Supporting Information for

Halogenated Compounds from Directed Fermentation of *Penicillium concentricum*, an Endophytic Fungus of the Liverwort *Trichocolea tomentella*

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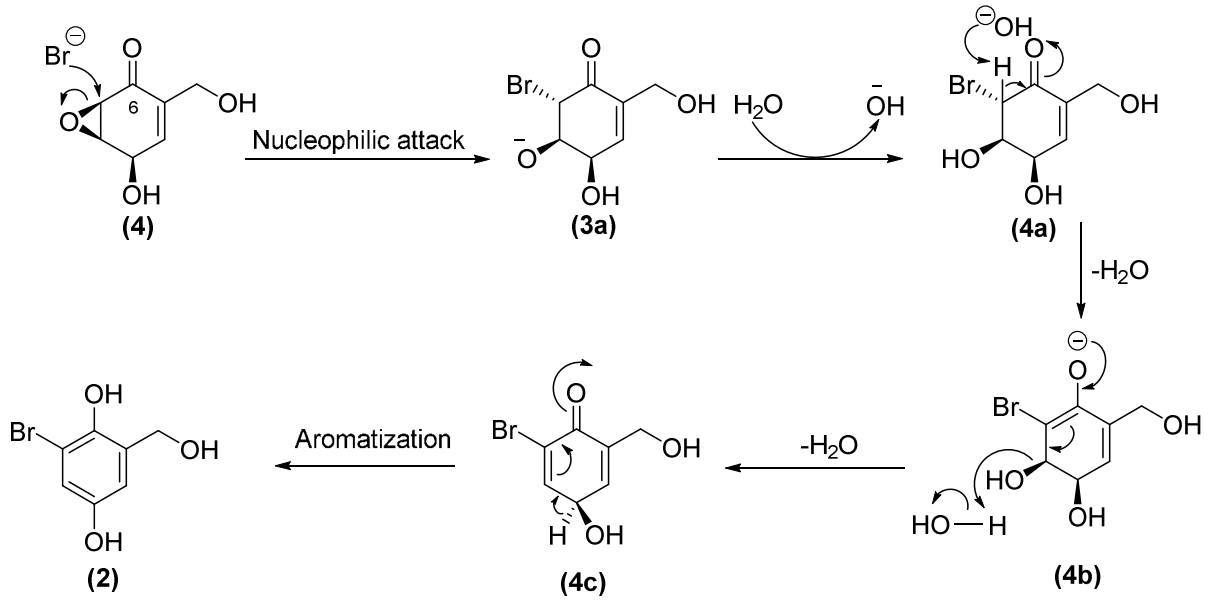
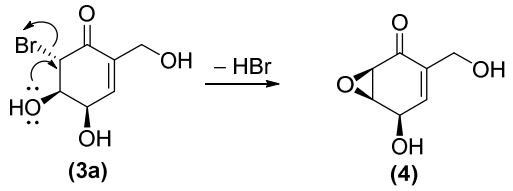
Chemical preparation of halohydrins (3a, 3b, 8a, 8b) and halogenated gentisyl alcohol analogues (2, 6). To confirm the non-enzymatic reaction, epoxydon (**4**) was first isolated from a 3-day epoxydon-rich fermentation of *P. concentricum* on rice medium. A saturated aqueous halogen salt solution such as KBr or KCl was then added to a methanolic solution of the isolated epoxydon and the reaction was stirred at room temperature for 24 hours. Semi-preparative HPLC of the reaction mixture (Figures S20 and S22) led to the isolation of **2**, **3a**, **3b**, **6**, **7**, **8a** and **8b**. These chemically produced compounds were identified by comparison of their spectroscopic characteristics (including UV characteristics, mass spectroscopy and NMR) with the isolated known compounds in the present study and those reported in the literatures. In addition, comparison of the HPLC chromatograms of the ethyl acetate extract of *P. concentricum* fermented on halogen salt (KCl or KBr) supplemented rice medium with that of the reaction mixture of epoxydon and KCl (Figure S20) on one hand and with that of KBr (Figure S22) on the other hand clearly demonstrated that compounds **2**, **3a**, **3b**, **6**, **7**, **8a**, and **8b** were not biosynthetically but chemically produced. This conclusion was also confirmed by co-injection of the extract obtained from fermentation in the presence of halogen salt and the reaction mixture of epoxydon and KCl or KBr (Figures S19 and S21). The chemical formation of the non-natural compounds has been depicted in scheme S1. The regioselective nucleophilic attack by bromine (or chlorine) ion occurs from the α-face opposite to the epoxide ring at the preferable α- position to the ketone (C-6).[28,29] The proposed mechanisms of formation of 2 is reported in Scheme S1. It

is worth to note that the brominated and chlorinated compounds (**2** and **6**, respectively) have been found to be the abundant compounds in the fifteen-day fermentation of *P. concentricum* on halogen salt (KBr and KCl) enriched rice medium.



Scheme S1. Proposed Chemical formation of 2-bromo-gentisyl alcohol (**2**) from epoxydon (**4**).



Scheme S2. Intramolecular S_N2 reaction of 6-dehydroxy-6α-bromogabosine C (**3a**) to form **4**.

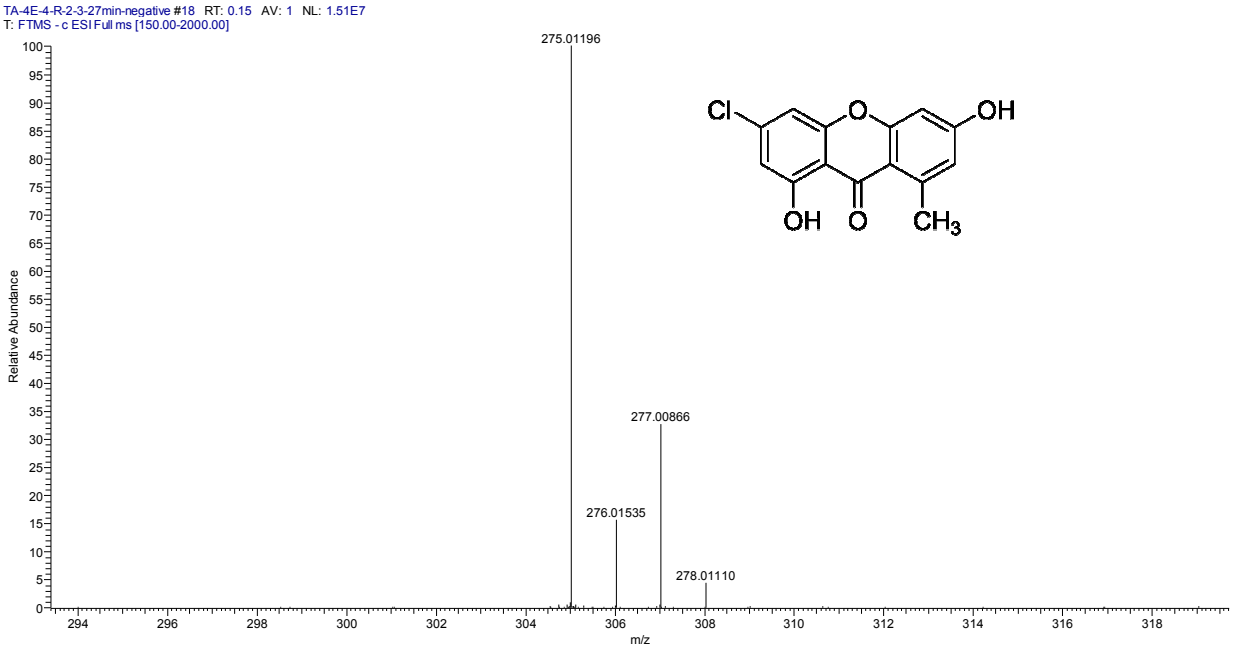


Figure S1. HRESIMS spectrum of compound **1**

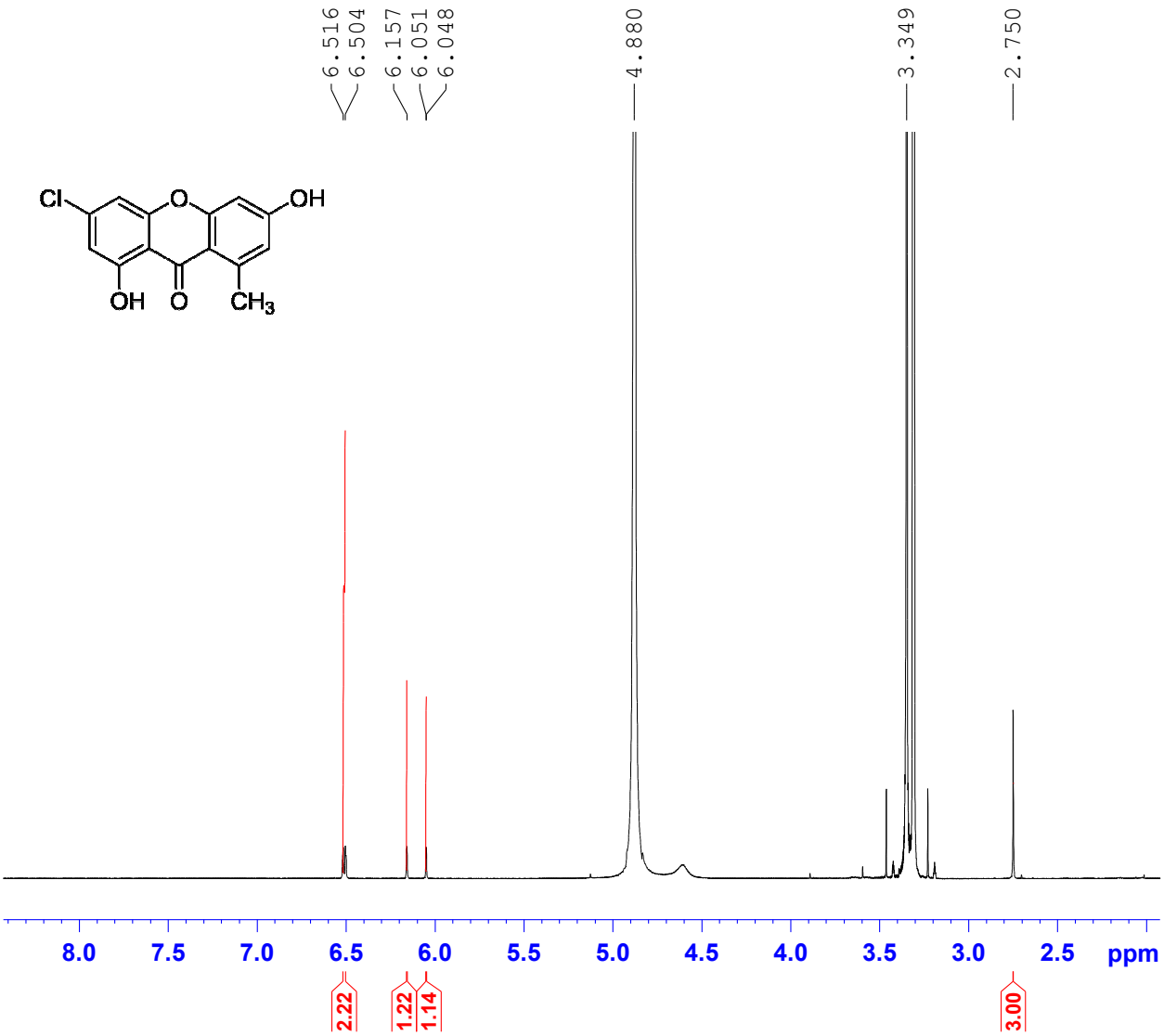


Figure S2. ^{1}H NMR spectrum of compound **1** in methanol-d_4 (700 MHz)

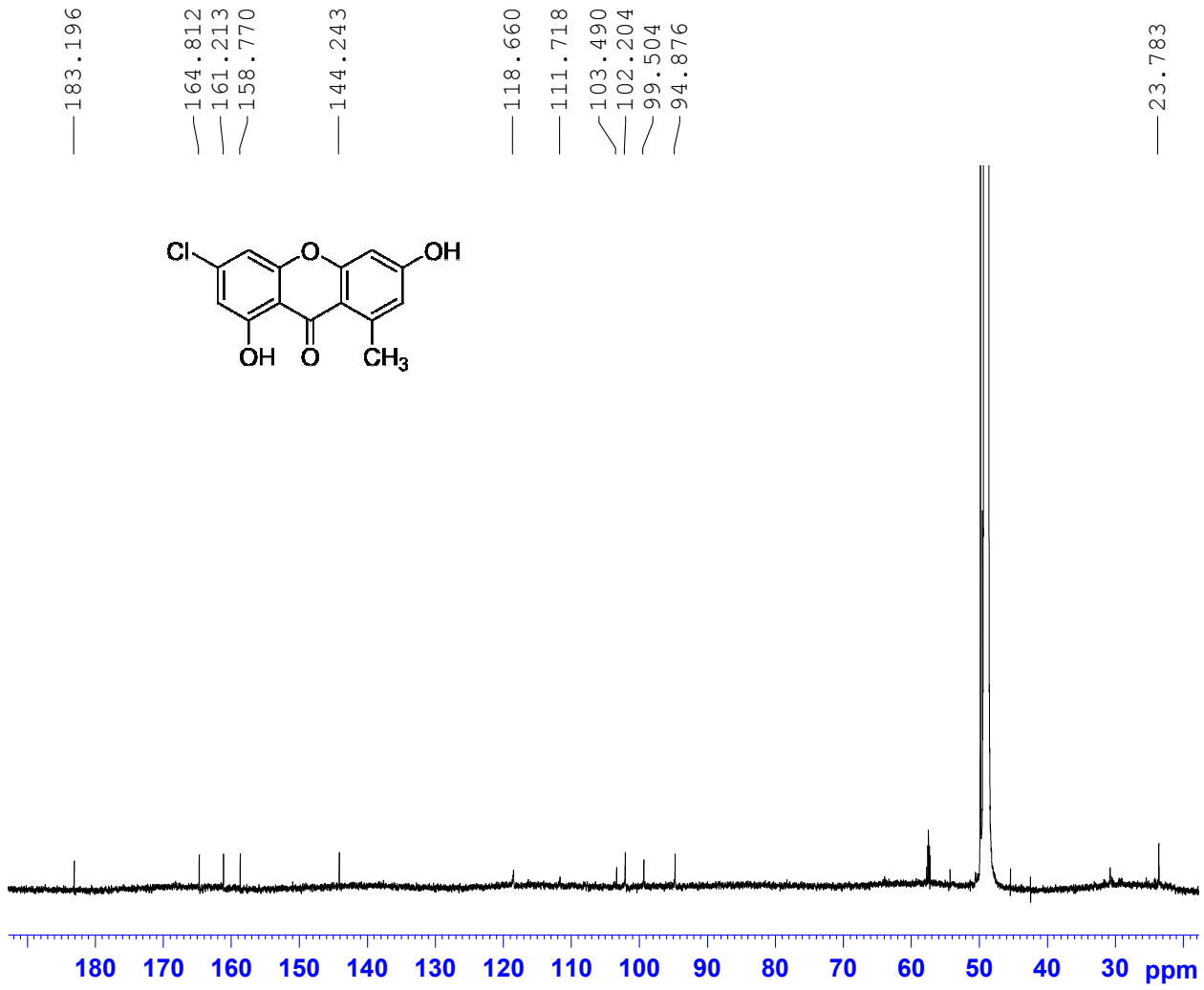


Figure S3. ^{13}C NMR spectrum of compound **1** in methanol-d_4 (175 MHz)

Figure S4. HSQC spectrum of compound **1** methanol-d_4 (400 MHz)

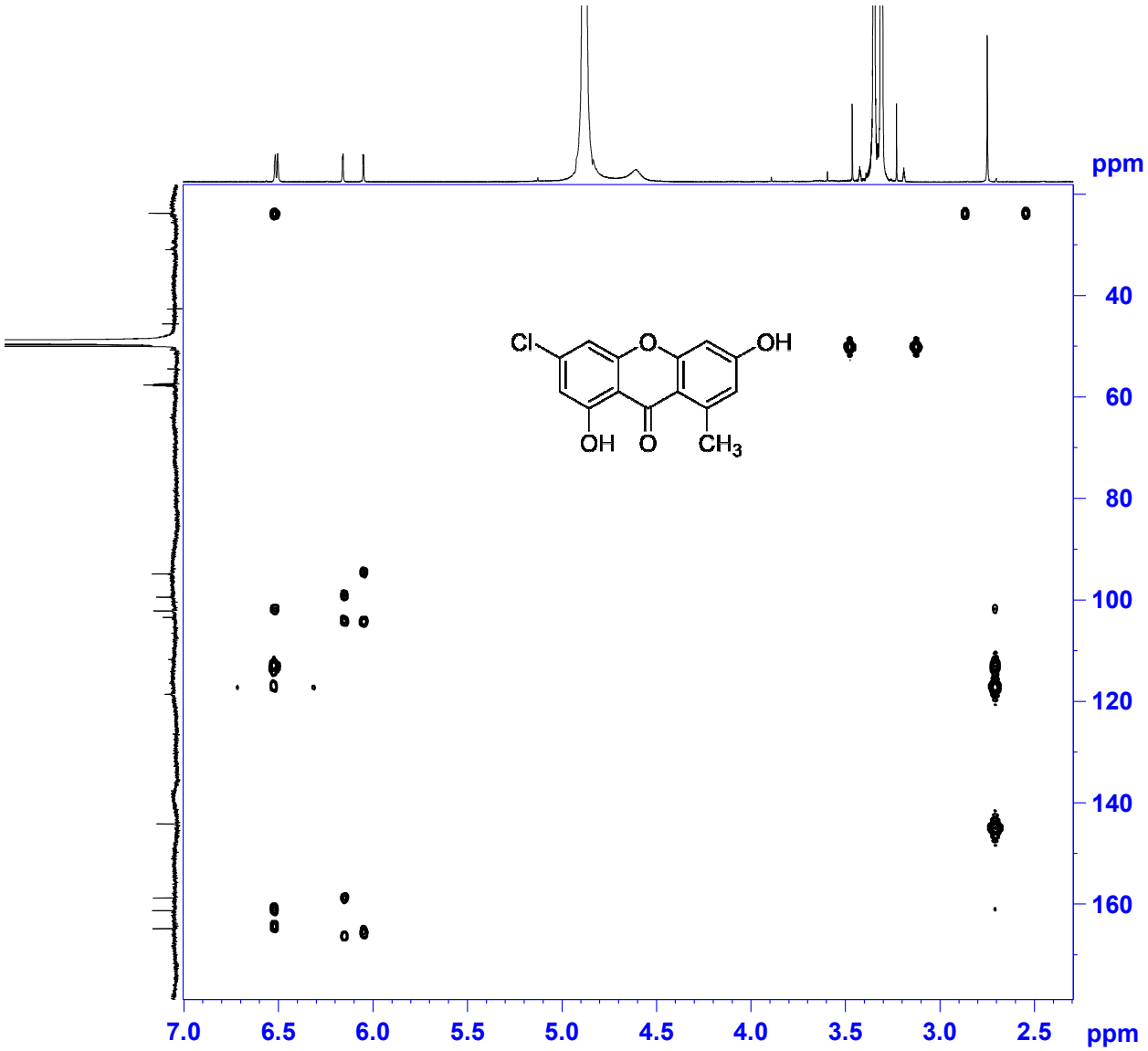


Figure S5. HMBC spectrum of compound **1** in methanol-d_4 (700 MHz)

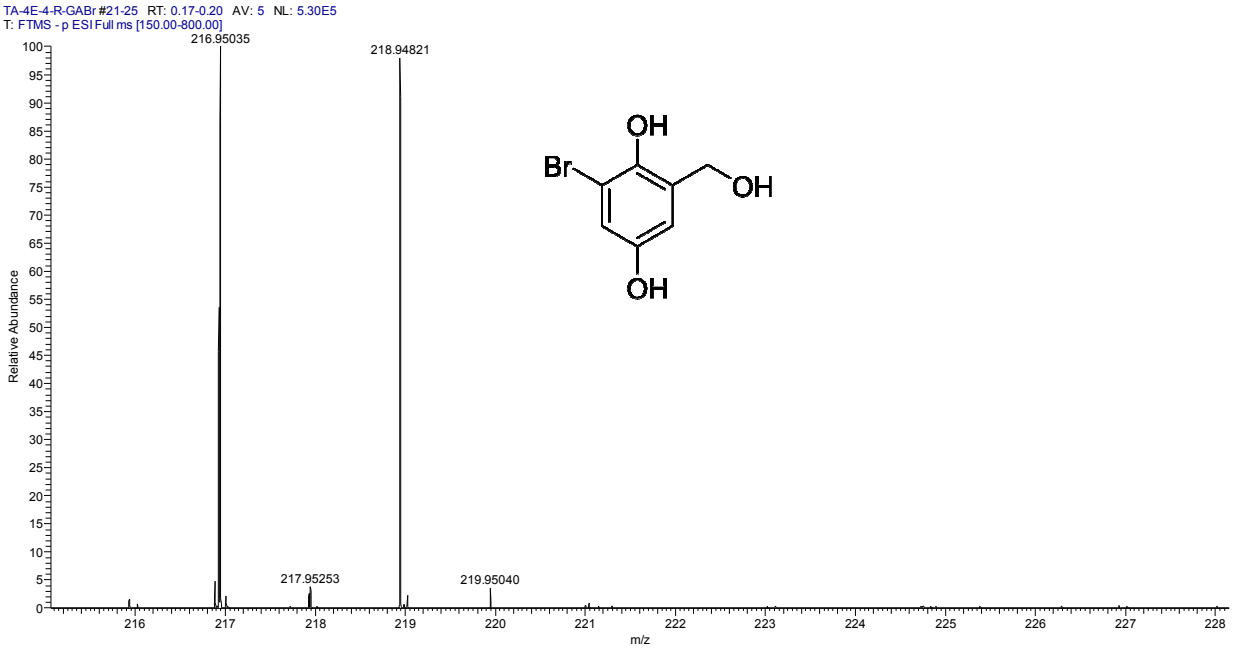


Figure S6. HRESIMS spectrum of compound **2**

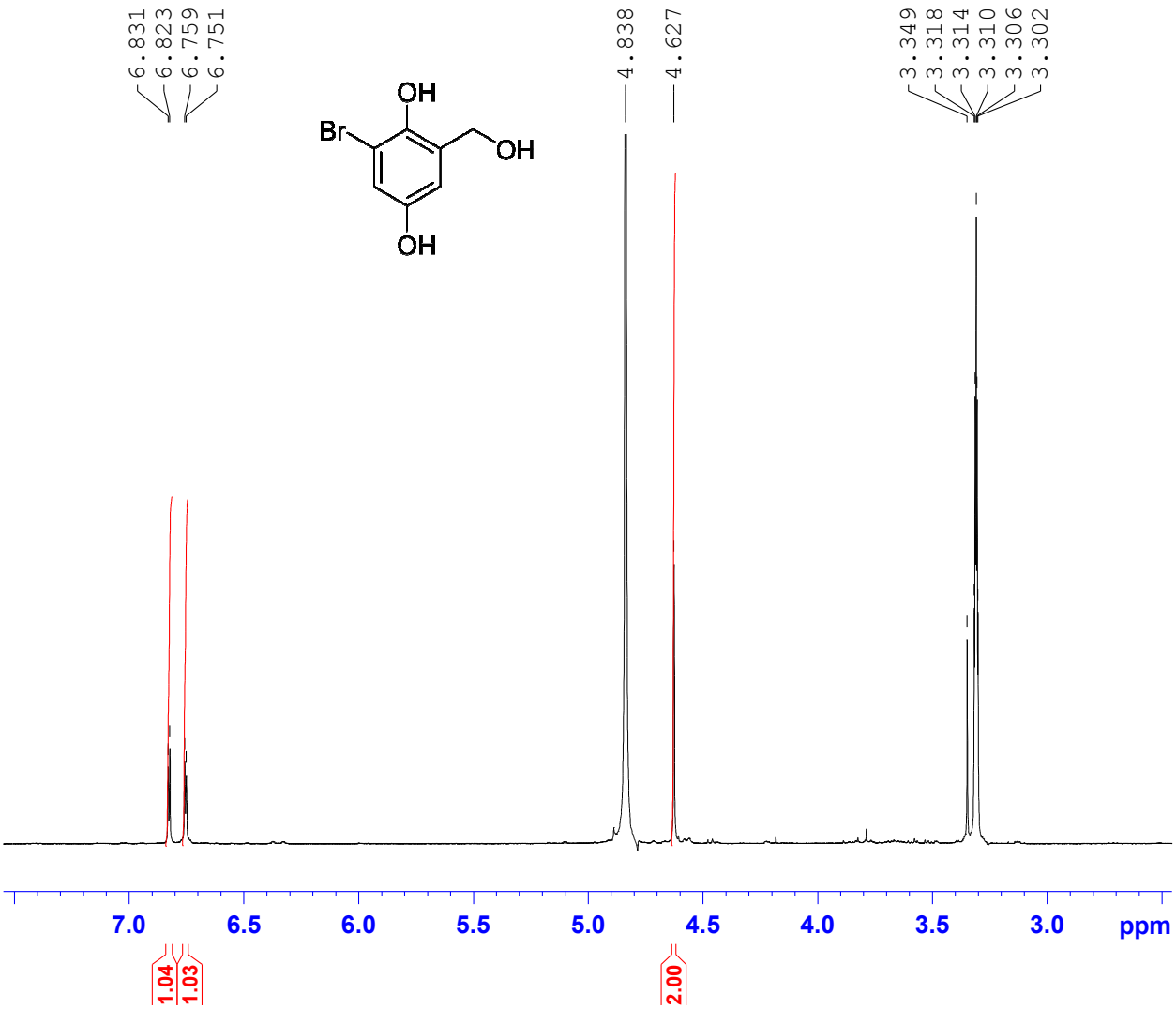


Figure S7. ^{1}H NMR spectrum of compound **2** in methanol-d_4 (400 MHz)

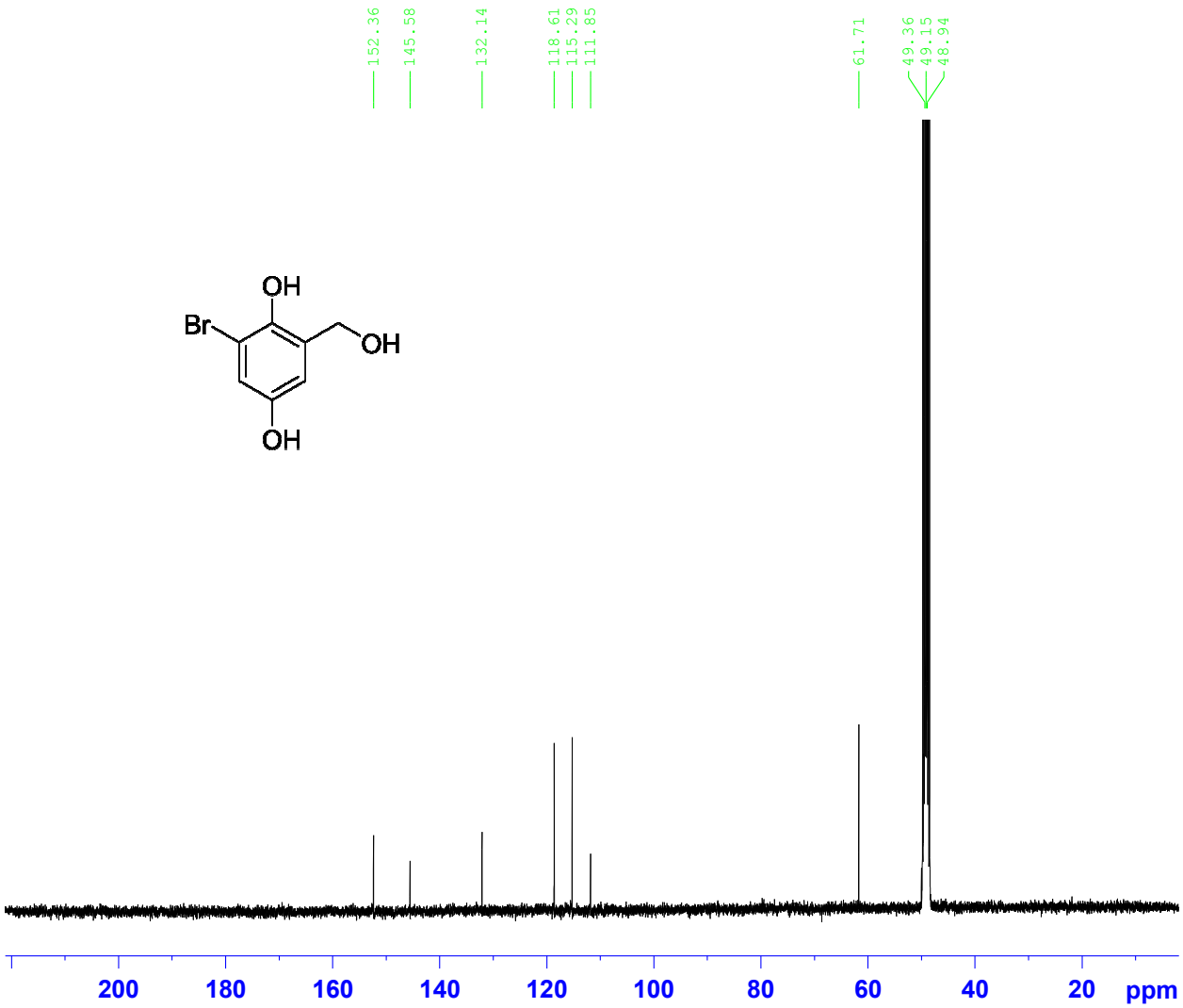


Figure S8. ^{13}C NMR spectrum of compound **2** in methanol-d_4 (100 MHz)

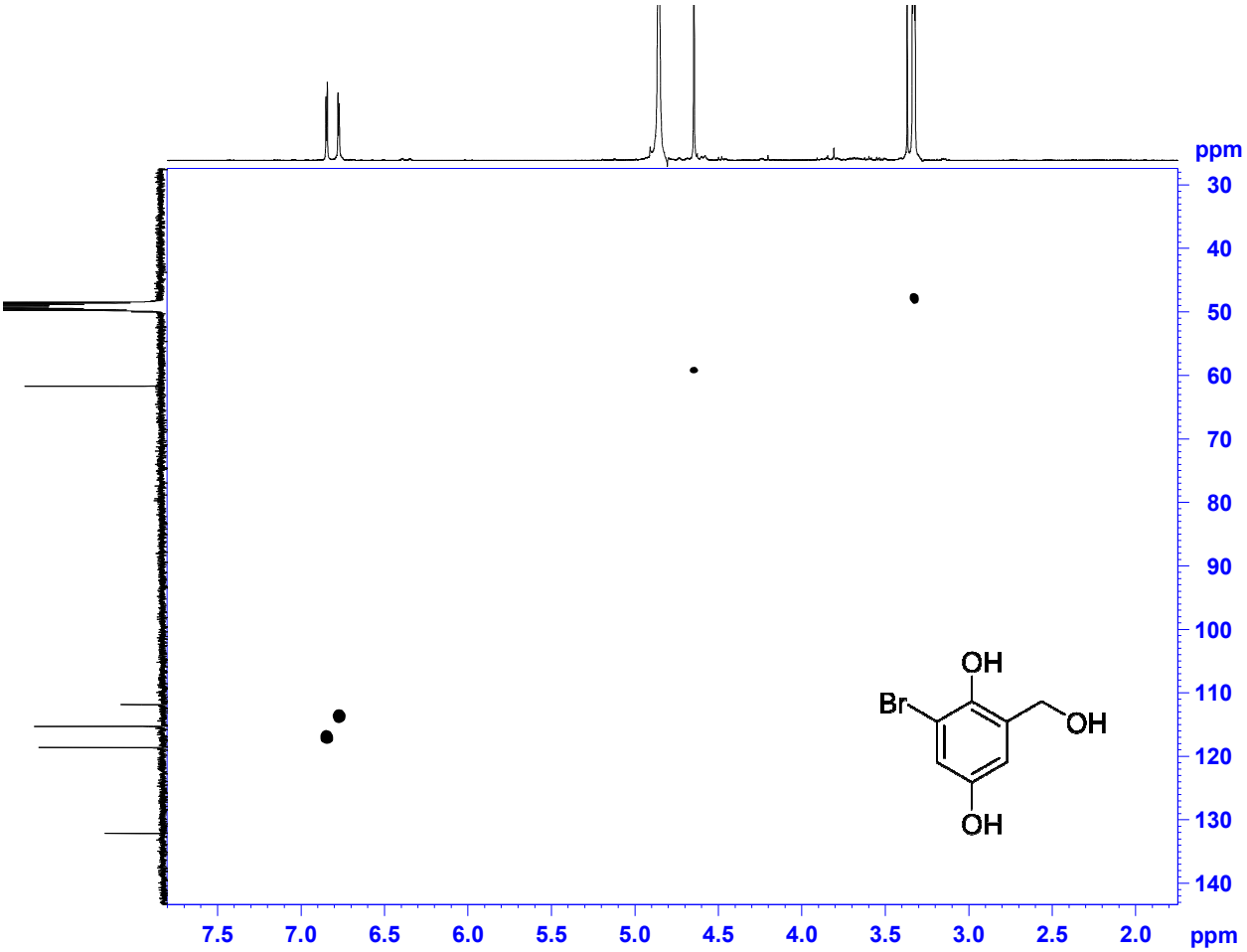


Figure S9. HSQC spectrum of compound **2** methanol-d_4 (400 MHz)

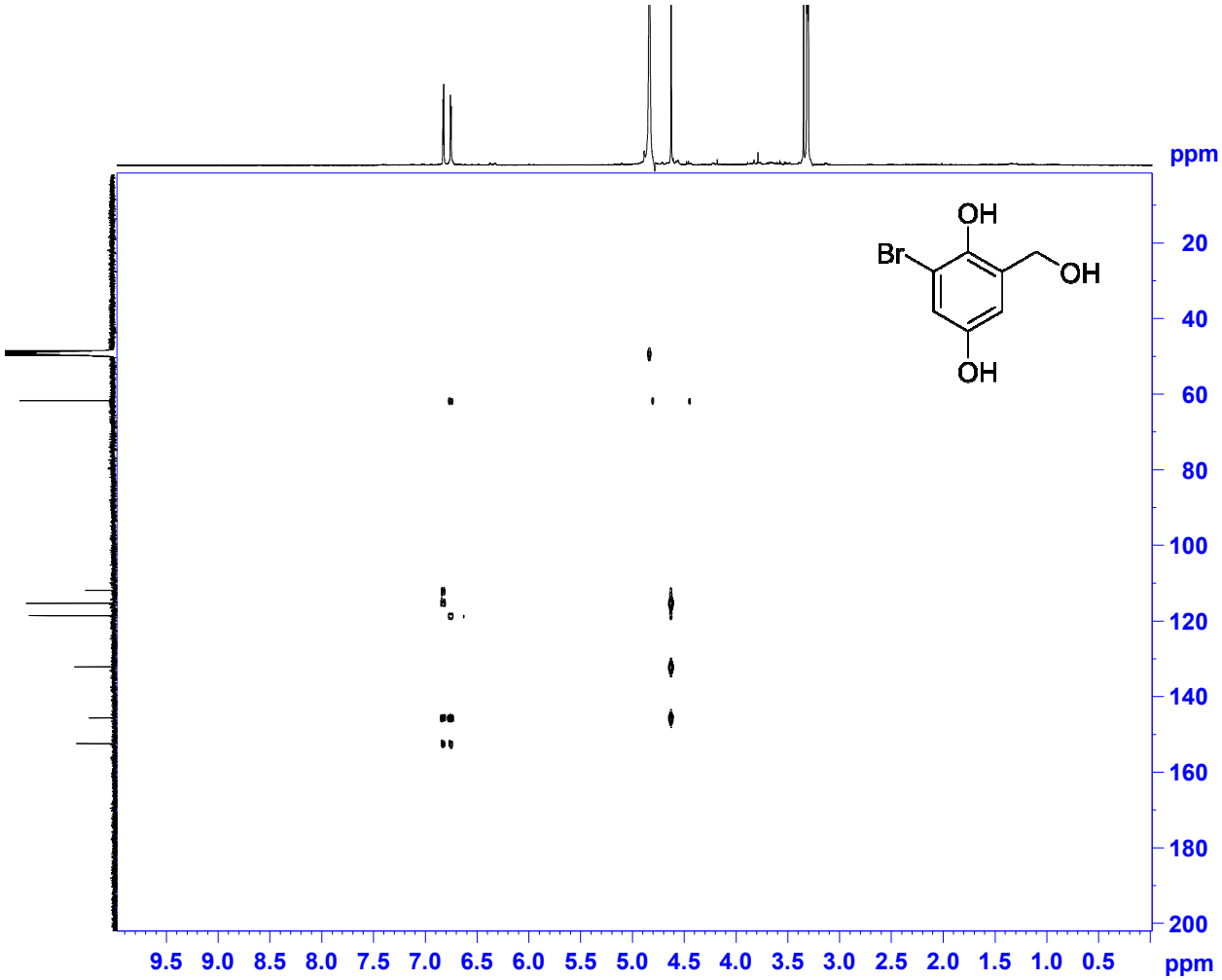


Figure S10. HMBC spectrum of compound **2** in methanol-d_4 (400 MHz)

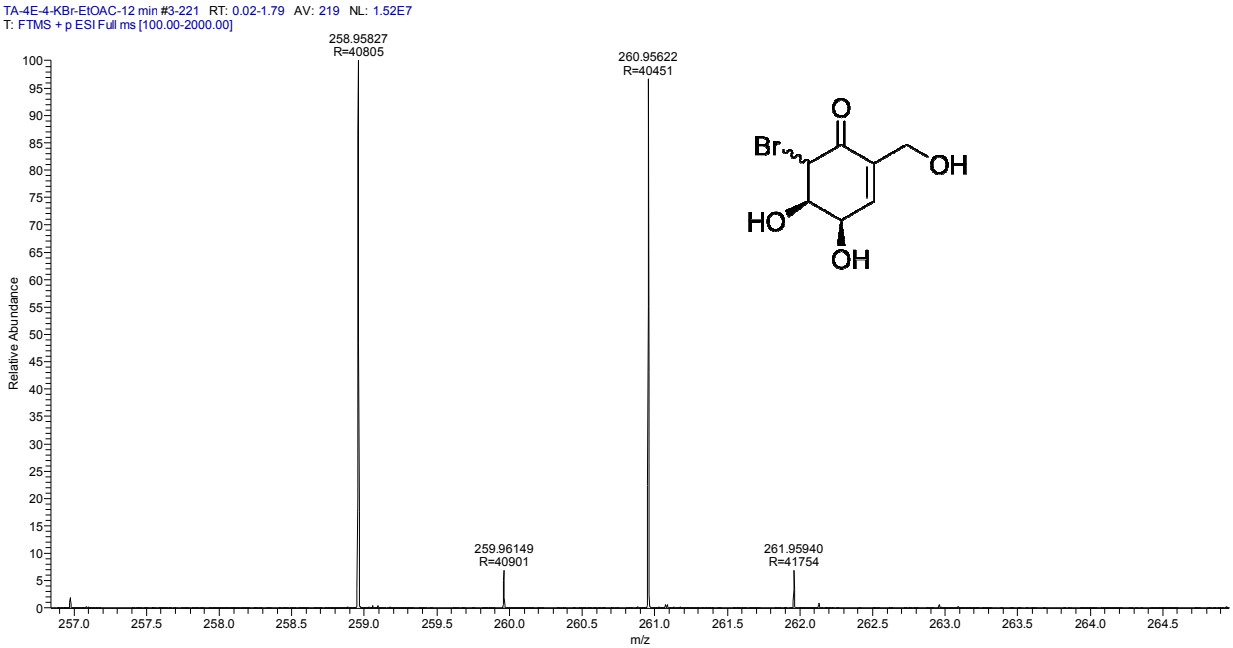


Figure S11. HRESIMS spectrum of compound **3**

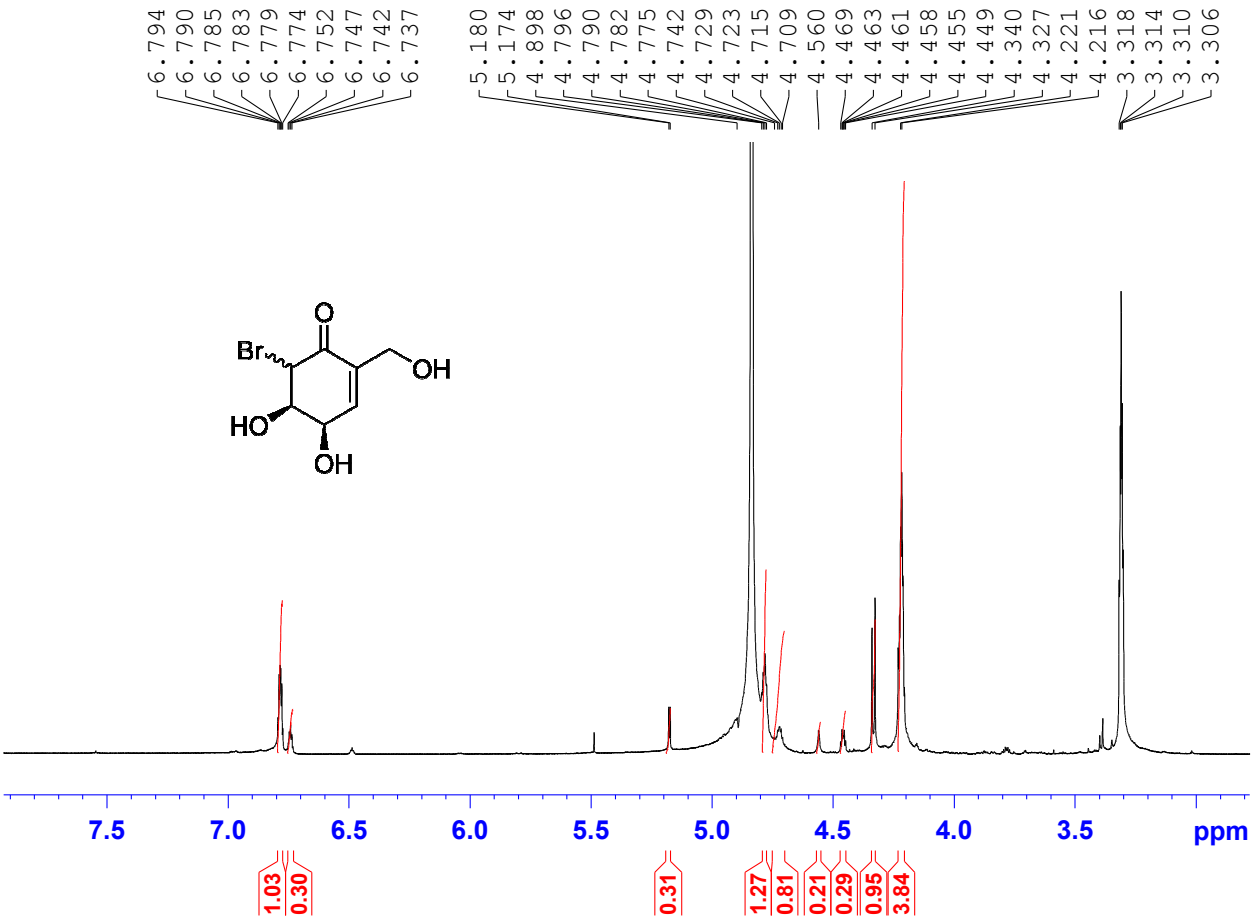


Figure S12. ^{1}H NMR spectrum of compound **3** in methanol-d_4 (400 MHz)

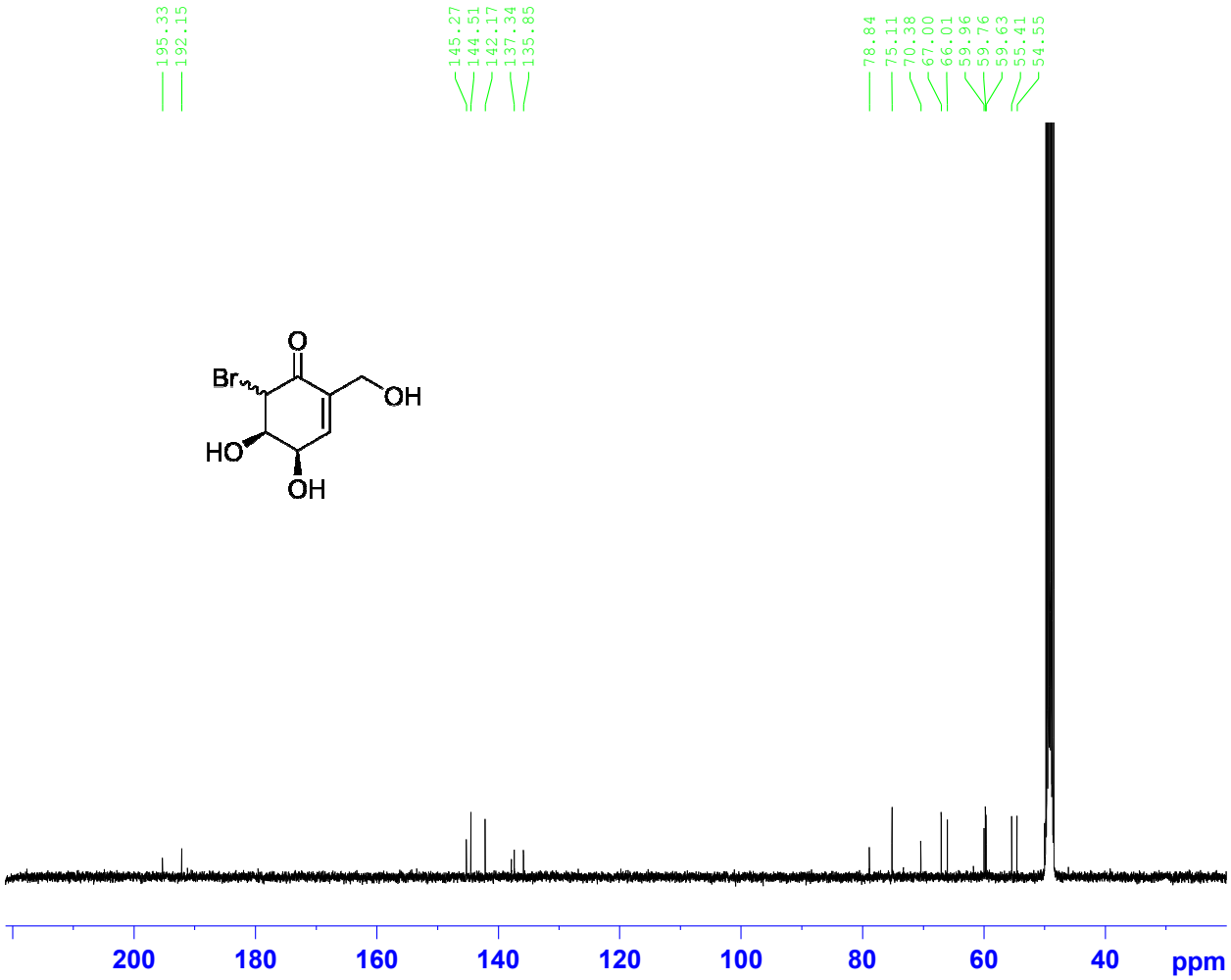


Figure S13. ^{13}C NMR spectrum of compound **3** in methanol-d_4 (100 MHz)

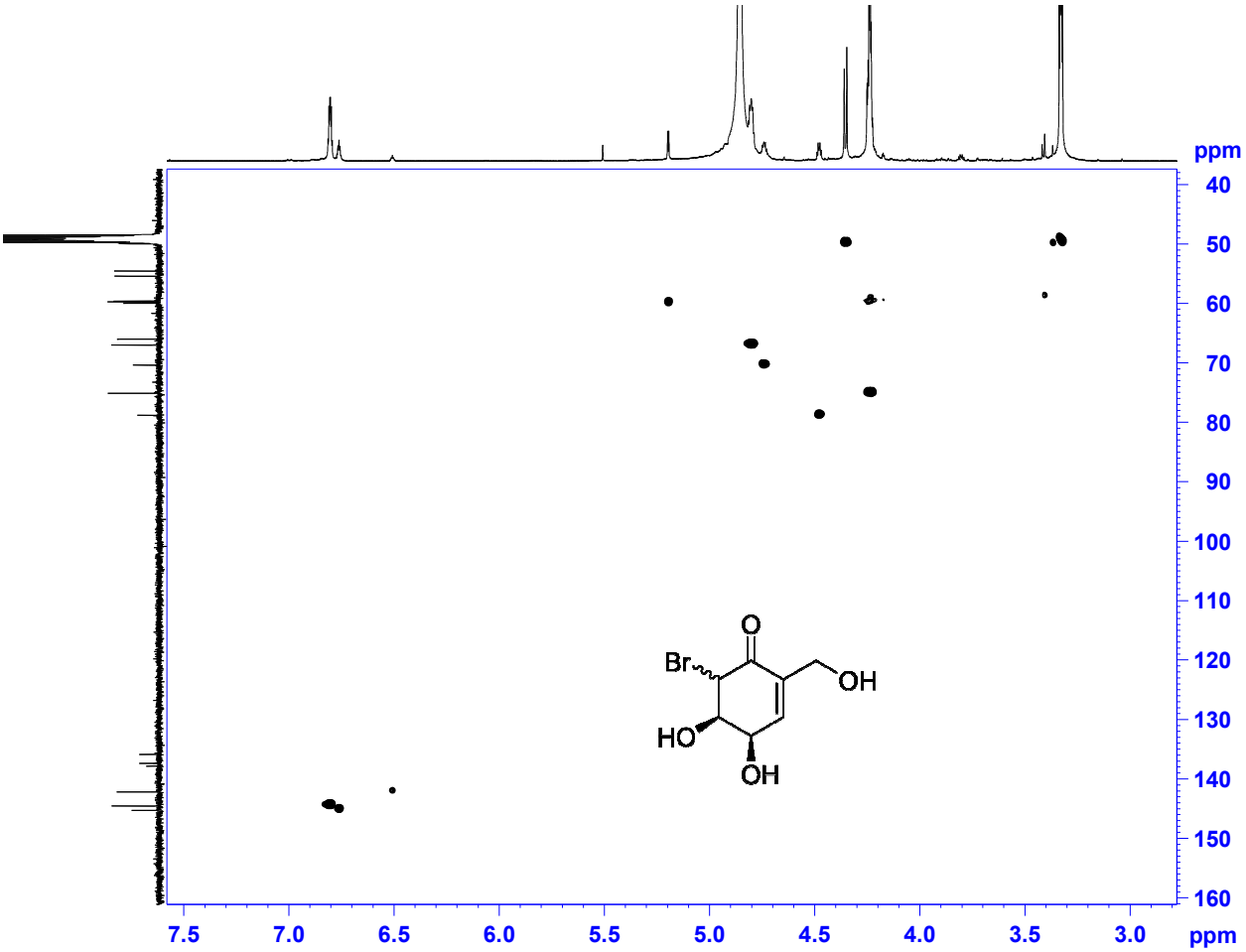


Figure S14. HSQC spectrum of compound **3** methanol-d_4 (400MHz)

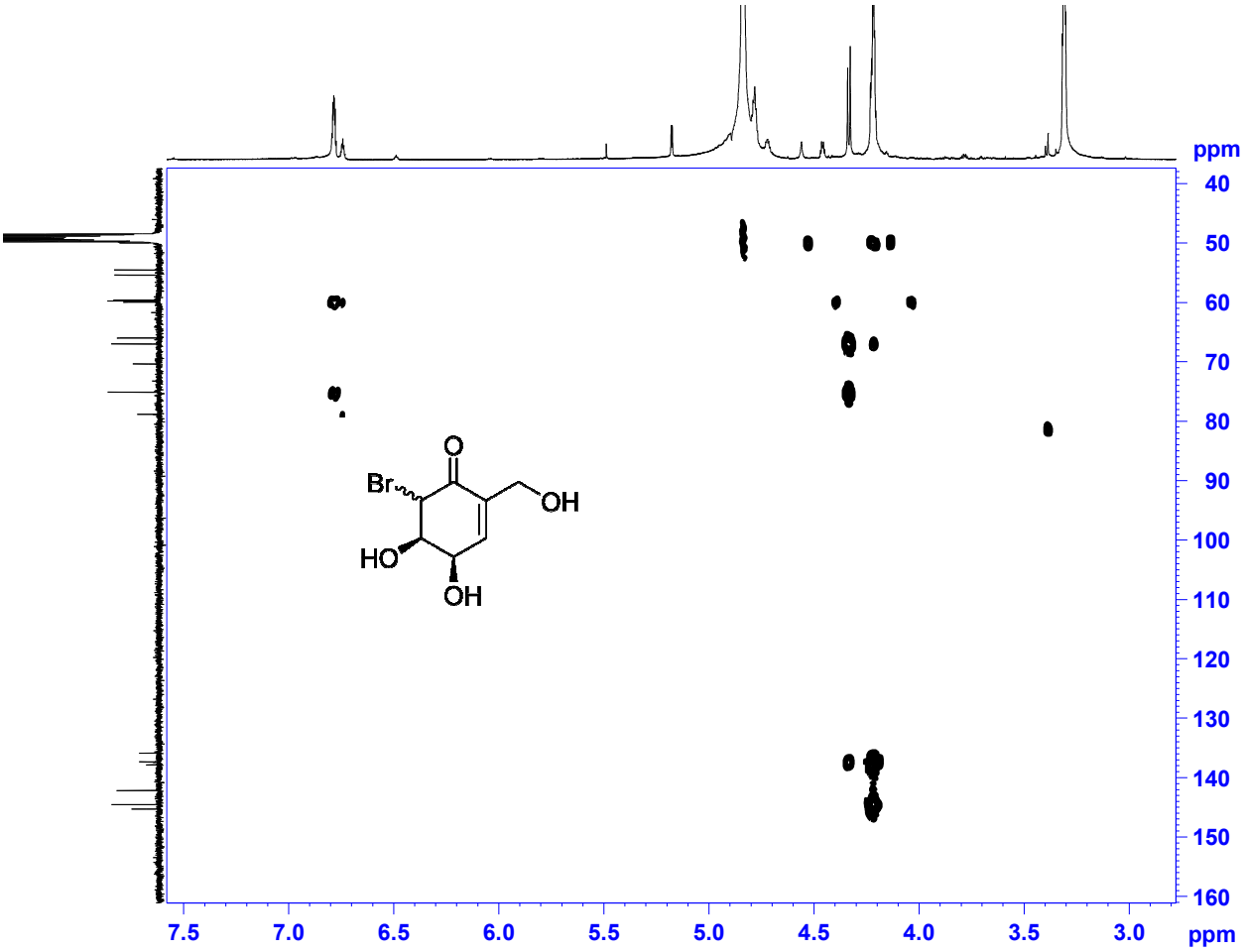


Figure S15. HMBC spectrum of compound **3** in methanol-d_4 (400 MHz)

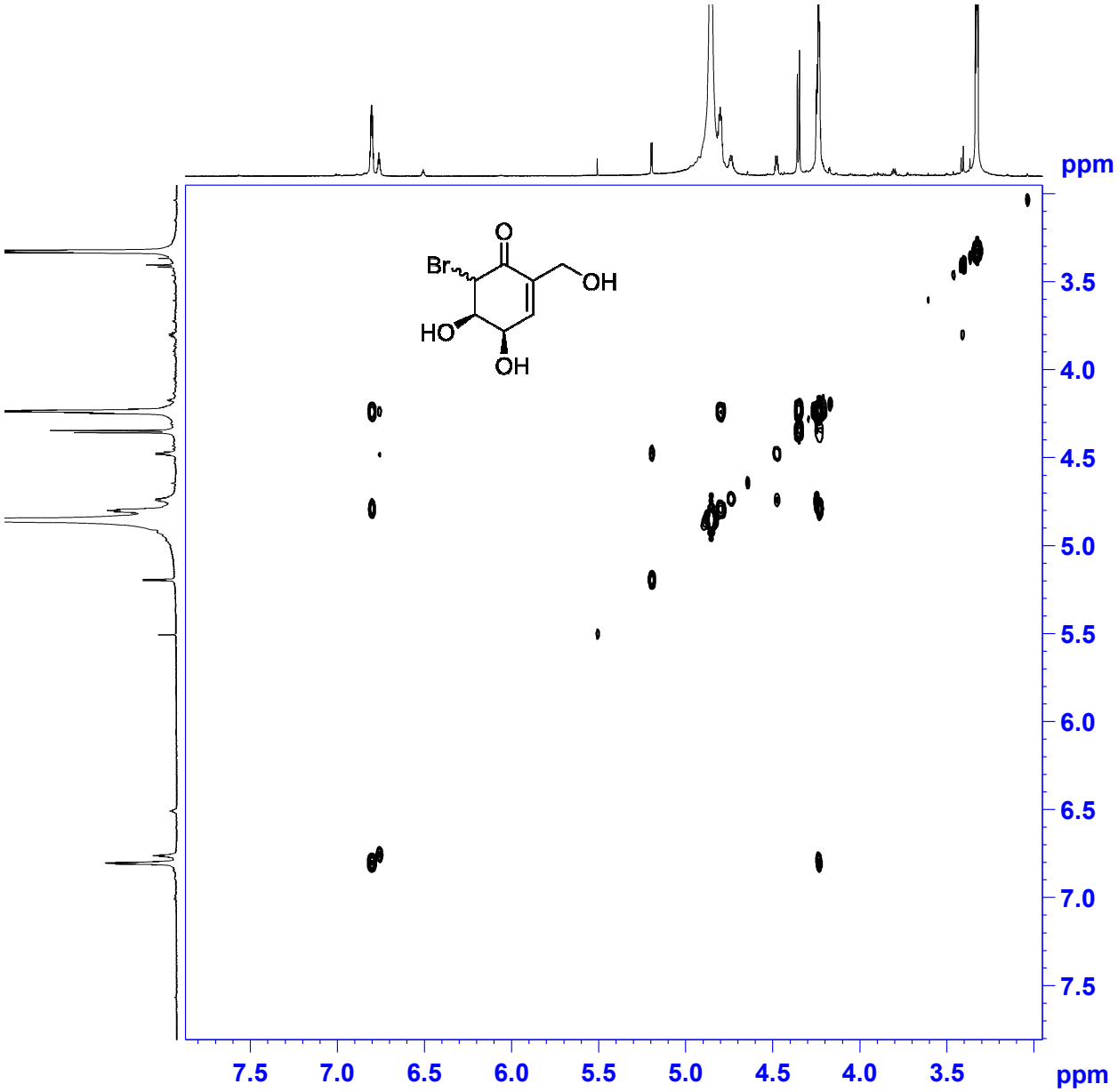


Figure S16. COSY spectrum of compound **3** in methanol-d_4 (400 MHz)

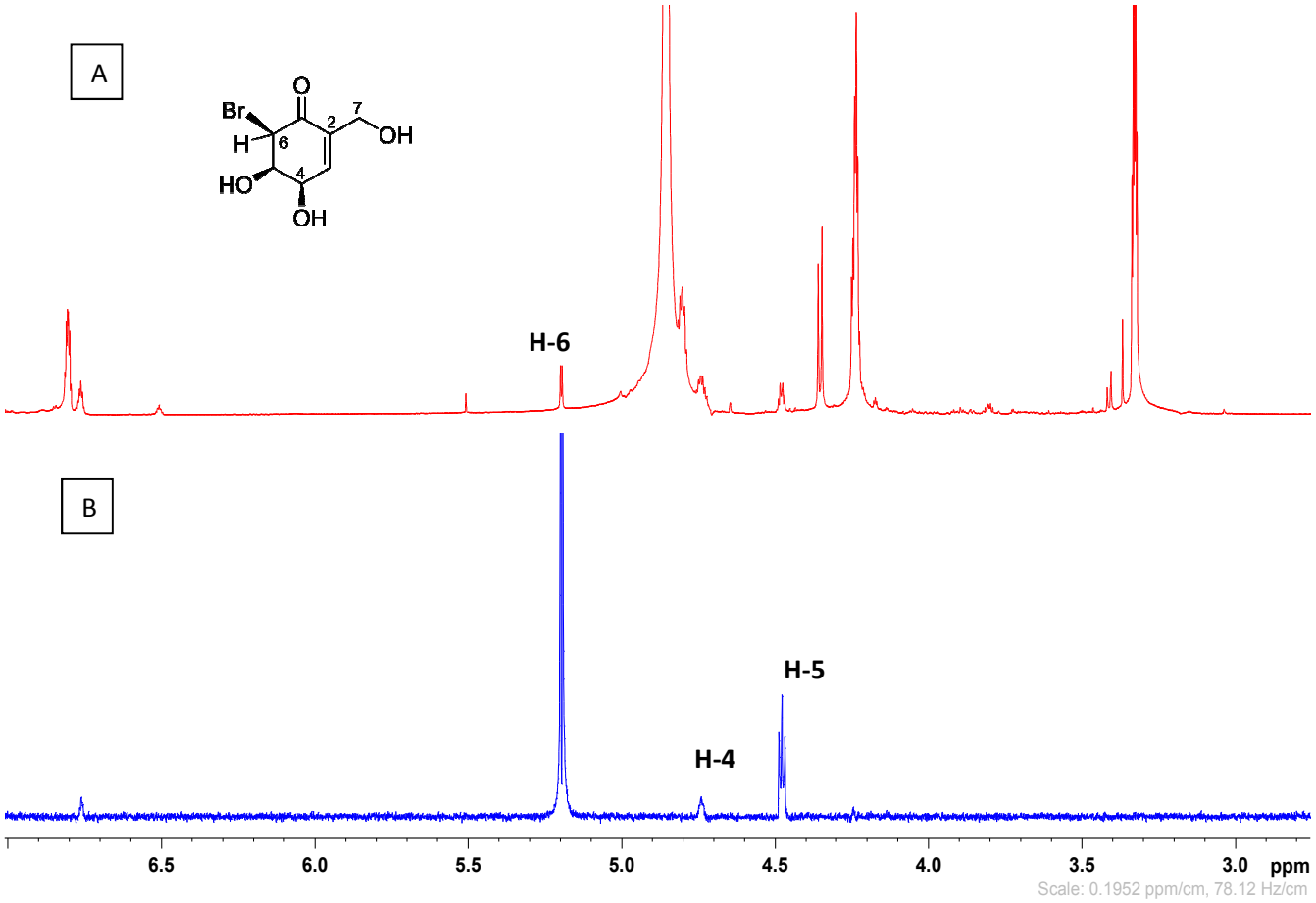


Figure S17. A: ^{1}H and B: 1D TOCSY (selective excitation at 5.1 ppm, H-6 of *cis* epimer) NMR spectra of compound **3a** and **3b** in methanol-d_4 (400 MHz)

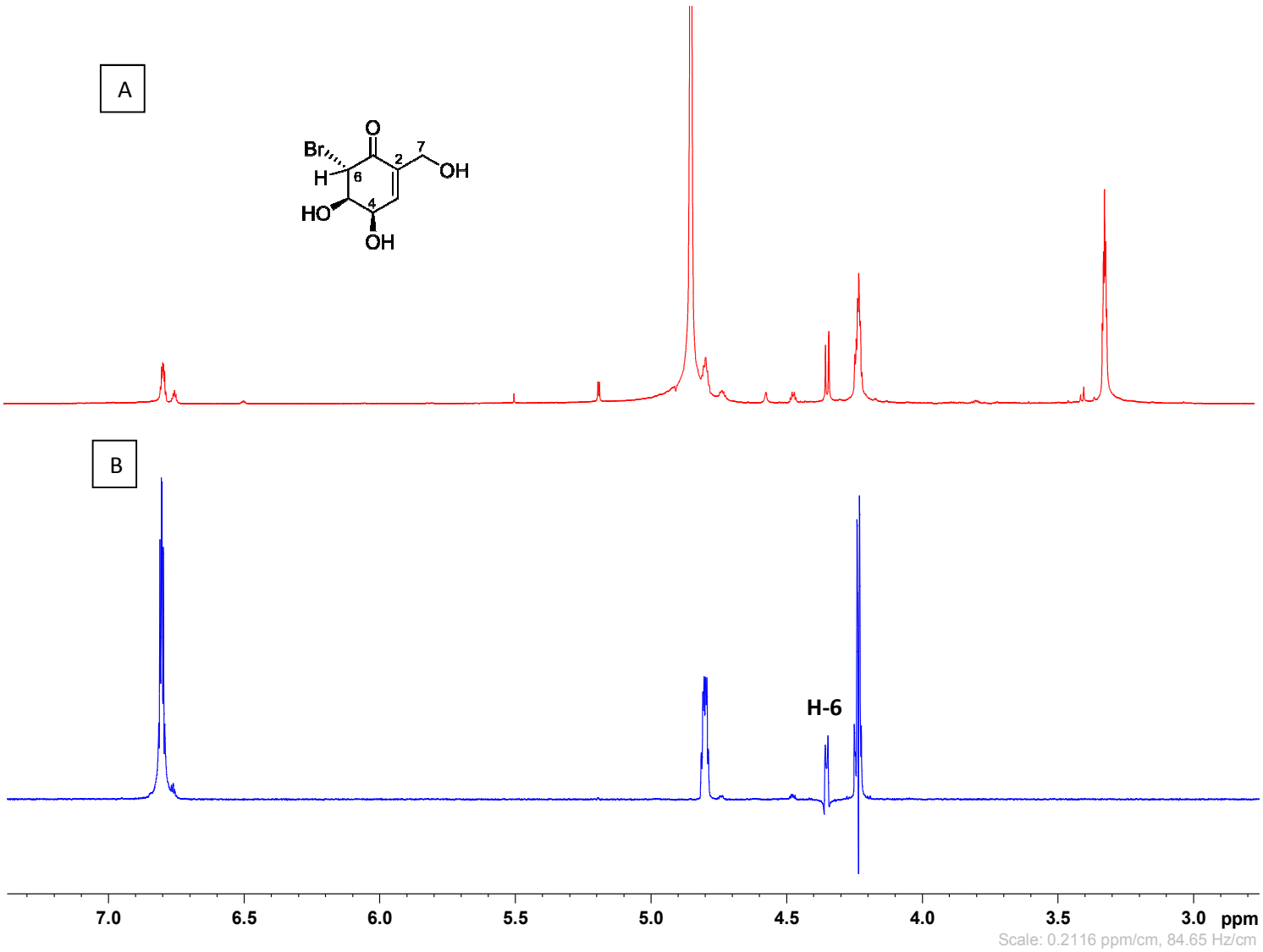


Figure S18. A: ^{1}H and B: 1D TOCSY (selective excitation at 4.3 ppm, H-6 of *trans* epimer) NMR spectra of compound **3a** and **3b** in methanol-d_4 (400 MHz)

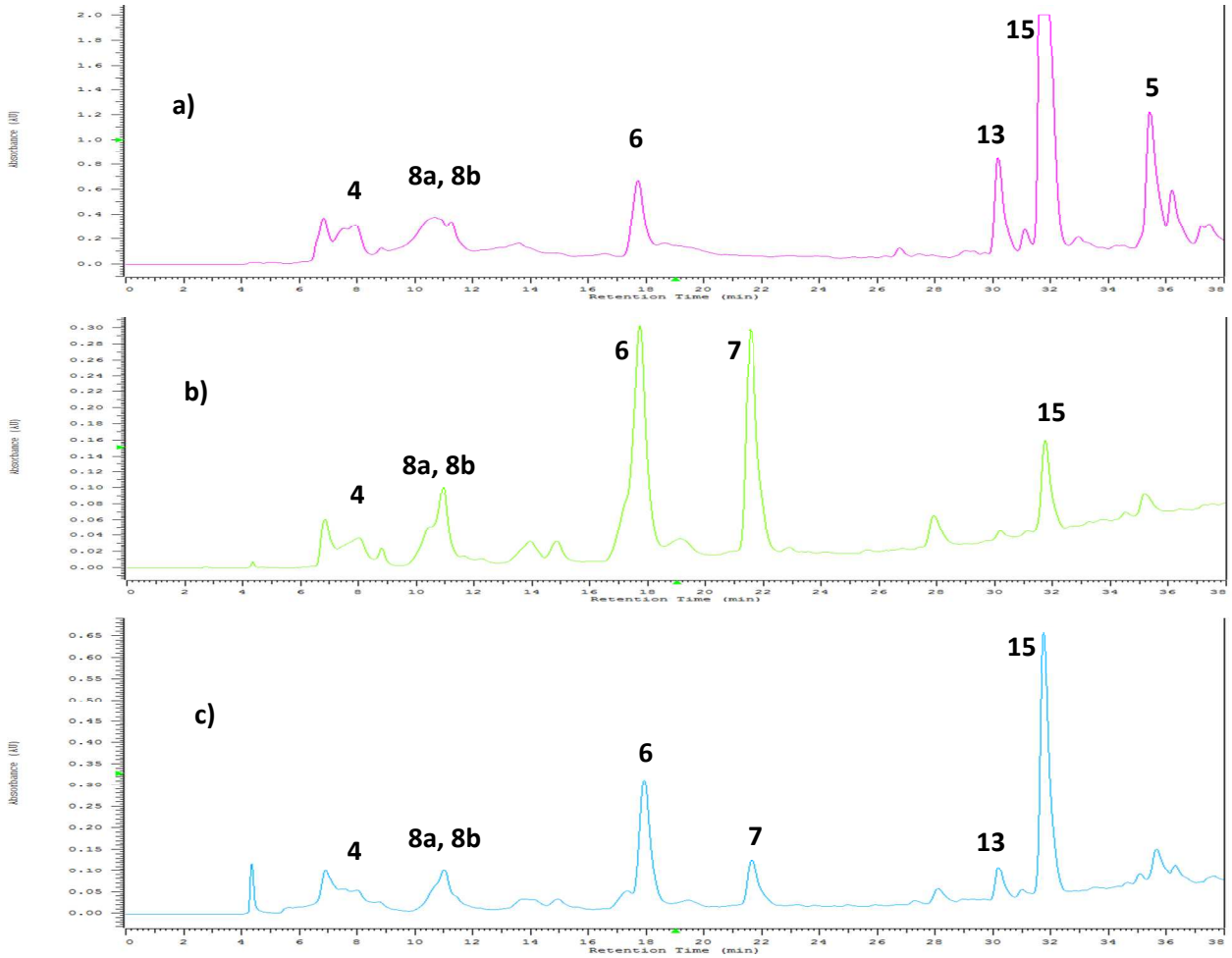


Figure S19. HPLC profile of metabolites produced by the culture of *P. concentricum* in KCl supplemented rice medium (**a**), chromatogram of KCl and epoxydon (**4**) reaction mixture (**b**) and co-injection of **a** and **b** (**c**) at 234 nm detection. Epoxydon (**4**), 6-dehydroxy-6α-chlorogabosine C (**8a**), 6-dehydroxy-6β-chlorogabosine C (**8b**), chlorogentisyl alcohol (**6**), hydroxychlorogentisyl quinone (**7**), dechlorogriseofulvin (**13**), griseofulvin (**15**), norlichxanthone (**5**).

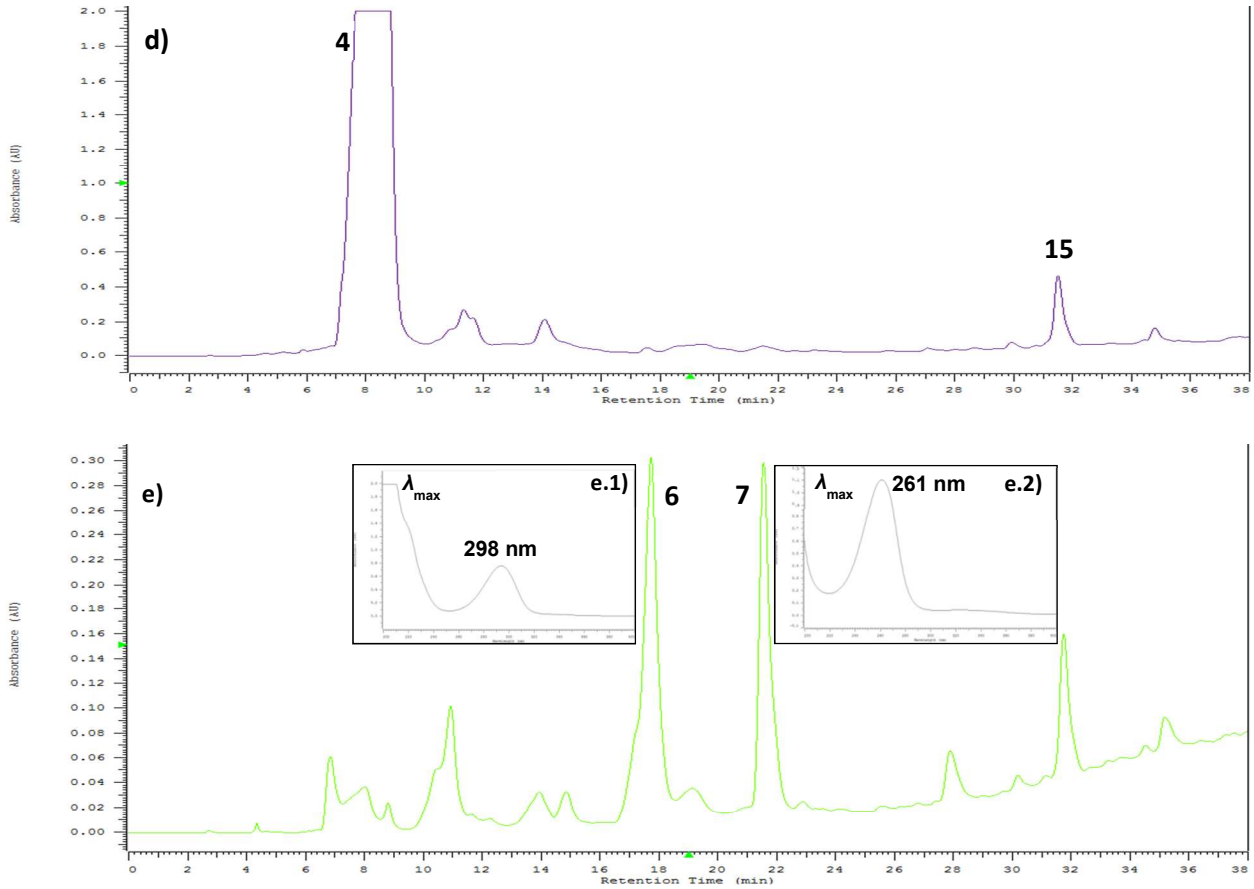


Figure S20. HPLC profile illustrating the non-enzymatic transformation of epoxydon (**4**) in chromatogram **d**) to compounds **6** and **7** (chromatogram **e**) in presence of KCl. UV detection at 234 nm. UV spectra of **6** and **7** are shown in **e.1** and **e.2**, respectively. MS and UV spectra of **7** showed characteristics features of hydroxychlorogentisyl quinone.

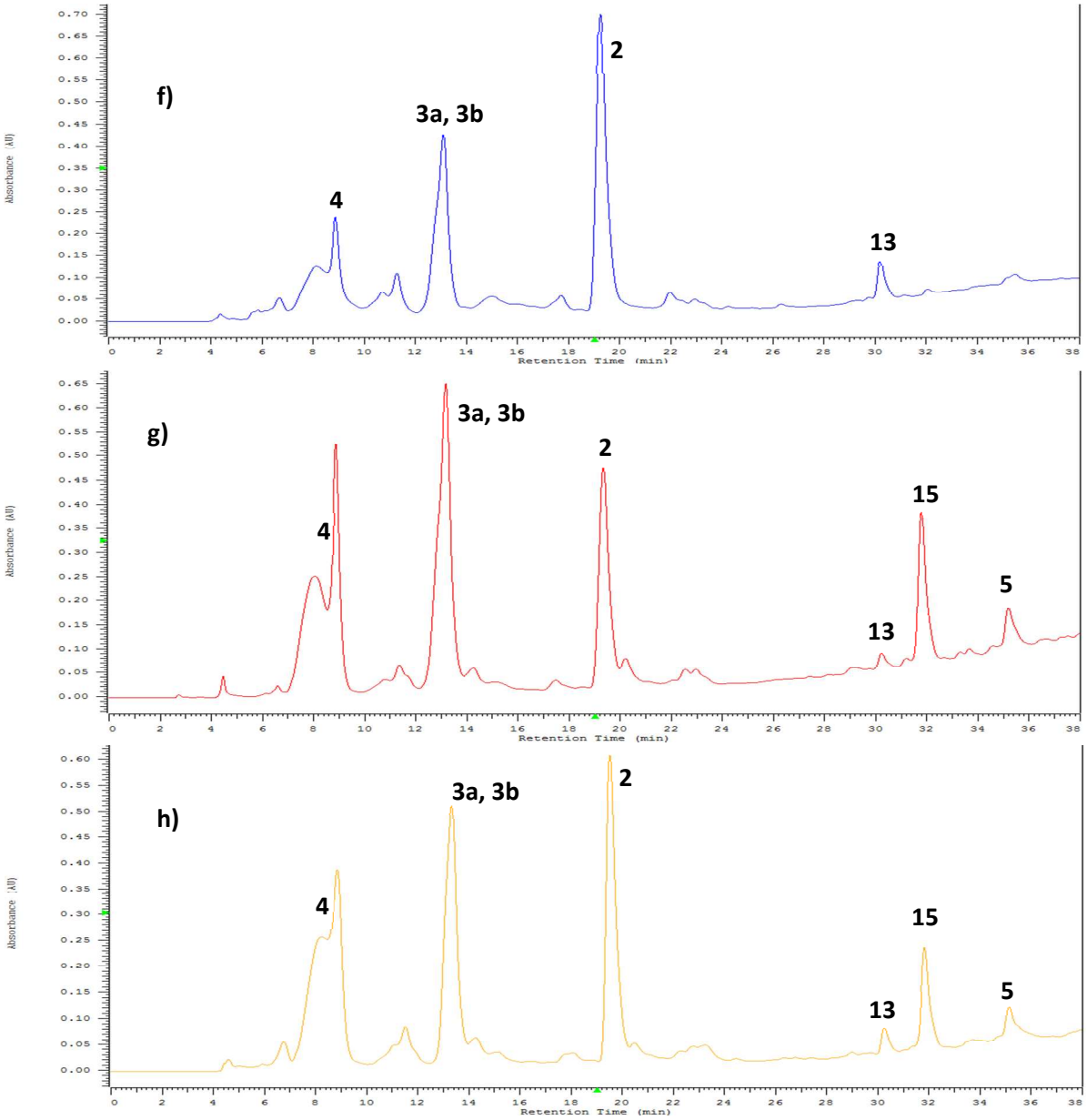


Figure S21. HPLC profile of metabolites produced by the culture of *P. concentricum* in KBr supplemented rice medium (**f**), chromatogram of KBr and epoxydon (**4**) reaction mixture (**g**), and co-injection of **f** and **g** (**h**) at 234 nm detection. Epoxydon (**4**), 6-dehydroxy-6α-bromogabosine C (**3a**), 6-dehydroxy-6β-bromogabosine C (**3b**) gentisyl alcohol bromide (**2**), dechlorogriseofulvin (**13**), griseofulvin (**15**), norlichxanthone (**5**). Griseofulvin (**15**) was not detected in fermentation of *P. concentricum* with KBr for 15 days (**f**).

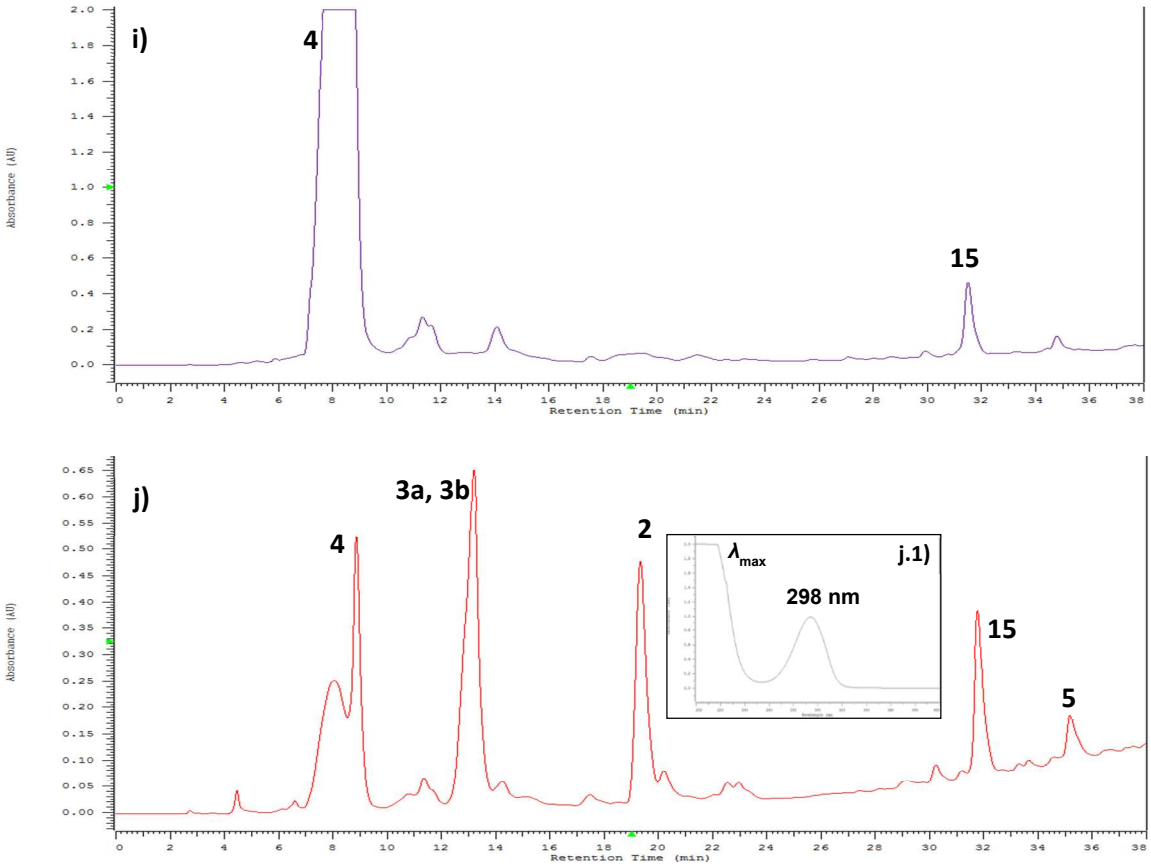


Figure S22. HPLC profile illustrating the non-enzymatic transformation of compound **4** in chromatogram **i** to compound **3a**, **3b** and **2** in chromatogram **j** in presence of KBr. UV detection at 234 nm. UV spectrum of **2** is shown in **j.1**.

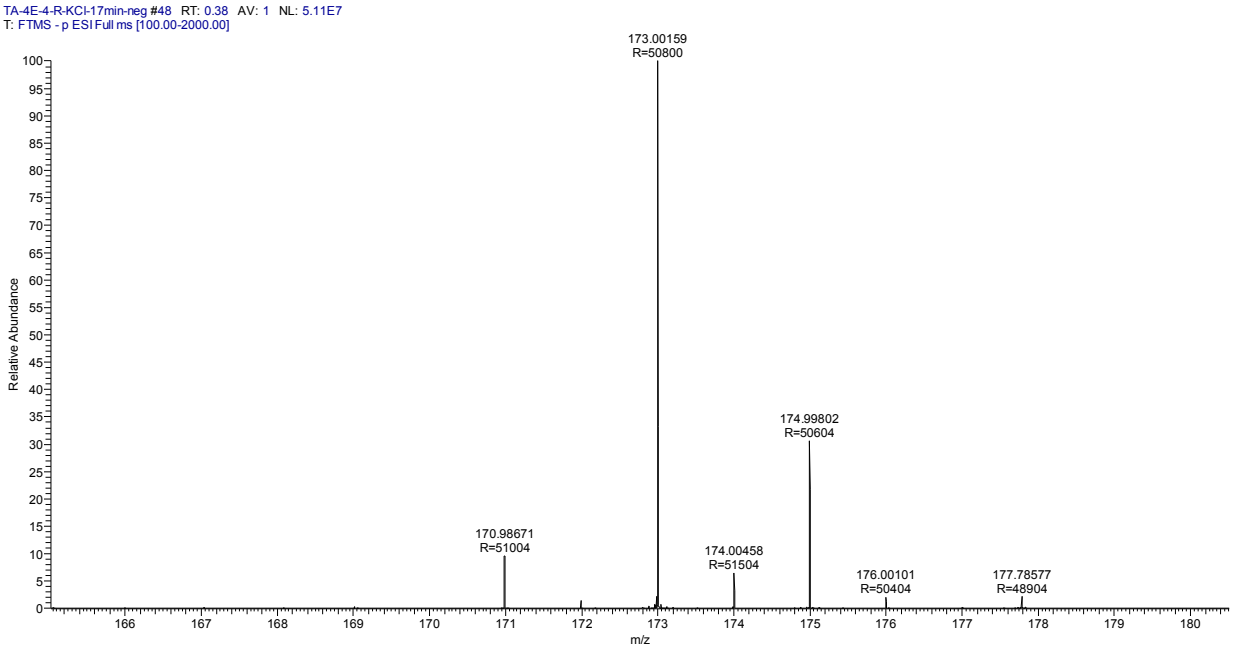


Figure S23. HRESIMS spectrum of compound **6**

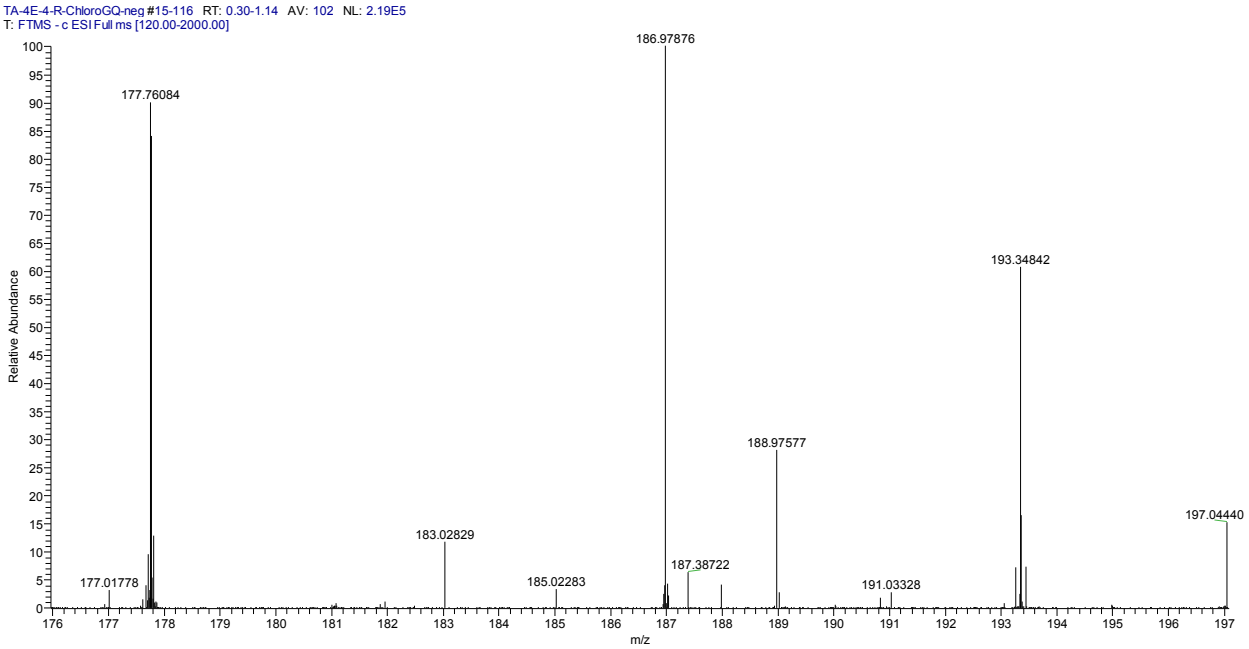


Figure S24. HRESIMS spectrum of peak #**7** in S20 (showing the presence of compound **7**)

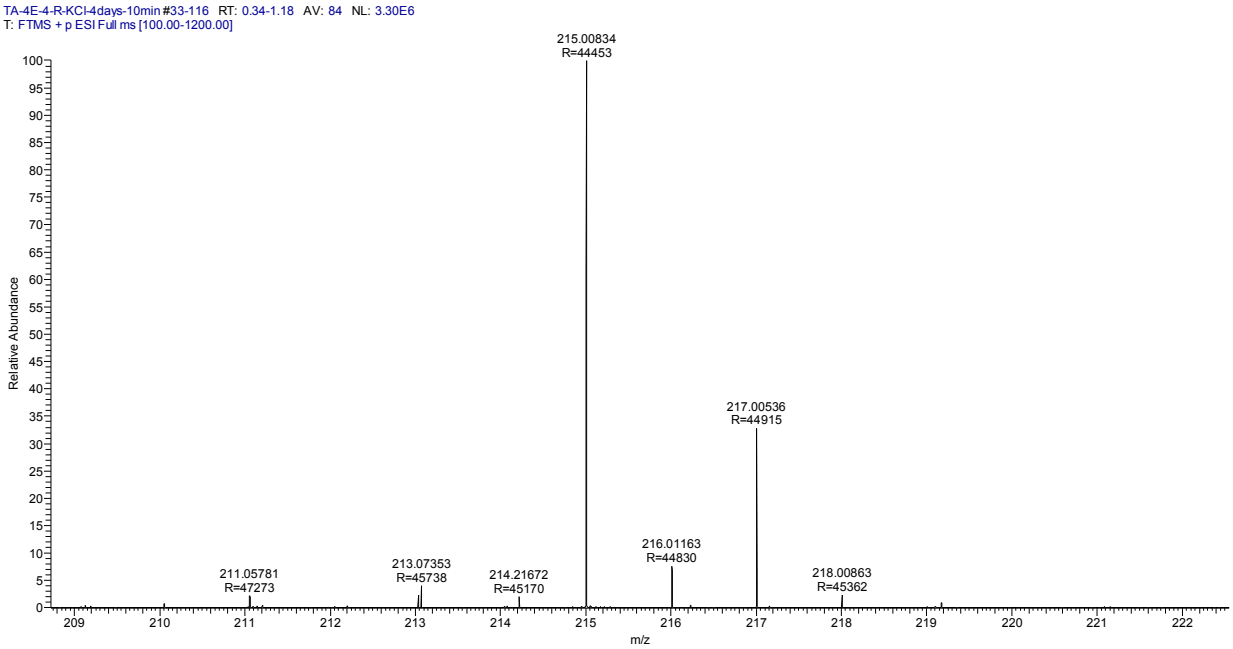


Figure S25. HRESIMS spectrum of compound **8**