments. Embodiments obtained by combining technical features or preferred technical features from one embodiment with technical features or preferred technical features from another embodiment are also included within the scope of the present application.

In another aspect, the present application provides a compound (an intermediate for preparing a compound of formula (I)) having the following structure: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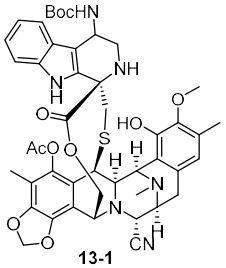
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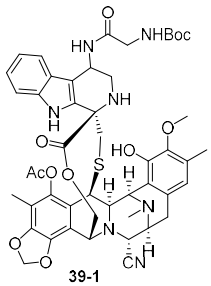
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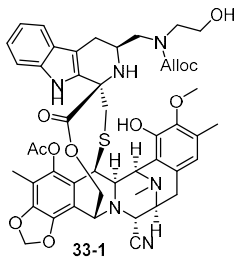
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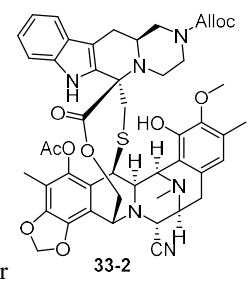
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In another aspect, the present application provides a pharmaceutical composition comprising a compound as described herein or a pharmaceutically acceptable salt, ester, stereoisomer, tautomer, polymorph, solvate, isotope-labeled compound, metabolite, or prodrug thereof, in a prophylactically or therapeutically effective amount, and one or more pharmaceutically acceptable carriers.

A further object of the present application is to provide a method for preparing the pharmaceutical composition of the present application, said method comprising combining the compound as described

herein or a pharmaceutically acceptable form thereof, or a mixture thereof, with one or more pharmaceutically acceptable carriers.

Pharmaceutically acceptable carriers usable in the pharmaceutical composition of the present application are pharmaceutically acceptable carriers, and examples of suitable pharmaceutically acceptable carriers are described in Remington’ s Pharmaceutical Sciences (2005).

The pharmaceutical composition may be administered in any form, provided that it achieves prevention, alleviation, inhibition, or cure of symptoms in human or animal patients. For example, various suitable dosage forms may be prepared according to the route of administration.

In other embodiments, administration of the compound or pharmaceutical composition of the present application may be combined with additional therapeutic methods. Said additional therapeutic methods may be selected from, but are not limited to: radiotherapy, chemotherapy, immunotherapy, or combinations thereof.

The present application also relates to a pharmaceutical formulation comprising the compound of the present application or a pharmaceutically acceptable form thereof, or a mixture thereof, as an active ingredient, or the pharmaceutical composition of the present application. In some embodiments, said formulation is in the form of a solid formulation, semi-solid formulation, liquid formulation, or gaseous formulation.

A further object of the present application is to provide an article of manufacture, for example, provided in the form of a kit. As used herein, the term “article of manufacture” is intended to include, but is not limited to, packages and packaging. The article of manufacture of the present application comprises: (a) a first container; (b) a pharmaceutical composition located in the first container, wherein said composition comprises: a first therapeutic agent, said first therapeutic agent comprising: the compound of the present application or a pharmaceutically acceptable form thereof, or a mixture thereof; (c) optionally, package insert instructions indicating that said pharmaceutical composition is useful for treating neoplastic disorders (as defined below); and (d) a second container.

Said first container is a container for holding the pharmaceutical composition. This container may be used for preparation, storage, transportation, and/or individual/bulk sale. The first container is intended to encompass bottles, jars, vials, flasks, syringes, tubes (e.g., for cream products), or any other container for preparation, containment, storage, or dispensing of pharmaceutical products.

Said second container is a container for holding the first container and optionally the package insert instructions. Examples of the second container include, but are not limited to, boxes (e.g., cardboard or plastic boxes), cases, cartons, bags (e.g., paper or plastic bags), pouches, and cloth sacks. Said package insert instructions may be physically attached to the exterior of the first container via ties, glue, staples, or other adhering means, or they may be placed inside the second container without any physical attachment to the first container. Alternatively, said package insert instructions are located on the outside of the second container. When located on the outside of the second container, it is preferred that said package

insert instructions be physically attached via ties, glue, staples, or other adhering means. Alternatively, they may be adjacent to or in contact with the exterior of the second container without physical attachment.

Said package insert instructions are trademarks, labels, markings, etc., which list information relating to the pharmaceutical composition contained within the first container. The listed information is typically determined by the regulatory authority (e.g., the U.S. Food and Drug Administration) governing the region where the article of manufacture is to be sold. It is preferred that said package insert instructions specifically list the indications for which the pharmaceutical composition is approved. Said package insert instructions may be made of any material from which the information contained therein or thereon can be read. It is preferred that said package insert instructions be a printable material (e.g., paper, plastic, cardboard, foil, adhesive paper, or plastic, etc.) on which the required information can be formed (e.g., printed or applied).

In another aspect, the present application provides the use of the compound as described herein or a pharmaceutically acceptable form thereof, or the pharmaceutical composition of the present application, in the manufacture of a medicament.

In another aspect, the present application provides the use of the compound as described herein or a pharmaceutically acceptable form thereof, or the pharmaceutical composition of the present application, in the manufacture of a medicament for preventing or treating a tumor or cancer.

In another aspect, the present application provides a method for preventing or treating a tumor, said method comprising administering to an individual in need thereof a compound as described herein or a pharmaceutically acceptable form thereof, or the pharmaceutical composition of the present application, in a prophylactically or therapeutically effective amount.

In another aspect, the present application provides a compound as described herein or a pharmaceutically acceptable form thereof, or the pharmaceutical composition of the present application, in a prophylactically or therapeutically effective amount, for preventing or treating a tumor or cancer.

In another aspect, the present application provides a compound as described herein or a pharmaceutically acceptable form thereof, or the pharmaceutical composition of the present application, in a prophylactically or therapeutically effective amount, in combination with additional therapeutic methods for preventing or treating a tumor or cancer, said additional therapeutic methods including, but not limited to: radiotherapy, chemotherapy, immunotherapy, or combinations thereof.

In some embodiments, said tumor or cancer include, but are not limited to, breast cancer, colorectal cancer, colon cancer, lung cancer, and prostate cancer, as well as bile duct cancer, bone cancer, bladder cancer, head and neck cancer, kidney cancer, liver cancer, gastrointestinal tissue cancer, esophageal cancer, ovarian cancer, pancreatic cancer, skin cancer, testicular cancer, thyroid cancer, uterine cancer, cervical cancer, and vulvar cancer, as well as leukemia (including chronic lymphocytic leukemia (CLL),

acute lymphoblastic leukemia (ALL), and chronic myeloid leukemia (CML)), multiple myeloma, and lymphoma.

In further preferred embodiments, the compounds of the present application may be used in combination with chemoradiotherapy or immunotherapy to prevent or treat tumors or cancer.

The dosing regimen may be adjusted to provide the optimal desired response. For example, when administered as an injectable, a single bolus injection, a bolus, and/or continuous infusion may be given, etc. For example, several divided doses may be administered over time, or the dose may be proportionally reduced or increased as indicated by urgent therapeutic needs. It should be noted that dose values may vary depending on the type and severity of the condition to be alleviated, and may include single or multiple doses. Generally, the therapeutic dose varies depending on considerations such as the age, sex, and general health status of the patient to be treated; the frequency of treatment and the nature of the desired effect; the extent of tissue damage; the duration of symptoms; and other variables adjustable by individual physicians. It should further be understood that for any particular individual, the specific dosing regimen should be adjusted over time based on individual needs and the professional judgment of the person administering or supervising administration of the composition. The amount and dosing regimen of administration of said pharmaceutical composition can be readily determined by those of ordinary skill in the clinical field. For example, the composition or compound of the present invention may be administered in divided doses ranging from four times daily to once every three days, with a dosage amount, for example, of 0.01 – 1000 mg per dose. The required dose may be administered once or multiple times to achieve the desired result. The pharmaceutical composition according to the present application may also be provided in unit dosage form.

General Terms and Definitions

Unless otherwise defined herein, all technical and scientific terms used herein are intended to have the same meaning as commonly understood by those skilled in the art. References to techniques used herein are intended to refer to those commonly understood in the art, including variations or equivalents thereof that would be apparent to those skilled in the art. Although the following terms are believed to be well understood by those skilled in the art, the following definitions are nevertheless set forth to better explain the present application.

The terms “comprising”, “including”, “having”, “containing”, “involving” and other variants thereof used herein are inclusive or open-ended and do not exclude additional unlisted elements or method steps. Those skilled in the art will understand that the above terms, such as “comprising” encompass the meaning of “consisting of”.

The term “about” refers to a range of ±10% of the stated value, preferably ±5%, and more preferably ±2%.

Unless otherwise stated, concentrations are by weight, and ratios (including percentages) are by molar amount.

The term “one or more” or similar expressions such as “at least one” may represent, for example, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more.

When lower and upper limits of a numerical range are disclosed, any number and any included range falling within that range are specifically disclosed. In particular, each numerical range disclosed herein (in the form “about a to b” or equivalently, “approximately a to b” or equivalently, “about a–b”) should be understood as encompassing each numerical value and range included within the broader range.

For example, the expression “C_{1-6}” should be understood as encompassing any subrange and each point value therein, such as C_{2-5}, C_{3-4}, C_{1-2}, C_{1-3}, C_{1-4}, C_{1-5}, etc., as well as C_1, C_2, C_3, C_4, C_5, C_6, etc. For example, the expression “C_{3-10}” should also be understood in a similar manner, e.g., encompassing any subrange and point value included therein, such as C_{3-9}, C_{6-9}, C_{6-8}, C_{6-7}, C_{7-10}, C_{7-9}, C_{7-8}, C_{8-9}, etc., as well as C_3, C_4, C_5, C_6, C_7, C_8, C_9, C_{10}, etc. As another example, the expression “3–10-membered” should be understood as encompassing any subrange and each point value therein, such as 3–4-membered, 3–5-membered, 3–6-membered, 3–7-membered, 3–8-membered, 3–9-membered, 4–5-membered, 4–6-membered, 4–7-membered, 4–8-membered, 5–7-membered, 5–8-membered, 6–7-membered, etc., as well as 3, 4, 5, 6, 7, 8, 9, 10-membered, etc. Similarly, the expression “5–10-membered” should also be understood in a similar manner, e.g., encompassing any subrange and point value included therein, such as 5–6-membered, 5–7-membered, 5–8-membered, 5–9-membered, 5–10-membered, 6–7-membered, 6–8-membered, 6–9-membered, 6–10-membered, 7–8-membered, etc., as well as 5, 6, 7, 8, 9, 10-membered, etc.

In the present specification, groups and their substituents may be selected by those skilled in the art to provide stable structural moieties and compounds. When a substituent is described by a conventional chemical formula written left to right, the substituent also includes the chemically equivalent substituent obtained when the structural formula is written right to left.

As used herein, alone or in combination with other groups, the term “alkyl” refers to a saturated, straight-chain or branched hydrocarbon group. As used herein, the term “C_{1-6} alkyl” refers to a saturated, straight-chain or branched hydrocarbon group having 1–6 carbon atoms (e.g., 1, 2, 3, 4, 5, or 6 carbon atoms). “C_{1-6} alkyl” includes, for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, isopentyl, neopentyl, or n-hexyl, etc. Alkyl groups in the present application are optionally substituted with one or more substituents as described herein.

In various parts of the present application, linking substituents are described. When the structure clearly requires a linking group, the Markush variables listed for that group should be understood as linking groups. For example, if the structure requires a linking group and the Markush group definition for that variable lists “alkyl,” then the “alkyl” should be understood as representing a linked alkylene group. For example, in certain specific structures, when an alkyl group is clearly indicated as a linking group, then that alkyl group represents a linked alkylene group; for instance, the C_{1-6} alkyl in the group “halo-C_{1-6} alkyl” should be understood as C_{1-6} alkylene.

As used herein, alone or in combination with other groups, the term “alkylene” refers to a saturated, straight-chain or branched divalent hydrocarbon group. As used herein, the term “C_{1-6} alkylene” refers to a saturated, straight-chain or branched divalent hydrocarbon group having 1–6 carbon atoms. “C_{1-6} alkylene” includes, for example and without limitation, methylene, ethylene, propylene, or butylene, etc. Alkylene groups in the present application are optionally substituted with one or more substituents as described herein.

In the present application, the term “cycloalkyl” refers to a saturated or partially saturated, monocyclic or polycyclic (such as bicyclic) non-aromatic hydrocarbon group. For example, “C_{3-12} cycloalkyl” or “3–12-membered cycloalkyl” refers to a cycloalkyl group having 3–12 ring carbon atoms (e.g., 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12). Common cycloalkyl groups include, but are not limited to, monocyclic cycloalkyl groups such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclobutene, cyclopentene, cyclohexene, etc.; or bicyclic cycloalkyl groups, including fused rings, bridged rings, or spiro rings, such as bicyclo[1.1.1]pentyl, bicyclo[2.2.1]heptyl, bicyclo[3.2.1]octyl, bicyclo[5.2.0]nonyl, decalinyl, etc.

In the present application, the term "cycloalkylene" refers to a saturated or partially saturated, monocyclic or polycyclic (such as bicyclic) non-aromatic divalent cyclic group. For example, "C_{3-12} cycloalkylene" or "3- to 12-membered cycloalkylene" refers to a cycloalkylene having 3 to 12 ring carbon atoms (e.g., 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12). Common cycloalkylenes include, but are not limited to, monocyclic cycloalkyls such as cyclopropylene, cyclobutylene, cyclopentylene, cyclohexylene, cycloheptylene, cyclobutenylene, cyclopentenylene, cyclohexenylene, etc.; or bicyclic cycloalkylenes, including fused rings, bridged rings, or spiro rings, such as bicyclo[1.1.1]pentylene, bicyclo[2.2.1]heptylene, bicyclo[3.2.1]octylene, bicyclo[5.2.0]nonylene, decahydronaphthylene, etc.

The term "heterocycloalkyl" refers to a saturated or partially saturated non-aromatic cyclic group containing at least one ring member selected from N, O, P, and S as a heteroatom; preferably, the number of such heteroatoms is 1, 2, 3, or 4 (e.g., 1 or 2 heteroatoms, independently selected from N). Examples include 3- to 8-membered, 3- to 6-membered, 4- to 12-membered, or 4- to 6-membered heterocycloalkyl groups. Furthermore, said heterocycloalkyl may contain 0, 1, 2, or 3 oxo groups. Specific examples include, but are not limited to, epoxyethyl, oxocyclobutyl, pyrrolidinyl, tetrahydrofuranyl, piperidinyl, piperazinyl, tetrahydropyranyl, homopiperazinyl, pyrrolidinonyl, etc.

The term "heterocycloalkylene" refers to a saturated or partially saturated non-aromatic divalent cyclic group containing at least one ring member selected from N, O, P, and S as a heteroatom; preferably, the number of such heteroatoms is 1, 2, 3, or 4 (e.g., 1 or 2 heteroatoms, independently selected from N). Examples include 3- to 8-membered, 3- to 6-membered, 4- to 12-membered, or 4- to 6-membered heterocycloalkylene groups. Furthermore, said heterocycloalkyl may contain 0, 1, 2, or 3 oxo groups. Specific examples include, but are not limited to, oxiranylene, oxetanylene, pyrrolidinylene, tetrahydrofuranylene, piperidinylene, piperazinylene, tetrahydropyranylene, homopiperazinylene, pyrrolidinonylene, etc.

In the present application, the term "halogen" refers to fluorine (F), chlorine (Cl), bromine (Br), or iodine (I).

In the present application, the term "hydroxy" refers to -OH.

In the present application, the term "cyano" refers to -CN.

In the present application, the term "nitro" refers to $-NO_2$.

In the present application, the term "amino" refers to $-NH_2$.

In the present application, the term "oxo group" refers to C(O), i.e., a carbonyl group.

When used alone or in combination with other groups in the present application, the term "haloalkyl" refers to an alkyl group as defined above wherein one or more hydrogen atoms are replaced by halogen atoms. For example, the term "C_{1-6} haloalkyl" or "halo-C_{1-6} alkyl" refers to a C_{1-6} alkyl group optionally substituted by one or more (e.g., 1–3) halogen atoms. Those skilled in the art will understand that when more than one halogen substituent is present, the halogens may be the same or different and may be located on the same or different carbon atoms. Examples of haloalkyl groups include, for example, $-CH_2F$, $-CHF_2$, $-CF_3$, $-CCl_3$, $-C_2F_5$, $-C_2Cl_5$, $-CH_2CF_3$, $-CH_2Cl$, or $-CH_2CH_2CF_3$, etc. The haloalkyl groups in the present application may optionally be substituted by one or more substituents described herein.

When used alone or in combination with other groups in the present application, the term "alkoxy" refers to an alkyl group as defined above attached to the parent molecular moiety via an oxygen atom. Examples of alkoxy groups include, but are not limited to, methoxy, ethoxy, propoxy, n-butoxy, tert-butoxy, pentoxy, etc.

As used herein, the term "independently" means that at least two groups (or moieties) having the same or similar ranges of values within a structure may have the same or different meanings under specific circumstances. For example, if substituent A and substituent B are each independently hydrogen, halogen, hydroxy, cyano, alkyl, or aryl, then when substituent A is hydrogen, substituent B may be hydrogen, halogen, hydroxy, cyano, alkyl, or aryl; similarly, when substituent B is hydrogen, substituent A may be hydrogen, halogen, hydroxy, cyano, alkyl, or aryl.

As used in the present application, the term "substituted" and its other variants herein refer to replacement of one or more (e.g., 1, 2, 3, or 4) atoms or groups (such as hydrogen atoms) on the specified atom by other equivalents, provided that the normal valence of the specified atom or group under the current circumstances is not exceeded and a stable compound can be formed. If an atom or group is described as "optionally substituted with...", it may either be substituted or unsubstituted. Unless otherwise stated, the point of attachment of a substituent may be at any suitable position of the substituent. When a bond of a substituent is shown crossing a bond between two connected atoms in a ring system, it indicates that the substituent may be attached to any ring atom of that ring system.

When any variable (e.g., R^a) appears multiple times in the definition of a compound, the definition of that variable at each occurrence is independent of its definitions at other occurrences; their meanings are mutually independent and do not affect one another. Thus, if a group is substituted by 1, 2, or 3 R^a groups, it means the group may be substituted by up to three R^a groups, and the definition of R^a at one position is independent of the definitions of R^a at other positions. Moreover, combinations of substituents and/or variables are permitted only if such combinations yield stable compounds. The term "optionally substituted by one or more R^a" encompasses both the unsubstituted form and forms substituted by one or more R^a. For example, "said C_{1-6} alkyl is optionally substituted by one or more R^a" refers to both C_{1-6} alkyl and C_{1-6} alkyl substituted by one or more R^a.

When a listed group is not explicitly indicated as having substituents, such a group refers solely to the unsubstituted form. For example, when "C_{1-6} alkyl" is not qualified by "substituted or unsubstituted," it refers only to the C_{1-6} alkyl itself or to "unsubstituted C_{1-6} alkyl."

As used herein, the compounds of the present invention may contain one or more chiral centers and exist in different optically active forms. When a compound contains one chiral center, the compound comprises enantiomers. The present application includes both enantiomers and mixtures thereof, such as racemic mixtures. Enantiomers may be resolved by methods known in the art, such as crystallization and chiral chromatography. When a compound of Formula I contains more than one chiral center, diastereomers may exist. The present application includes resolved optically pure specific isomers as well as mixtures of diastereomers. Diastereomers may be resolved by methods known in the art, such as crystallization and chiral chromatography.

The term "stereoisomer" includes conformational isomers and configurational isomers, wherein configurational isomers primarily include cis-trans isomers and optical isomers. The compounds described herein may exist as stereoisomers and thus encompass all possible stereoisomeric forms, including but not limited to cis-trans isomers, enantiomers, diastereomers, atropisomers, etc. The compounds of the present invention may also exist as any combination or mixture of the aforementioned stereoisomers, such as meso forms, racemates, equimolar mixtures of atropisomers, single enantiomers, single diastereomers or mixtures thereof, or single atropisomers or mixtures thereof.

The term "tautomer" refers to functional group isomers resulting from the rapid migration of an atom within a molecule between two positions.

As used herein, solid lines ( ), solid wedges ( ), or dashed wedges ( ) may be used to depict carbon-carbon bonds of the compounds of the present application. Use of a solid line to depict a bond attached to an asymmetric carbon atom indicates that all possible stereoisomers at that carbon atom are included (e.g., specific enantiomers, racemic mixtures, etc.). Use of a solid or dashed wedge to depict a bond attached to an asymmetric carbon atom indicates that the depicted stereoisomer exists. When present in a racemic mixture, solid and dashed wedges define relative stereochemistry rather than absolute stereochemistry. Unless otherwise indicated, the compounds of the present invention may exist as stereoisomers (including cis and trans isomers, optical isomers (e.g., R and S enantiomers), diastereomers,

geometric isomers, rotamers, conformational isomers, atropisomers, and mixtures thereof). Compounds of the present invention may exhibit more than one type of isomerism and may consist of mixtures thereof (e.g., racemic mixtures and diastereomeric pairs).

In the present application, unless otherwise specified, the structures described herein also include compounds that differ only in the presence or absence of one or more isotopically enriched atoms. For example, compounds that are identical to those described herein except that hydrogen atoms are replaced by deuterium or tritium, or carbon atoms are replaced by carbon-13 or carbon-14, fall within the scope of the present application.

The present application also encompasses all possible crystalline forms or polymorphs of the compounds of the application, which may be a single polymorph or a mixture of more than one polymorph in any ratio.

Unless otherwise stated, the terms "or" and "and" as used herein mean "and/or."

Unless otherwise stated, the symbol " " or "  " appearing in specific groups herein denotes a point of attachment; the two symbols are interchangeable.

The term "pharmaceutically acceptable form" refers to, but is not limited to, pharmaceutically acceptable salts, esters, stereoisomers, tautomers, polymorphs, solvates, isotope-labeled compounds, metabolites, or prodrugs thereof.

It should also be understood that certain compounds of the present application may be used in their free form for therapy, or, where appropriate, in the form of their pharmaceutically acceptable derivatives. In the present application, pharmaceutically acceptable derivatives include, but are not limited to, pharmaceutically acceptable salts, esters, solvates, metabolites, or prodrugs that, upon administration to a patient in need thereof, provide directly or indirectly the compound of the present application or its metabolite. Accordingly, when the term "compound of the present application" is used herein, it is intended to encompass the various derivative forms described above.

Pharmaceutically acceptable salts of the compounds of the present application include acid addition salts and base addition salts. Suitable acid addition salts are formed from acids that yield pharmaceutically acceptable salts. Suitable base addition salts are formed from bases that yield pharmaceutically acceptable salts. For a general review of suitable salts, see, for example, "*Remington's Pharmaceutical Sciences*", Mack Publishing Company, Easton, Pa., (2005); and "*Handbook of Pharmaceutical Salts: Properties, Selection, and Use*", Stahl and Wermuth (Wiley-VCH, Weinheim, Germany, 2002). Methods for preparing pharmaceutically acceptable salts of the compounds of the present application are known to those skilled in the art.

As used herein, the term "ester" refers to esters derived from the compounds described herein, including physiologically hydrolyzable esters (which hydrolyze under physiological conditions to release the free

acid or alcohol form of the compound of the present application). The compounds of the present application themselves may also be esters.

The compounds of the present application may exist as solvates (preferably hydrates), wherein the compound includes a polar solvent, particularly water, methanol, or ethanol, as a structural element of the crystal lattice. The amount of polar solvent, particularly water, may be present in stoichiometric or non-stoichiometric ratios.

Those skilled in the art will understand that not all nitrogen-containing heterocycles can form N-oxides, as nitrogen requires an available lone pair of electrons to be oxidized to an oxide. Those skilled in the art will recognize nitrogen-containing heterocycles capable of forming N-oxides. Those skilled in the art will also recognize that tertiary amines can form N-oxides. Synthetic methods for preparing N-oxides of heterocycles and tertiary amines are well known to those skilled in the art and include oxidation of heterocycles and tertiary amines with peracids such as peracetic acid and m-chloroperbenzoic acid (mCPBA), hydrogen peroxide, alkyl hydroperoxides such as tert-butyl hydroperoxide, sodium perborate, and dioxiranes such as dimethyldioxirane. These methods for preparing N-oxides have been extensively described and reviewed in the literature; see, for example: T. L. Gilchrist, *Comprehensive Organic Synthesis*, vol. 7, pp. 748–750 (A. R. Katritzky and A. J. Boulton, Eds., Academic Press); and G. W. H. Cheeseman and E. S. G. Werstiuk, *Advances in Heterocyclic Chemistry*, vol. 22, pp. 390–392 (A. R. Katritzky and A. J. Boulton, Eds., Academic Press).

Also included within the scope of the present application are metabolites of the compounds of the application, i.e., substances formed in vivo upon administration of the compounds of the application. Metabolites of a compound can be identified using techniques well known in the art, and their activity can be characterized by experimental methods. Such products may be generated, for example, by oxidation, reduction, hydrolysis, amidation, deamidation, esterification, enzymatic cleavage, etc., of the administered compound. Thus, the present application includes metabolites of the compounds of the application, including compounds prepared by contacting the compounds of the application with a mammal for a time sufficient to produce their metabolites.

The present application further encompasses prodrugs of the compounds of the application, which are certain derivatives of the compounds of the application that themselves may possess little or no pharmacological activity but, upon administration into or onto the body, are converted, e.g., by hydrolytic cleavage, into the compounds of the application having the desired activity. Typically, such prodrugs are functional group derivatives of the compound that are readily converted in vivo to the therapeutically active compound. For additional information regarding the use of prodrugs, see "Pro-drugs as Novel Delivery Systems," Vol. 14, ACS Symposium Series (T. Higuchi and V. Stella). Prodrugs of the present application may be prepared, for example, by replacing appropriate functional groups present in the compounds of the application with certain moieties known to those skilled in the art as "pro-moieties" (e.g., as described in "Design of Prodrugs," H. Bundgaard (Elsevier, 1985)).

The present application also encompasses compounds of the application containing protecting groups. In any process for preparing the compounds of the present application, it may be necessary and/or desirable to protect sensitive or reactive groups on any relevant molecule, thereby forming chemically protected forms of the compounds of the application. This may be accomplished using conventional protecting groups, such as those described in T. W. Greene & P. G. M. Wuts, Protective Groups in Organic Synthesis, John Wiley & Sons, 2006, which references are incorporated herein by reference. Protecting groups may be removed at an appropriate subsequent stage using methods known in the art.

The present application also encompasses methods for preparing the compounds described herein. It should be understood that the compounds of the present application may be synthesized using the methods described hereinbelow, as well as synthetic methods known in the field of synthetic organic chemistry or variations thereof familiar to those skilled in the art. Preferred methods include, but are not limited to, those described below. Reactions may be carried out in solvents or solvent mixtures suitable for the reagents and materials employed and appropriate for achieving the desired transformation.

The terms "active ingredient", "therapeutic agent", "active substance", or "active agent" refer to a chemical entity that effectively treats one or more symptoms of a target disorder or condition.

As used herein, the term "effective amount" (e.g., "therapeutically effective amount" or "prophylactically effective amount") refers to an amount of the active ingredient that, upon administration, achieves the intended effect to some degree, such as alleviating one or more symptoms of the disorder being treated or preventing the onset of the disorder or its symptoms.

Unless otherwise stated, as used herein, the term "treatment" means reversing, ameliorating, inhibiting the progression of the disorder or condition to which the term applies or one or more symptoms thereof, or preventing such disorder or condition or one or more symptoms thereof.

As used herein, the term "individual" includes human or non-human animals. Exemplary human individuals include human individuals suffering from a disease (e.g., a disease described herein) (referred to as patients) or normal individuals. In the present application, the term "non-human animal" encompasses all vertebrates, such as non-mammals (e.g., birds, amphibians, reptiles) and mammals, including non-human primates, livestock, and/or domesticated animals (e.g., sheep, dogs, cats, cows, pigs, etc.).

Without departing from common knowledge in the art, the above-mentioned preferred conditions may be arbitrarily combined to obtain various preferred embodiments of the present application.

All reagents and raw materials used in the present application are commercially available.

The advantageous effects of the present application lie in that the novel, highly active ecteinascidin derivatives provided herein achieve at least one of the following technical effects: (1) high inhibitory activity against tumor cells; (2) excellent physicochemical properties (e.g., solubility, physical and/or

chemical stability); (3) excellent safety profile (lower toxicity and/or fewer side effects, wider therapeutic window), etc.

Brief Description of the Drawings

Figure 1 shows body weight changes in SD rats following an initial intravenous injection of 0.04 mg/kg, and subsequent injections of 0.3 mg/kg of Compound 26, Compound 25, or lurbinectedin nine days later, as described in Efficacy Test Example 2.

Figure 2 shows food intake changes in SD rats following an initial intravenous injection of 0.04 mg/kg, and subsequent injections of 0.3 mg/kg of Compound 26, Compound 25, or lurbinectedin nine days later, as described in Efficacy Test Example 2.

Figure 3 shows food intake changes in SD rats following an initial intravenous injection of 0.1 mg/kg, and subsequent injections of 0.1 mg/kg of Compound 26, Compound 25, or lurbinectedin nine days later, as described in Efficacy Test Example 2.

Detailed Description

The present application includes all combinations of the specific embodiments described herein. Further embodiments of the application and the full scope of its applicability will become apparent from the detailed description provided below. However, it should be understood that although the detailed description and specific examples indicate preferred embodiments of the application, they are provided for illustrative purposes only, as various changes and modifications within the spirit and scope of the application will become apparent to those skilled in the art from this detailed description. All publications, patents, and patent applications cited herein, including citations, are incorporated herein by reference in their entirety for all purposes. The present application is further illustrated by the following examples, but is not limited thereby to the scope of the examples set forth herein. Experimental methods for which specific conditions are not indicated in the following examples were carried out according to conventional methods and conditions, or as specified in product manuals.

Mass spectrometry (MS) was performed using an Agilent (ESI) mass spectrometer, manufacturer: Agilent, model: Agilent 6120B.

Preparative high-performance liquid chromatography (HPLC) was performed using a Shimadzu LC-8A preparative liquid chromatograph equipped with a YMC ODS column (250 × 20 mm).

Purification by thin-layer chromatography (TLC) was carried out using GF 254 silica gel plates (0.4 – 0.5 nm) manufactured in Yantai.

Reaction progress was monitored by thin-layer chromatography (TLC) or liquid chromatography-mass spectrometry (LC-MS). Eluent systems used included, but were not limited to: dichloromethane/methanol, n-hexane/ethyl acetate, and petroleum ether/ethyl acetate. The volume ratios of solvents were adjusted according to the polarity of the compounds, or modified by addition of triethylamine or similar agents.

Column chromatography was generally performed using Qingdao Marine silica gel (200 – 300 mesh) as the stationary phase. Eluent systems included, but were not limited to, dichloromethane/methanol and n-hexane/ethyl acetate. The solvent volume ratios were adjusted according to compound polarity, and small amounts of triethylamine or similar agents could also be added for adjustment.

Unless otherwise specified in the examples, reactions were conducted at room temperature (20 °C–30 °C).

Unless specifically indicated otherwise, reagents used in the examples were purchased from companies such as Acros Organics, Aldrich Chemical Company, PharmaBlock Sciences (Nanjing), Annokey, or Shanghai Synchem Co., Ltd.

The above examples do not limit the scope of the present application in any manner. In addition to those described herein, numerous modifications of the application will be apparent to those skilled in the art based on the foregoing description. Such modifications are also intended to fall within the scope of the appended claims. All references cited herein (including all patents, patent applications, journal articles, books, and any other disclosures) are incorporated herein by reference in their entirety.

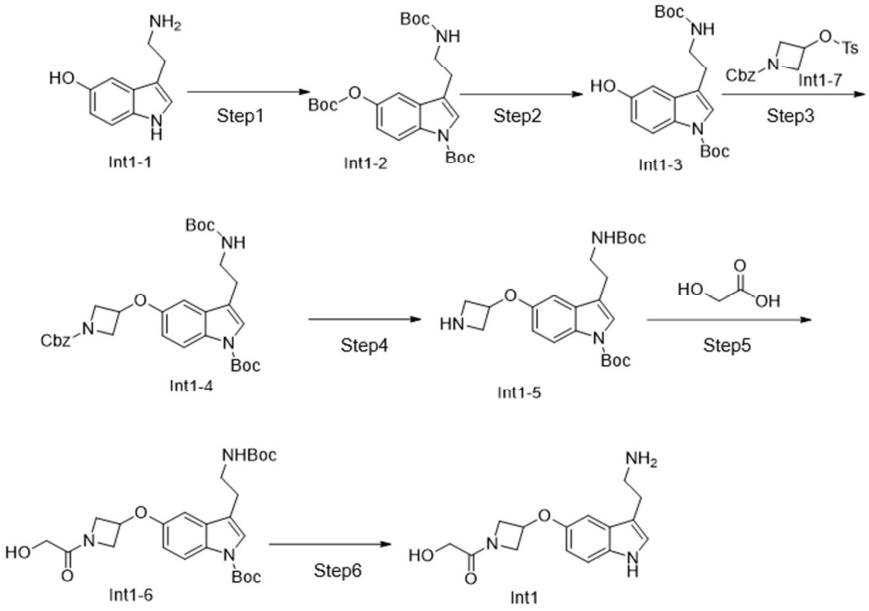
In conventional synthetic procedures, preparation examples, working examples, and intermediate synthesis examples, starting materials were commercially available and sourced from suppliers such as Shanghai Leyan, Shanghai Shaoyuan, Bide Pharmatech, and Aladdin Reagent. Key starting materials M24 and the reference compound lurbinectedin were both procured from Zhejiang Zhongke Chuangyue. The meanings of the abbreviations are listed in the table below.

Abbreviation	Meaning	Abbreviation	Meaning
DMF	N,N-Dimethylformamide	HOBT	1-Hydroxybenzotriazole
DIEA	Diisopropylethylamine	LC-MS	Liquid Chromatography-Mass Spectrometry
HPLC	High-Performance Liquid Chromatography	TLC	Thin-Layer Chromatography
HATU	O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate	AcOH	Acetic acid
Ethyl acetate	EA	DMSO	Dimethyl sulfoxide
DIPEA	N,N-Diisopropylethylamine	EtOH	Ethanol

Boc_2O	Di-tert-butyl dicarbonate	AllocCl	Allyl chloroformate
ACN	Acetonitrile	$Pd(PPh_3)_4$	Tetrakis(triphenylphosphine)palladium
$NaCNBH_3$	Sodium cyanoborohydride	THF	Tetrahydrofuran
SO3.Py	Pyridine sulfur trioxide	p-TsOH	p-Toluenesulfonic acid
Pd/C	Palladium on carbon	DCM	Dichloromethane
TMP	2,2,6,6-Tetramethylpiperidine	HOAT	N-Hydroxy-7-azabenzotriazole

Synthesis of Intermediates:

Intermediate Preparation Example 1: Preparation of Compound **Int1**



Step 1: Preparation of Compound **Int1-2**

Compound **Int1-1** (2.00 g, 11.35 mmol) was dissolved in anhydrous tetrahydrofuran (50 mL). Boc_2O (6.40 g, 29.5 mmol), triethylamine (2.50 g, 25 mmol), and DMAP (0.70 g, 5.7 mmol) were added, and the mixture was reacted at room temperature for two hours. After TLC indicated complete reaction, the tetrahydrofuran was removed under reduced pressure. Ethyl acetate and water were added to the residue, and the mixture was stirred and separated. The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford crude **Int1-2** (3 g, 70% yield), which was used directly in the next step.

Step 2: Preparation of Compound **Int1-3**

Lithium hydroxide (1.3 g, 54.27 mmol) was dissolved in a mixture of methanol (30 mL) and water (10 mL) with stirring. Compound **Int1-2** (3.0 g, 6.3 mmol) was then added, and the mixture was stirred at room temperature for 2 hours. After TLC indicated complete reaction, the pH was adjusted to 6–7 with 1 M aqueous HCl. Ethyl acetate was added, and the mixture was stirred and separated. The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography to afford **Int1-3** (1.5 g, 63% yield).

Step 3: Preparation of Compound **Int1-4**

Compound **Int1-3** (1.5 g, 4.0 mmol, 1.0 eq) and compound **Int1-7** (1.6 g, 4.38 mmol) were dissolved in DMF (30 mL), followed by addition of cesium carbonate (2.60 g, 8.00 mmol). The reaction mixture was heated to 65° C with stirring and maintained at this temperature for 6 hours. After LC-MS confirmed complete reaction, the mixture was cooled to room temperature. Ethyl acetate and water were added, and the mixture was stirred and separated. The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography to afford **Int1-4** (2.0 g, 89% yield).

Step 4: Preparation of Compound **Int1-5**

Compound **Int1-4** (2.0 g, 3.54 mmol) was dissolved in anhydrous tetrahydrofuran (50 mL). 10% Pd/C (0.2 g) was added, and after purging with hydrogen, the mixture was heated to 35° C and stirred overnight. After LC-MS monitoring indicated completion of the reaction, the mixture was cooled to room temperature and filtered directly. The filter cake was washed with methanol, and the combined organic filtrate was concentrated to afford **Int1-5** (1.4 g, 93% yield), which was used directly in the next step.

Step 5: Preparation of compound **Int1-6**

Compound **Int1-5** (1.1 g, 2.55 mmol), glycolic acid (0.21 g, 2.8 mmol), HATU (1.14 g, 3.01 mmol), and DIEA (0.98 g, 7.65 mmol) were dissolved in DMF (20 mL), and the mixture was stirred at room temperature for 2 h. After completion of the reaction as monitored by LCMS, ethyl acetate and water were added to the reaction mixture. The mixture was stirred and then separated. The organic layer was dried over anhydrous sodium sulfate, concentrated under reduced pressure, and the residue was purified by column chromatography to afford **Int1-6** (1.1 g, 63% yield).

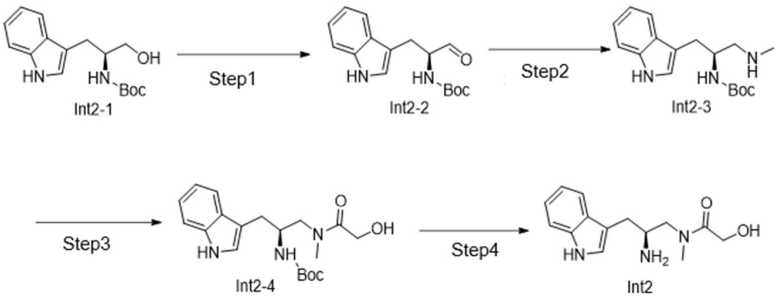
Step 6: Preparation of hydrochloride salt of compound **Int1**

Compound **Int1-6** (1.1 g, 2.24 mmol) was dissolved in 1,4-dioxane (3 mL), and hydrogen chloride/1,4-dioxane (3 mL, 10 mmol) was added. The mixture was stirred at room temperature for 2 h. After monitoring the reaction by LCMS, the reaction mixture was concentrated under reduced pressure to give the hydrochloride salt of **Int1** (0.67 g, 92% yield).

MS m/z (ESI): 290.0 $[M+H]^+$

1H NMR (400 MHz, DMSO-d6) δ 10.90 (d, *J* = 2.5 Hz, 1H), 8.03 (s, 3H), 7.31 (dd, *J* = 8.7, 5.0 Hz, 1H), 7.23 (d, J = 2.4 Hz, 1H), 6.97 (d, *J* = 2.4 Hz, 1H), 6.73 (dd, *J* = 8.7, 2.5 Hz, 1H), 5.10 – 5.05 (m, 1H), 4.70 – 4.65 (m, 1H), 4.42 – 4.38 (m 1H), 4.18 – 4.14 (m, 1H), 3.96 (s, 2H), 3.83 – 3.80 (m, 1H), 3.10 – 2.97 (m, 4H).

Intermediate Preparation Example 2: Preparation of compound **Int2**



Step 1: Preparation of compound **Int2-2**

Compound **Int2-1** (4.0 g, 13.78 mmol) was dissolved in a mixed solvent of DMSO (20 mL) and DCM (10 mL). TEA (3.2 g, 31.4 mmol) was added, and the reaction mixture was purged with nitrogen, cooled to 0 ° C, and a solution of SO_3 • Py (4.4 g, 27.56 mmol) in DMSO (20 mL) was added dropwise slowly. The reaction was maintained at 0 ° C for 2 h. After completion of the reaction as monitored by LCMS, ice-water and ethyl acetate were added. The mixture was stirred and then separated. The organic layer was dried over anhydrous sodium sulfate, concentrated under reduced pressure, and the residue was purified by column chromatography to afford **Int2-2** (3.8 g, 90% yield).

Step 2: Preparation of compound **Int2-3**

Compound **Int2-2** (3.50 g, 0.012 mol), NaOAc (4.92 g, 0.060 mol), and methylamine hydrochloride (3.96 g, 0.060 mol) were added to MeOH (40 mL) and the mixture was reacted at room temperature for 2 h. Subsequently, $NaCNBH_3$ (1.50 g, 0.024 mmol) was added, and stirring was continued for 2 h. After monitoring the reaction by TLC, the reaction mixture was concentrated under reduced pressure. Saturated sodium bicarbonate and DCM were added to the residue. The mixture was stirred and then separated. The organic layer was dried over anhydrous sodium sulfate, concentrated under reduced pressure, and the residue was purified by column chromatography to afford **Int2-3** (1.9 g, 52.7% yield).

Step 3: Preparation of compound **Int2-4**

Compound **Int2-3** (1.2 g, 3.96 mmol), glycolic acid (0.34 g, 4.35 mmol), HATU (1.65 g, 4.35 mmol), and DIEA (0.78 g, 9.90 mmol) were dissolved in DMF (8 mL) and the mixture was reacted at room temperature for 2 h. After completion of the reaction as monitored by LCMS, saturated sodium bicarbonate and ethyl acetate were added to the reaction mixture. The mixture was stirred and then

separated. The organic layer was dried over anhydrous sodium sulfate, concentrated under reduced pressure, and the residue was purified by column chromatography to afford **Int2-4** (1.0 g, 71.4% yield).

Step 4: Preparation of compound **Int2**

Compound **Int2-4** (500 mg, 1.38 mmol) was dissolved in ethyl acetate (5 mL), cooled to 0 ° C, and hydrogen chloride/ethyl acetate (2 N, 10 mL) was added. After addition was complete, the mixture was allowed to warm naturally to room temperature and reacted for 2 h. After completion of the reaction as monitored by LCMS, the reaction mixture was concentrated under reduced pressure to dryness to give the hydrochloride salt of compound **Int2** (400 mg), which was used directly in the next step without further purification.

MS m/z (ESI): 261.9 $[M+H]^+$

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.05 (s, 1H), 7.97 (s, 3H), 7.61 (d, J = 7.9 Hz, 1H), 7.39 (d, J = 8.1 Hz, 1H), 7.30 (d, J = 2.4 Hz, 1H), 7.11 (t, J = 7.5 Hz, 1H), 7.03 (t, J = 7.5 Hz, 1H), 4.06 (s, 2H), 4.03 (t, J = 7.1 Hz, 1H), 3.63 – 3.64 (m, 1H), 3.39 (d, J = 10.0 Hz, 1H), 3.11 – 2.92 (m, 2H), 2.83 (s, 3H).

Intermediate Preparation Example 3: Preparation of compound **Int3**



Step 1: Preparation of compound **Int3-2**

Compound **Int3-1** (5.0 g, 0.034 mol) was dissolved in methanol (50 mL), cooled to 0 ° C, and sodium acetate (14.0 g, 0.170 mol) and methylamine hydrochloride (11.0 g, 0.170 mol) were added sequentially. The reaction mixture was then heated to 45 ° C and reacted for 4 h. After completion of the reaction as monitored by LCMS, the reaction mixture was cooled and filtered, and the filtrate was concentrated under reduced pressure to dryness. The residue was dissolved in dichloromethane (60 mL), acetic acid (1.9 g, 0.032 mol) was added, and the mixture was cooled to 0 ° C. TMSCN (9.5 g, 0.096 mol) was then added dropwise slowly with stirring. After addition was complete, the mixture was allowed to warm naturally to room temperature and reacted for 16 h. After completion of the reaction as monitored by LCMS, saturated sodium bicarbonate and DCM were added to the reaction mixture for extraction. The mixture was stirred and then separated. The organic layer was dried over anhydrous sodium sulfate, concentrated under reduced pressure, and the residue was purified by column chromatography to afford **Int3-2** (4 g, 63.4% yield).

Step 2: Preparation of compound **Int3-3**

Compound **Int3-2** (4.0 g, 0.021 mol) was dissolved in THF (40 mL), and DIEA (5.4 g, 0.042 mol) and (Boc)₂O (5.5 g, 0.025 mol) were added. The mixture was stirred at 60 ° C for 16 h, cooled to room temperature, concentrated under reduced pressure, and the residue was purified by column chromatography to afford **Int3-3** (0.6 g, 10% yield).

Step 3: Preparation of compound **Int3**

Compound **Int3-3** (600 mg, 2.1 mmol) was dissolved in a mixed solution of EtOH (40 mL) and aqueous ammonia (30%, 10 mL). Raney Ni (100 mg) was added, the system was purged with hydrogen three times, pressurized to 1.5 MPa, and the mixture was stirred at 50 ° C for 16 h. Completion of the reaction was confirmed by LCMS. The reaction mixture was concentrated under reduced pressure, and the residue was purified by column chromatography to afford **Int3** (410 mg, 67.7% yield).

MS m/z (ESI): 290.2 $[M+H]^+$

Intermediate Preparation Example 4: Preparation of compound **Int4**

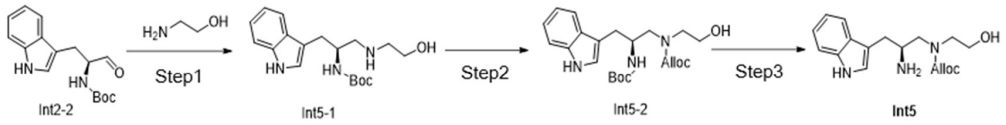


Compound **Int4** was synthesized by a method analogous to that described in Intermediate Preparation Example 3.

MS m/z (ESI): 276.4 $[M+H]^+$

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (s, 1H), 7.65 (d, *J* = 7.9 Hz, 1H), 7.37 (d, *J* = 8.1 Hz, 1H), 7.24 – 7.18 (m, 1H), 7.15 – 7.08 (m, 2H), 5.09 (s, 1H), 4.98 (d, *J* = 7.4 Hz, 1H), 3.21 – 3.13 (m, 2H), 1.45 (s, 9H).

Intermediate Preparation Example 5: Preparation of compound **Int5**



Step 1: Preparation of compound **Int5-1**

Compound **Int2-2** (2.5 g, 8.6 mmol) was dissolved in EtOH (40 mL). AcOH (1.0 g, 17.2 mmol), ethanolamine (1.1 g, 17.2 mmol), and $NaCNBH_3$ (1.6 g, 25.8 mmol) were added sequentially. The mixture was stirred at room temperature for 4 h, and completion of the reaction was monitored by TLC. The reaction mixture was concentrated under reduced pressure. Saturated sodium bicarbonate and ethyl acetate

were added to the residue. The mixture was stirred and then separated. The organic layer was dried over anhydrous sodium sulfate, concentrated under reduced pressure, and the residue was purified by column chromatography to afford **Int5-1** (2.6 g, 91% yield).

Step 2: Preparation of compound **Int5-2**

Compound **Int5-1** (2.6 g, 7.80 mmol) and DIEA (2.0 g, 15.61 mmol) were dissolved in ACN (30 mL). Under nitrogen protection, the mixture was cooled to 0 ° C, and AllocCl (1.8 g, 15.61 mmol) was added dropwise slowly. After addition was complete, the mixture was allowed to warm naturally to room temperature and stirred for 16 h. Completion of the reaction was confirmed by LCMS. Saturated sodium bicarbonate and ethyl acetate were added to the reaction mixture. The mixture was stirred and then separated. The organic layer was dried over anhydrous sodium sulfate, concentrated under reduced pressure, and the residue was purified by column chromatography to afford **Int5-2** (1 g, 71% yield).

MS m/z (ESI): 418.2 $[M+H]^+$

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (s, 1H), 7.60 (d, *J* = 7.9 Hz, 1H), 7.38 – 7.36 (s, 1H), 7.22 – 7.17(m, 1H), 7.16 – 7.04 (m, 2H), 5.94 – 5.79 (m, 1H), 5.25 – 5.12 (m, 2H), 4.60 – 4.45 (m, 2H), 4.37 – 4.25 (m, 1H), 3.79 – 3.56 (m, 4H), 3.28 – 2.97 (m, 2H), 2.99 – 2.88 (m, 2H), 1.40 (s, 9H).

Step 3: Preparation of compound **Int5**

Compound **Int5-2** (0.5 g, 1.57 mmol) was dissolved in DCM (3 mL), and trifluoroacetic acid (1 mL) was added. The mixture was stirred at room temperature for 1 h. After completion of the reaction as monitored by LCMS, the reaction mixture was concentrated under reduced pressure to dryness to give the trifluoroacetate salt of compound **Int5** (0.33 g), which was used directly in the next step.

Intermediate Preparation Example 6: Preparation of compound **Int6**



Step 1: Preparation of compound **Int6-2**

LiHMDS (1.12 mL, 6.06 mmol, 2 N) was added to a reaction flask under nitrogen protection and cooled to −78 ° C. A solution of Int6-1 (776.1 mg, 3.03 mmol) in tetrahydrofuran (5 mL) was then added dropwise. After addition was complete, the reaction was maintained at this temperature for 1.5 h. Subsequently, a solution of isobutyl chloroformate (0.32 mL, 3.64 mmol) in tetrahydrofuran (3 mL) was added dropwise while maintaining the temperature. After addition was complete, the mixture was allowed to warm naturally to room temperature and reacted for 2 h. LCMS indicated completion of the reaction. The mixture was cooled to 0 ° C, and saturated NH_4Cl solution and ethyl acetate were added. The

mixture was stirred and then separated. The organic layer was dried over anhydrous sodium sulfate, concentrated under reduced pressure, and the residue was purified by column chromatography to afford **Int6-2** (0.82 g, 76% yield).

Step 2: Preparation of compound **Int6-3**

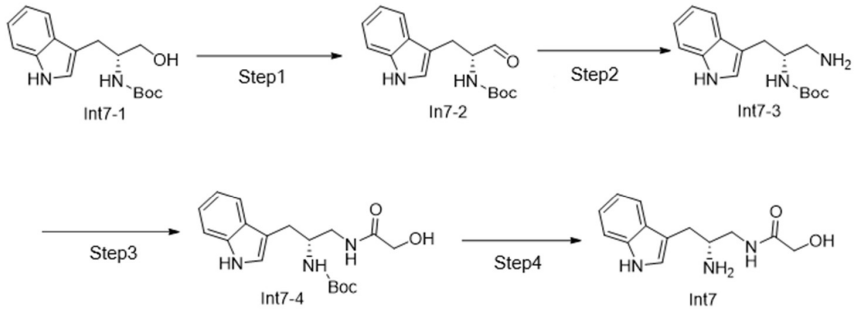
Compound **Int6-2** (500 mg, 1.40 mmol) was dissolved in a mixed solution of dichloromethane/trifluoroacetic acid (5 mL, dichloromethane/trifluoroacetic acid = 4/1) and reacted at room temperature for 2 h. After completion of the reaction, the mixture was concentrated under reduced pressure. Saturated sodium bicarbonate solution and DCM were added to the residue. The mixture was stirred and then separated. The organic layer was dried over anhydrous sodium sulfate, concentrated under reduced pressure, and the residue was purified by preparative TLC to afford **Int6-3** (250 mg, 69% yield).

Step 3: Preparation of compound **Int6**

Compound **Int6-3** (300 mg, 1.17 mmol) was dissolved in tetrahydrofuran (4 mL), cooled to 0 ° C, and a solution of lithium aluminum hydride (2.3 mL, 5.85 mmol) in tetrahydrofuran was added dropwise. The mixture was reacted at room temperature for 2 h. After completion of the reaction as confirmed by LCMS, water was added dropwise to quench the reaction. The mixture was filtered, washed with methanol, concentrated, and the residue was purified by preparative HPLC to afford compound **Int6** (50 mg, 22% yield).

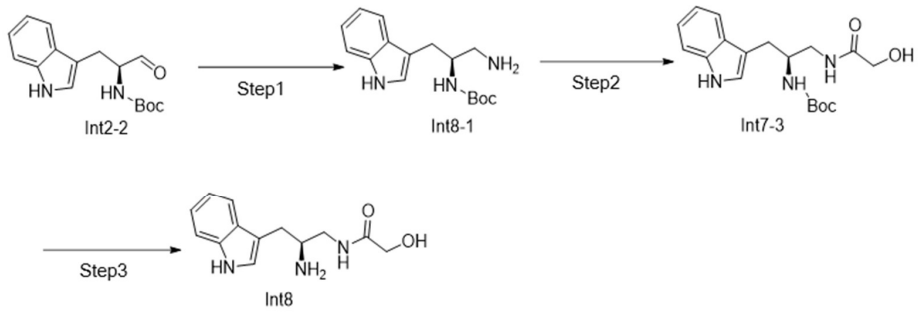
MS m/z (ESI): 191.1 $[M+H]^+$

Intermediate Preparation Example 7: Preparation of compound **Int7**



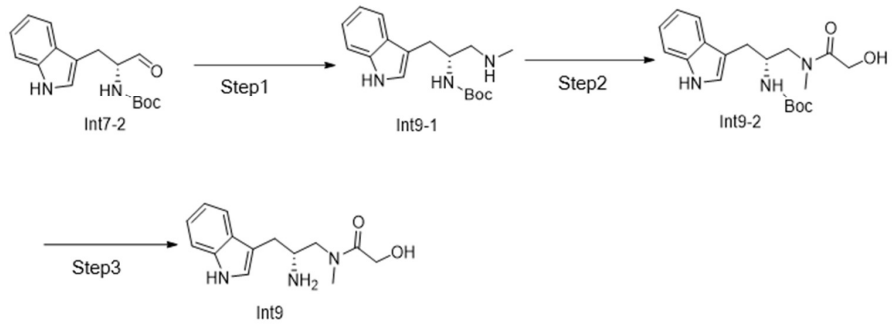
Compound Int7 was synthesized by a method analogous to that described in Intermediate Preparation Example 2.

Intermediate Preparation Example 8: Preparation of compound **Int8**



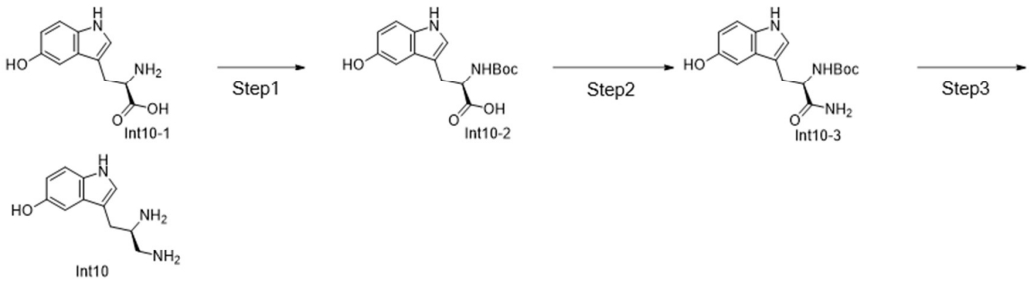
Compound Int8 was synthesized according to the method described in Intermediate Preparation Example 2.

Intermediate Preparation Example 9: Preparation of compound **Int9**



Compound Int9 was synthesized according to the method described in Intermediate Preparation Example 2.

Intermediate Preparation Example 10: Preparation of compound **Int10**



Step 1: Preparation of compound **Int10-2**

Compound **Int10-1** (2.0 g, 9.1 mmol) was dissolved in THF (40 mL), and 2 N aqueous sodium bicarbonate solution (30 mL) was added. After stirring at room temperature until homogeneous, di-tert-butyl dicarbonate (2.4 g, 10.9 mmol) was added, and the reaction was continued for 2 h. After completion of the reaction as monitored by LCMS, the reaction mixture was concentrated under reduced pressure to

remove THF. Ethyl acetate was added to the residue, and the pH was adjusted to approximately 6 with saturated aqueous citric acid solution under stirring. The mixture was then separated. The organic layer was dried over anhydrous sodium sulfate, concentrated under reduced pressure, and the residue was purified by column chromatography to afford **Int10-2** (2.5 g, 86% yield).

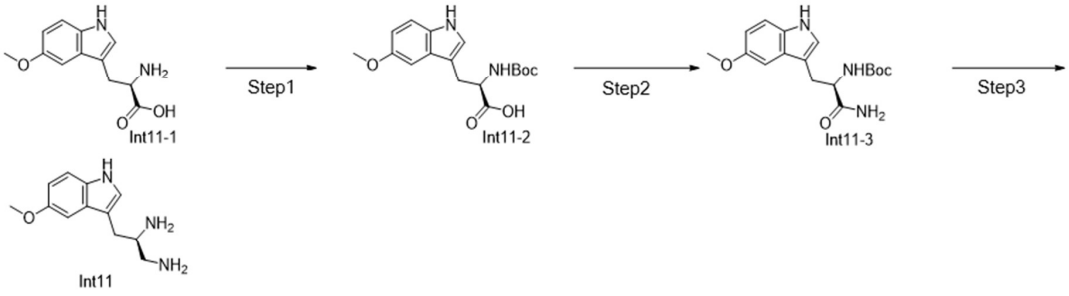
Step 2: Preparation of compound **Int10-3**

Compound **Int10-2** (2.50 g, 7.8 mmol) and ammonium chloride (0.54 g, 10.1 mmol) were dissolved in DMF (20 mL). HATU (3.56 g, 9.36 mmol) and DIEA (2.6 g, 20.2 mmol) were added sequentially. The mixture was stirred at room temperature for 4 h, and completion of the reaction was confirmed by LCMS. Ethyl acetate and saturated aqueous ammonium chloride solution were added. The mixture was stirred and then separated. The organic layer was dried over anhydrous sodium sulfate, concentrated under reduced pressure, and the residue was purified by column chromatography to afford **Int10-3** (2 g, 80% yield).

Step 3: Preparation of compound **Int10**

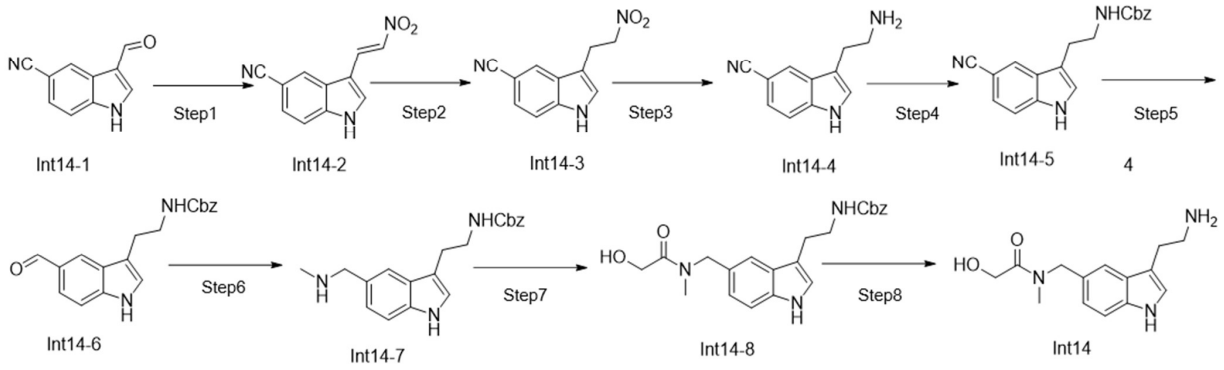
Compound **Int10-3** (2 g, 6.26 mmol) was dissolved in anhydrous tetrahydrofuran (10 mL), cooled to 0 ° C, and a solution of borane-tetrahydrofuran solution (1 N, 50 mL) was added slowly. After addition was complete, the mixture was allowed to warm naturally to room temperature and reacted for 4 h. After completion of the reaction as monitored by LCMS, the reaction mixture was cooled to 0 ° C, and anhydrous methanol was added slowly under controlled temperature until borane was completely quenched. Subsequently, 2 N aqueous hydrochloric acid was added slowly under controlled temperature until the pH of the mixture reached approximately 3. After addition was complete, the mixture was allowed to warm naturally to room temperature and stirred for 2 h. The reaction mixture was concentrated under reduced pressure, and the residue was purified by reverse-phase column chromatography to afford compound **Int10** (0.83 g, 65% yield).

Intermediate Preparation Example 11: Preparation of compound **Int11**



Compound **Int11** was synthesized according to the method described in **Intermediate Preparation Example 10**.

Intermediate Preparation Example 12: Preparation of compound Int14



Step 1: Preparation of compound **Int14-2**

Ammonium acetate (13.50 g, 176.47 mmol) was dissolved in nitromethane (200 mL), and compound **Int14-1** (10.00 g, 58.80 mmol) was added. Under nitrogen protection, the mixture was heated to 105 ° C and reacted for 2 hours. After completion of the reaction as monitored by TLC, the mixture was cooled to room temperature and filtered. The filter cake was washed with H_2O/MeOH (V/V = 1/1), and the solid was dried under reduced pressure to afford compound **Int14-2** (10.30 g, 82% yield).

Step 2: Preparation of compound **Int14-3**

Compound **Int14-2** (5.00 g, 23.47 mmol) was dissolved in a mixed solution of MeOH (25 mL) and DMF (25 mL). Sodium borohydride (4.30 g, 117.30 mmol) was added at 0 ° C, and the mixture was stirred at room temperature for 2 hours. After completion of the reaction as monitored by TLC, the pH was adjusted to 7 with 2 N dilute hydrochloric acid solution. DCM was added, the mixture was stirred and then separated. The organic layer was dried over anhydrous sodium sulfate, concentrated under reduced pressure, and the residue was purified by column chromatography to afford compound **Int14-3** (1.77 g, 35% yield).

Step 3: Preparation of compound **Int14-4**

Compound **Int14-3** (1.77 g, 8.20 mmol) was dissolved in MeOH (20 mL), followed by addition of a suspension of zinc powder (5.00 g, 82.00 mmol) in 2 N HCl (20 mL). The reaction mixture was heated to 85 ° C with stirring and stirred for 2 hours. After the reaction was confirmed complete by LCMS, the reaction mixture was cooled to room temperature, and 1 N NaOH solution was added to adjust the pH to 11. DCM was then added, and the mixture was stirred and separated. The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford compound **Int14-4** (800 mg, 53% yield), which was used directly in the next step.

Step 4: Preparation of compound **Int14-5**

Compound **Int14-4** (750 mg, 4.00 mmol) was dissolved in anhydrous tetrahydrofuran (2 mL). An aqueous solution (6 mL) of $NaCO_3$ (510 mg, 4.86 mmol) was added, and after nitrogen purging, benzyl

chloroformate (884 mg, 5.20 mmol) was added at 0 ° C. The mixture was stirred at room temperature overnight. After monitoring the reaction by LCMS, ethyl acetate was added. The mixture was stirred and separated. The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography to give compound **Int14-5** (700 mg, 55% yield).

Step 5: Preparation of compound **Int14-6**

Compound **Int14-5** (650 mg, 2.00 mmol) was dissolved in pyridine (8 mL). Acetic acid (4 mL), an aqueous solution of sodium hypophosphite (4 mL, 10 g/35 mL), and Raney nickel (4 g) were added. The mixture was stirred at room temperature for 3 h under nitrogen atmosphere. After the reaction was confirmed complete by LCMS, the reaction mixture was filtered. To the filtrate were added ethyl acetate and an aqueous solution of copper sulfate. The layers were separated, and the organic layer was washed with water, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to afford compound **Int14-6** (600 mg, 91% yield).

Step 6: Preparation of compound **Int14-7**

Compound **Int14-6** (550 mg, 1.71 mmol) was dissolved in MeOH (5 mL). Methanamine hydrochloride (572 mg, 8.54 mmol) and sodium acetate (700 mg, 8.54 mmol) were added, and the mixture was stirred at room temperature for 1 h. Sodium cyanoborohydride (211 mg, 3.41 mmol) was then added, and stirring was continued at room temperature for another 1 h. After monitoring the reaction by LCMS, water and DCM were added to the reaction mixture. The mixture was stirred and separated. The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography to give compound **Int14-7** (240 mg, 38% yield).

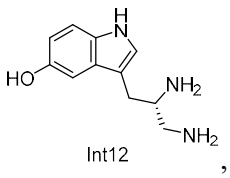
Step 7: Preparation of compound **Int14-8**

Compound **Int14-7** (220 mg, 0.65 mmol) was dissolved in DMF (2 mL). Glycolic acid (54 mg, 0.70 mmol), DMAP (39 mg, 0.32 mmol), HOAT (442 mg, 3.25 mmol), and EDCI (620 mg, 3.25 mmol) were added, and the mixture was stirred at room temperature for 2 h. After the reaction was confirmed complete by LCMS, the reaction mixture was purified by reverse-phase medium-pressure preparative chromatography to give compound **Int14-8** (200 mg, 78% yield).

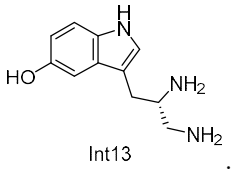
Step 7: Preparation of compound **Int14**

Compound **Int14-8** (170 mg, 0.43 mmol) was dissolved in trifluoroethanol (2 mL). Acetic acid (25 mg, 0.43 mmol) and Pd/C (85 mg, 10%) were added, and the mixture was stirred at room temperature overnight under a hydrogen atmosphere. After the reaction was confirmed complete by LCMS, the reaction mixture was filtered, and the filtrate was concentrated under reduced pressure to afford compound **Int14** (100 mg, 89% yield), which was used directly in the next step.

Intermediates Int12 and Int13 were synthesized according to the method described in Intermediate Preparation Example 10, using the corresponding starting materials. Their structures are as follows:

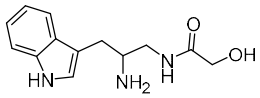


Int12 ,



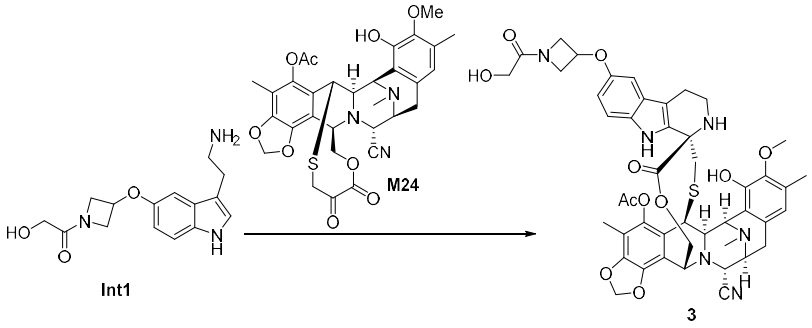
Int13 .

Intermediate Int15 was synthesized according to the method described in Intermediate Preparation Example 2, using the corresponding starting material.



Int15

Example 1: Synthesis of compound **3**



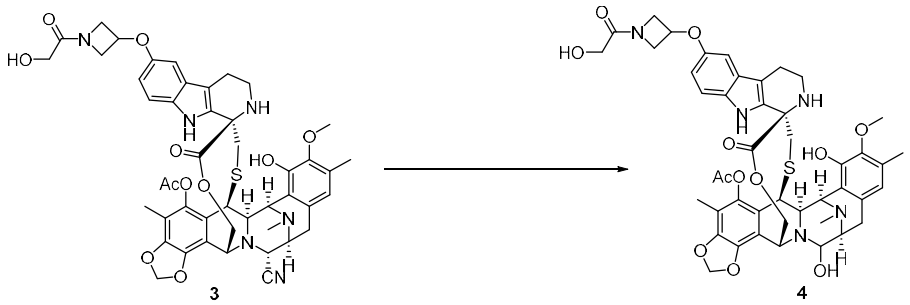
Compound **M24** (100 mg, 0.16 mmol) and hydrochloride salt of compound **Int1** (260 mg, 0.80 mmol) were dissolved in anhydrous ethanol (5 mL). Sodium acetate (164 mg, 2.00 mmol) and acetic acid (120 mg, 2.00 mmol) were added, and the mixture was stirred at 60 ° C overnight. After the reaction was confirmed complete by LCMS, the mixture was cooled to room temperature and concentrated under reduced pressure. The residue was treated with ethyl acetate and saturated aqueous sodium bicarbonate solution. The mixture was stirred and separated. The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by Pre-TLC to give compound **3** (65 mg, 45% yield).

MS m/z (ESI): 893.4 $[M+H]^+$

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (s, 1H), 7.17 (d, *J* = 8.8 Hz, 1H), 6.66 (d, *J* = 8.7 Hz, 2H), 6.59 (d, *J* = 2.4 Hz, 1H), 6.22 (s, 1H), 6.02 (s, 1H), 5.81 (s, 1H), 5.08 (d, *J* = 11.7 Hz, 1H), 5.00 (d, *J* = 7.4 Hz, 1H), 4.56 (s, 1H), 4.48 – 4.36 (m, 2H), 4.33 (s, 1H), 4.27 (d, *J* = 4.6 Hz, 1H), 4.17 – 4.07 (m, 3H), 4.00 (s,

2H), 3.81 (s, 3H), 3.42 (d, J = 9.9 Hz, 2H), 3.15 – 3.05 (m, 2H), 2.97 – 2.75 (m, 3H), 2.58 – 2.52 (m, 4H), 2.37 (s, 3H), 2.26 (s, 3H), 2.22 (s, 3H), 2.06 (s, 3H).

Example 2: Synthesis of compound **4**

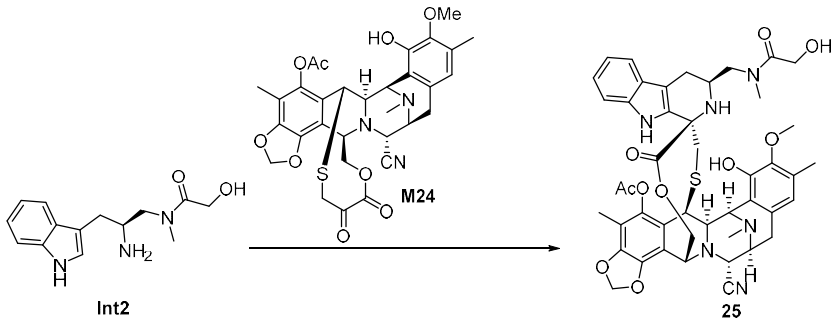


Compound **3** (30 mg, 0.034 mmol) was dissolved in ACN (3 mL) and water (2 mL). Silver nitrate (143 mg, 0.840 mmol) was added, and the mixture was stirred at room temperature for 12 hours in the dark. After the reaction was confirmed complete by LCMS, saturated aqueous sodium bicarbonate solution was added, and the mixture was stirred and separated. The organic layer was retained, and the aqueous layer was extracted once with dichloromethane. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by preparative HPLC to give compound **26** (1.5 mg, 4% yield).

MS m/z (ESI): 866.3 $[M\text{-}OH]^+$

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (s, 1H), 7.19 (d, J = 8.7 Hz, 1H), 6.68 (d, J = 8.7 Hz, 2H), 6.61 (s, 1H), 6.22 (s, 1H), 6.01 (s, 1H), 5.22 (d, J = 11.5 Hz, 1H), 5.04 – 5.02 (m, 1H), 4.86 (s, 1H), 4.52 – 4.43 (m, 4H), 4.23 – 4.09 (m, 4H), 4.03 (s, 2H), 3.84 (s, 3H), 3.55 – 3.52 (m, 1H), 3.25 – 3.17 (m, 2H), 3.05 – 2.83 (m, 3H), 2.62 – 2.53 (m, 4H), 2.40 (s, 3H), 2.28 (s, 3H), 2.23 (s, 3H), 2.07 (s, 3H).

Example 3: Synthesis of compound **25**



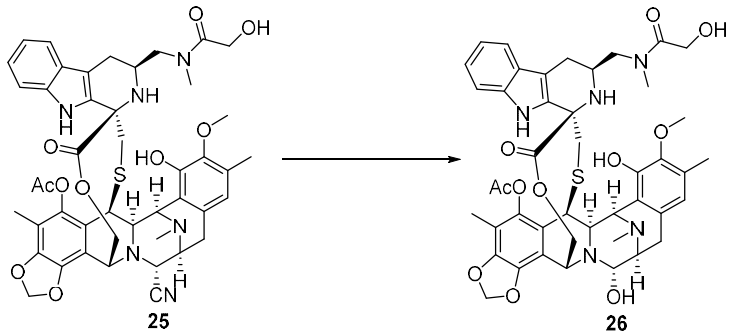
Compound **M24** (40 mg, 0.06 mmol) and hydrochloride salt of compound **Int2** (100 mg, 0.35 mmol) were dissolved in anhydrous ethanol (1 mL) and acetic acid (2 mL). Sodium acetate (7.38 mg, 0.09 mmol) was

added, and the mixture was stirred at 60 ° C overnight. After the reaction was confirmed complete by LCMS, the reaction mixture was cooled to room temperature. Ethyl acetate and saturated aqueous sodium bicarbonate solution were added to the residue. The mixture was stirred and separated. The organic layer was separated and dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by Pre-TLC to give compound **25** (20 mg, 43% yield).

MS m/z (ESI): 865.3 $[M+H]^+$

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (s, 1H), 7.36 – 7.32 (m, 1H), 7.25 – 7.20 (m, 1H), 7.16 – 7.08 (m, 1H), 7.04 – 6.99(m, 1H), 6.59 (d, *J* = 8.0 Hz, 1H), 6.25 (d, *J* = 4.4 Hz, 1H), 6.04 (s, 1H), 5.82 (s, 1H), 5.15 – 5.09 (m, 1H), 4.63 – 4.58 (m, 1H), 4.43 – 4.15 (m, 5H), 4.11 – 4.05 (m, 1H), 3.83 (d, *J* = 13.1 Hz, 3H), 3.64 – 3.62 (m, 1H), 3.55 – 3.41 (m, 3H), 3.40 – 3.20 (m, 1H), 3.04 (s, 2H), 2.96 – 2.91 (m, 4H), 2.63 – 2.35 (m, 4H), 2.30 (s, 6H), 2.15 (s, 3H), 2.05 (s, 3H).

Example 4: Synthesis of compound **26**

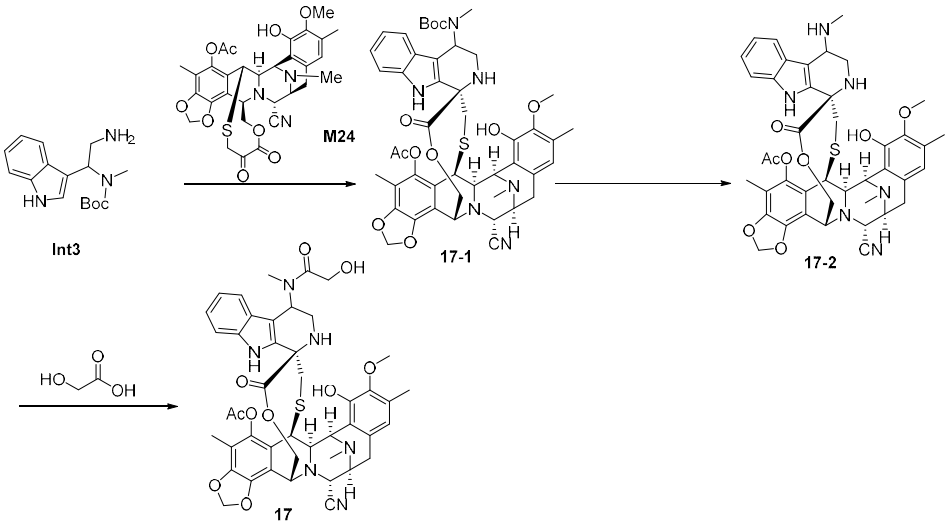


Compound **25** (20 mg, 0.023 mmol) was dissolved in ACN (3 mL) and water (2 mL). Silver nitrate (98 mg, 0.577 mmol) was added, and the mixture was stirred at room temperature for 12 hours in the dark. After the reaction was confirmed complete by LCMS, saturated aqueous sodium bicarbonate solution was added, and the mixture was stirred and separated. The organic layer was retained, and the aqueous layer was extracted once with dichloromethane. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by preparative HPLC to give compound **26** (3 mg, 15.6% yield).

MS m/z (ESI): 838.3 $[M-OH]^+$

1H NMR (400 MHz, $CDCl_3$) δ 7.34 (t, *J* = 7.2 Hz, 1H), 7.22 (d, *J* = 6.3 Hz, 1H), 7.13 – 7.06 (m, 1H), 7.06 – 6.94 (m, 1H), 6.65 – 6.54 (m, 1H), 6.24 – 6.18 (m, 1H), 6.01 (t, *J* = 1.7 Hz, 1H), 5.22 (d, *J* = 11.8 Hz, 1H), 4.90 (s, 1H), 4.51 (s, 2H), 4.26 (dd, *J* = 15.8, 11.4 Hz, 2H), 4.17 (d, *J* = 7.5 Hz, 2H), 4.11 (s, 1H), 3.84 (d, *J* = 2.6 Hz, 1H), 3.81 (s, 2H), 3.56 (s, 1H), 3.24 (d, *J* = 9.0 Hz, 1H), 3.04 (d, *J* = 3.3 Hz, 2H), 2.99 (d, *J* = 11.7 Hz, 1H), 2.93 (d, *J* = 4.0 Hz, 2H), 2.86 (d, *J* = 9.1 Hz, 1H), 2.64 – 2.46 (m, 3H), 2.43 – 2.32 (m, 3H), 2.30 (d, J = 3.0 Hz, 6H), 2.27 – 2.19 (m, 2H), 2.16 (d, *J* = 11.4 Hz, 1H), 2.13-2.08 (m, 3H).

Example 5: Synthesis of compound **17**



Step 1: Preparation of compound **17-1**

Compound **17-1** was synthesized according to a method similar to that described in Example 1.

MS m/z (ESI): 893.6 $[M+H]^+$

Step 2: Preparation of compound **17-2**

Compound **17-1** (48 mg, 2.1 mmol) was dissolved in DCM (2 mL), and TFA (0.5 mL) was added. The mixture was stirred at room temperature for 2 h, and the reaction was monitored by LCMS until completion. The reaction mixture was concentrated to dryness under reduced pressure. The residue was adjusted to pH 8 with saturated aqueous sodium bicarbonate solution and extracted with DCM three times. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford crude compound **17-2** (40 mg), which was used directly in the next step.

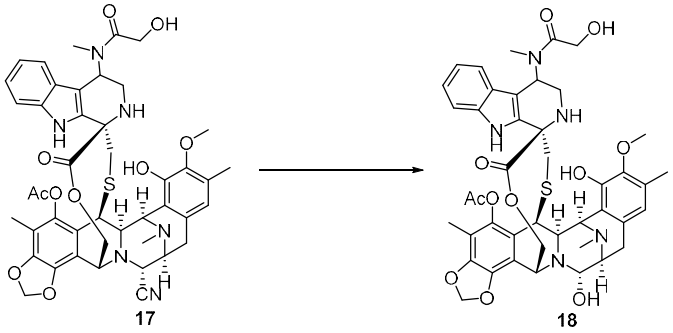
Step 3: Preparation of compound **17**

Compound **17-2** (23.8 mg, 0.030 mmol) was dissolved in DMF (1.5 mL). Glycolic acid (3.0 mg, 0.039 mol), HATU (14.9 mg, 0.039 mmol), and DIEA (11.6 mg, 0.090 mmol) were added sequentially. The mixture was stirred at room temperature for 2 h, and the reaction was monitored by LCMS until completion. Ethyl acetate and saturated aqueous sodium bicarbonate solution were added. The mixture was stirred and separated. The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by Pre-TLC to give compound **17** (16 mg, 62% yield).

MS m/z (ESI): 851.5 $[M+H]^+$

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.56 (d, *J* = 8.3 Hz, 1H), 6.47 – 6.42 (m, 1H), 6.05 (d, *J* = 5.0 Hz, 1H), 5.98 (s, 1H), 5.75 (d, *J* = 9.5 Hz, 1H), 5.49 (d, *J* = 9.8 Hz, 1H), 5.35 (s, 1H), 5.03 – 4.95 (m, 1H), 4.59 (s, 1H), 4.33 (d, *J* = 7.7 Hz, 1H), 4.28 – 4.20 (m, 2H), 4.16 – 4.09 (m, 3H), 3.81 – 3.77 (m, 3H), 3.74 – 3.70 (m, 1H), 3.65 (d, *J* = 3.2 Hz, 3H), 3.52 – 3.49 (m, 1H), 3.43 – 3.39 (m, 1H), 2.93 – 2.82 (m, 3H), 2.61 – 2.58 (m, 1H), 2.48 (s, 1H), 2.45 (s, 1H), 2.31 (dd, *J* = 6.5, 2.9 Hz, 4H), 2.29 – 2.23 (m, 3H), 2.21 (s, 3H), 2.05 (s, 3H).

Example 6: Synthesis of compound **18**

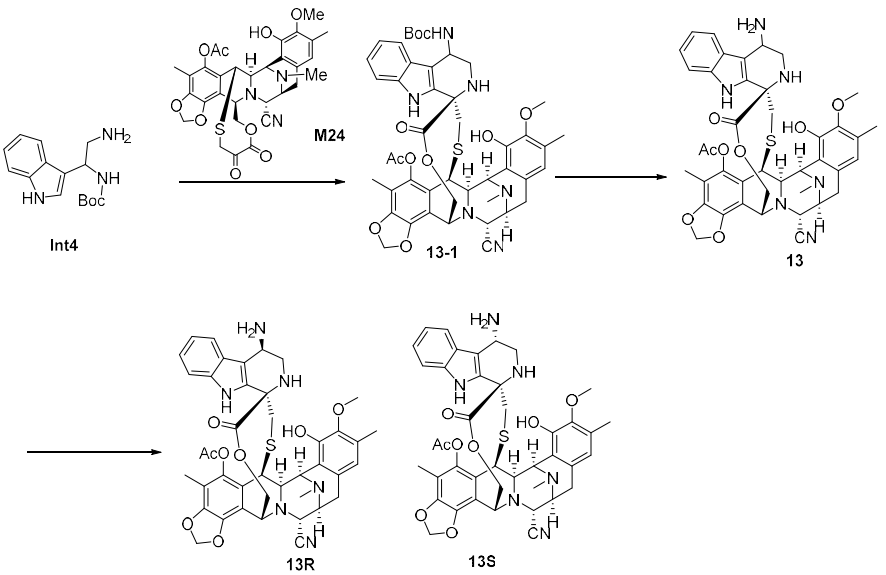


Compound **18** was synthesized according to a method similar to that described in Example 2.

MS m/z (ESI): 824.4 $[M\text{-}OH]^+$

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 – 7.21 (m, 2H), 7.07 (t, *J* = 7.3 Hz, 1H), 6.95 (t, *J* = 7.5 Hz, 1H), 6.56 (d, *J* = 8.8 Hz, 1H), 6.15 (s, 1H), 5.93 (s, 1H), 5.73 – 5.68 (m, 1H), 5.10 – 5.05 (m, 1H), 4.79 – 4.74 (m, 1H), 4.44 – 4.37 (m, 2H), 4.26 – 4.22 (m, 1H), 4.12 – 4.01 (m, 3H), 3.77 – 3.70 (m, 3H), 3.62 – 3.59(m, 1H), 3.43 (d, *J* = 7.9 Hz, 1H), 3.19 – 3.12 (m, 1H), 3.08 – 2.96 (m, 1H), 2.96 – 2.72 (m, 4H), 2.60 (d, *J* = 2.6 Hz, 2H), 2.48 (d, *J* = 3.8 Hz, 2H), 2.34 – 2.27 (m, 3H), 2.27 – 2.22 (m, 3H), 2.19 (d, *J* = 6.3 Hz, 2H), 2.13 (d, *J* = 2.6 Hz, 2H), 2.00 (s, 3H).

Example 7: Synthesis of compounds **13, 13R, 13S**



Step 1: Preparation of compound **13-1**

Compound **13-1** was synthesized according to a method similar to that described in Example 1.

Step 2: Preparation of compound **13**

Crude compound **13** was synthesized according to a method similar to Step 2 of Example 5. **Compound 13 was purified by Pre-TLC to afford compound 13.**

MS m/z (ESI): 779.3$[M+H]^+$

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (s, 1H), 7.82 (s, 1H), 7.56 (d, *J* = 7.8 Hz, 1H), 7.22 (d, *J* = 8.2 Hz, 1H), 7.11 (t, *J* = 7.6 Hz, 1H), 7.03 (t, *J* = 7.4 Hz, 1H), 6.65 (s, 1H), 6.25 (d, *J* = 1.4 Hz, 1H), 6.03 (d, *J* = 1.4 Hz, 1H), 5.10 (d, *J* = 11.8 Hz, 1H), 4.53 (s, 1H), 4.35 (s, 1H), 4.33 – 4.24 (m, 2H), 4.17 (s, 2H), 3.78 (s, 4H), 3.43 (d, *J* = 4.7 Hz, 1H), 3.39 (s, 1H), 2.90 (d, *J* = 5.1 Hz, 4H), 2.78 (d, *J* = 11.9 Hz, 2H), 2.46 (d, *J* = 16.0 Hz, 2H), 2.37 (s, 3H), 2.25 (s, 3H), 2.21 (d, *J* = 3.3 Hz, 3H), 2.04 (s, 3H).

The purified compound 13 was further purified by reverse-phase medium-pressure preparative chromatography under the following conditions:

Column: Agela technologies C18, 20 – 35 μm, 100 A, 120 g

Mobile phase: Purified water (0.1% HCl)/acetonitrile

Gradient: 100% purified water to 100% acetonitrile; product eluted at 50% acetonitrile

Peak 1 and Peak 2 had retention times of 1.415 min and 1.392 min, respectively, on LCMS.

Characterization of the first peak (1.415 min): 13R or 13S:

MS m/z (ESI): 779.3[M+H]$^+$

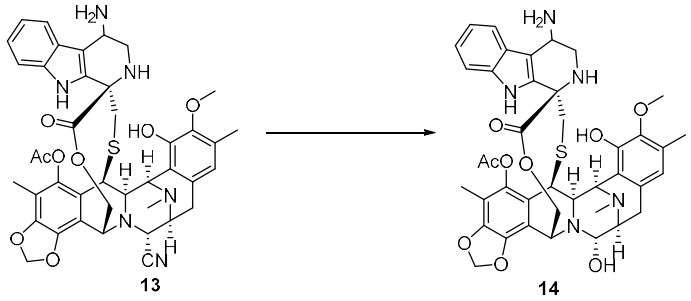
^{1}H NMR (400 MHz, DMSO-d_6) δ 10.81 (s, 1H), 8.95 (s, 1H), 7.93 (s, 3H), 7.64 (d, J = 6.4 Hz, 1H), 7.40 (d, J = 6.4 Hz, 1H), 7.11 (t, J = 6.4 Hz, 1H), 7.02 (t, J = 6.4 Hz, 1H), 6.53 (s, 1H), 6.25 (d, J = 16.8 Hz, 2H), 5.06 (d, J = 11.2 Hz, 1H), 4.71-4.57 (m, 1H), 4.55-4.47 (m, 1H), 4.44-4.38 (m, 1H), 4.37-4.28 (m, 1H), 4.09 (s, 1H), 4.07-4.04 (m, 1H), 3.67 (s, 3H), 3.43-3.40 (m, 1H), 3.35-3.25 (m, 1H), 2.99-2.92 (m, 3H), 2.73 – 2.69 (m, 1H), 2.32 (s, 3H), 2.30 (s, 3H), 2.22-2.08 (m, 4H), 2.00 (s, 3H), 1.99-1.94 (m, 1H).

Characterization of the second peak (1.392 min): 13R or 13S:

MS m/z (ESI): 779.3[M+H]$^+$

^{1}H NMR (400 MHz, DMSO) δ 10.67 (s, 1H), 9.02 (s, 1H), 8.24 (s, 3H), 7.74 (d, J = 6.4 Hz, 1H), 7.42 (d, J = 6.4 Hz, 1H), 7.12 (t, J = 6.4 Hz, 1H), 7.02 (t, J = 6.4 Hz, 1H), 6.49 (s, 1H), 6.25 (d, J = 16.8 Hz, 2H), 5.15 (d, J = 11.2 Hz, 1H), 4.68-4.57 (m, 1H), 4.54-4.42 (m, 1H), 4.38-4.26 (brs, 2H), 4.23-4.20 (m, 1H), 4.14 (s, 1H), 3.66 (s, 3H), 3.34-3.26 (m, 1H), 3.14-3.03 (m, 1H), 3.01-2.84 (m, 3H), 2.56 – 2.53(m, 1H), 2.31 (s, 3H), 2.29 (s, 3H), 2.22-2.11 (m, 3H), 2.10-2.01 (m, 2H), 1.97 (s, 3H).

Example 8: Synthesis of compound **14**

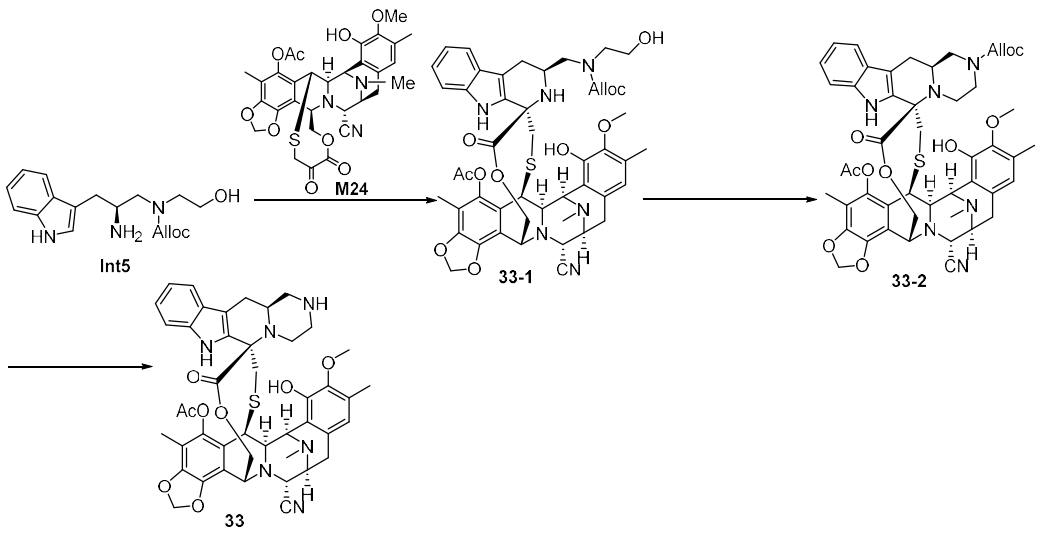


Compound **14** was synthesized according to a method similar to that described in Preparation Example 2.

MS m/z (ESI): 770.9 [M+H]$^+$

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, J = 25.9 Hz, 1H), 7.15 (s, 1H), 7.08 – 6.94 (m, 1H), 6.51 (s, 1H), 6.16 (d, J = 11.4 Hz, 1H), 5.92 (d, J = 6.9 Hz, 1H), 5.00 (d, J = 10.9 Hz, 1H), 4.76 (d, J = 26.5 Hz, 1H), 4.37 (d, J = 13.9 Hz, 1H), 4.21 (s, 1H), 4.14 (s, 1H), 4.10 (s, 1H), 4.01 (d, J = 11.2 Hz, 1H), 3.74 (d, J = 5.5 Hz, 3H), 3.62 (d, J = 18.1 Hz, 1H), 3.42 (s, 1H), 3.23 (s, 1H), 3.13 (s, 1H), 2.99 – 2.69 (m, 7H), 2.34 (s, 2H), 2.32 (s, 2H), 2.28 (s, 2H), 2.21 (s, 2H), 2.13 (d, J = 5.5 Hz, 3H), 2.05 (s, 3H), 1.96 (s, 2H).

Example 9: Synthesis of compound **33**



Step 1: Preparation of compound **33-1**

Compound **33-1** was synthesized according to a method similar to that described in Preparation Example 1.

Step 2: Preparation of compound **33-2**

Compound **33-1** (85 mg, 0.09 mmol) and TEA (27 mg, 0.27 mmol) were dissolved in anhydrous DCM (4 mL) and cooled to 0 ° C. Ms_2O (32.5 mg, 0.184 mmol) was then added, and the mixture was allowed to warm to room temperature and stirred for 2 h. The reaction was quenched by addition of saturated aqueous sodium bicarbonate solution (3 mL), and the mixture was heated to 45 ° C and stirred overnight. The reaction was monitored by LCMS until completion. The reaction mixture was directly extracted with DCM. The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by Pre-TLC to give compound **33-2** (28 mg, 25% yield).

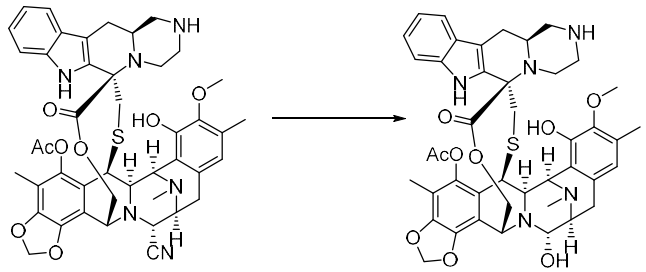
Step 3: Preparation of compound **33**

Compound **33-2** (16 mg, 0.018 mmol), acetic acid (5.4 mg, 0.09 mmol), and $Pd(PPh_3)_4$ (2.0 mg, 0.002 mmol) were added to DCM (2 mL). Under nitrogen atmosphere, Bu_3SnH (52 mg, 0.18 mmol) was added, and the mixture was reacted at room temperature for 2 h after addition. After the reaction was confirmed complete by LCMS, saturated ammonium chloride solution and dichloromethane were added to the reaction mixture. The mixture was stirred and separated. The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by preparative HPLC to give compound **33** (8 mg, 50% yield).

MS m/z (ESI): 819.4 $[M+H]^+$

H NMR (400 MHz, $CDCl_3$) δ 7.36 (d, *J* = 7.9 Hz, 1H), 7.19 – 6.99 (m, 4H), 6.50 (s, 1H), 6.33 (s, 1H), 6.14 (s, 1H), 5.03 (d, *J* = 11.2 Hz, 1H), 4.48 – 4.41 (m, 2H), 4.28 (d, *J* = 4.7 Hz, 1H), 4.21 – 4.18 (m, 1H), 4.05 – 4.02 (m, 1H), 3.84 (s, 3H), 3.69 (d, *J* = 4.7 Hz, 1H), 3.44 (d, *J* = 9.2 Hz, 1H), 3.18 (d, *J* = 12.0 Hz, 1H), 3.00 – 2.69 (m, 7H), 2.61 – 2.55 (m, 2H), 2.49 – 2.36 (m, 2H), 2.32 (s, 6H), 2.20 (s, 3H), 2.02 (s, 3H).

Example 10: Synthesis of compound **34**

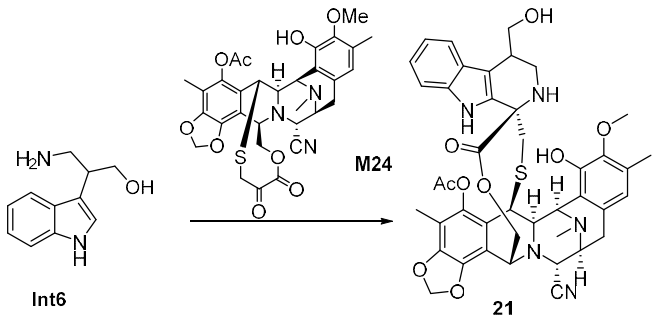


Compound **34** was synthesized by a method analogous to that described in Example 2.

MS m/z (ESI): 810.3 $[M+H]^+$

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, *J* = 7.9 Hz, 1H), 7.05 (d, *J* = 7.3 Hz, 2H), 7.00 (d, *J* = 7.4 Hz, 2H), 6.95 – 6.92 (m, 1H), 6.40 (s, 1H), 6.20 (d, *J* = 3.6 Hz, 1H), 6.00 (d, *J* = 3.6 Hz, 1H), 5.04 – 4.96 (m, 1H), 4.29 – 4.23 (m, 1H), 4.16 – 3.98 (m, 2H), 3.87 – 3.80 (m, 1H), 3.75 (s, 3H), 3.71 (s, 1H), 3.65 (d, *J* = 4.9 Hz, 1H), 3.42 (s, 1H), 3.19 – 3.03 (m, 3H), 2.90 – 2.82 (m, 3H), 2.82 – 2.44 (m, 7H), 2.36 – 2.25 (m, 3H), 2.22 (s, 3H), 2.21 (s, 3H), 2.19 – 2.14 (m, 1H), 2.09 (s, 3H), 2.06 – 1.96 (m, 1H).

Example 11: Synthesis of compound **21**

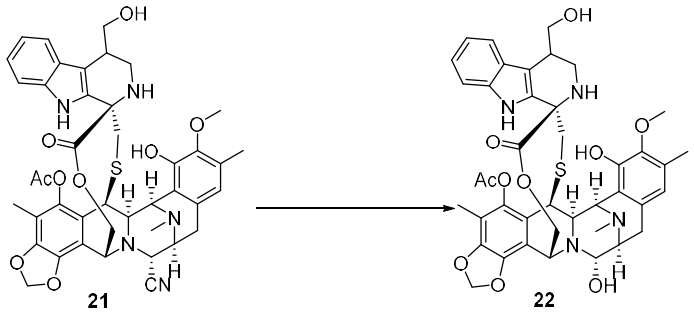


Compound **21** was synthesized by a method analogous to that described in Example 1.

MS m/z (ESI): 794.3 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.07 (s, 1H), 8.77 (s, 1H), 7.42 (d, J = 7.9 Hz, 1H), 7.33 (d, J = 8.1 Hz, 1H), 7.00 (t, J = 7.5 Hz, 1H), 6.89 (t, J = 7.5 Hz, 1H), 6.48 (s, 1H), 6.23 (d, J = 19.4 Hz, 2H), 5.11 (d, J = 11.6 Hz, 1H), 4.69 (s, 1H), 4.51 – 4.37 (m, 2H), 4.20 (d, J = 4.6 Hz, 1H), 4.14 (d, J = 11.7 Hz, 1H), 4.09 (s, 1H), 3.82 (d, J = 9.8 Hz, 2H), 3.66 (s, 3H), 2.98 – 2.92 (m, 1H), 2.82 – 2.71 (m, 5H), 2.67 (s, 1H), 2.33 (d, J = 4.6 Hz, 1H), 2.27 (d, J = 7.2 Hz, 6H), 2.06 (s, 3H), 2.00 – 1.98 (m, 1H), 1.96 (s, 3H).

Example 12: Synthesis of compound **22**

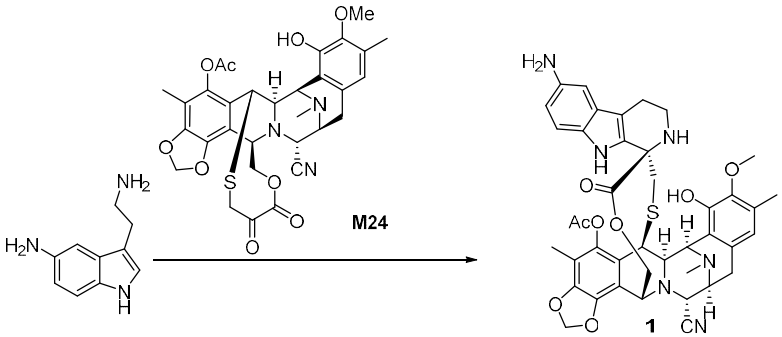


Compound **22** was synthesized by a method analogous to that described in Example 2.

MS m/z (ESI): 785.4 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.05 (d, J = 8.8 Hz, 1H), 8.65 (s, 1H), 7.56 – 7.19 (m, 2H), 6.99 – 6.90 (m, 2H), 6.48 (s, 1H), 6.23 (d, J = 7.0 Hz, 1H), 6.13 (s, 1H), 5.04 (dd, J = 22.9, 11.4 Hz, 1H), 4.68 (d, J = 13.7 Hz, 1H), 4.35 – 4.30 (m, 2H), 4.12 – 4.09 (m, 2H), 3.83 – 3.81 (m, 1H), 3.66 (s, 3H), 3.64 – 3.51 (m, 2H), 3.11 – 2.99 (m, 4H), 2.78 – 2.69 (m, 4H), 2.29 (s, 3H), 2.27(s, 3H), 2.07 – 2.03 (m, 4H), 1.96 – 1.92 (m, 4H).

Example 13: Synthesis of compound **1**

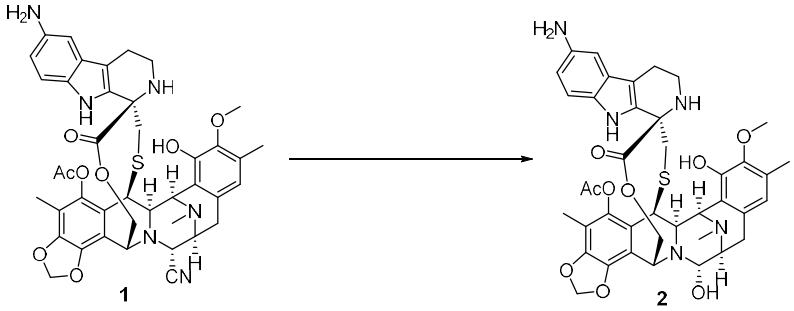


Compound **1** was synthesized by a method analogous to that described in Example 1.

MS m/z (ESI): 779.4 $[M+H]^+$.

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.62 (s, 1H), 8.80 (s, 1H), 7.03 (d, J = 8.6 Hz, 1H), 6.52 – 6.46 (m, 2H), 6.42 (dd, J = 8.6, 2.1 Hz, 1H), 6.23 (d, J = 7.8 Hz, 2H), 5.34 (t, J = 4.7 Hz, 1H), 5.07 (d, J = 11.2 Hz, 1H), 4.47 (d, J = 2.7 Hz, 2H), 4.22 – 4.19 (m, 1H), 4.10 (s, 1H), 4.07 (s, 2H), 3.67 (s, 3H), 3.21 – 3.08 (m, 2H), 2.85 – 2.69 (m, 6H), 2.36 – 2.33 (m, 2H), 2.30 (s, 3H), 2.27 (s, 3H), 2.06 (s, 3H), 2.04 – 2.02 (s, 1H), 1.99 (s, 3H).

Example 14: Synthesis of compound **2**

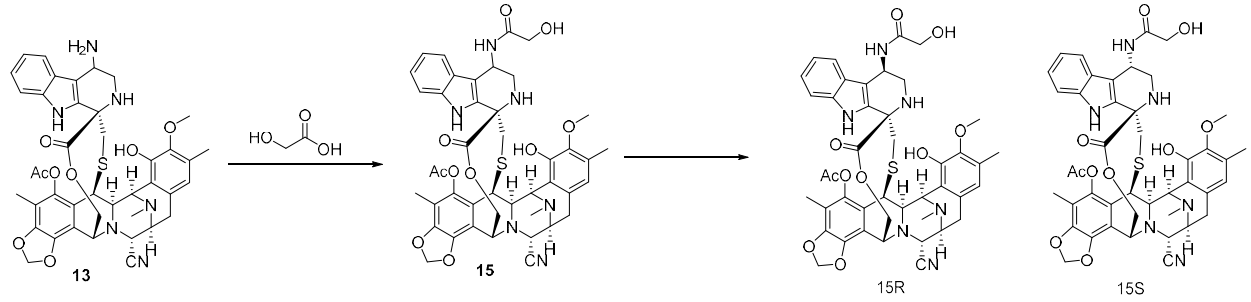


Compound **2** was synthesized by a method analogous to that described in Example 2.

MS m/z (ESI): 770.4 $[M+H]^+$.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.03 (s, 1H), 6.68 (s, 2H), 6.56 (d, J = 8.8 Hz, 1H), 6.19 (s, 1H), 5.99 (s, 1H), 5.34 – 5.28 (m, 2H), 5.19 (d, J = 11.5 Hz, 1H), 4.89 – 4.84 (m, 1H), 4.52 – 4.50 (m, 2H), 4.22 – 4.08 (m, 2H), 3.82 (s, 3H), 3.23 – 3.08 (m, 2H), 2.92 – 2.42 (m, 6H), 2.37 (s, 3H), 2.26 – 2.22 (m, 7H), 2.05 (s, 3H), 2.04 – 2.02 (m, 1H).

Example 15: Synthesis of compounds **15, 15R, and 15S**



Compound **13** (50 mg, 0.064 mmol) was dissolved in DMF (1.5 mL), followed by sequential addition of glycolic acid (5.8 mg, 0.077 mol), HATU (29.4 mg, 0.077 mmol), and DIEA (16.5 mg, 0.128 mmol). The reaction mixture was stirred at room temperature for 2 h, and completion of the reaction was monitored by LCMS. Ethyl acetate and saturated aqueous sodium bicarbonate were added, the mixture was stirred and

then separated. The organic layer was dried over anhydrous sodium sulfate, concentrated under reduced pressure, and the residue was purified by preparative TLC to afford compound **15** (40 mg, 75% yield).

Compound 15:

MS m/z (ESI): 837.2 $[M+H]^+$

Compound 15 was further purified by reversed-phase medium-pressure preparative chromatography under the following conditions:

Column: Agela technologies C18, 20-35 uM, 100 A, 120 g

Mobile phase: Purified Water (0.1% formic acid)/acetonitrile

Gradient: 100% purified water to 100% acetonitrile; product eluted at 50% acetonitrile

Peaks 1 and 2 exhibited retention times of 1.651 min and 1.587 min, respectively, on LCMS.

Characterization of the first peak (1.651 min): 15R or 15S (15 mg, 28% yield):

MS m/z (ESI): 837.2 $[M+H]^+$

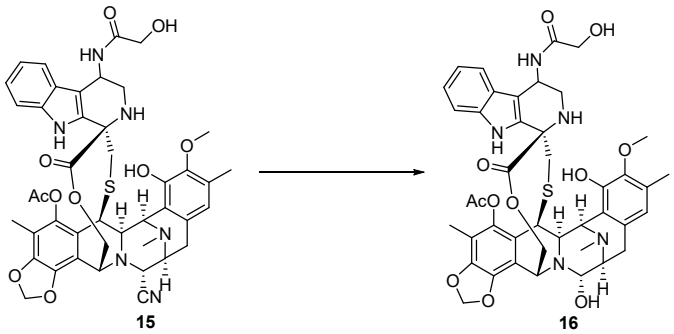
^{1}H NMR (400 MHz, DMSO) δ 10.49 (s, 1H), 8.82 (s, 1H), 7.43 (d, J = 6.4 Hz, 1H), 7.34 (d, J = 6.4 Hz, 1H), 7.29 (d, J = 8.8 Hz, 1H), 7.04 (t, J = 6.4 Hz, 1H), 6.92 (t, J = 6.4 Hz, 1H), 6.49 (s, 1H), 6.24 (d, J = 16.8 Hz, 2H), 5.43 (t, J = 5.6 Hz, 1H), 5.10-5.07 (m, 1H), 4.98-4.96 (m, 1H), 4.48-4.47 (m, 2H), 4.21-4.20 (m, 1H), 4.08-4.05 (m, 3H), 3.81-3.68 (m, 2H), 3.65 (s, 3H), 3.45-3.42 (m, 1H), 3.38-3.35 (m, 1H), 3.23-3.19 (m, 1H), 2.90-2.78 (m, 2H), 2.76-2.72 (m, 1H), 2.69-2.66 (m, 2H), 2.31 (s, 3H), 2.23 (s, 3H), 2.06 (s, 3H), 1.99 (s, 3H), 1.98-1.96 (m, 1H), 1.85-1.83 (m, 1H).

Characterization of the second peak (1.587 min): 15R or 15S (12 mg, 22.6% yield):

MS m/z (ESI): 837.2 $[M+H]^+$

^{1}H NMR (400 MHz, DMSO) δ 10.39 (s, 1H), 8.81 (s, 1H), 7.50 (d, J = 6.4 Hz, 1H), 7.36 (d, J = 6.4 Hz, 1H), 7.30 (d, J = 8.8 Hz, 1H), 7.04 (t, J = 6.4 Hz, 1H), 6.90 (t, J = 6.4 Hz, 1H), 6.48 (s, 1H), 6.24 (d, J = 16.8 Hz, 2H), 5.39 (t, J = 5.6 Hz, 1H), 5.13-5.10 (m, 1H), 4.97-4.92 (m, 1H), 4.48-4.47 (m, 2H), 4.21-4.20 (m, 1H), 4.14-4.09 (m, 2H), 3.86-3.85 (m, 2H), 3.65 (s, 3H), 3.40-3.38 (m, 1H), 3.21-3.20 (m, 1H), 2.95-2.76 (m, 4H), 2.63-2.59 (m, 1H), 2.30 (s, 3H), 2.24 (s, 3H), 2.06 (s, 3H), 2.05-2.02 (m, 1H), 1.98 (s, 3H), 1.93-1.82 (m, 1H).

Example 16: Synthesis of compound **16**

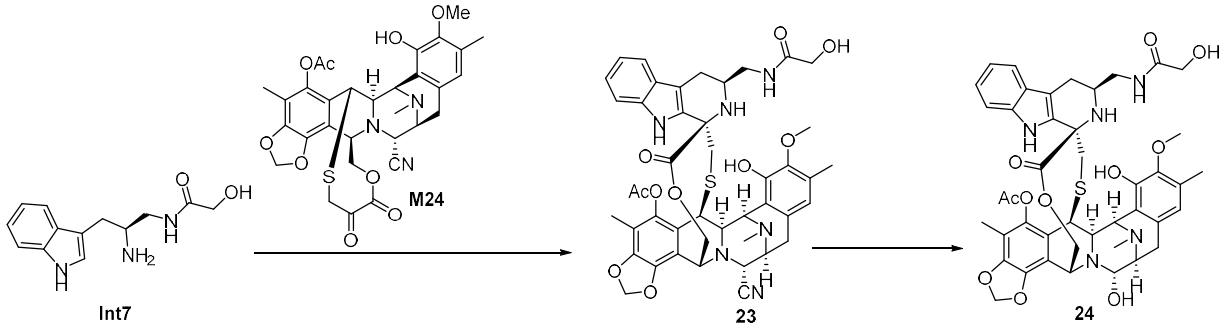


Compound **16** was synthesized by a method analogous to that described in Example 2.

MS m/z (ESI): 828.7 $[M+H]^+$

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, *J* = 24.5 Hz, 1H), 7.61-7.43 (m, 1H), 7.30 (s, 1H), 7.14 (t, *J* = 7.7 Hz, 1H), 7.09-6.97 (m, 1H), 6.88 (s, 1H), 6.64 (s, 1H), 6.23 (d, *J* = 3.2 Hz, 1H), 6.01 (s, 1H), 5.97-5.64 (m, 1H), 5.46-5.08 (m, 3H), 4.94 (s, 1H), 4.70-4.44 (m, 2H), 4.29-4.03 (m, 4H), 3.92-3.79 (m, 5H), 3.53-3.40 (m, 2H), 2.94-2.67 (m, 4H), 2.58-2.16 (m, 9H), 2.18-1.94 (m, 5H).

Example 17: Synthesis of compounds **23 and 24**



Step 1: Synthesis of compound 23

Compound **M24** (50 mg, 0.08 mmol) and compound **Int7** (40 mg, 0.16 mmol) were dissolved in anhydrous ethanol (1 mL) and acetic acid (2 mL), followed by addition of sodium acetate (7.38 mg, 0.09 mmol). The mixture was stirred overnight at 60 ° C. After LCMS indicated complete conversion, the reaction mixture was cooled to room temperature. Ethyl acetate and saturated aqueous sodium bicarbonate were added, the mixture was stirred and then separated. The organic phase was separated and dried over anhydrous sodium sulfate, concentrated under reduced pressure, and the residue was purified by reversed-phase preparative HPLC to afford compound **23** (37 mg, 55% yield).

MS m/z (ESI): 851.2 $[M+H]^+$

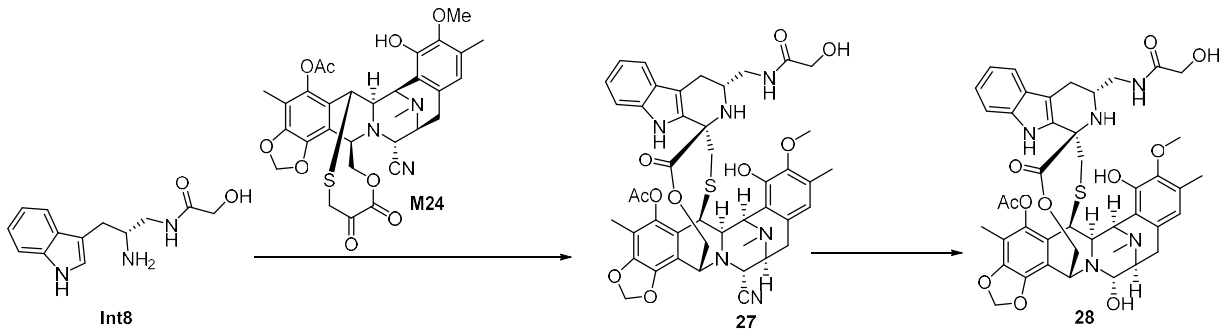
^{1}H NMR (400 MHz, DMSO-d_6) δ 9.92 (s, 1H), 8.77 (s, 1H), 7.74 (t, J = 5.6 Hz, 1H), 7.36 – 7.25 (m, 2H), 7.02 (t, J = 7.6 Hz, 1H), 6.91 (t, J = 7.4 Hz, 1H), 6.47 (s, 1H), 6.29 – 6.20 (m, 2H), 5.58 (t, J = 5.7 Hz, 1H), 5.17 (d, J = 10.8 Hz, 1H), 4.60 – 4.43 (m, 2H), 4.30 – 4.18 (m, 2H), 4.15 (s, 1H), 3.90 – 3.84 (m, 2H), 3.69 (s, 3H), 3.46 – 3.39 (m, 2H), 3.26 – 3.19 (m, 2H), 3.00 – 2.88 (m, 1H), 2.85 – 2.70 (m, 3H), 2.42 – 2.34 (m, 1H), 2.29 (s, 3H), 2.24 – 2.14 (m, 5H), 2.01 (s, 3H), 1.95 (s, 3H), 1.86 (s, 1H).

Step 2: Synthesis of compound 24

Compound 24 was synthesized by a method analogous to that described in Example 4.

MS m/z (ESI): 842.2 $[M+H]^+$

Example 18: Synthesis of compounds **27 and 28**



Compounds 27 and 28 were synthesized by methods analogous to those described in Examples 2 and 3, respectively.

Compound **27**:

MS m/z (ESI): 851.2 $[M+H]^+$

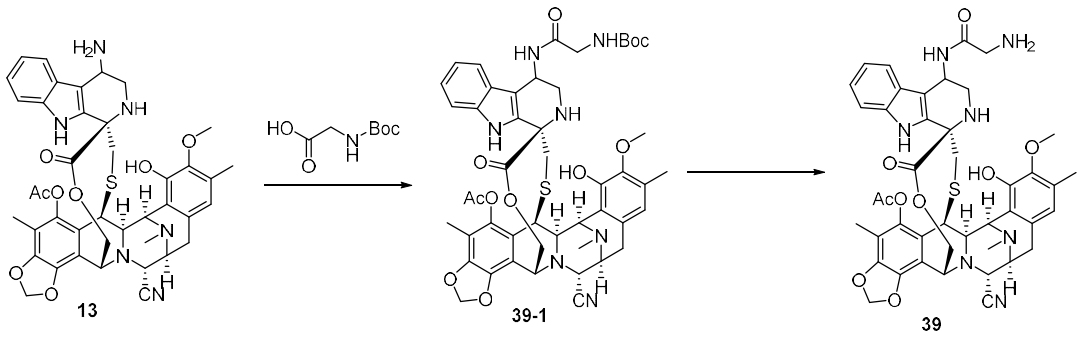
^{1}H NMR (400 MHz, DMSO-d_6) δ 10.16 (s, 1H), 8.77 (s, 1H), 7.60 – 7.50 (m, 1H), 7.40 – 7.25 (m, 2H), 7.03 (t, J = 7.6 Hz, 1H), 6.91 (t, J = 7.8 Hz, 1H), 6.53 (s, 1H), 6.25 (d, J = 11.4 Hz, 2H), 5.55 (t, J = 5.5 Hz, 1H), 5.08 (d, J = 11.0 Hz, 1H), 4.60 – 4.43 (m, 2H), 4.20 (d, J = 3.9 Hz, 1H), 4.15 – 4.04 (m, 2H), 3.87 (d, J = 5.5 Hz, 2H), 3.69 – 3.56 (m, 4H), 3.46 – 3.40 (m, 1H), 3.25 – 3.15 (m, 1H), 3.05 – 2.93 (m, 1H), 2.95 – 2.80 (m, 2H), 2.63 – 2.57 (m, 1H), 2.40 – 2.28 (m, 4H), 2.19 (s, 3H), 2.15 – 2.05 (m, 2H), 2.04 – 1.99 (m, 7H), 1.81 (s, 1H).

Compound 28:

MS m/z (ESI): 842.2 $[M+H]^+$

^{1}H NMR (400 MHz, $CDCl_3$) δ 12.52 (s, 1H), 7.66-7.52 (m, 1H), 7.35-7.26 (m, 2H), 7.18-6.97 (m, 2H), 6.75 (s, 2H), 6.25 (s, 1H), 6.07-6.01 (m, 2H), 5.15 (d, *J* = 11.5 Hz, 2H), 4.90-4.89 (m, 2H), 4.65 (s, 1H), 4.33 (s, 1H), 4.17-4.09 (m, 4H), 3.97-3.83 (m, 6H), 3.51-3.50 (m, 2H), 3.18-3.14 (m, 2H), 2.65-2.58 (m, 4H), 2.38-2.35 (m, 4H), 2.31-2.14 (m, 4H), 2.08 (s, 3H), 2.02 (m, 1H).

Example 19: Synthesis of compound **39**



Step 1: Preparation of compound **39-1**

To a solution of compound 13 (95 mg, 0.12 μmol) in DMF (2 mL) were added Boc-glycine (64 mg, 0.36 μmol), HATU (45.6 mg, 0.12 μmol), and HOAt (27.2 mg, 0.12 μmol). The mixture was stirred at room temperature, followed by addition of TMP (43.6 mg, 0.36 μmol). The reaction mixture was stirred at room temperature for one hour. The reaction mixture was directly purified by reversed-phase preparative chromatography and lyophilized to afford compound **39-1** (65 mg, 58.0% yield).

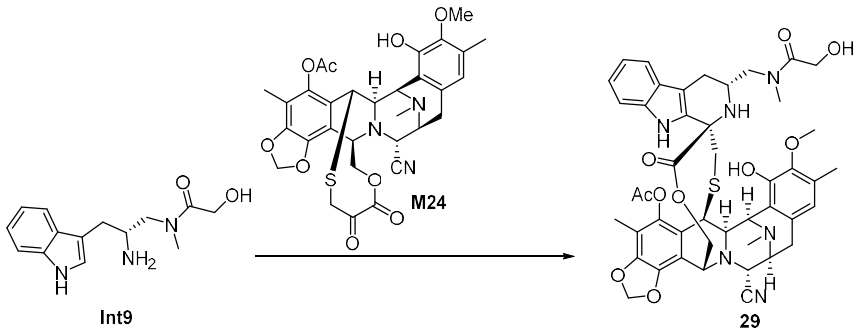
Step 2: Preparation of compound **39**

To a solution of 39-1 (60 mg, 0.06 mmol) in $MeNO_2$ (1.0 mL) was added $ZnBr_2$ (40.53 mg, 0.18 mmol) at room temperature. The reaction mixture was stirred at room temperature for 3 hours and then concentrated. The reaction mixture was purified by reversed-phase HPLC and lyophilized to afford compound **39** as a white solid (45 mg, 84.9% yield).

MS m/z (ESI): 836.2 $[M+H]^+$

^{1}HNMR (400 MHz, DMSO-d_6) δ 10.49 – 10.37 (m, 1H), 8.82 (s, 1H), 8.33 (s, 1H), 8.07 – 7.89 (m, 1H), 7.49 – 7.26 (m, 2H), 7.04 (t, J = 7.6 Hz, 1H), 6.95 – 6.85 (m, 1H), 6.48 (d, J = 5.0 Hz, 1H), 6.36 – 6.17 (m, 2H), 5.17 – 5.01 (m, 1H), 4.94 (s, 1H), 4.48 (s, 2H), 4.20 (s, 1H), 4.13 – 4.01 (m, 2H), 3.65 (s, 3H), 3.21 (s, 3H), 3.10 (s, 1H), 3.00 – 2.60 (m, 5H), 2.36 – 2.26 (m, 3H), 2.26 – 2.20 (m, 3H), 2.12 – 2.07 (m, 1H), 2.08 – 2.02 (m, 3H), 2.02 – 1.95 (m, 3H), 1.94 – 1.75 (m, 2H).

Example 20: Synthesis of compound **29**

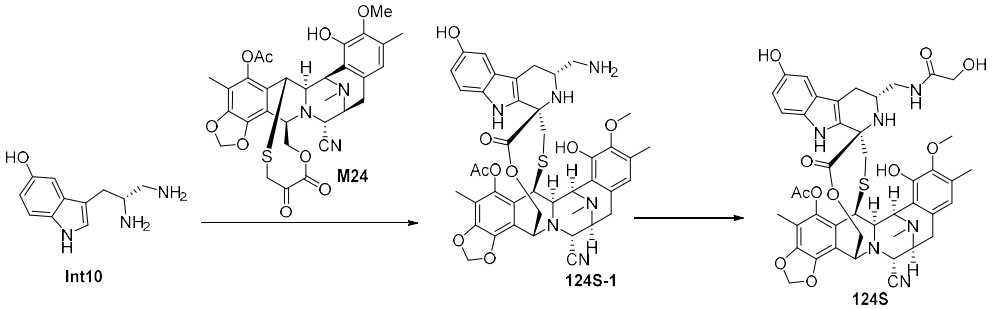


Compound **M24** (150 mg, 0.24 mmol) and compound **Int9** (213 mg, 0.7 mmol) were dissolved in anhydrous ethanol (4 mL) and acetic acid (4 mL), and the mixture was stirred overnight at 70 ° C. After LCMS indicated complete conversion, the reaction mixture was cooled to room temperature. Ethyl acetate and saturated aqueous sodium bicarbonate were added, the mixture was stirred and then separated. The organic layer was dried over anhydrous sodium sulfate, concentrated under reduced pressure, and the residue was purified by reversed-phase HPLC to afford compound **29** (18 mg, 8.6% yield).

MS m/z (ESI): 865.3 $[M+H]^+$

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, *J* = 12.4 Hz, 1H), 7.30 (t, *J* = 7.3 Hz, 1H), 7.27 – 7.20 (m, 1H), 7.10 – 7.01 (m, 1H), 6.96 (q, *J* = 8.0 Hz, 1H), 6.49 (d, *J* = 22.3 Hz, 1H), 6.17 (dd, *J* = 2.8, 1.3 Hz, 1H), 5.96 (d, *J* = 1.2 Hz, 1H), 5.71 (d, *J* = 3.2 Hz, 1H), 4.96 (d, *J* = 11.7 Hz, 1H), 4.57 (s, 1H), 4.31 (d, *J* = 4.8 Hz, 1H), 4.26 – 4.18 (m, 2H), 4.16 (d, *J* = 2.7 Hz, 2H), 4.13 – 4.06 (m, 1H), 3.74 (d, *J* = 1.0 Hz, 3H), 3.66 – 3.54 (m, 2H), 3.44 (s, 1H), 3.40 (d, *J* = 5.1 Hz, 3H), 3.09 (s, 1H), 3.07 – 2.94 (m, 1H), 2.93 (s, 3H), 2.54 (ddd, *J* = 31.3, 14.7, 3.1 Hz, 1H), 2.43 – 2.33 (m, 1H), 2.25 (s, 3H), 2.19 (s, 3H), 2.10 (d, *J* = 1.3 Hz, 5H), 2.02 (s, 3H).

Example 21: Synthesis of compound **124S**



Step 1: Preparation of compound **124S-1**

Compound **M24** (100 mg, 0.16 mmol), compound **Int10** (65 mg, 0.32 mmol), and sodium acetate (138 mg, 1.60 mmol) were dissolved in acetic acid (4 mL). The reaction mixture was stirred at 65 ° C for 2

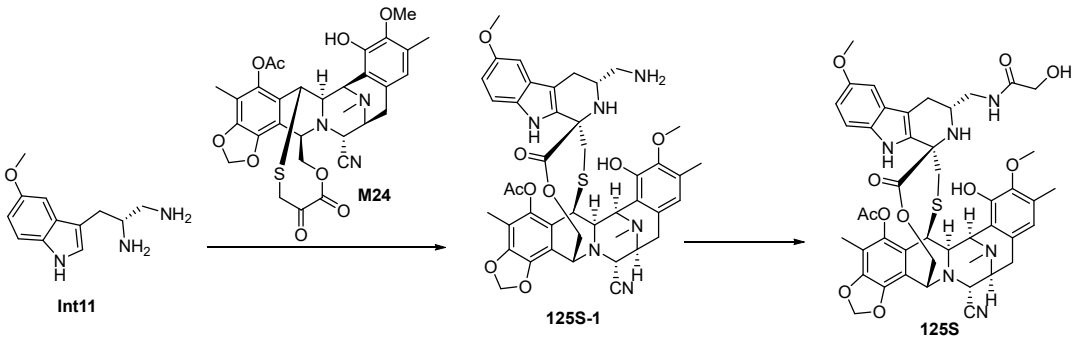
hours. The solution was concentrated, and the crude residue was diluted with ethyl acetate and water. The pH was adjusted to 9 with saturated aqueous sodium bicarbonate. The aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over anhydrous sodium sulfate, filtered, concentrated, and purified by silica gel column chromatography to afford compound **124S-1** (72 mg, 60% yield).

Step 2: Preparation of compound **124S**

Compound **124-1** (27 mg, 0.033 mmol) was dissolved in DMF (1.5 mL), followed by sequential addition of glycolic acid (3.0 mg, 0.039 mol), HATU (14.9 mg, 0.039 mmol), and DIEA (11.6 mg, 0.090 mmol). The reaction mixture was stirred at room temperature for 2 h, and completion of the reaction was monitored by LCMS. Ethyl acetate and saturated aqueous sodium bicarbonate were added, the mixture was stirred and then separated. The organic layer was separated and dried over anhydrous sodium sulfate, concentrated under reduced pressure, and the residue was purified by reversed-phase preparative HPLC to afford compound **124S** (10 mg, 35% yield).

MS m/z (ESI): 867.5 $[M+H]^+$

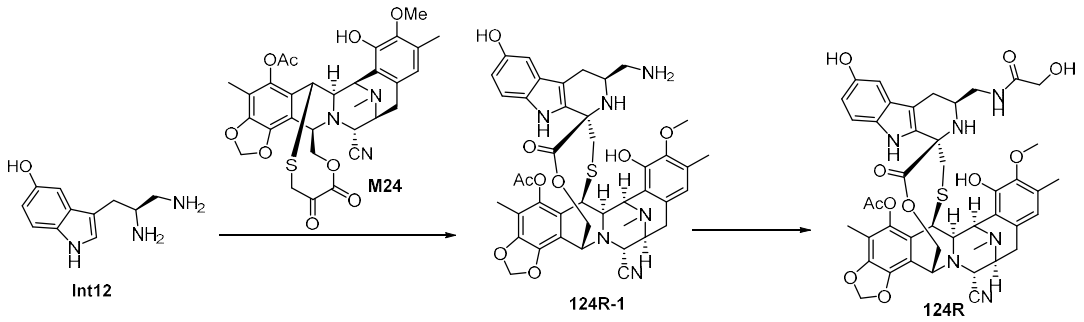
Example 22: Synthesis of compound **125S**



Compound **125S** was synthesized by the method described in Example 21.

MS m/z (ESI): 881.4 $[M+H]^+$

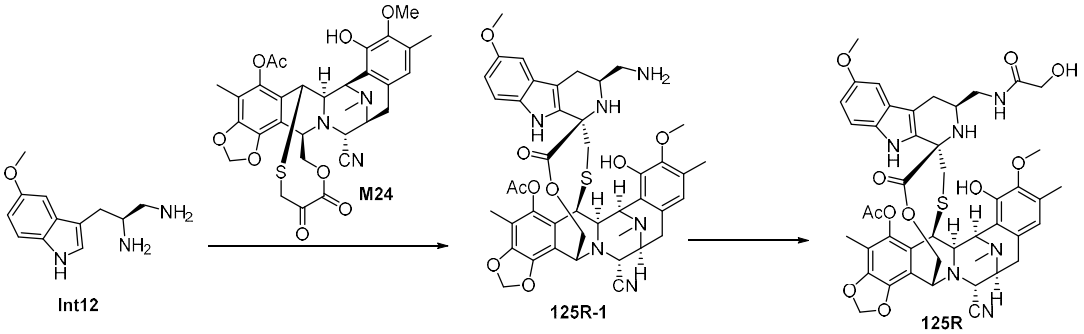
Example 23: Synthesis of compound **124R**



Compound **124R** was synthesized by the method described in Example 21.

MS m/z (ESI): 867.5 $[M+H]^+$

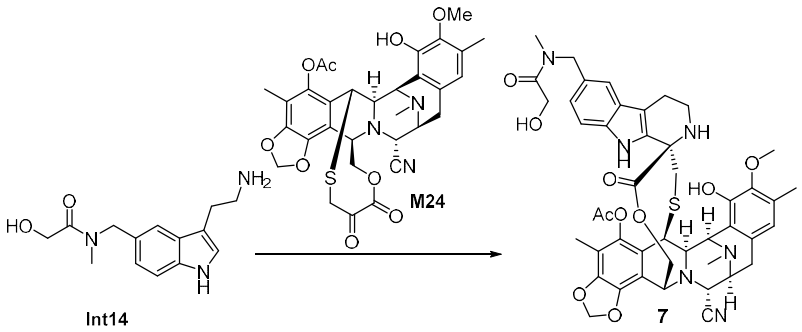
Example 24: Synthesis of compound **125R**



Compound **125R** was synthesized by the method described in Example 21.

MS m/z (ESI): 881.4 $[M+H]^+$

Example 25: Synthesis of compound **7**



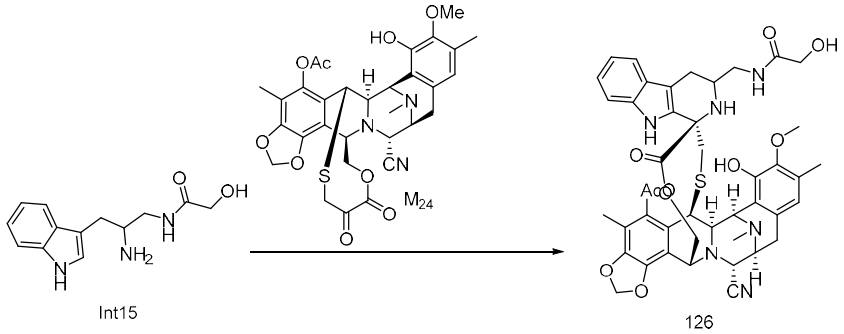
Compound Int14 (180 mg, 0.43 mmol) was dissolved in trifluoroethanol (2 mL), and M24 (89 mg, 0.14 mmol) was added. The mixture was stirred at 60 ° C for 2 h. After LCMS indicated complete conversion,

the reaction mixture was subjected to reversed-phase preparative HPLC, and the collected fractions were lyophilized to afford compound 7 (38.79 mg, 33% yield).

MS m/z (ESI): 865.4 $[M+H]^+$

^1H NMR (400 MHz, $CDCl_3$) δ 10.19 (d, *J* = 14.8 Hz, 1H), 8.76 (s, 1H), 7.28 – 7.34 (m, 1H), 7.19 (d, *J* = 15.6, 1H), 6.89 – 6.93 (m, 1H), 6.49 (s, 1H), 6.24 (d, *J* = 15.2, 2H), 5.08 (d, *J* = 10.8, 1H), 4.52 (s, 1H), 4.46 (d, *J* = 12.8, 3H), 4.17 – 4.21 (m, 2H), 4.08 (d, *J* = 11.2 Hz, 3H), 3.66 (s, 3H), 3.12 – 3.20 (m, 4H), 2.62 – 2.90 (m, 9H), 2.39 – 2.47 (m, 1H), 2.28 (d, *J* = 12.4 Hz, 6H), 2.06 (s, 4H), 1.99 (s, 3H)

Example 26: Synthesis of compound 126



Compound 126 was synthesized by a method analogous to that described in Example 3.

MS m/z (ESI): 865.3 $[M+H]^+$

Efficacy Test Example 1: In Vitro Antiproliferative Activity of Compounds Against Tumor Cells

Test Objective

To evaluate the inhibitory activity on in vitro proliferation of the drug compound against NCI-H82, SKOV-3, OVCAR-3, NCI-H1781, MKN-45, LS174T, and BT474 tumor cells. Cells were treated in vitro with the compound at various concentrations. After 6 days of incubation, cell proliferation was assessed using the CTG reagent (CellTiter-Glo® Luminescent Cell Viability Assay, Promega, Cat. No.: G7558). The in vitro activity of the compound was evaluated based on its IC_{50} value.

Experimental Methods

The following describes the method for testing the inhibitory activity on in vitro proliferation of NCI-H82 cells as an example to illustrate the method used in this application for evaluating the inhibitory activity on in vitro proliferation of the claimed compounds against tumor cells. This method is also applicable, but not limited, to testing the inhibitory activity on in vitro proliferation of other tumor cells.

1. Cell culture: NCI-H82 cells were cultured in RPMI-1640 medium supplemented with 10% FBS.

2. Cell preparation: Logarithmically growing NCI-H82 cells were washed once with PBS, followed by digestion with 2 – 3 mL trypsin for 2 – 3 min. After complete digestion, 10 – 15 mL of culture medium was added to resuspend the digested cells. The cell suspension was centrifuged at 1000 rpm for 5 min, the supernatant was discarded, and the cells were resuspended in 10 – 20 mL of culture medium to prepare a single-cell suspension.

3. Cell plating: The NCI-H82 single-cell suspension was mixed thoroughly, and viable cell density was adjusted to 6×10^4 cells/mL using culture medium. The adjusted cell suspension was mixed again and seeded into 96-well cell culture plates at 50 μL per well. The plates were incubated in an incubator for 18 hours (37° C, 5% CO_2).

4. Compound preparation: The compound was dissolved in DMSO to prepare a stock solution with an initial concentration of 10 mM. Nine concentrations of the small-molecule compound were tested, with the highest concentration being 1 μM and serial 3-fold dilutions.

5. Sample addition: Different concentrations of test samples were added to the culture plates, with each sample tested in duplicate wells. The plates were incubated in an incubator for 6 days (37 °C, 5% CO_2).

6. Color development procedure: The 96-well cell culture plates were removed, and 50 μL of CTG reagent was added to each well, followed by incubation at room temperature for 10 minutes.

7. Plate reading: The 96-well cell culture plates were removed and placed into a microplate reader to measure chemiluminescence.

Data analysis: Data were processed and analyzed using Microsoft Excel and GraphPad Prism 5.

Table 1. IC_{50} values of the compounds disclosed herein for inhibitory activity on in vitro proliferation of the indicated cells

Compound No.	NCI-H82	SKOV-3	OVCAR-3	NCI-H1781	MKN-45	LS174T	BT474
	IC_{50} (nM)						
lurbinectedin	0.19	1.01	0.68	0.38	0.63	0.72	2.81
Compound 1	0.12	0.55	0.24	/	/	/	1.08
Compound 2	0.21	0.85	0.38	0.36	0.46	0.77	/
Compound 3	0.12	0.7	0.26	/	/	/	/
Compound 7	/	/	/	/	/	/	1.00
Compound 15	/	0.62	/	/	/	0.49	1.12
Compound 15R or 15S Peak 1	/	0.46	/	/	/	0.43	1.11

Compound 15R or 15S Peak 2	/	0.64	/	/	/	0.51	1.15
Compound 17	/	0.93	/	/	/	/	/
Compound 18	/	0.83	/	/	/	/	/
Compound 23	/	/	/	/	/	/	2.66
Compound 25	0.07	0.31	0.24	0.11	0.22	0.24	1.16
Compound 27	/	0.98	0.02	/	0.58	0.43	0.98
Compound 29	/	/	/	/	/	/	0.30

Conclusion: According to the results in Table 1, the compounds disclosed herein exhibit superior inhibitory activity on proliferation against at least one of the tumor cell lines—NCI-H82, SKOV-3, OVCAR-3, NCI-H1781, MKN-45, LS174T, or BT474—compared to the reference compound lurbinectedin.

Efficacy Test Example 2: Toxicological Study of Different Compounds Administered Intravenously to SD Rats

Objective

Three test articles were administered once intravenously to Sprague-Dawley rats to observe acute toxic responses induced by the three test articles in SD rats, thereby comparing their toxic effects and providing data support for subsequent safety evaluation.

Dose:

Group	**Compound**	**Test sample**					**Number of animals**	
		First dose (mg/kg)	**Concentration of first dose (mg/mL)**	***Second dose (mg/kg)***	***Concentration of second dose (mg/mL)***	**Administration volume (mL/kg)**	**Female**	**Male**
G1	Compound 26	0.04	0.008	***0.3***	***0.06***	5	3	3
G2	Compound 26	0.1	0.02	***0.1***	***0.02***	5	3	3
G3	Compound 25	0.04	0.008	***0.3***	***0.06***	5	3	3
G4	Compound 25	0.1	0.02	***0.1***	***0.02***	5	3	3
G5	lurbinectedin	0.04	0.008	***0.3***	***0.06***	5	3	3
G6	lurbinectedin	0.1	0.02	***0.1***	***0.02***	5	3	3
First dose on D1; second dose on D9								

Observation: Sprague-Dawley (SD) rats administered a single intravenous dose of 0.04 mg/kg or 0.1 mg/kg of Compound 26, Compound 25, or lurbinectedin showed no obvious signs of toxicity. Nine days later, rats in groups G1, G3, and G5 were injected with 0.3 mg/kg of Compound 26, Compound 25, or lurbinectedin, respectively, and all exhibited body weight loss. Rats in the Compound 25 and Compound 26 groups gradually recovered starting from day 2 or 3 post-dosing, whereas those in the lurbinectedin group showed further significant weight loss. In the lurbinectedin group, both male and female rats exhibited perianal soiling due to loose stools; additionally, female rats displayed piloerection, hunched posture, reduced activity, and reddish secretions around the eyes and nose. No obvious clinical signs were observed in the other dosing groups. Furthermore, all female rats in the lurbinectedin group (G5) died on day 18, while rats in all other groups survived. Clinical pathology results showed that serum ALT, AST, GGT, and DBIL levels increased following administration of both Compound 26 and lurbinectedin, with more pronounced changes observed in the lurbinectedin group. In hematology, the lurbinectedin group exhibited marked decreases in EO and PLT, whereas no significant changes in these parameters were observed in the Compound 26 group. No significant abnormalities were observed in either serum tests or routine blood tests following administration of Compound 25. Nine days later, Compound 26, Compound 25, or lurbinectedin was administered again at 0.1 mg/kg to groups G2, G4, and G6, respectively, and no obvious toxic reactions were observed. Experimental results are shown in Figures 1 – 3.

Conclusion: At 0.3 mpk, Compound 25 and Compound 26 demonstrated good tolerability in SD rats, with significantly better toxicity profiles than lurbinectedin.

Efficacy Test Example 3: Toxicological study of different compounds administered intravenously to SD rats

Objective

Seven test articles were administered as a single intravenous dose to Sprague-Dawley rats to observe acute toxic responses and compare their toxicological profiles, thereby providing data to support subsequent safety evaluations.

Dose:

Group	**Compound**	**Test sample**			**Number of animals**	
		Dosage (mg/kg)	**Drug concentration (mg/mL)**	**Administration volume (mL/kg)**	**Female**	**Male**
G1	Compound 1	2.4	0.48	5	3	3
G2	Compound 15R or 15S (peak 1)	2.4	0.48	5	3	3
G3	Compound 15R or 15S (peak 2)	2.4	0.48	5	3	3

G4	Compound 23	2.4	0.48	5	3	3
G5	Compound 27	2.4	0.48	5	3	3
G6	lurbinectedin	0.3	0.06	5	3	3

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Observation: Sprague-Dawley (SD) rats received a single intravenous dose of Compound 1, Compound 15, Compound 23, Compound 27, or lurbinectedin, respectively. In group G6, both male and female rats exhibited perianal soiling due to loose stools; female rats also showed piloerection, hunched posture, reduced activity, and reddish secretions around the eyes and nose. No obvious clinical signs were observed in the other dosing groups. Additionally, all female rats in group G6 died on day 5, and one male rat died; all animals in the remaining groups survived until the scheduled necropsy date.

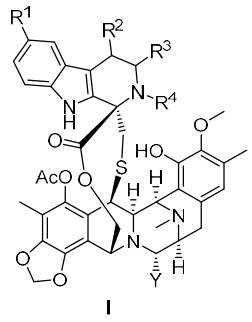
On Day 3, serum biochemistry showed markedly elevated CK in group G4; in group G5, CK, ALT, and AST were markedly elevated but returned to normal by Day 7; in group G6, serum ALT, AST, GGT, and DBIL were elevated, and hematology revealed decreased RET, WBC, LYMPH, MONO, EO, and PLT.

Conclusion: At 2.4 mpk, Compound 1, Compound 15R, Compound 15S, Compound 23, and Compound 27 demonstrated good tolerability in SD rats, with significantly better toxicity profiles than lurbinectedin.

The above examples do not limit the scope of the present application in any manner. In addition to those described herein, various modifications of the application will be apparent to those skilled in the art based on the foregoing description. Such modifications are also intended to fall within the scope of the appended claims. All references cited herein (including all patents, patent applications, journal articles, books, and any other disclosures) are incorporated herein by reference in their entirety.

Claims

1. A compound of formula (I), or a pharmaceutically acceptable salt, ester, stereoisomer, tautomer, polymorph, solvate, isotope-labeled compound, metabolite, or prodrug thereof:



I

wherein,

R^1 is hydrogen, deuterium, halogen, -OH, -CN, -NH_2, C_{1-6} alkyl, -OC_{1-6} alkyl, -NHC_{1-6} alkyl, -NH-S(O)$_2$-R^{1-2}, -C(O)R^{1-2}, C(O)-N(R^{1-1})R^{1-2}, -C_{1-6} alkylene-N(R^{1-1})-C(O)R^{1-2}, -O-C_{3-12} cycloalkyl, -O-(4 to 12-membered heterocycloalkylene)-C(O)R^{1-2}, -O-C_{3-12} cycloalkylene-N(R^{1-1})-C(O)R^{1-2}, -O-C(O)-N(R^{1-1})R^{1-2}, -N(R^{1-1})-C(O)R^{1-2}, -N(R^{1-1})-C(O)-OR^{1-2}, -N(R^{1-1})-(4 to 12-membered heterocycloalkylene)-C(O)R^{1-2}, -N(R^{1-1})-C_{3-12} cycloalkylene-N(R^{1-3})-C(O)R^{1-2}, -(4 to 12-membered heterocycloalkylene)-C(O)R^{1-2}, -(4 to 12-membered heterocycloalkylene)-N(R^{1-1})-C(O)R^{1-2}, -N(R^{1-1})C(O)C_{3-12} cycloalkyl, (4 to 12-membered heterocycloalkylene), or -N(R^{1-1})C(O)(4 to 12-membered heterocycloalkyl), wherein said C_{1-6} alkyl, C_{1-6} alkylene, C_{3-12} cycloalkyl, C_{3-12} cycloalkylene, 4 to 12-membered heterocycloalkylene, and 4 to 12-membered heterocycloalkyl are each optionally substituted with one or more substituents selected from halogen, -OH, -SH, -NH_2, -NHC_{1-6} alkyl, -SC_{1-6} alkyl, -C_{1-6} alkylene-OH, -C_{1-6} alkylene-SH, -C_{1-6} alkylene-S(C_{1-6} alkyl), and -C_{1-6} alkylene-NH_2;

R^2 is hydrogen, deuterium, halogen, -C_{1-6} alkyl, -OH, -O-C(O)-N(R^{2-1})R^{2-2}, -C(O)R^{2-2}, C(O)-N(R^{2-1})R^{2-2}, -NH_2, -NHC_{1-6} alkyl, -NHC(O)C_{1-6} alkyl, -N(R^{2-1})-C(O)-OR^{2-2}, -N(R^{2-1})-C(O)-N(R^{2-1})R^{2-2}, -NHC(O)C_{3-12} cycloalkyl, -NHC(O)(4 to 12-membered heterocycloalkyl), -N(C_{1-6} alkyl)C(O)C_{1-6} alkyl, -N(C_{1-6} alkyl)C(O)C_{3-12} cycloalkyl, C(O)(4 to 12-membered heterocycloalkyl), -N(C_{1-6} alkyl)C(O)(4 to 12-membered heterocycloalkyl), or -NH-S(O)$_2$-R^{2-2}, wherein said C_{1-6} alkyl, C_{3-12} cycloalkyl, and 4 to 12-membered heterocycloalkyl are each optionally substituted with one or more substituents selected from halogen, -OH, -O-$NHCH_3$, -SH, -NH_2, -NHC_{1-6} alkyl, and -SC_{1-6} alkyl;

R^3 is hydrogen, deuterium, -C_{1-6} alkyl, -CH_2-NHC_{1-6} alkyl, -CH_2-NHC(O)C_{1-6} alkyl, -CH_2-OC(O)-N$R^{3-1}R^{3-2}$, -CH_2-NR^{3-1}C(O)NR^{3-1}-R^{3-2}, -CH_2-NR^{3-1}C(O)O-R^{3-2}, -CH_2-NHC(O)C_{3-12} cycloalkyl, -CH_2-NHC(O)(4 to 12-membered heterocycloalkyl), -CH_2-N(C_{1-6} alkyl)C(O)C_{1-6} alkyl, -CH_2-N(C_{1-6} alkyl)C(O)C_{3-12} cycloalkyl, -CH_2-N(C_{1-6} alkyl)C(O)(4 to 12-membered heterocycloalkyl), -CH_2NH-S(O)$_2$-

R^{3-2}, $-CH_2-S(O)_2-R^{3-2}$, or $-C(O)R^{3-2}$, wherein said C_{1-6} alkyl, C_{3-12} cycloalkyl, and 4 to 12-membered heterocycloalkyl are each optionally substituted with one or more substituents selected from halogen, cyclopropyl, -OH, $-O-NHCH_3$, -SH, $-NH_2$, $-NHC_{1-6}$ alkyl, and $-SC_{1-6}$ alkyl;

R^4 is hydrogen, deuterium, $-C_{1-6}$ alkyl, $-C(O)C_{1-6}$ alkyl, $-C(O)C_{3-12}$ cycloalkyl, or -C(O)(4 to 12-membered heterocycloalkyl), wherein said C_{1-6} alkyl, C_{3-12} cycloalkyl, and 4 to 12-membered heterocycloalkyl are each optionally substituted with one or more substituents selected from halogen, -OH, -SH, $-NH_2$, $-NHC_{1-6}$ alkyl, and $-SC_{1-6}$ alkyl;

or R^3 and R^4, together with the atoms to which they are attached, form a 5- to 12-membered heterocycloalkyl; said 5- to 12-membered heterocycloalkyl is optionally substituted with one or more substituents selected from halogen, oxo group, -OH, -CN, $-NH_2$, $-NHC_{1-6}$ alkyl, $-N(C_{1-6}$ alkyl$)_2$, $-C_{1-6}$ alkyl, $-C_{1-6}$ alkylene-OH, $-C(O)C_{1-6}$ alkylene-OH, $-C(O)-C_{3-12}$ cycloalkylene-OH, and -C(O)-(4 to 12-membered heterocycloalkylene)-OH;

R^{1-1}, R^{2-1}, and R^{3-1} are each independently hydrogen, deuterium, C_{1-6} alkyl, or halo-C_{1-6} alkyl;

R^{1-2}, R^{2-2}, and R^{3-2} are each independently C_{1-6} alkyl, C_{3-12} cycloalkyl, or 4 to 12-membered heterocycloalkyl; said C_{1-6} alkyl, C_{3-12} cycloalkyl, and 4 to 12-membered heterocycloalkyl are each optionally substituted with one or more substituents independently selected from halogen, -OH, $-O-NHCH_3$, -SH, $-NH_2$, $-NHC_{1-6}$ alkyl, and $-SC_{1-6}$ alkyl;

Y is -OH or -CN.

2. The compound of claim 1, or a pharmaceutically acceptable salt, ester, stereoisomer, tautomer, polymorph, solvate, isotope-labeled compound, metabolite, or prodrug thereof, characterized in that the compound satisfies at least one of the following conditions:

(1) R^1 is deuterium, halogen, -OH, -CN, $-NH_2$, C_{1-6} alkyl, $-NH-S(O)_2-R^{1-2}$, $-C(O)R^{1-2}$, $C(O)-N(R^{1-1})R^{1-2}$, $-C_{1-6}$ alkylene-$N(R^{1-1})-C(O)R^{1-2}$, $-O-C_{3-12}$ cycloalkyl, -O-(4 to 12-membered heterocycloalkylene)-$C(O)R^{1-2}$, $-O-C_{3-12}$ cycloalkylene-$N(R^{1-1})-C(O)R^{1-2}$, $-O-C(O)-N(R^{1-1})R^{1-2}$, $-N(R^{1-1})-C(O)R^{1-2}$, $-N(R^{1-1})-C(O)-OR^{1-2}$, $-N(R^{1-1})$-(4 to 12-membered heterocycloalkylene)-$C(O)R^{1-2}$, $-N(R^{1-1})-C_{3-12}$ cycloalkylene-$N(R^{1-3})-C(O)R^{1-2}$, -(4 to 12-membered heterocycloalkylene)-$C(O)R^{1-2}$, -(4 to 12-membered heterocycloalkylene)-$N(R^{1-1})-C(O)R^{1-2}$, $-N(R^{1-1})C(O)C_{3-12}$ cycloalkyl, (4 to 12-membered heterocycloalkylene), or $-N(R^{1-1})C(O)$(4 to 12-membered heterocycloalkyl), wherein said C_{1-6} alkyl, C_{1-6} alkylene, C_{3-12} cycloalkyl, C_{3-12} cycloalkylene, 4 to 12-membered heterocycloalkylene, and 4 to 12-membered heterocycloalkyl are each optionally substituted with one or more substituents selected from halogen, -OH, -SH, $-NH_2$, $-O-NHCH_3$, $-NHC_{1-6}$ alkyl, $-SC_{1-6}$ alkyl, $-C_{1-6}$ alkylene-OH, $-C_{1-6}$ alkylene-SH, $-C_{1-6}$ alkylene-S(C_{1-6} alkyl), and $-C_{1-6}$ alkylene-NH_2;

(2) R^2 is halogen, $-C_{1-6}$ alkyl, -OH, $-O-C(O)-N(R^{2-1})R^{2-2}$, $-C(O)R^{2-2}$, $C(O)-N(R^{2-1})R^{2-2}$, $-NH_2$, $-NHC_{1-6}$ alkyl, $-NHC(O)C_{1-6}$ alkyl, $-N(R^{2-1})-C(O)-OR^{2-2}$, $-N(R^{2-1})-C(O)-N(R^{2-1})R^{2-2}$, $-NHC(O)C_{3-12}$ cycloalkyl, $-NHC(O)$(4 to 12-membered heterocycloalkyl), $-N(C_{1-6}$ alkyl$)C(O)C_{1-6}$ alkyl, $-N(C_{1-6}$ alkyl$)C(O)C_{3-12}$

cycloalkyl, C(O)(4 to 12-membered heterocycloalkyl), -N(C_{1-6} alkyl)C(O)(4 to 12-membered heterocycloalkyl), or -NH-S(O)$_2$-R^{2-2}, wherein said C_{1-6} alkyl, C_{3-12} cycloalkyl, and 4 to 12-membered heterocycloalkyl are each optionally substituted with one or more substituents selected from halogen, -OH, -O-NHCH$_3$, -SH, -NH$_2$, -NHC_{1-6} alkyl, and -SC_{1-6} alkyl;

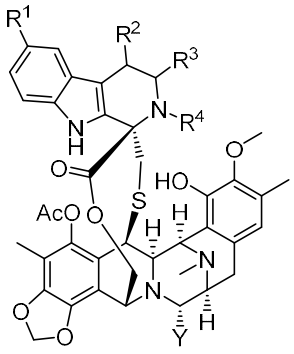
(3) R^3 is -CH$_2$-NHC_{1-6} alkyl, -CH$_2$-NHC(O)C_{1-6} alkyl, -CH$_2$-OC(O)-$NR^{3-1}R^{3-2}$, -CH$_2$-NR^{3-1}C(O)NR^{3-1}-R^{3-2}, -CH$_2$-NR^{3-1}C(O)O-R^{3-2}, -CH$_2$-NHC(O)C_{3-12} cycloalkyl, -CH$_2$-NHC(O)(4 to 12-membered heterocycloalkyl), -CH$_2$-NHC(O)C_{3-12} cycloalkyl, -CH$_2$-N(C_{1-6} alkyl)C(O)C_{1-6} alkyl, -CH$_2$-N(C_{1-6} alkyl)C(O)C_{3-12} cycloalkyl, -CH$_2$-N(C_{1-6} alkyl)C(O)(4 to 12-membered heterocycloalkyl), -CH$_2$NH-S(O)$_2$-R^{3-2}, -CH$_2$-S(O)$_2$-R^{3-2}, or -C(O)R^{3-2}, wherein said C_{1-6} alkyl, C_{3-12} cycloalkyl, and 4 to 12-membered heterocycloalkyl are each optionally substituted with one or more substituents selected from halogen, cyclopropyl, -OH, -O-NHCH$_3$, -SH, -NH$_2$, -NHC_{1-6} alkyl, and -SC_{1-6} alkyl;

(4) R^4 is C_{1-6} alkyl, -C(O)C_{1-6} alkyl, -C(O)C_{3-12} cycloalkyl, or -C(O)(4 to 12-membered heterocycloalkyl), wherein said C_{1-6} alkyl, C_{3-12} cycloalkyl, and 4 to 12-membered heterocycloalkyl are each optionally substituted with one or more substituents selected from halogen, -OH, -SH, -NH$_2$, -NHC_{1-6} alkyl, and -SC_{1-6} alkyl; and

(5) R^3 and R^4, together with the atoms to which they are attached, form a 5- to 12-membered heterocycloalkyl; said 5- to 12-membered heterocycloalkyl is optionally substituted with one or more substituents selected from halogen, oxo group, -OH, -CN, -NH$_2$, -NHC_{1-6} alkyl, -N(C_{1-6} alkyl)$_2$, C_{1-6} alkyl, -C_{1-6} alkylene-OH, -C(O)C_{1-6} alkylene-OH, -C(O)-C_{3-12} cycloalkylene-OH, and -C(O)-(4 to 12-membered heterocycloalkylene)-OH.

3. The compound of claim 1, or a pharmaceutically acceptable salt, ester, stereoisomer, tautomer, polymorph, solvate, isotope-labeled compound, metabolite, or prodrug thereof, characterized in that

the compound of formula (I) is a compound having the structure of formula (IA), (IB), (Ia), or (Ib):



IA

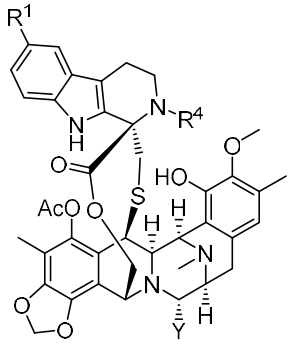
wherein,

R^1 is hydrogen, halogen, -OH, or -OC_{1-6} alkyl;

R^2 is hydrogen or deuterium; R^3 is -CH_2-NHC_{1-6} alkyl, -CH_2-NHC(O)C_{1-6} alkyl, -CH_2-OC(O)-$NR^{3-1}R^{3-2}$, -CH_2-NR^{3-1}C(O)NR^{3-1}-R^{3-2}, -CH_2-NR^{3-1}C(O)O-R^{3-2}, -CH_2-NHC(O)C_{3-12} cycloalkyl, -CH_2-NHC(O)(4 to 12-membered heterocycloalkyl), -CH_2-NHC(O)C_{3-12} cycloalkyl, -CH_2-N(C_{1-6} alkyl)C(O)C_{1-6} alkyl, -CH_2-N(C_{1-6} alkyl)C(O)C_{3-12} cycloalkyl, -CH_2-N(C_{1-6} alkyl)C(O)(4 to 12-membered heterocycloalkyl), -CH_2NH-S(O)$_2$-R^{3-2}, -CH_2-S(O)$_2$-R^{3-2}, or -C(O)R^{3-2}, wherein said C_{1-6} alkyl, C_{3-12} cycloalkyl, and 4 to 12-membered heterocycloalkyl are each optionally substituted with one or more substituents selected from halogen, cyclopropyl, -OH, -O-$NHCH_3$, -SH, -NH_2, -NHC_{1-6} alkyl, and -SC_{1-6} alkyl; R^4 is hydrogen or C_{1-6} alkyl;

or R^2 is hydrogen or deuterium; R^3 and R^4, together with the atoms to which they are attached, form a 5- to 12-membered heterocycloalkyl; said 5- to 12-membered heterocycloalkyl is optionally substituted with one or more substituents selected from -C(O)C_{1-6} alkylene-OH;

or R^2 is halogen, -C_{1-6} alkyl, -OH, -O-C(O)-N(R^{2-1})R^{2-2}, -C(O)R^{2-2}, C(O)-N(R^{2-1})R^{2-2}, -NH_2, -NHC_{1-6} alkyl, -NHC(O)C_{1-6} alkyl, -N(R^{2-1})-C(O)-OR^{2-2}, -N(R^{2-1})-C(O)-N(R^{2-1})R^{2-2}, -NHC(O)C_{3-12} cycloalkyl, -NHC(O)(4 to 12-membered heterocycloalkyl), -N(C_{1-6} alkyl)C(O)C_{1-6} alkyl, -N(C_{1-6} alkyl)C(O)C_{3-12} cycloalkyl, C(O)(4 to 12-membered heterocycloalkyl), -N(C_{1-6} alkyl)C(O)(4 to 12-membered heterocycloalkyl), or -NH-S(O)$_2$-R^{2-2}, wherein said C_{1-6} alkyl, C_{3-12} cycloalkyl, and 4 to 12-membered heterocycloalkyl are each optionally substituted with one or more substituents selected from halogen, -OH, -O-$NHCH_3$, -SH, -NH_2, -NHC_{1-6} alkyl, and -SC_{1-6} alkyl; R^3 is hydrogen or deuterium; R^4 is hydrogen or C_{1-6} alkyl;



IB

Y is -OH or -CN;

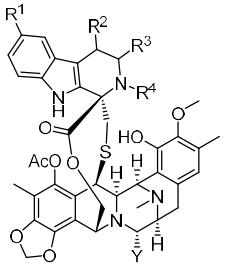
wherein,

R^1 is -OH, -CN, -NH_2, C_{1-6} alkyl, -NH-S(O)$_2$-R^{1-2}, -C(O)R^{1-2}, C(O)-N(R^{1-1})R^{1-2}, -C_{1-6} alkylene-N(R^{1-1})-C(O)R^{1-2}, -O-C_{3-12} cycloalkyl, -O-(4 to 12-membered heterocycloalkylene)-C(O)R^{1-2}, -O-C_{3-12} cycloalkylene-N(R^{1-1})-C(O)R^{1-2}, -O-C(O)-N(R^{1-1})R^{1-2}, -N(R^{1-1})-C(O)R^{1-2}, -N(R^{1-1})-C(O)-OR^{1-2}, -N(R^{1-1})-(4 to 12-membered heterocycloalkylene)-C(O)R^{1-2}, -N(R^{1-1})-C_{3-12} cycloalkylene-N(R^{1-3})-C(O)R^{1-2}, -(4 to 12-membered heterocycloalkylene)-C(O)R^{1-2}, -(4 to 12-membered heterocycloalkylene)-N(R^{1-1})-C(O)R^{1-2}, -N(R^{1-1})C(O)C_{3-12} cycloalkyl, (4 to 12-membered heterocycloalkylene), or -N(R^{1-1})C(O)(4 to 12-membered heterocycloalkyl), wherein said C_{1-6} alkyl, C_{1-6} alkylene, C_{3-12} cycloalkyl, C_{3-12} cycloalkylene,

4 to 12-membered heterocycloalkylene, and 4 to 12-membered heterocycloalkyl are each optionally substituted with one or more substituents selected from halogen, -OH, -SH, $-NH_2$, $-O-NHCH_3$, $-NHC_{1-6}$ alkyl, $-SC_{1-6}$ alkyl, $-C_{1-6}$ alkylene-OH, $-C_{1-6}$ alkylene-SH, $-C_{1-6}$ alkylene-S(C_{1-6} alkyl), and $-C_{1-6}$ alkylene-NH_2;

R^4 is hydrogen or $-C_{1-6}$ alkyl;

Y is -OH or -CN;



Ia

wherein,

R^1 is hydrogen, deuterium, halogen, -OH, -CN, $-NH_2$, C_{1-6} alkyl, halo-C_{1-6} alkyl, $-OC_{1-6}$ alkyl, -O-halo-C_{1-6} alkyl, $-NHC_{1-6}$ alkyl, -O-halo-C_{1-6} alkyl, or -NH-halo-C_{1-6} alkyl;

R^2 is hydrogen, deuterium, halogen, C_{1-6} alkyl, -OH, $-NH_2$, $-NHC_{1-6}$ alkyl, $-NHC(O)C_{1-6}$ alkyl, $-NHC(O)C_{3-12}$ cycloalkyl, -NHC(O)(4 to 12-membered heterocycloalkyl), $-N(C_{1-6}$ alkyl)$C(O)C_{1-6}$ alkyl, $-N(C_{1-6}$ alkyl)$C(O)C_{3-12}$ cycloalkyl, or $-N(C_{1-6}$ alkyl)C(O)(4 to 12-membered heterocycloalkyl), wherein said C_{1-6} alkyl, C_{3-12} cycloalkyl, or 4 to 12-membered heterocycloalkyl is optionally substituted with one or more substituents selected from halogen, -OH, -SH, $-NH_2$, $-NHC_{1-6}$ alkyl, and $-SC_{1-6}$ alkyl;

R^3 is H or $-CH_2-NR^{3a}R^{3b}$;

R^{3a} is hydrogen or C_{1-6} alkyl; said C_{1-6} alkyl is optionally substituted with one or more substituents selected from halogen, -OH, -SH, $-NH_2$, $-NHC_{1-6}$ alkyl, and $-SC_{1-6}$ alkyl;

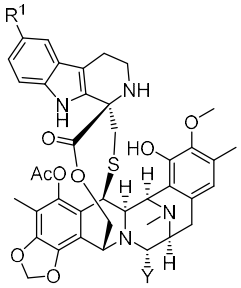
R^{3b} is $-C(O)C_{1-6}$ alkyl, $-C(O)C_{3-12}$ cycloalkyl, or -C(O)(4 to 12-membered heterocycloalkyl), wherein said C_{1-6} alkyl, C_{3-12} cycloalkyl, or 4 to 12-membered heterocycloalkyl is optionally substituted with one or more substituents selected from halogen, -OH, -SH, $-NH_2$, $-NHC_{1-6}$ alkyl, and $-SC_{1-6}$ alkyl;

R^4 is hydrogen, deuterium, C_{1-6} alkyl, $-C(O)C_{1-6}$ alkyl, $-C(O)C_{3-12}$ cycloalkyl, or -C(O)(4 to 12-membered heterocycloalkyl), wherein said C_{1-6} alkyl, C_{3-12} cycloalkyl, or 4 to 12-membered heterocycloalkyl is optionally substituted with one or more substituents selected from halogen, -OH, -SH, $-NH_2$, $-NHC_{1-6}$ alkyl, and $-SC_{1-6}$ alkyl;

or R^3 and R^4, together with the atoms to which they are attached, form a 5- to 12-membered heterocycloalkyl; said 5- to 12-membered heterocycloalkyl is optionally substituted with one or more substituents selected from halogen, oxo group, -OH, -CN, $-NH_2$, $-NHC_{1-6}$ alkyl, $-N(C_{1-6}$ alkyl$)_2$, $-C_{1-6}$ alkyl, $-C_{1-6}$ alkylene-OH, $-C(O)C_{1-6}$ alkylene-OH, $-C(O)-C_{3-12}$ cycloalkylene-OH, and -C(O)-(4 to 12-membered heterocycloalkylene)-OH;

Y is -OH or -CN;

provided that R^2 and R^3 are not both H;



Ib

wherein,

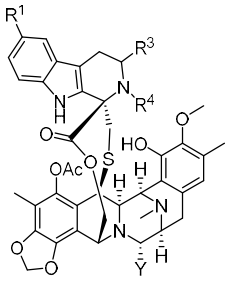
R^1 is $-NH_2$, $-C_{1-6}$ alkylene-$N(R^{1-1})$-$C(O)R^{1-2}$, -O-C_{3-12} cycloalkyl, -O-(4 to 12-membered heterocycloalkylene)-$C(O)R^{1-2}$, -O-C_{3-12} cycloalkylene-$N(R^{1-1})$-$C(O)R^{1-2}$, $-N(R^{1-1})$-(4 to 12-membered heterocycloalkylene)-$C(O)R^{1-2}$, $-N(R^{1-1})$-C_{3-12} cycloalkylene-$N(R^{1-3})$-$C(O)R^{1-2}$, -(4 to 12-membered heterocycloalkylene)-$C(O)R^{1-2}$, -(4 to 12-membered heterocycloalkylene)-$N(R^{1-1})$-$C(O)R^{1-2}$, $-N(R^{1-1})C(O)C_{3-12}$ cycloalkyl, or $-N(R^{1-1})C(O)$(4 to 12-membered heterocycloalkyl), wherein said C_{1-6} alkyl, C_{1-6} alkylene, C_{3-12} cycloalkyl, C_{3-12} cycloalkylene, 4 to 12-membered heterocycloalkylene, or 4 to 12-membered heterocycloalkyl is optionally substituted with one or more substituents selected from halogen, -OH, -SH, $-NH_2$, $-NHC_{1-6}$ alkyl, $-SC_{1-6}$ alkyl, $-C_{1-6}$ alkylene-OH, $-C_{1-6}$ alkylene-SH, $-C_{1-6}$ alkylene-S(C_{1-6} alkyl), and $-C_{1-6}$ alkylene-NH_2;

R^{1-1} is hydrogen, deuterium, C_{1-6} alkyl, or halo-C_{1-6} alkyl;

R^{1-2} is C_{1-6} alkyl, C_{3-12} cycloalkyl, or 4 to 12-membered heterocycloalkyl; said C_{1-6} alkyl, C_{3-12} cycloalkyl, or 4 to 12-membered heterocycloalkyl is optionally substituted with one or more substituents selected from halogen, -OH, -SH, $-NH_2$, $-NHC_{1-6}$ alkyl, and $-SC_{1-6}$ alkyl;

Y is -OH or -CN.

4. The compound of any one of claims 1-3, or a pharmaceutically acceptable salt, ester, stereoisomer, tautomer, polymorph, solvate, isotope-labeled compound, metabolite, or prodrug thereof, wherein the compound of formula (I) is a compound having the structure of formula (IA-1), (IA-2), (Ia-1), or (Ia-2),



IA-1

wherein,

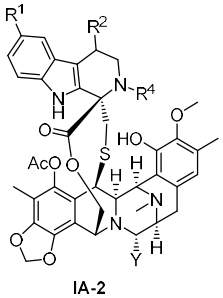
R^1 is hydrogen, halogen, -OH, or -OC_{1-6} alkyl;

R^3 is -CH_2-NHC_{1-6} alkyl, -CH_2-$NHC(O)C_{1-6}$ alkyl, -CH_2-$OC(O)$-$NR^{3-1}R^{3-2}$, -CH_2-$NR^{3-1}C(O)NR^{3-1}$-R^{3-2}, -CH_2-$NR^{3-1}C(O)O$-R^{3-2}, -CH_2-$NHC(O)C_{3-12}$ cycloalkyl, -CH_2-NHC(O)(4 to 12-membered heterocycloalkyl), -CH_2-$NHC(O)C_{3-12}$ cycloalkyl, -CH_2-$N(C_{1-6}$ alkyl)$C(O)C_{1-6}$ alkyl, -CH_2-$N(C_{1-6}$ alkyl)$C(O)C_{3-12}$ cycloalkyl, -CH_2-$N(C_{1-6}$ alkyl)C(O)(4 to 12-membered heterocycloalkyl), -CH_2NH-$S(O)_2$-R^{3-2}, -CH_2-$S(O)_2$-R^{3-2}, or -$C(O)R^{3-2}$, wherein said C_{1-6} alkyl, C_{3-12} cycloalkyl, and 4 to 12-membered heterocycloalkyl are each optionally substituted with one or more substituents selected from halogen, cyclopropyl, -OH, -O-$NHCH_3$, -SH, -NH_2, -NHC_{1-6} alkyl, and -SC_{1-6} alkyl;

R^4 is hydrogen or C_{1-6} alkyl;

or R^3 and R^4, together with the atoms to which they are attached, form a 5- to 12-membered heterocycloalkyl; said 5- to 12-membered heterocycloalkyl is optionally substituted with one or more substituents selected from -$C(O)C_{1-6}$ alkylene-OH;

Y is -OH or -CN;



IA-2

wherein,

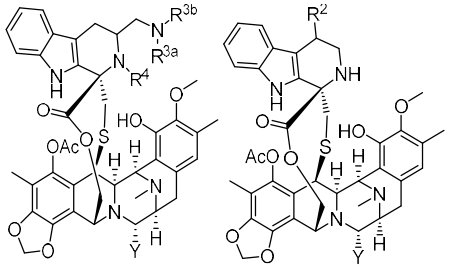
R^1 is hydrogen, halogen, -OH, or -OC_{1-6} alkyl;

R^2 is halogen, -C_{1-6} alkyl, -OH, -O-$C(O)$-$N(R^{2-1})R^{2-2}$, -$C(O)R^{2-2}$, $C(O)$-$N(R^{2-1})R^{2-2}$, -NH_2, -NHC_{1-6} alkyl, -$NHC(O)C_{1-6}$ alkyl, -$N(R^{2-1})$-$C(O)$-OR^{2-2}, -$N(R^{2-1})$-$C(O)$-$N(R^{2-1})R^{2-2}$, -$NHC(O)C_{3-12}$ cycloalkyl, -

NHC(O)(4 to 12-membered heterocycloalkyl), -N(C_{1-6} alkyl)C(O)C_{1-6} alkyl, -N(C_{1-6} alkyl)C(O)C_{3-12} cycloalkyl, C(O)(4 to 12-membered heterocycloalkyl), -N(C_{1-6} alkyl)C(O)(4 to 12-membered heterocycloalkyl), or -NH-S(O)$_2$-R^{2-2}, wherein said C_{1-6} alkyl, C_{3-12} cycloalkyl, and 4 to 12-membered heterocycloalkyl are each optionally substituted with one or more substituents selected from halogen, -OH, -O-$NHCH_3$, -SH, -NH_2, -NHC_{1-6} alkyl, and -SC_{1-6} alkyl;

R^4 is hydrogen or C_{1-6} alkyl;

Y is -OH or -CN;



Ia-1 Ia-2

wherein,

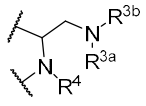
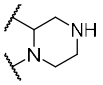
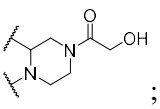
Y, R^2, R^{3a}, R^{3b}, and R^4 are as defined in any one of claims 1-3;

preferably, in the compounds of formula (Ia) or (Ia-1),

R^{3a} is hydrogen or -CH_3;

R^{3b} is -C(O)C_{1-6} alkylene-OH;

R^4 is hydrogen;

or,  is  or  ;

Y is -OH or -CN.

5. The compound of any one of claims 1-3, or a pharmaceutically acceptable salt, ester, stereoisomer, tautomer, polymorph, solvate, isotope-labeled compound, metabolite, or prodrug thereof, wherein it satisfies at least one of the following conditions:

(1) the number of heteroatoms in said 4 to 12-membered heterocycloalkylene and 4 to 12-membered heterocycloalkyl is one or more, each heteroatom being independently selected from N, O, and S;

preferably, said 4 to 12-membered heterocycloalkylene and 4 to 12-membered heterocycloalkyl are 4 to 6-membered heterocycloalkylene and 4 to 6-membered heterocycloalkyl; the number of heteroatoms is one or two, and the heteroatoms are independently selected from N;

(2) in the compounds of formula (I) or (Ia), R^1 is hydrogen, halogen, -OH, -CN, $-NH_2$, $-CH_3$, $-OCH_3$, or $-NHCH_3$;

preferably, R^1 is hydrogen, deuterium, -F, -Cl, -OH, $-CH_3$, $-OCH_3$, $-NH_2$, or $-NHCH_3$;

(3) in the compounds of formula (I), (Ia), or (Ia-2), R^2 is -OH, $-NH_2$, C_{1-6} alkyl, $-NHC_{1-6}$ alkyl, $-NHC(O)C_{1-6}$ alkyl, $-N(C_{1-6}$ alkyl$)C(O)C_{1-6}$ alkyl, or $-N(C_{1-6}$ alkyl$)C(O)C_{3-12}$ cycloalkyl, wherein said C_{1-6} alkyl, C_{3-12} cycloalkyl, or 4 to 12-membered heterocycloalkyl is optionally substituted with one or more substituents selected from -OH, -SH, $-NH_2$, $-NHCH_3$, and $-SCH_3$; preferably, R^2 is -OH, $-NH_2$, $-C_{1-6}$ alkylene-OH, $-NHC(O)C_{1-6}$ alkylene-OH, $-N(C_{1-6}$ alkyl$)C(O)C_{1-6}$ alkylene-OH, $-NHC(O)C_{1-6}$ alkylene-NH_2, or $-N(C_{1-6}$ alkyl$)C(O)C_{1-6}$ alkylene-NH_2;

preferably, R^2 is -OH, $-NH_2$, $-C_{1-6}$ alkylene-OH, $-NHC(O)C_{1-6}$ alkylene-OH, or $-N(C_{1-6}$ alkyl$)C(O)C_{1-6}$ alkylene-OH;

more preferably, R^2 is -OH, $-NH_2$, $-C_{1-3}$ alkylene-OH, $-NHC(O)C_{1-3}$ alkylene-OH, $-N(C_{1-3}$ alkyl$)C(O)C_{1-3}$ alkylene-OH, $-NHC(O)C_{1-3}$ alkylene-NH_2, or $-N(C_{1-6}$ alkyl$)C(O)C_{1-3}$ alkylene-NH_2;

(4) in the compounds of formula (I) or (Ia), R^{3a} is hydrogen or C_{1-3} alkyl;

preferably, R^{3a} is hydrogen or $-CH_3$;

(5) in the compounds of formula (I) or (Ia), R^{3b} is $-C(O)C_{1-6}$ alkyl or $-C(O)C_{3-6}$ cycloalkyl, wherein said C_{1-6} alkyl or C_{3-6} cycloalkyl is optionally substituted with one or more substituents selected from -OH, -SH, $-NH_2$, $-NHCH_3$, and $-SCH_3$;

preferably, R^{3b} is $-C(O)C_{1-6}$ alkylene-OH;

more preferably, R^{3b} is $-C(O)C_{1-3}$ alkylene-OH;

(6) in the compounds of formula (I), (Ia), or (Ia-1), R^4 is hydrogen, deuterium, $-C_{1-6}$ alkyl, or $-C(O)C_{1-6}$ alkylene-OH;

(7) in the compounds of formula (I) or (Ia), R^3 and R^4, together with the atoms to which they are attached, form a 5- to 6-membered heterocycloalkyl, said 5- to 6-membered heterocycloalkyl being optionally substituted with one or more substituents selected from halogen, oxo group, -OH, -CN, $-NH_2$, $-NHC_{1-6}$ alkyl, $-N(C_{1-6}$ alkyl$)_2$, $-C_{1-6}$ alkyl, $-C_{1-6}$ alkyl-OH, $-C(O)C_{1-6}$ alkylene-OH, $-C(O)-C_{3-12}$ cycloalkylene-OH, -C(O)-(4 to 12-membered heterocycloalkylene)-OH;

preferably, R^3 and R^4, together with the atoms to which they are attached, form a piperazinyl group, said piperazinyl group being optionally substituted with one or more substituents selected from halogen, oxo

group, -OH, -CN, -NH_2, -NHC_{1-6} alkyl, -$N(C_{1-6}$ alkyl$)_2$, -C_{1-6} alkyl, -C_{1-6} alkyl-OH, -$C(O)C_{1-6}$ alkylene-OH, -$C(O)$-C_{3-12} cycloalkylene-OH, -$C(O)$-(4 to 12-membered heterocycloalkylene)-OH;

(8) in the compounds of formula (I) or (Ib), R^{1-1} is hydrogen, deuterium, or -C_{1-6} alkyl;

preferably, R^{1-1} is hydrogen, deuterium, or -CH_3;

(9) in the compounds of formula (I) or (Ib), R^{1-2} is C_{1-6} alkyl, C_{3-6} cycloalkyl, or 4 to 6-membered heterocycloalkyl; said C_{1-6} alkyl, C_{3-6} cycloalkyl, or 4 to 6-membered heterocycloalkyl is optionally substituted with one or more substituents selected from halogen, -OH, -SH, -NH_2, -NHC_{1-6} alkyl, and -SC_{1-6} alkyl;

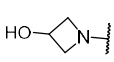
preferably, R^{1-2} is -C_{1-6} alkylene-OH or -C_{3-6} cycloalkylene-OH;

more preferably, R^{1-2} is -NH_2, -C_{1-3} alkylene-OH, or -C_{3-4} cycloalkylene-OH;

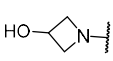
(10) in the compounds of formula (I) or (Ib), R^1 is -NH_2, -C_{1-6} alkylene-NH-$C(O)R^{1-2}$, -C_{1-6} alkylene-$N(CH_3)$-$C(O)R^{1-2}$, -O-(4 to 6-membered heterocycloalkylene)-$C(O)R^{1-2}$, -O-C_{3-6} cycloalkylene-NH-$C(O)R^{1-2}$, -O-C_{3-6} cycloalkylene-$N(CH_3)$-$C(O)R^{1-2}$, -NH-(4 to 6-membered heterocycloalkylene)-$C(O)R^{1-2}$, -$N(CH_3)$-(4 to 6-membered heterocycloalkylene)-$C(O)R^{1-2}$, -$NHC(O)C_{3-6}$ cycloalkyl, -$N(CH_3)C(O)C_{3-6}$ cycloalkyl, -NHC(O)(4 to 6-membered heterocycloalkyl), or -$N(CH_3)C(O)$(4 to 6-membered heterocycloalkyl), wherein said C_{1-6} alkylene, C_{3-6} cycloalkyl, C_{3-6} cycloalkylene, 4 to 6-membered heterocycloalkyl, or 4 to 6-membered heterocycloalkylene is optionally substituted with one or more substituents selected from halogen, -OH, -NH_2, -$NHCH_3$, -C_{1-6} alkylene-OH;

preferably, R^1 is -NH_2, -O-(4 to 6-membered heterocycloalkylene)-$C(O)R^{1-2}$, or -C_{1-6} alkylene-$N(CH_3)$-$C(O)R^{1-2}$;

(11) in the compounds of formula (I) or (Ia), R^{2-1} is hydrogen or C_{1-3} alkyl; preferably H or CH_3;

(12) in the compounds of formula (I) or (Ia), R^{2-2} is C_{1-6} alkyl, C_{3-12} cycloalkyl, or 4 to 12-membered heterocycloalkyl; said C_{1-6} alkyl, C_{3-12} cycloalkyl, 4 to 12-membered heterocycloalkyl is optionally substituted with one or more substituents independently selected from halogen and -OH; preferably substituted with -OH; preferably, R^{2-2} is -CH_2OH, -CH_2CH_2OH, -$CH(OH)CH_3$, -$CH_2ONH(CH_3)$,  or  ;

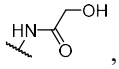
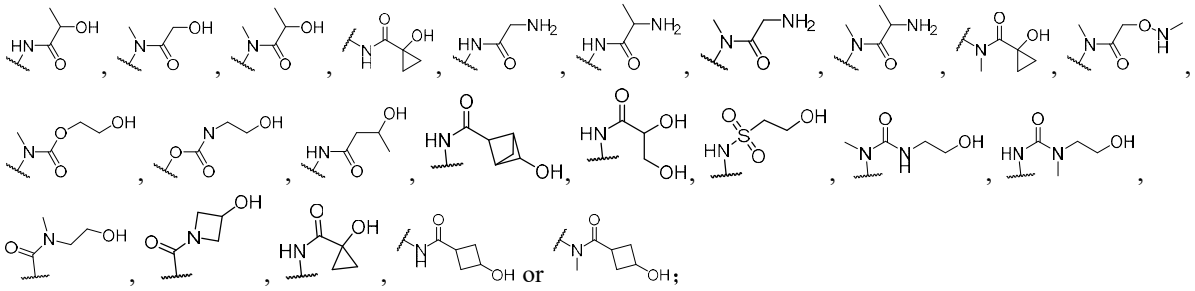
(11) in the compounds of formula (I) or (Ia), R^{3-1} is hydrogen or C_{1-3} alkyl; preferably hydrogen or -CH_3;

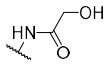
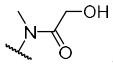
(12) in the compounds of formula (I) or (Ia), R^{3-2} is C_{1-6} alkyl, C_{3-12} cycloalkyl, or 4 to 12-membered heterocycloalkyl; said C_{1-6} alkyl, C_{3-12} cycloalkyl, 4 to 12-membered heterocycloalkyl is optionally substituted with one or more substituents independently selected from halogen and -OH; preferably substituted with -OH; preferably, R^{3-2} is -CH_2OH, -CH_2CH_2OH, -$CH(OH)CH_3$, -CH_2O-$NHCH_3$, -$CH_2ONH(CH_3)$,  or  ;

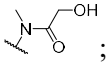
(13) in the compounds of formula (I) or (Ia), R^3 is H, -C(O)R^{3-2}, -CH_2-NHC(O)C_{1-6} alkyl, -CH_2-N(C_{1-6} alkyl)C(O)C_{1-6} alkyl, -CH_2-NR^{3-1}C(O)O-R^{3-2}, -CH_2-OC(O)-$NR^{3-1}R^{3-2}$, -CH_2NH-S(O)$_2$-R^{3-2}, -CH_2-NR^{3-1}C(O)NR^{3-1}-R^{3-2}, -CH_2-NHC(O)C_{3-12} cycloalkyl; said C_{1-6} alkyl, C_{3-12} cycloalkyl, and 4 to 12-membered heterocycloalkyl are each optionally substituted with one or more substituents selected from cyclopropyl, -OH, -O-$NHCH_3$.

6. The compound of claim 1, or a pharmaceutically acceptable salt, ester, stereoisomer, tautomer, polymorph, solvate, isotope-labeled compound, metabolite, or prodrug thereof, characterized in that it satisfies at least one of the following conditions:

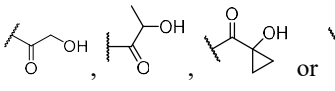
(1) In the compounds of formulae (I) and (Ia), R^1 is hydrogen, halogen, -OH, -CN, -NH_2, -CH_3, -OCH_3, or -$NHCH_3$; preferably hydrogen, F, -OH, or -OCH_3; more preferably hydrogen;

(2) In the compounds of formulae (I), (Ia), and (Ia-2), R^2 is -OH, -NH_2, -$NHCH_3$, -CH_2OH,  , 

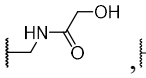
Preferably, R^2 is -OH, -NH_2, -CH_2OH,  or  ;

More preferably, R^2 is -NH_2, -CH_2OH, or  ;

(3) In the compounds of formulae (I), (Ia), and (Ia-1), R^{3a} is -CH_3;

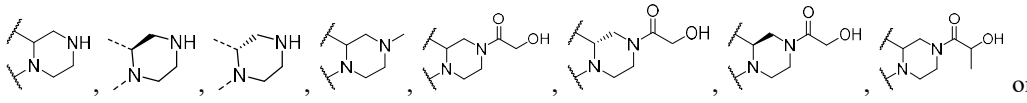
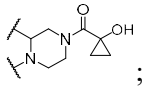
(4) In the compounds of formulae (I), (Ia), and (Ia-1), R^{3b} is  ;

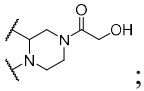
preferably, R^{3b} is  ;

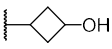
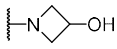
(5) In the compounds of formulae (I), (Ia), and (Ia-1), -CH_2-$NR^{3a}R^{3b}$ is  ;

(6) In the compounds of formulae (I), (Ia), and (Ia-1), R^4 is hydrogen or  ;

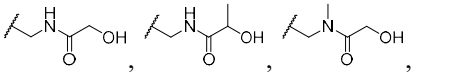
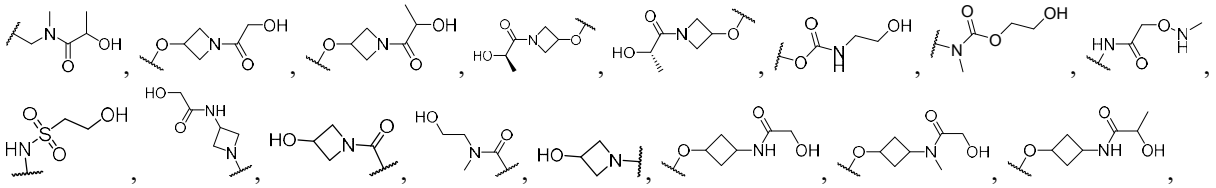
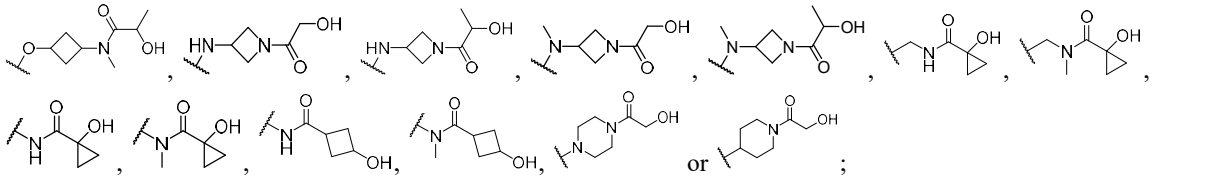
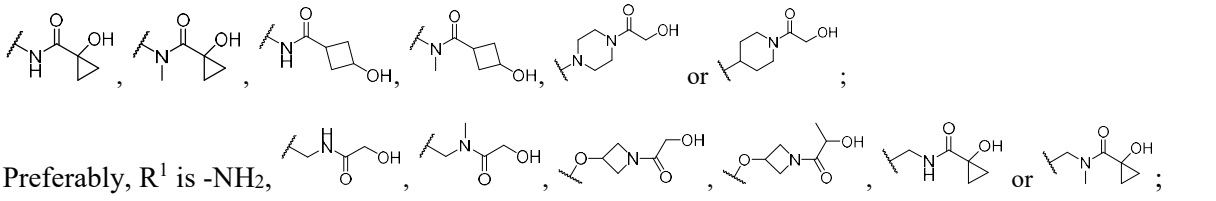
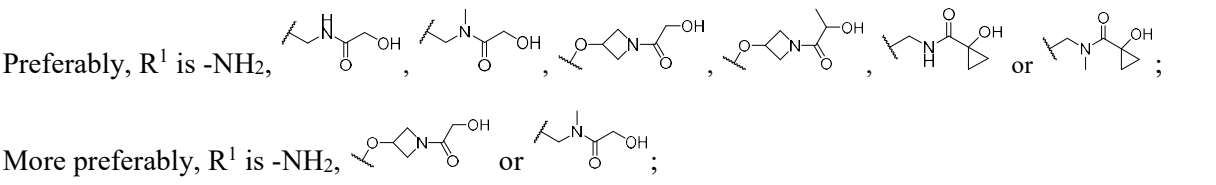
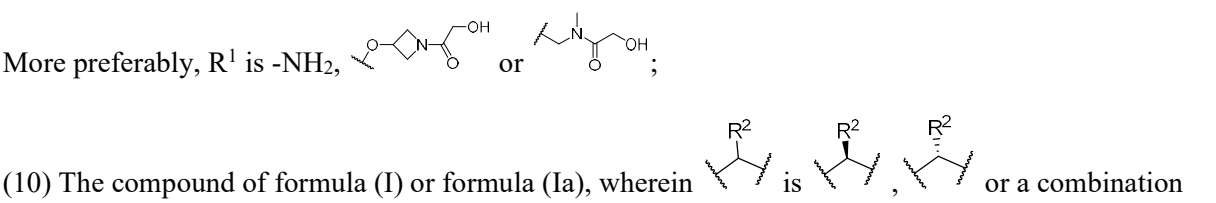
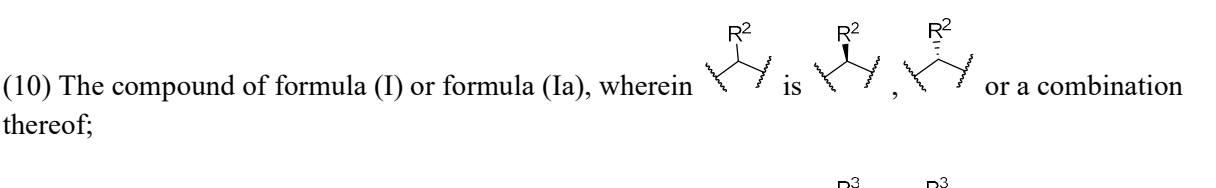
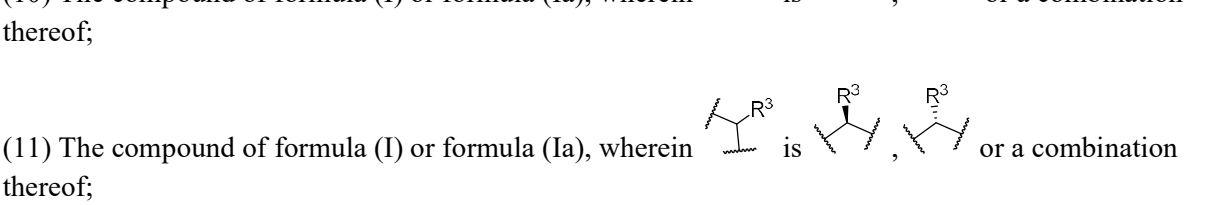
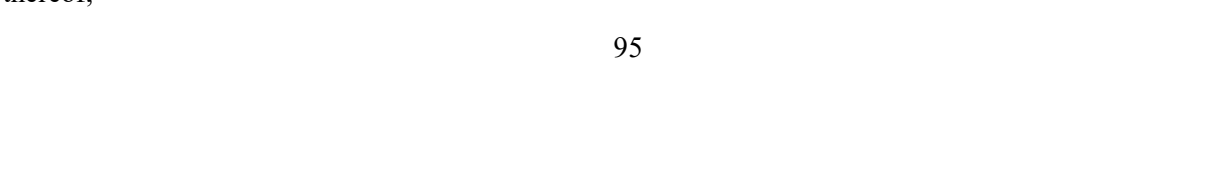
Preferably, R^4 is hydrogen;

(7) In the compounds of formulae (I), (Ia), and (Ia-1), R^3 and R^4, together with the atoms to which they are attached, form  ,  ;

Preferably,  or  ;

(8) In the compounds of formulae (I) and (Ib), R^{1-2} is $-CH_2OH$, $-CH(CH_3)OH$, $-CH_2CH_2OH$, $-CH_2ONH(CH_3)$,  ,  or  ;

Preferably, R^{1-2} is $-CH_2OH$, $-CH(CH_3)OH$, or  ;

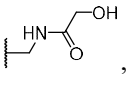
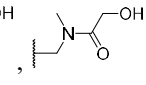
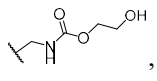
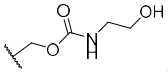
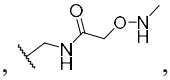
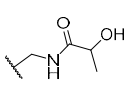
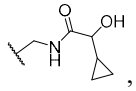
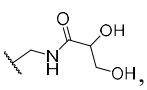
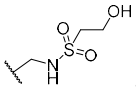
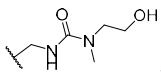
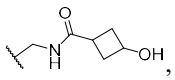
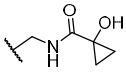
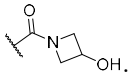
(9) In the compounds of formulae (I) and (Ib), R^1 is $-NH_2$, -OH,  ,  , ,  ,  ,  ,  ,  ,  , ,  , .

Preferably, R^1 is $-NH_2$, ;

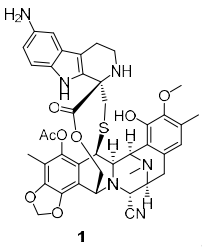
More preferably, R^1 is $-NH_2$, or ;

(10) The compound of formula (I) or formula (Ia), wherein is , or a combination thereof;

(11) The compound of formula (I) or formula (Ia), wherein is , or a combination thereof;

(12) The compound of formula (I) or formula (Ia), wherein R^3 is H,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  or  .

7. The compound according to claim 1, or a pharmaceutically acceptable salt, ester, stereoisomer, tautomer, polymorph, solvate, isotope-labeled compound, metabolite or prodrug thereof, characterized in that the compound is any one of the following structures: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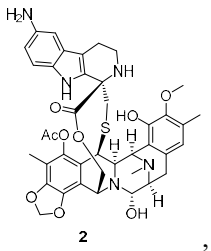
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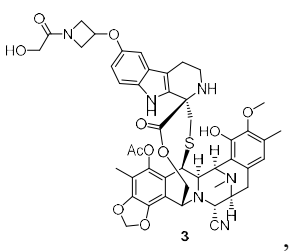
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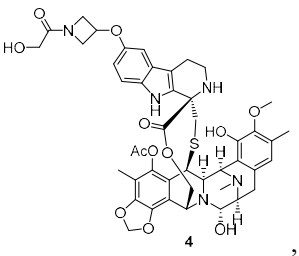
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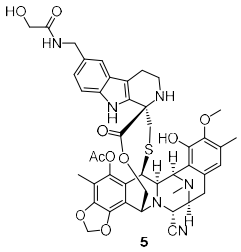
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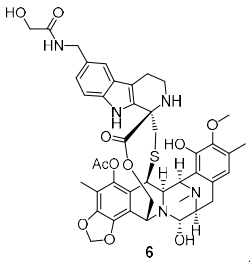
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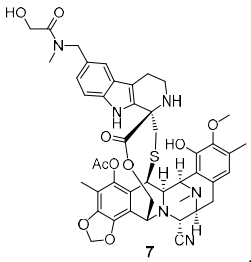
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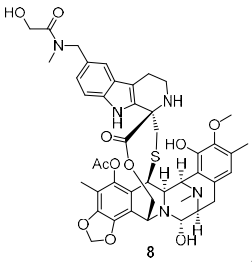
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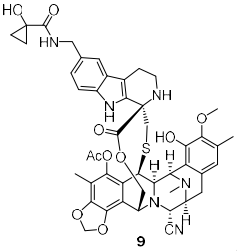
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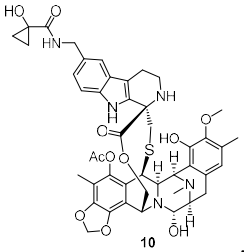
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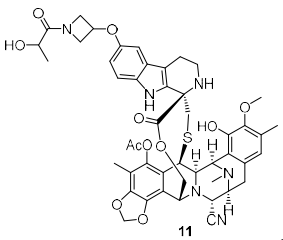
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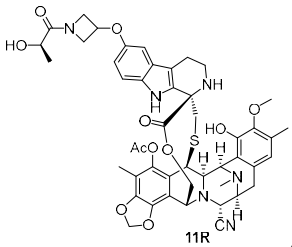
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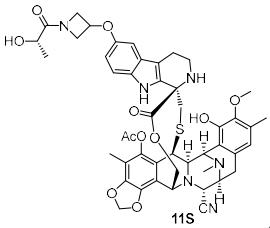
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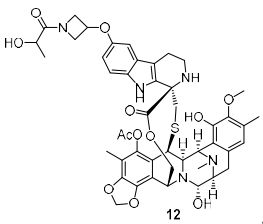
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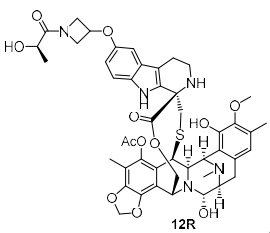
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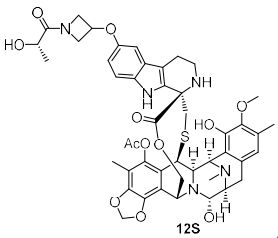
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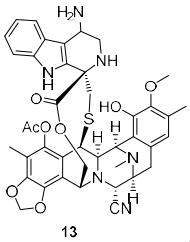
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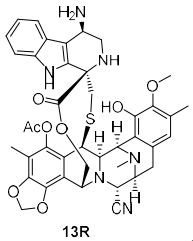
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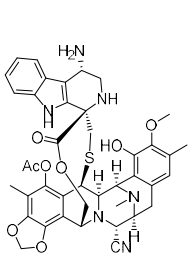

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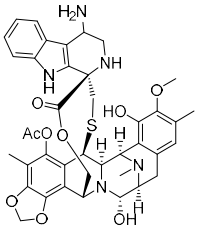

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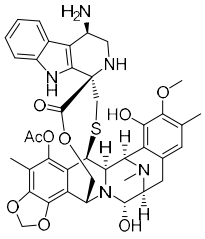

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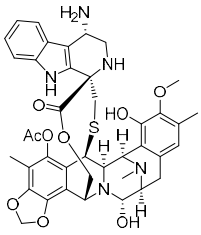

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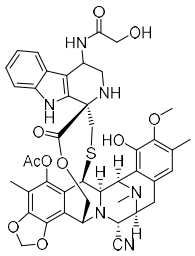

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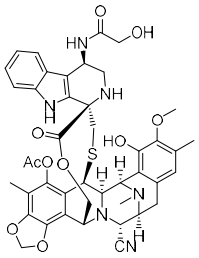

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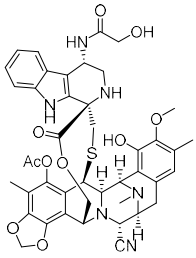

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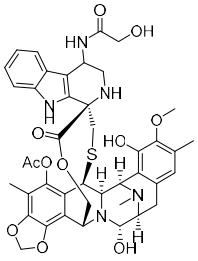

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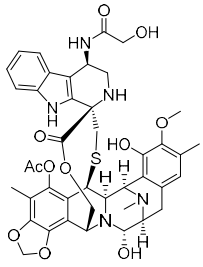

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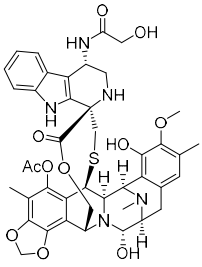

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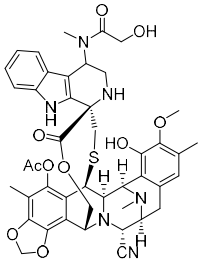

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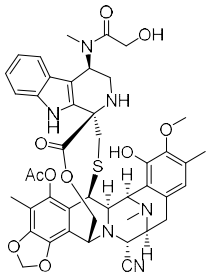

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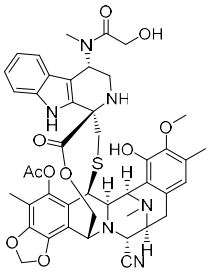

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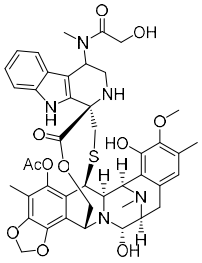

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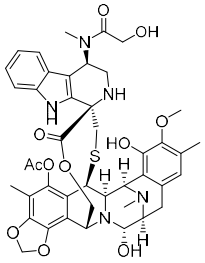

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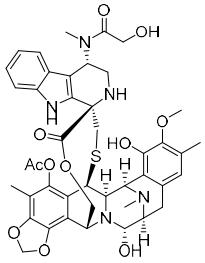

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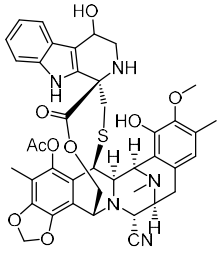

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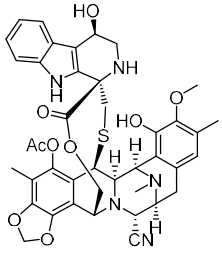

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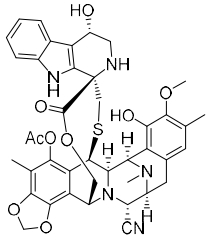

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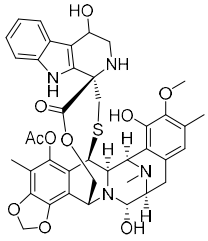

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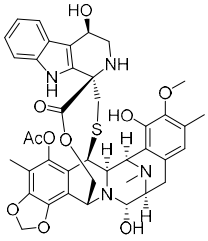

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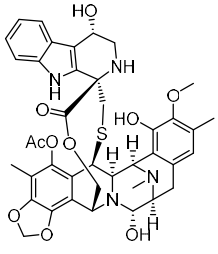

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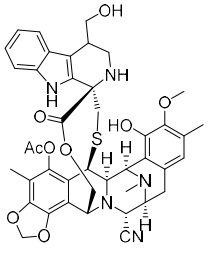

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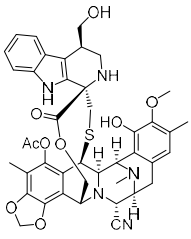

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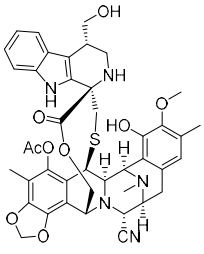

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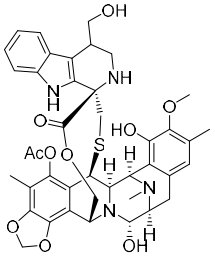

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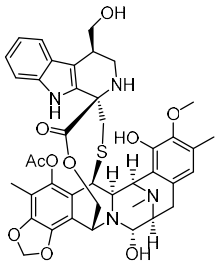
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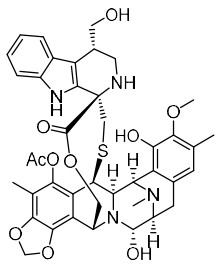
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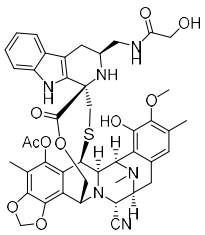
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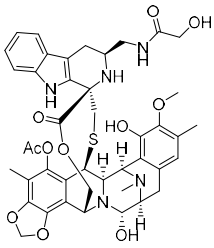
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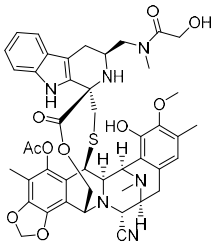
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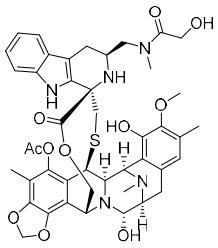
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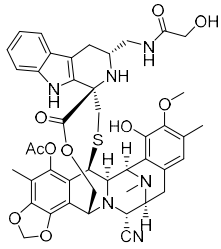
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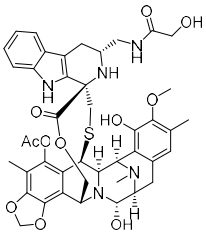
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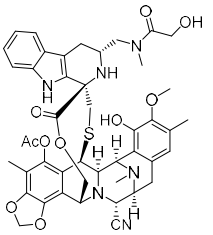
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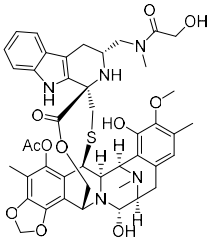
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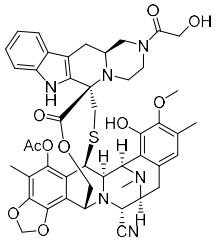
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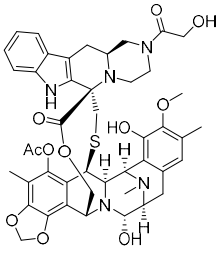
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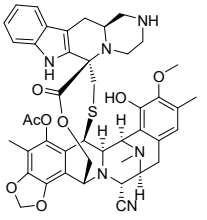
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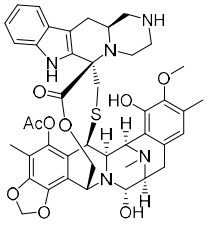
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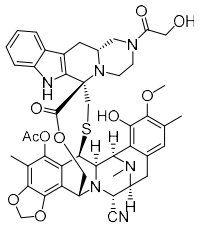
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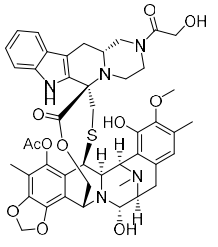
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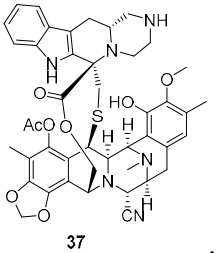
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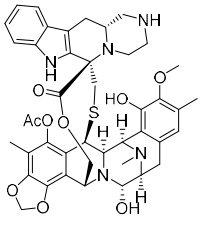
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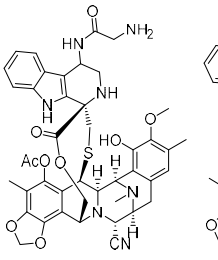
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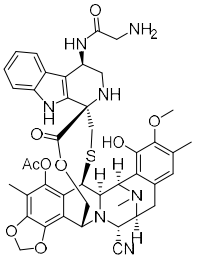
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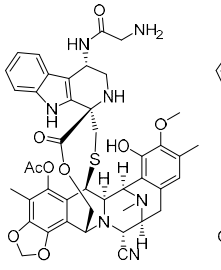
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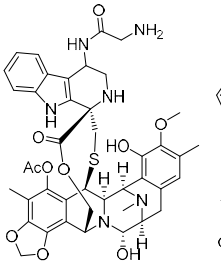
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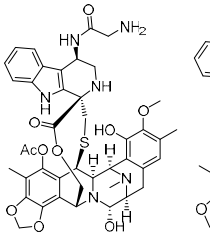
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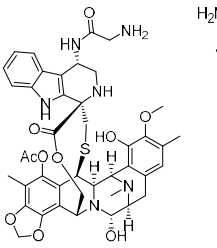
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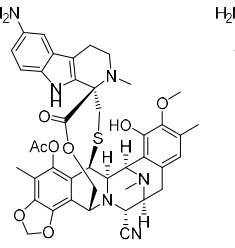
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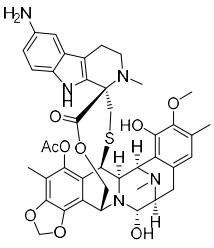
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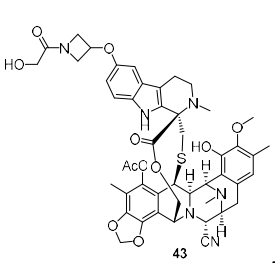
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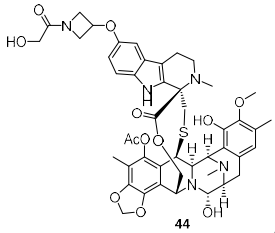
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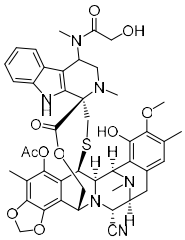
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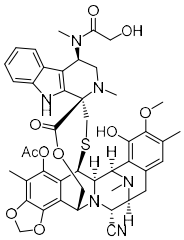
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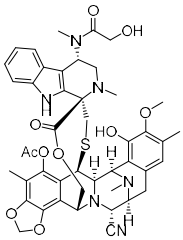
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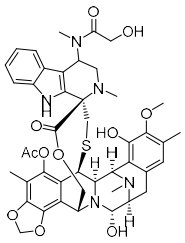
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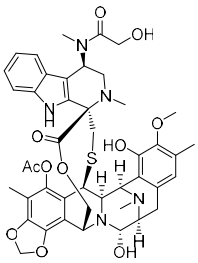
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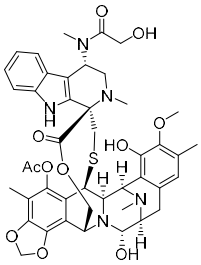
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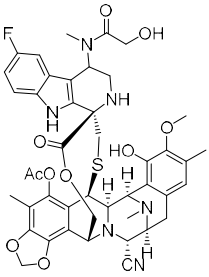
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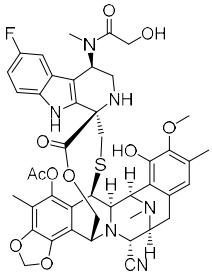
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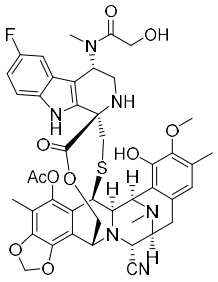
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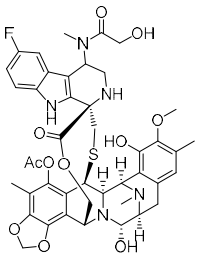
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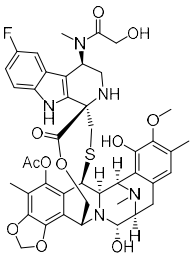
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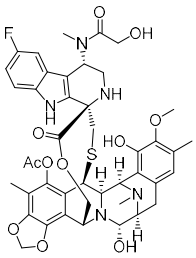
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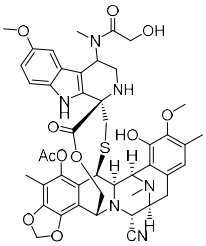
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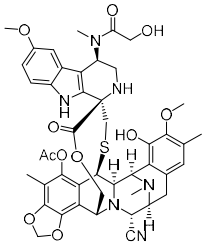
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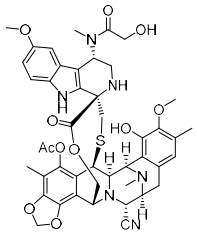
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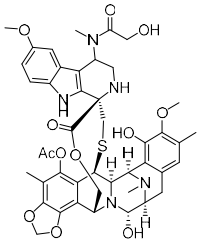
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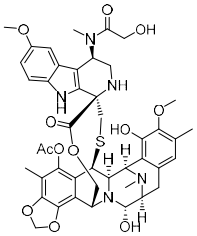
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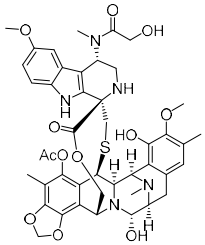
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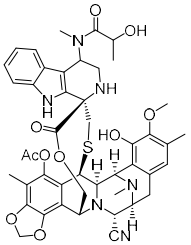
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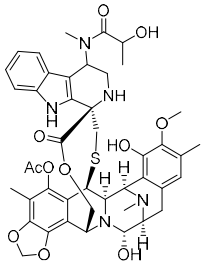
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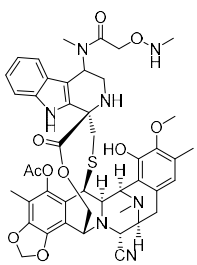
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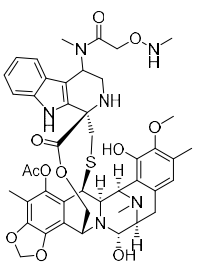
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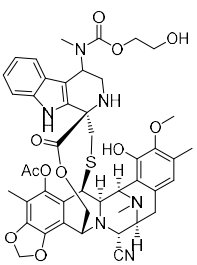
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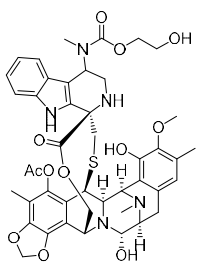
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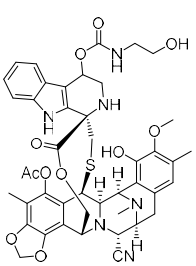
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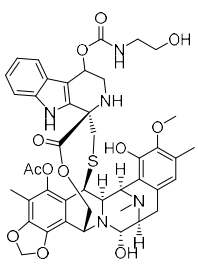

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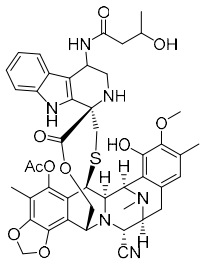

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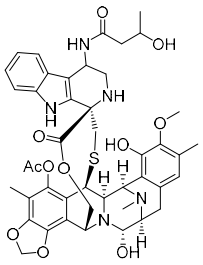

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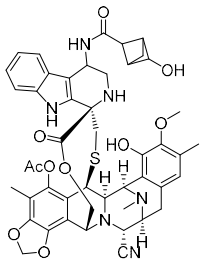

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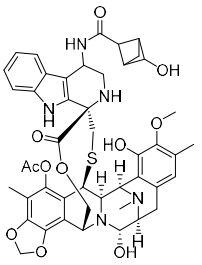

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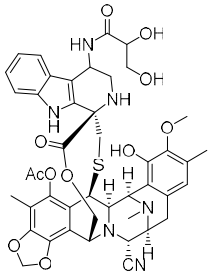

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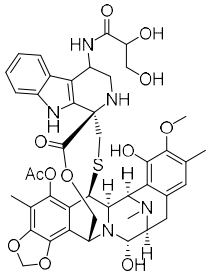

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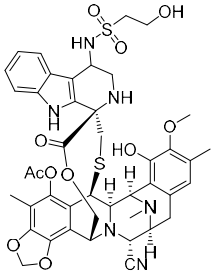

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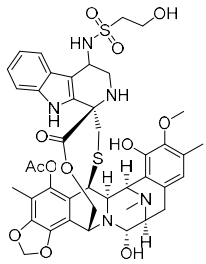

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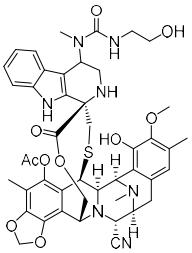

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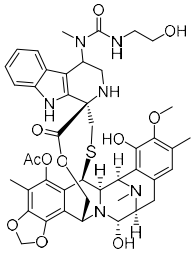

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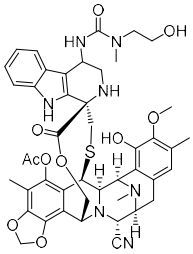

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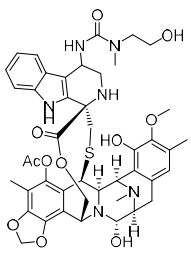

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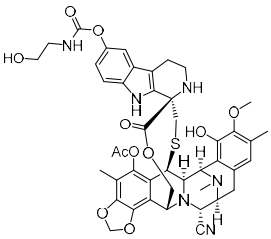

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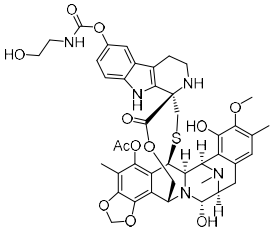

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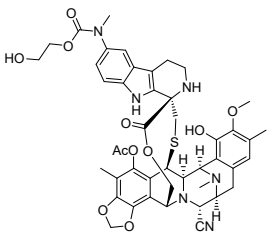

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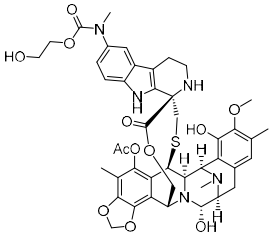

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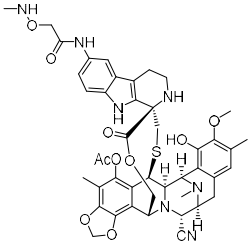

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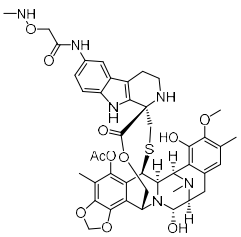

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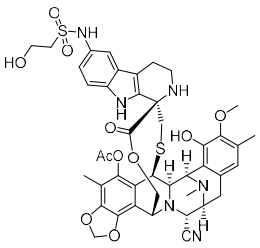

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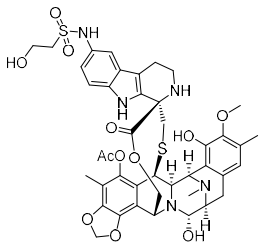

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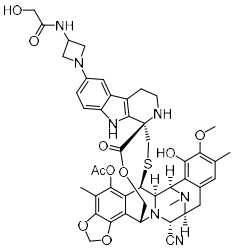

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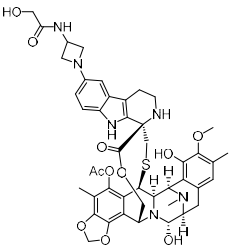

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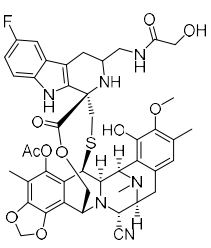

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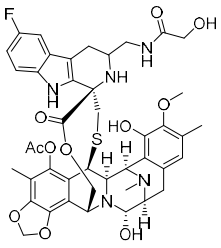
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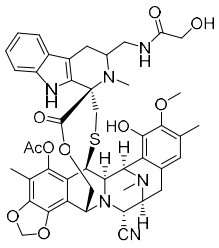
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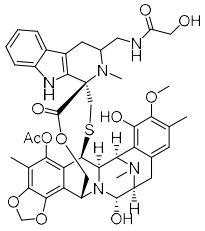
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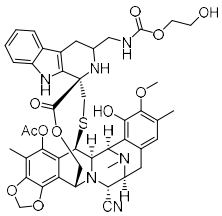
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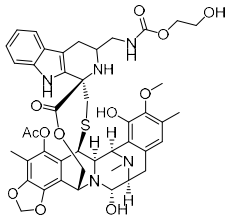
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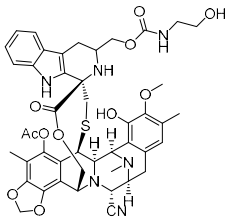
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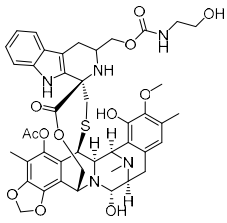
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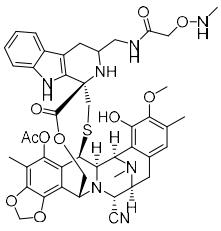
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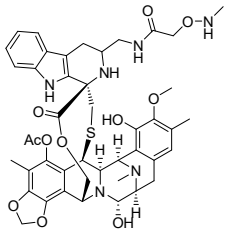
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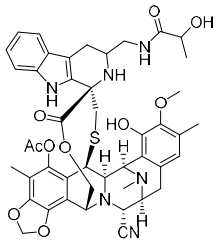
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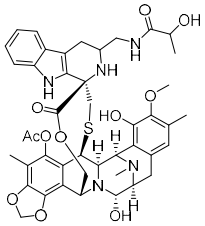
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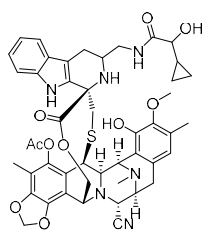
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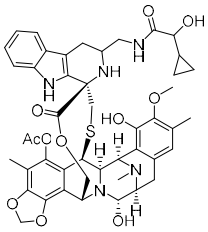
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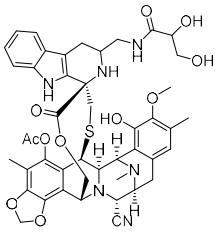
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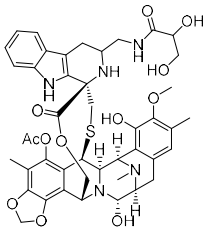
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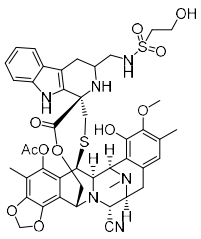
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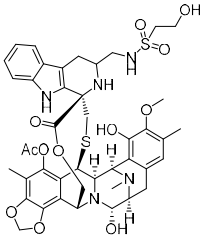
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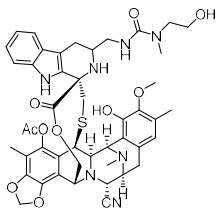
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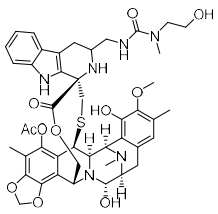
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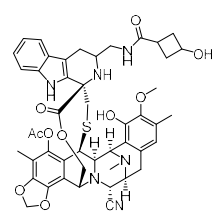
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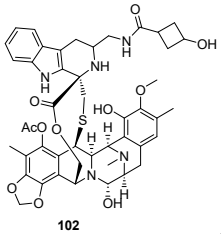
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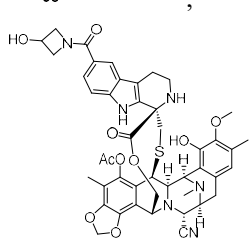
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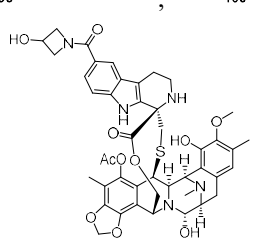
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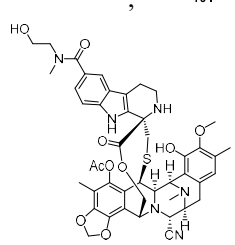
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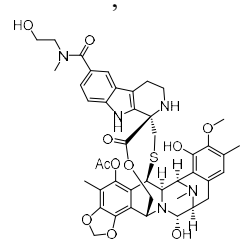
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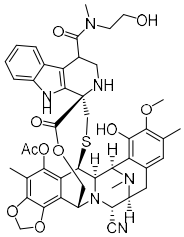
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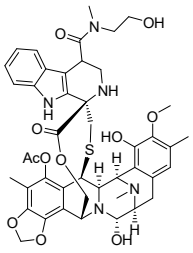
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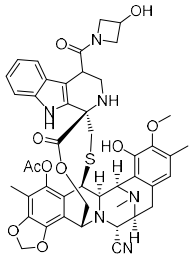
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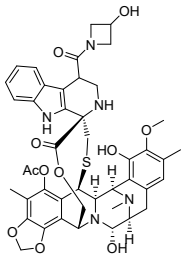
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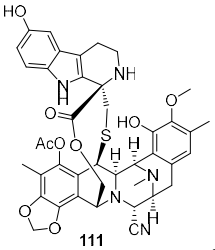
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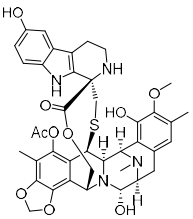
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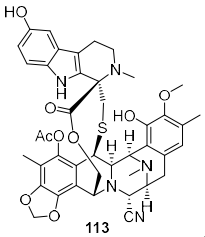
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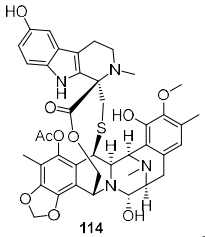
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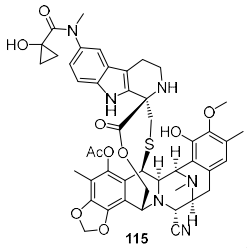
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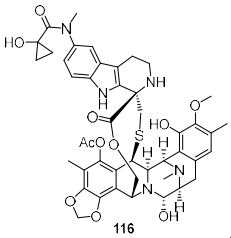
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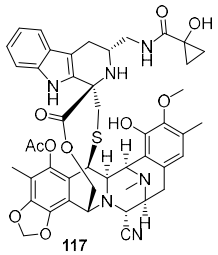
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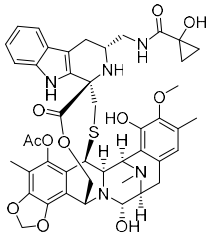
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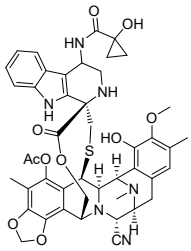
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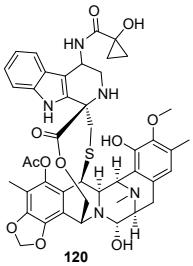
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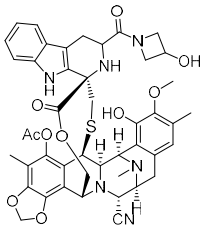
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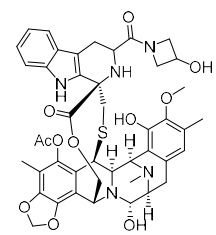
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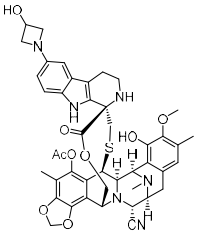
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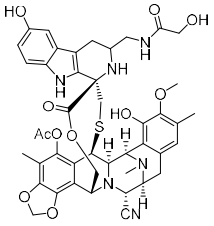
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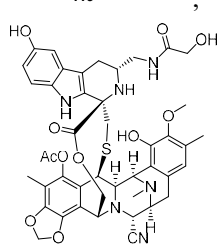
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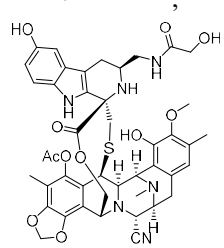
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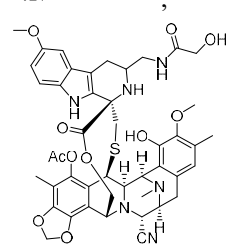
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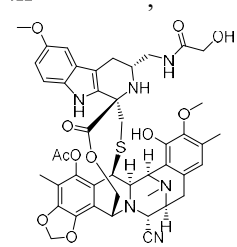
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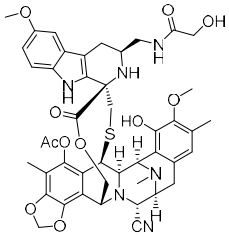
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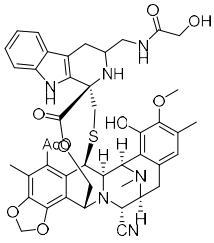
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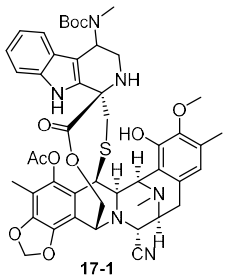

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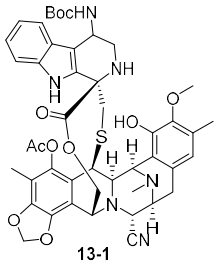

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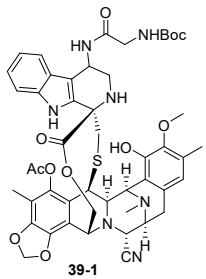

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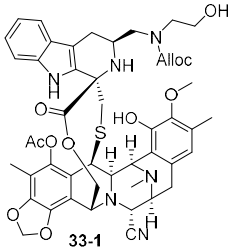

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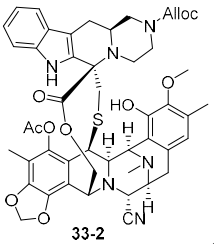

33-2 .

9. A pharmaceutical composition, characterized in that it comprises the compound according to any one of claims 1 – 7 or a pharmaceutically acceptable salt, ester, stereoisomer, tautomer, polymorph, solvate, isotope-labeled compound, metabolite or prodrug thereof, and one or more pharmaceutically acceptable carriers.

10. Use of a substance A in the preparation of a medicament for preventing or treating a tumor or cancer, characterized in that said substance A is the compound according to any one of claims 1 – 7 or a pharmaceutically acceptable salt, ester, stereoisomer, tautomer, polymorph, solvate, isotope-labeled compound, metabolite or prodrug thereof, or the pharmaceutical composition according to claim 9;

wherein said tumor or cancer is preferably breast cancer, colorectal cancer, colon cancer, lung cancer, prostate cancer, cholangiocarcinoma, bone cancer, bladder cancer, head and neck cancer, kidney cancer, liver cancer, gastrointestinal tissue cancer, esophageal cancer, ovarian cancer, pancreatic cancer, skin cancer, testicular cancer, thyroid cancer, uterine cancer, cervical cancer, vulvar cancer, leukemia, multiple myeloma, and lymphoma;

wherein said leukemia is preferably chronic lymphocytic leukemia (CLL), acute lymphoblastic leukemia (ALL), and chronic myeloid leukemia (CML).