In vitro and molecular docking evaluation of anticholinesterase and antidiabetic effects of compounds from *Terminalia macroptera* Guill. & Perr. (Combretaceae)

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Abstract: Abstract: Alzheimer's disease (AD) and diabetes are non-communicable diseases with global impacts. Inhibitors of acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) are suitable therapies for AD, while α-amylase and α-glucosidase inhibitors are employed as antidiabetic agents. Compounds were isolated from the medicinal plant *Terminalia macroptera* and evaluated for their AChE, BChE, α-amylase and α-glucosidase inhibitions. From ^{1}H and ^{13}C NMR data, the compounds were identified as 3,3'-di-O-methyl ellagic acid (1), 3,3',4'-tri-O-methyl ellagic ac-id-4-O-β-D-xylopyranoside (2), 3,3',4'-tri-O-methyl ellagic acid-4-O-β-D-glucopyranoside (3), 3,3'-di-O-methyl ellagic acid-4-O-β-D-glucopyranoside (4), myricetin-3-O-rhamnoside (5), shi-kimic acid (6), arjungenin (7), terminolic acid (8), 24-deoxysericoside (9), arjunglucoside I (10) and chebuloside II (11). The derivatives of ellagic acid (1-4) showed moderate to good inhibition of cholinesterases with the most potent being 3,3'-di-O-methyl ellagic acid with IC_{50} of 46.77±0.90 μg/mL and 50.48±1.10 μg/mL against AChE and BChE respectively. The compounds exhibited potential inhibition of α-amylase and α-glucosidase especially the phenolic compounds (1-5). Myricetin-3-O-rhamnoside had the highest α-amylase inhibition with an IC_{50} value of 65.17±0.43 μg/mL compared to acarbose with IC_{50} of 32.25±0.36 μg/mL. Two compounds, 3,3'-di-O-methyl ellagic acid (IC_{50} = 74.18±0.29 μg/mL) and myricetin-3-O-rhamnoside (IC_{50} = 69.02±0.65 μg/mL) were more active than the standard acarbose (IC_{50} = 87.70±0.68 μg/mL) in the α-glucosidase as-say. For α-glucosidase and α-amylase, molecular docking results of 1-11 reveal that these com-pounds may fit well into the binding sites of target enzymes, establishing stable complexes with negative binding energies in the range of -4.03 to -10.20 kcalmol^{-1}. Though not all compounds showed binding affinities with cholinesterases, some had negative binding energies indicating that the inhibition is thermodynamically favorable.

Keywords: *Terminalia macroptera*; diabetes; Alzheimer's disease; cholinesterase inhibition; α-glucosidase inhibition; α-amylase inhibition; molecular

List of supplementary materials

Figure S1: Figure S1 Free binding energies (kcal/mol), hydrogen bonding, number of closest residues to the docked isolated compounds into the binding site of α-glucosidase, and α-amylase.
Figure S2: Figure S2. Free binding energies, hydrogen bonding, number of closest residues to the docked isolated compounds into the binding site of acetylcholinesterase, and butyrylcholinesterase.
Figure S3: ^{1}H NMR and ^{13}C NMR spectra of compounds 1-11.

Figure S1 Free binding energies (kcal/mol), hydrogen bonding, number of closest residues to the docked isolated compounds into the binding site of α-glucosidase, and α-amylase.

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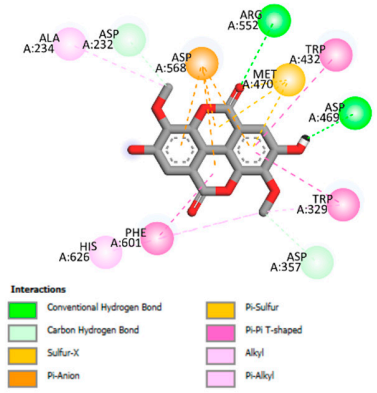
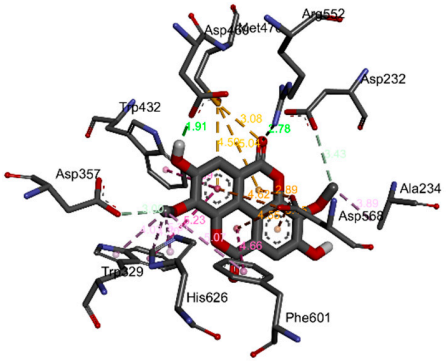
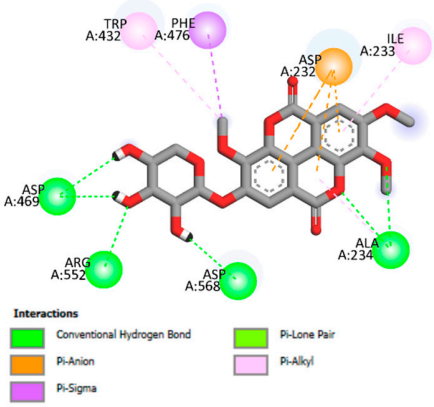
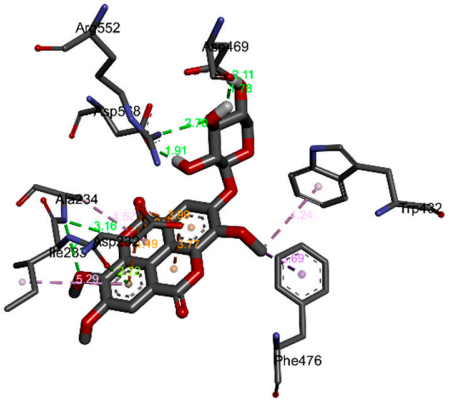
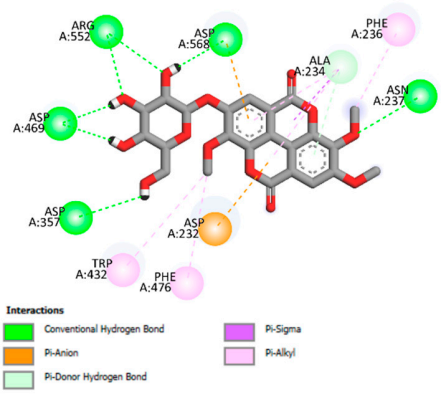
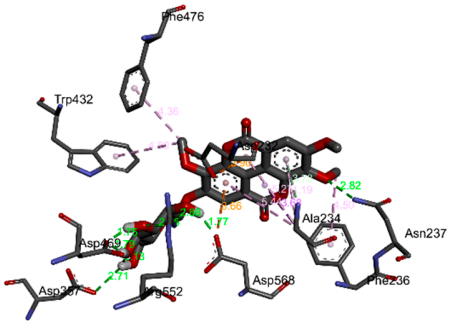
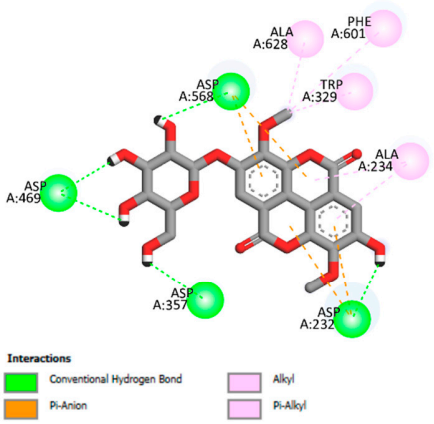
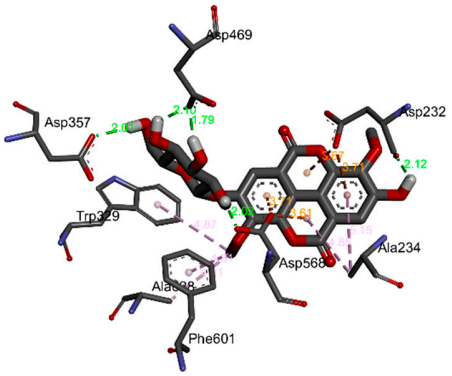
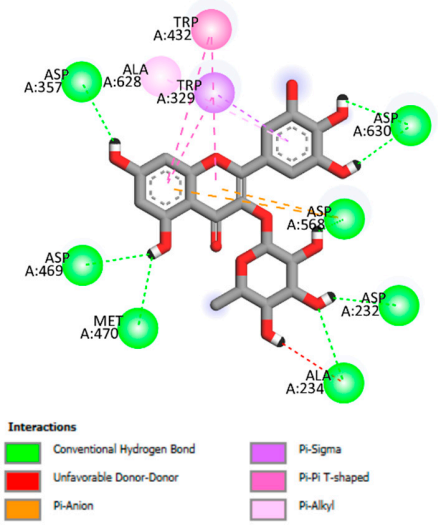
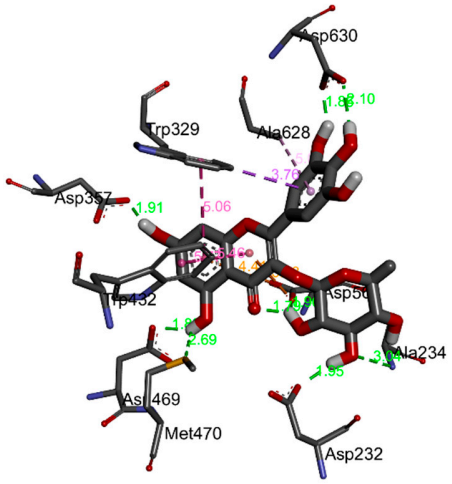
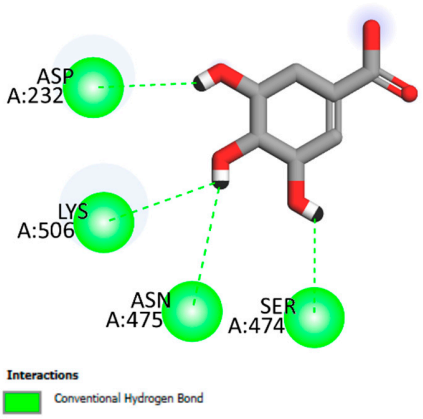
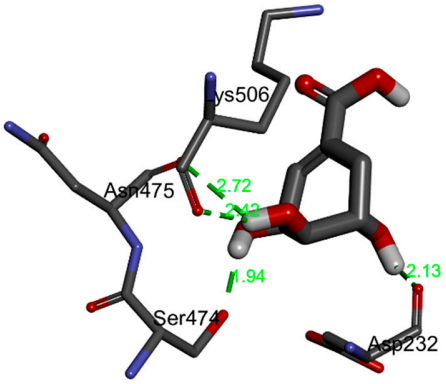
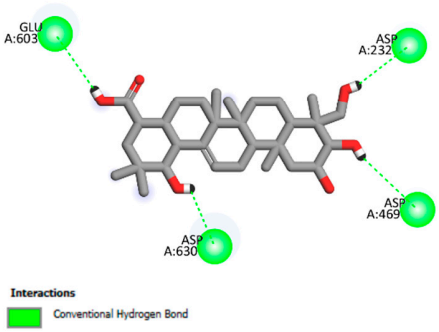
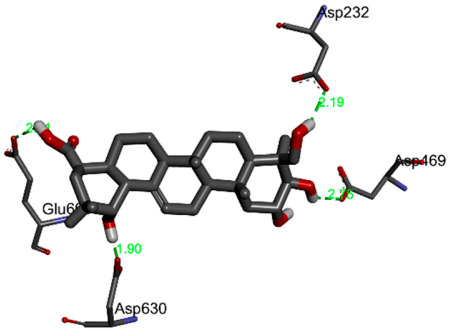
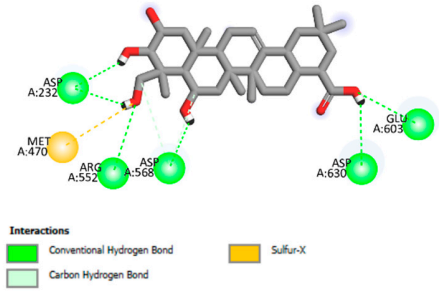
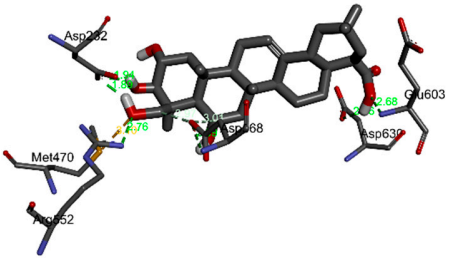
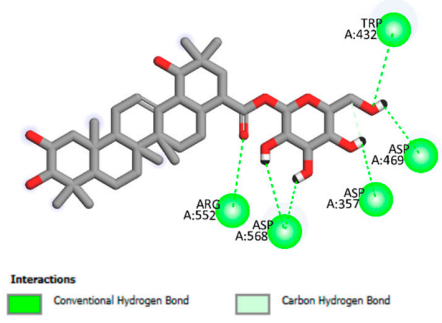
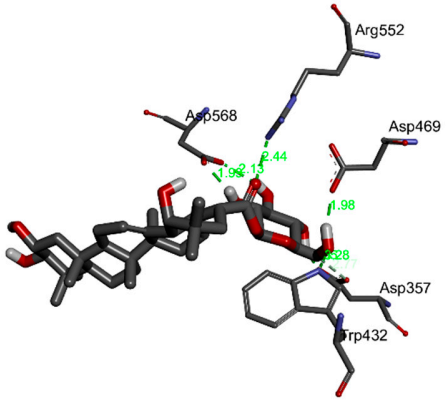
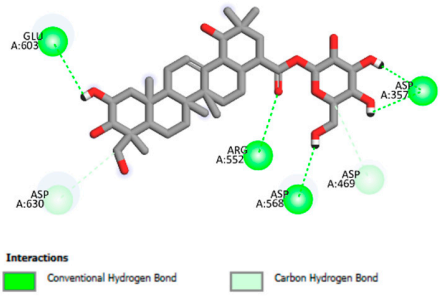
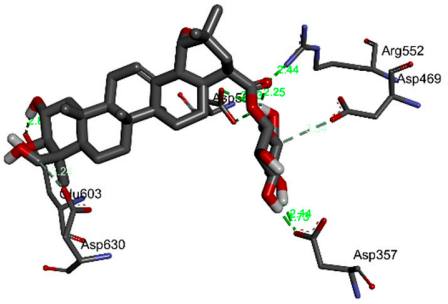
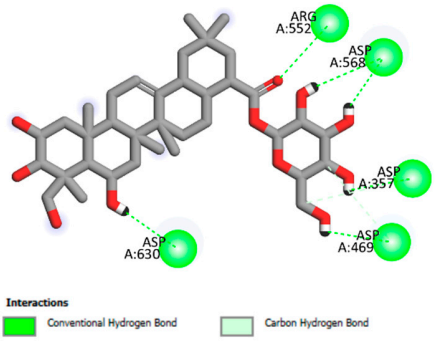
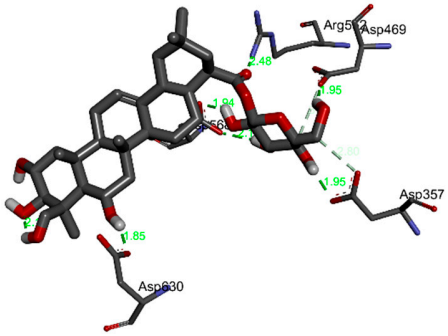
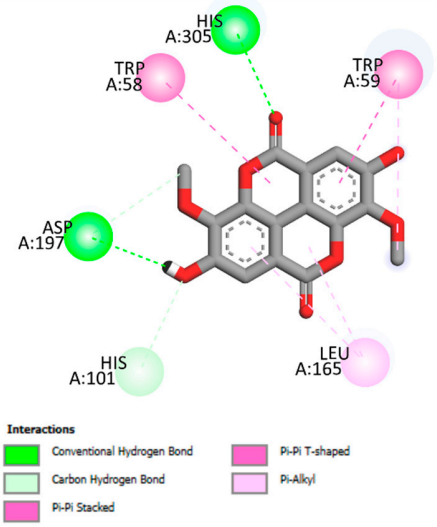
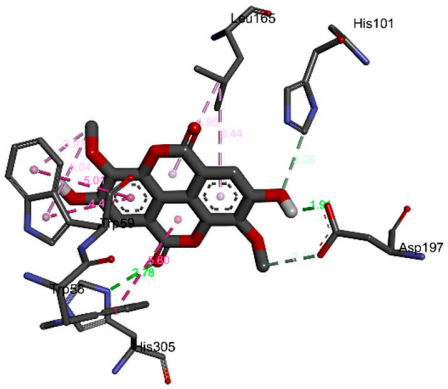
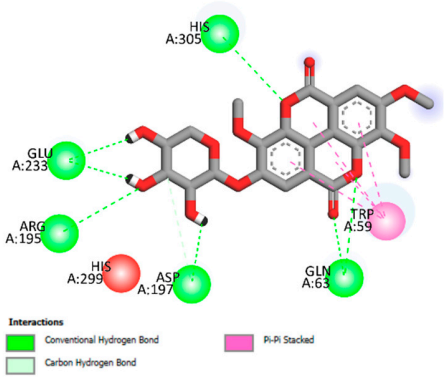
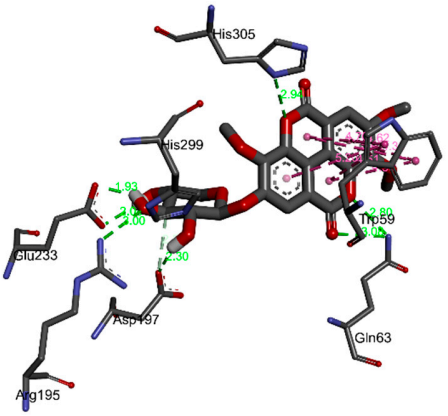
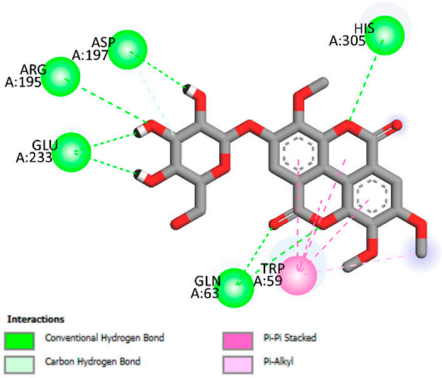
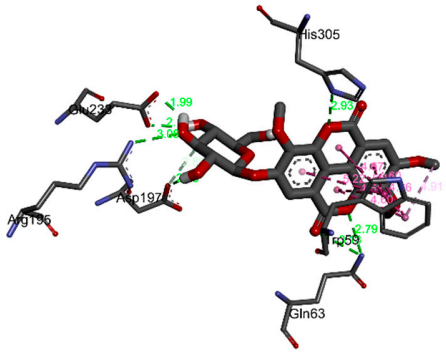
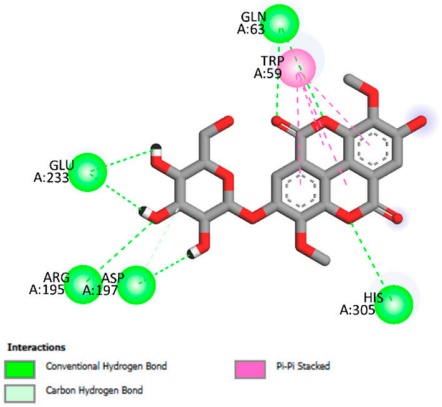
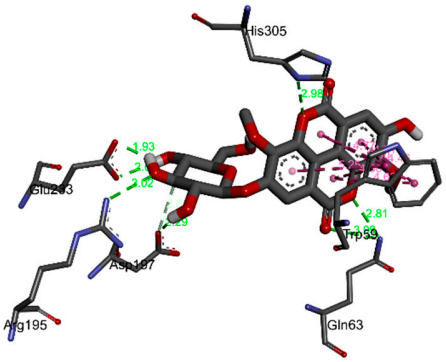
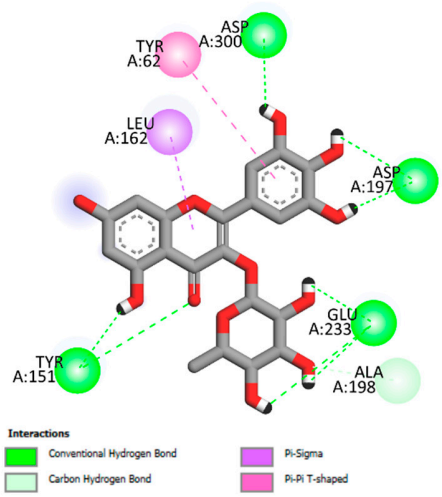
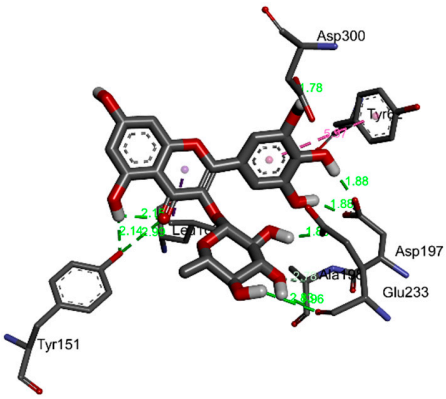
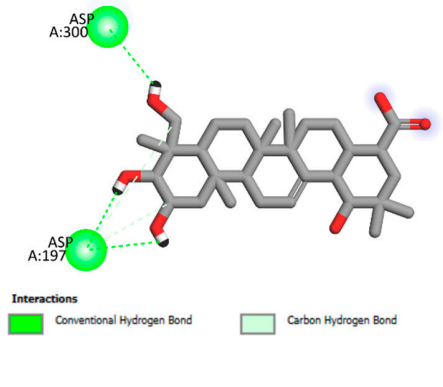
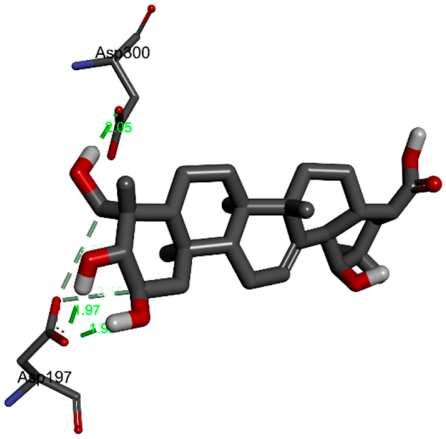
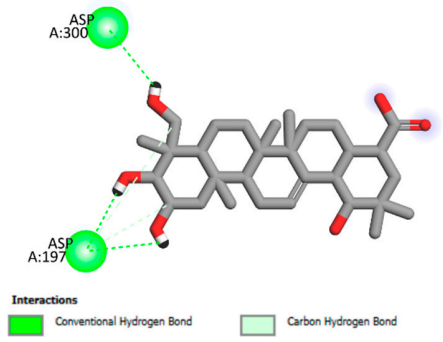
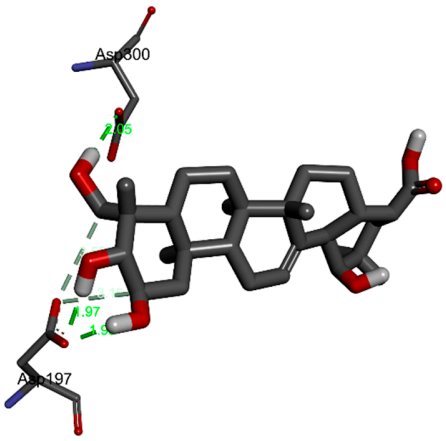
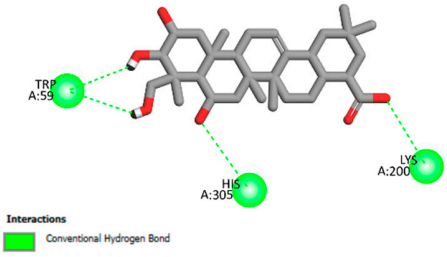
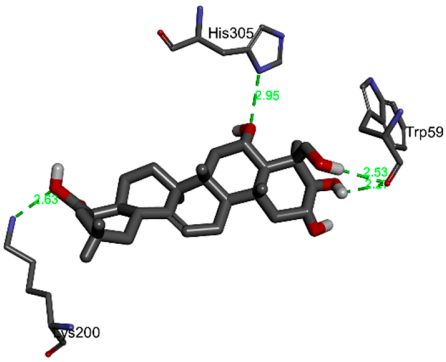
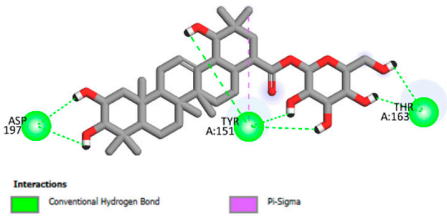
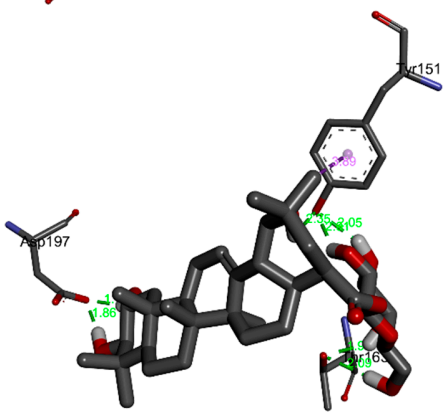
1	-5.97	2		
2	-7.86	6		

3	-7.54	7		
4	-7.78	5		
5	-7.30	8		

6	-4.03	4		
7	-7.27	4		
8	-6.71	6		
9	-10.16	6		

10	-9.60	5		
11	-10.20	6		
1	-6.22	2		
2	-9.41	7		

3	-8.84	7		
4	-8.72	7		
5	-7.83	7		

6	-4.72	4		
7	-8.78	3		
8	-10.18	4		
9	-8.84	7		

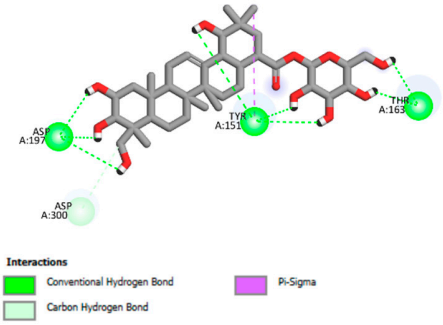
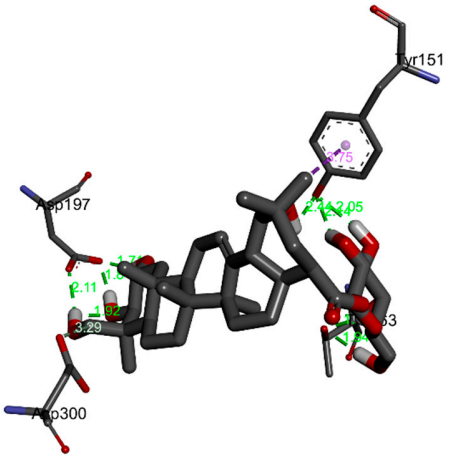
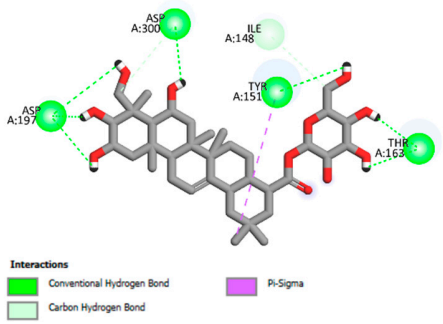
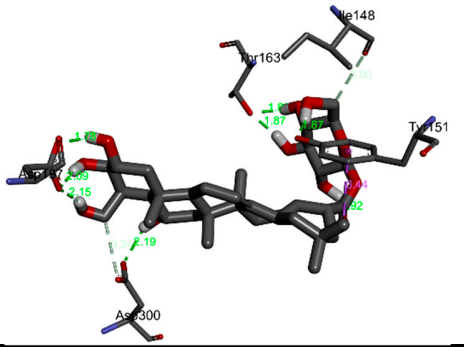
10	-8.95	8		
11	-9.60	7		

Figure S2. Free binding energies, hydrogen bonding, number of closest residues to the docked isolated compounds into the binding site of acetylcholinesterase, and butyrylcholinesterase.

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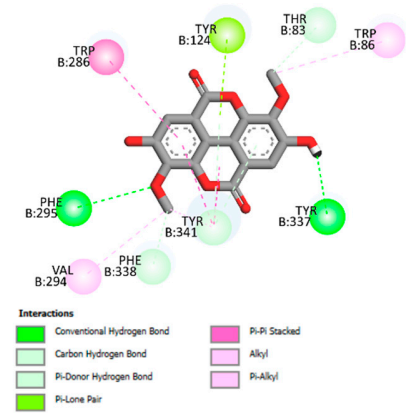
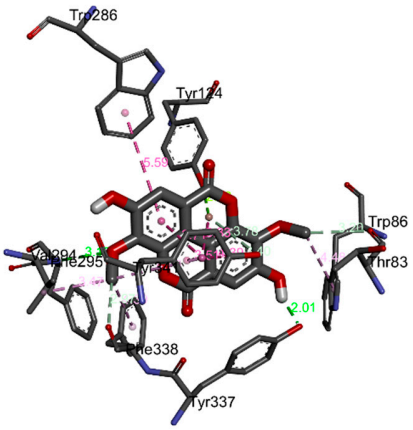
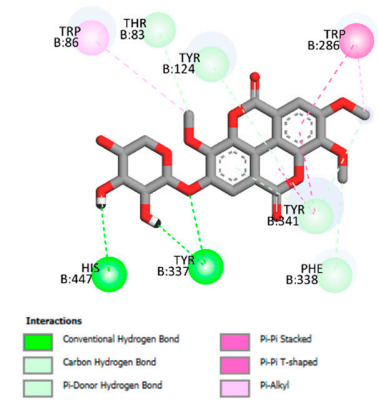
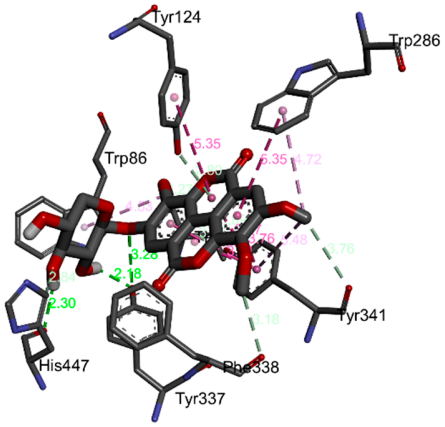
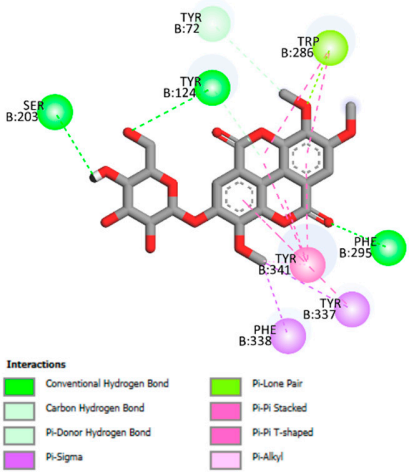
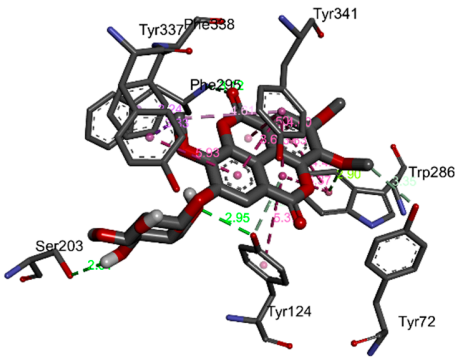
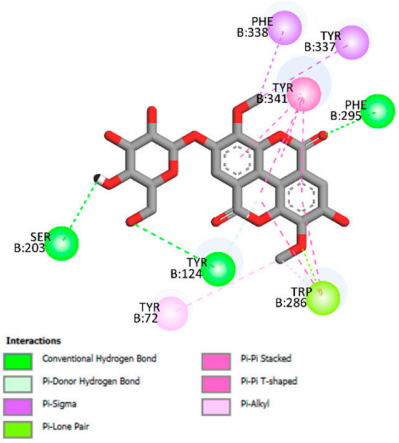
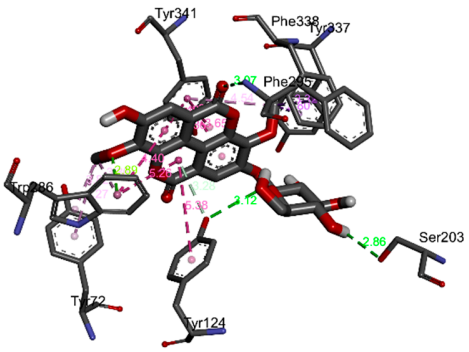
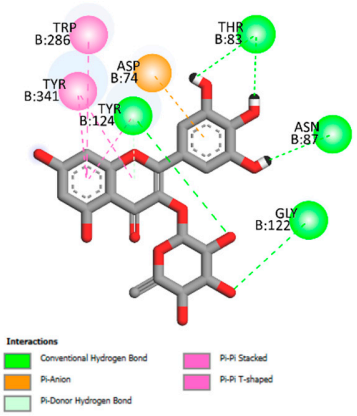
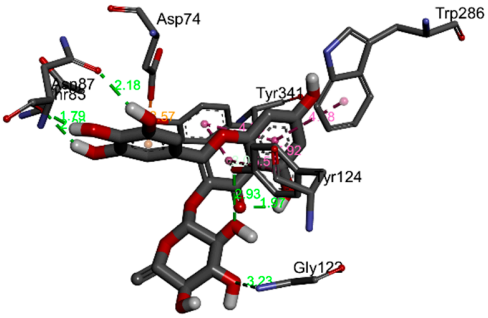
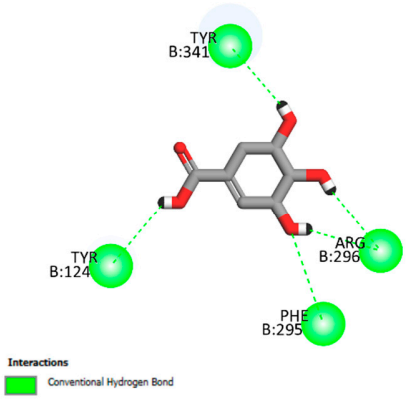
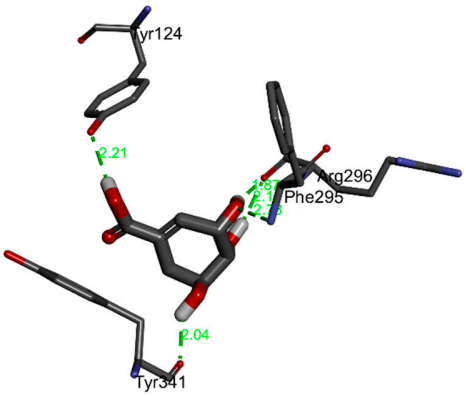
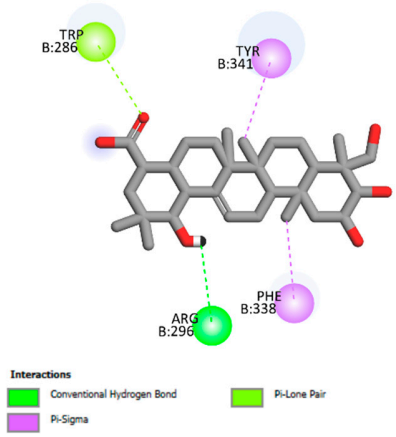
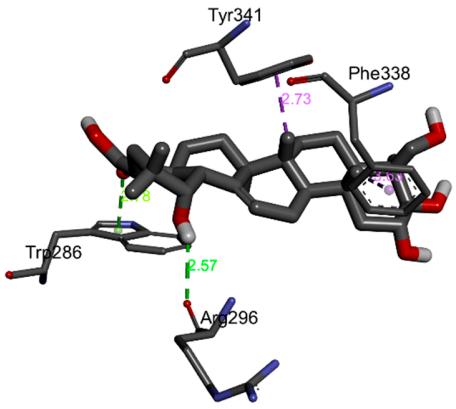
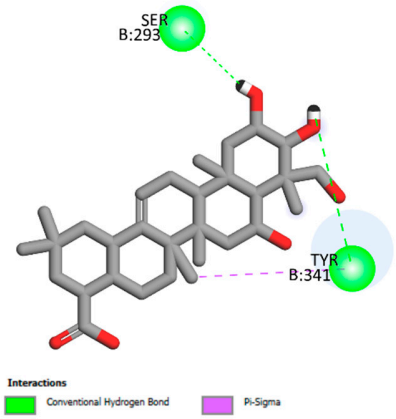
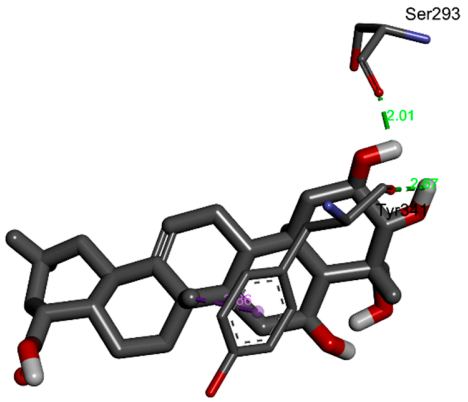
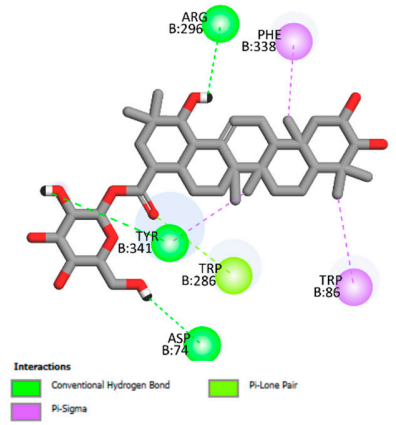
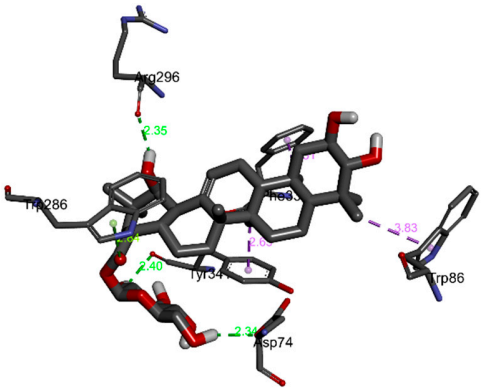
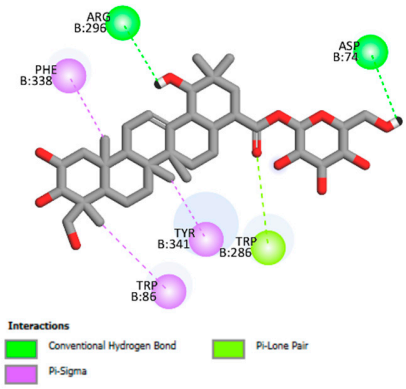
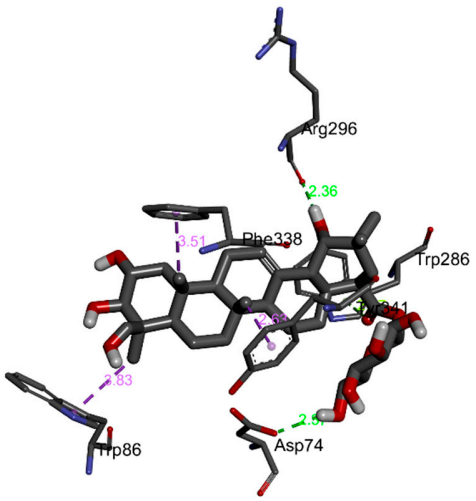
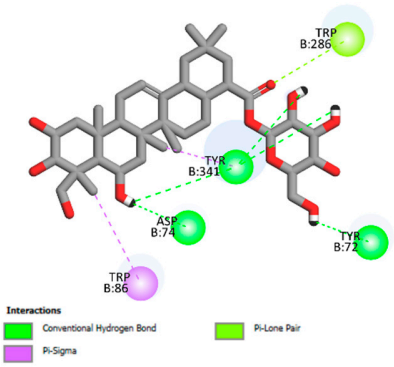
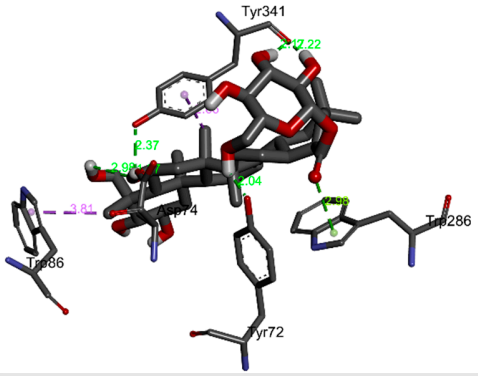
1	-8.21	2		

2	-10.08	3		
3	-10.21	3		
4	-9.86	3		

5	-8.45	5		
6	-4.13	5		
7	-7.10	1		

8	-7.56	2		
9	-6.13	3		
10	-5.72	2		

11	-6.57	5		
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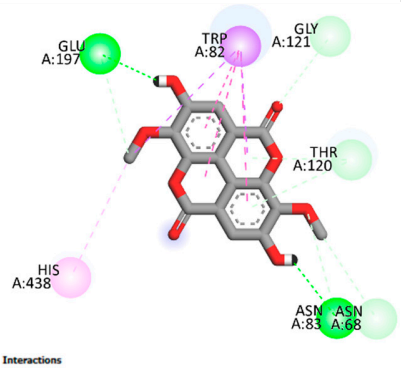
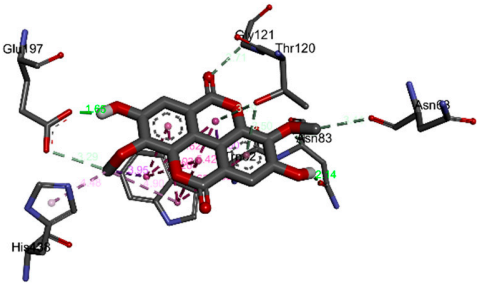
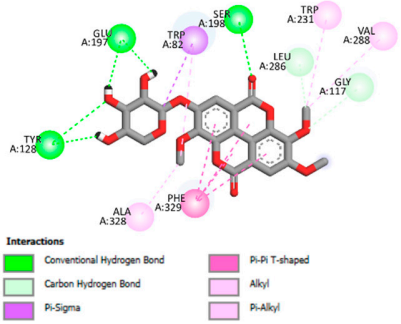
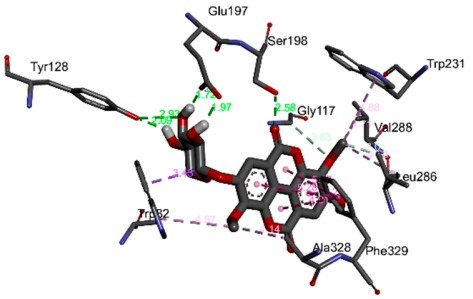
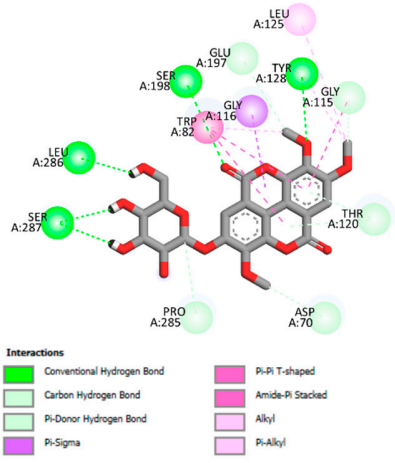
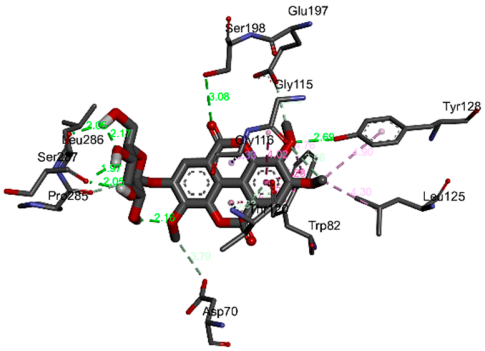
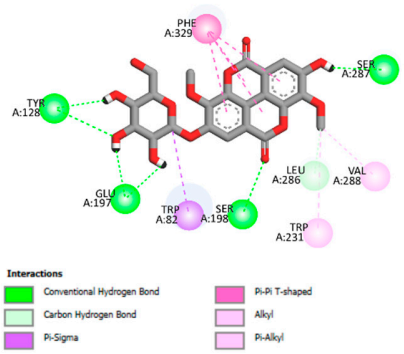
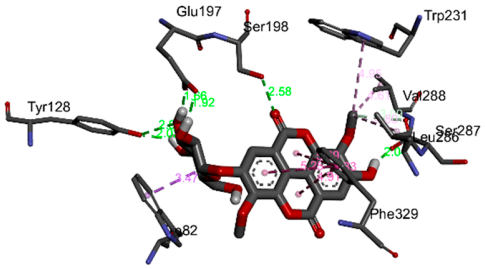
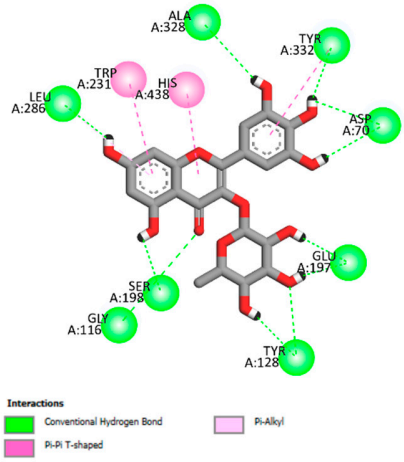
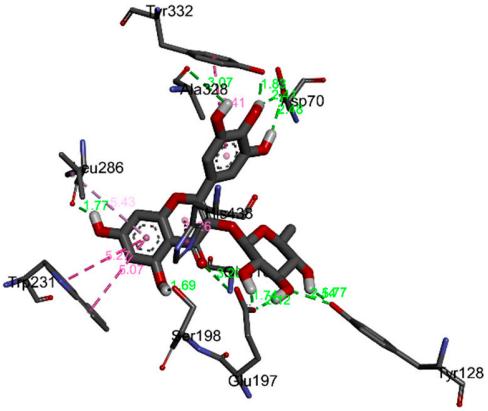
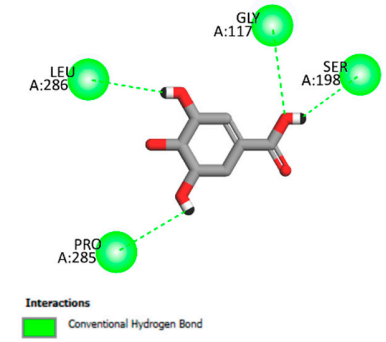
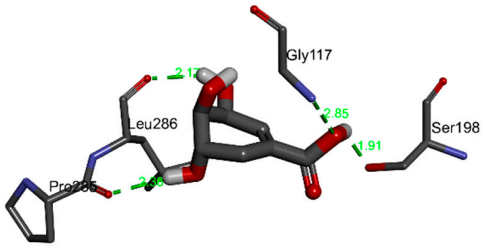
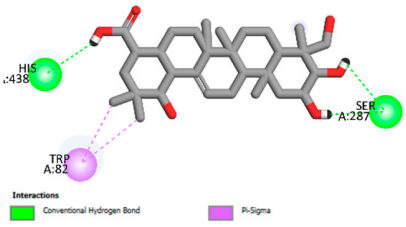
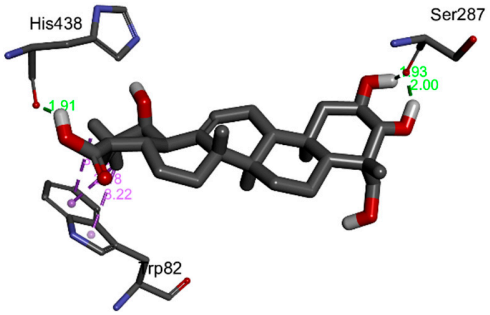
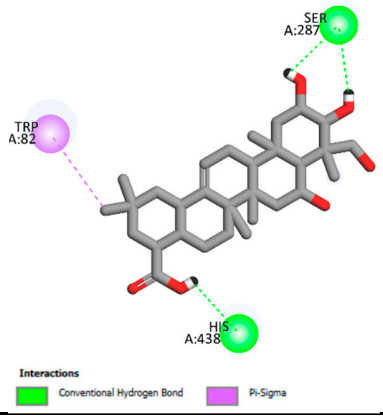
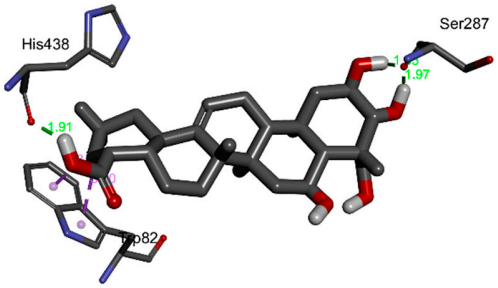
1	-7.83	2		
2	-8.10	5		
3	-8.04	5		

4	-8.14	6		
5	-9.66	11		
6	-5.13	4		
7	-5.00	3		

8	-6.77	3		

* NB for No Binding affinity; NA for not applicable

Figure S3: ^{1}H NMR and ^{13}C NMR spectra of compounds 1-11.

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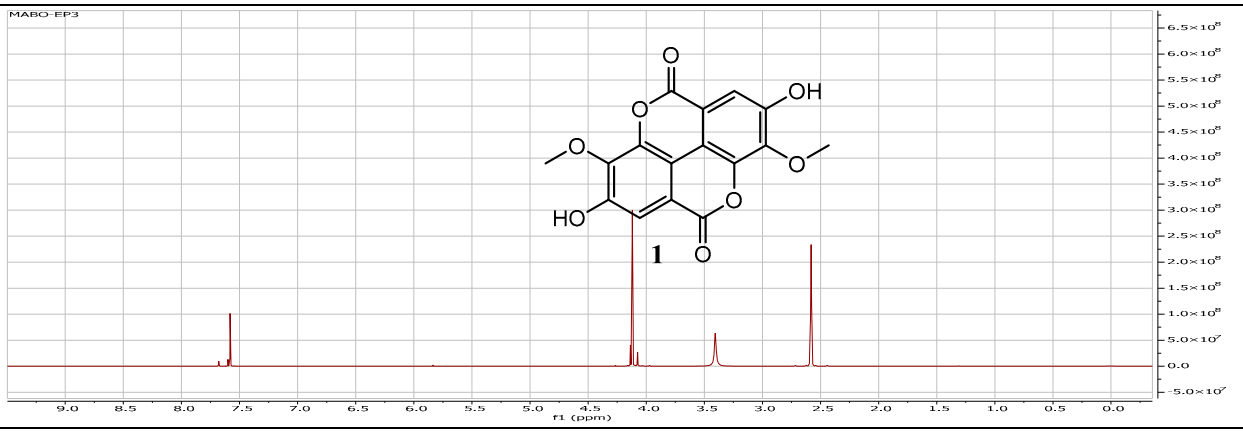

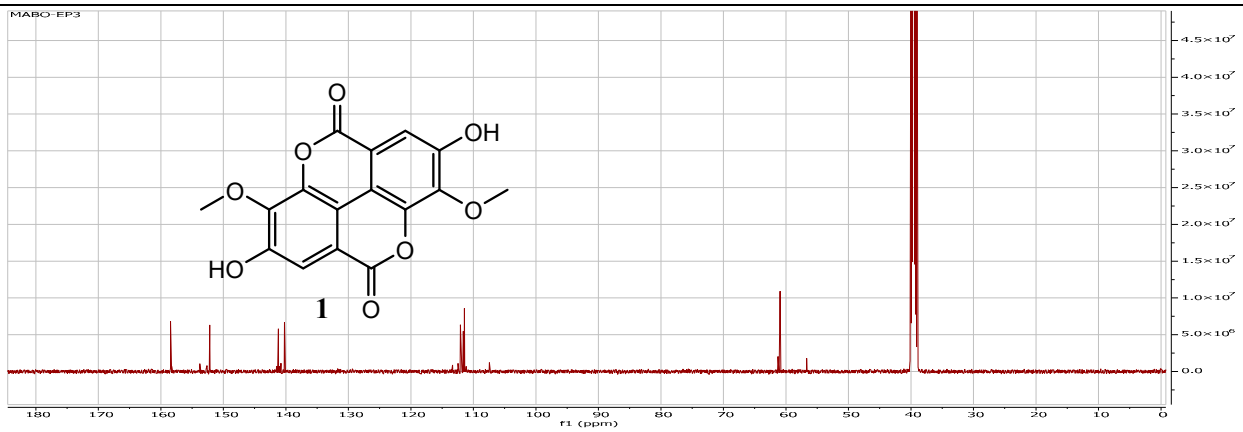

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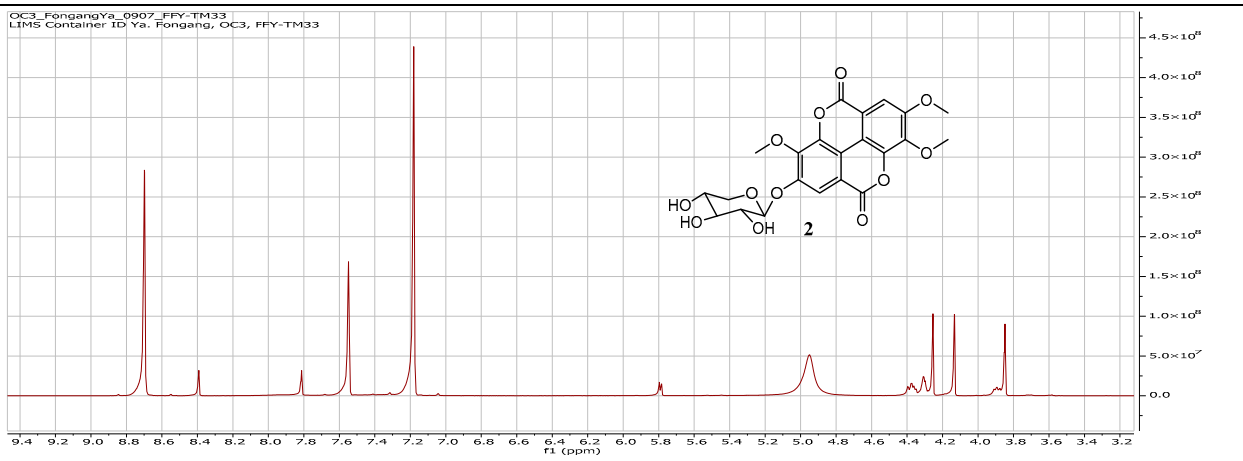

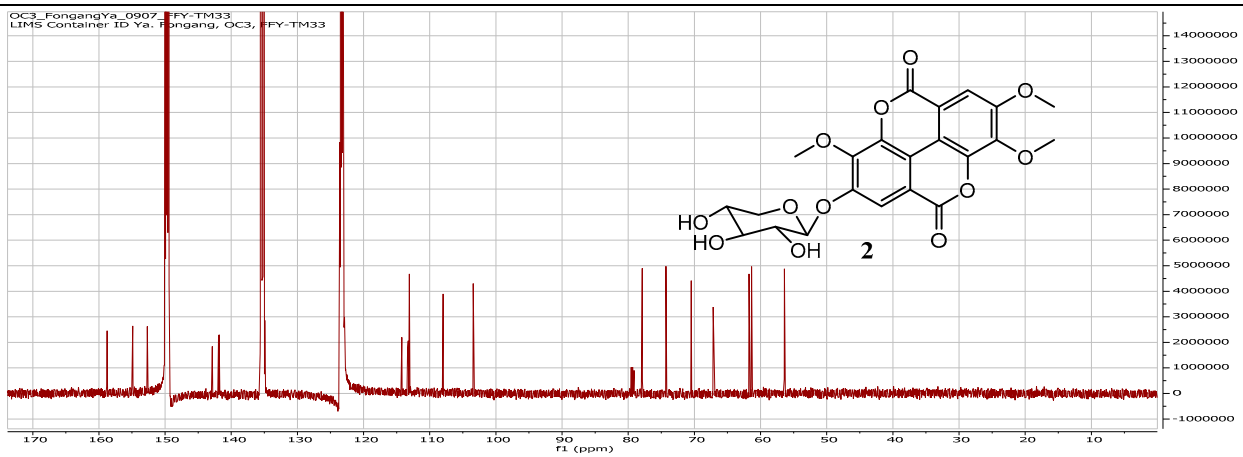

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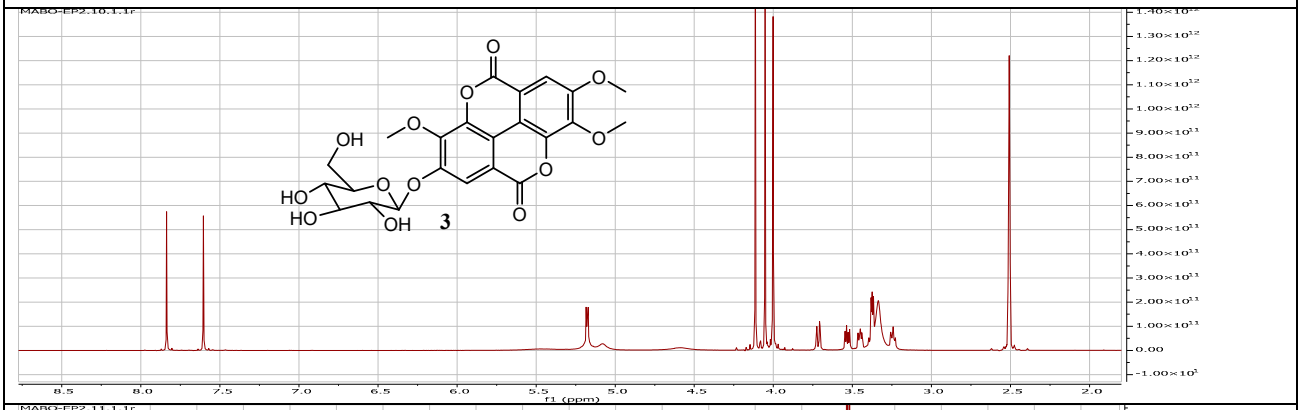

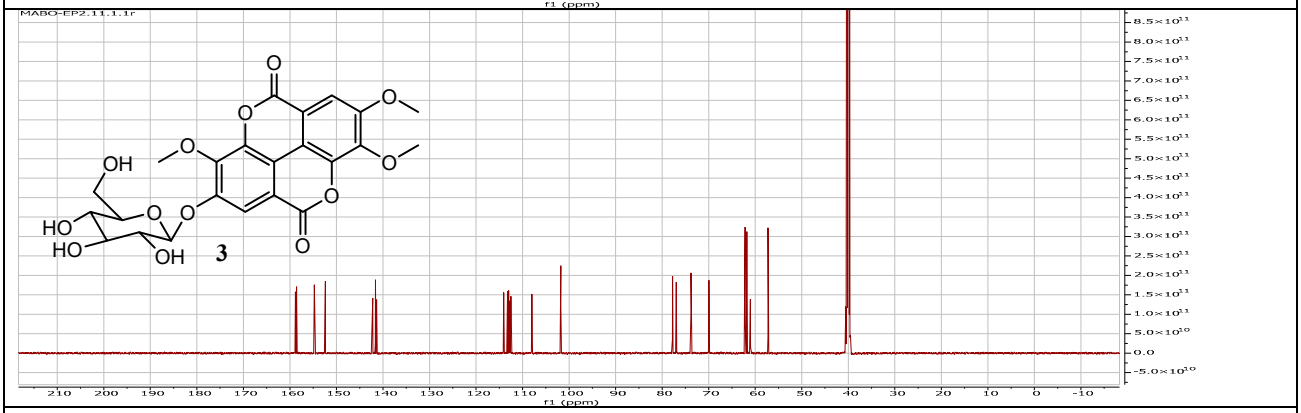

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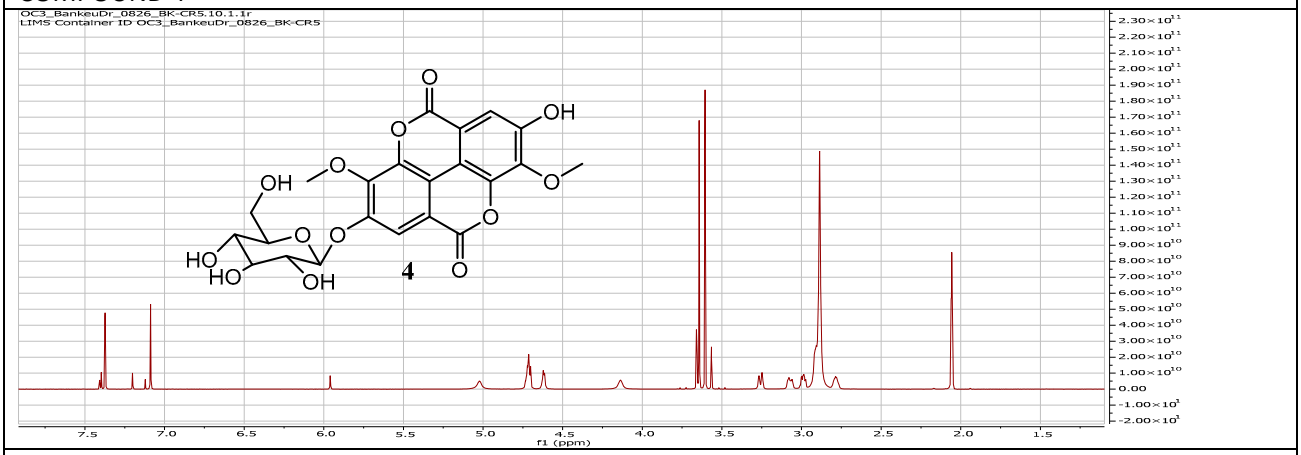

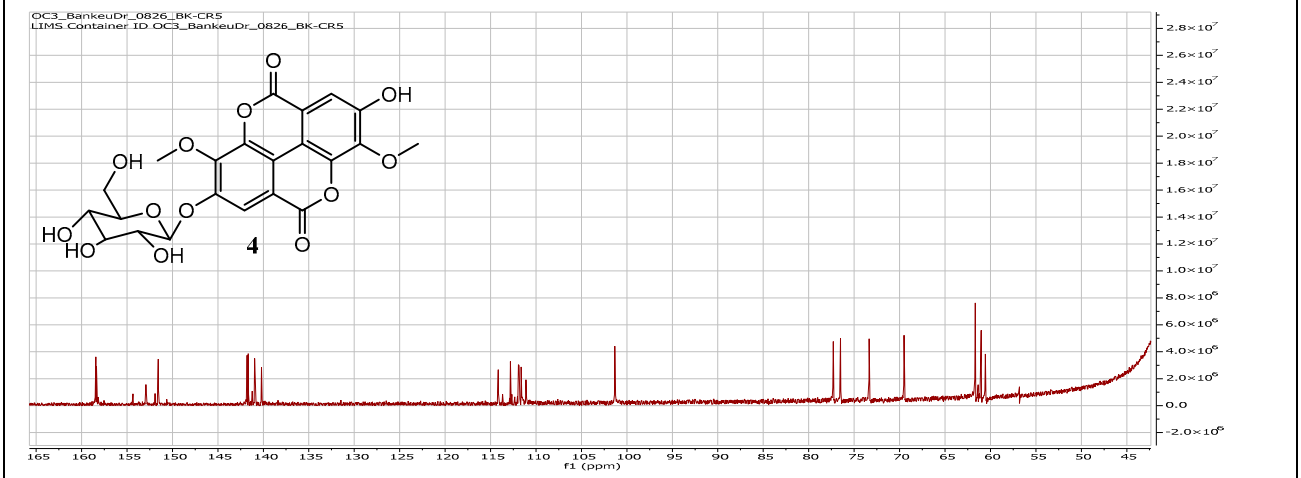

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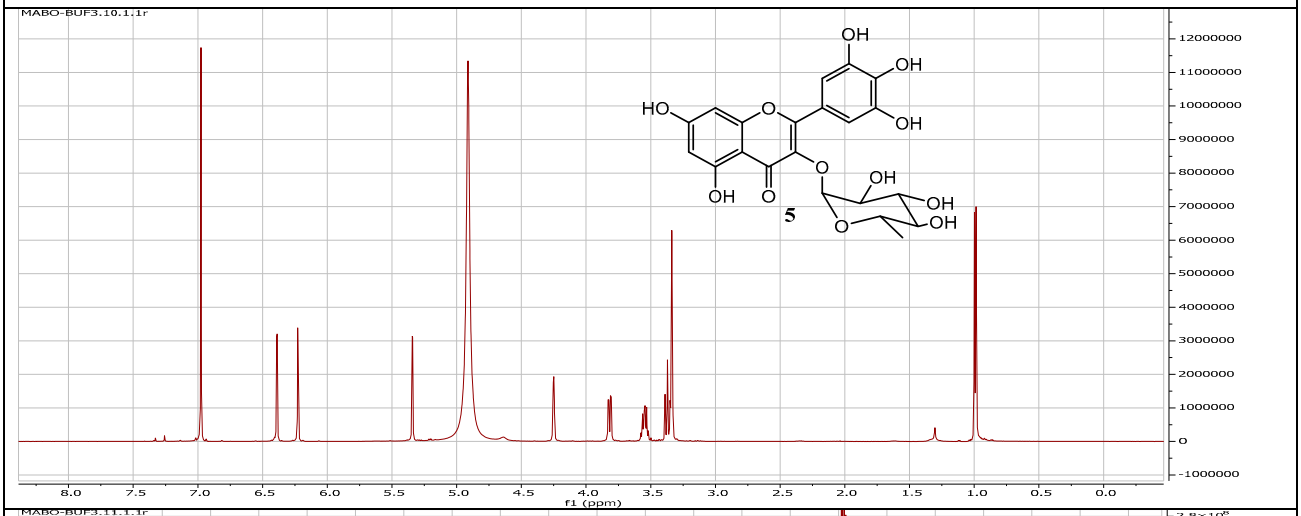

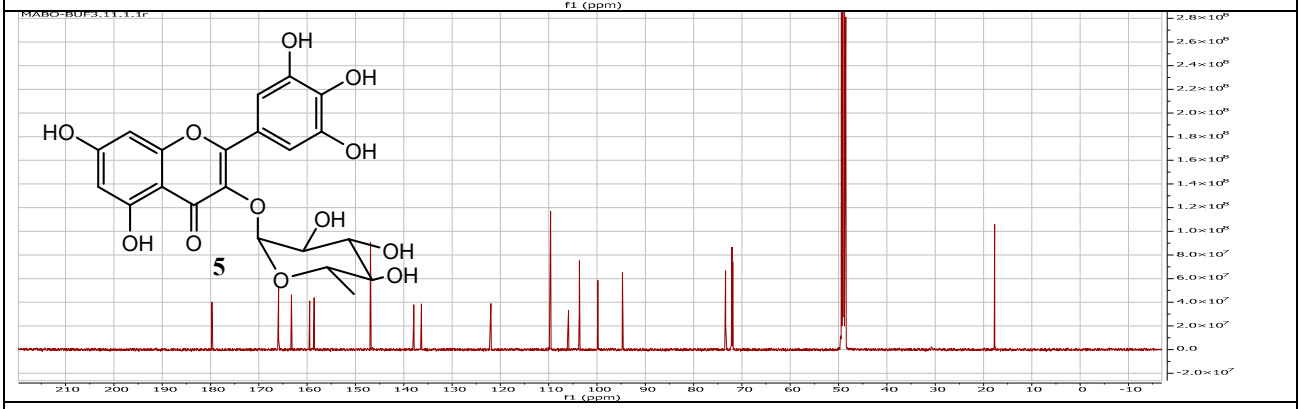

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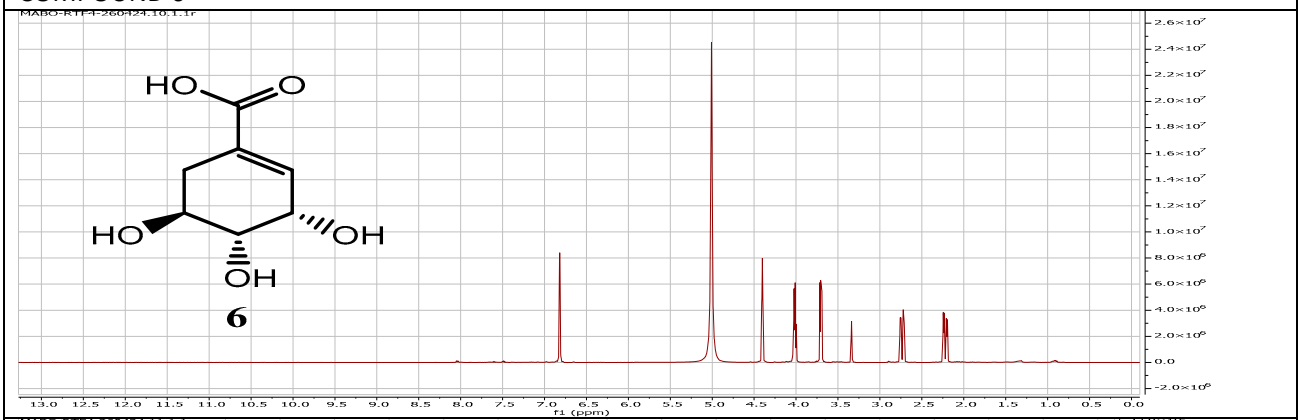

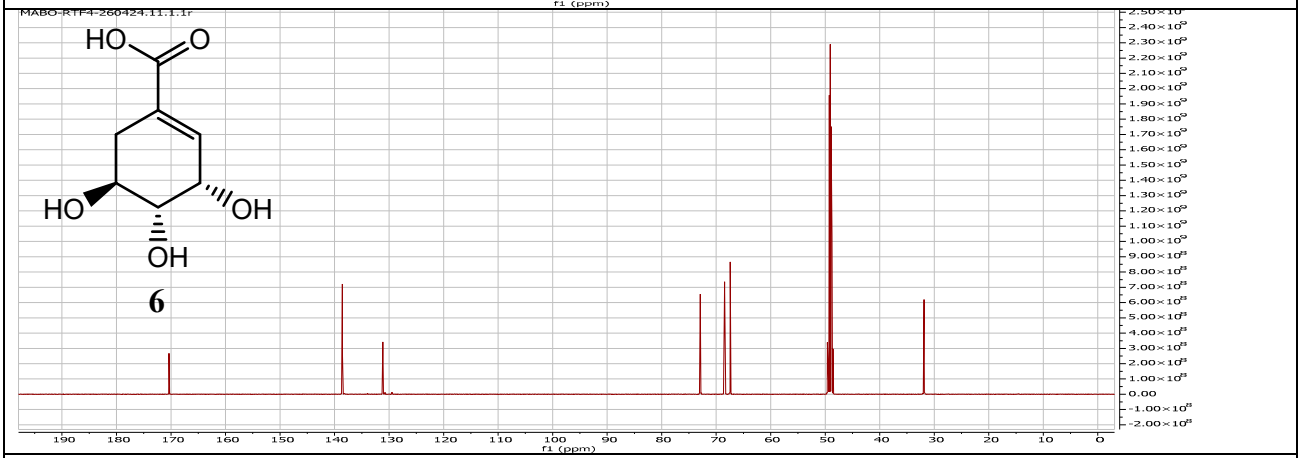

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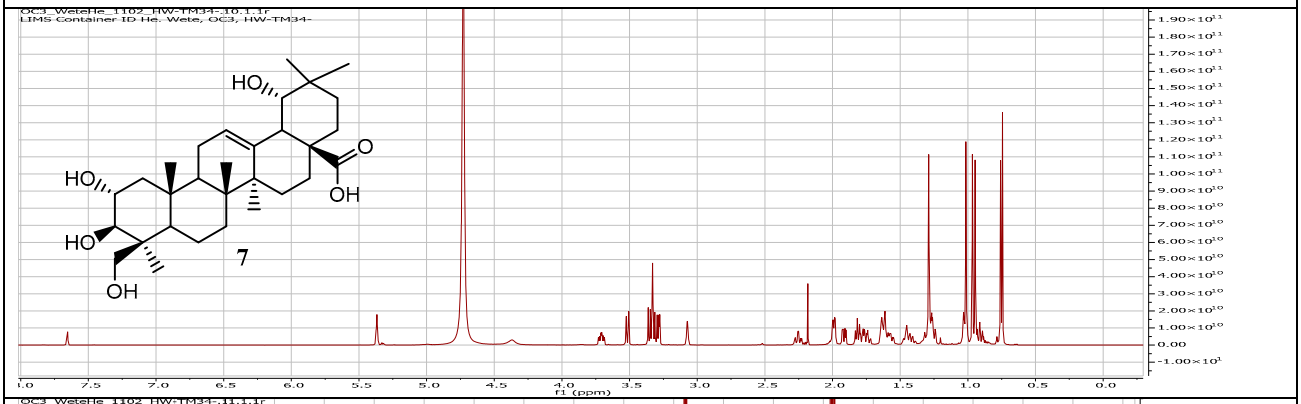

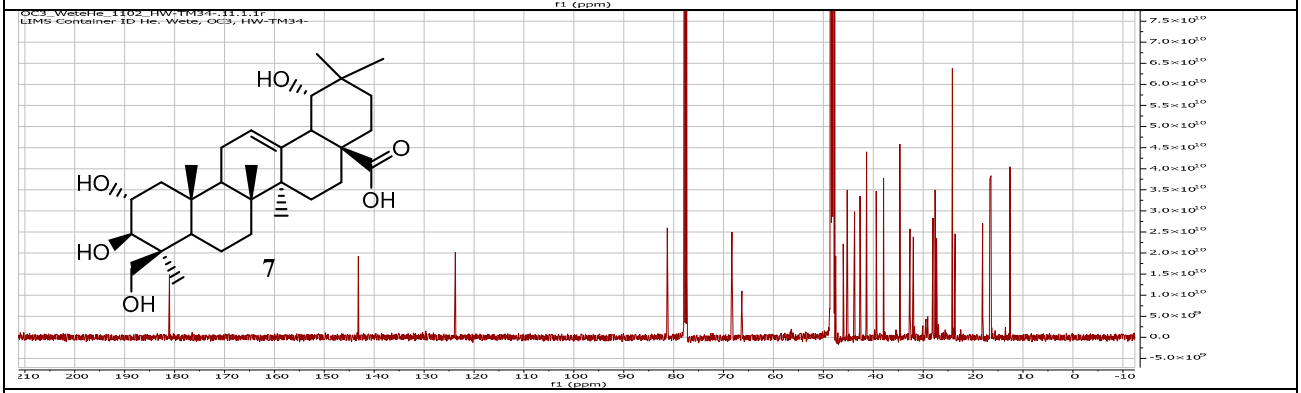

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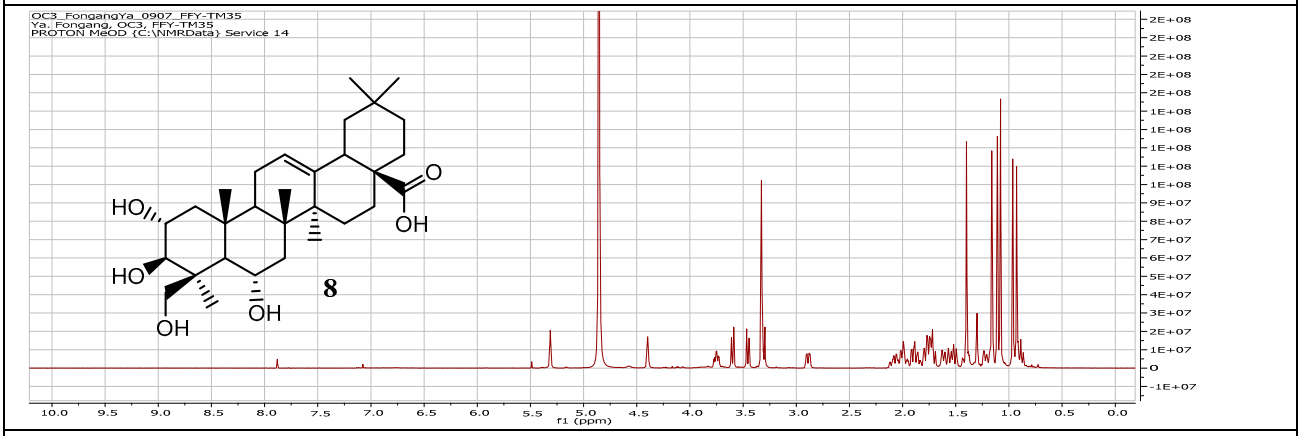

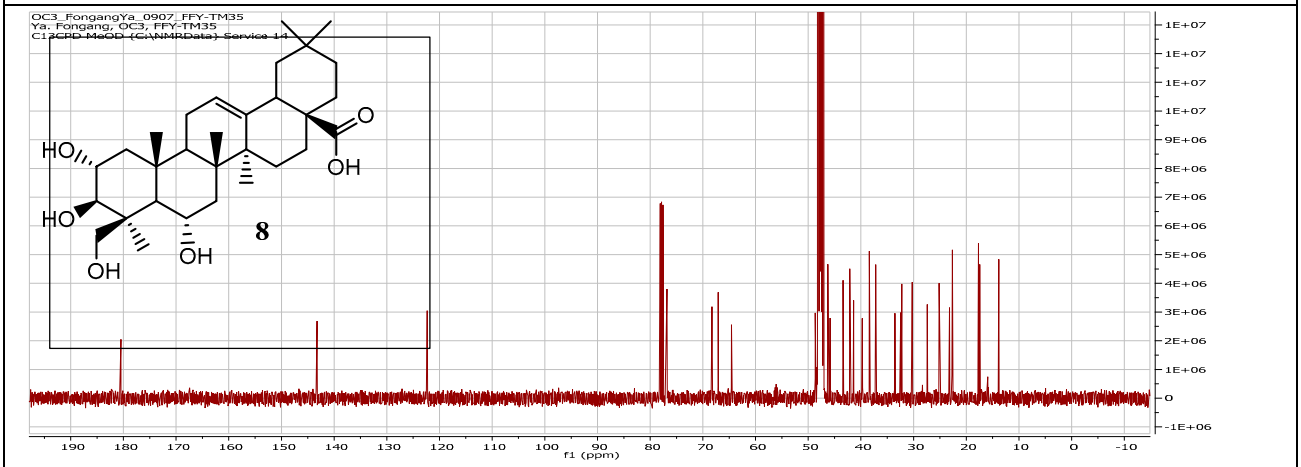

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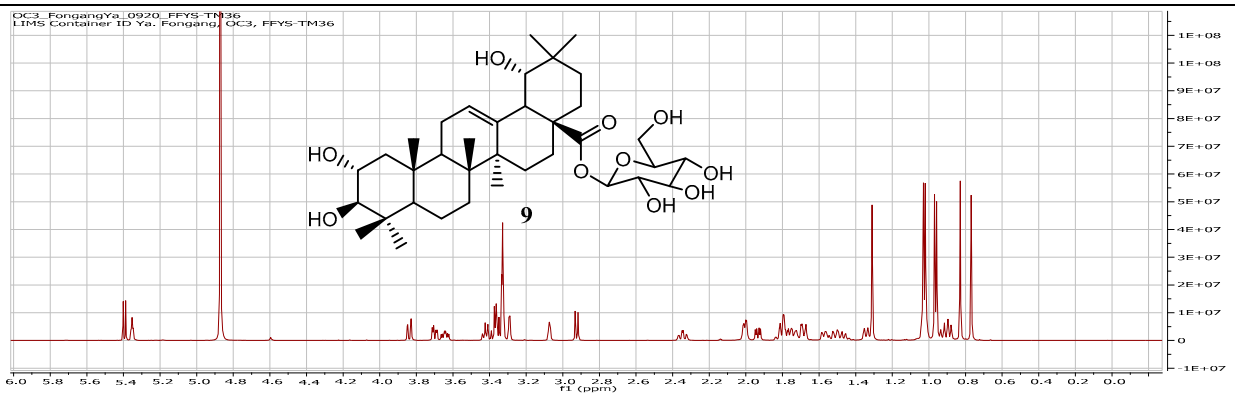

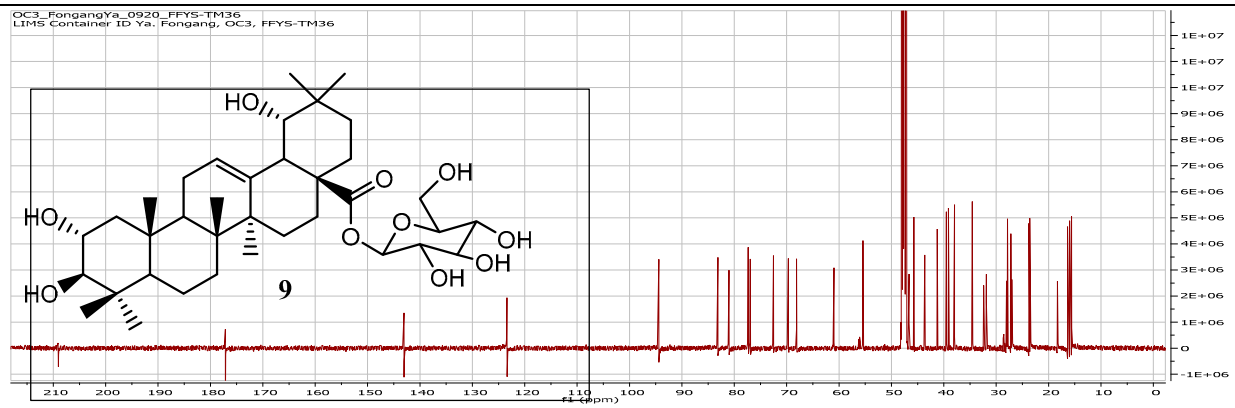

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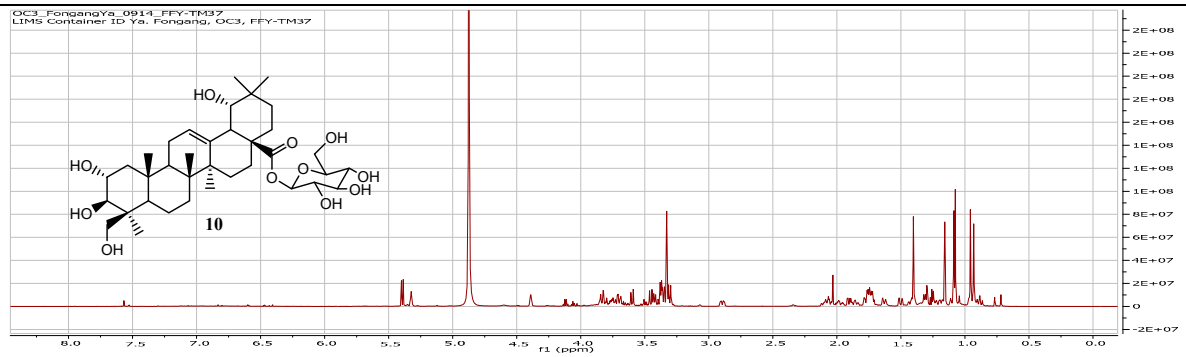

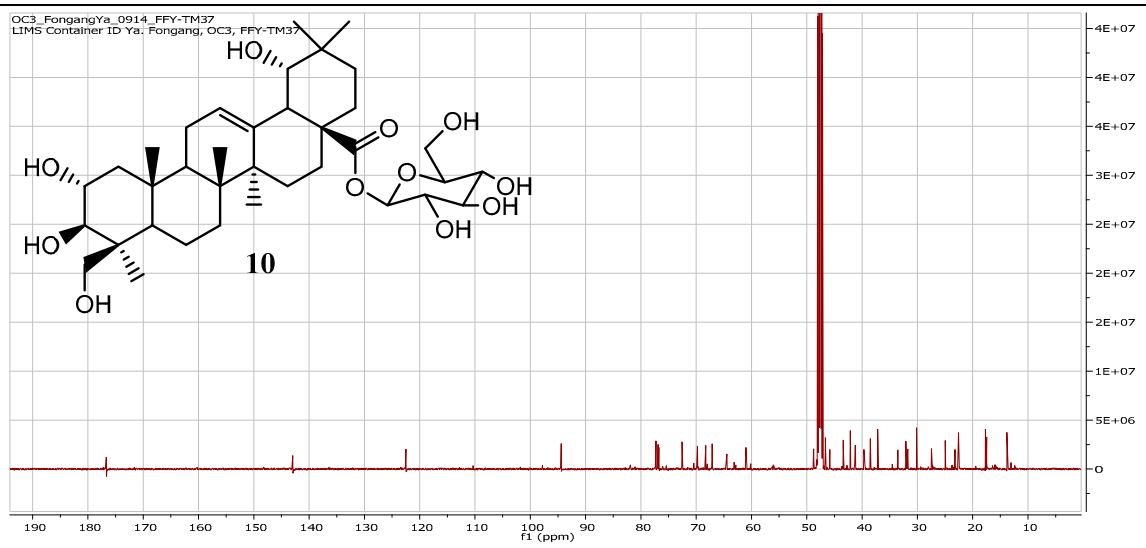

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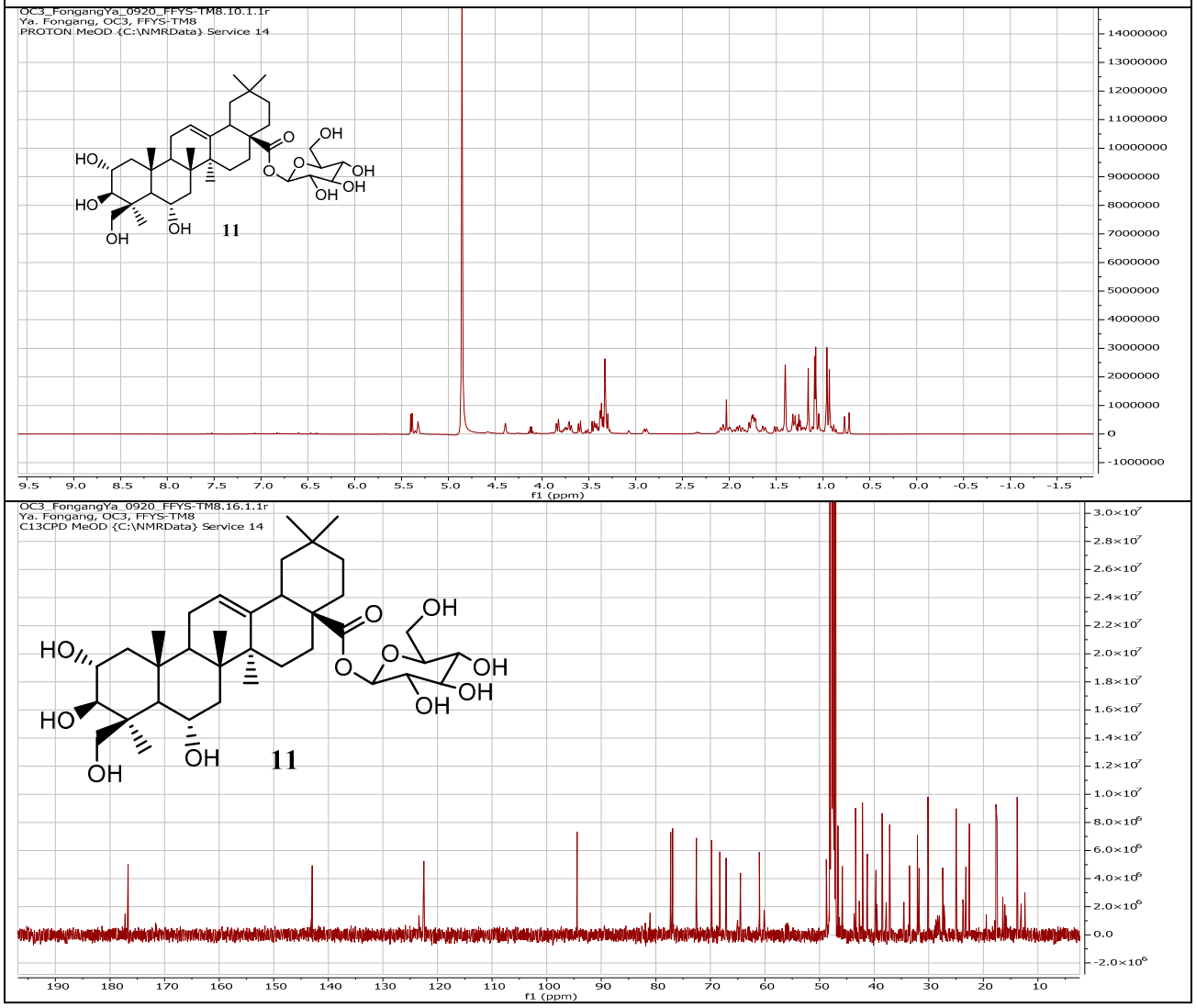
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