

Supporting Information for

***In Vitro* Identification of Oridonin Hybrids as Potential Anti-TNBC
Agents inducing Cell Cycle Arrest and Apoptosis by Regulation of
p21, γ H2AX and Cleaved PARP**

Jinhua Ning,^{1‡} Nini Zhan,^{1‡} Zhanpan Wu,¹ Yuzhe Li,¹ Die Zhang,¹ Yadian Shi,¹ Yingxun Zhou,¹

Chuan-Huizi Chen,^{*1} and Wenbin Jin^{*1}.

¹ Key Laboratory of External Drug Delivery System and Preparation Technology in Universities
of Yunnan and Faculty of Chinese Materia Medica, Yunnan University of Chinese Medicine,
Kunming, Yunnan, China

[‡]These authors contributed equally.

*Corresponding authors: Wenbin Jin and Chuan-Huizi Chen

For W. B. J., email: 14900326r@connect.polyu.hk

For C.H.Z C., email: huizipurple@163.com

Table of Content

Figure S1-S36	^1H and ^{13}C spectra of compounds
Figure S37-S69	HRMS spectra of compounds
Figure S70-S72	HPLC-purity spectra of compounds
Table S1	Plasma stability of oridonin and compound 11a

Figure S1. ^1H and ^{13}C NMR spectra of **5,6,14-trihydroxy-4,4-dimethyl-8-methylenedecahydro-1H-6,11b-(epoxymethano)-6a,9-methanocyclohepta[a]naphthalene-1,7(8H)-dione (1)**

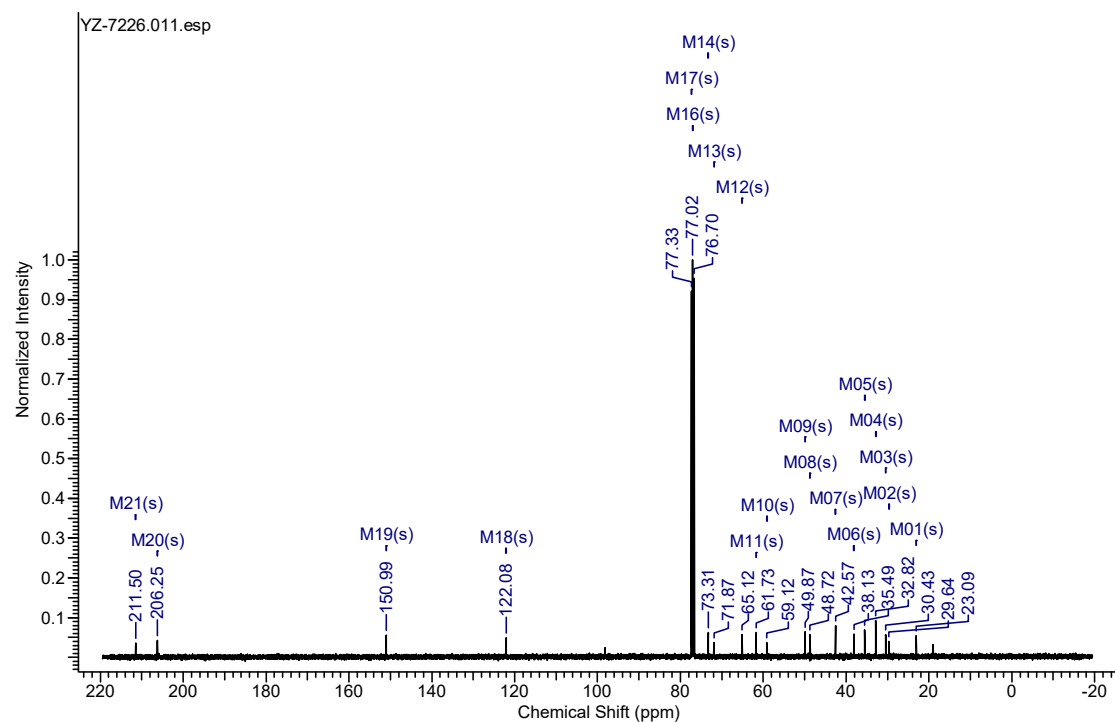
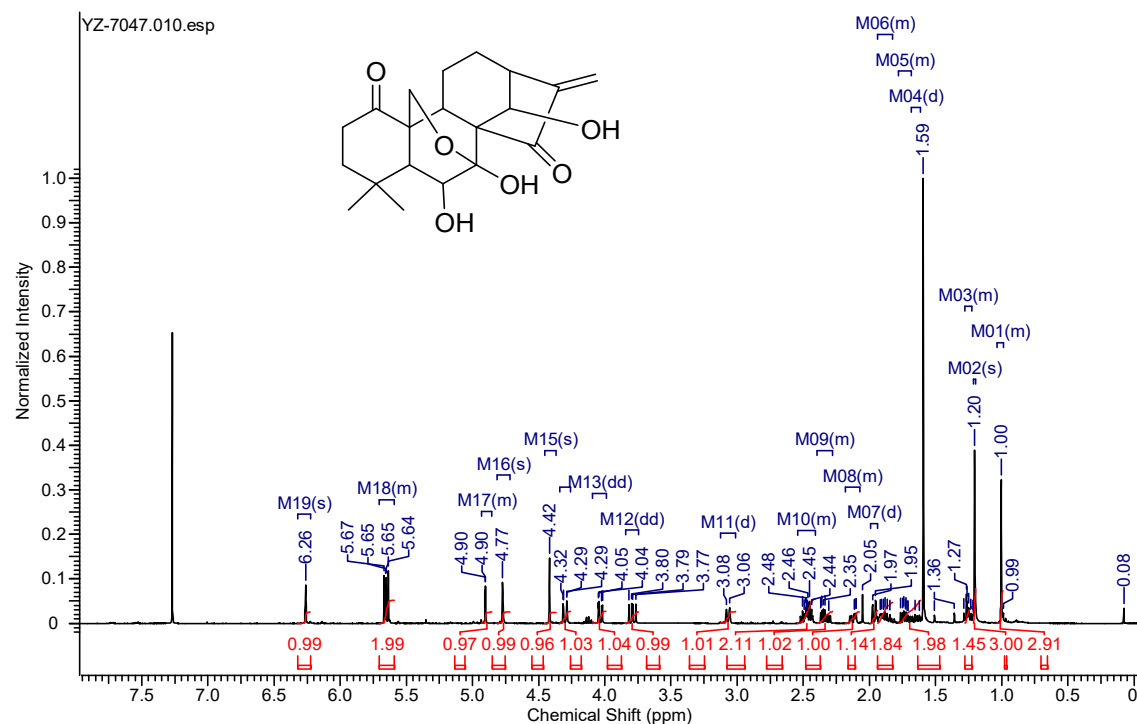


Figure S2. ^1H and ^{13}C NMR spectra of **5,6-dihydroxy-4,4-dimethyl-8-methylene-1,7-dioxododecahydro-1H-6,11b-(epoxymethano)-6a,9-methanocyclohepta[a]naphthalen-14-yl 2-(3,4,5-trimethoxyphenyl)acetate (1a)**

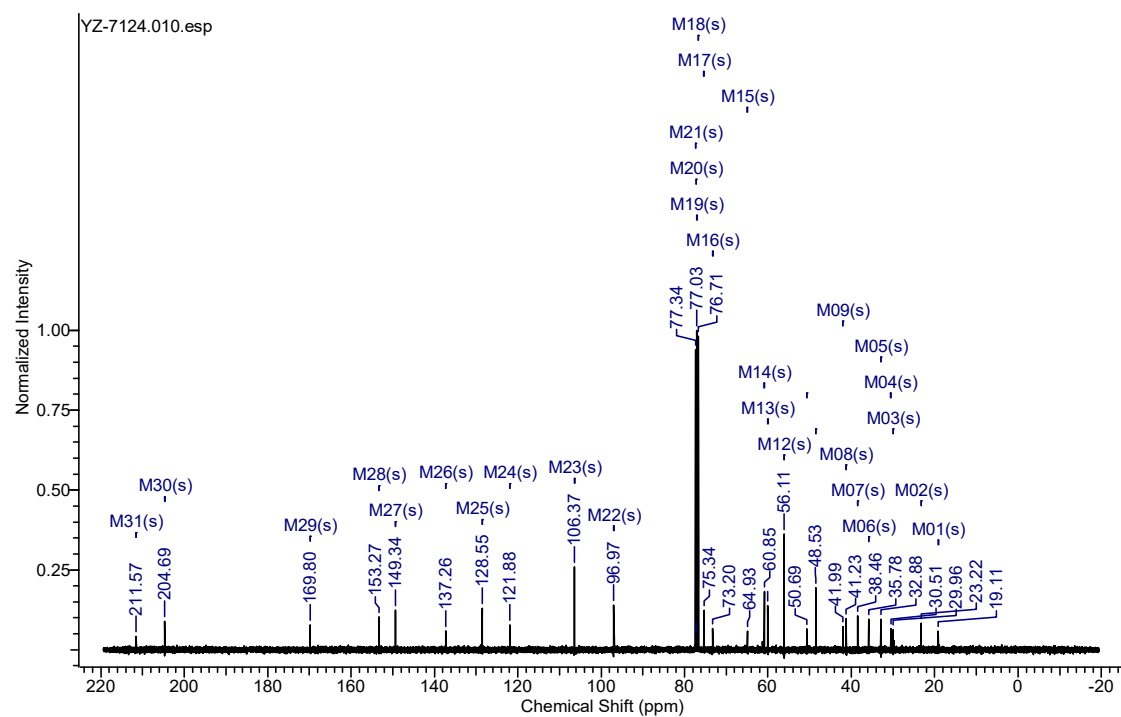
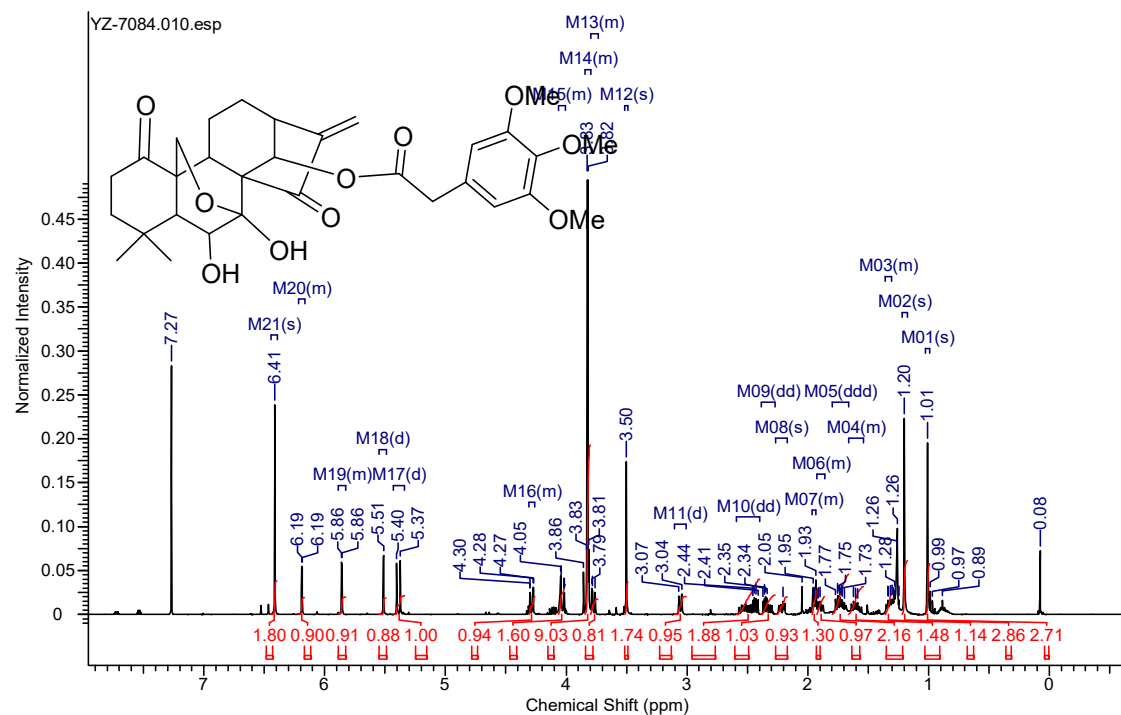


Figure S3. ^1H and ^{13}C NMR spectra of **5,6-dihydroxy-4,4-dimethyl-8-methylene-1,7-dioxododecahydro-1H-6,11b-(epoxymethano)-6a,9-methanocyclohepta[a]naphthalen-14-yl 2-(3,4-dimethoxyphenyl)acetate (1b)**

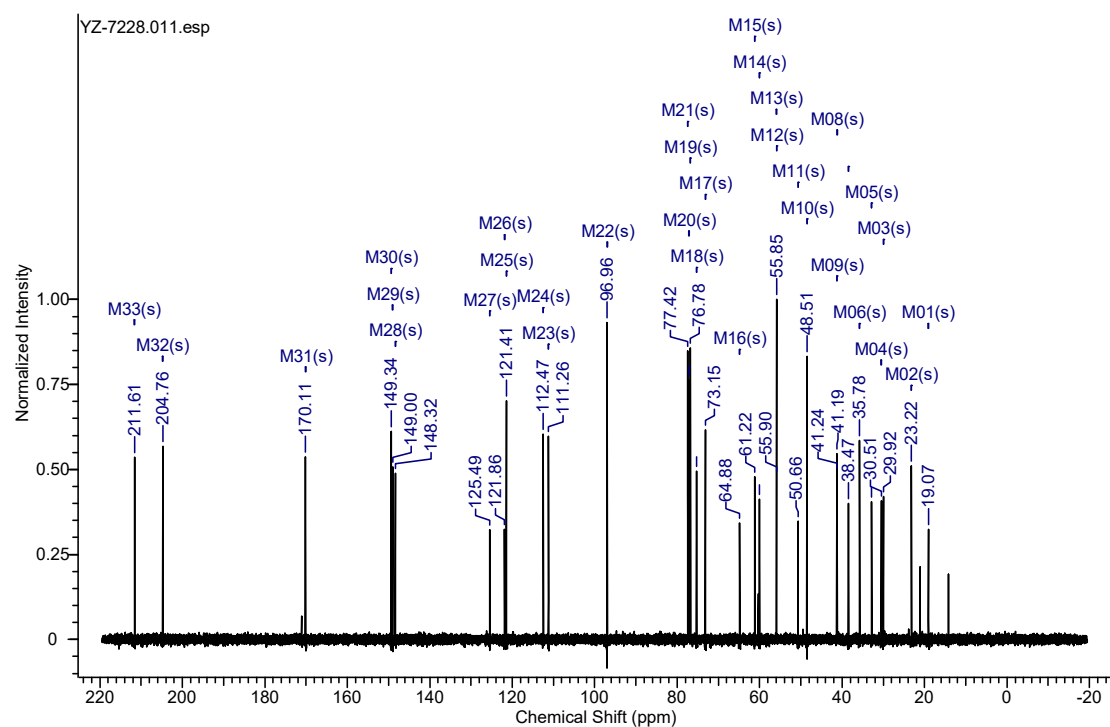
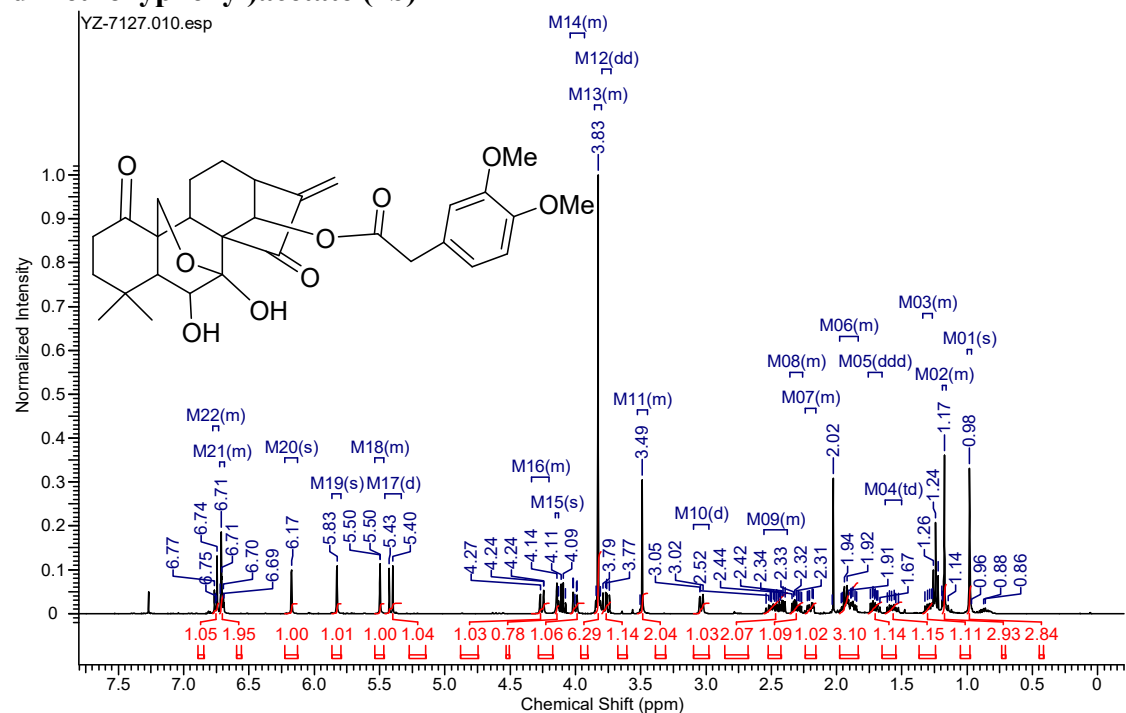


Figure S4. ^1H and ^{13}C NMR spectra of **5,6-dihydroxy-4,4-dimethyl-8-methylene-1,7-dioxododecahydro-1H-6,11b-(epoxymethano)-6a,9-methanocyclohepta[a]naphthalen-14-yl 2-(4-methoxyphenyl)acetate (1c)**

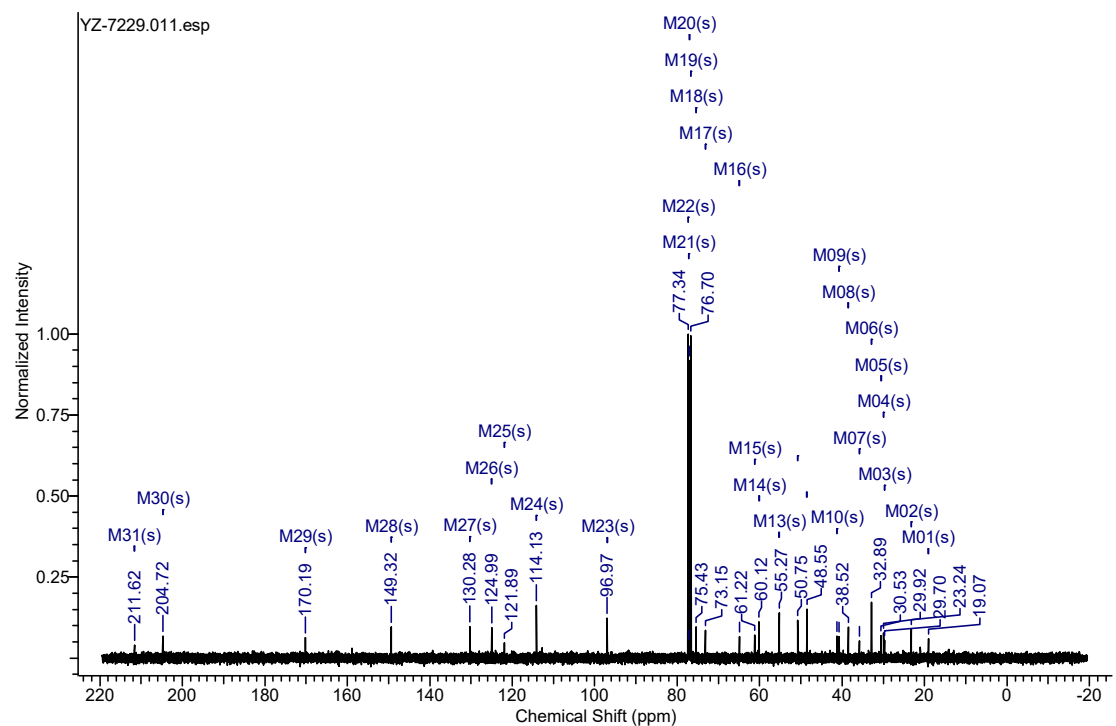
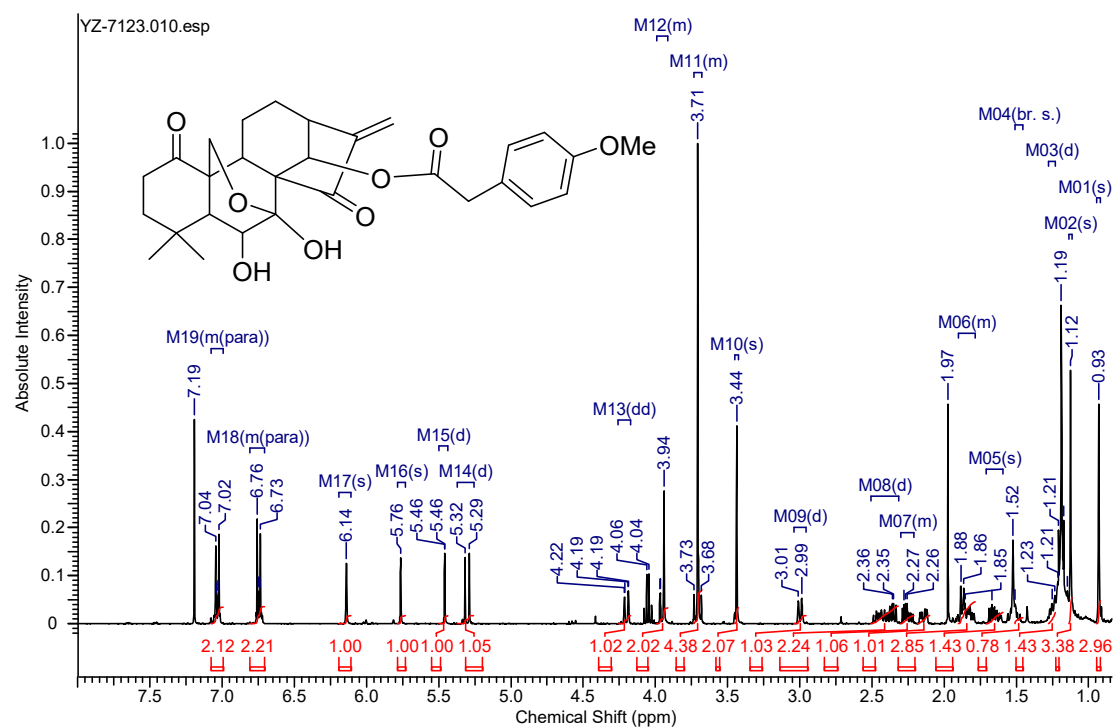


Figure S5. ^1H and ^{13}C NMR spectra of **5,6-dihydroxy-4,4-dimethyl-8-methylene-1,7-dioxododecahydro-1H-6,11b-(epoxymethano)-6a,9-methanocyclohepta[a]naphthalen-14-yl 2-(2-bromophenyl)acetate (1d)**

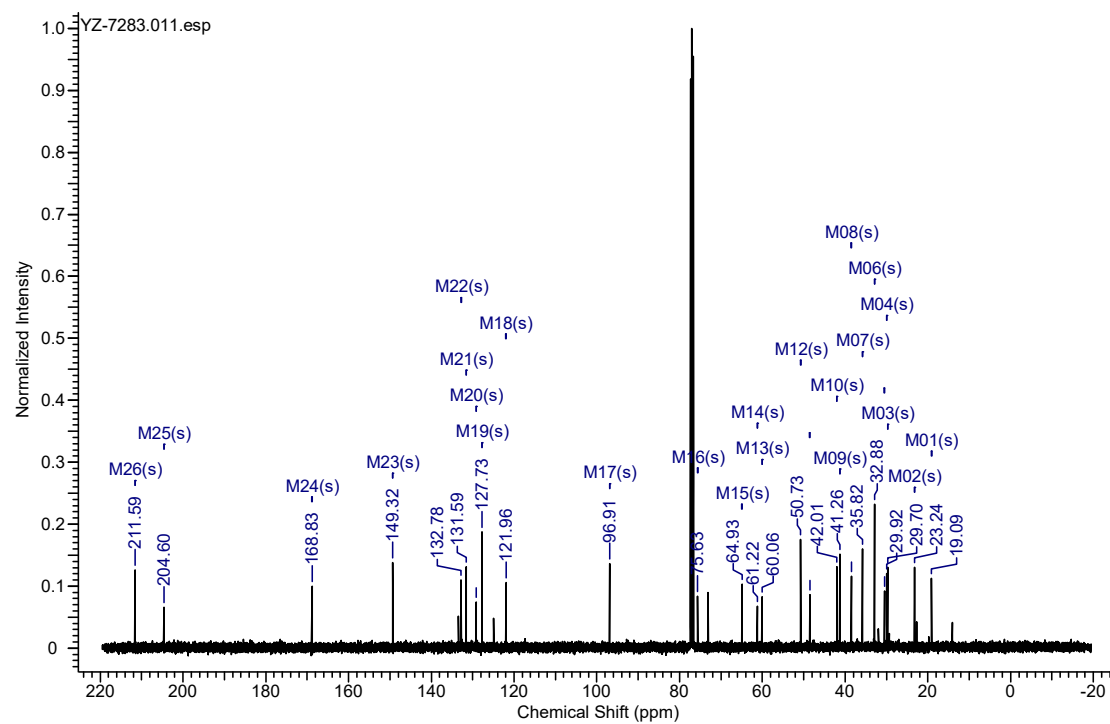
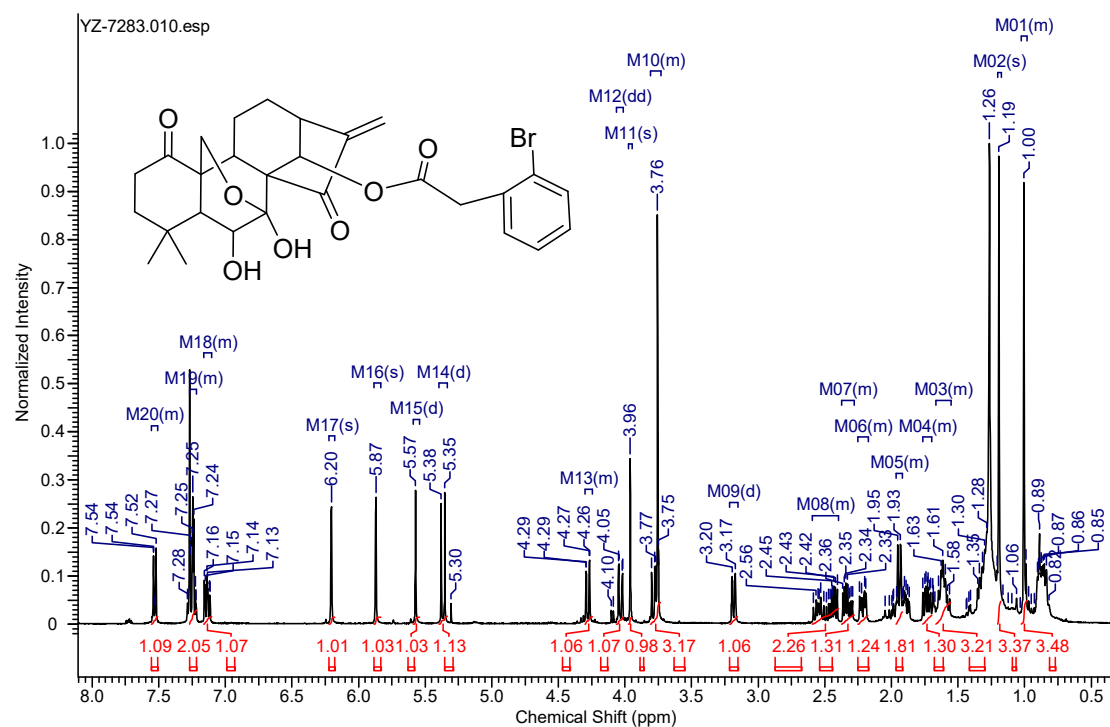


Figure S6. ^1H and ^{13}C NMR spectra of **5,6-dihydroxy-4,4-dimethyl-8-methylene-1,7-dioxododecahydro-1H-6,11b-(epoxymethano)-6a,9-methanocyclohepta[a]naphthalen-14-yl 4-(bis(2-chloroethyl)amino)benzoate (1e)**

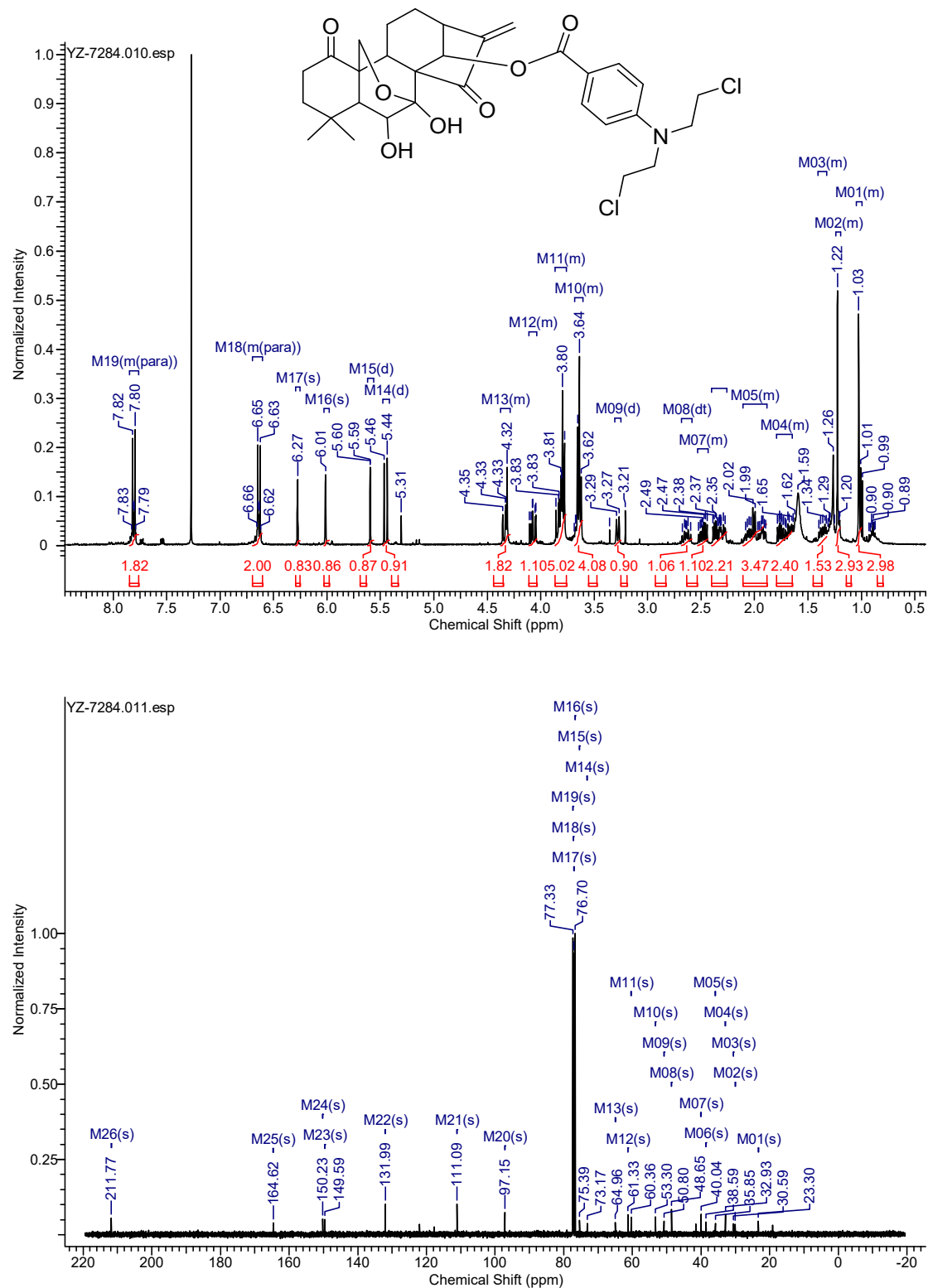


Figure S7. ^1H and ^{13}C NMR spectra of **5,6-dihydroxy-4,4-dimethyl-8-methylene-1,7-dioxododecahydro-1H-6,11b-(epoxymethano)-6a,9-methanocyclohepta[a]naphthalen-14-yl 2-(4-(bis(2-chloroethyl)amino)phenyl)acetate (1f)**

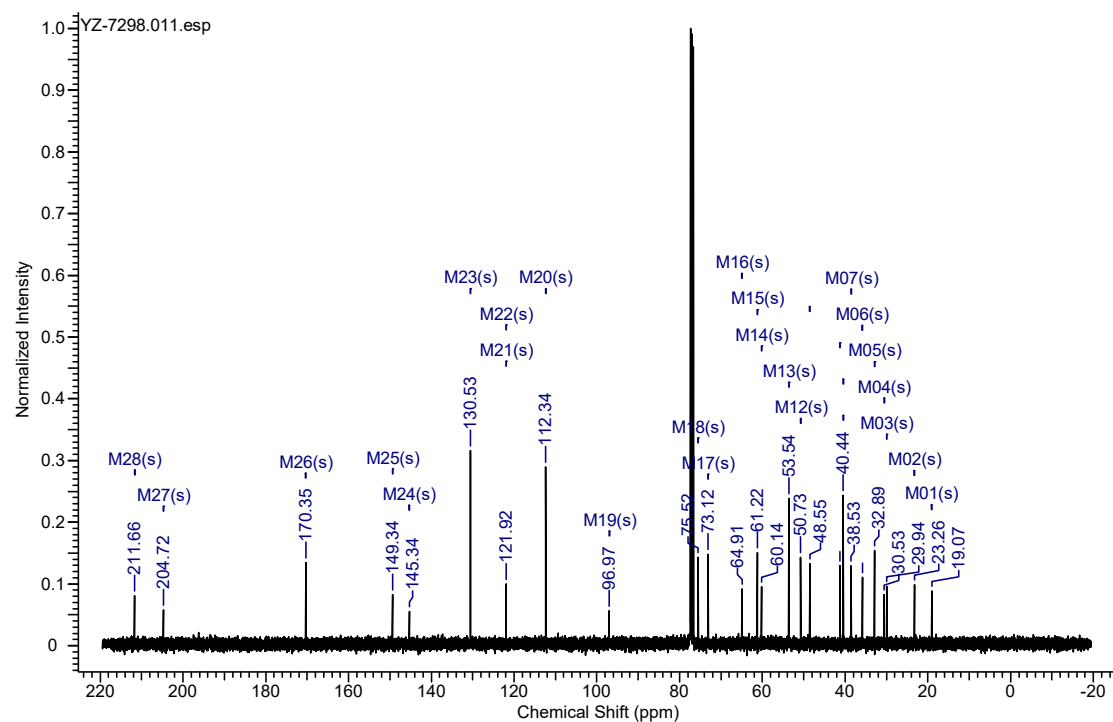
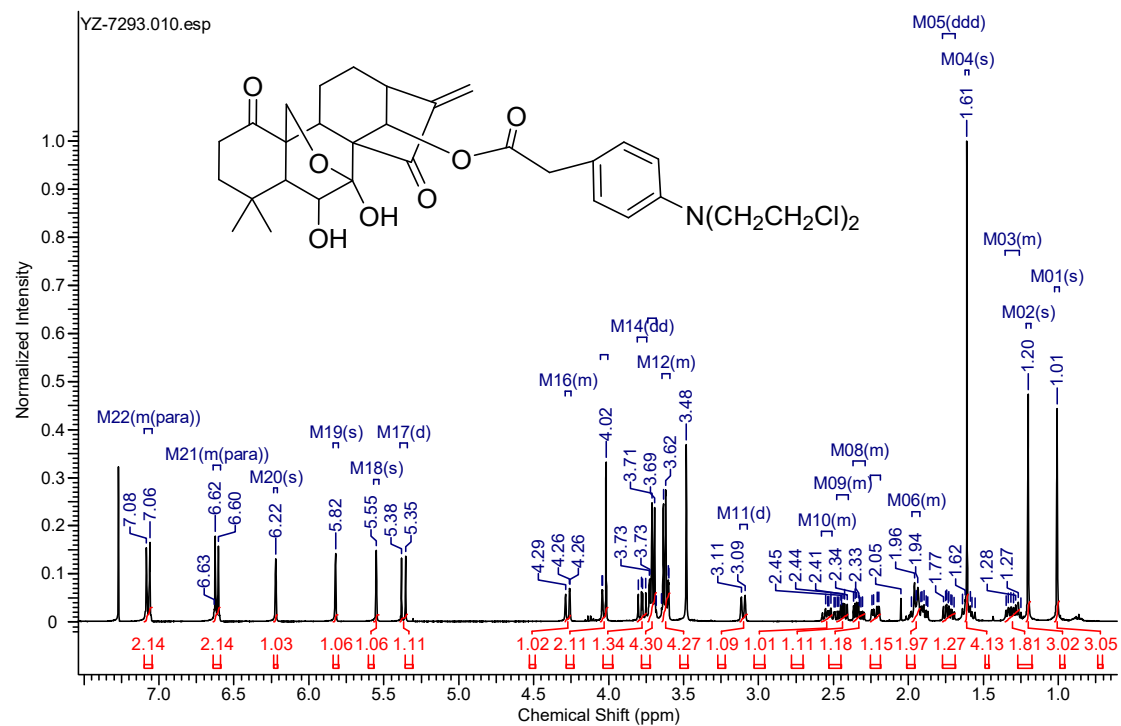


Figure S8. ^1H and ^{13}C NMR spectra of **5,6-dihydroxy-4,4-dimethyl-8-methylene-1,7-dioxododecahydro-1H-6,11b-(epoxymethano)-6a,9-methanocyclohepta[a]naphthalen-14-yl adamantane-1-carboxylate (1g)**

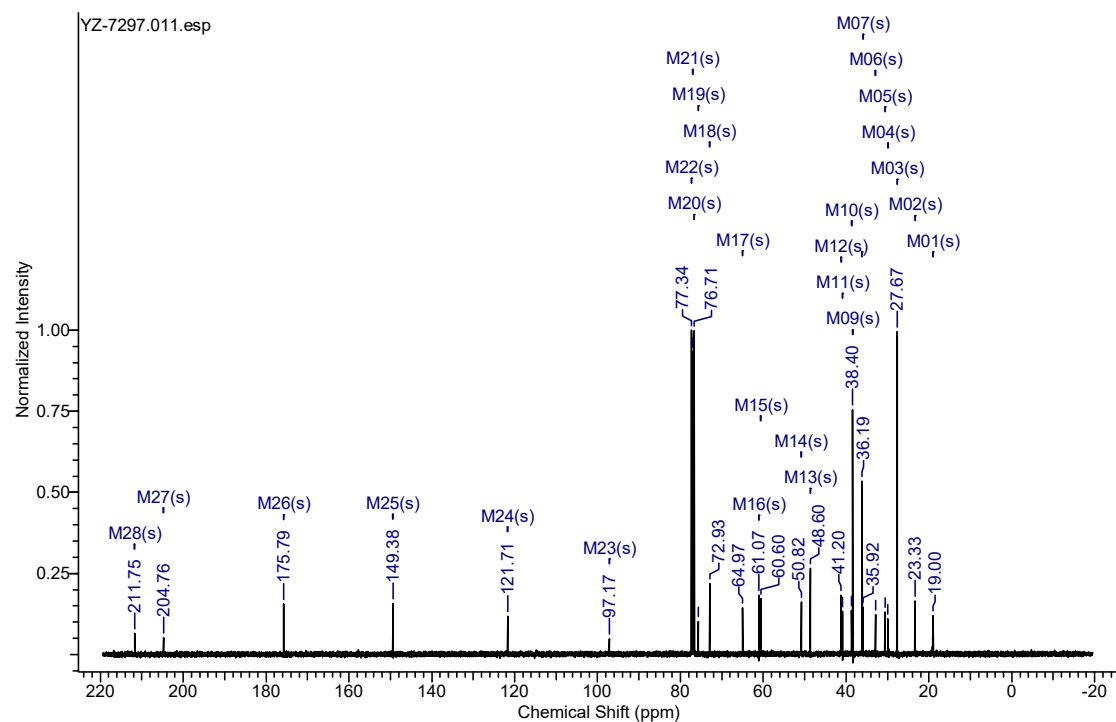
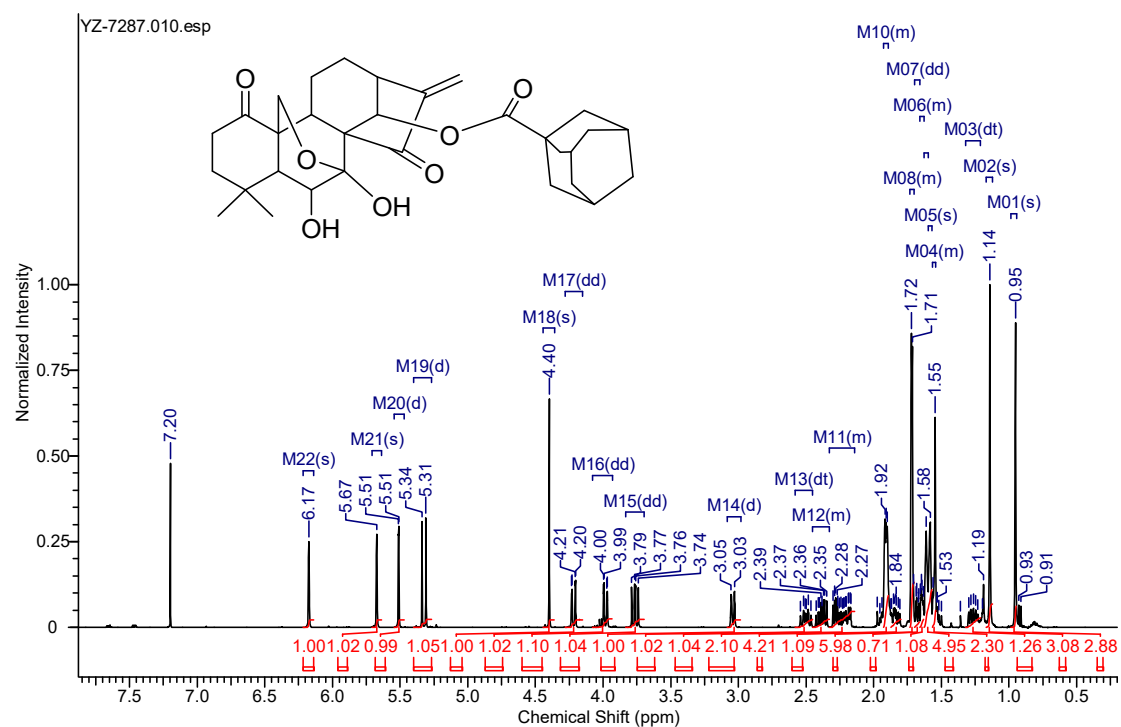


Figure S9. ^1H and ^{13}C NMR spectra of **5,6-dihydroxy-4,4-dimethyl-8-methylene-1,7-dioxododecahydro-1H-6,11b-(epoxymethano)-6a,9-methanocyclohepta[a]naphthalen-14-yl (E)-3-(4-(dimethylamino)phenyl)acrylate (1h)**

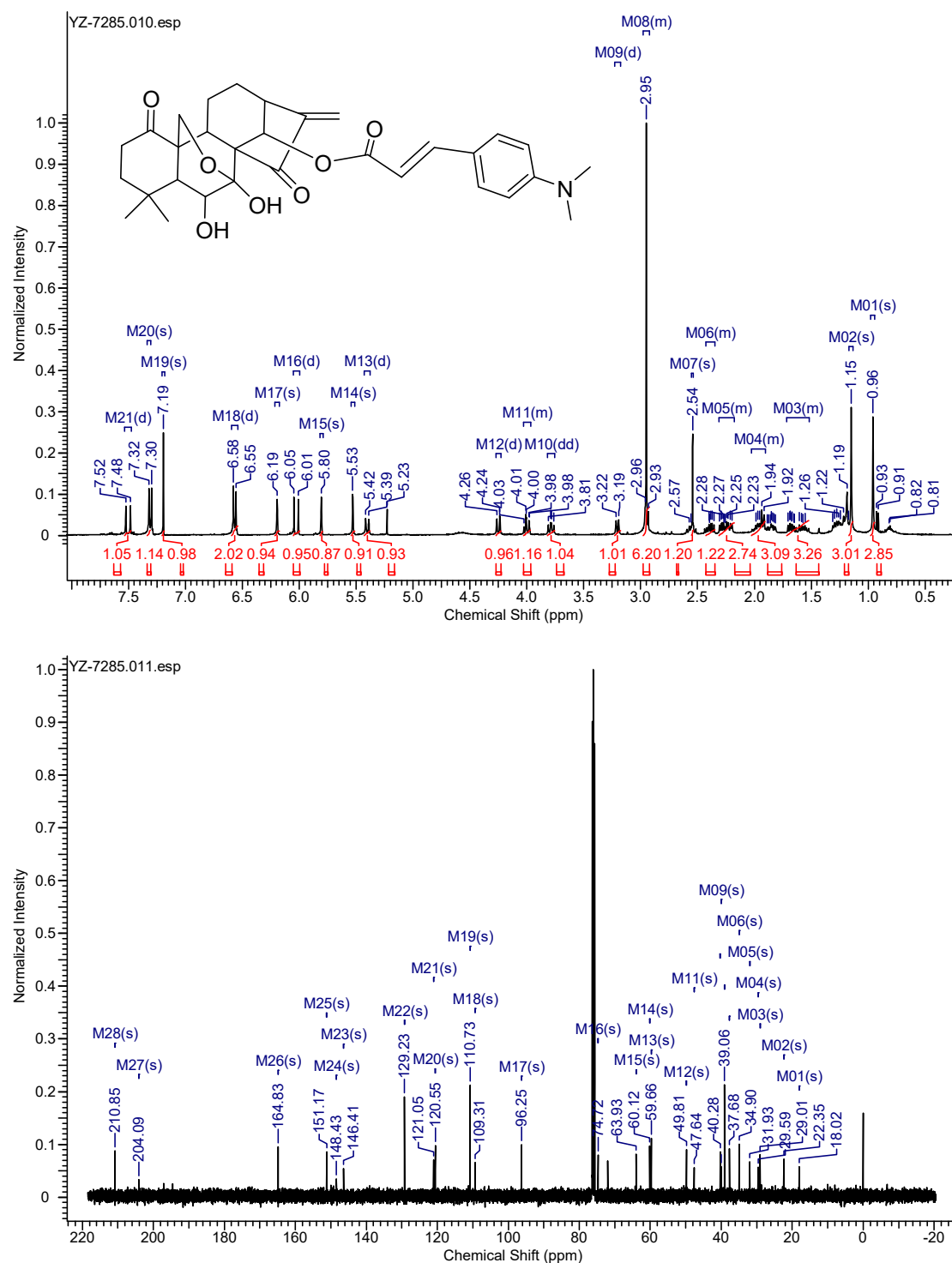


Figure S10. ^1H and ^{13}C NMR spectra of **4,4-dimethyl-8-methylene-1,6,7-trioxadodecahydro-1H-5,11b-(epoxymethano)-6a,9-methanocyclohepta[a]naphthalen-14-yl 2-(3,4,5-trimethoxyphenyl)acetate (2a)**

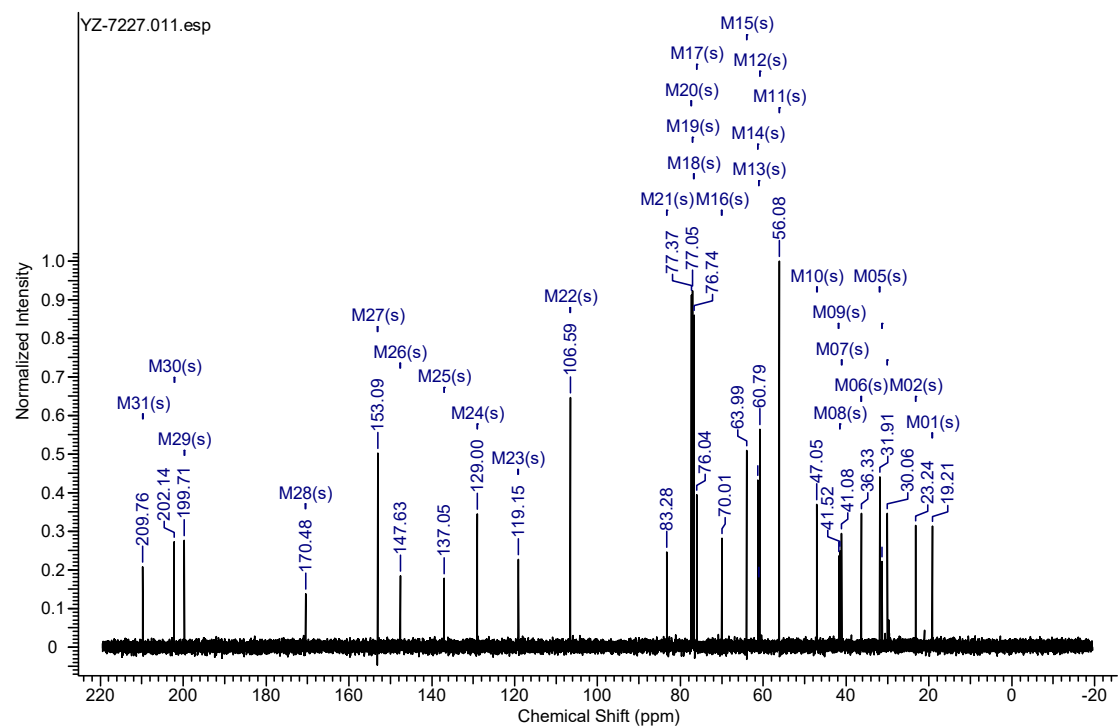
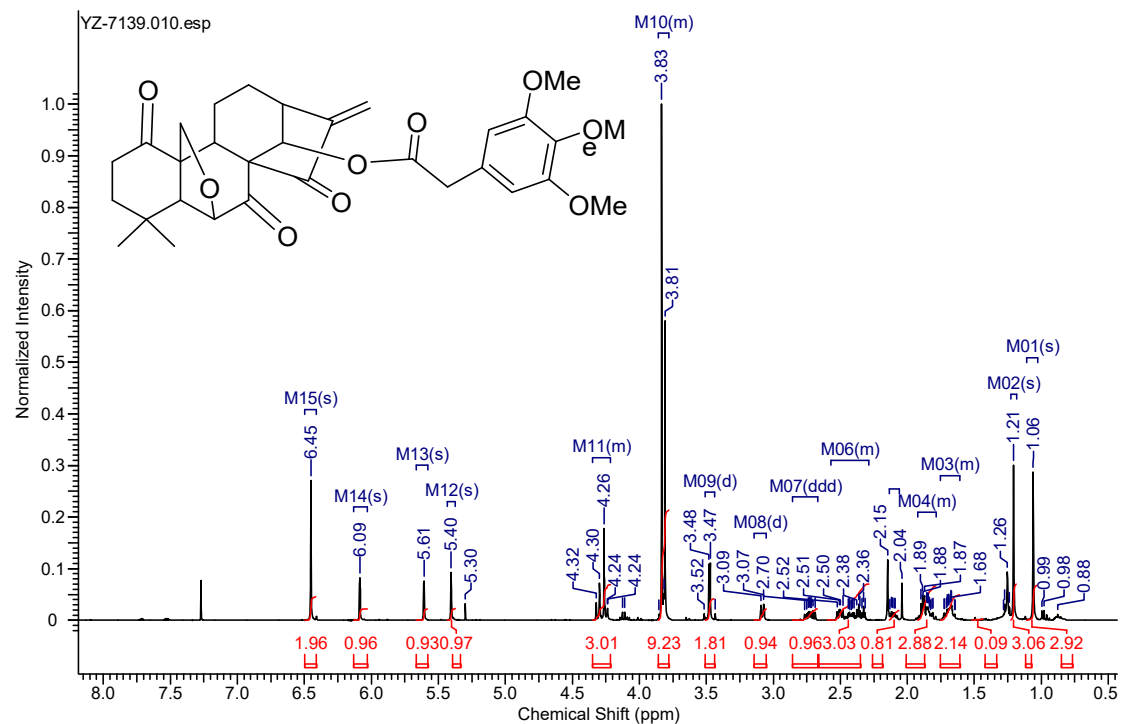


Figure S11. ^1H and ^{13}C NMR spectra of **4,4-dimethyl-8-methylene-1,6,7-trioxadodecahydro-1H-5,11b-(epoxymethano)-6a,9-methanocyclohepta[a]naphthalen-14-yl 2-(3,4-dimethoxyphenyl)acetate (2b)**

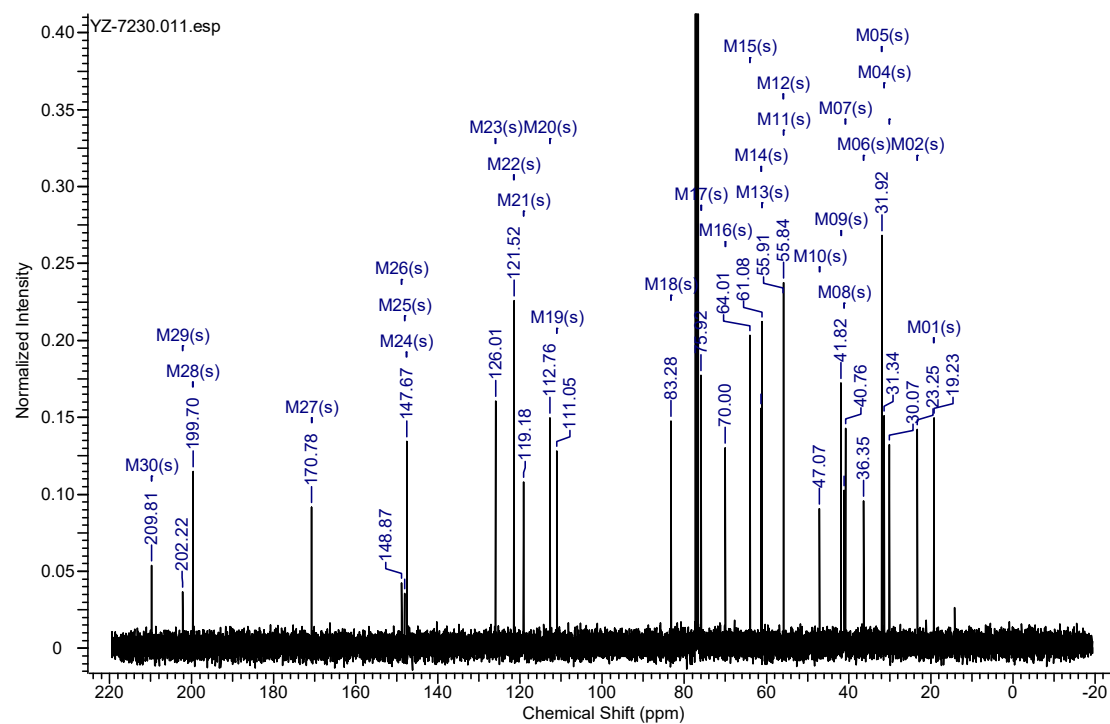
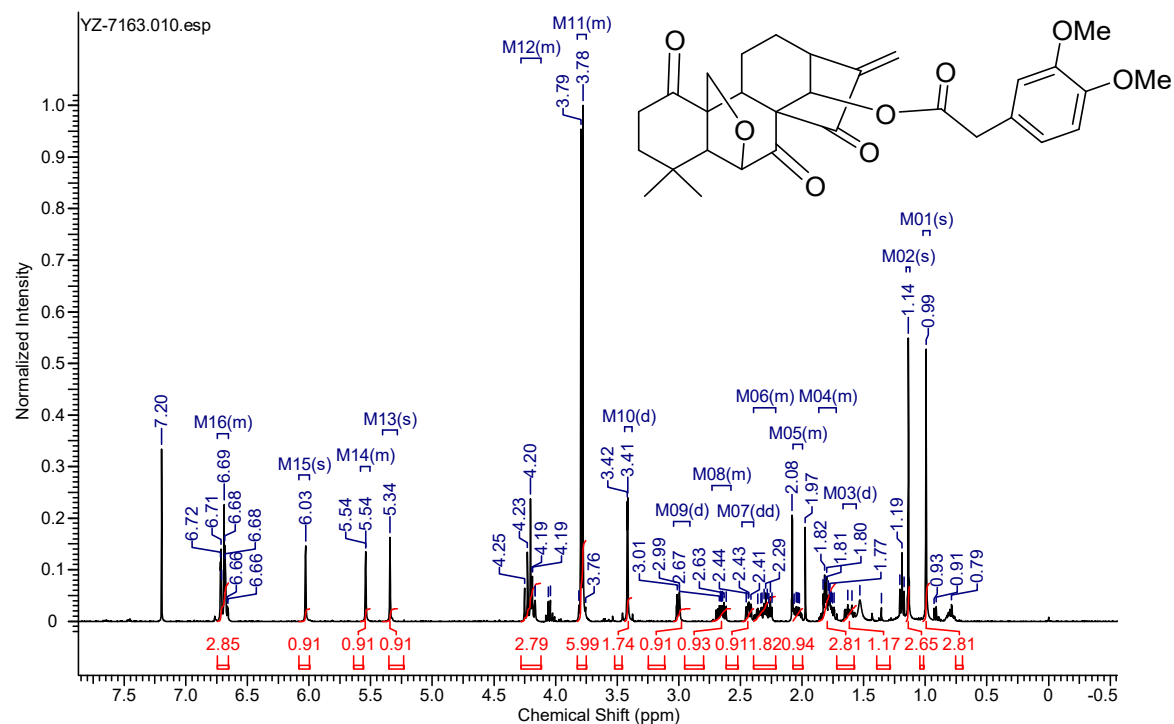


Figure S12. ^1H and ^{13}C NMR spectra of **4,4-dimethyl-8-methylene-1,6,7-trioxododecahydro-1H-5,11b-(epoxymethano)-6a,9-methanocyclohepta[a]naphthalen-14-yl 2-(4-methoxyphenyl)acetate (2c)**

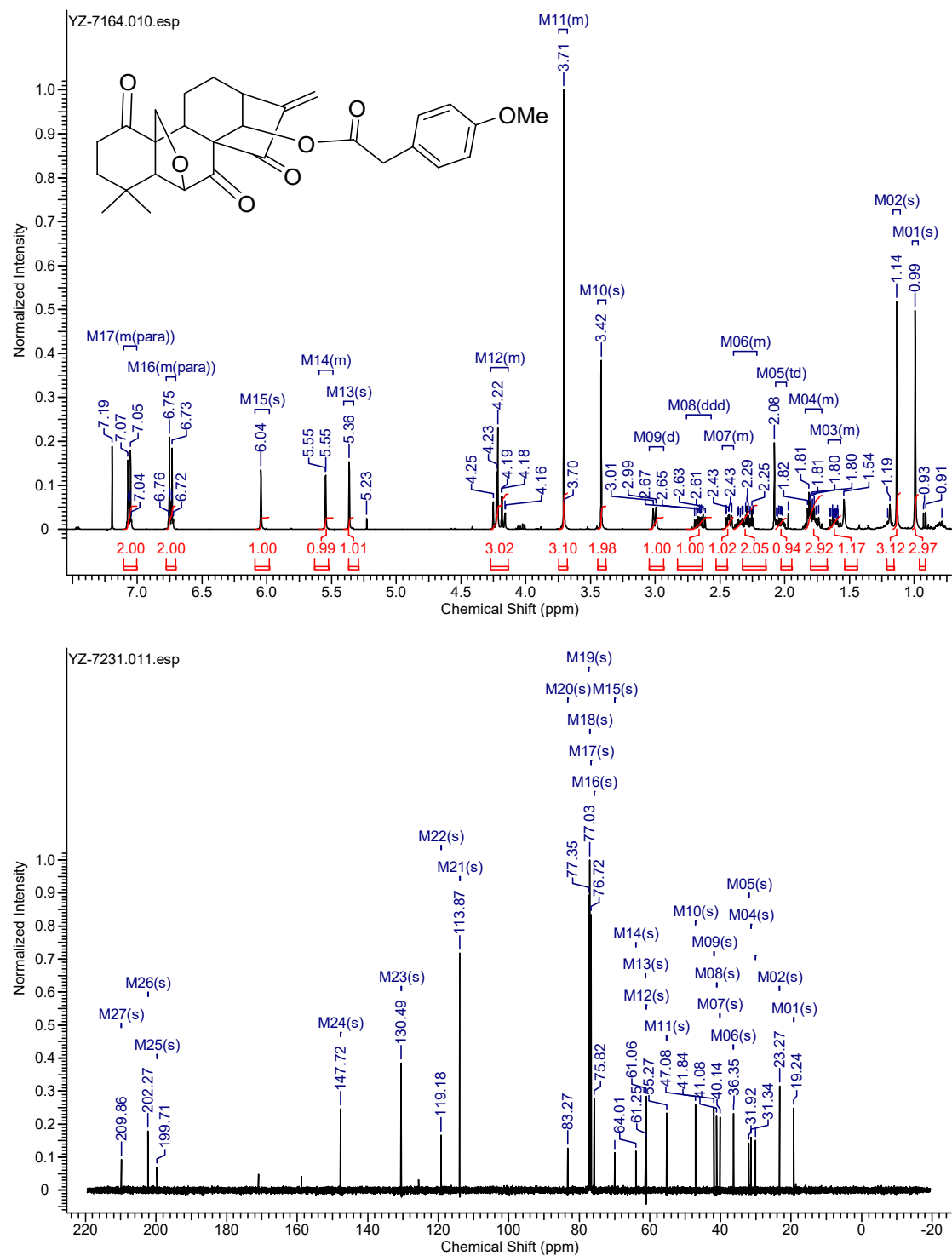


Figure S13. ^1H and ^{13}C NMR spectra of **4,4-dimethyl-8-methylene-1,6,7-trioxadodecahydro-1H-5,11b-(epoxymethano)-6a,9-methanocyclohepta[a]naphthalen-14-yl 2-(2-bromophenyl)acetate (2d)**

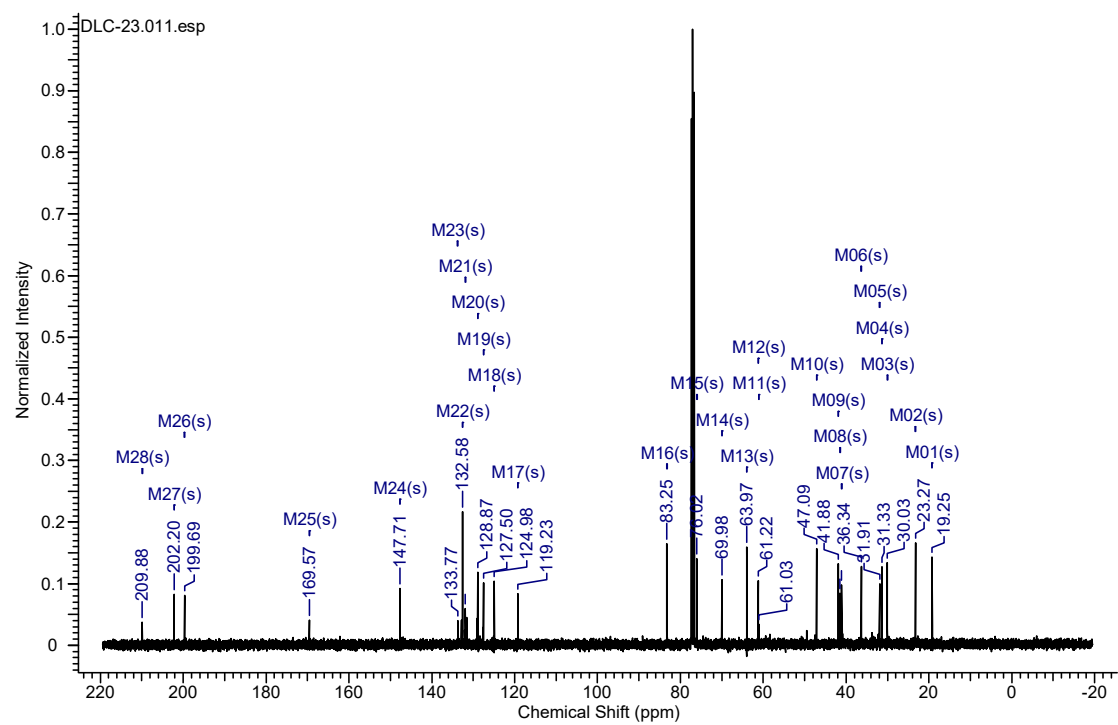
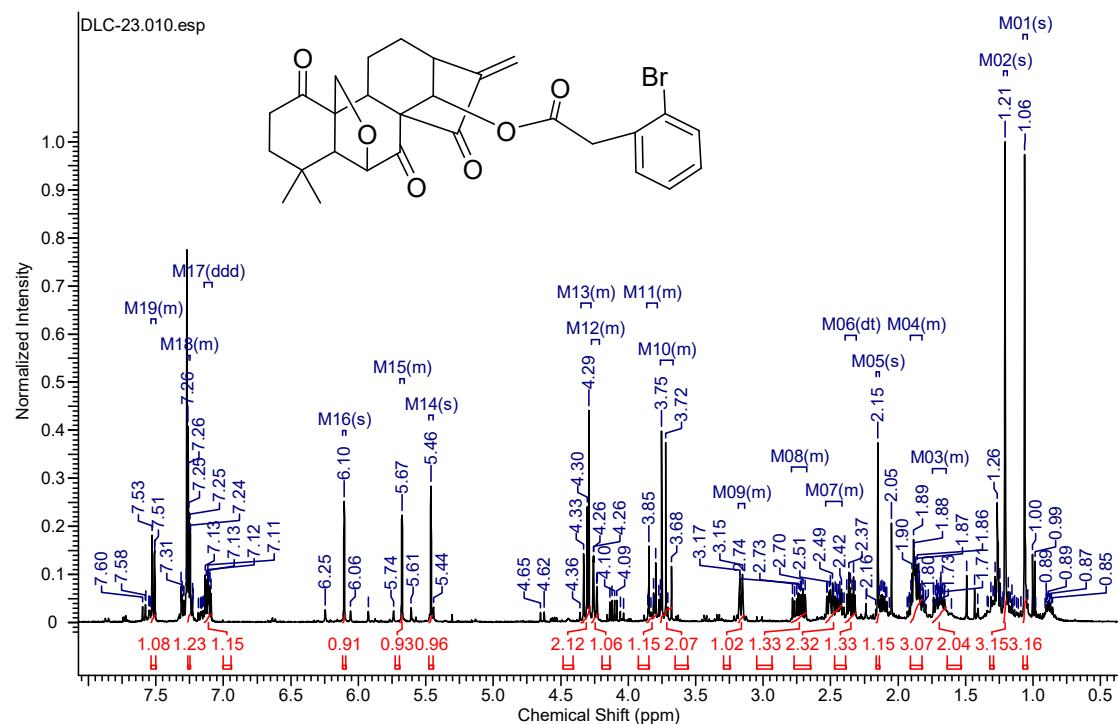


Figure S14. ^1H and ^{13}C NMR spectra of **4,4-dimethyl-8-methylene-1,6,7-trioxadodecahydro-1H-5,11b-(epoxymethano)-6a,9-methanocyclohepta[a]naphthalen-14-yl 4-(bis(2-chloroethyl)amino)benzoate (2e)**

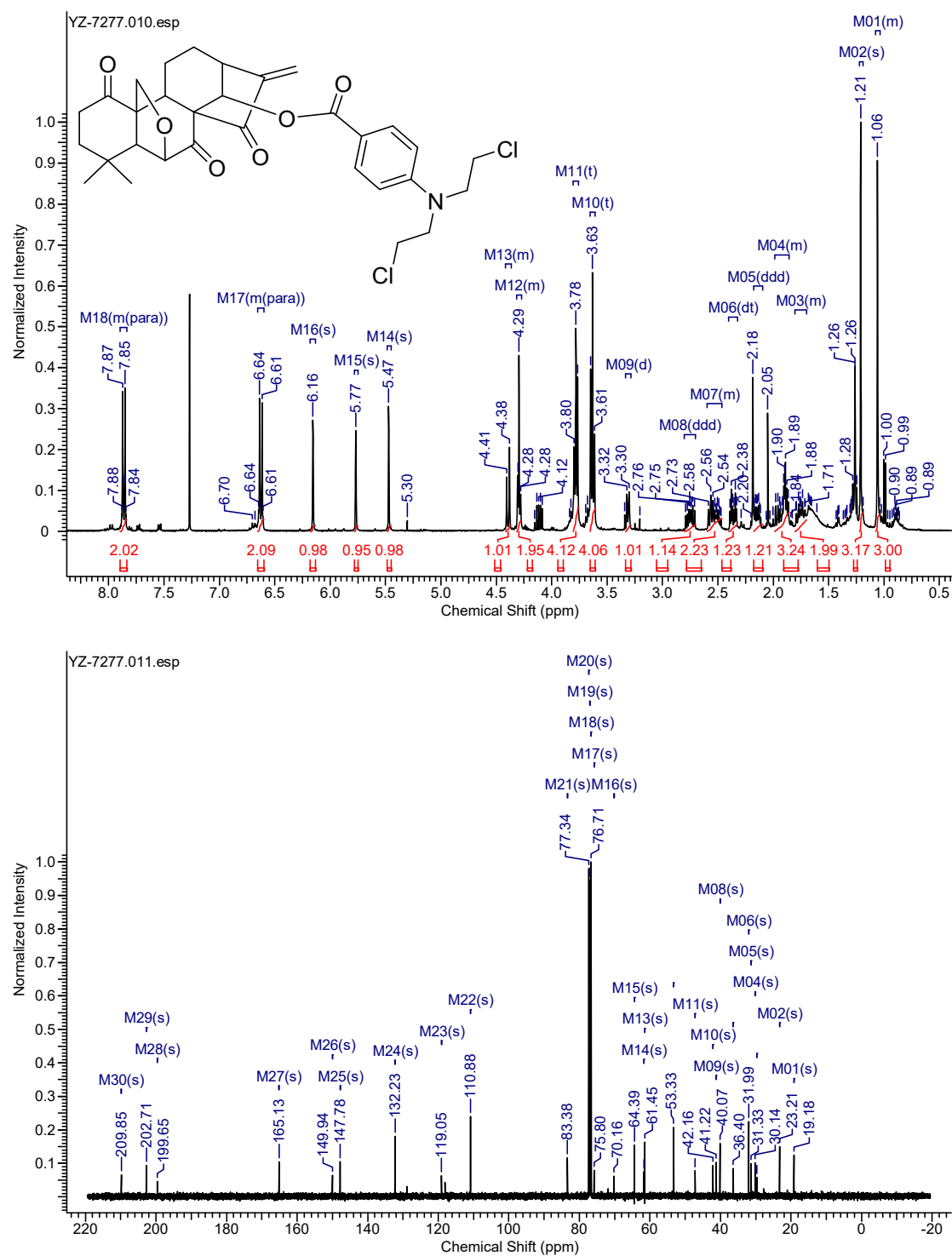


Figure S15. ^1H and ^{13}C NMR spectra of **4,4-dimethyl-8-methylene-1,6,7-trioxadodecahydro-1H-5,11b-(epoxymethano)-6a,9-methanocyclohepta[a]naphthalen-14-yl 2-(4-(bis(2-chloroethyl)amino)phenyl)acetate (2f)**

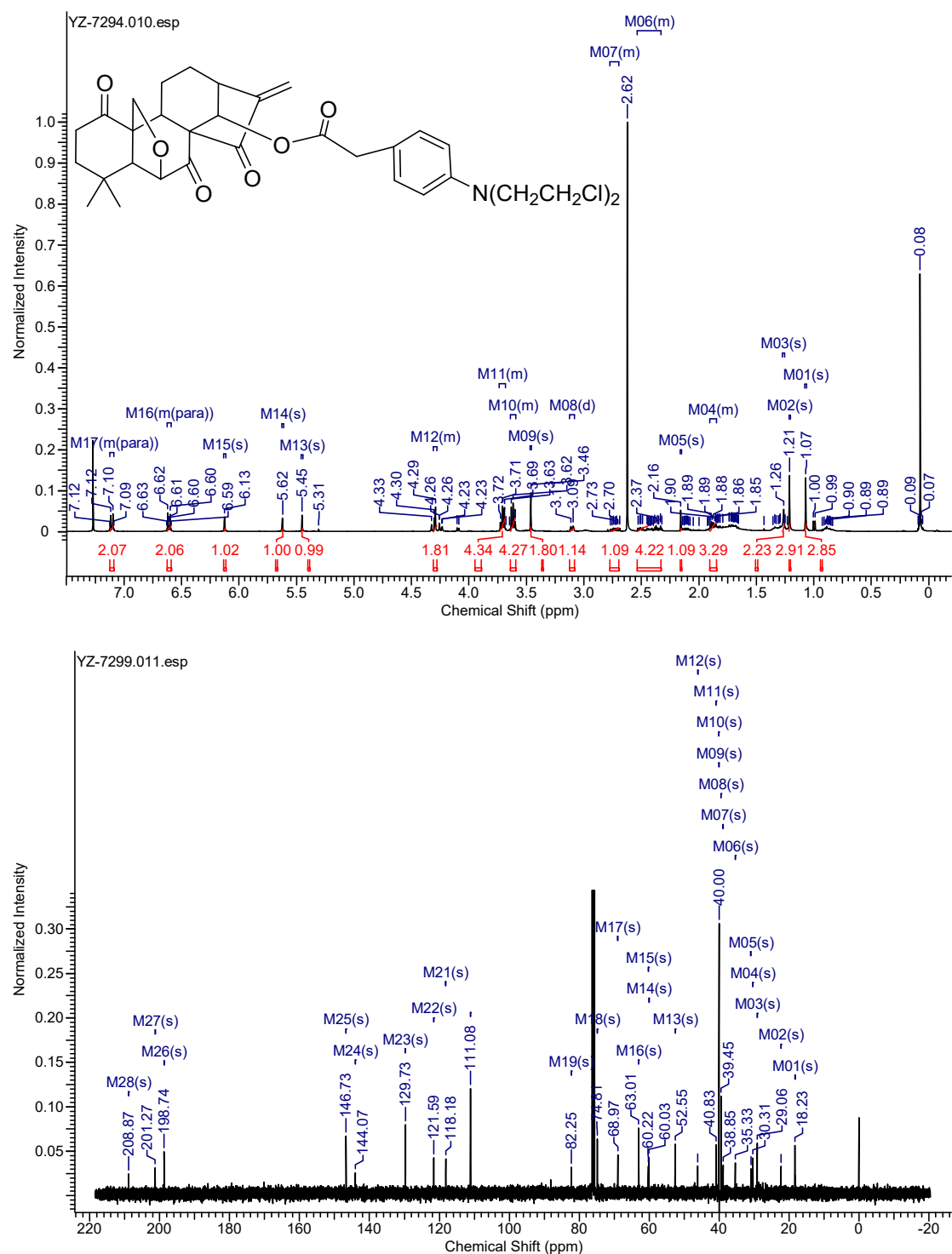


Figure S16. ^1H and ^{13}C NMR spectra of **4,4-dimethyl-8-methylene-1,6,7-trioxadodecahydro-1H-5,11b-(epoxymethano)-6a,9-methanocyclohepta[a]naphthalen-14-yl adamantane-1-carboxylate (2g)**

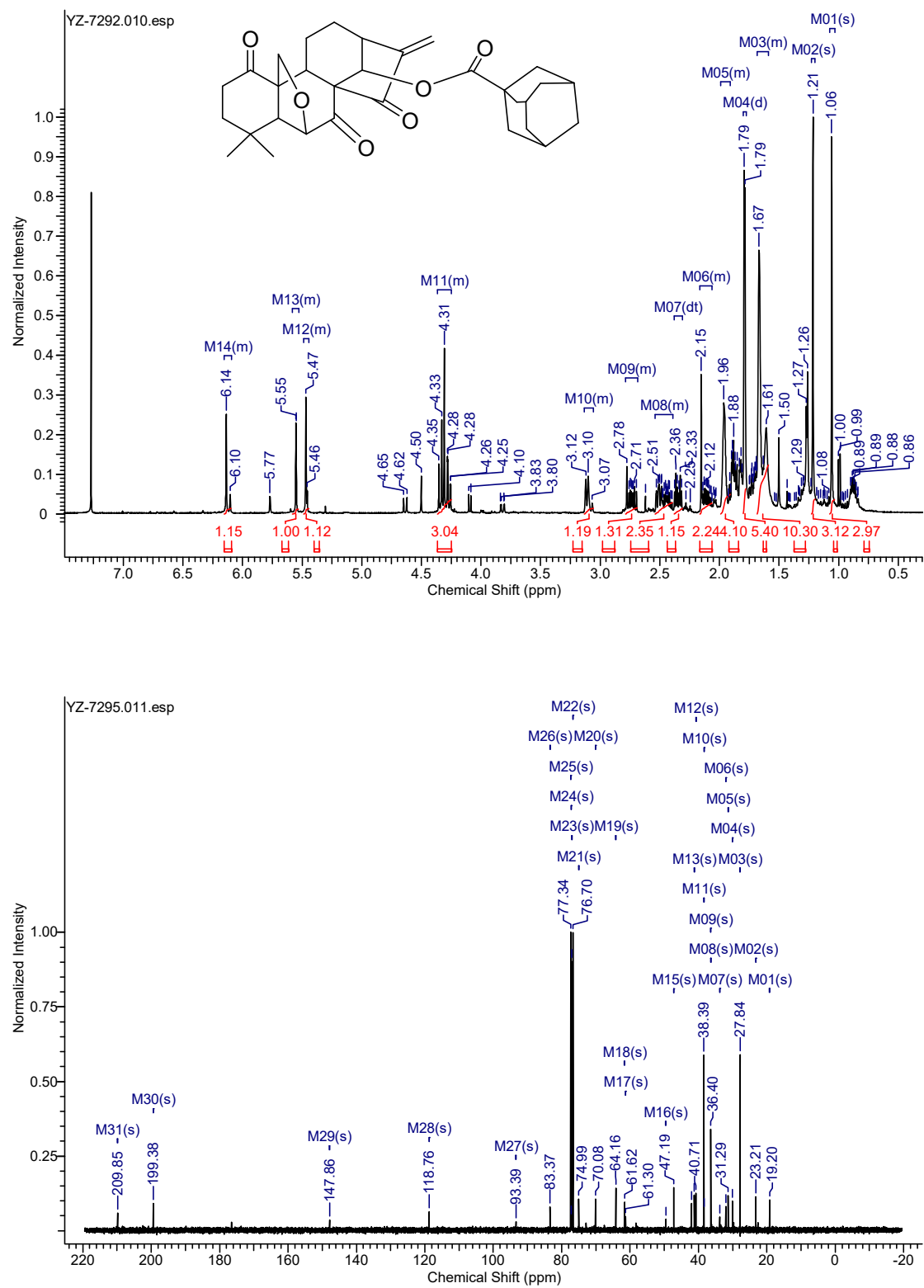


Figure S17. ^1H NMR spectra of **(3S,3aR,3a1R,6aS,7S,11S,11aS)-7,11-dihydroxy-5,5,8,8-tetramethyl-15-methylenedecahydro-2H-6a,11a-(epoxymethano)-3,3a1-ethanophenanthro[1,10-de][1,3]dioxin-14-one (3)**

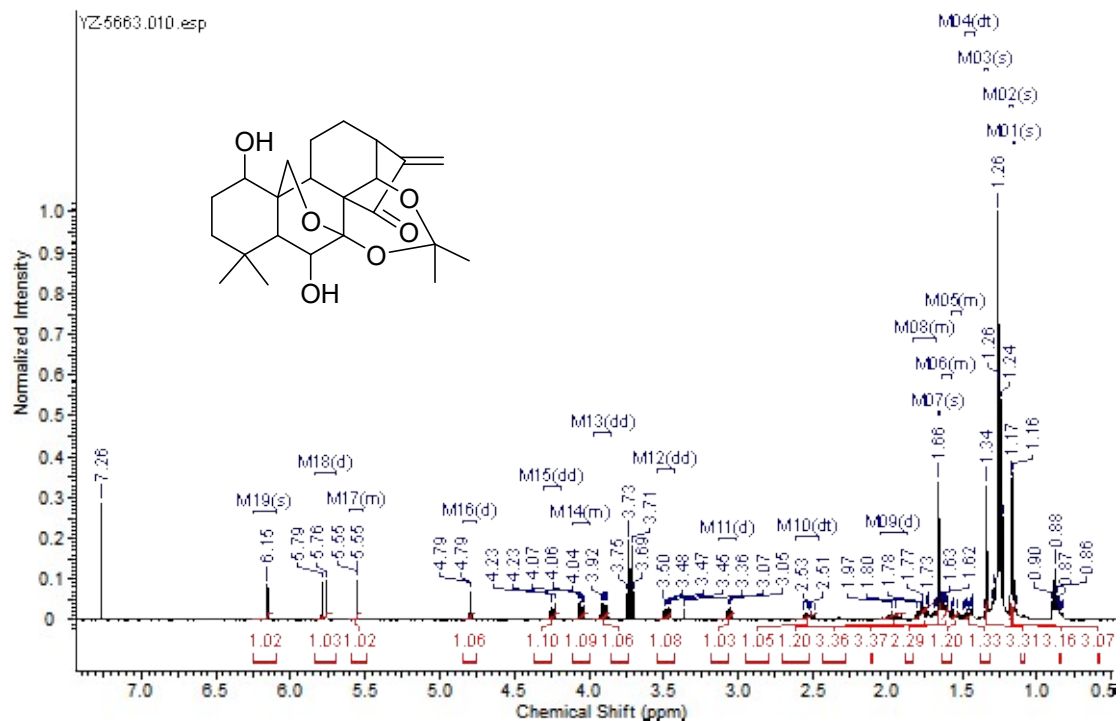


Figure S18. ^1H NMR spectra of
(3S,3aR,3a1R,6aS,7S,11S,11aS)-7-hydroxy-5,5,8,8-tetramethyl-15-methylene-14-oxodecahydro-2H-6a,11a-(epoxymethano)-3,3a1-ethanophenanthro[1,10-de][1,3]dioxin-11-yl methanesulfonate (4)

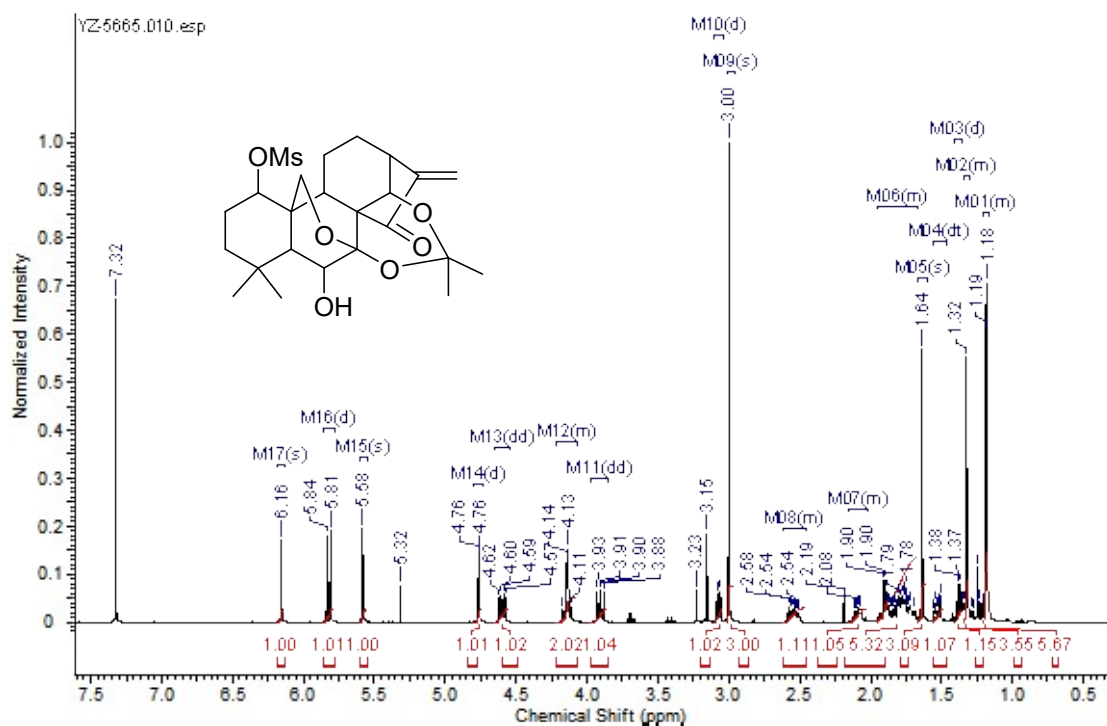


Figure S19. ^1H NMR spectra of
(3S,3aR,3a1R,6aS,7S,11aR)-7-hydroxy-5,5,8,8-tetramethyl-15-methylene-
1,3,3a,7,7a,8,9,11b-octahydro-2H-6a,11a-(epoxymethano)-3,3a1-
ethanophenanthro[1,10-de][1,3]dioxin-14-one (5)

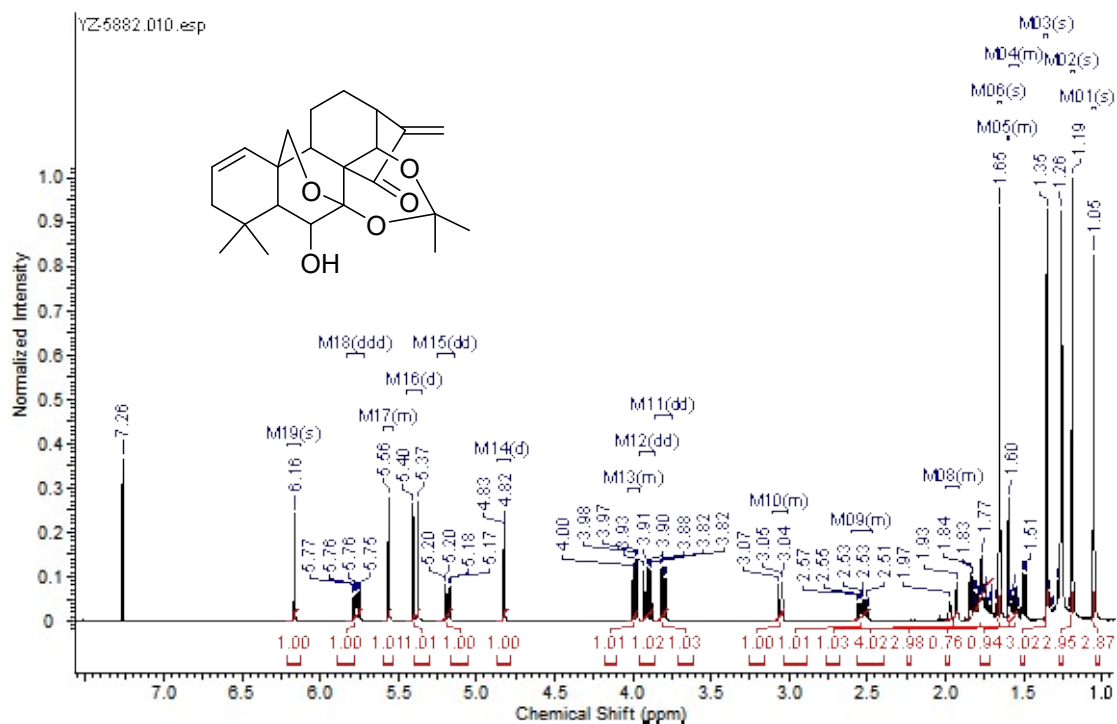


Figure S20. ^1H and ^{13}C NMR spectra of **5,6,14-trihydroxy-4,4-dimethyl-8-methylene-4,4a,5,6,9,10,11,11a-octahydro-3H-6,11b-(epoxymethano)-6a,9-methanocyclohepta[a]naphthalen-7(8H)-one (6)**

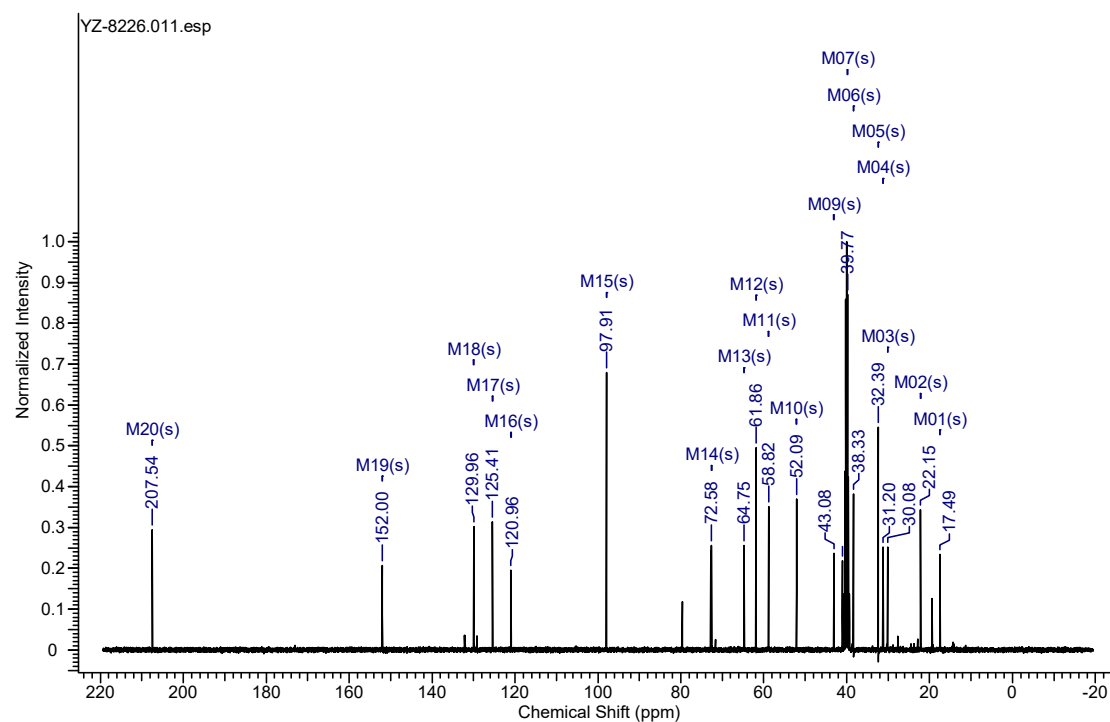
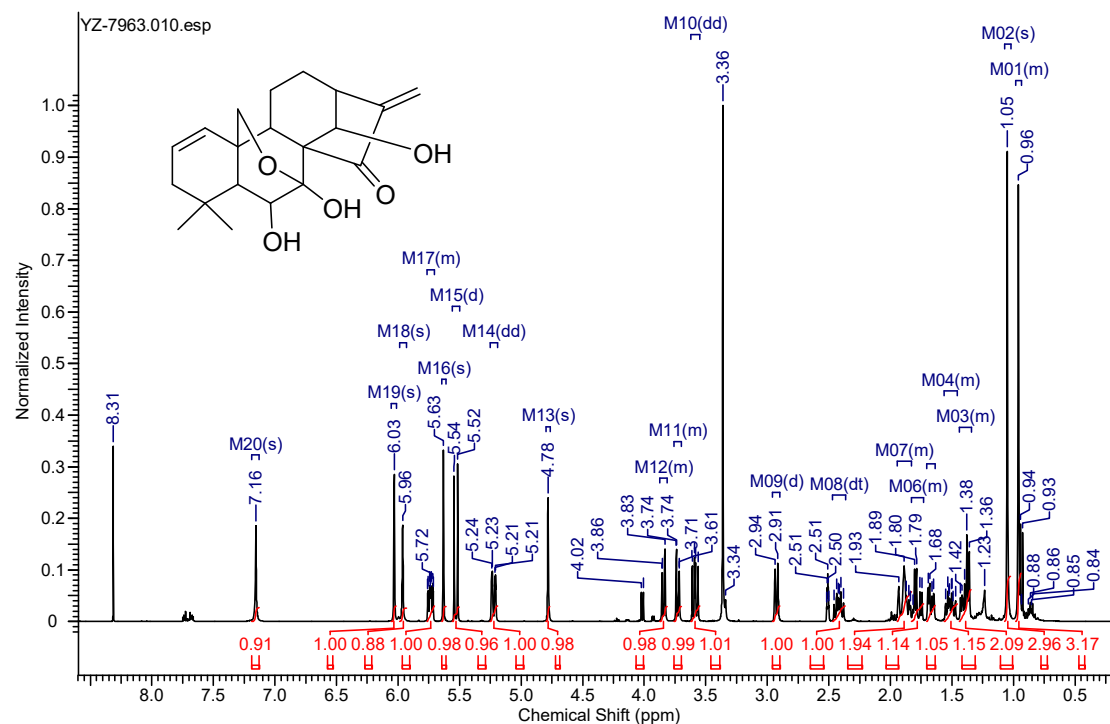


Figure S21. ^1H and ^{13}C NMR spectra of **5,6-dihydroxy-4,4-dimethyl-8-methylene-7-oxo-4,4a,5,6,7,8,9,10,11,11a-decahydro-3H-6,11b-(epoxymethano)-6a,9-methanocyclohepta[a]naphthalen-14-yl 2-(3,4,5-trimethoxyphenyl)acetate (6a)**

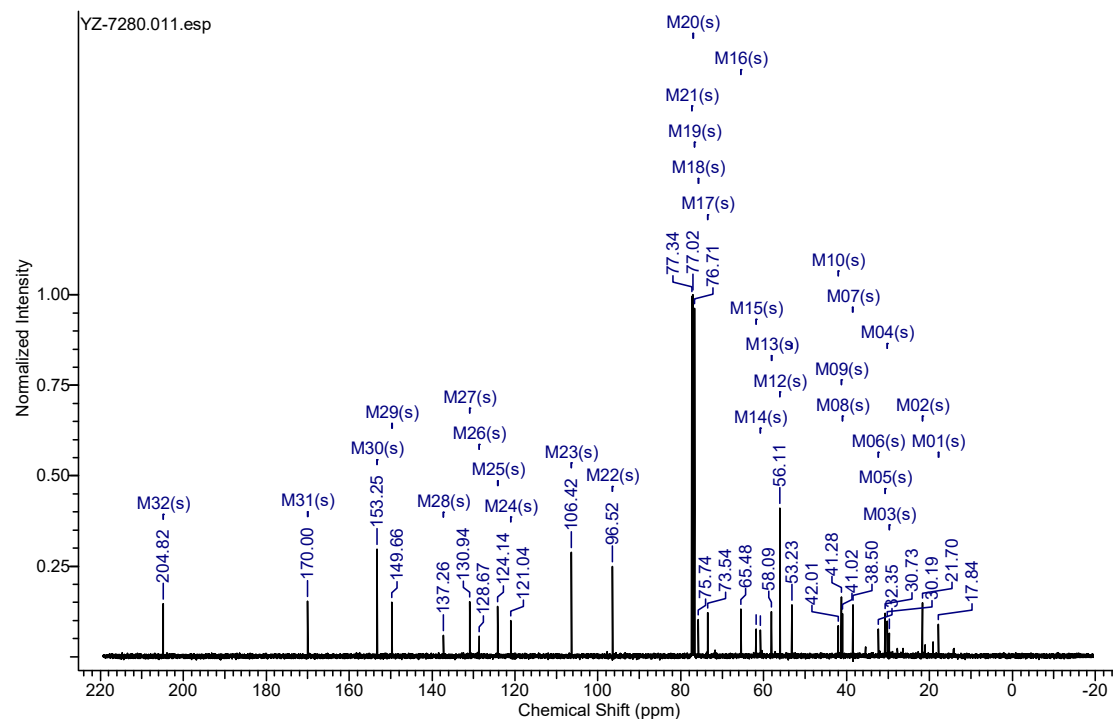
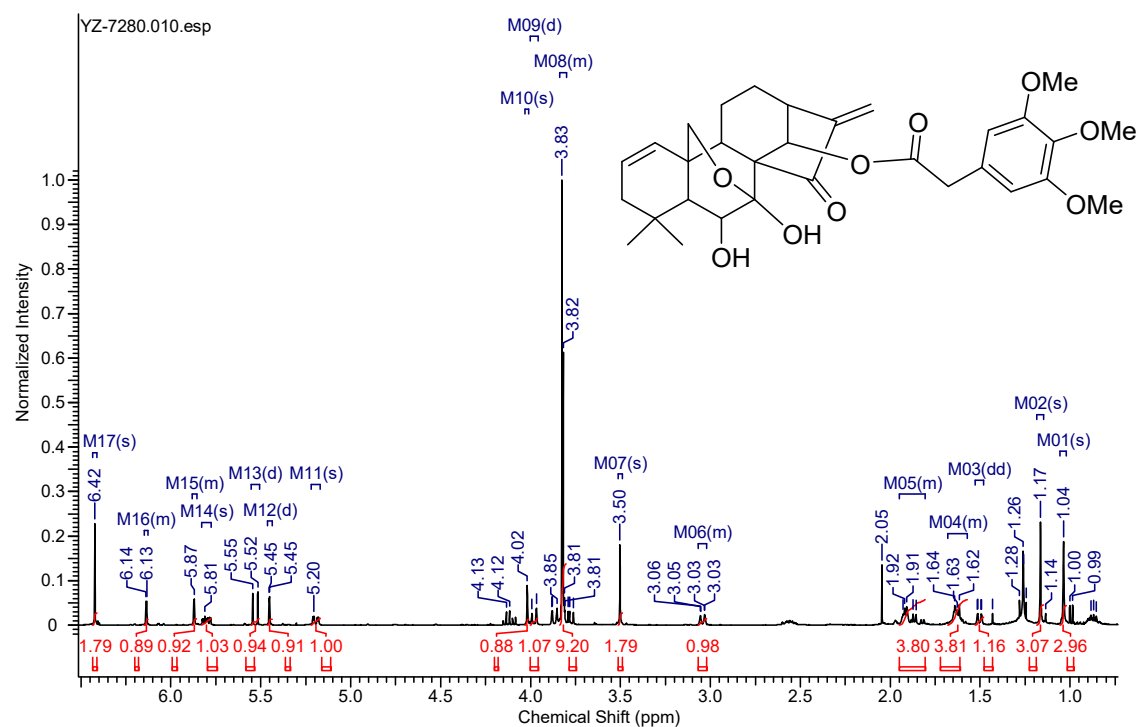


Figure S22. ^1H and ^{13}C NMR spectra of **5,6-dihydroxy-4,4-dimethyl-8-methylene-7-oxo-4,4a,5,6,7,8,9,10,11,11a-decahydro-3H-6,11b-(epoxymethano)-6a,9-methanocyclohepta[a]naphthalen-14-yl 2-(3,4-dimethoxyphenyl)acetate (6b)**

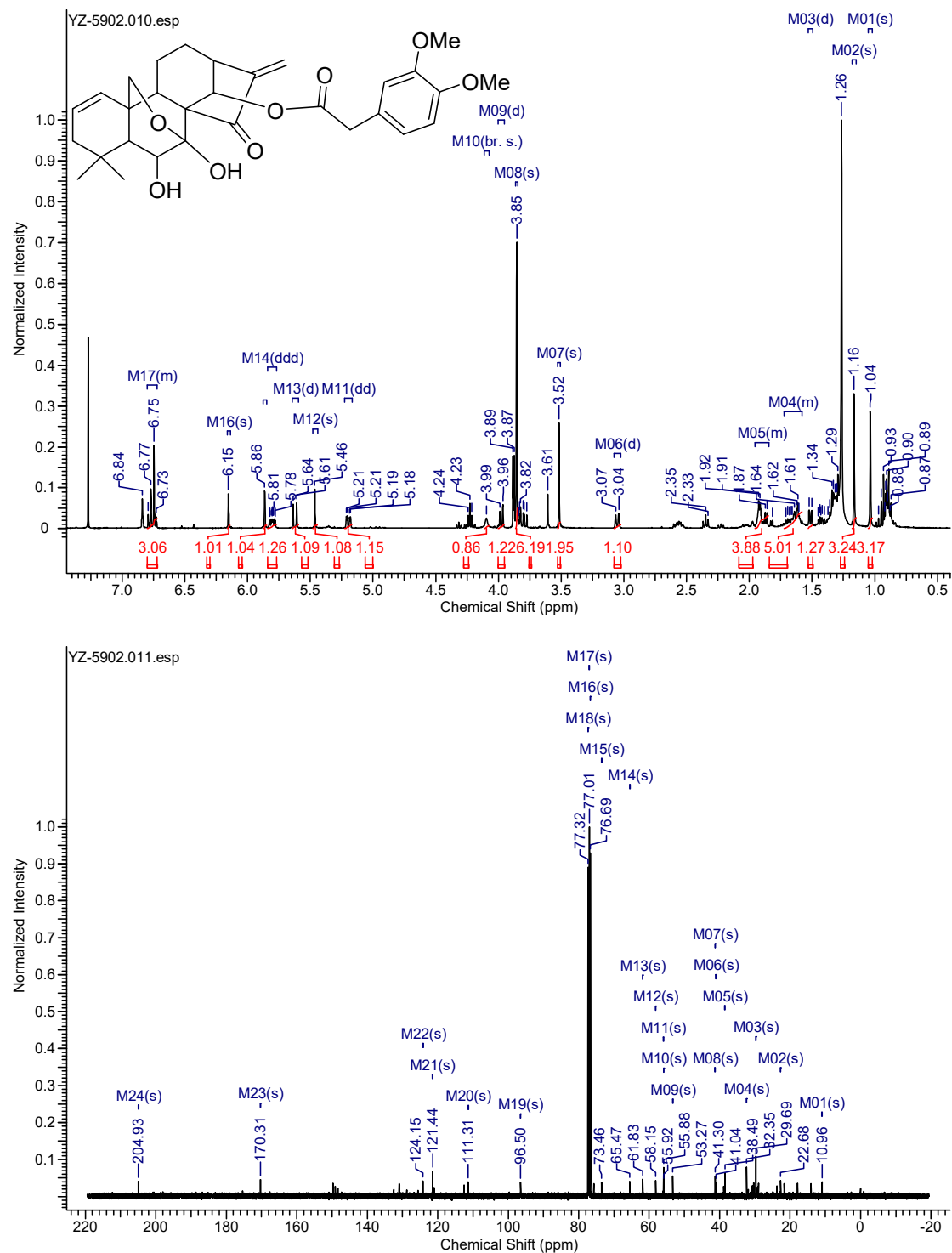


Figure S23. ^1H and ^{13}C NMR spectra of **5,6-dihydroxy-4,4-dimethyl-8-methylene-7-oxo-4,4a,5,6,7,8,9,10,11,11a-decahydro-3H-6,11b-(epoxymethano)-6a,9-methanocyclohepta[a]naphthalen-14-yl 2-(4-methoxyphenyl)acetate (6c)**

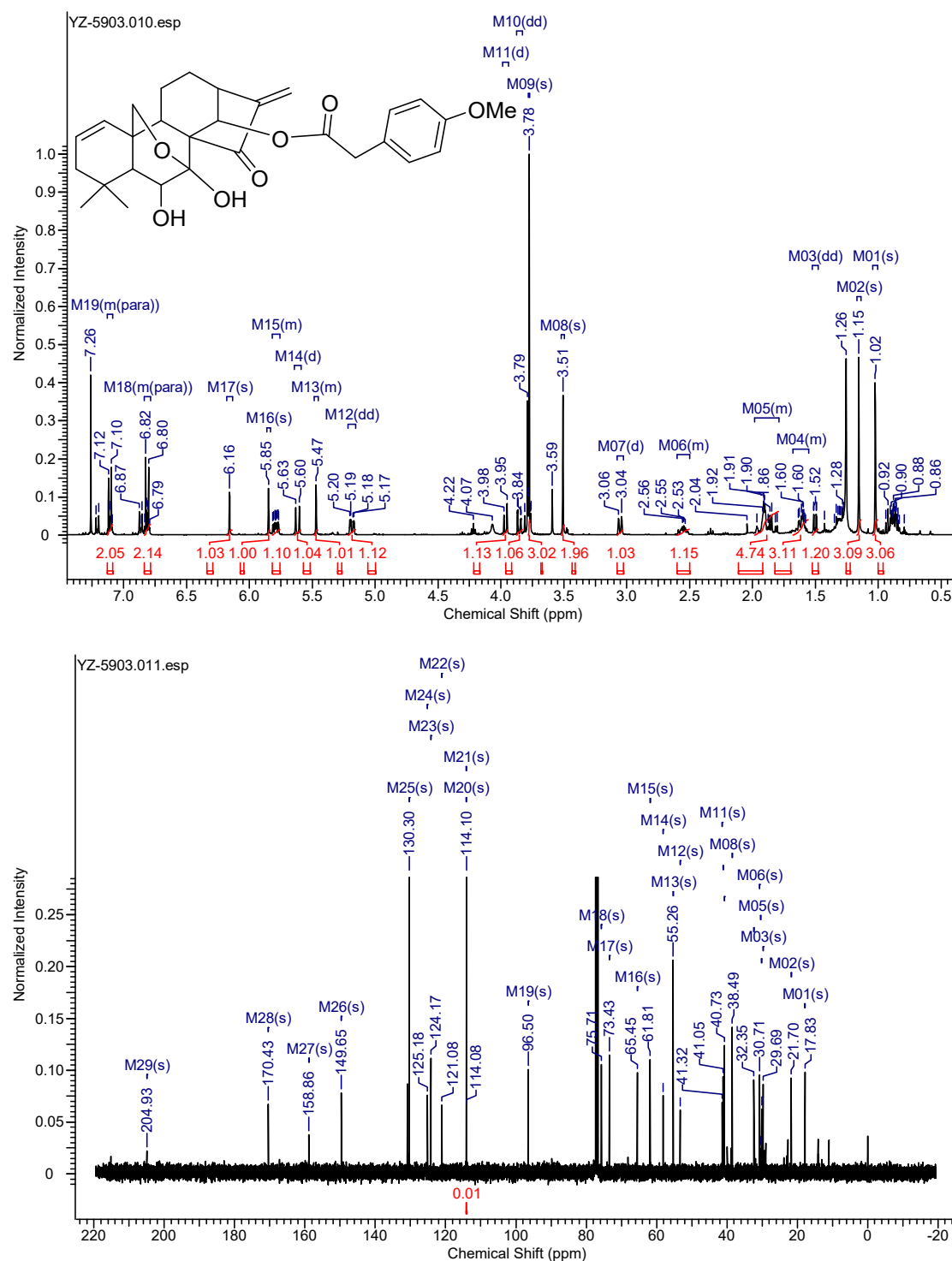


Figure S24. ^1H and ^{13}C NMR spectra of **5,6-dihydroxy-4,4-dimethyl-8-methylene-7-oxo-4,4a,5,6,7,8,9,10,11,11a-decahydro-3H-6,11b-(epoxymethano)-6a,9-methanocyclohepta[a]naphthalen-14-yl adamantane-1-carboxylate (6d)**

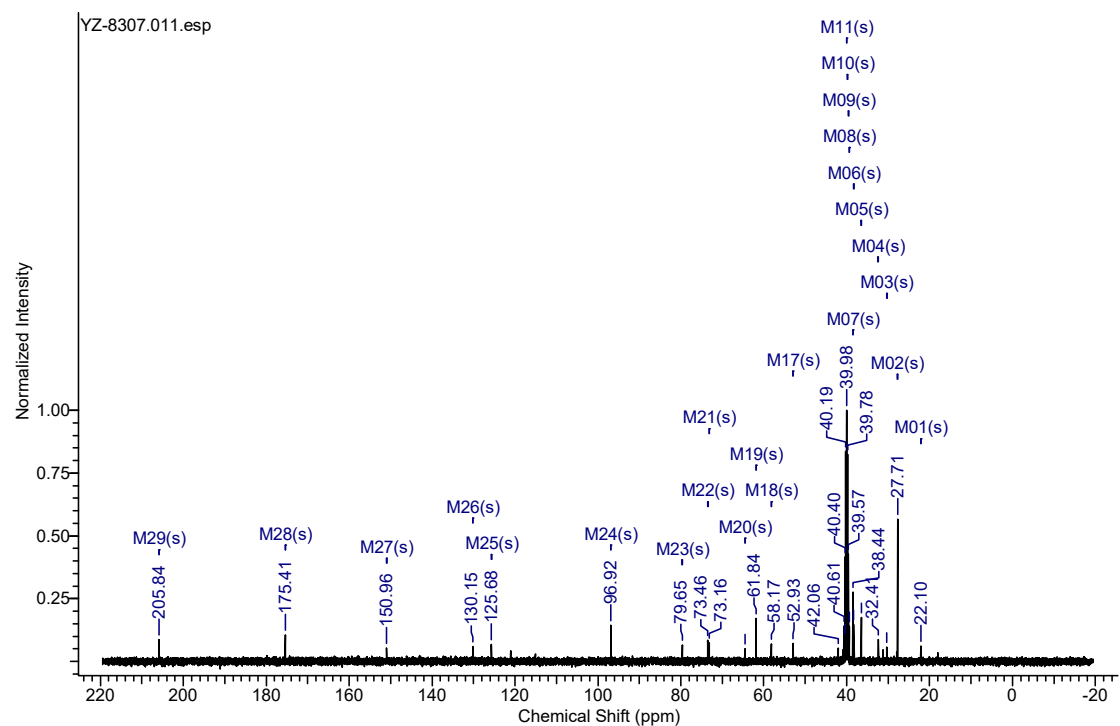
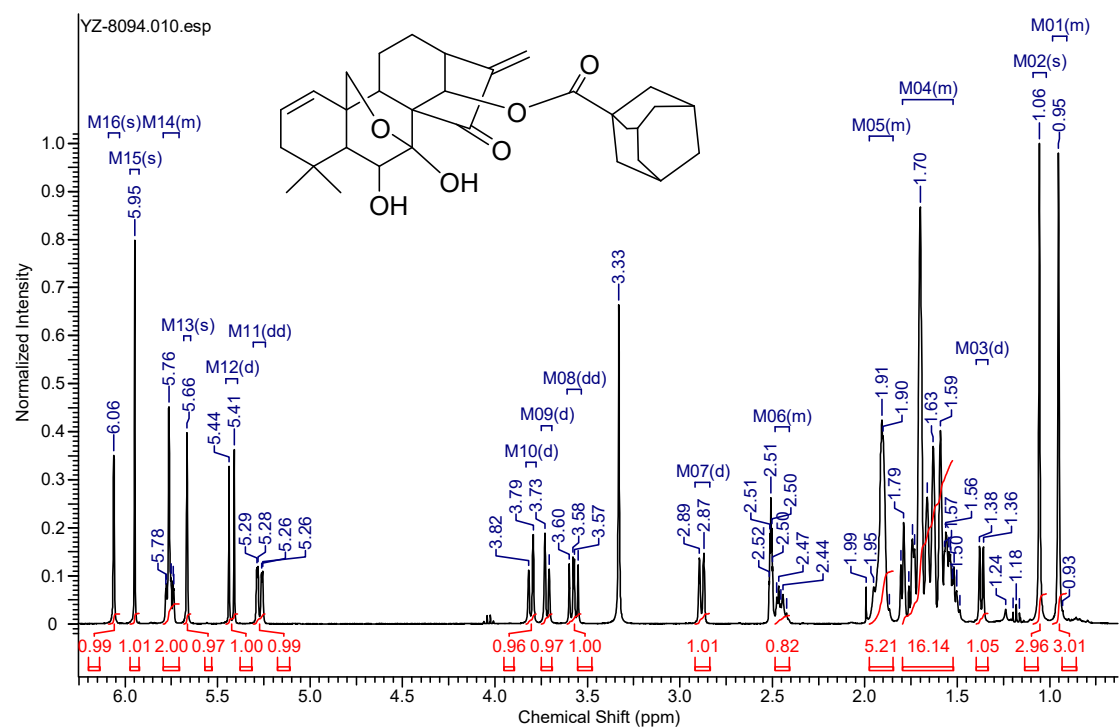


Figure S25. ^1H and ^{13}C NMR spectra of **5,6-dihydroxy-4,4-dimethyl-8-methylene-7-oxo-4,4a,5,6,7,8,9,10,11,11a-decahydro-3H-6,11b-(epoxymethano)-6a,9-methanocyclohepta[a]naphthalen-14-yl 4-(bis(2-chloroethyl)amino)benzoate (6e).**

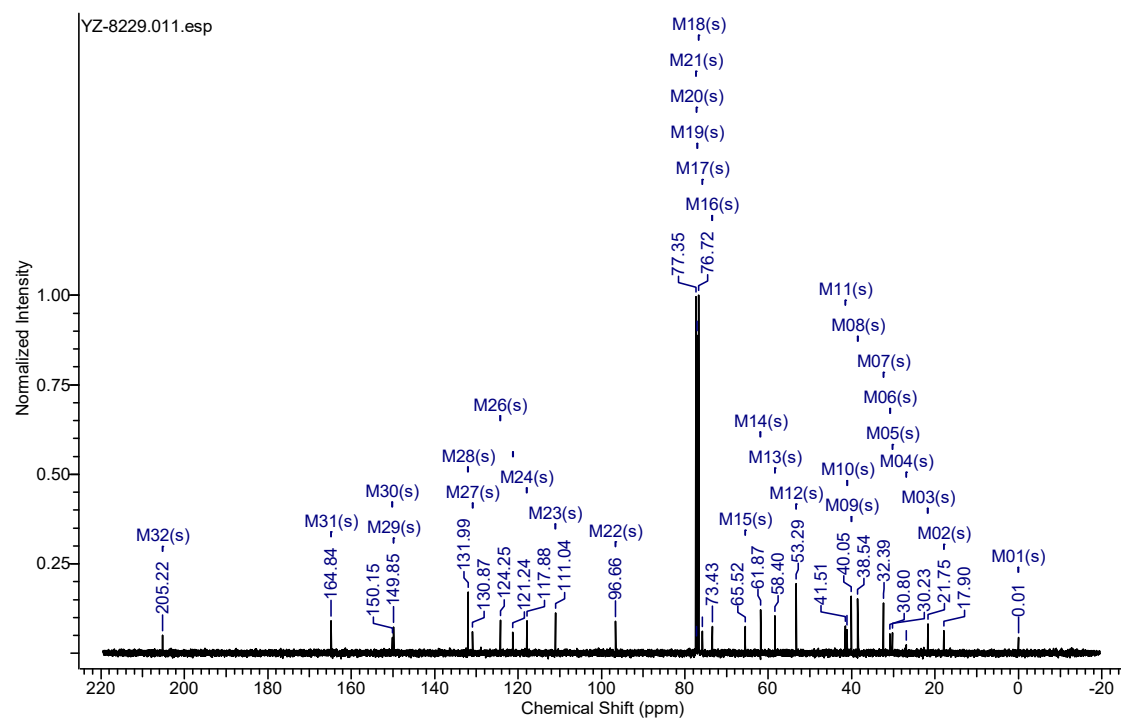
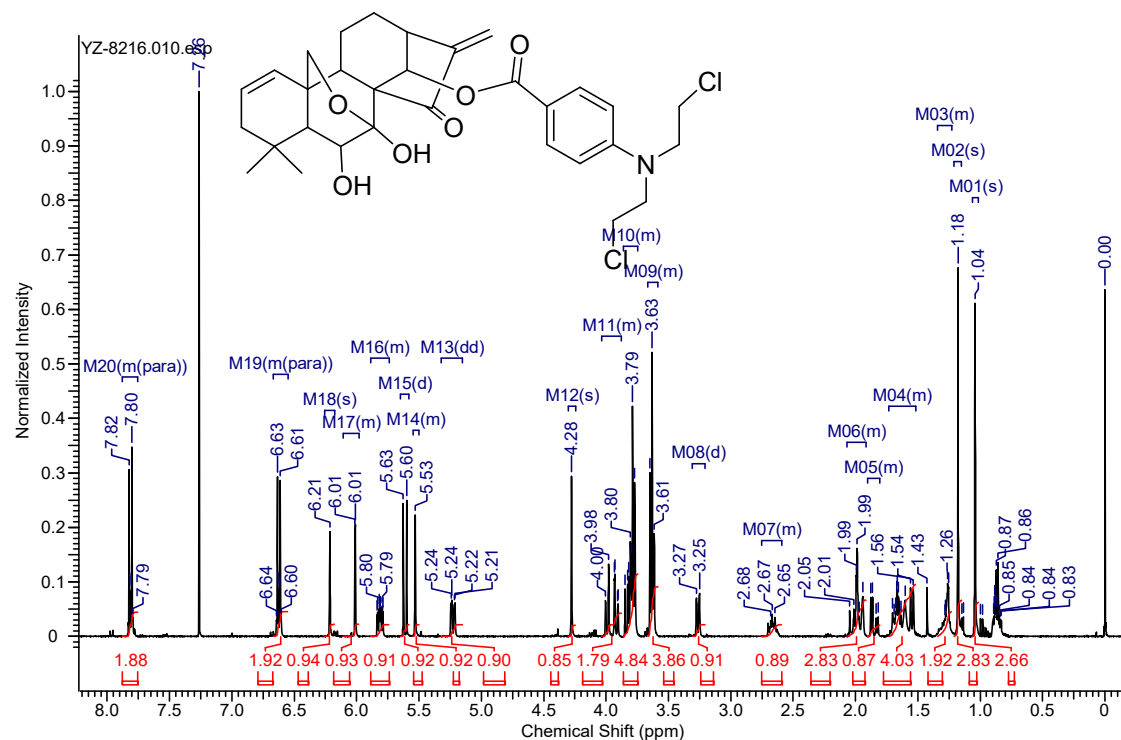


Figure S26. ^1H and ^{13}C NMR spectra of **14-hydroxy-4,4-dimethyl-8-methylene-3,4,4a,5,9,10,11,11a-octahydro-6H-5,11b-(epoxymethano)-6a,9-methanocyclohepta[a]naphthalene-6,7(8H)-dione (7)**.

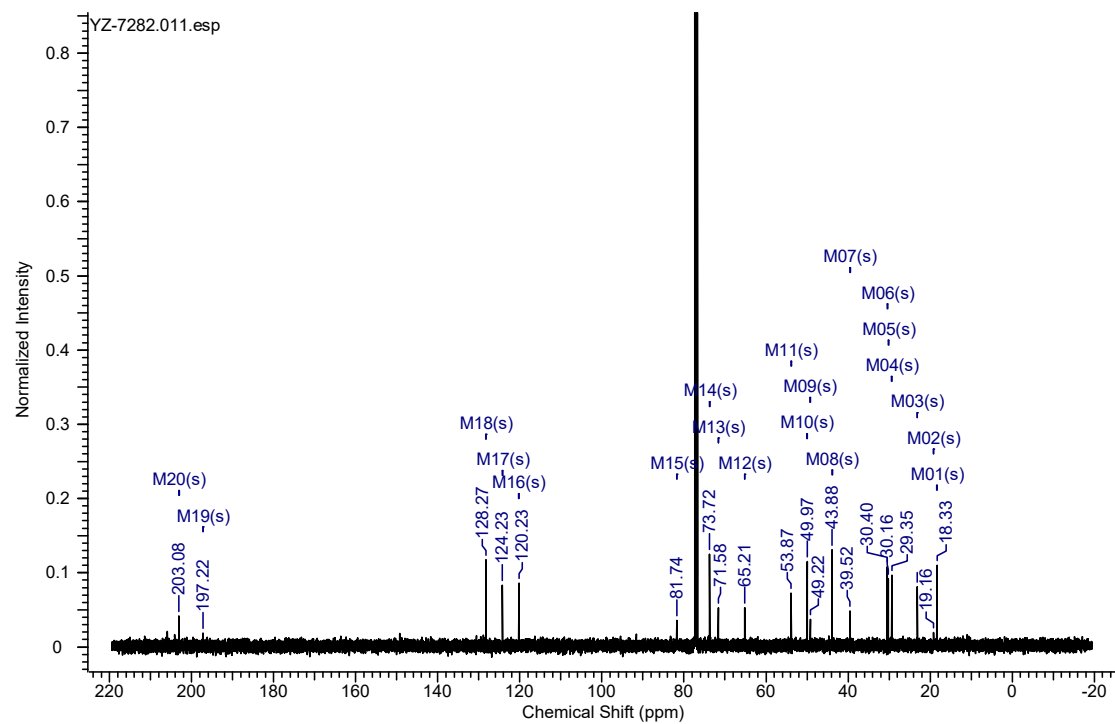
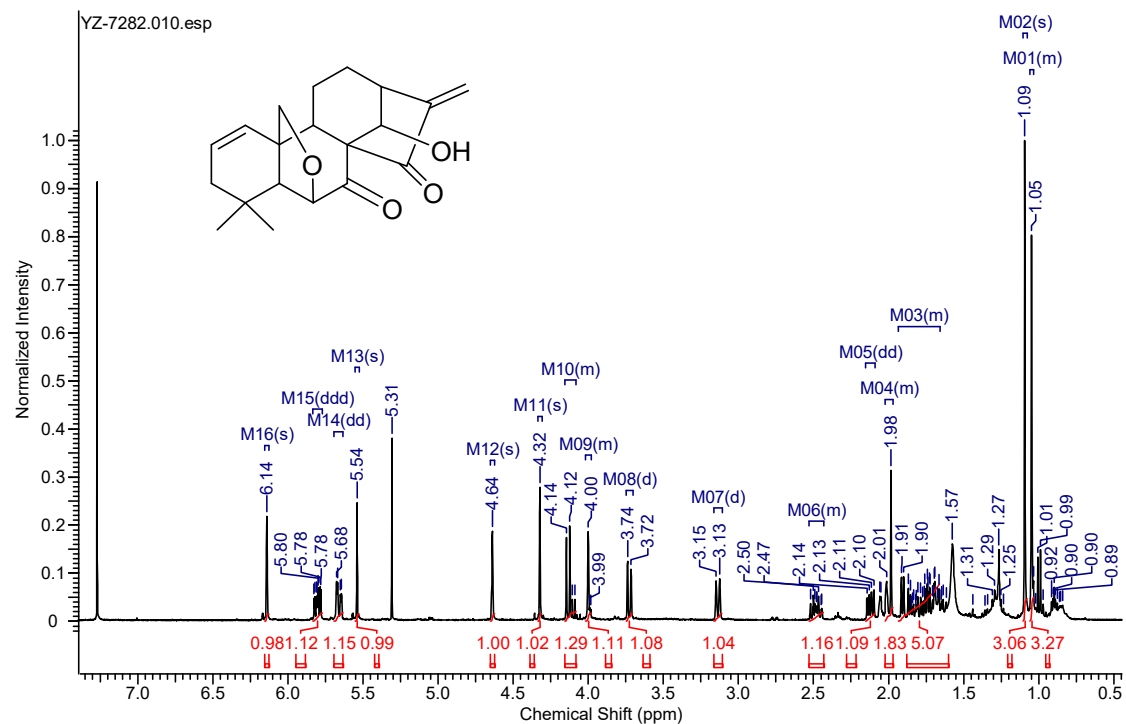


Figure S27. ^1H and ^{13}C NMR spectra of **4,4-dimethyl-8-methylene-6,7-dioxo-4,4a,5,6,7,8,9,10,11,11a-decahydro-3H-5,11b-(epoxymethano)-6a,9-methanocyclohepta[a]naphthalen-14-yl 2-(3,4,5-trimethoxyphenyl)acetate (7a)**

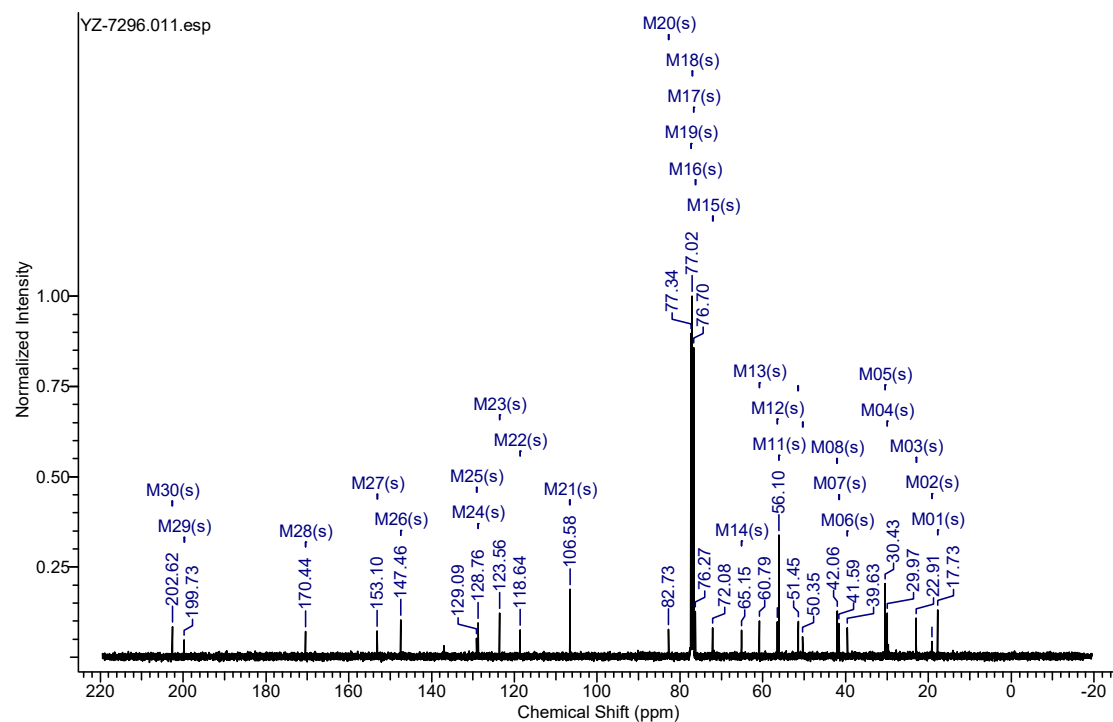
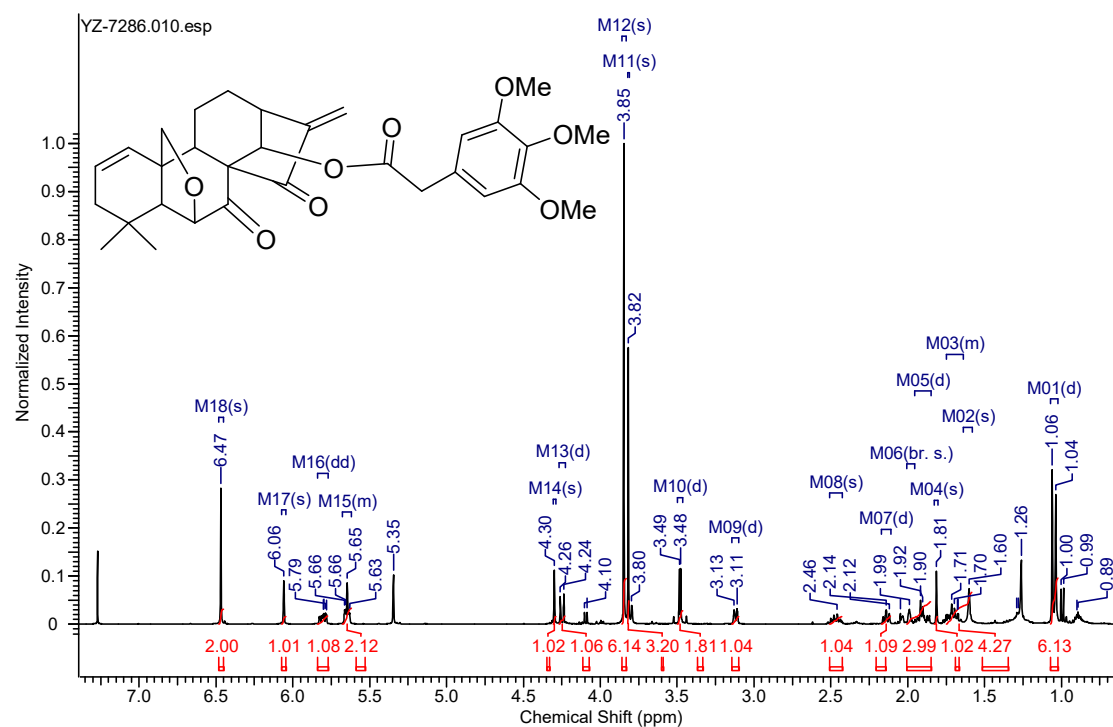


Figure S28. ^1H and ^{13}C NMR spectra of **4,4-dimethyl-8-methylene-6,7-dioxo-4,4a,5,6,7,8,9,10,11,11a-decahydro-3H-5,11b-(epoxymethano)-6a,9-methanocyclohepta[a]naphthalen-14-yl adamantane-1-carboxylate (7d).**

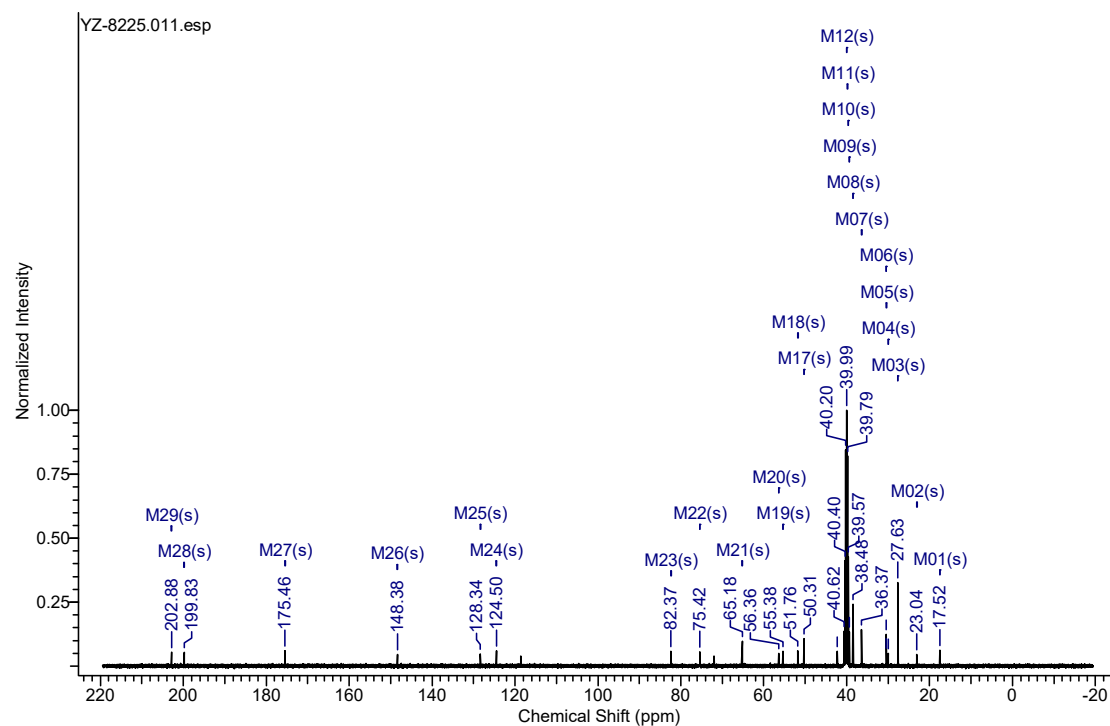
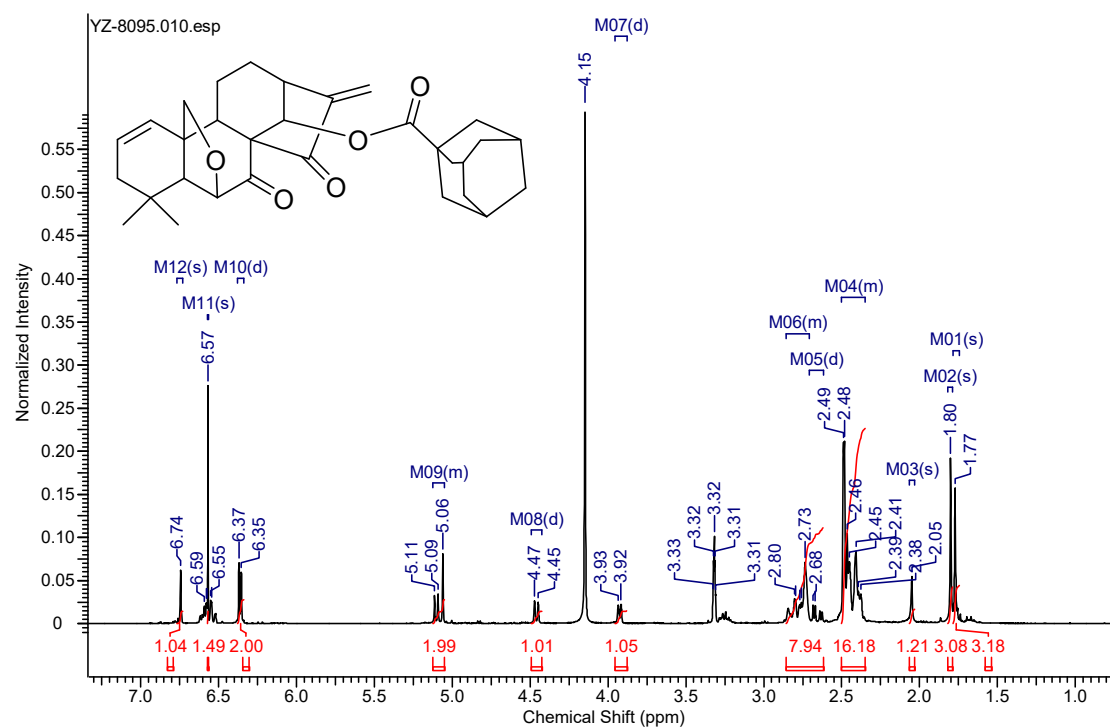


Figure S29. ^1H and ^{13}C NMR spectra of **4,4-dimethyl-8-methylene-6,7-dioxo-4,4a,5,6,7,8,9,10,11,11a-decahydro-3H-5,11b-(epoxymethano)-6a,9-methanocyclohepta[a]naphthalen-14-yl 4-(bis(2-chloroethyl)amino)benzoate (7e)**

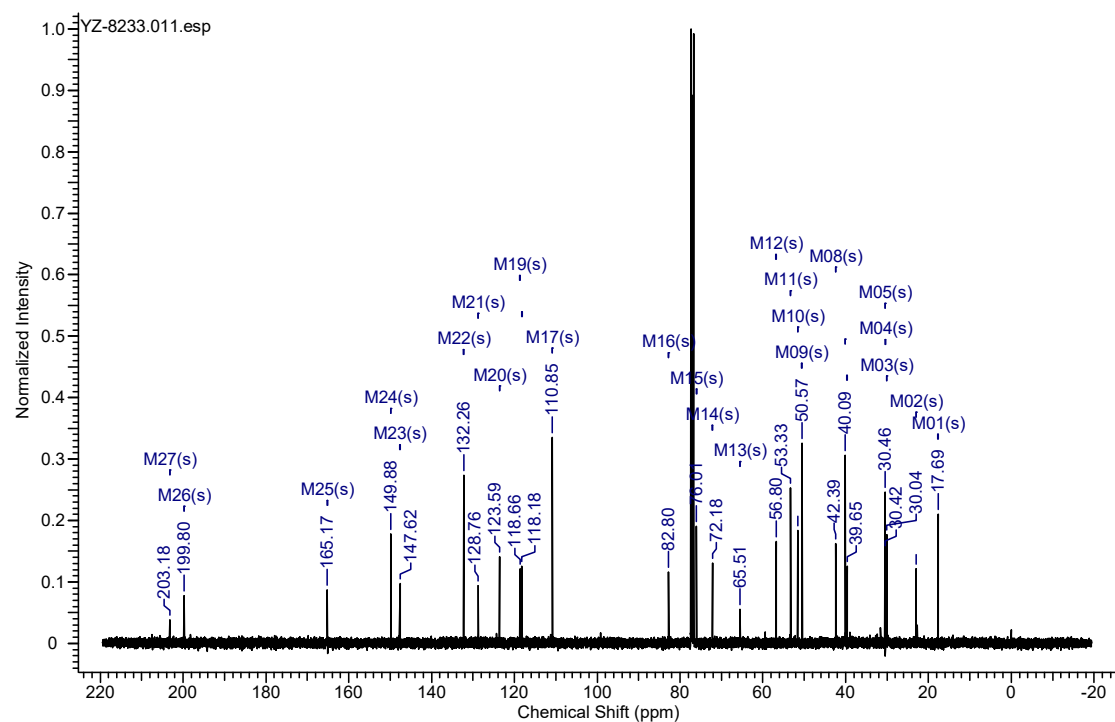
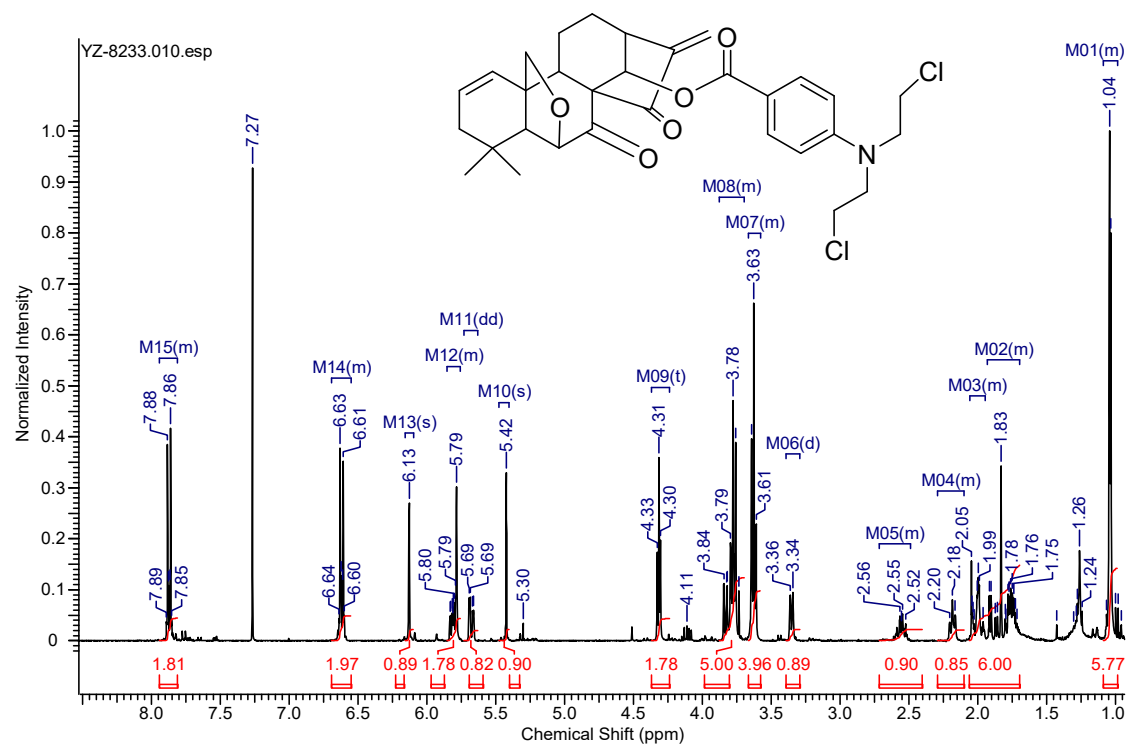


Figure S30. ^1H and ^{13}C NMR spectra of **5,6,14-trihydroxy-4,4-dimethyl-8-methylene-7-oxododecahydro-1H-6,11b-(epoxymethano)-6a,9-methanocyclohepta[a]naphthalen-1-yl acetate (9)**.

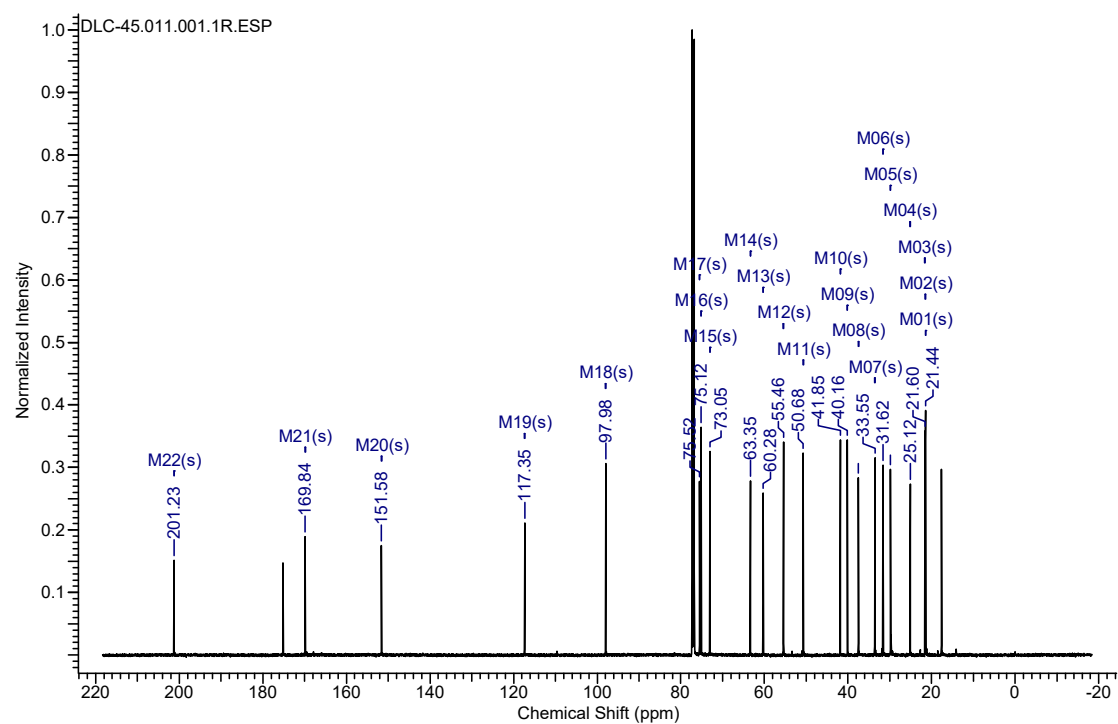
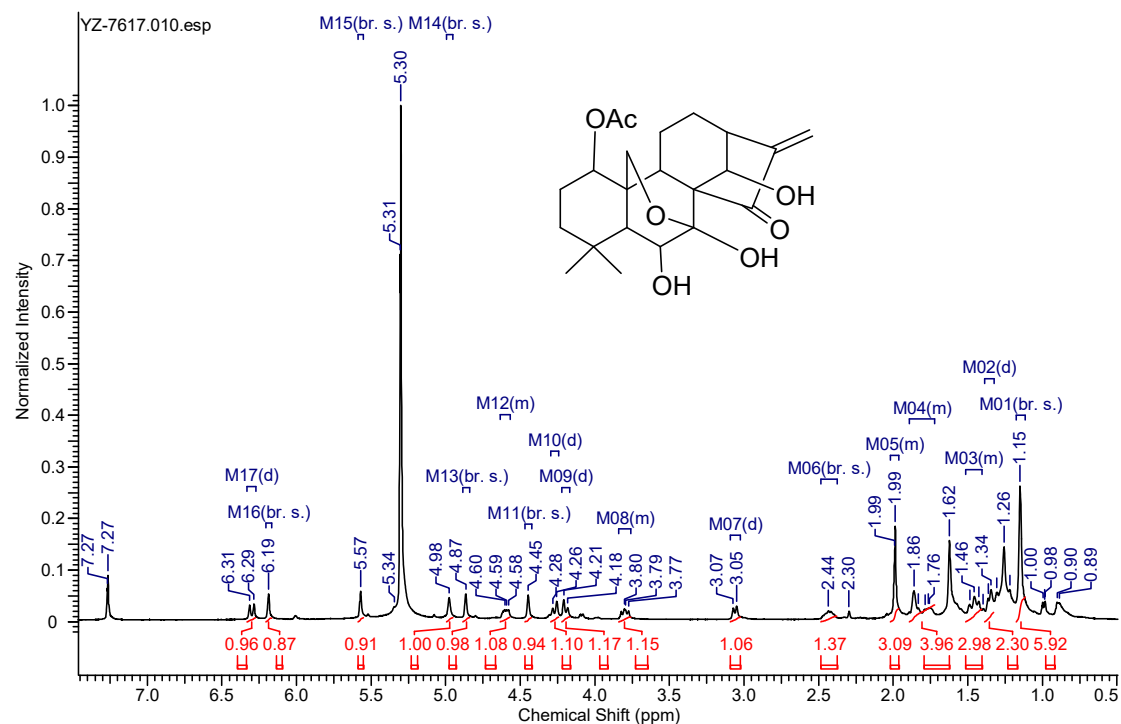


Figure S31. ^1H and ^{13}C NMR spectra of **1-acetoxy-5,6-dihydroxy-4,4-dimethyl-8-methylene-7-oxododecahydro-1H-6,11b-(epoxymethano)-6a,9-methanocyclohepta[a]naphthalen-14-yl adamantane-1-carboxylate (9a)**

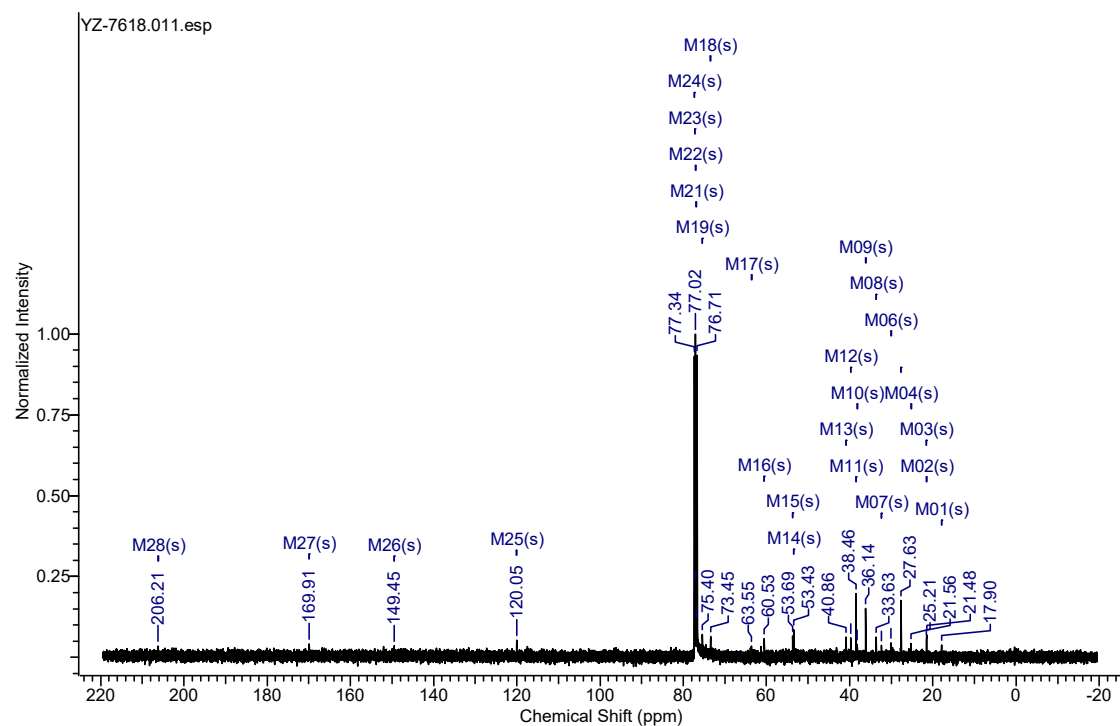
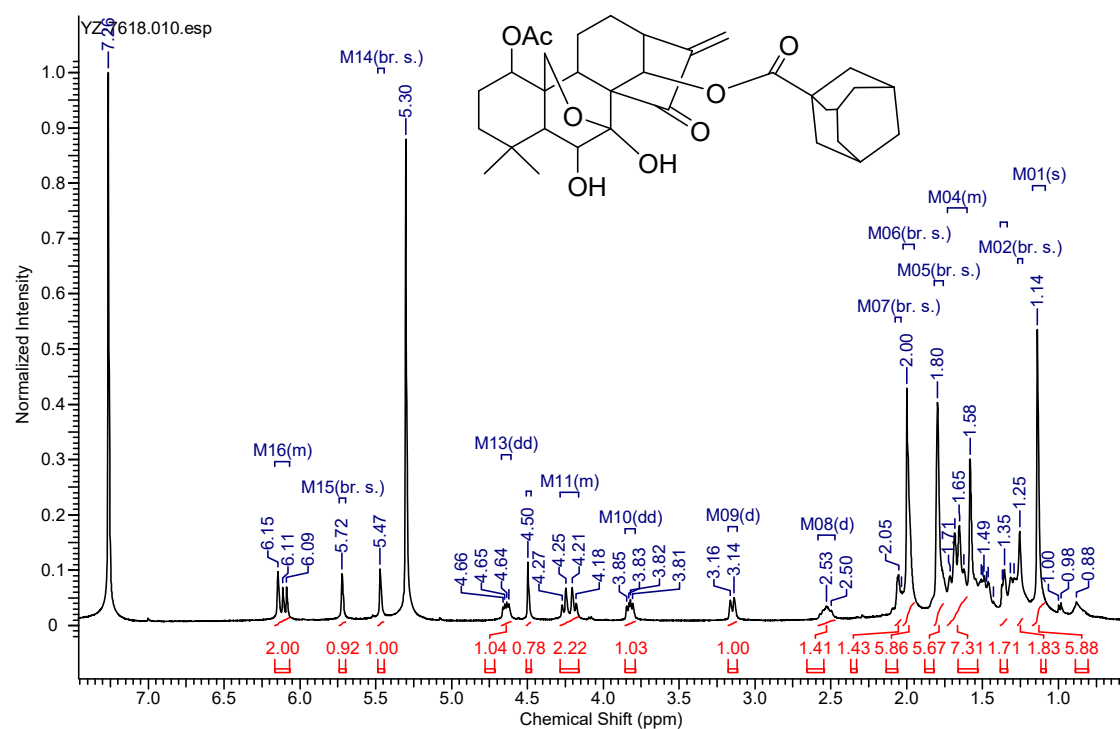


Figure S33. ^1H and ^{13}C NMR spectra of **1,5,6-Trihydroxy-4,4-dimethyl-8-methylene-7-oxododecahydro-1H-6,11b-(epoxymethano)-6a,9-methanocyclohepta[a]naphthalen-14-yl adamantane-1-carboxylate (11a)**

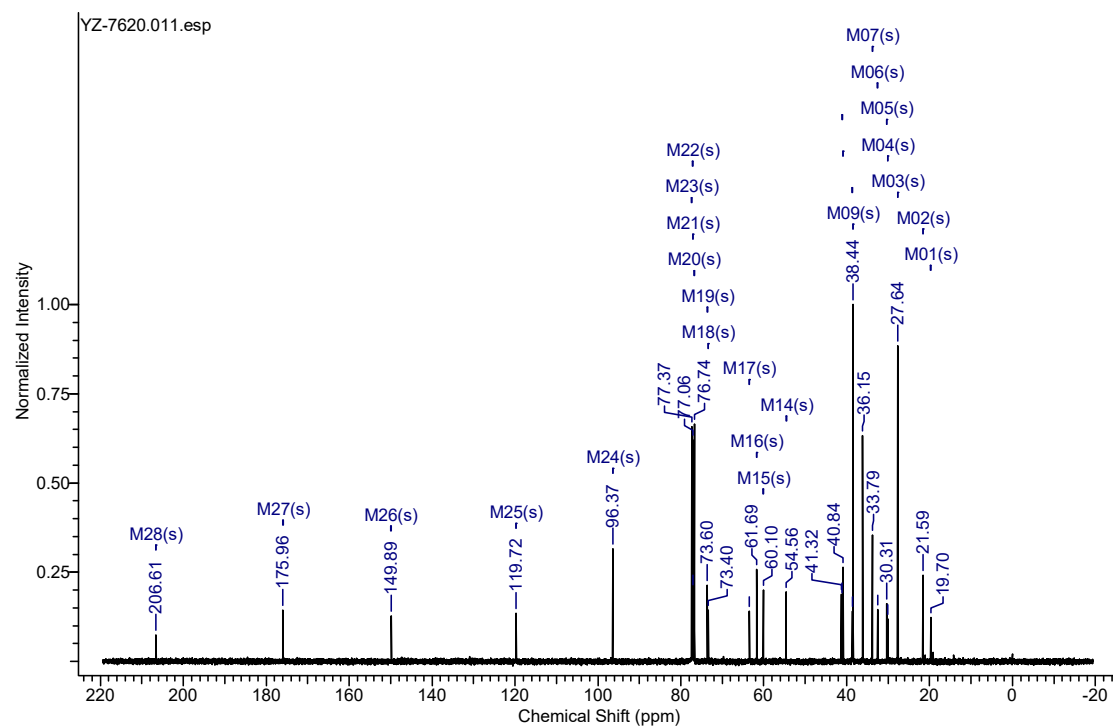
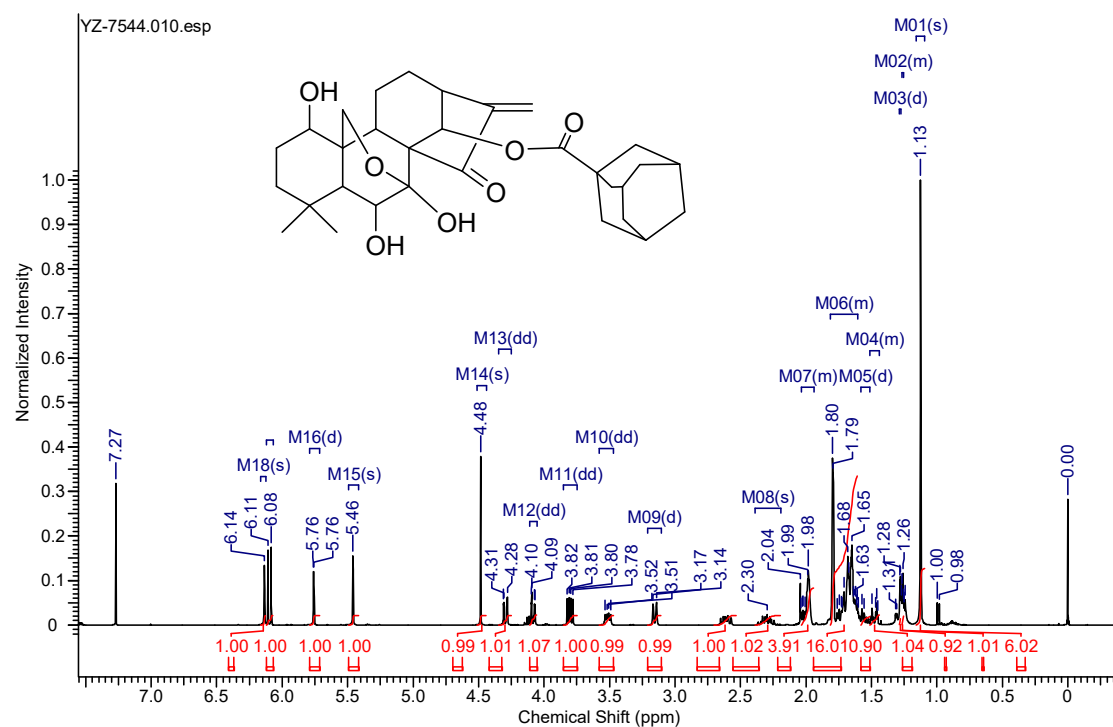


Figure S34. ^1H and ^{13}C NMR spectra of **1,5,6-trihydroxy-4,4-dimethyl-8-methylene-7-oxododecahydro-1H-6,11b-(epoxymethano)-6a,9-methanocyclohepta[a]naphthalen-14-yl 4-(bis(2-chloroethyl)amino)benzoate (11b)**

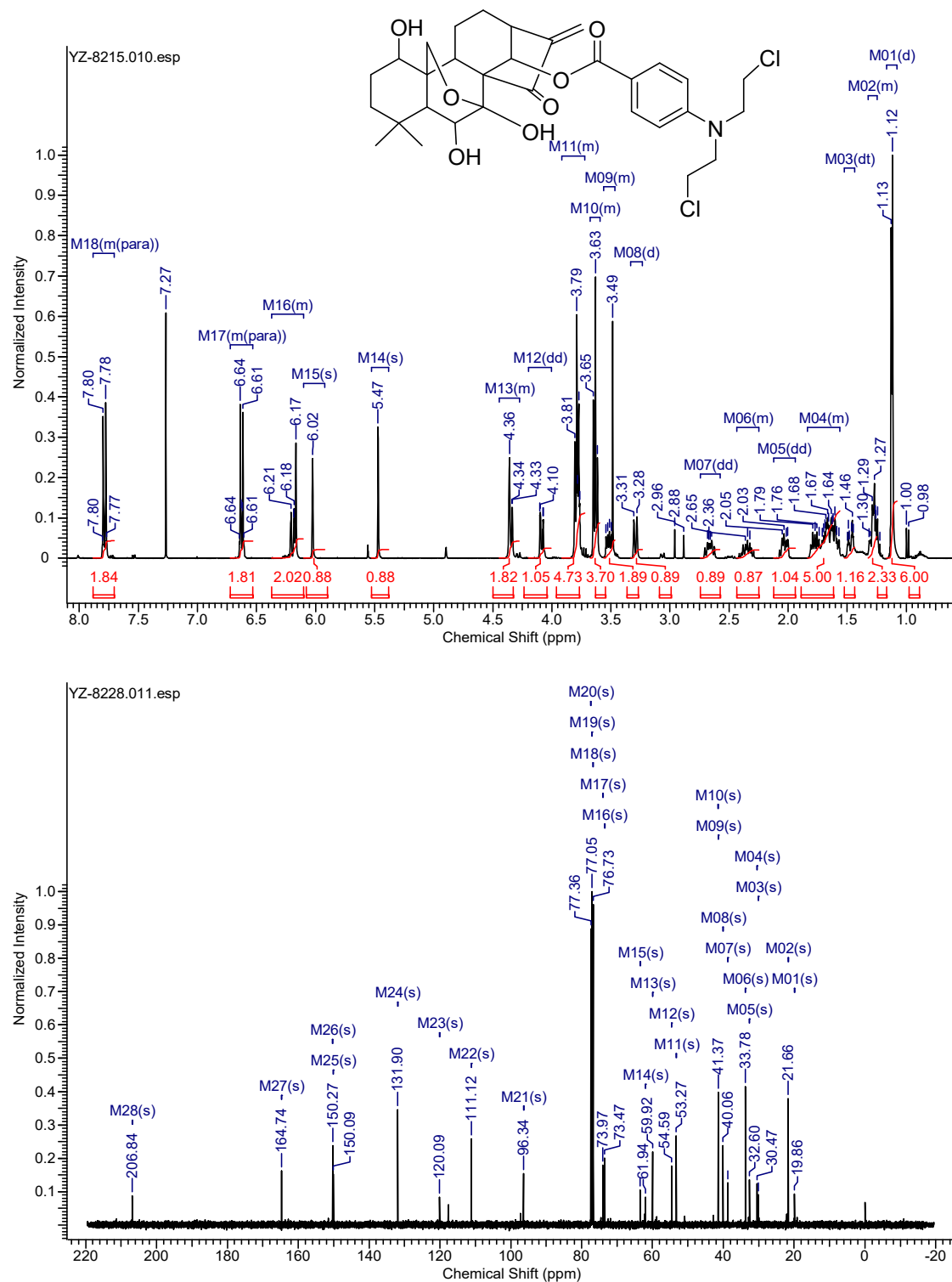


Figure S35. ^1H and ^{13}C NMR spectra of **1-hydroxy-4,4-dimethyl-8-methylene-6,7-dioxododecahydro-1H-5,11b-(epoxymethano)-6a,9-methanocyclohepta[a]naphthalen-14-yl adamantane-1-carboxylate (12a)**

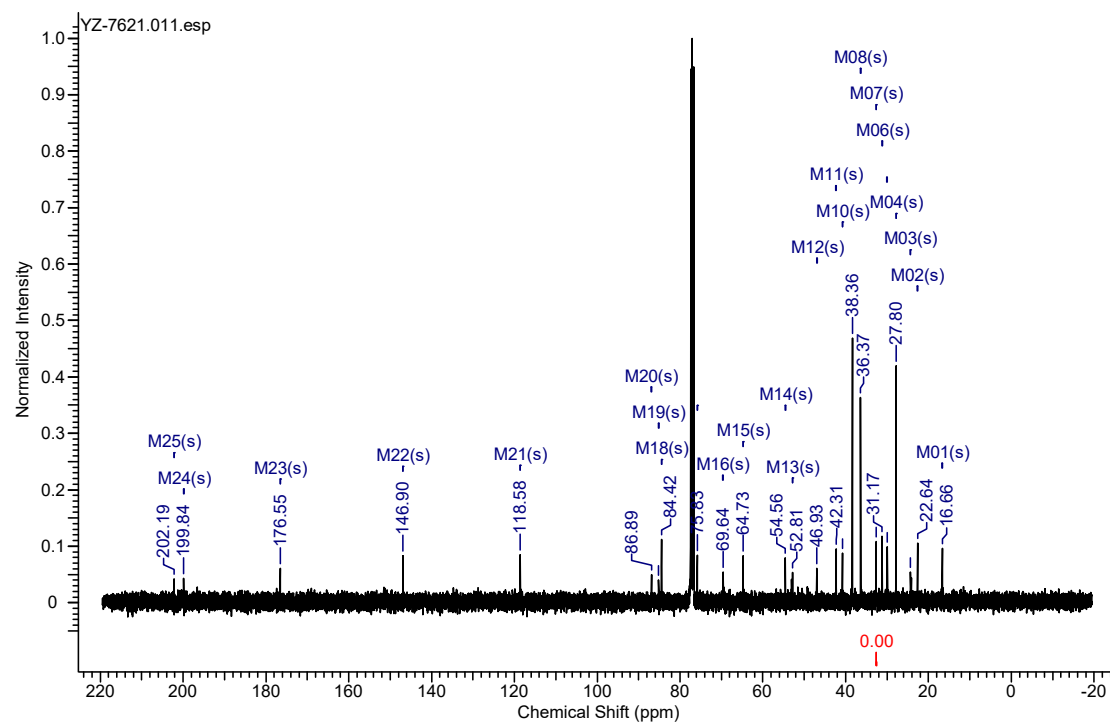
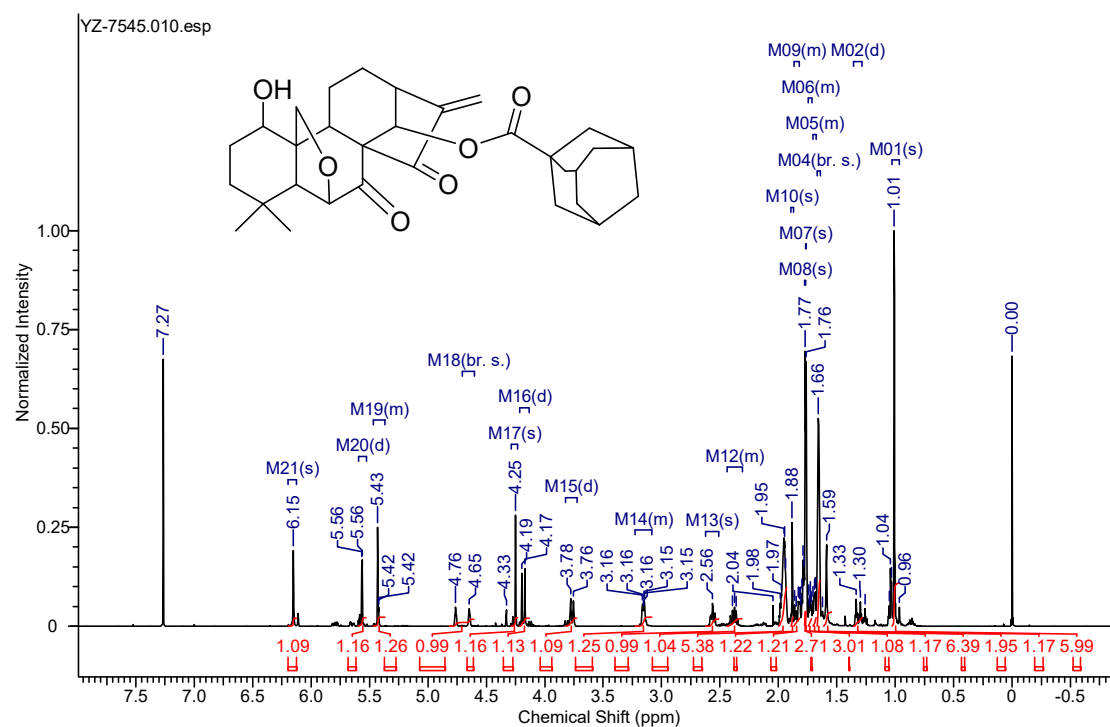


Figure S36. ^1H and ^{13}C NMR spectra of **1-hydroxy-4,4-dimethyl-8-methylene-6,7-dioxododecahydro-1H-5,11b-(epoxymethano)-6a,9-methanocyclohepta[a]naphthalen-14-yl 4-(bis(2-chloroethyl)amino)benzoate (12b)**

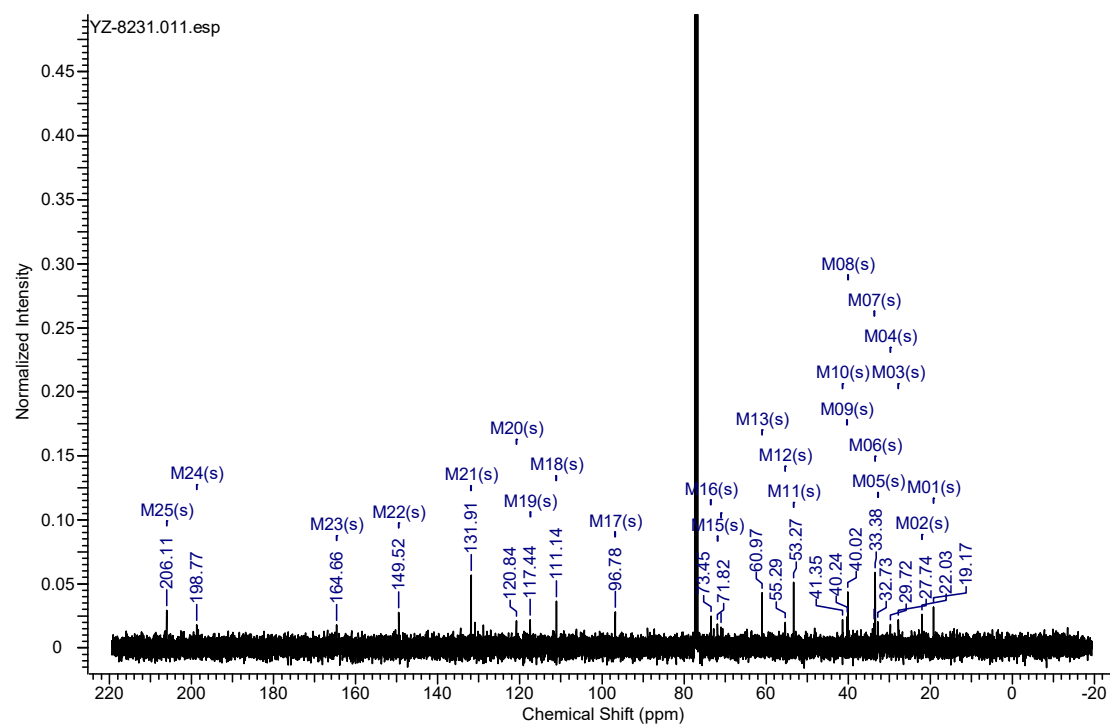
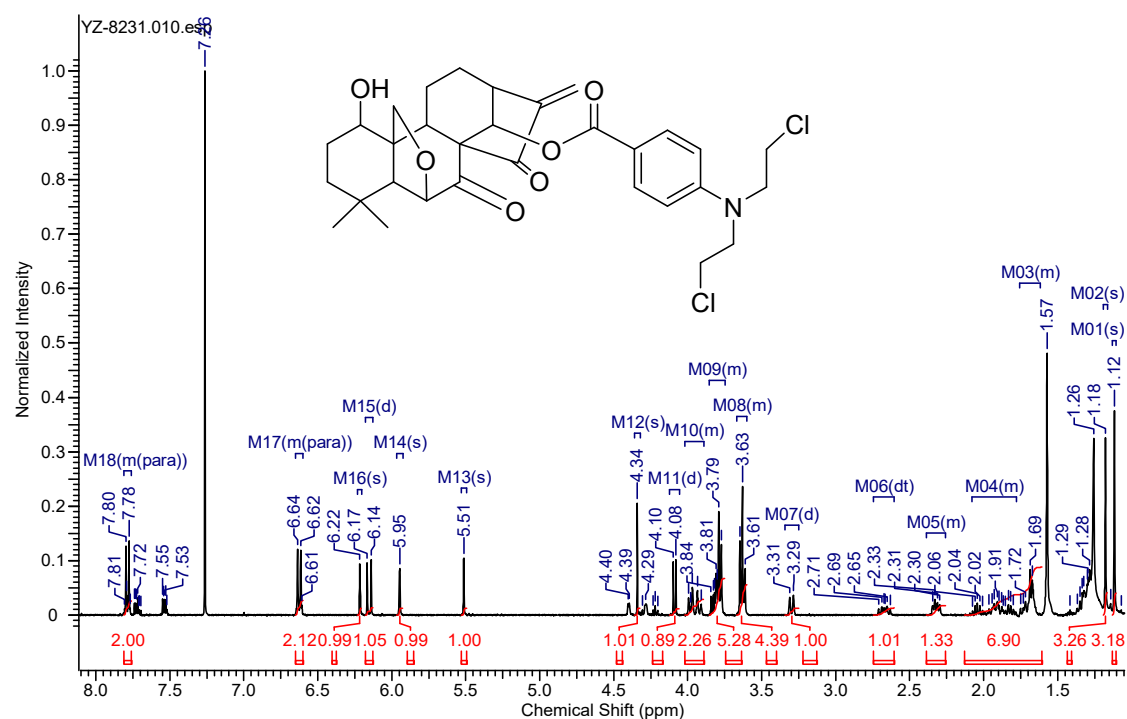


Figure S37. HRMS spectra of **5,6,14-trihydroxy-4,4-dimethyl-8-methylenedecahydro-1H-6,11b-(epoxymethano)-6a,9-methanocyclohepta[a]naphthalene-1,7(8H)-dione (1)**

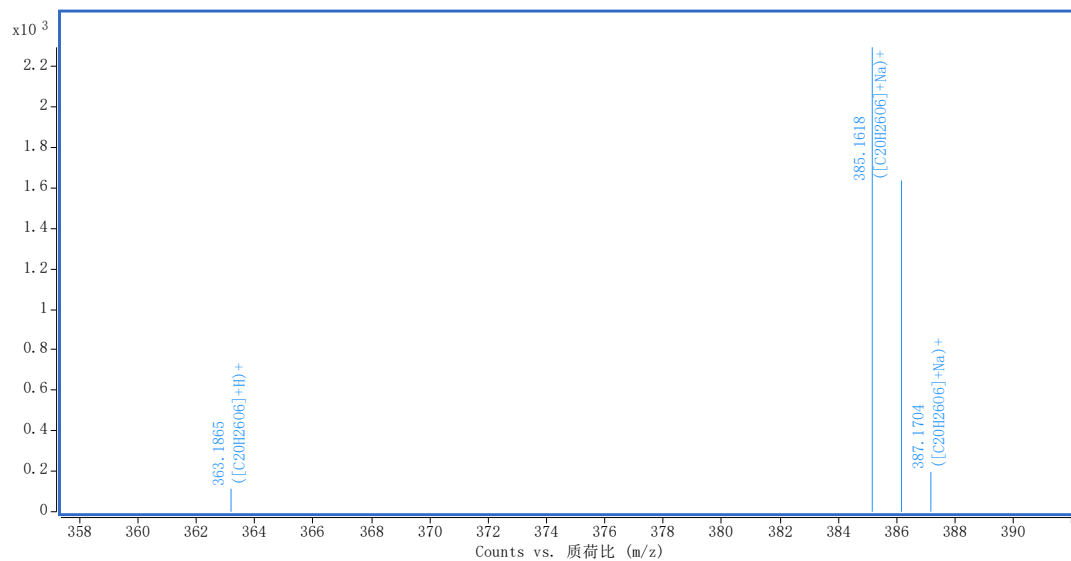


Figure S38. HRMS spectra of **5,6-dihydroxy-4,4-dimethyl-8-methylene-1,7-dioxododecahydro-1H-6,11b-(epoxymethano)-6a,9-methanocyclohepta[a]naphthalen-14-yl 2-(3,4,5-trimethoxyphenyl)acetate (1a)**

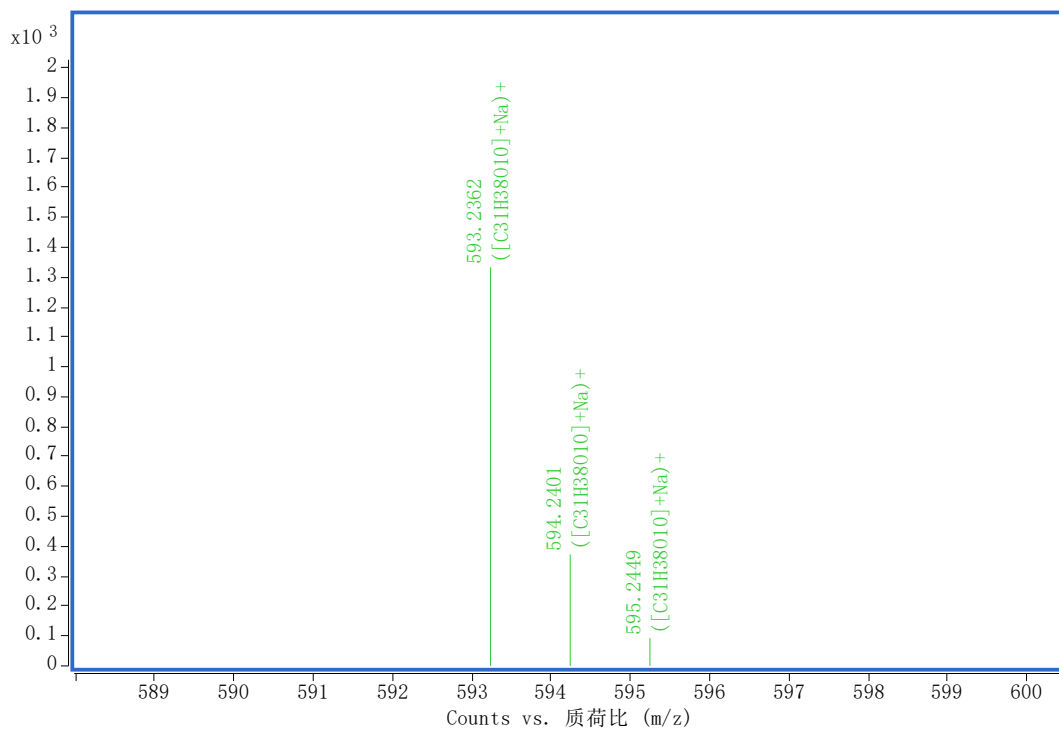


Figure S39. HRMS spectra of **5,6-dihydroxy-4,4-dimethyl-8-methylene-1,7-dioxododecahydro-1H-6,11b-(epoxymethano)-6a,9-methanocyclohepta[a]naphthalen-14-yl 2-(3,4-dimethoxyphenyl)acetate (1b)**

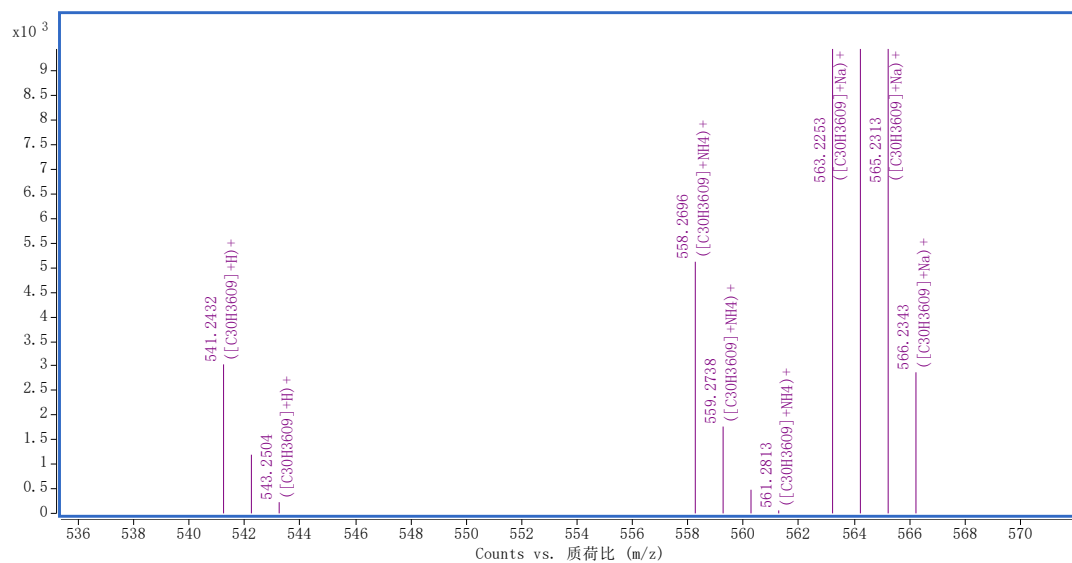


Figure S40. HRMS spectra of **5,6-dihydroxy-4,4-dimethyl-8-methylene-1,7-dioxododecahydro-1H-6,11b-(epoxymethano)-6a,9-methanocyclohepta[a]naphthalen-14-yl 2-(4-methoxyphenyl)acetate (1c)**

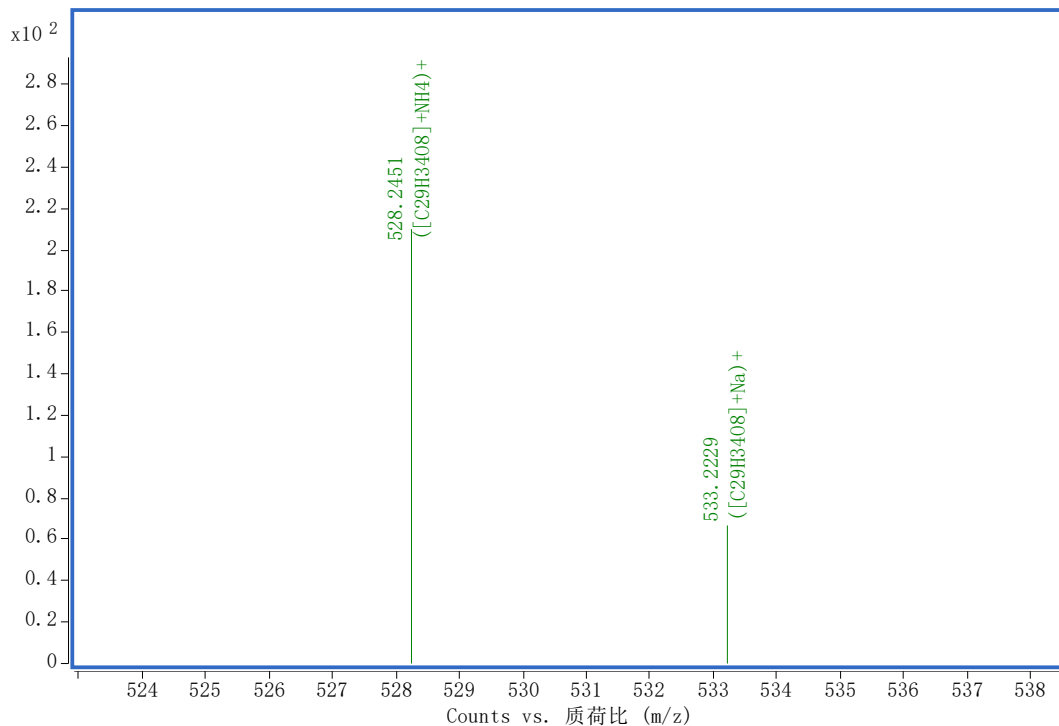


Figure S41. HRMS spectra of **5,6-dihydroxy-4,4-dimethyl-8-methylene-1,7-dioxododecahydro-1H-6,11b-(epoxymethano)-6a,9-methanocyclohepta[a]naphthalen-14-yl 2-(2-bromophenyl)acetate (1d)**

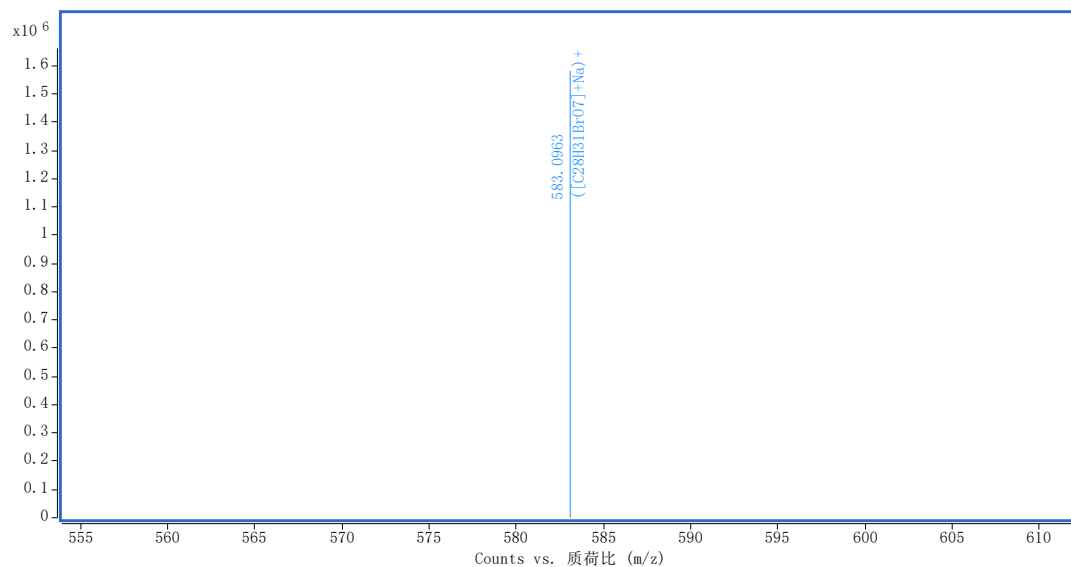


Figure S42. HRMS spectra of **5,6-dihydroxy-4,4-dimethyl-8-methylene-1,7-dioxododecahydro-1H-6,11b-(epoxymethano)-6a,9-methanocyclohepta[a]naphthalen-14-yl 4-(bis(2-chloroethyl)amino)benzoate (1e)**

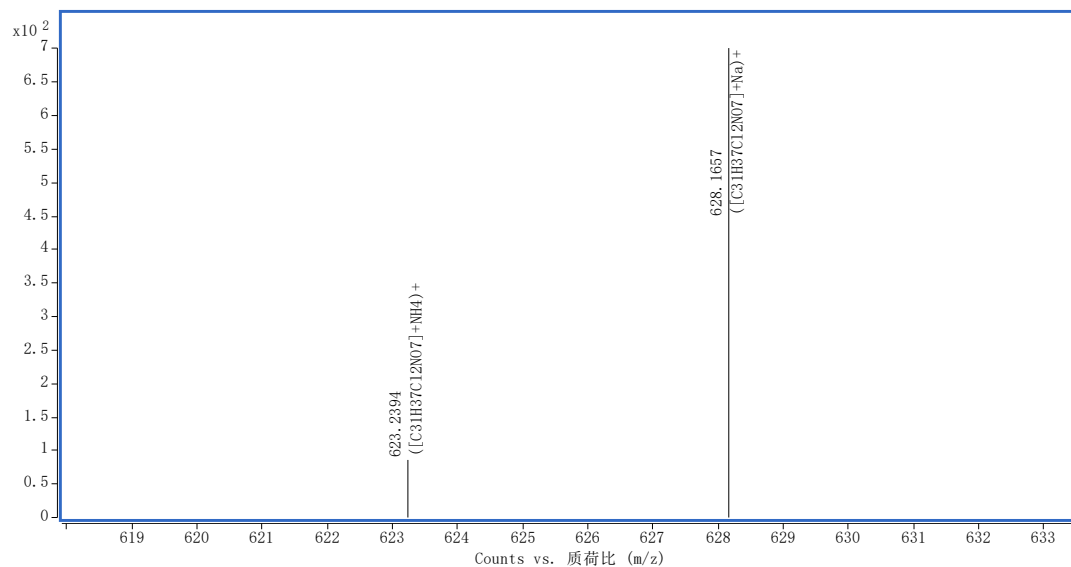


Figure S43. HRMS spectra of
5,6-dihydroxy-4,4-dimethyl-8-methylene-1,7-dioxododecahydro-1H-6,11b-
(epoxymethano)-6a,9-methanocyclohepta[a]naphthalen-14-yl 2-(4-(bis(2-
chloroethyl)amino)phenyl)acetate (1f)

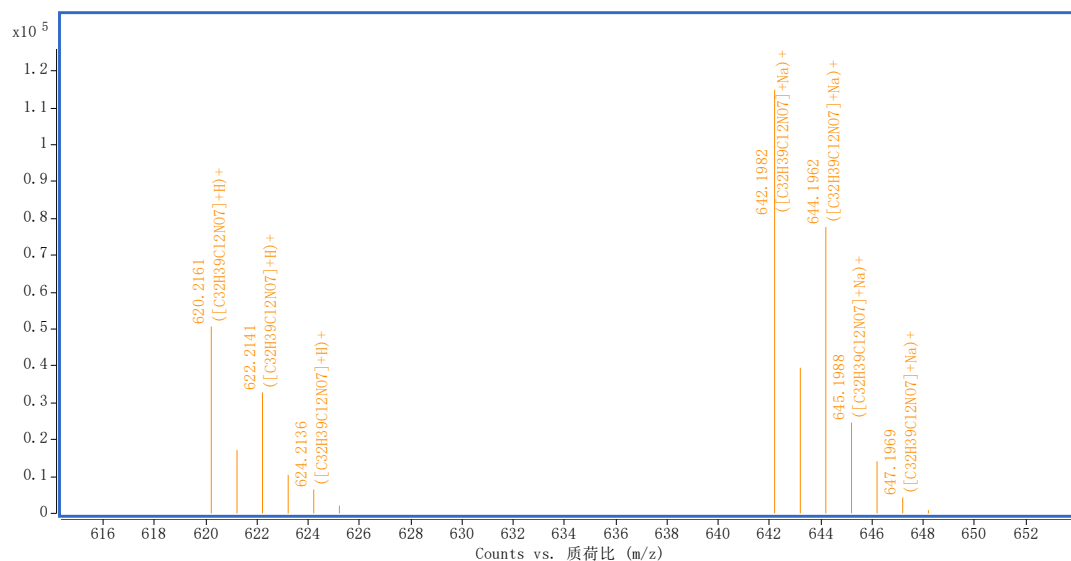


Figure S44. HRMS spectra of
5,6-dihydroxy-4,4-dimethyl-8-methylene-1,7-dioxododecahydro-1H-6,11b-
(epoxymethano)-6a,9-methanocyclohepta[a]naphthalen-14-yl adamantane-1-
carboxylate (1g)

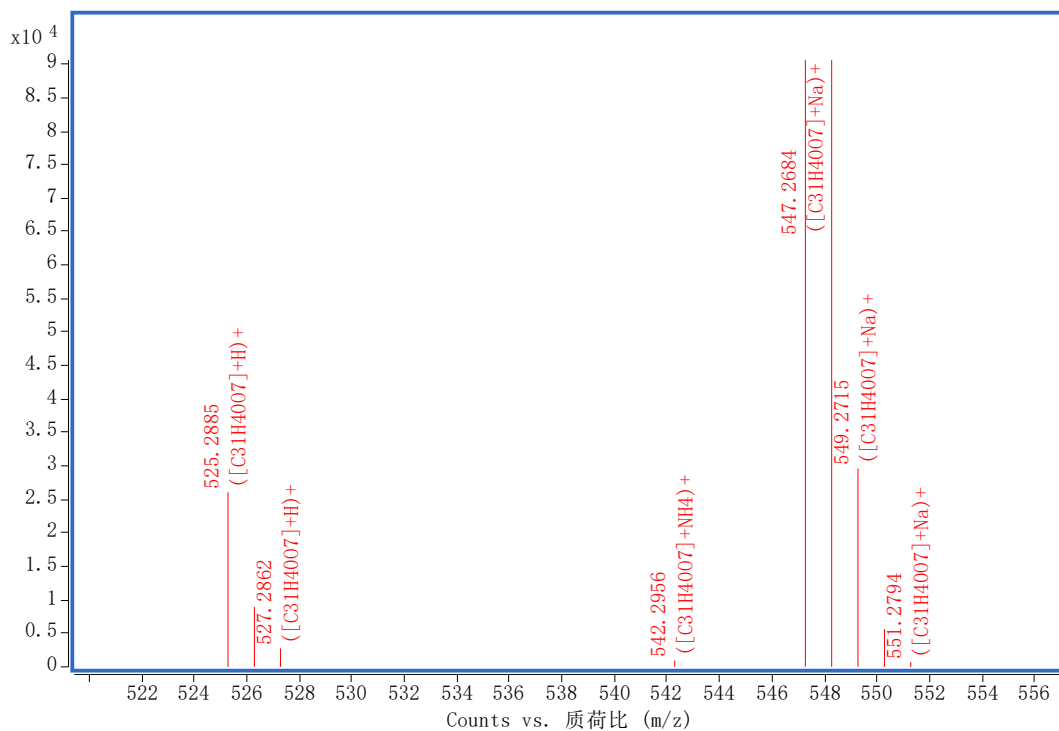


Figure S45. HRMS spectra of
5,6-dihydroxy-4,4-dimethyl-8-methylene-1,7-dioxododecahydro-1H-6,11b-
(epoxymethano)-6a,9-methanocyclohepta[a]naphthalen-14-yl (E)-3-(4-
(dimethylamino)phenyl)acrylate (1h)

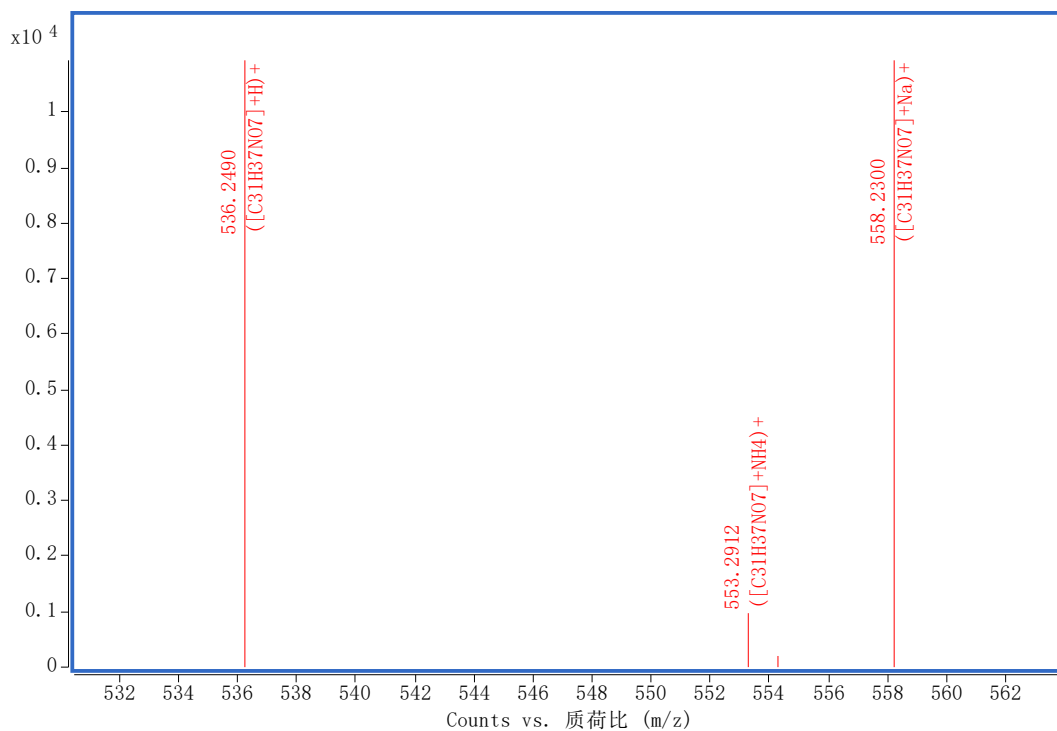


Figure S46. HRMS spectra of
4,4-dimethyl-8-methylene-1,6,7-trioxododecahydro-1H-5,11b-(epoxymethano)-
6a,9-methanocyclohepta[a]naphthalen-14-yl 2-(3,4,5-trimethoxyphenyl)acetate
(2a)

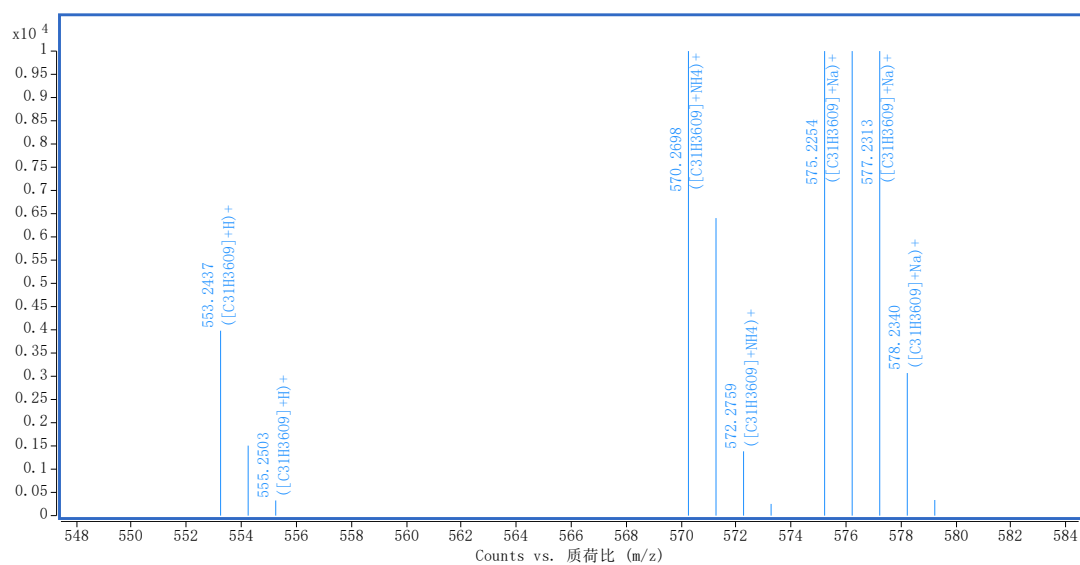


Figure S47. HRMS spectra of **4,4-dimethyl-8-methylene-1,6,7-trioxododecahydro-1H-5,11b-(epoxymethano)-6a,9-methanocyclohepta[a]naphthalen-14-yl 2-(3,4-dimethoxyphenyl)acetate (2b)**

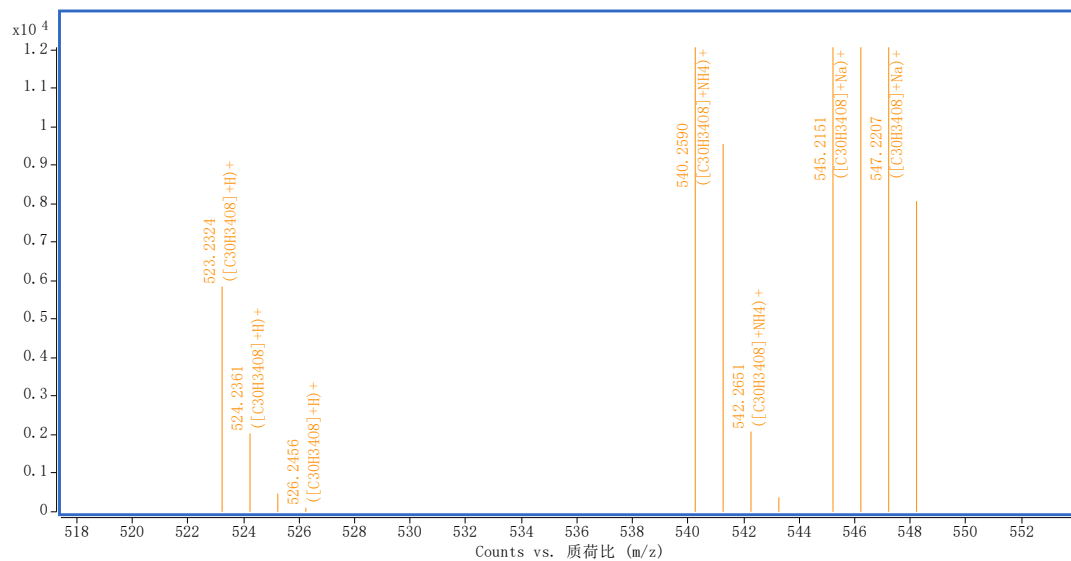


Figure S48. HRMS spectra of **4,4-dimethyl-8-methylene-1,6,7-trioxododecahydro-1H-5,11b-(epoxymethano)-6a,9-methanocyclohepta[a]naphthalen-14-yl 2-(4-methoxyphenyl)acetate (2c)**

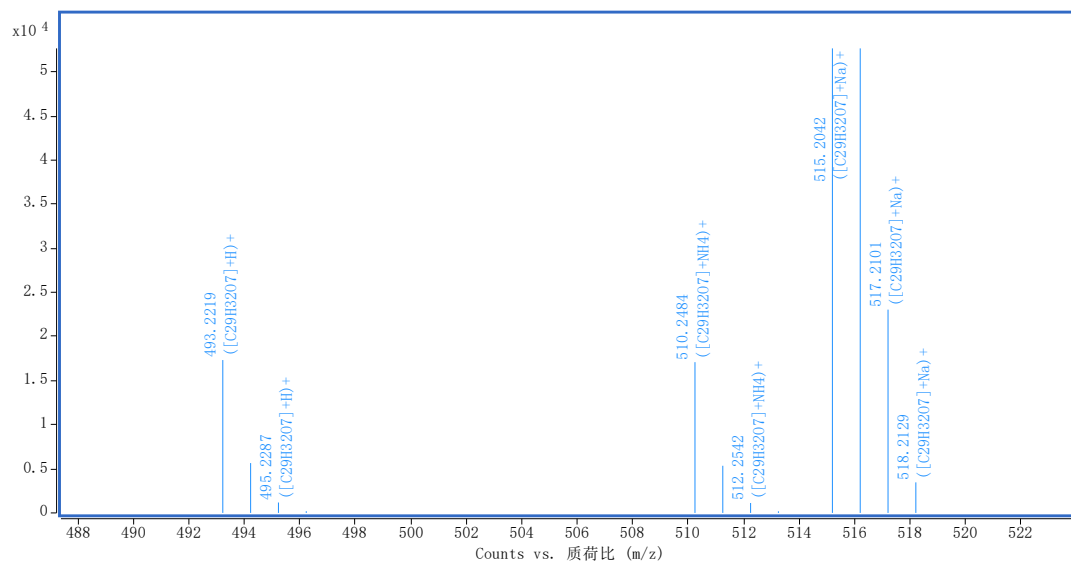


Figure S49. HRMS spectra of
4,4-dimethyl-8-methylene-1,6,7-trioxododecahydro-1H-5,11b-(epoxymethano)-6a,9-methanocyclohepta[a]naphthalen-14-yl 2-(2-bromophenyl)acetate (2d)

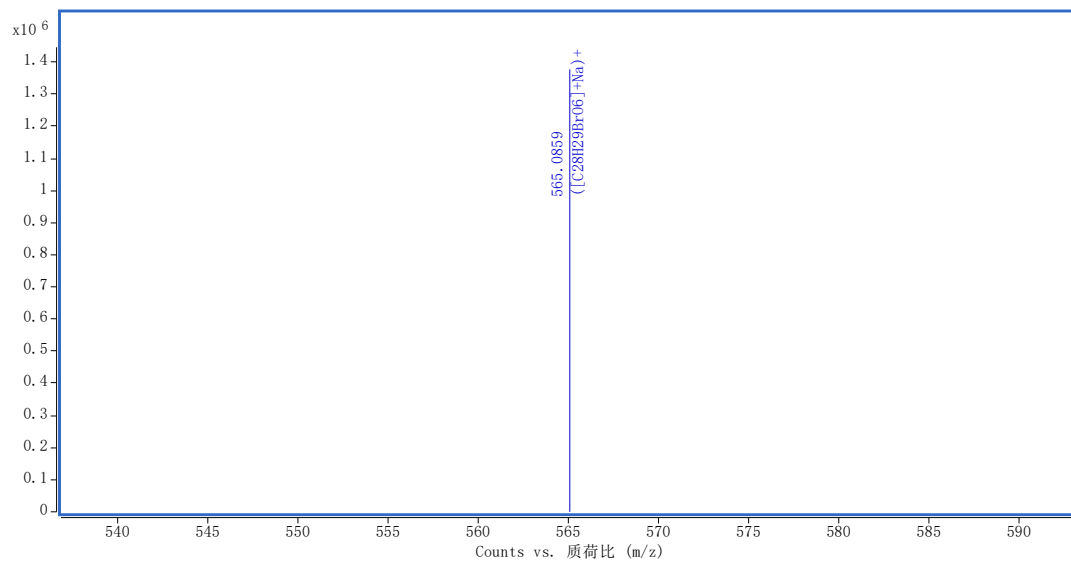


Figure S50. HRMS spectra of
4,4-dimethyl-8-methylene-1,6,7-trioxododecahydro-1H-5,11b-(epoxymethano)-6a,9-methanocyclohepta[a]naphthalen-14-yl 4-(bis(2-chloroethyl)amino)benzoate (2e)

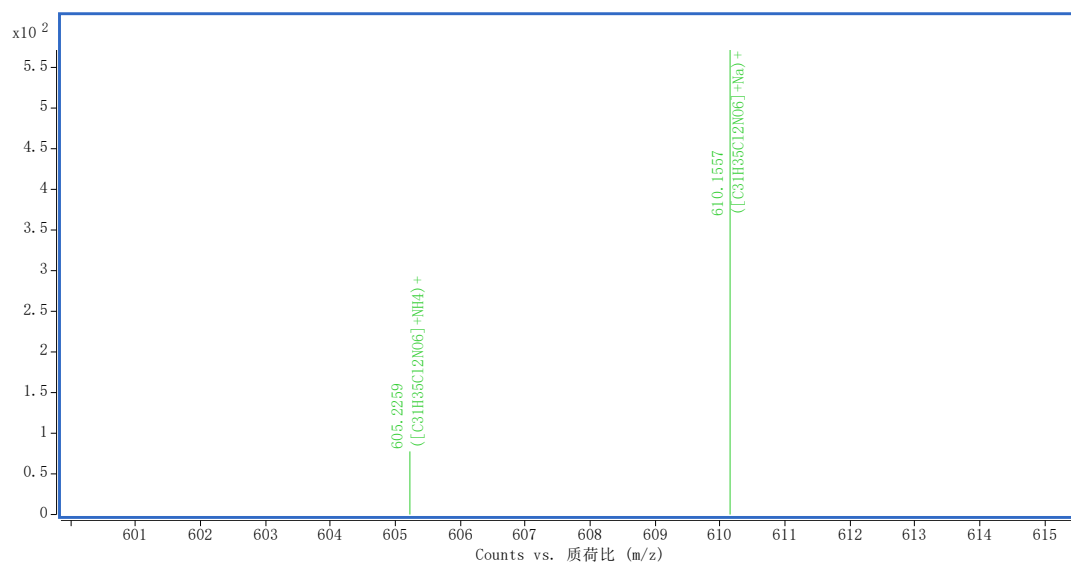


Figure S51. HRMS spectra of **4,4-dimethyl-8-methylene-1,6,7-trioxododecahydro-1H-5,11b-(epoxymethano)-6a,9-methanocyclohepta[a]naphthalen-14-yl 2-(4-(bis(2-chloroethyl)amino)phenyl)acetate (2f)**

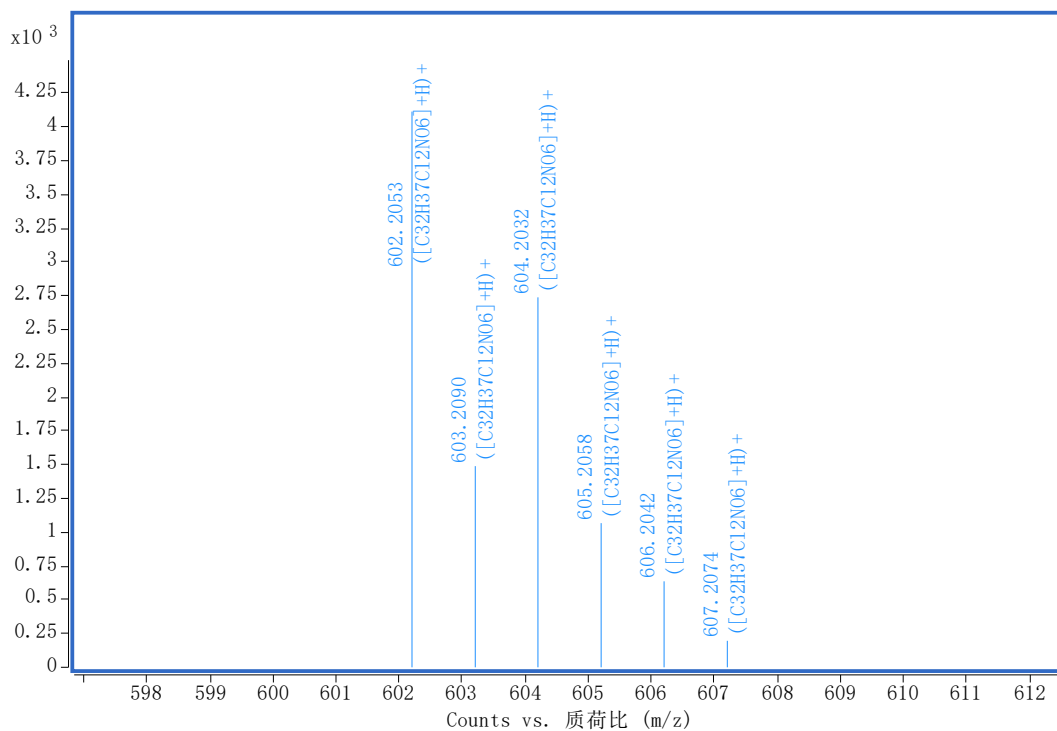


Figure S52. HRMS spectra of **4,4-dimethyl-8-methylene-1,6,7-trioxododecahydro-1H-5,11b-(epoxymethano)-6a,9-methanocyclohepta[a]naphthalen-14-yl adamantane-1-carboxylate (2g)**

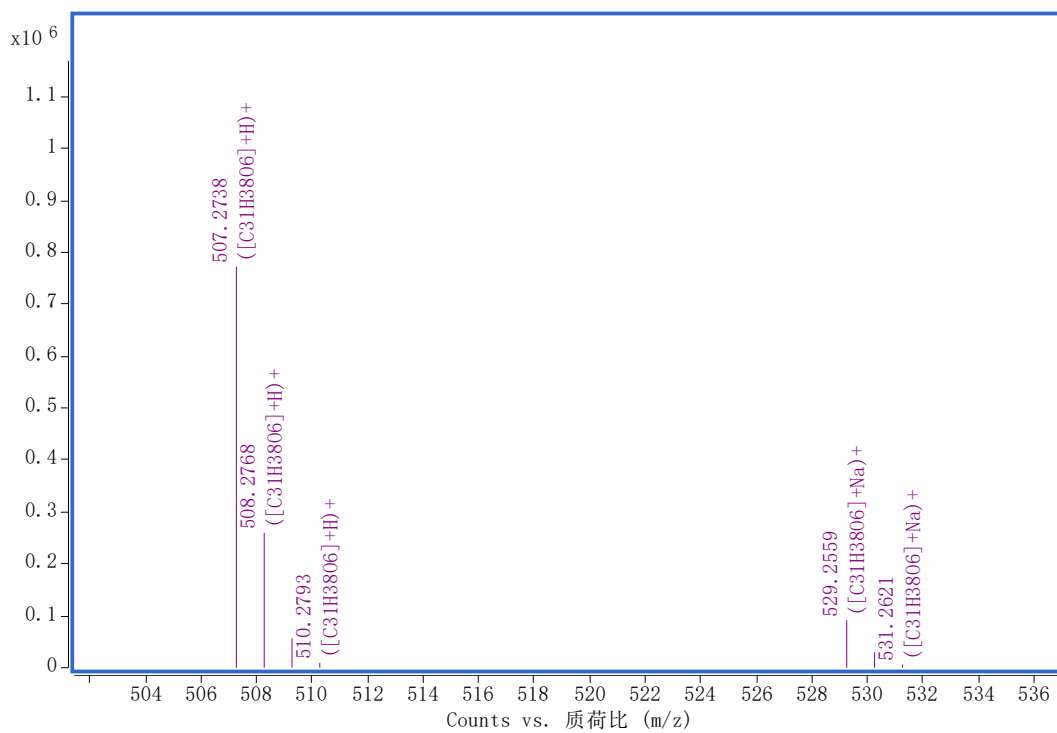


Figure S53. HRMS spectra of **5,6,14-trihydroxy-4,4-dimethyl-8-methylene-4,4a,5,6,9,10,11,11a-octahydro-3H-6,11b-(epoxymethano)-6a,9-methanocyclohepta[a]naphthalen-7(8H)-one (6)**

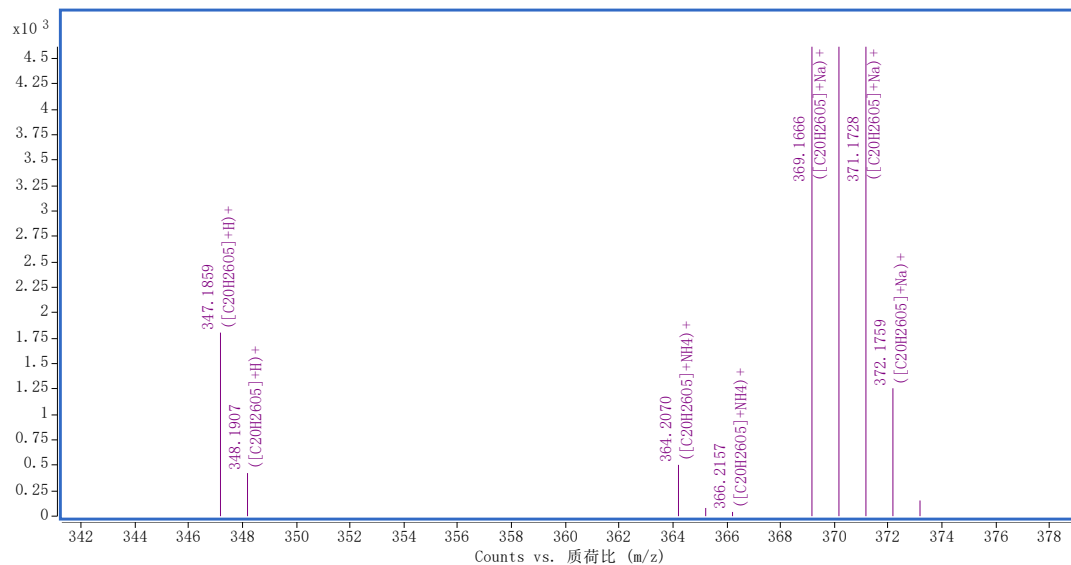


Figure S54. HRMS spectra of **5,6-dihydroxy-4,4-dimethyl-8-methylene-7-oxo-4,4a,5,6,7,8,9,10,11,11a-decahydro-3H-6,11b-(epoxymethano)-6a,9-methanocyclohepta[a]naphthalen-14-yl 2-(3,4,5-trimethoxyphenyl)acetate (6a)**

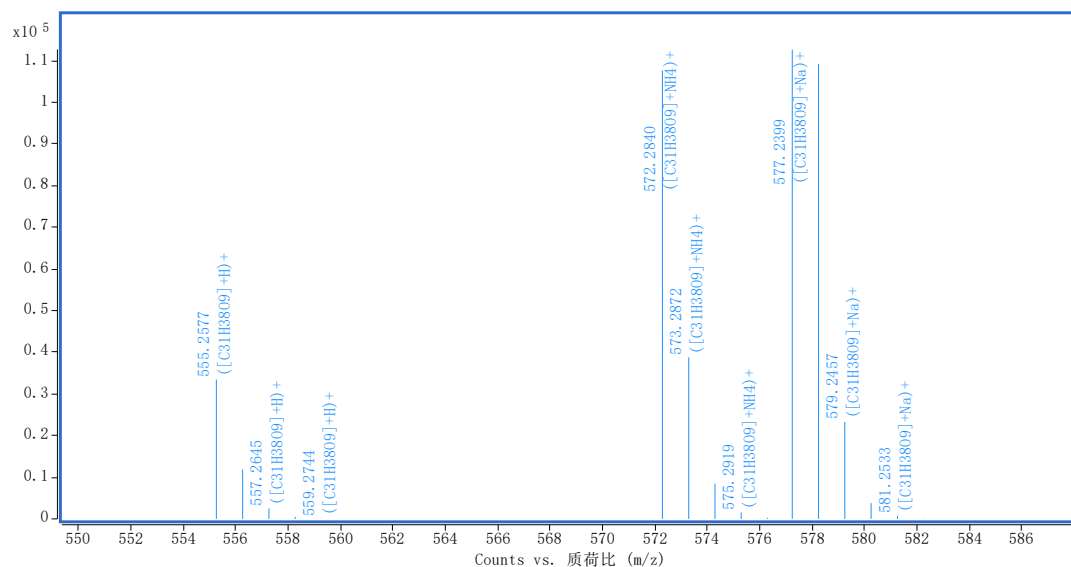


Figure S55. HRMS spectra of **5,6-dihydroxy-4,4-dimethyl-8-methylene-7-oxo-4,4a,5,6,7,8,9,10,11,11a-decahydro-3H-6,11b-(epoxymethano)-6a,9-methanocyclohepta[a]naphthalen-14-yl 2-(3,4-dimethoxyphenyl)acetate (6b)**

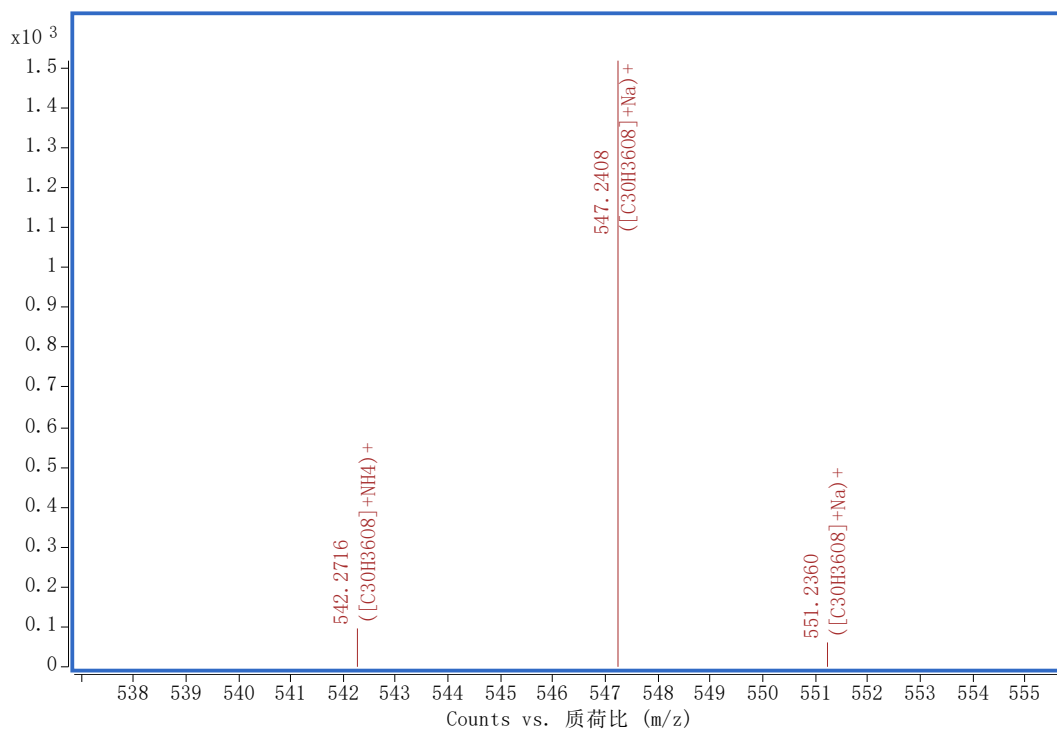


Figure S56. HRMS spectra of **5,6-dihydroxy-4,4-dimethyl-8-methylene-7-oxo-4,4a,5,6,7,8,9,10,11,11a-decahydro-3H-6,11b-(epoxymethano)-6a,9-methanocyclohepta[a]naphthalen-14-yl 2-(4-methoxyphenyl)acetate (6c)**

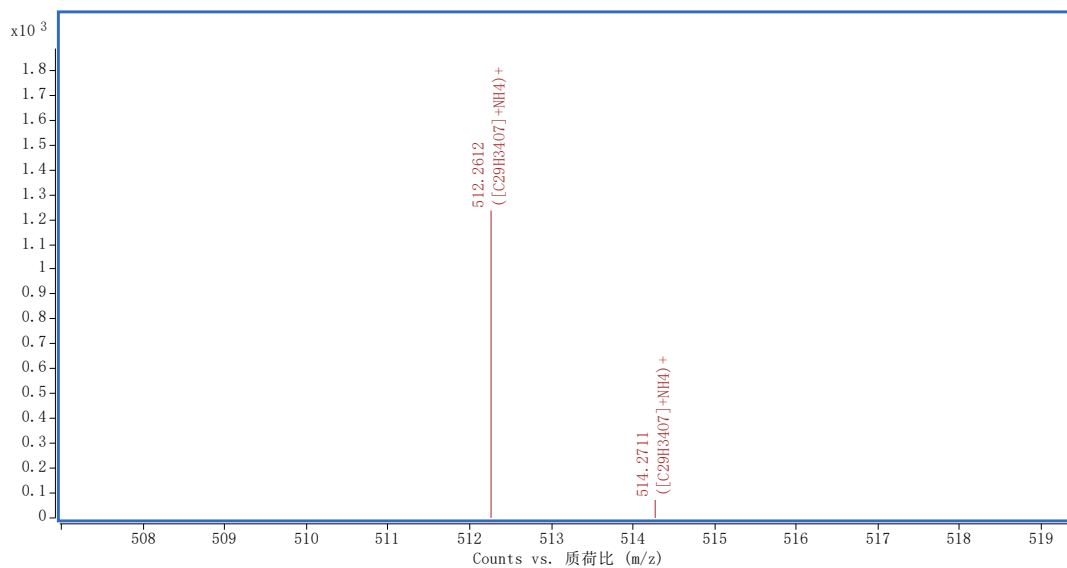


Figure S57. HRMS spectra of **5,6-dihydroxy-4,4-dimethyl-8-methylene-7-oxo-4,4a,5,6,7,8,9,10,11,11a-decahydro-3H-6,11b-(epoxymethano)-6a,9-methanocyclohepta[a]naphthalen-14-yl adamantane-1-carboxylate (6d)**

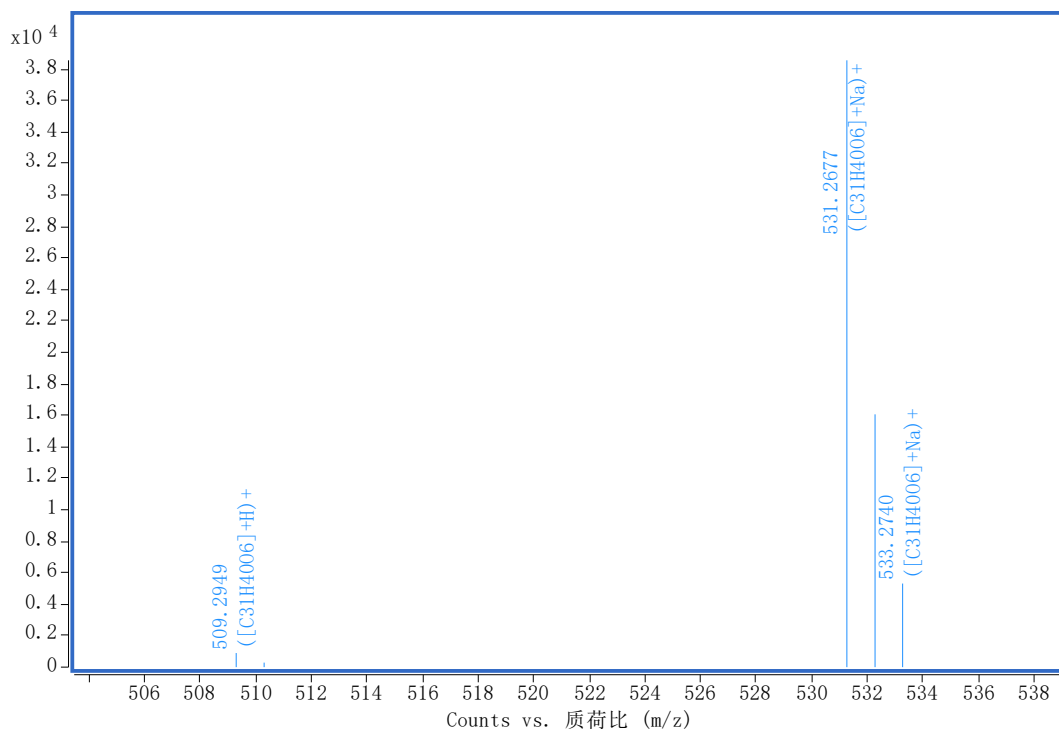


Figure S58. HRMS spectra of **5,6-dihydroxy-4,4-dimethyl-8-methylene-7-oxo-4,4a,5,6,7,8,9,10,11,11a-decahydro-3H-6,11b-(epoxymethano)-6a,9-methanocyclohepta[a]naphthalen-14-yl 4-(bis(2-chloroethyl)amino)benzoate (6e).**

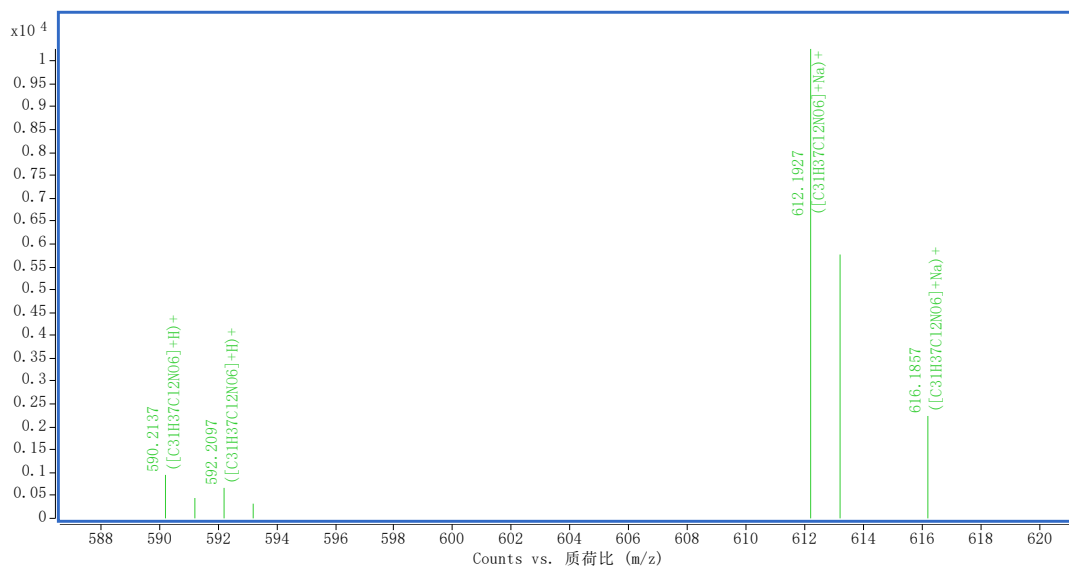


Figure S59. HRMS spectra of
14-hydroxy-4,4-dimethyl-8-methylene-3,4,4a,5,9,10,11,11a-octahydro-6H-5,11b-(epoxymethano)-6a,9-methanocyclohepta[a]naphthalene-6,7(8H)-dione (7)

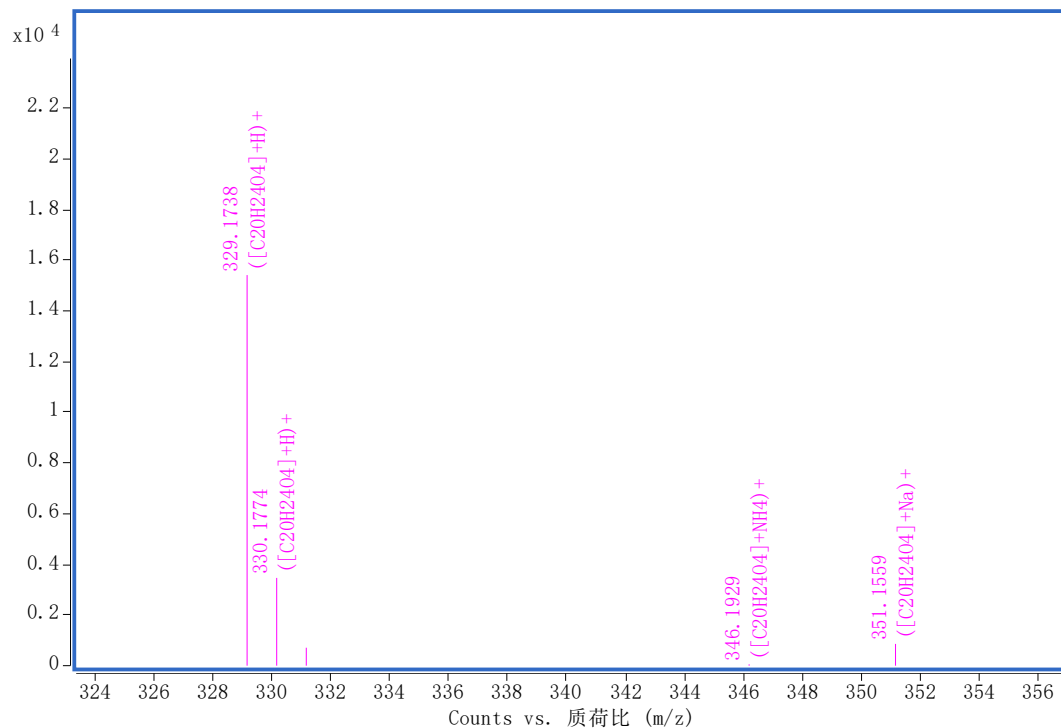


Figure S60. HRMS spectra of
4,4-dimethyl-8-methylene-6,7-dioxo-4,4a,5,6,7,8,9,10,11,11a-decahydro-3H-5,11b-(epoxymethano)-6a,9-methanocyclohepta[a]naphthalen-14-yl 2-(3,4,5-trimethoxyphenyl)acetate (7a)

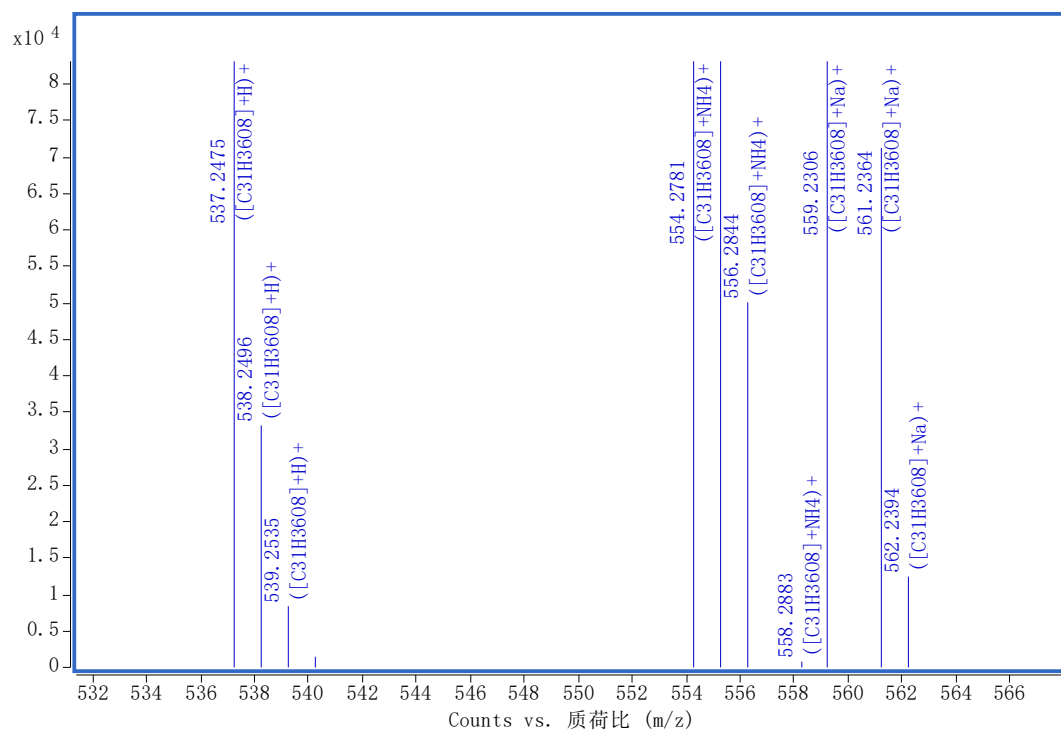


Figure S61. HRMS spectra of **4,4-dimethyl-8-methylene-6,7-dioxo-4,4a,5,6,7,8,9,10,11,11a-decahydro-3H-5,11b-(epoxymethano)-6a,9-methanocyclohepta[a]naphthalen-14-yl adamantane-1-carboxylate (7d).**

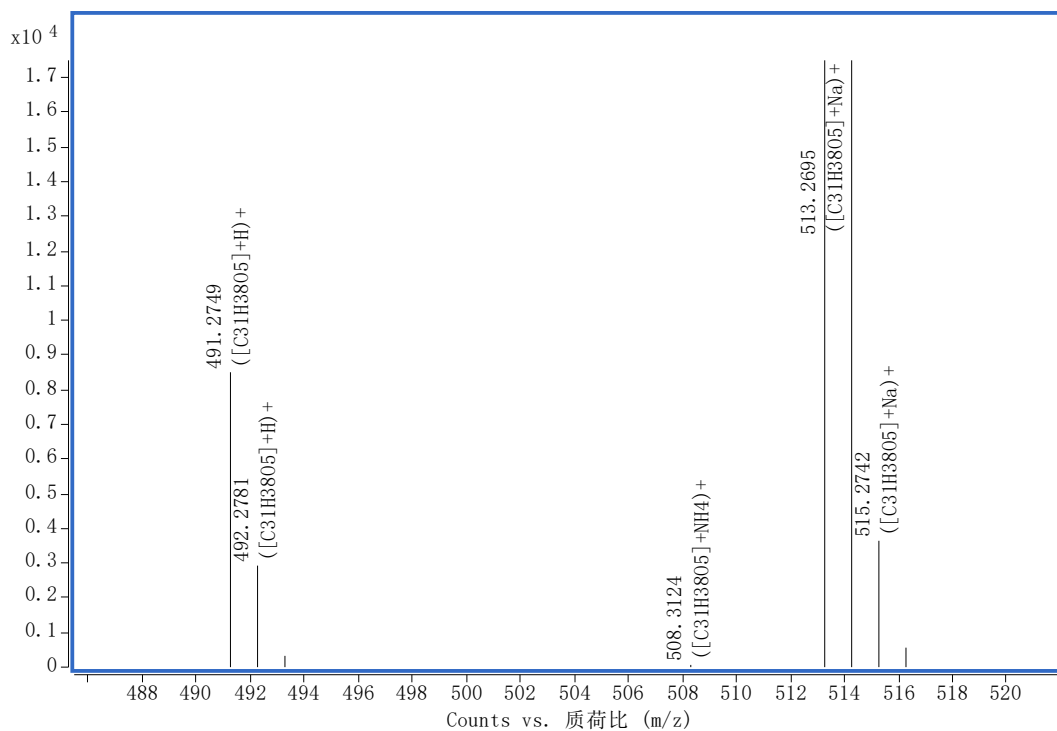


Figure S62. HRMS spectra of **4,4-dimethyl-8-methylene-6,7-dioxo-4,4a,5,6,7,8,9,10,11,11a-decahydro-3H-5,11b-(epoxymethano)-6a,9-methanocyclohepta[a]naphthalen-14-yl 4-(bis(2-chloroethyl)amino)benzoate (7e)**

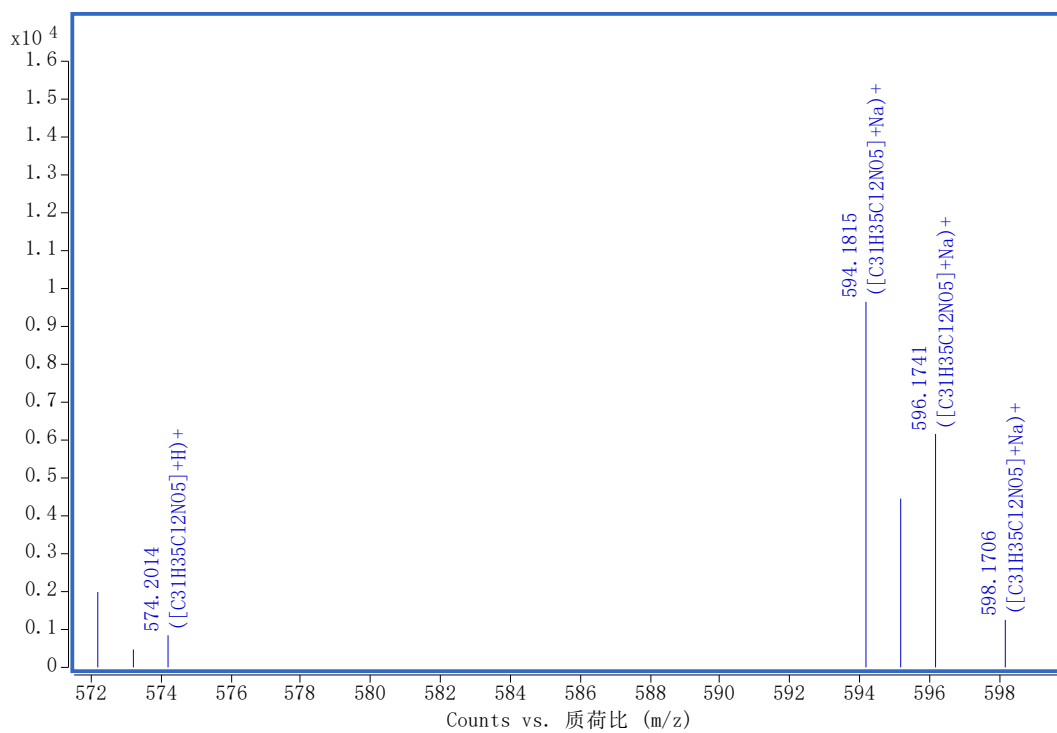


Figure S63. HRMS spectra of **5,6,14-trihydroxy-4,4-dimethyl-8-methylene-7-oxododecahydro-1H-6,11b-(epoxymethano)-6a,9-methanocyclohepta[a]naphthalen-1-yl acetate (9)**.

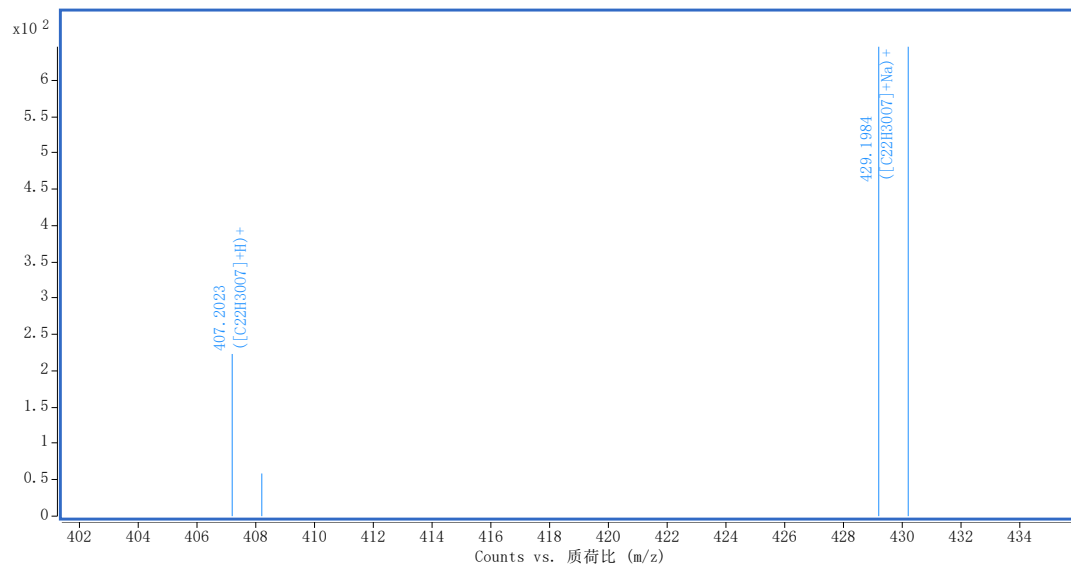


Figure S64. HRMS spectra of **1-acetoxy-5,6-dihydroxy-4,4-dimethyl-8-methylene-7-oxododecahydro-1H-6,11b-(epoxymethano)-6a,9-methanocyclohepta[a]naphthalen-14-yl adamantane-1-carboxylate (9a)**.

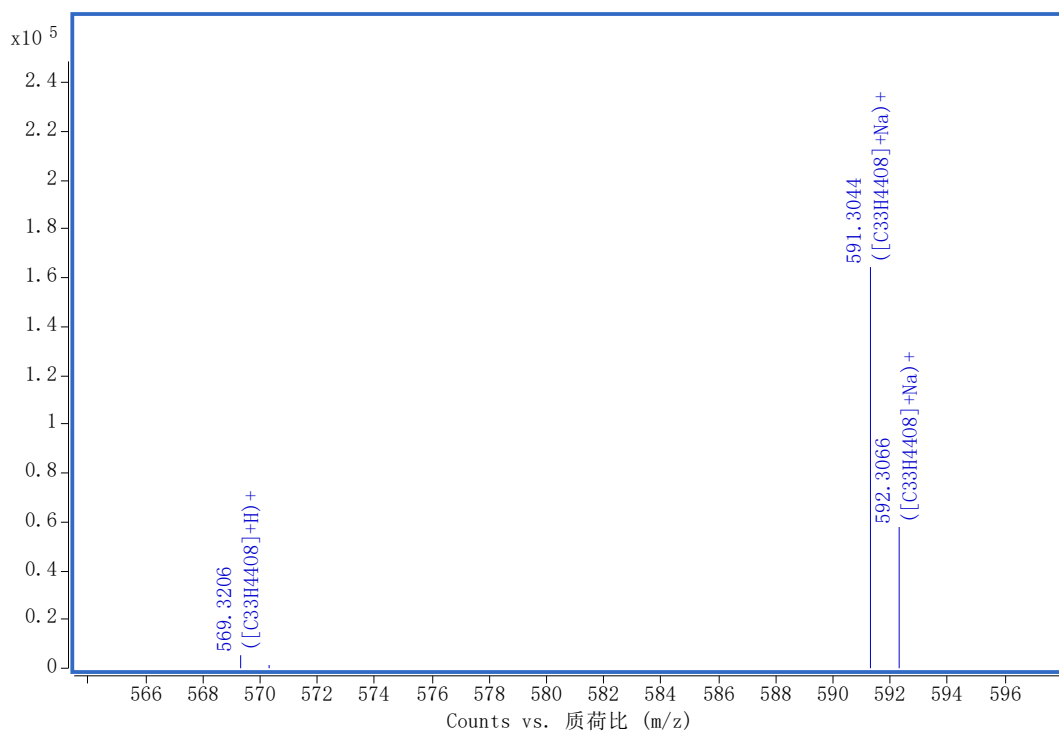


Figure S65. HRMS spectra of
1-acetoxy-4,4-dimethyl-8-methylene-6,7-dioxododecahydro-1H-5,11b-
(epoxymethano)-6a,9-methanocyclohepta[a]naphthalen-14-yl adamantane-1-
carboxylate (10a)

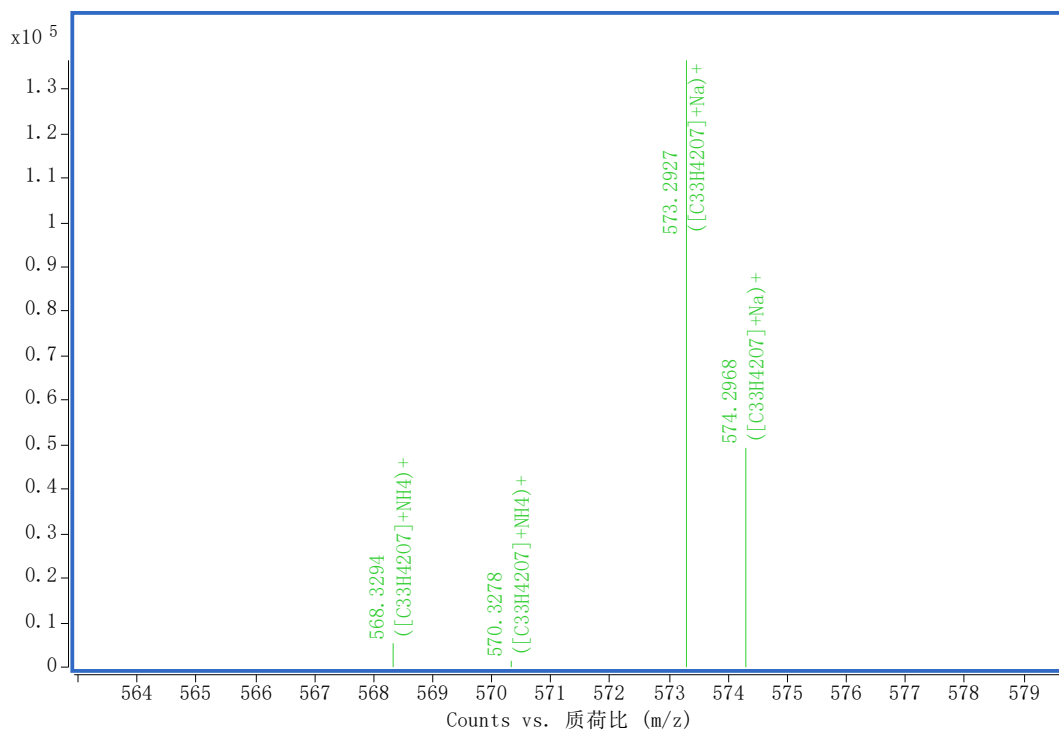


Figure S66. HRMS spectra of
1,5,6-Trihydroxy-4,4-dimethyl-8-methylene-7-oxododecahydro-1H-6,11b-
(epoxymethano)-6a,9-methanocyclohepta[a]naphthalen-14-yl adamantane-1-
carboxylate (11a)

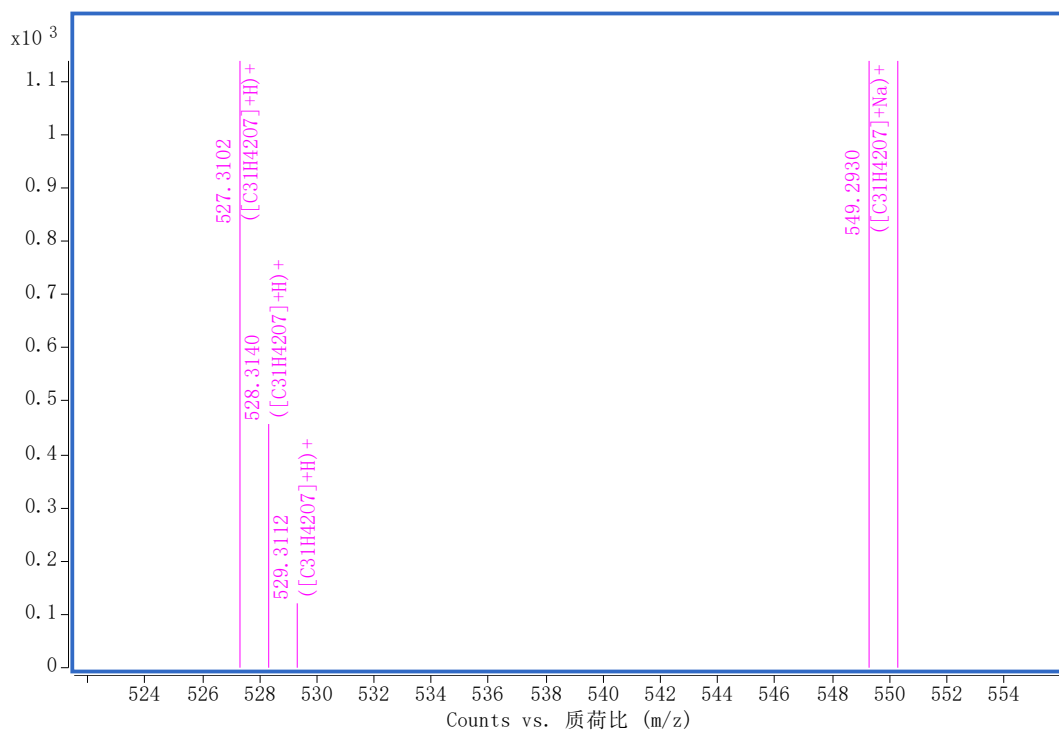


Figure S67. HRMS spectra of
1,5,6-trihydroxy-4,4-dimethyl-8-methylene-7-oxododecahydro-1H-6,11b-
(epoxymethano)-6a,9-methanocyclohepta[a]naphthalen-14-yl 4-(bis(2-
chloroethyl)amino)benzoate (11b)

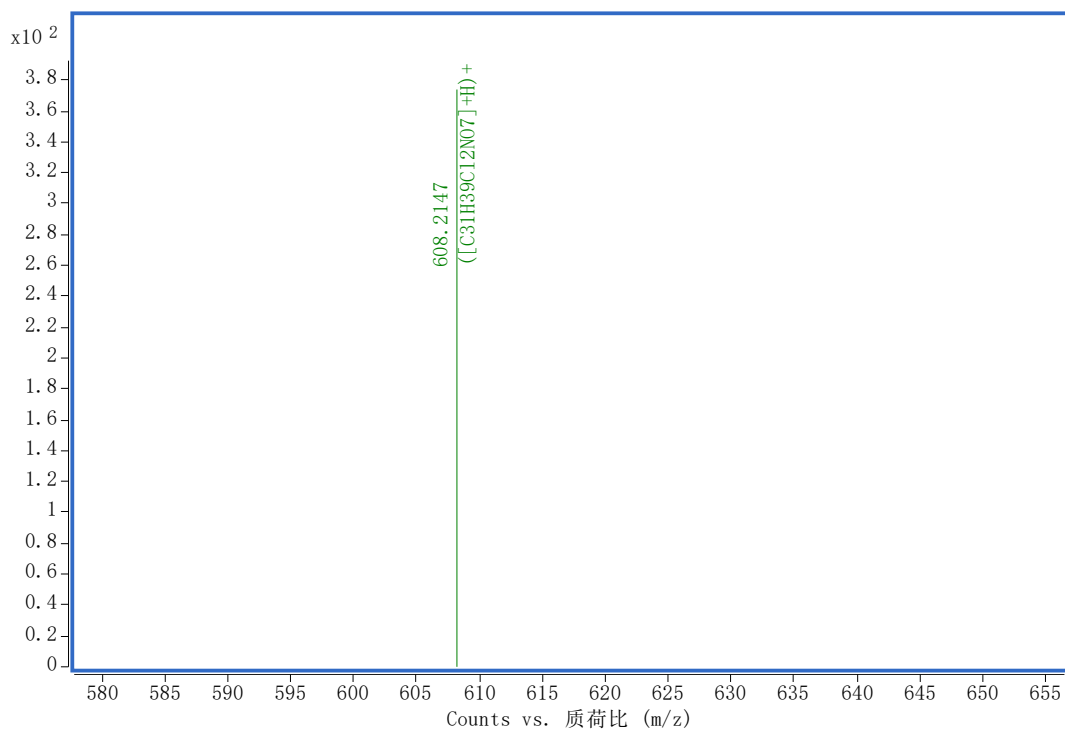


Figure S68. HRMS spectra of
1-hydroxy-4,4-dimethyl-8-methylene-6,7-dioxododecahydro-1H-5,11b-
(epoxymethano)-6a,9-methanocyclohepta[a]naphthalen-14-yl adamantane-1-
carboxylate (12a)

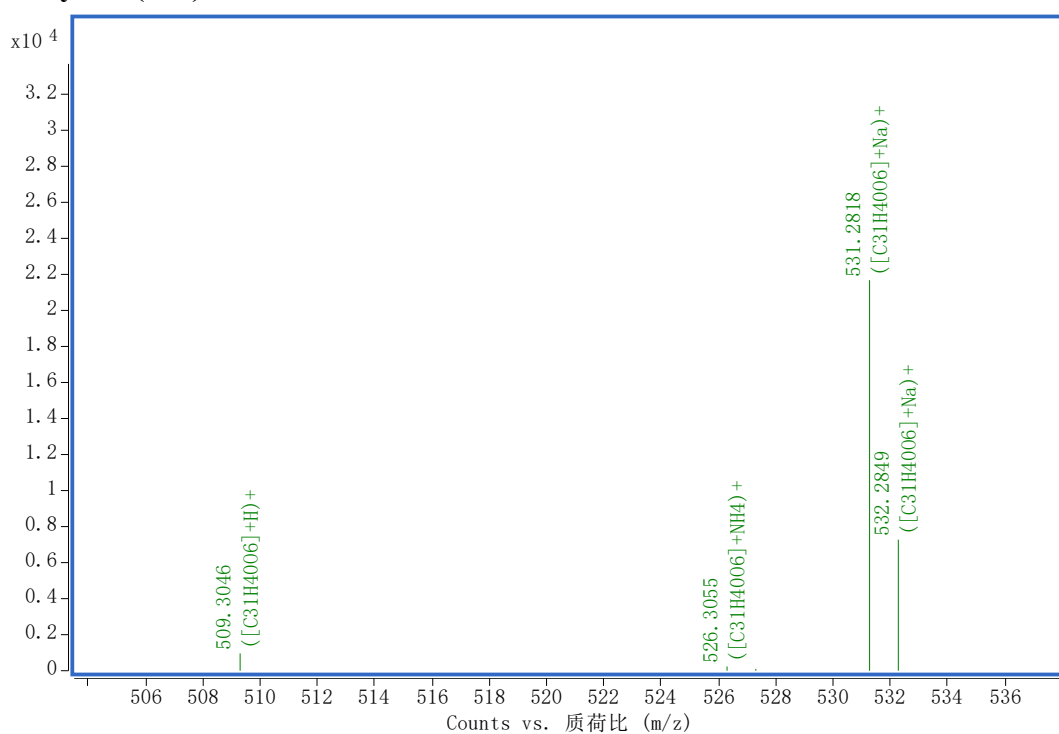


Figure S69. HRMS spectra of **1-hydroxy-4,4-dimethyl-8-methylene-6,7-dioxododecahydro-1H-5,11b-(epoxymethano)-6a,9-methanocyclohepta[a]naphthalen-14-yl 4-(bis(2-chloroethyl)amino)benzoate (12b)**

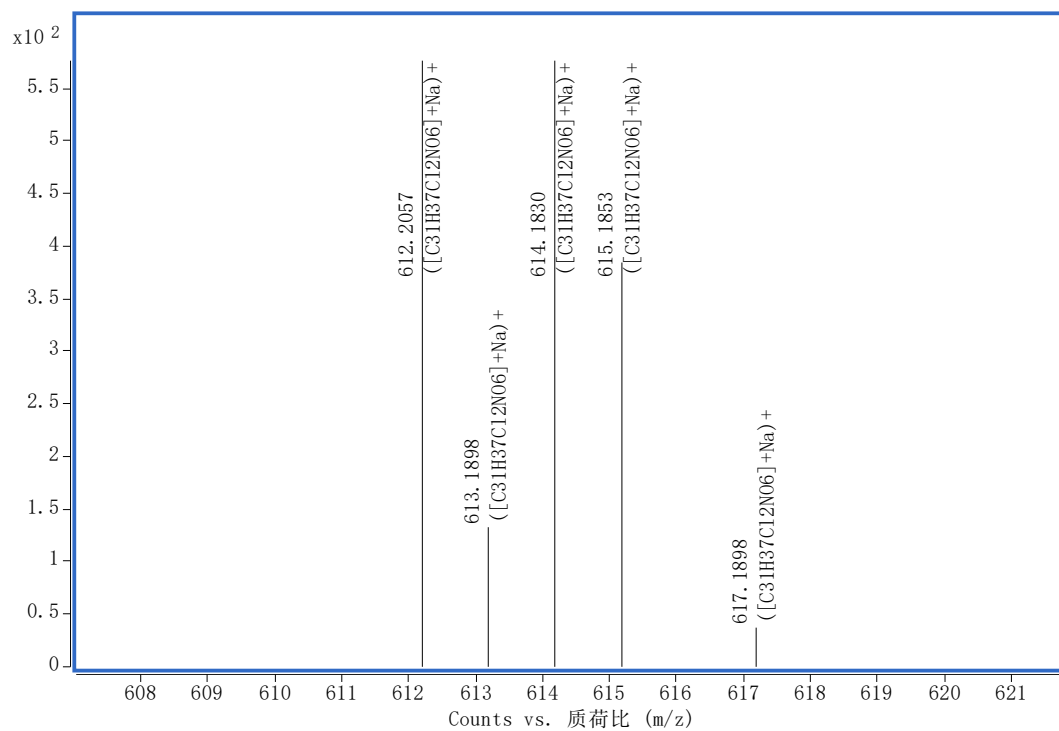
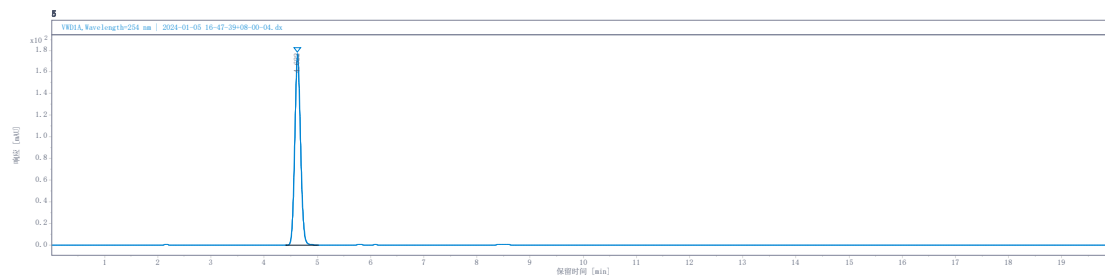
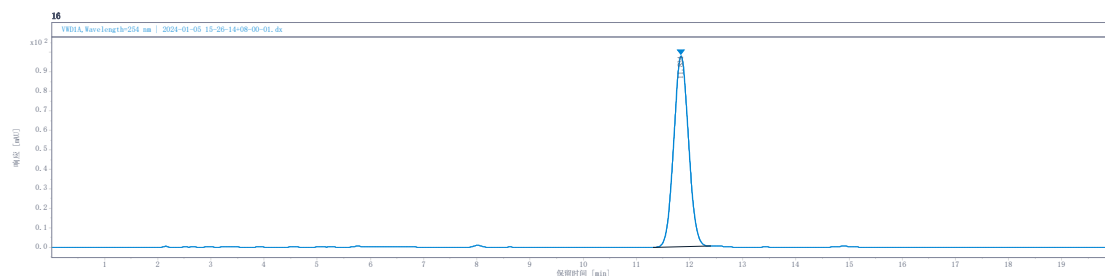


Figure S70. HPLC-purity spectra of **5,6,14-trihydroxy-4,4-dimethyl-8-methylene-4,4a,5,6,9,10,11,11a-octahydro-3H-6,11b-(epoxymethano)-6a,9-methanocyclohepta[a]naphthalen-7(8H)-one (6)**



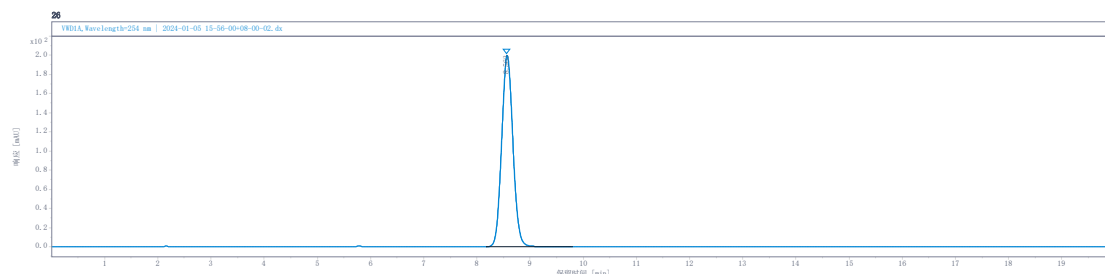
RT (min)	A (mAU·s)	A %	H (mAU)	H%
4.622	1331.522	100.000	176.940	100.00

Figure S71. HPLC-purity spectra of **1-acetoxy-5,6-dihydroxy-4,4-dimethyl-8-methylene-7-oxododecahydro-1H-6,11b-(epoxymethano)-6a,9-methanocyclohepta[a]naphthalen-14-yl adamantane-1-carboxylate (9a)**



RT (min)	A (mAU·s)	A %	H (mAU)	H%
11.834	1897.914	100.000	97.914	100.00

Figure S72. HPLC-purity spectra of **1,5,6-Trihydroxy-4,4-dimethyl-8-methylene-7-oxododecahydro-1H-6,11b-(epoxymethano)-6a,9-methanocyclohepta[a]naphthalen-14-yl adamantane-1-carboxylate (11a)**



RT (min)	A (mAU·s)	A %	H (mAU)	H%
8.563	2941.279	100.000	200.100	100.00

Table S1 Plasma stability of oridonin and compound 11a

Summary			
Compound ID	Time Point (min)	% Remaining	T _{1/2} (min)
		Human	Human
Oridonin	0	100.0	143.8
	10	60.6	
	30	47.5	
	60	39.8	
	120	31.8	
11a	0	100.0	143.8
	10	96.3	
	30	85.6	
	60	64.6	
	120	58.0	
Propantheline bromide	0	100.0	9.7
	10	74.2	
	30	25.2	
	60	2.2	
	120	0.0	

The Initial Report in Human Plasma						
Sample_ID	Time (min)	Analyte Peak Area	IS Peak Area	Aa/Ai	% Remainin g (n=2)	Ln (% Remainin g)
Oridonin_H_0	0	1.95E+05	3.07E+05	0.6335	100.0	0.00
Oridonin_H_0		1.53E+05	2.78E+05	0.5525		
Oridonin_H_10	10	1.01E+05	2.74E+05	0.3688	60.6	-0.50
Oridonin_H_10		9.62E+04	2.75E+05	0.3497		
Oridonin_H_30	30	7.65E+04	2.72E+05	0.2811	47.5	-0.74
Oridonin_H_30		7.64E+04	2.71E+05	0.2820		
Oridonin_H_60	60	6.62E+04	2.71E+05	0.2443	39.8	-0.92
Oridonin_H_60		6.32E+04	2.78E+05	0.2273		
Oridonin_H_120	120	5.45E+04	2.99E+05	0.1820	31.8	-1.15
Oridonin_H_120		5.21E+04	2.68E+05	0.1949		
11a_H_0	0	2.27E+05	2.76E+04	8.2170	100.0	0.00
11a_H_0		2.19E+05	2.86E+04	7.6775		
11a_H_10	10	2.13E+05	2.64E+04	8.0600	96.3	-0.04
11a_H_10		2.17E+05	2.99E+04	7.2530		
11a_H_30	30	2.02E+05	3.01E+04	6.7357	85.6	-0.16
11a_H_30		1.91E+05	2.78E+04	6.8758		
11a_H_60	60	1.32E+05	3.01E+04	4.3945	64.6	-0.44
11a_H_60		1.75E+05	2.98E+04	5.8710		
11a_H_120	120	1.43E+05	2.96E+04	4.8163	58.0	-0.54
11a_H_120		1.35E+05	3.07E+04	4.4073		
Propantheline bromide_H_0	0	6.66E+06	2.41E+06	2.7626	100.0	0.00
Propantheline bromide_H_0		6.66E+06	2.41E+06	2.7660		
Propantheline bromide_H_10	10	4.53E+06	2.40E+06	1.8922	70.1	-0.35
Propantheline bromide_H_10		4.82E+06	2.43E+06	1.9858		
Propantheline bromide_H_30	30	1.16E+06	2.47E+06	0.4713	18.9	-1.67
Propantheline bromide_H_30		1.37E+06	2.40E+06	0.5708		
Propantheline bromide_H_60	60	1.03E+05	2.44E+06	0.0421	1.5	-4.19
Propantheline bromide_H_60		1.01E+05	2.42E+06	0.0416		
Propantheline bromide_H_120	120	0.00E+00	2.40E+06	0.0000	0.1	
Propantheline bromide_H_120		1.00E+04	2.44E+06	0.0041		