Dual Inhibition of Acetylcholinesterase and *β*-Secretase by Metabolites from *Echinocactus grusonii* Hildm.: *In Silico* and *In Vitro* Investigations

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Abstract

Targeting acetylcholinesterase (AChE) and *β*-secretase (BACE-1) is a promising multi-faceted approach for treating neurological disorders. In our study, the chemical investigation of *Echinocactus grusonii* Hildm. (Cactaceae) led to the isolation and identification of seven compounds, including three flavonoids, naringenin **1**, kaempferol **2**, and isokaempferide **3**, one megastigmane glycoside, vomifoliol-9-*O*-*β*-D-glucopyranoside **4**, and three alkaloids, *N*-chloromethyl hordenine **5**, *N*-acetyl hordenine **6**, and *N*-acetyl-*N*-chloromethyl-*N*-methyl tyramine **7**. Compounds **5** and **7** were identified as previously undescribed halogenated alkaloids. Biological evaluation revealed that all compounds exhibited promising acetylcholinesterase inhibitory activity (IC_{50} = 0.076–2.255 µg/mL), as well as significant inhibition of β-secretase (BACE1) with IC_{50} values ranging from 0.066 to 7.189 µg/mL. Docking, molecular dynamics, and binding energy calculations suggested that compounds **4** and **5** are promising AChE inhibitors, while compounds **3**, **4**, and **7** are leading candidates against BACE1. Collectively, this study underscores the potential of *Echinocactus grusonii* as a rich source of bioactive lead compounds for developing novel therapeutics for pharmaceutical applications.

Keywords: Cactaceae, Halogenated alkaloids, Hordenine derivatives, Anti-Alzheimer compounds, Anti-cholinesterase activity, Anti-BACE1 activity

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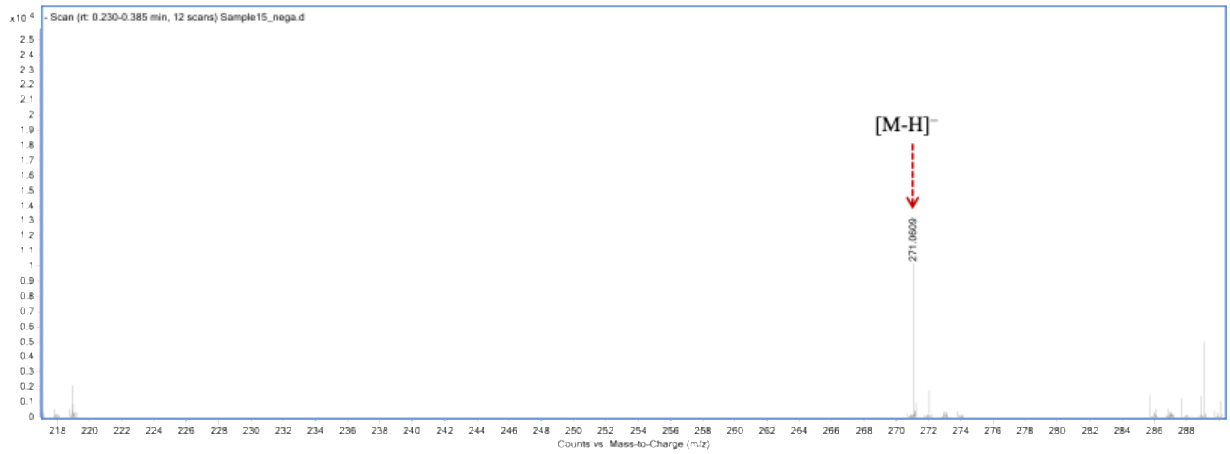

Figure S1: HR-MS spectrum of compound 1

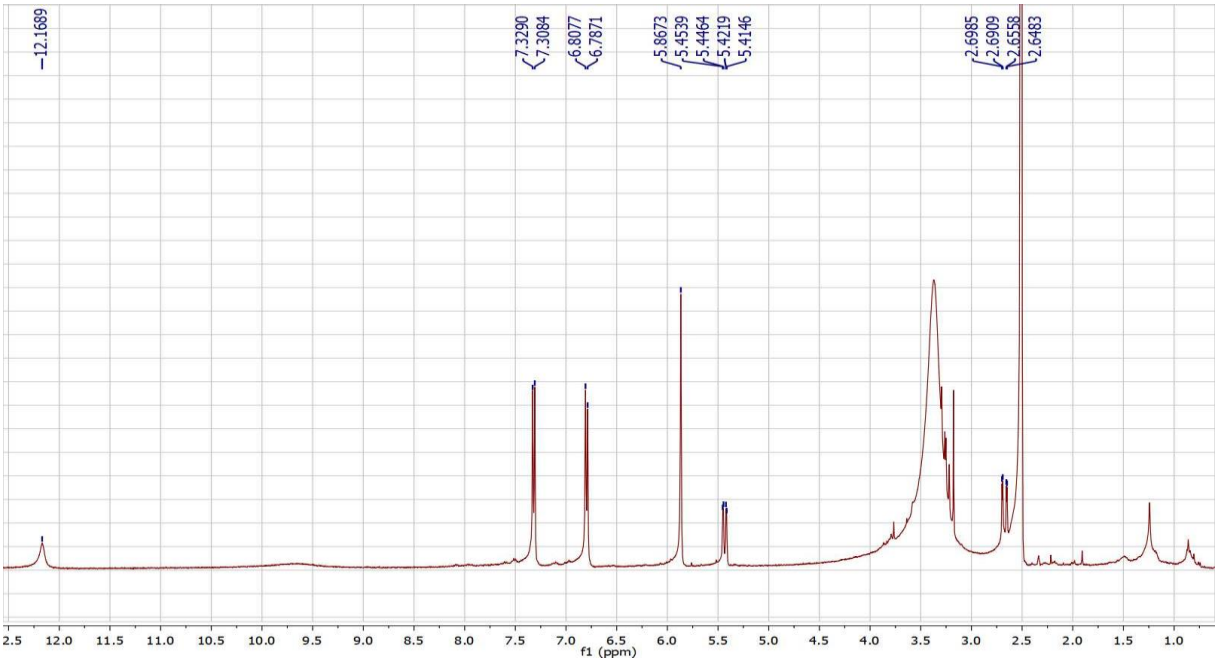

Figure S2: ^{1}H NMR spectrum of compound 1

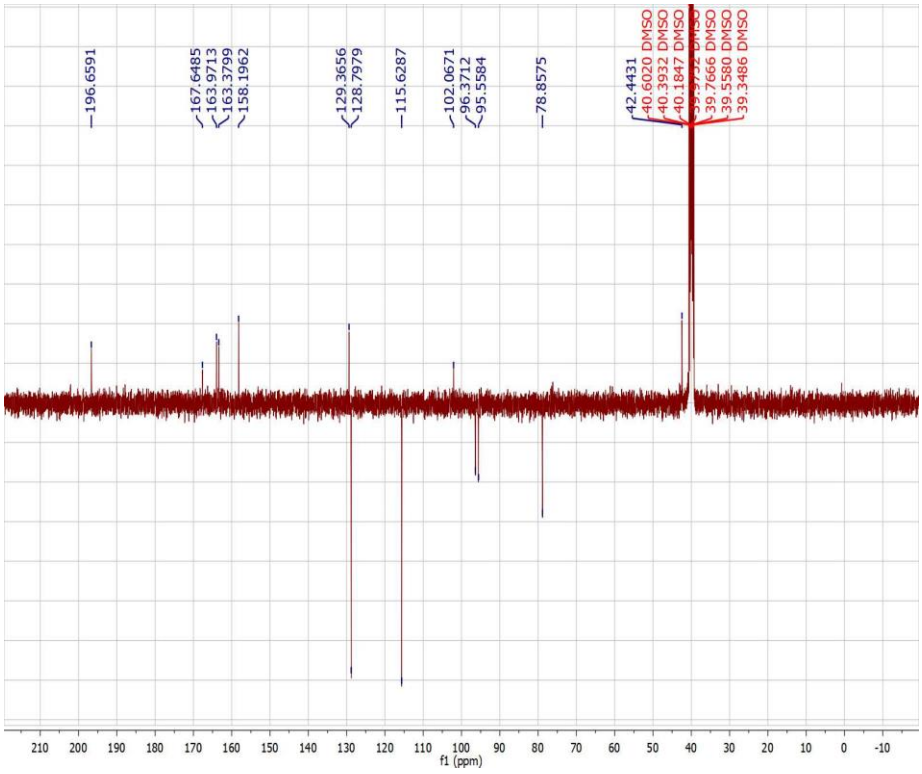

Figure S3: APT NMR spectrum of compound 1

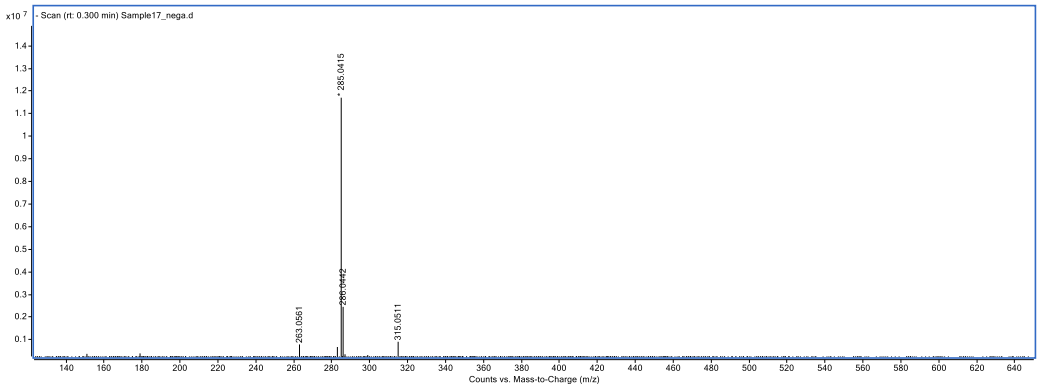

Figure S4: HR-MS spectrum of compound 2

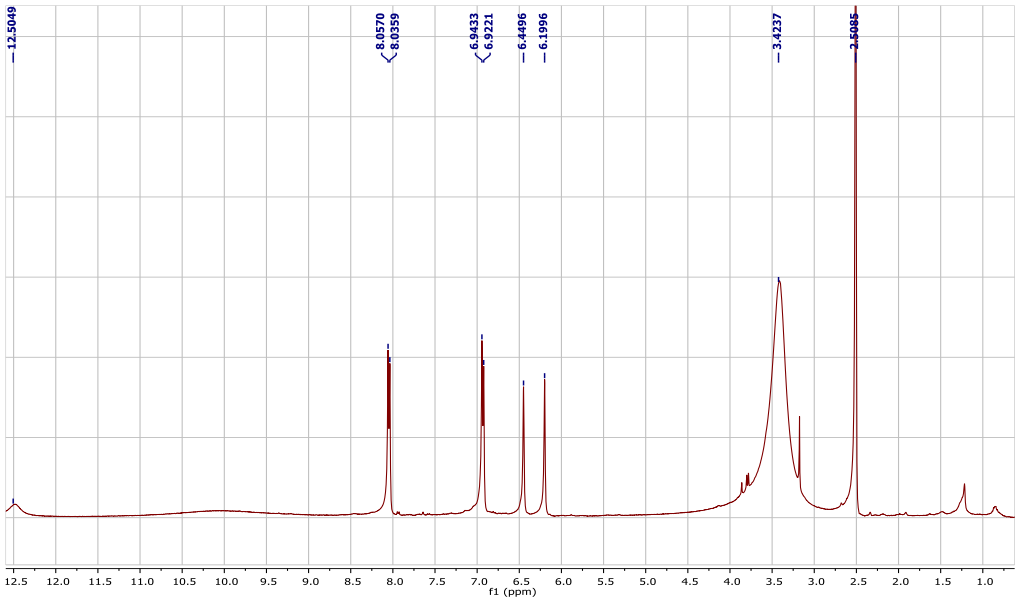

Figure S5: ^{1}H NMR spectrum of compound 2

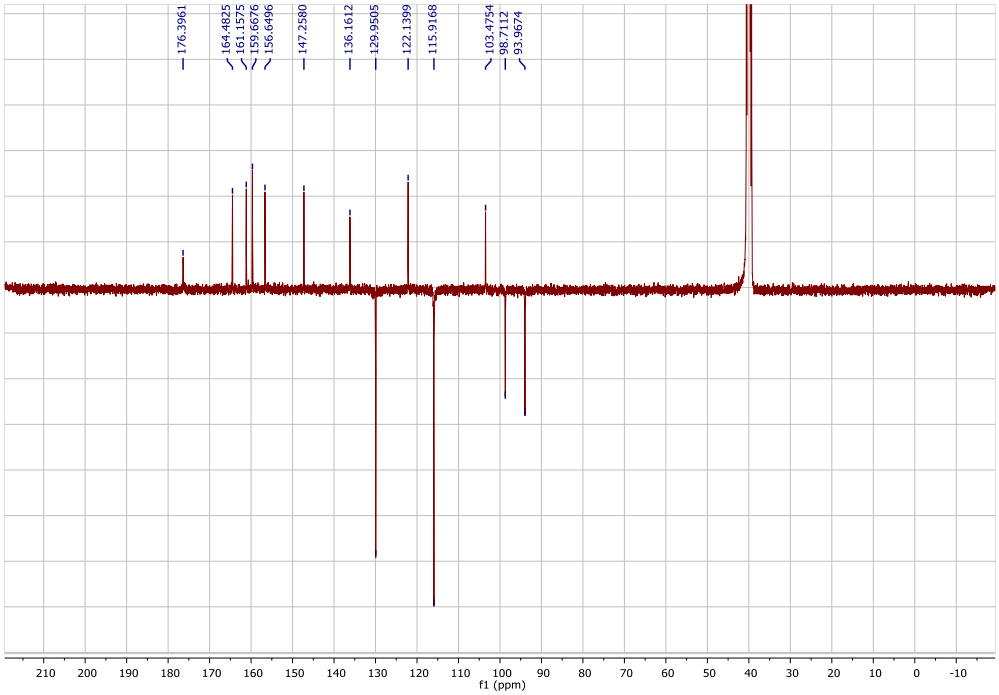

Figure S6: APT NMR spectrum of compound 2

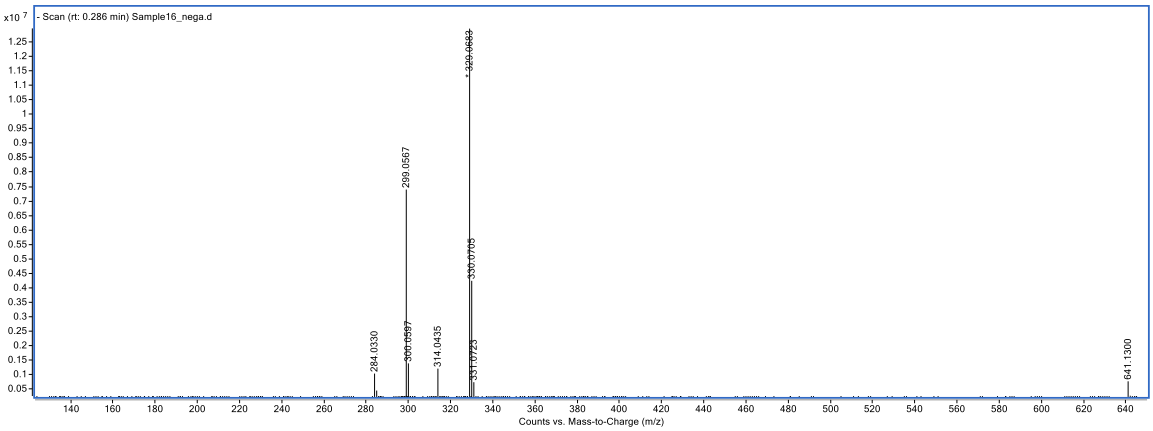

Figure S7: HR-MS spectrum of compound 3

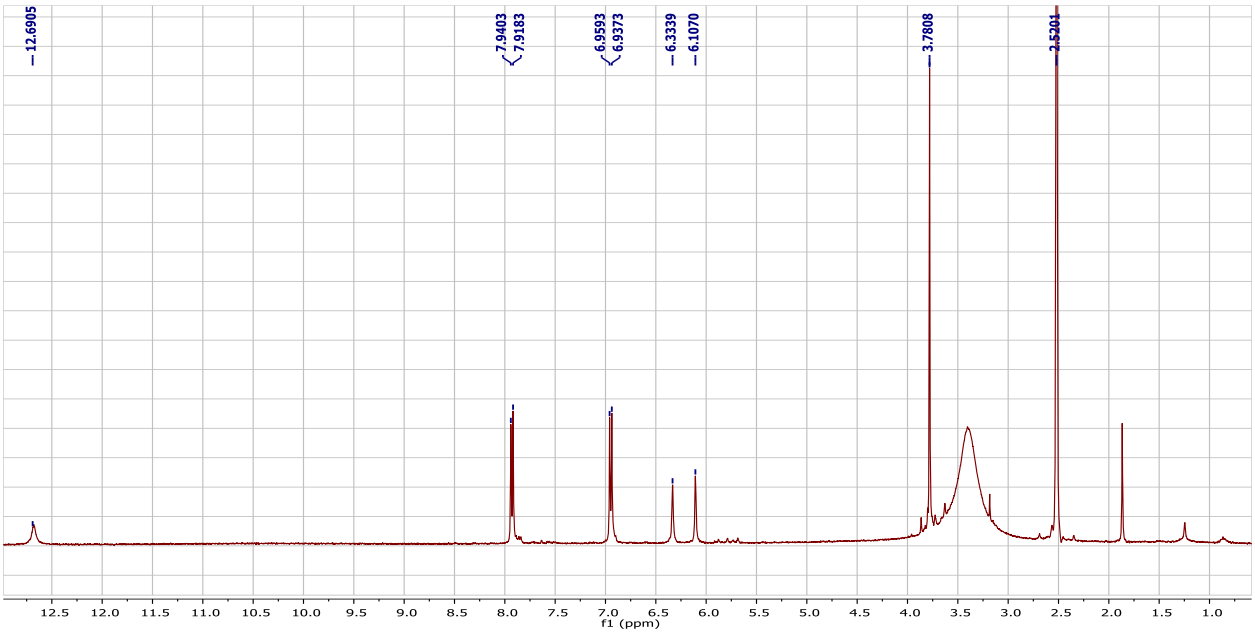

Figure S8: ^{1}H NMR spectrum of compound 3

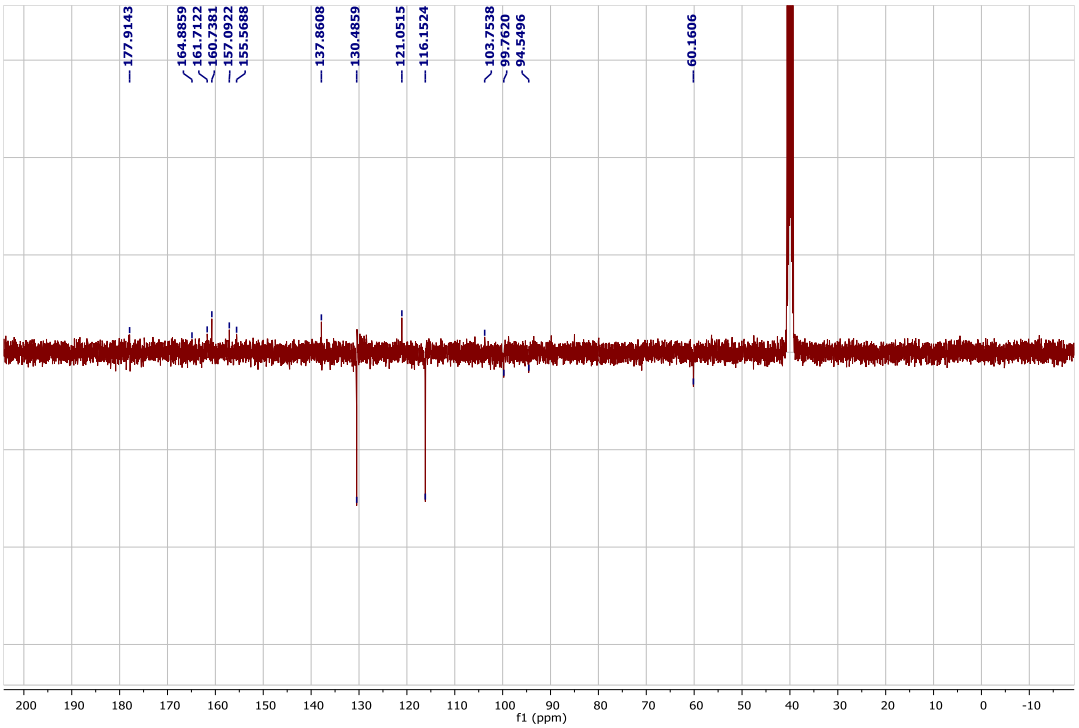

Figure S9: APT NMR spectrum of compound 3

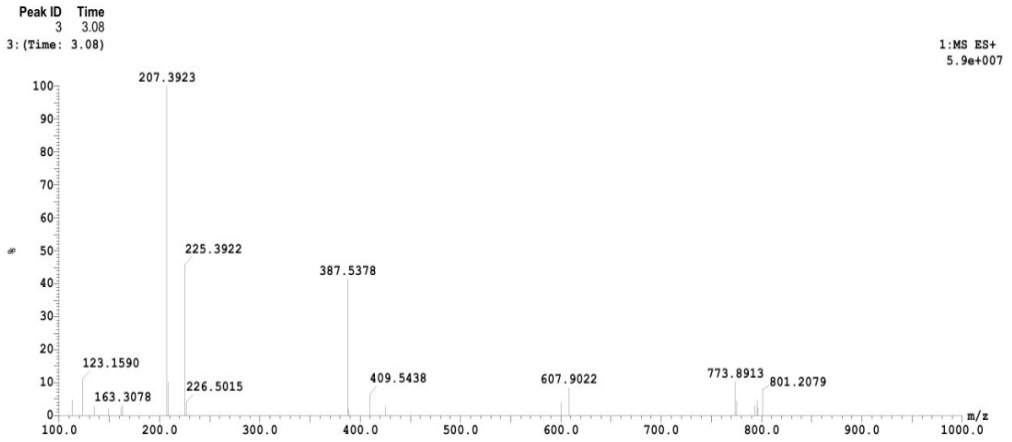

Figure S10: ESI-MS spectrum of compound 4

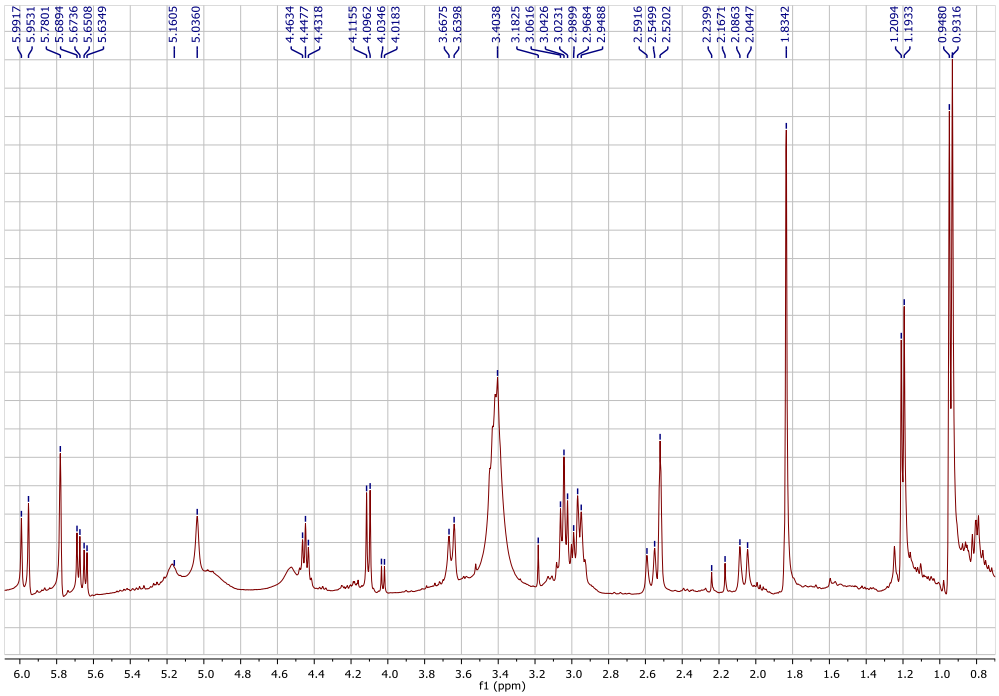

Figure S11: ^{1}H NMR spectrum of compound 4

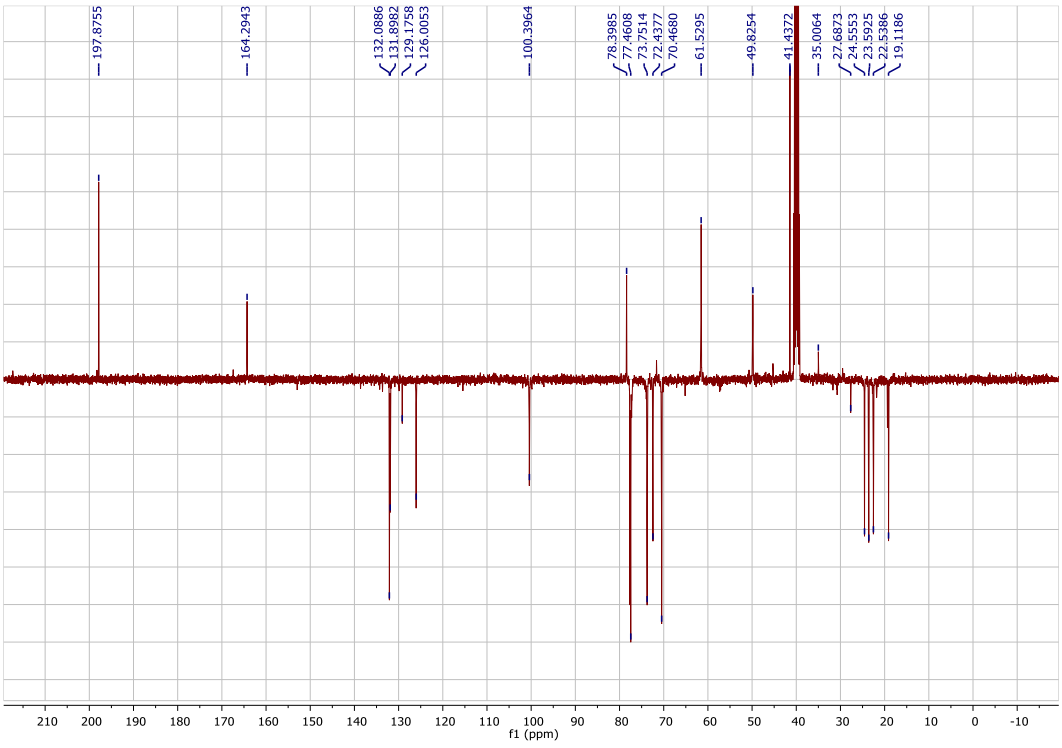

Figure S12: APT NMR spectrum of compound 4

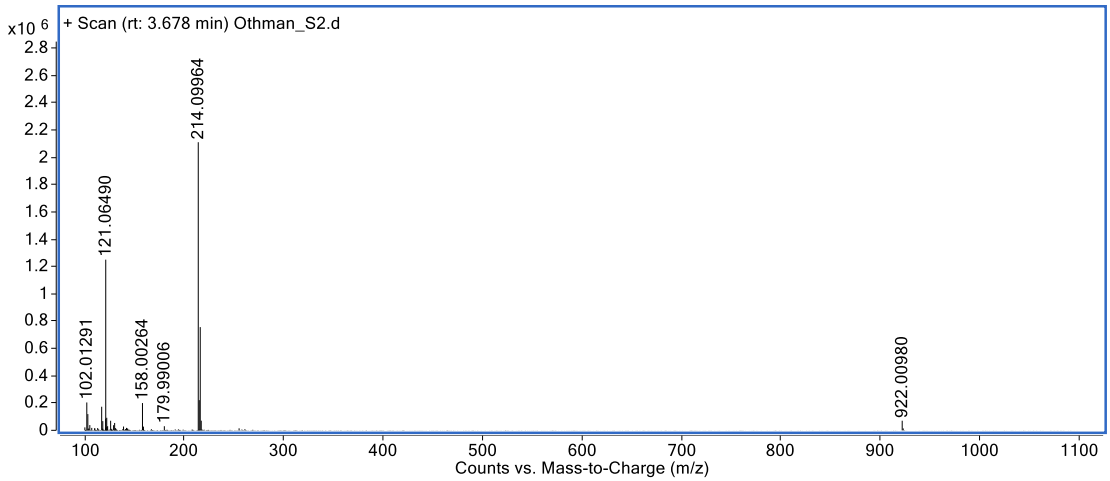

Figure S13: HR-MS spectrum of compound 5

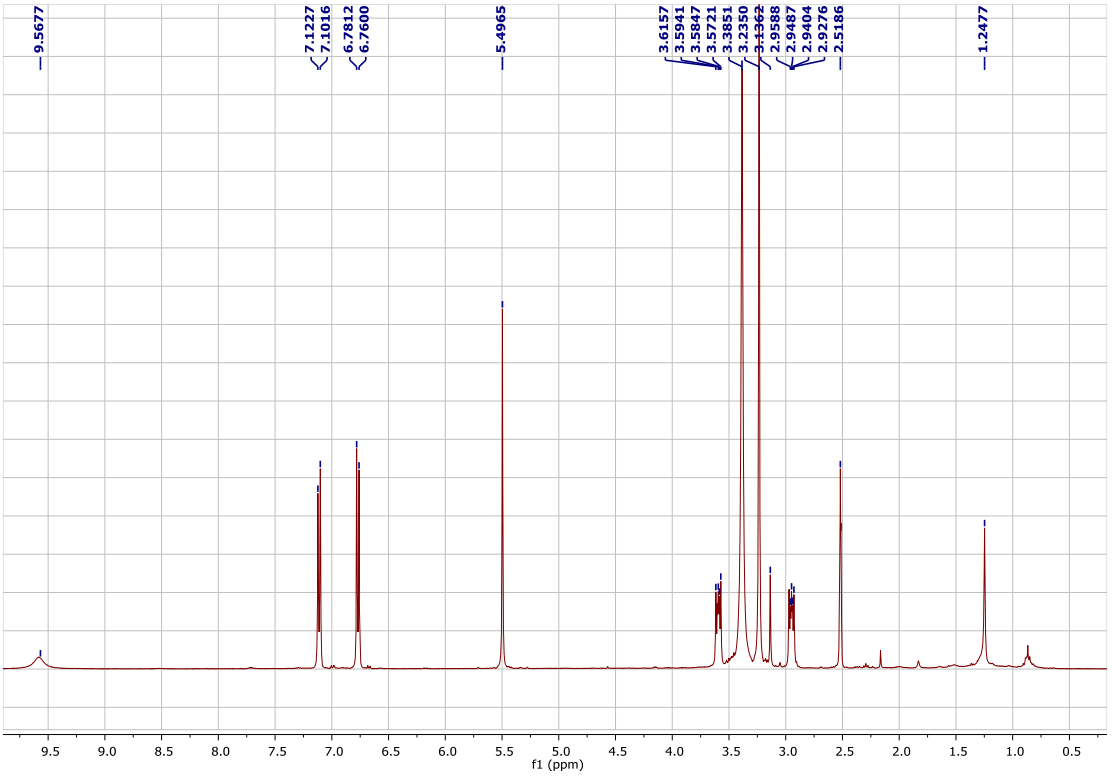

Figure S14: ^{1}H NMR spectrum of compound 5

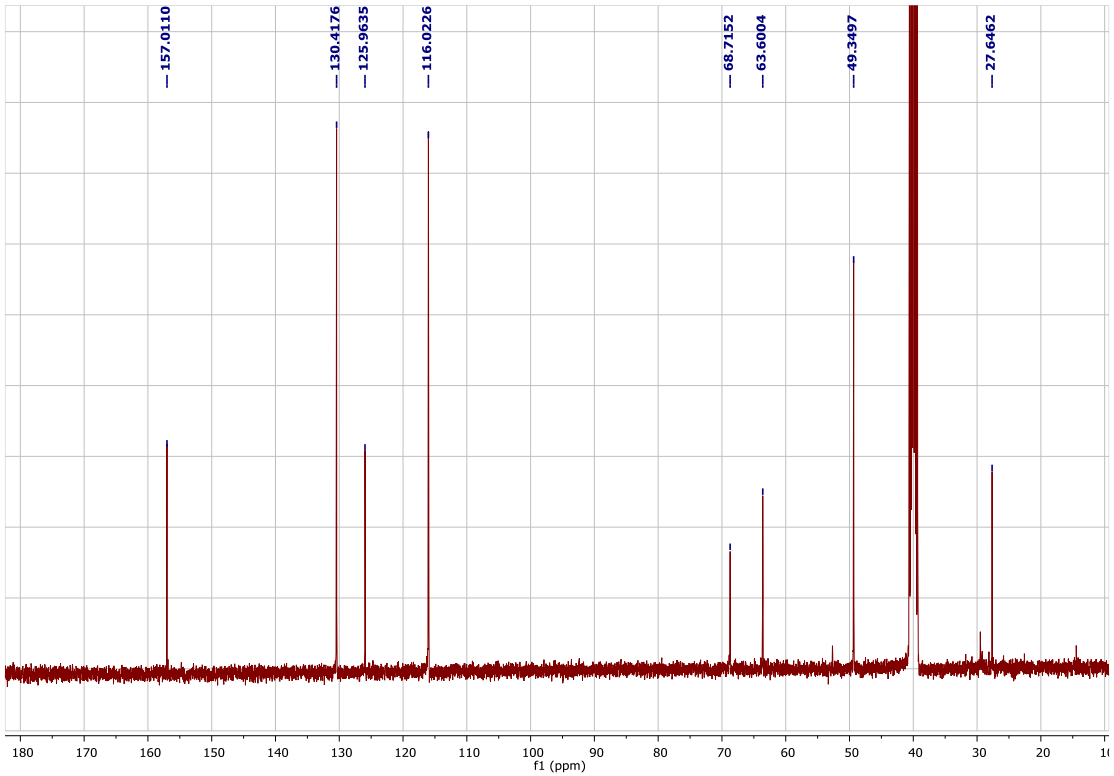

Figure S15: ^{13}C NMR spectrum of compound 5

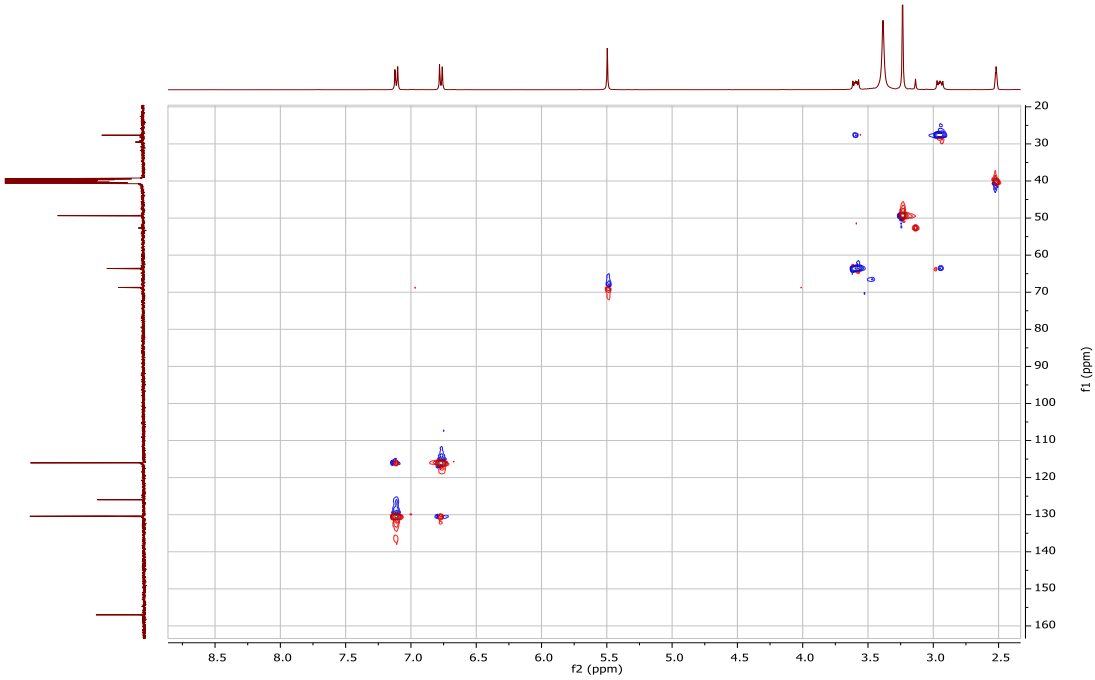

Figure S16: HSQC spectrum of compound 5

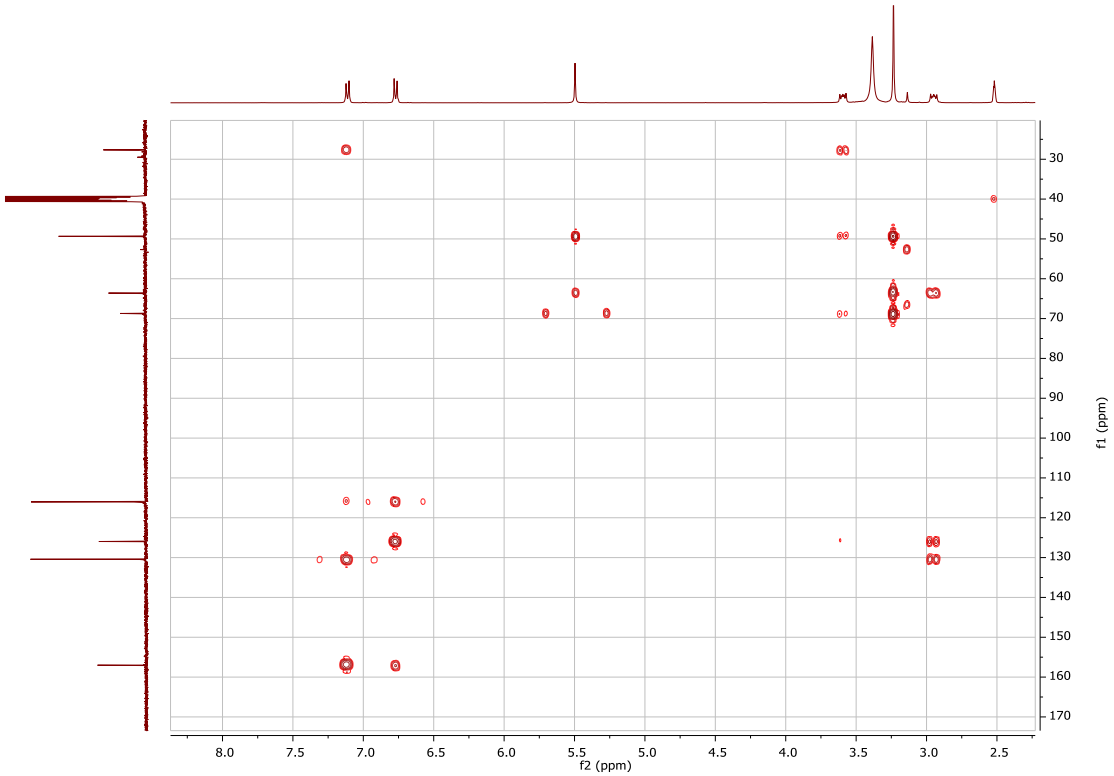

Figure S17: HMBC spectrum of compound 5

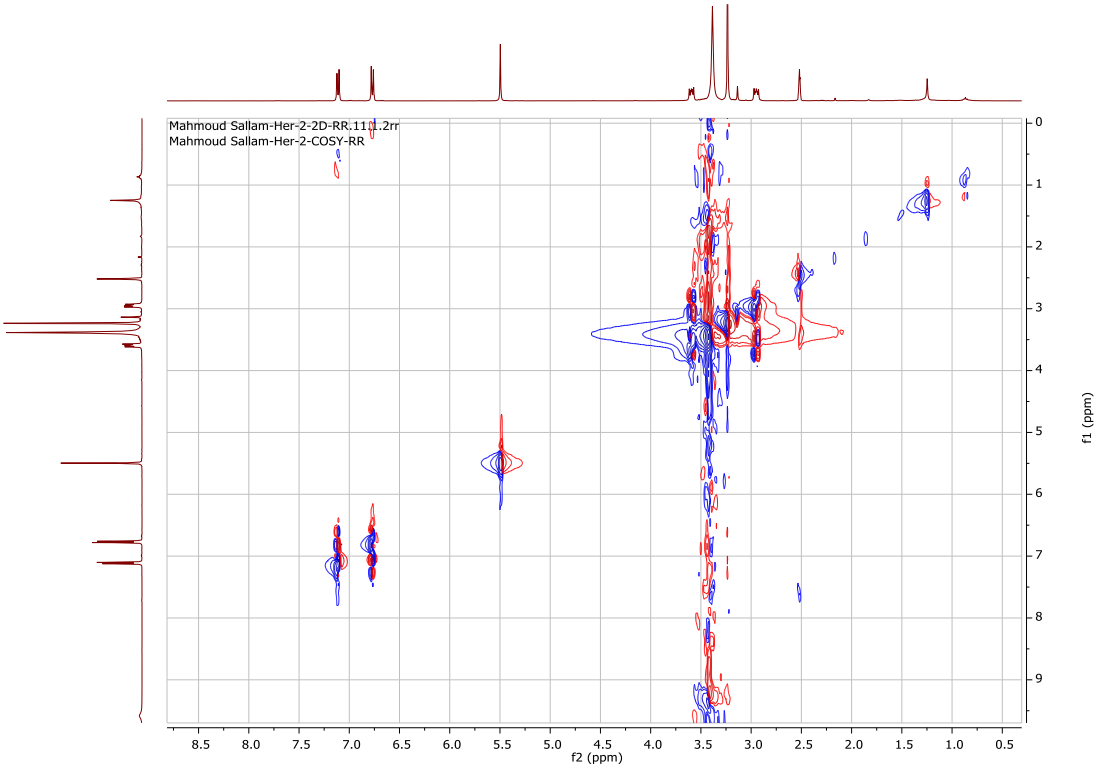

Figure S18: COSY spectrum of compound 5

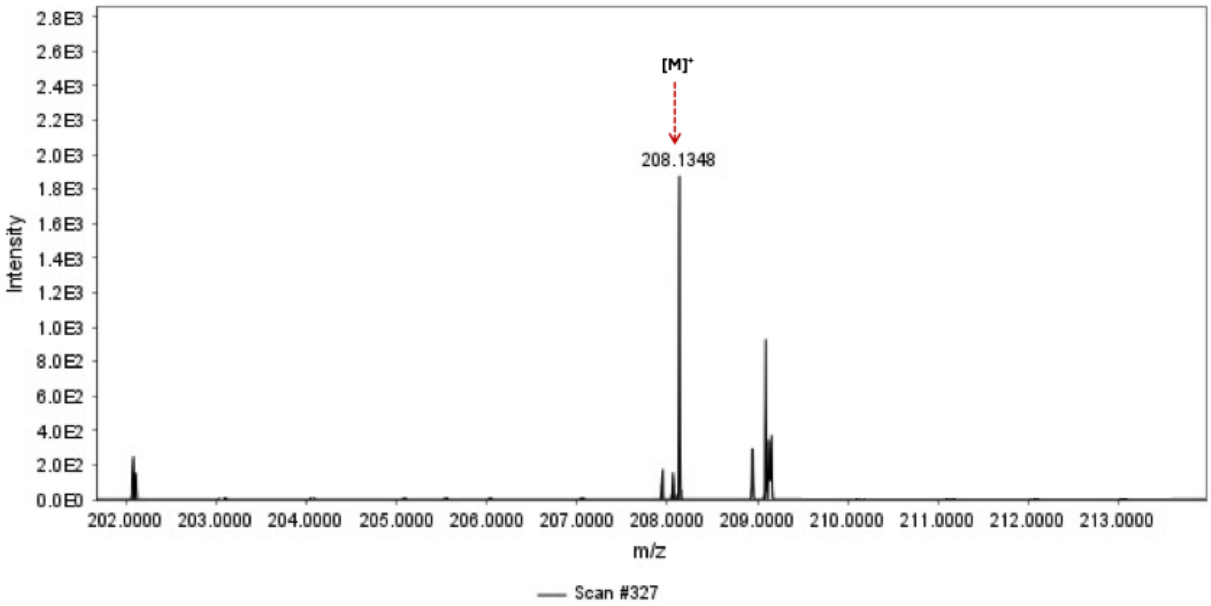

Figure S19: HR-MS spectrum of compound 6

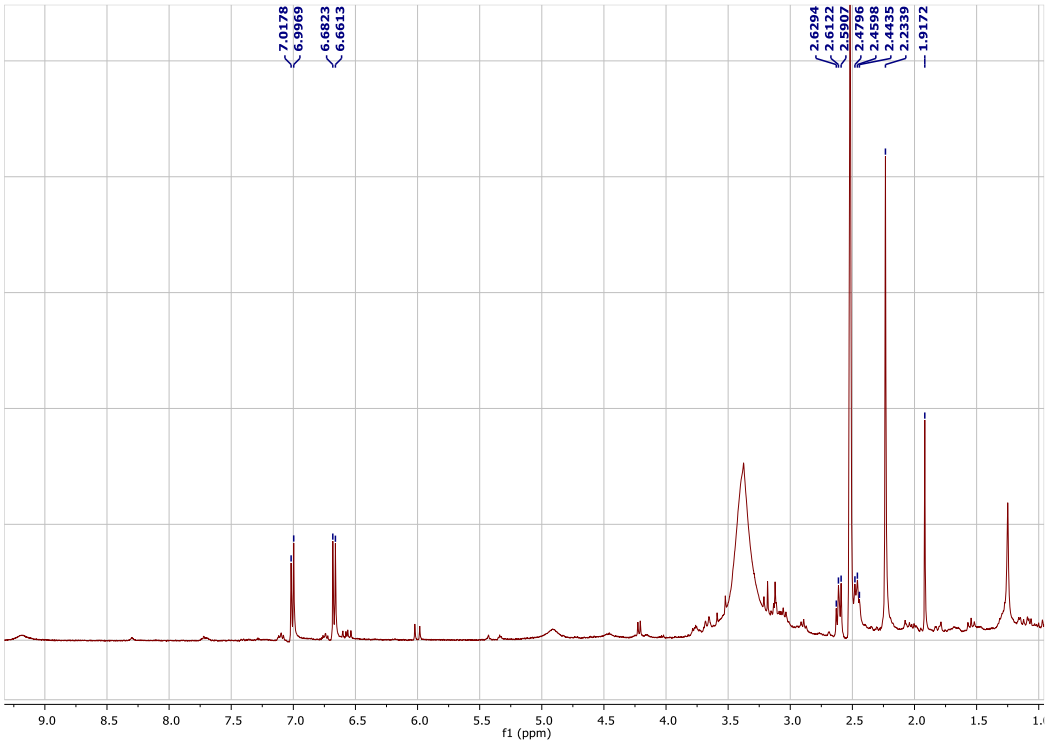

Figure S20: ^{1}H NMR spectrum of compound 6

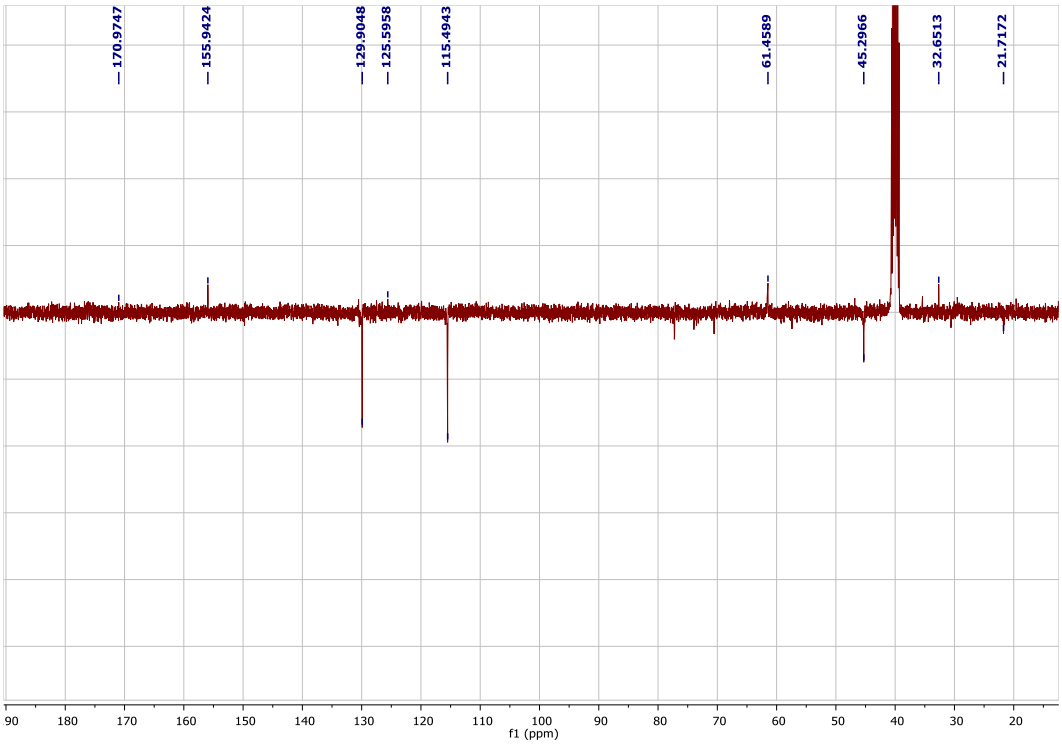

Figure S21: APT spectrum of compound 6

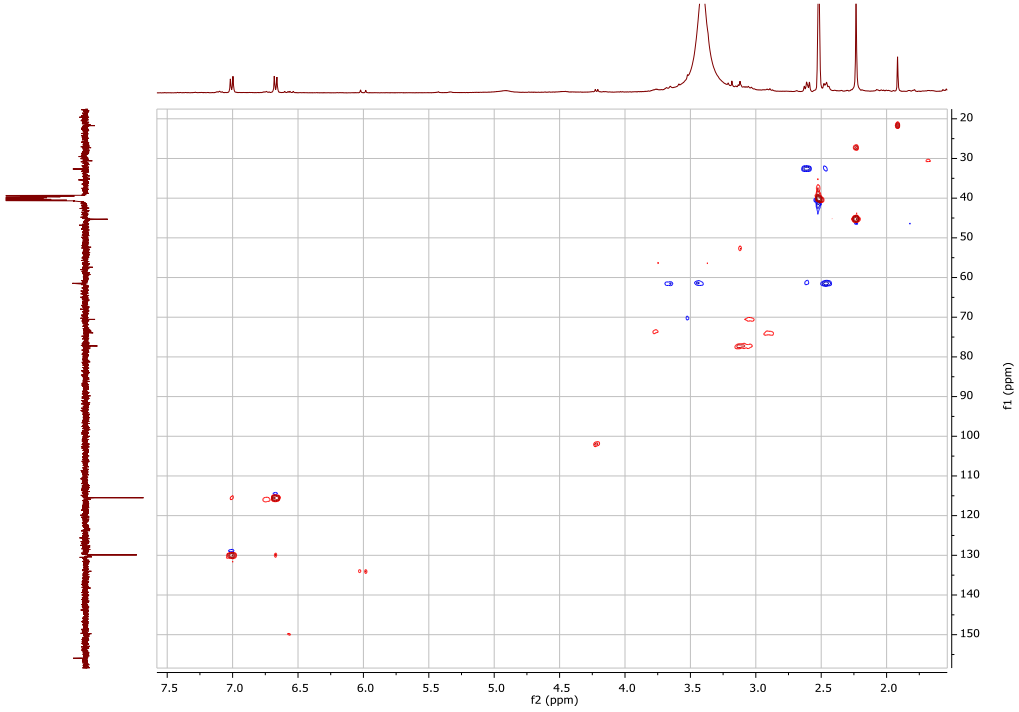

Figure S22: HSQC spectrum of compound 6

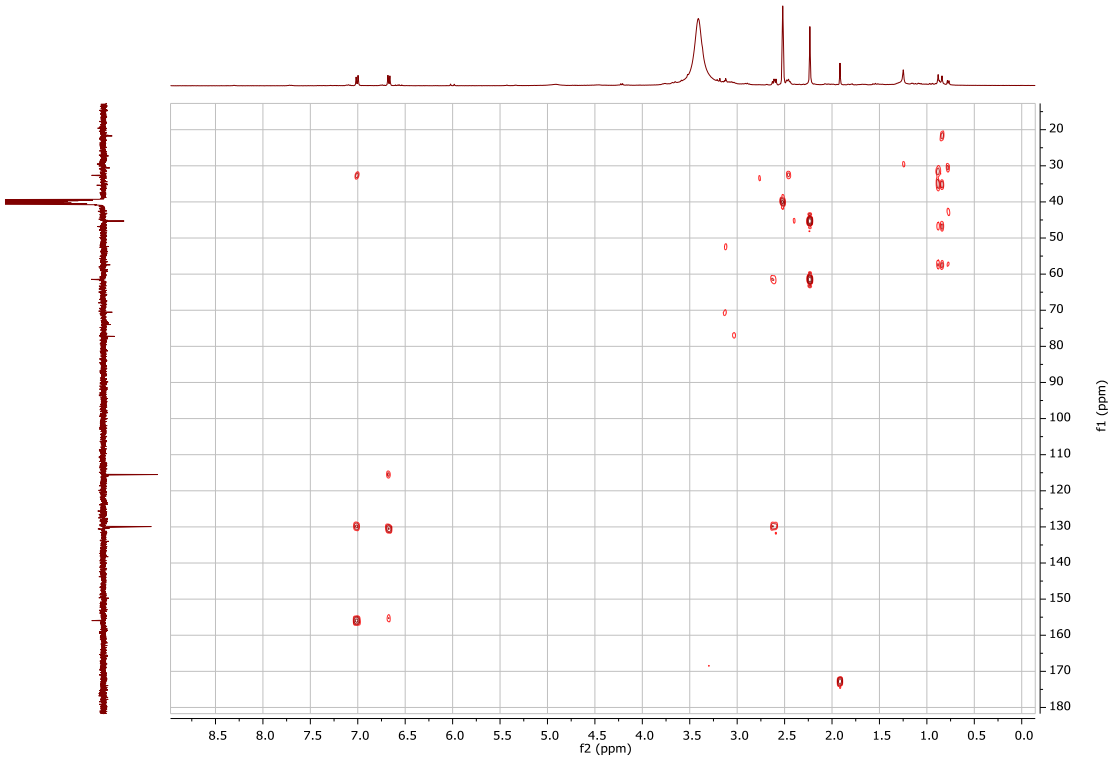

Figure S23: HMBC spectrum of compound 6

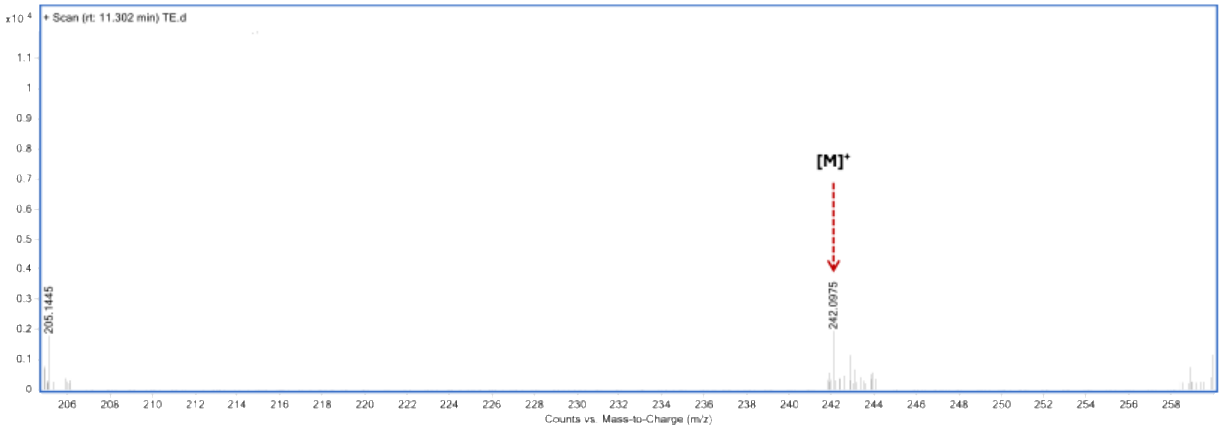

Figure S24: HR-MS spectrum of compound 7

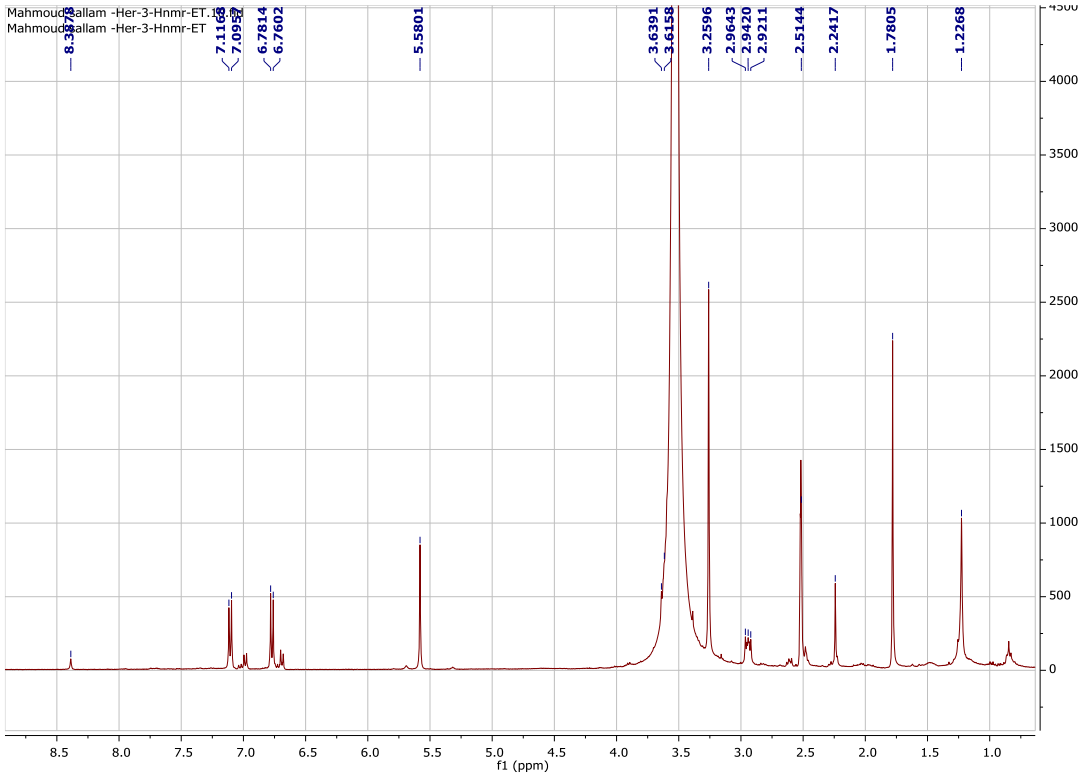

Figure S25: ^{1}H NMR spectrum of compound 7

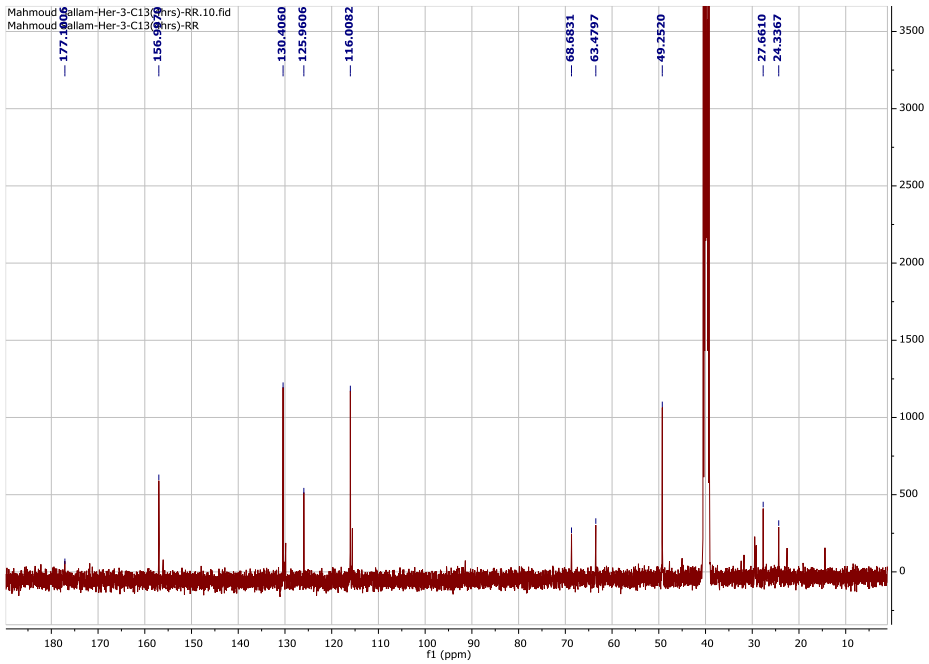

Figure S26: ^{13}C NMR spectrum of compound 7

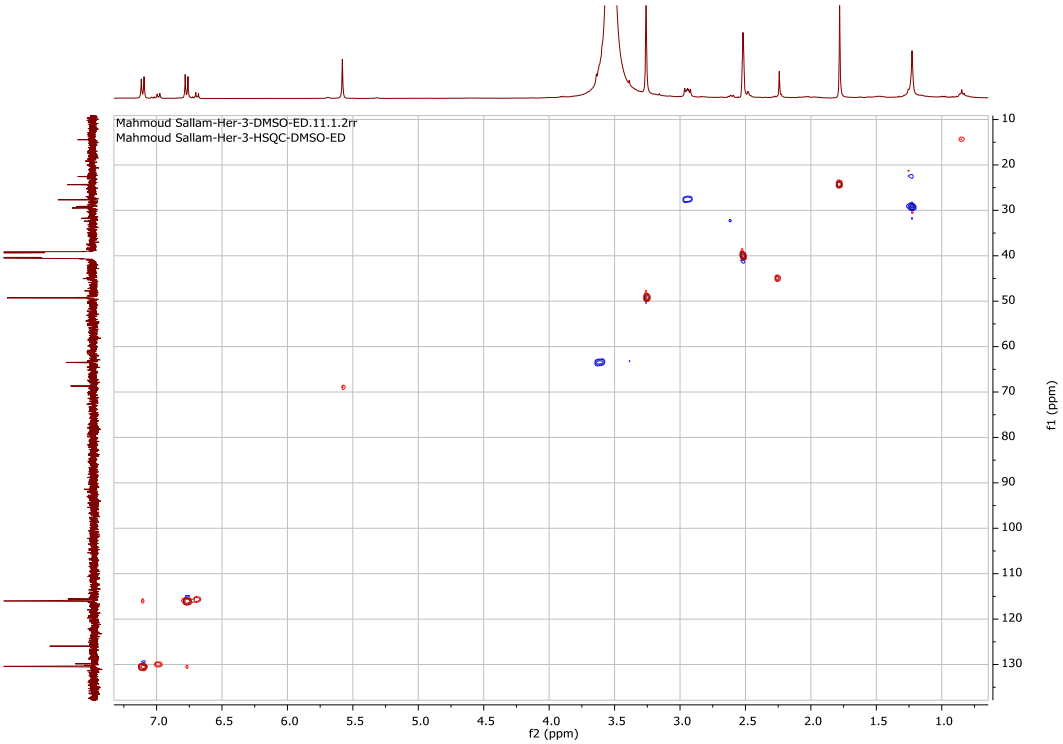

Figure S27: HSQC spectrum of compound 7

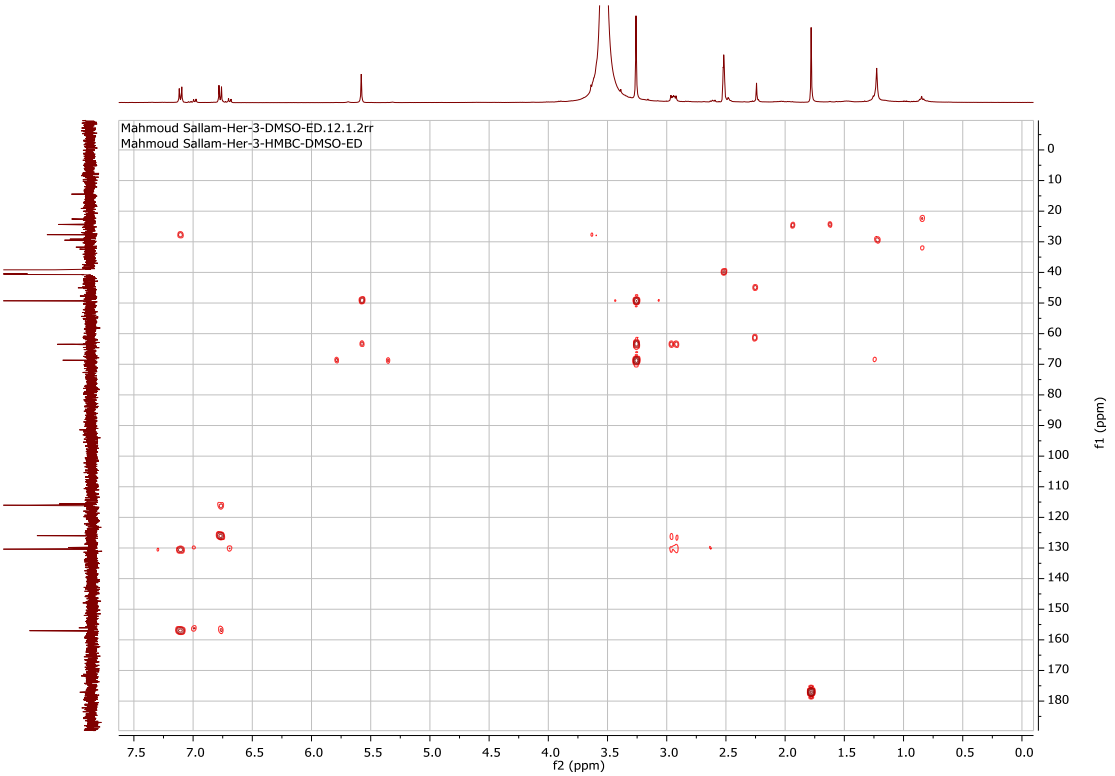

Figure S28: HMBC spectrum of compound 7

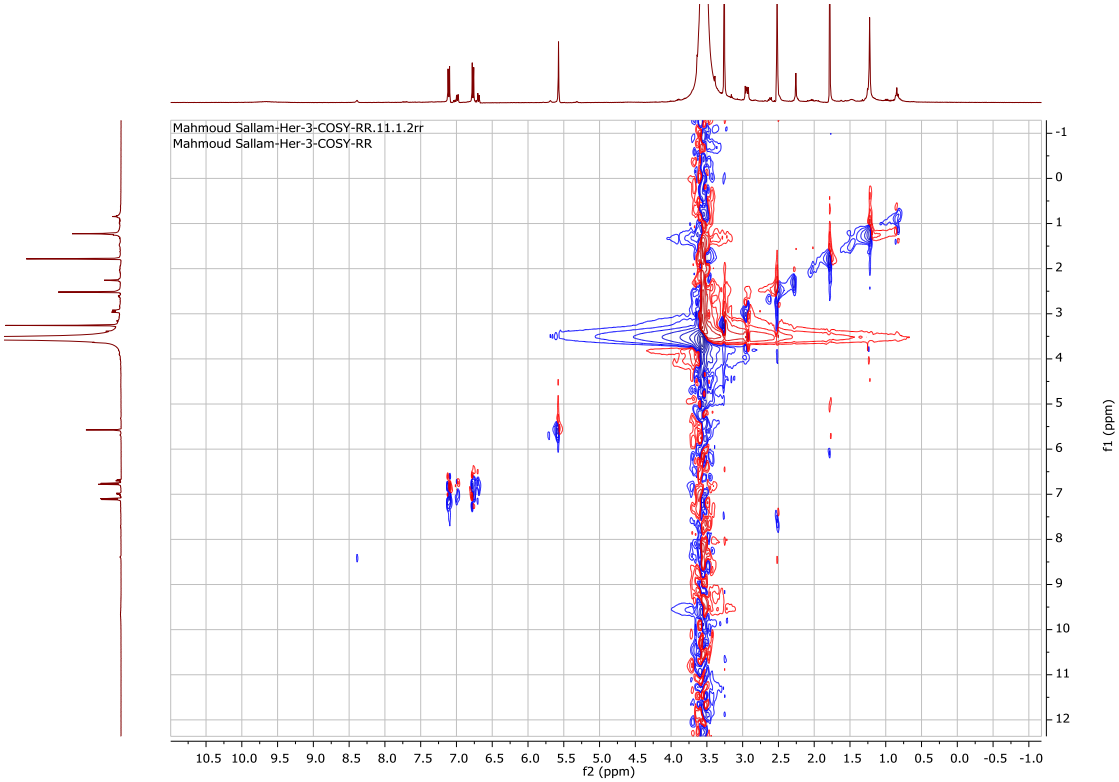

Figure S29: COSY spectrum of compound 7