SUPPORTING INFORMATION

Aspirin Vs Ibuprofen: Unveiling Distinct Cyclooxygenase-1/2 Behaviour and Dual Efficacy of Their Synthesized Analogues via Molecular Modeling and *In-Vitro* Biological Assessment

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Scheme S1. Synthesis of intermediate (iii)

Figure S1. IR, ^{1}H-NMR, ^{13}C-NMR and HRMS spectra of Compound 1.

Figure S2. IR, ^{1}H-NMR, ^{13}C-NMR and HRMS spectra of Compound 2.

Figure S3. IR, ^{1}H-NMR, ^{13}C-NMR and HRMS spectra of Compound 3.

Figure S4. IR, ^{1}H-NMR, ^{13}C-NMR and HRMS spectra of Compound 4.

Figure S5. IR, ^{1}H-NMR, ^{13}C-NMR and HRMS spectra of Compound 6.

Figure S6. IR, ^{1}H-NMR, ^{13}C-NMR and HRMS spectra of Compound 7.

Figure S7. IR, ^{1}H-NMR, ^{13}C-NMR and HRMS spectra of Compound 8.

Figure S8. IR, ^{1}H-NMR, ^{13}C-NMR and HRMS spectra of Compound 11.

Figure S9. IR, ^{1}H-NMR, ^{13}C-NMR and HRMS spectra of Compound 12.

Figure S10. List of compounds with inappropriate ADMET profile.

Figure S11. 2D diagram showing the redocked poses of celecoxib in the binding pocket of COX-1 and COX-2.

Figure S12. Orientation of celecoxib within the side pocket and main catalytic pocket of COX-2

Figure S13. (A) 3D diagram showing penetration of celecoxib (red), aspirin (green) and ibuprofen (pink) in the side pocket of COX-2. 2D representations of predicted binding modes of celecoxib (B), ibuprofen (C) and aspirin (D).

Figure S14. 2D interaction diagrams of aspirin and ibuprofen with the key residues of COX-1 binding pocket.

Figure S15. Correlation of Normalized Docking Score and number of heavy atoms

Figure S16. RMSD plots of compounds 3, 12, and Aspirin with COX-1 during the 2nd (A) and 3rd (B) replica Simulation.

Figure S17. RMSD plots of compounds 3, 12, and Aspirin with COX-2 during the 2nd (A) and 3rd (B) replica Simulation.

Figure S18. RMSF plots of compounds 3 (red), 12 (green), and aspirin (black) with COX-1 during the 2nd (A) and 3rd (B) replica Simulation.

Figure S19. RMSF plots of compounds 3 (red), 12 (green), and aspirin (black) with COX-2 during the 2nd (A) and 3rd (B) replica Simulation.

Figure S20. The hydrogen bonding population graph between inhibitors and COX-1 in three replicas of 100 ns Simulations .

Figure S21: The hydrogen bonding population graph between inhibitors and COX-2 in three replicas of 100 ns Simulations.

Figure S22. Cumulative diagram of RMSD, RMSF, and binding-free energy of compounds 3, 12, and aspirin with COX-1 and COX-2 during three replica simulations

Figure S23. Data for the calculation of IC50 value of compounds 3, 12, and aspirin with COX-1 enzyme.

Figure S24. Data for the calculation of IC50 value of compounds 3, 12, and aspirin with COX-2 enzyme.

Figure S25. Data for the calculation of IC50 value of compounds 3, 12, and aspirin for the antiplatelet activity.

Figure S26. Structures of newly synthesized compounds with numbering.

Table S1. ADMET features of compounds other than those selected for synthesis.

Table S2. Predicted physicochemical, medicinal, excretion and toxicological parameters from SwissADME, Osiris DataWarrior and ADMETlab tools

Table S3. Interactions of compounds 3,12, aspirin, ibuprofen, and celecoxib with COX-1 from Discovery Studio Visualizer

Table S4. Interactions of compounds 3,12, aspirin, ibuprofen, and celecoxib with COX-2 from Discovery Studio Visualizer

Table S5. Average RMSD analysis of compounds 3, 12, and aspirin with COX-1 and COX-2 isozymes during the three replicas.

Table S6. Average RMSF analysis of compounds 3, 12, and aspirin with COX-1 and COX-2 isozymes during the three replicas.

Table S7. Binding free energy components of COX-1 and Aspirin.

Table S8. Binding free energy components of *COX-1,* and Compound 3.

Table S9. Binding free energy components of COX-1 and Compound 12.

Table S10. Binding free energy components of *COX-2* and Aspirin.

Table S11. Binding free energy components of *COX-2* and Compound 3

Table S12. Binding free energy components of *COX-2* and Compound12

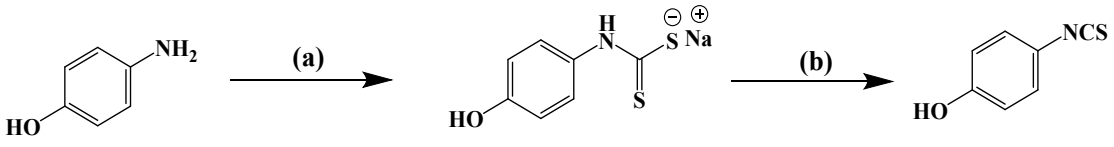
Table S13. Average Binding free energy (kcal/mol) and Docking Energy of Com3, Com12, and Aspirin with COX-1/COX-2 enzyme.

Table S14. The percentage inhibition of compounds 3 , 12, and aspirin against COX-1 and COX-2 enzymes at specific concentrations

Table S15. Percentage inhibition of compounds 3, 12, and aspirin on AA-induced platelet aggregation at specific concentrations

Table S16. SMILEs for compounds are given in the manuscript.

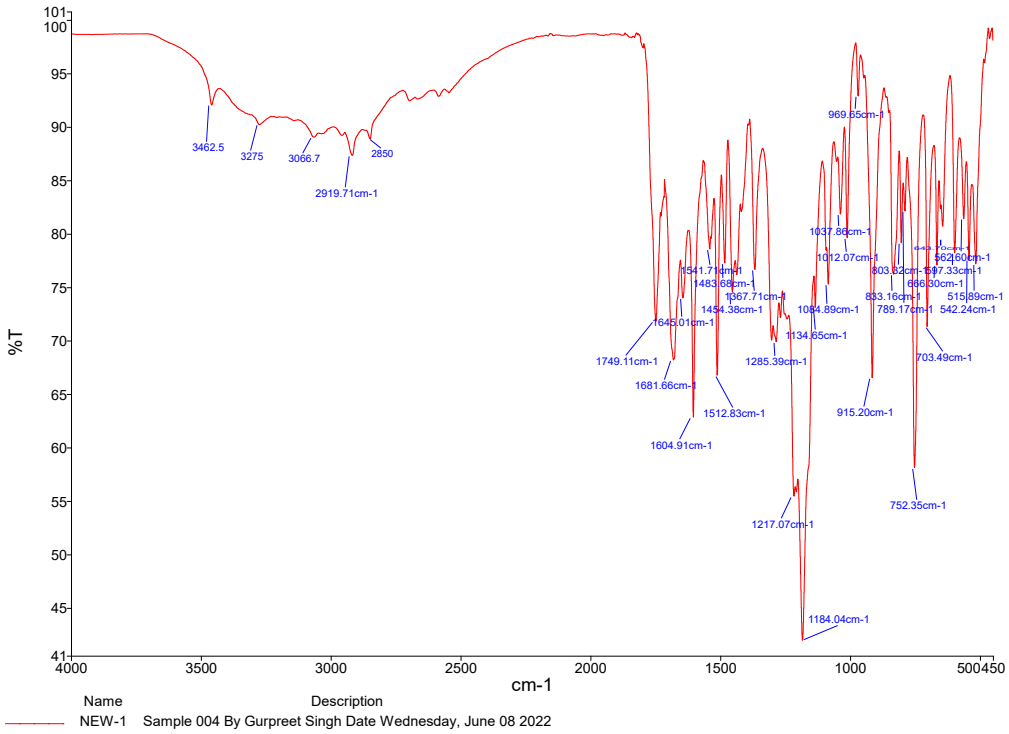
Scheme S1. Synthesis of intermediate (iii)

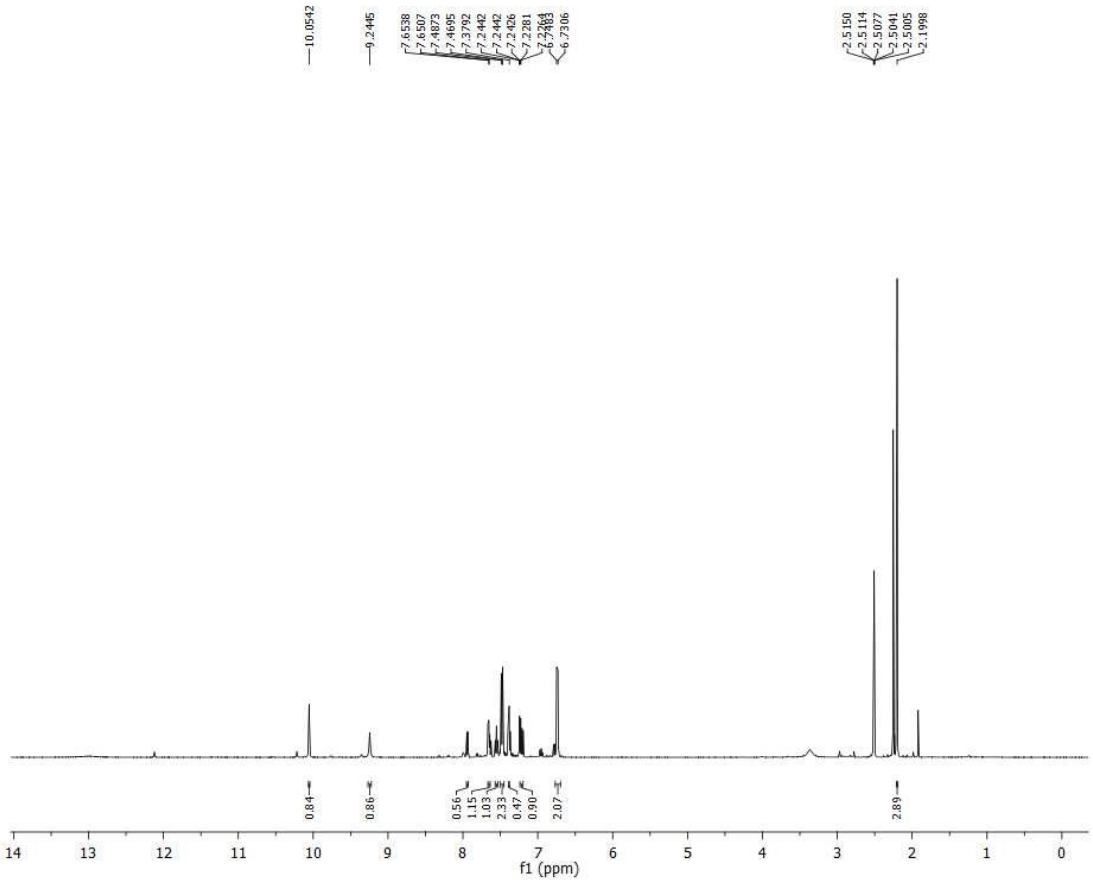


(i) **(ii)** **(iii)**

Reagents and conditions: (a) CS_2, acetone, sodium acetate, rt, stirring 4-5 h; (b) $FeCl_3$, acetone, sodium acetate, rt, stirring 4-5 h.

Figure S1. IR, ^{1}H-NMR, ^{13}C-NMR, and HRMS spectra of Compound 1

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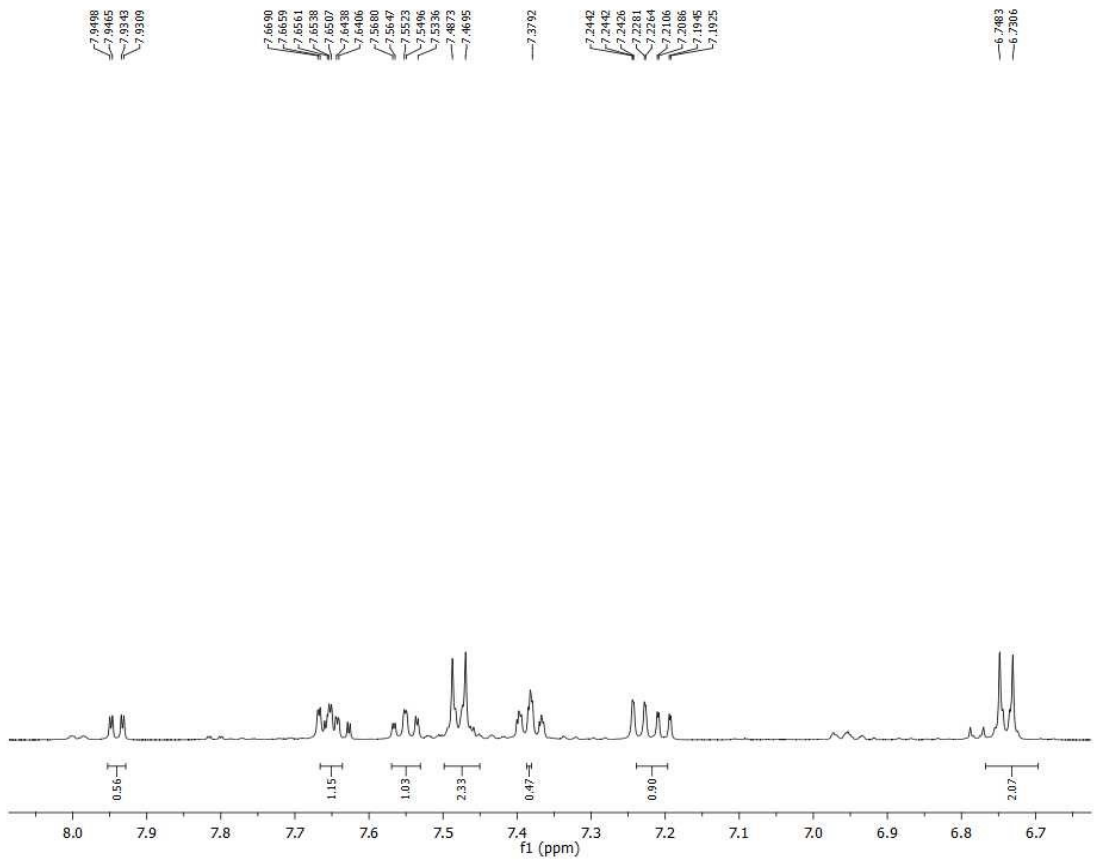
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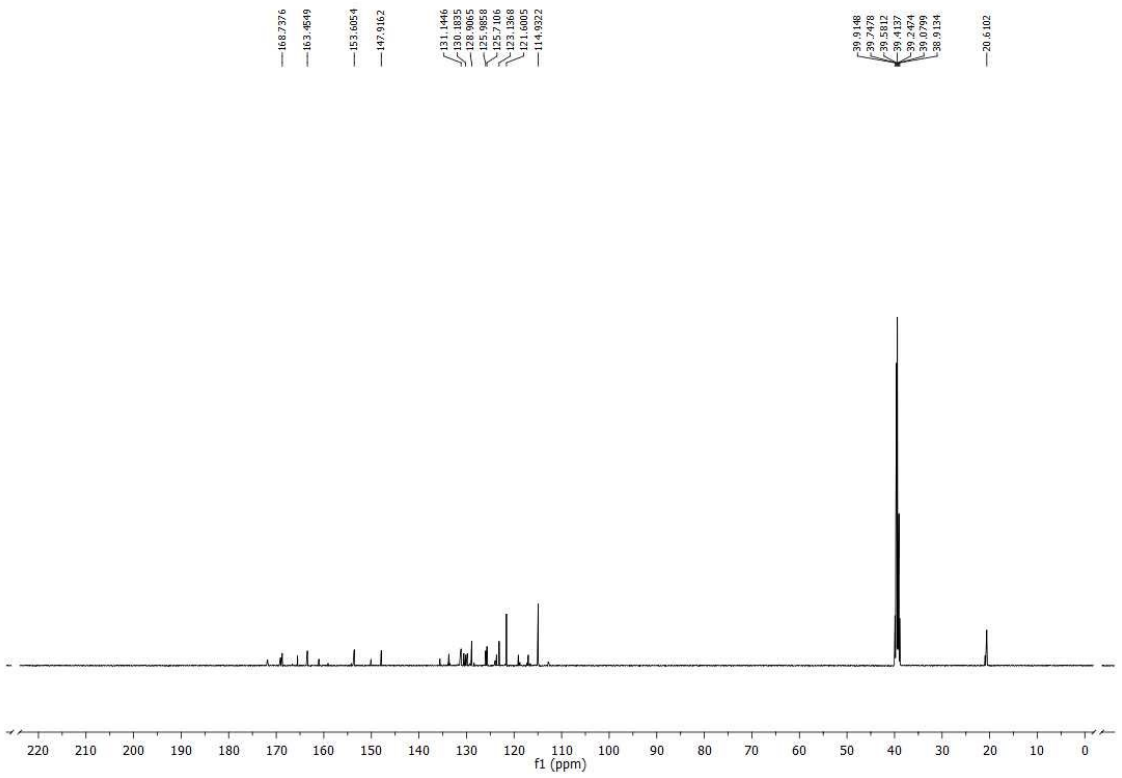

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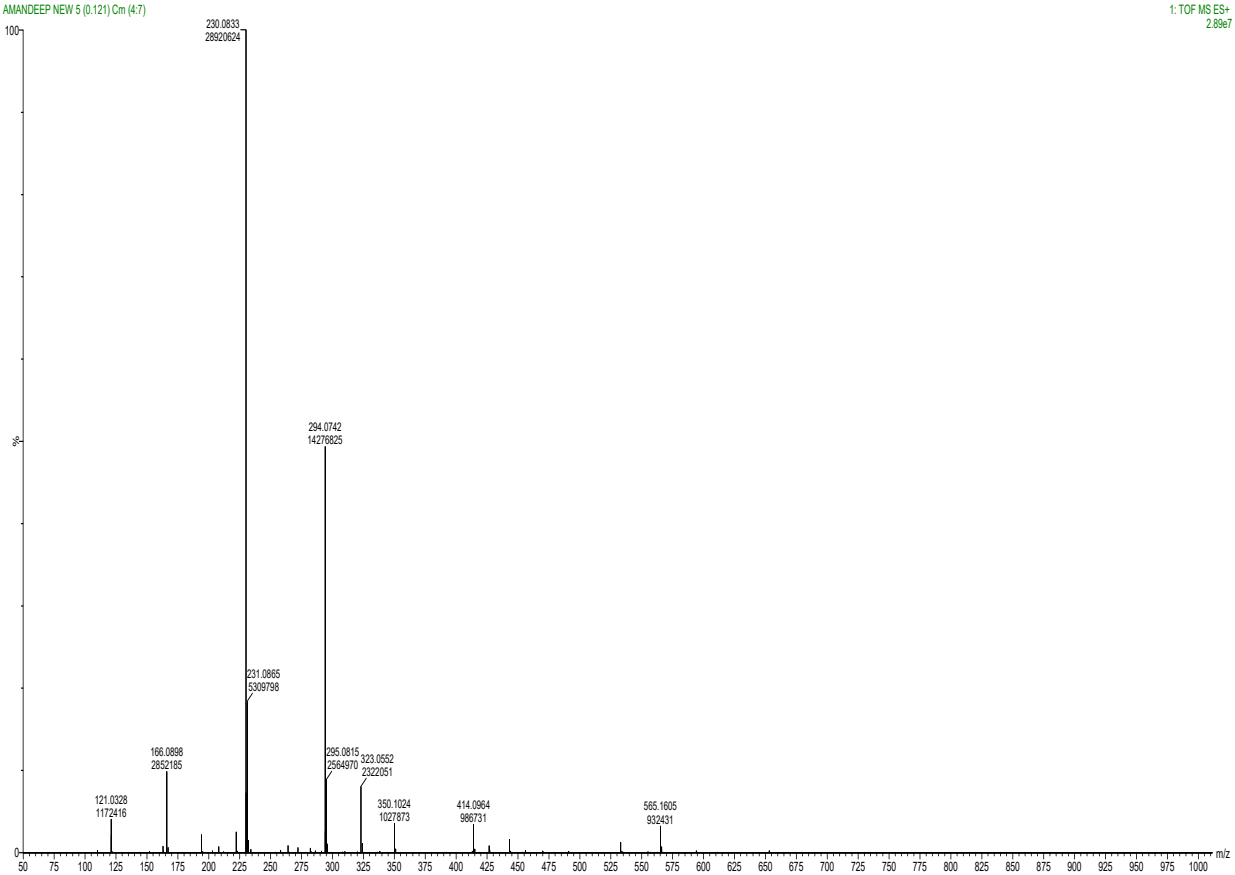

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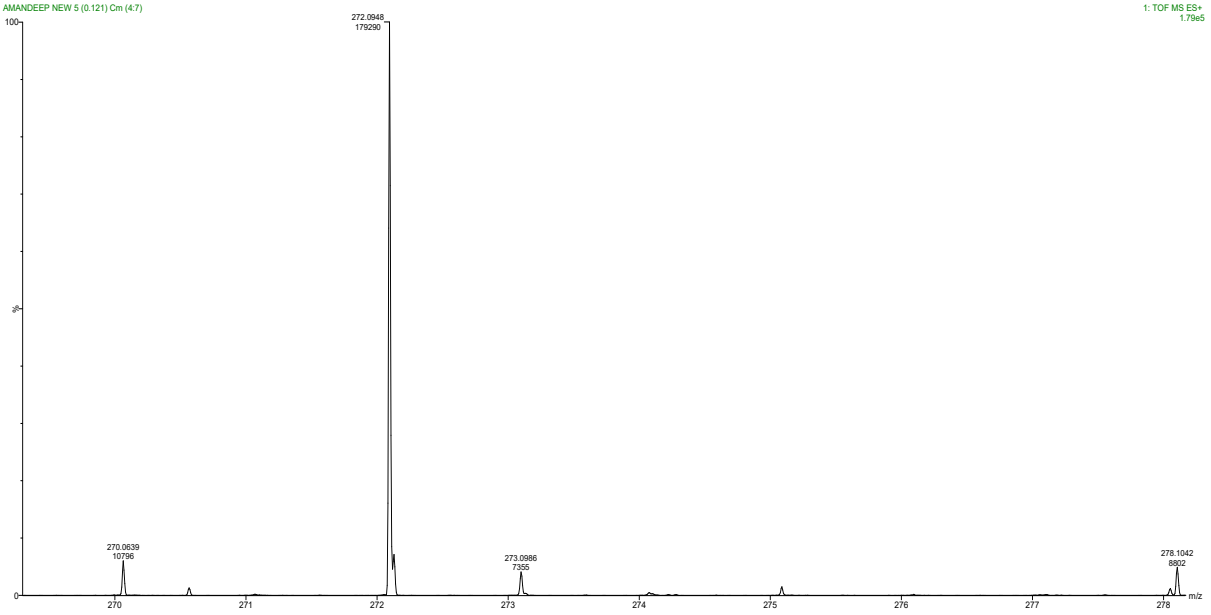

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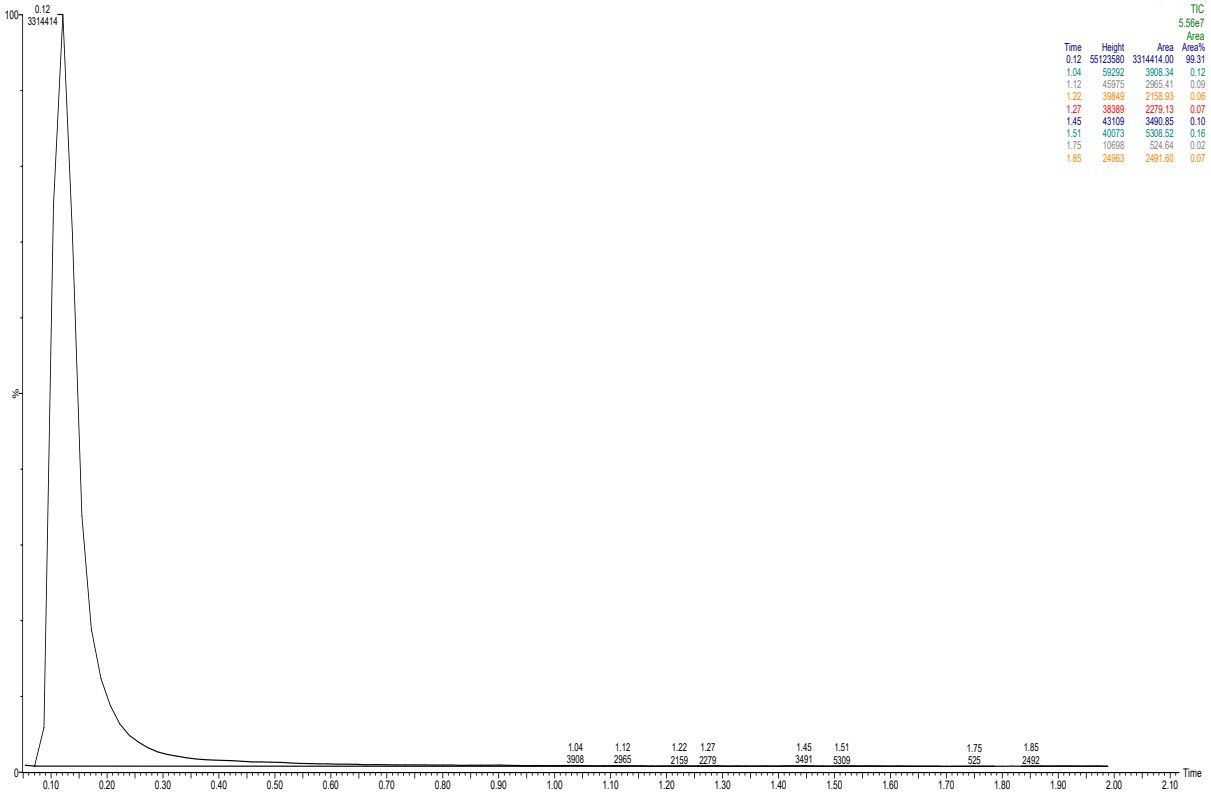

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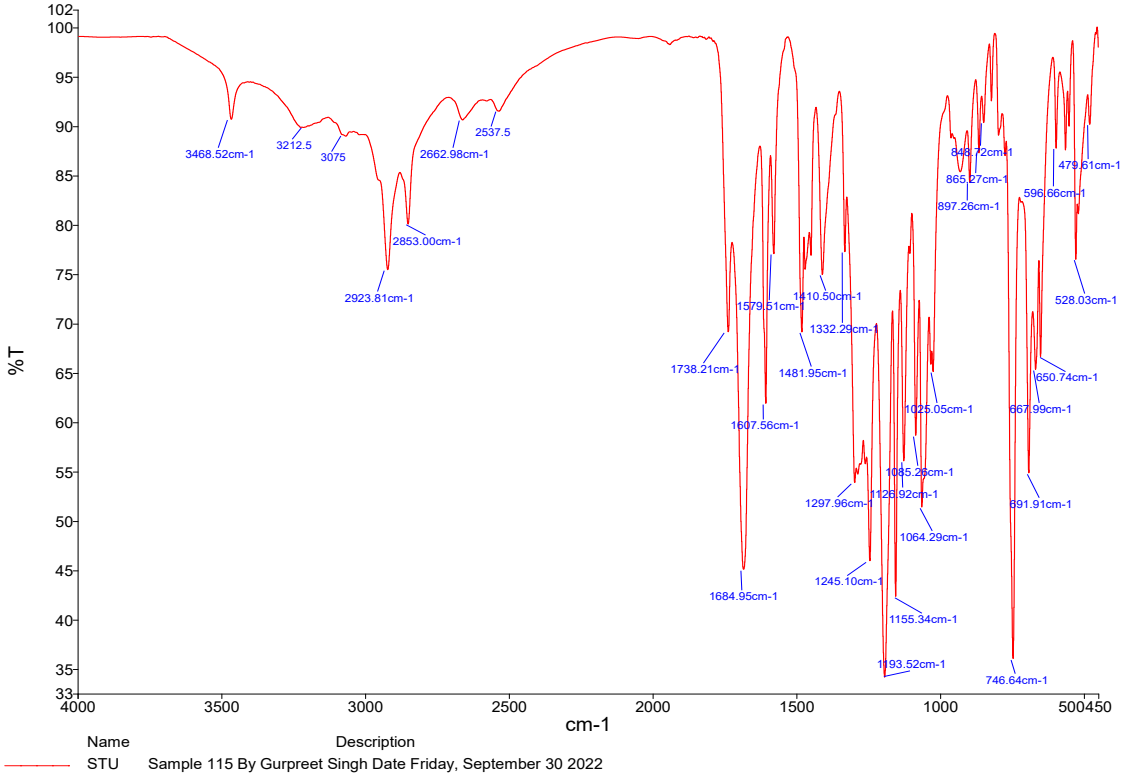
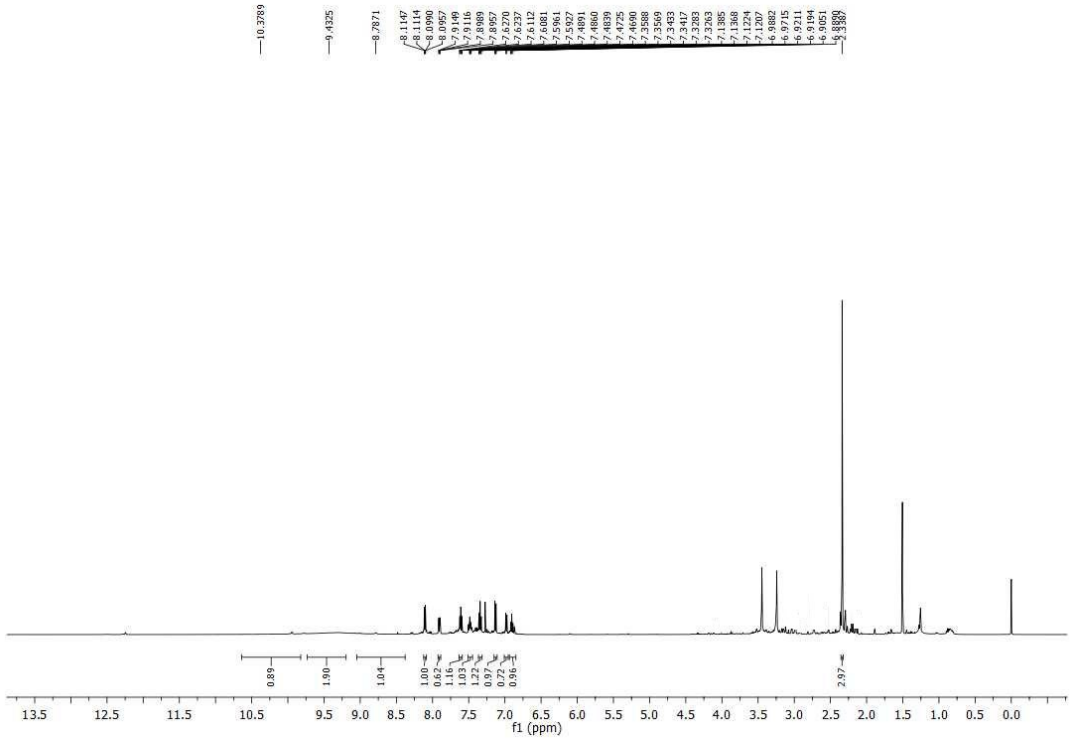
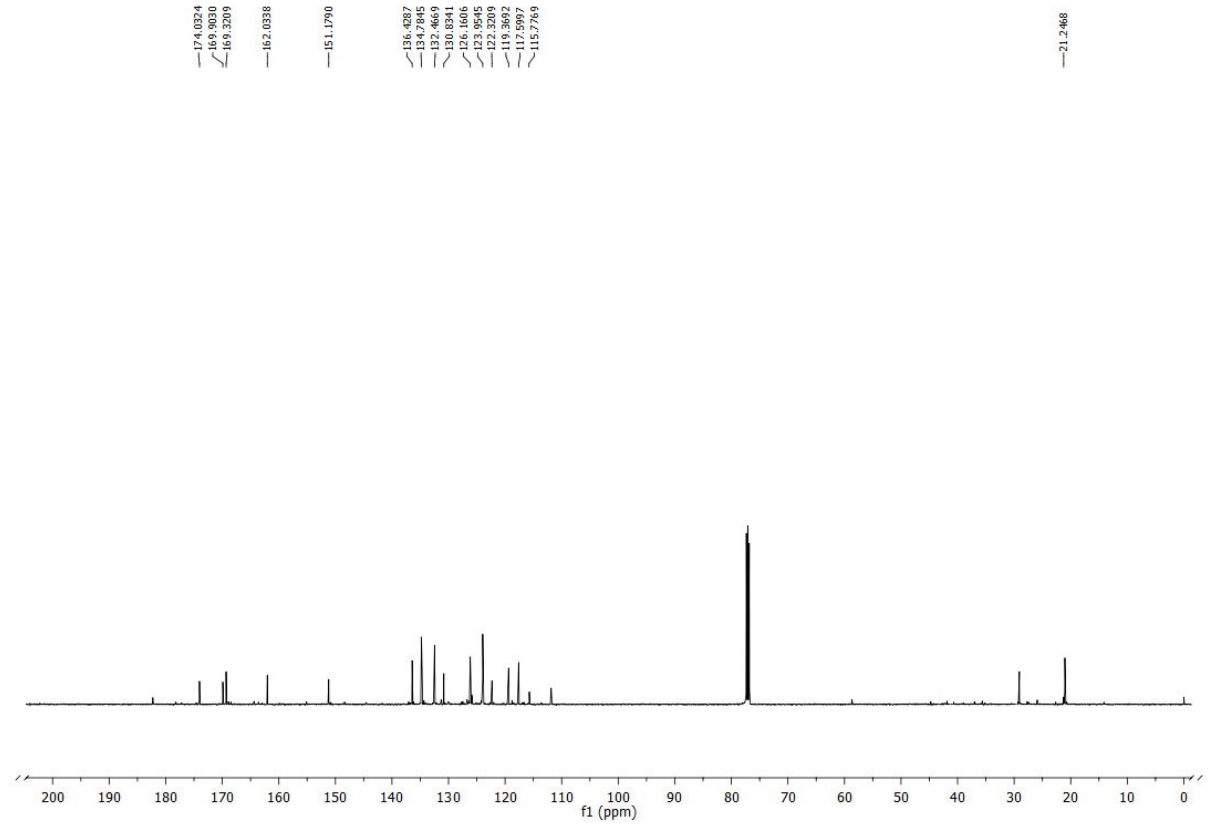
Figure S2. IR, ^{1}H-NMR, ^{13}C-NMR, and HRMS spectra of Compound 2.



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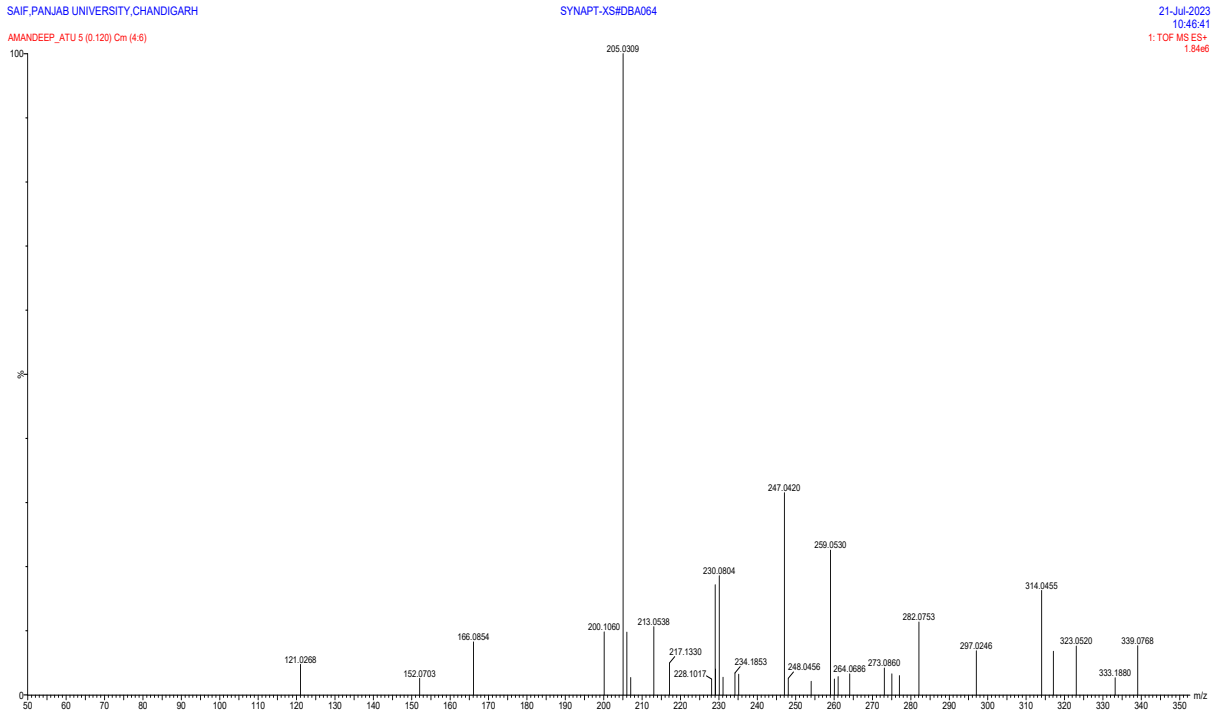
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SAIF,PANJAB UNIVERSITY,CHANDIGARH

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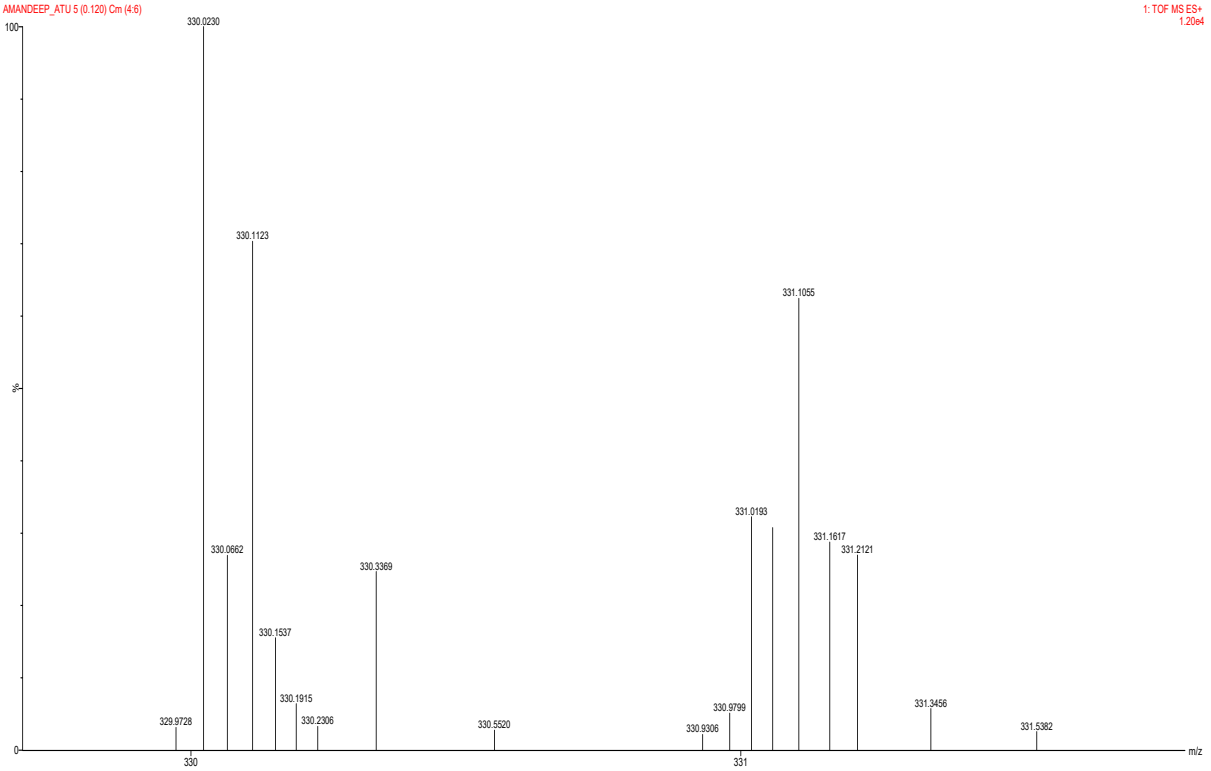

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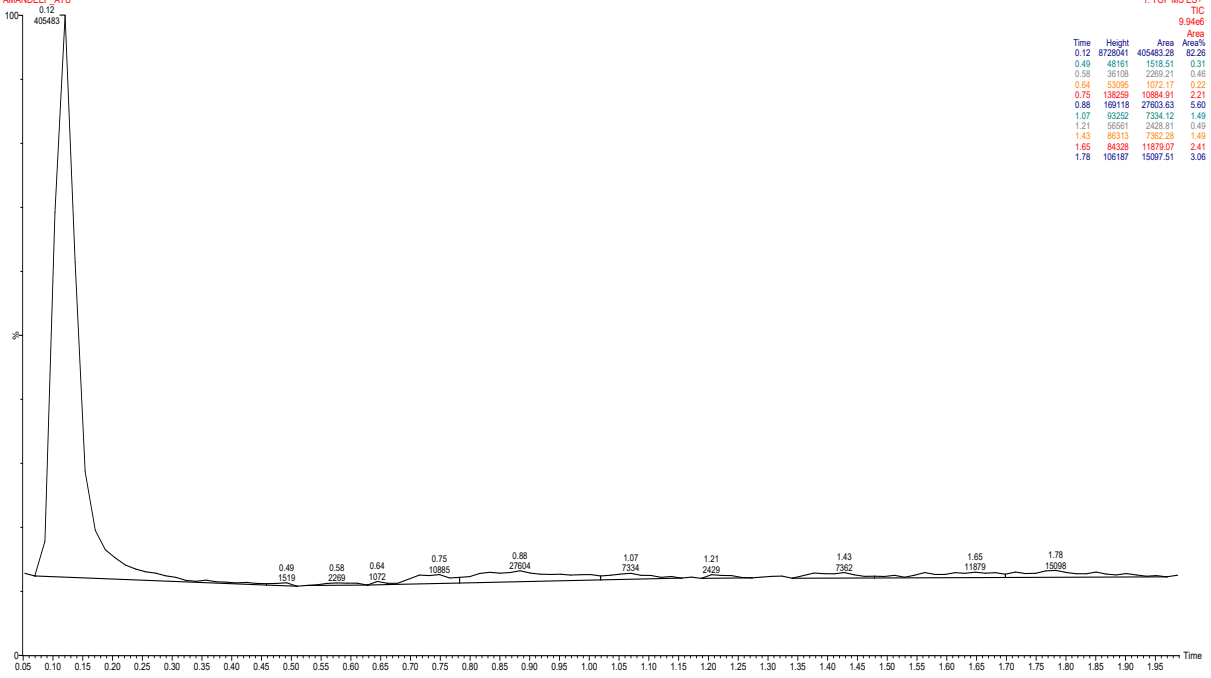
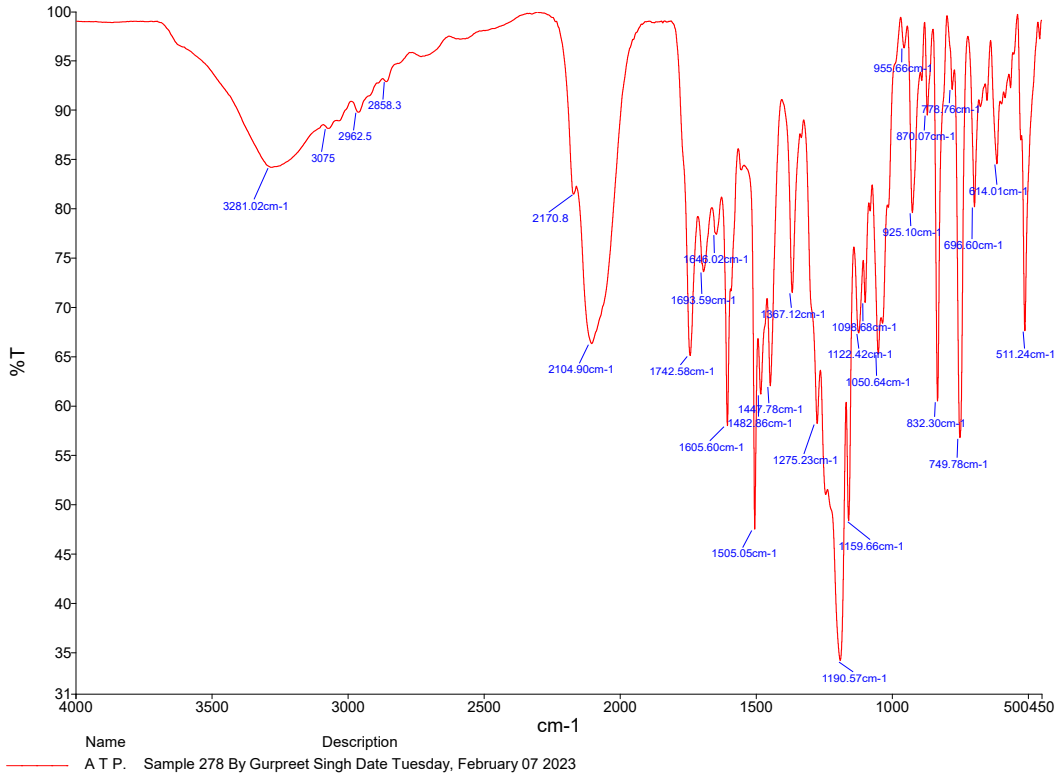
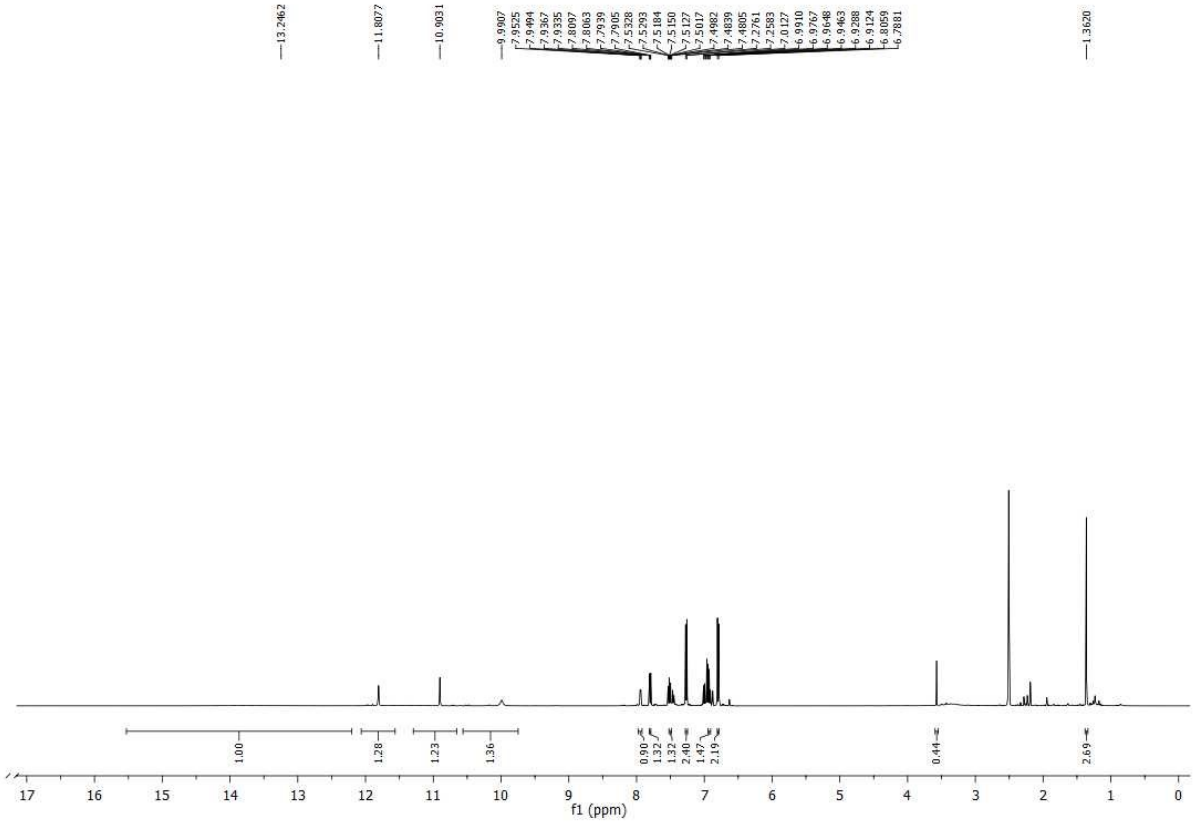
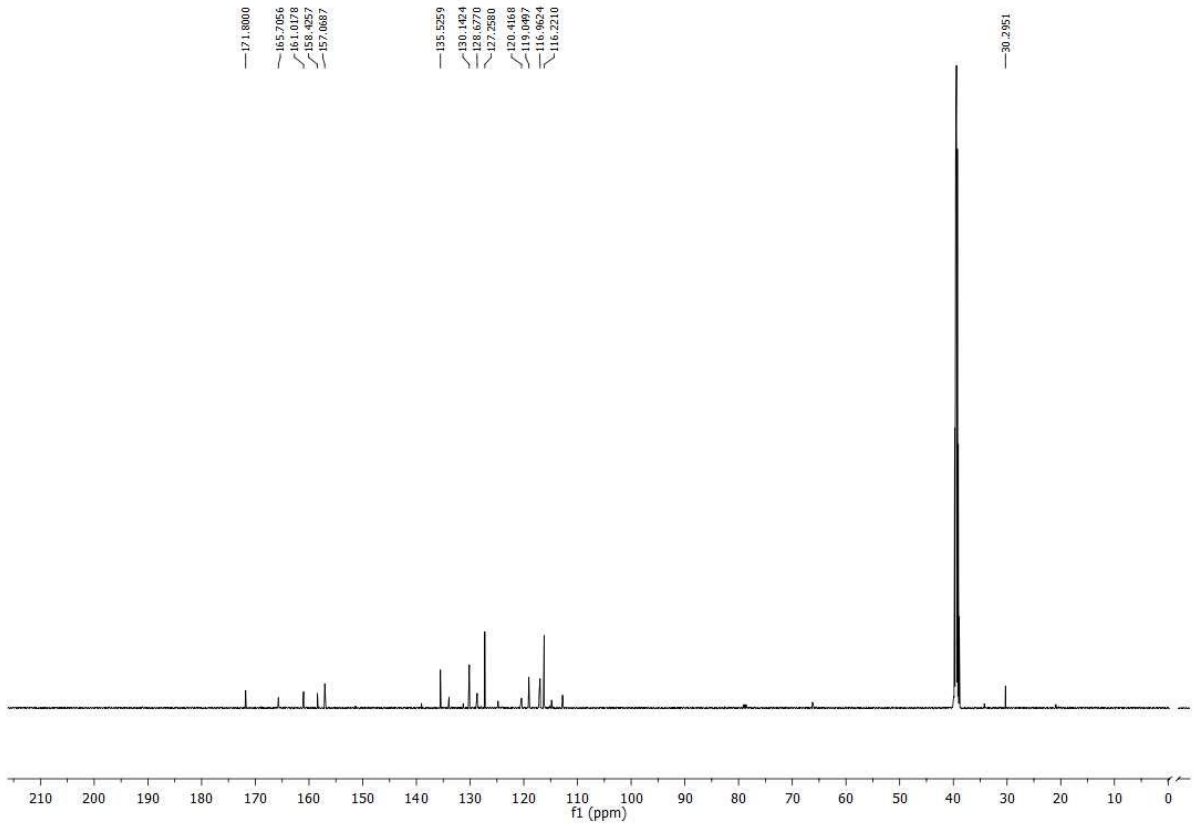


Figure S3. IR, ^{1}H-NMR, ^{13}C-NMR, and HRMS spectra of Compound 3.



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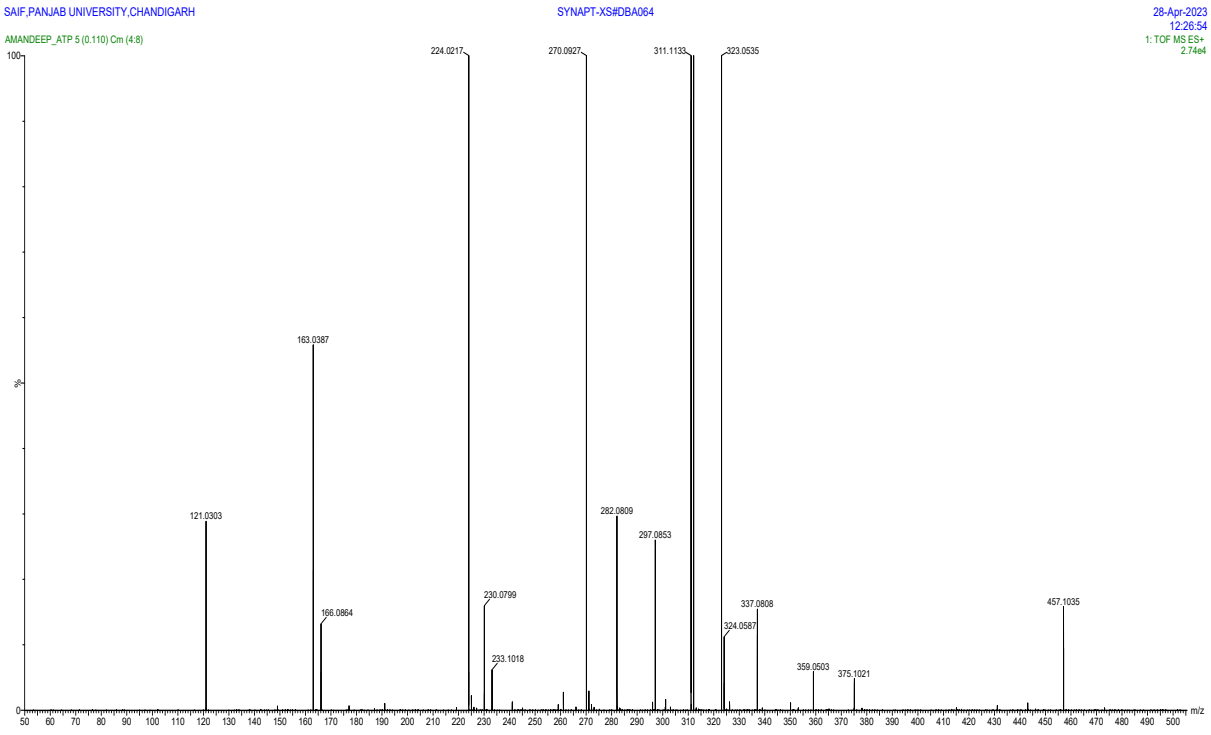
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SAIF,PANJAB UNIVERSITY,CHANDIGARH

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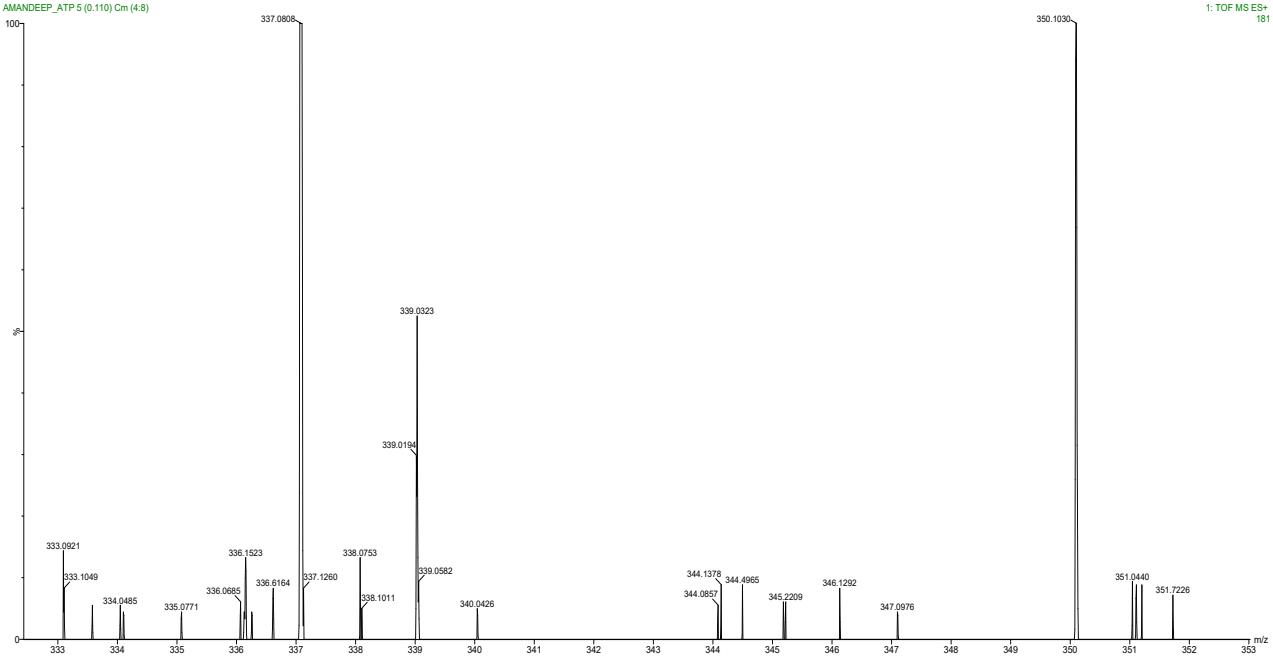

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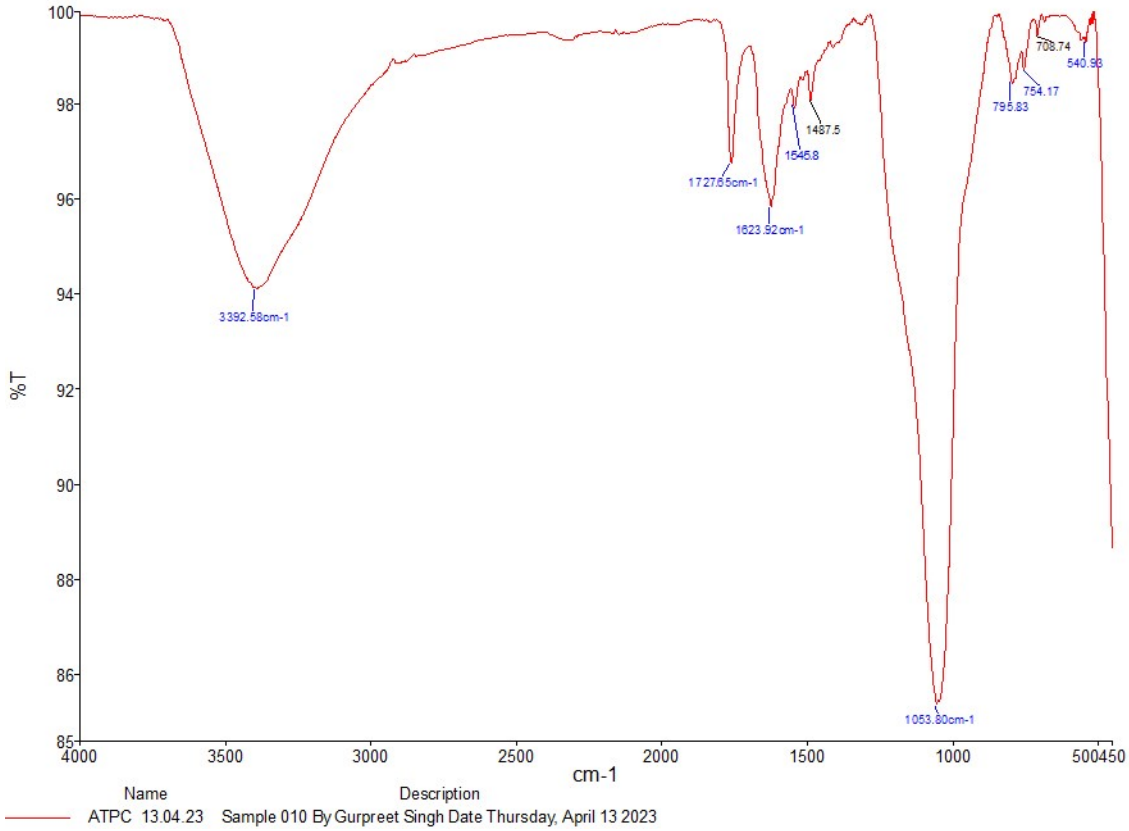

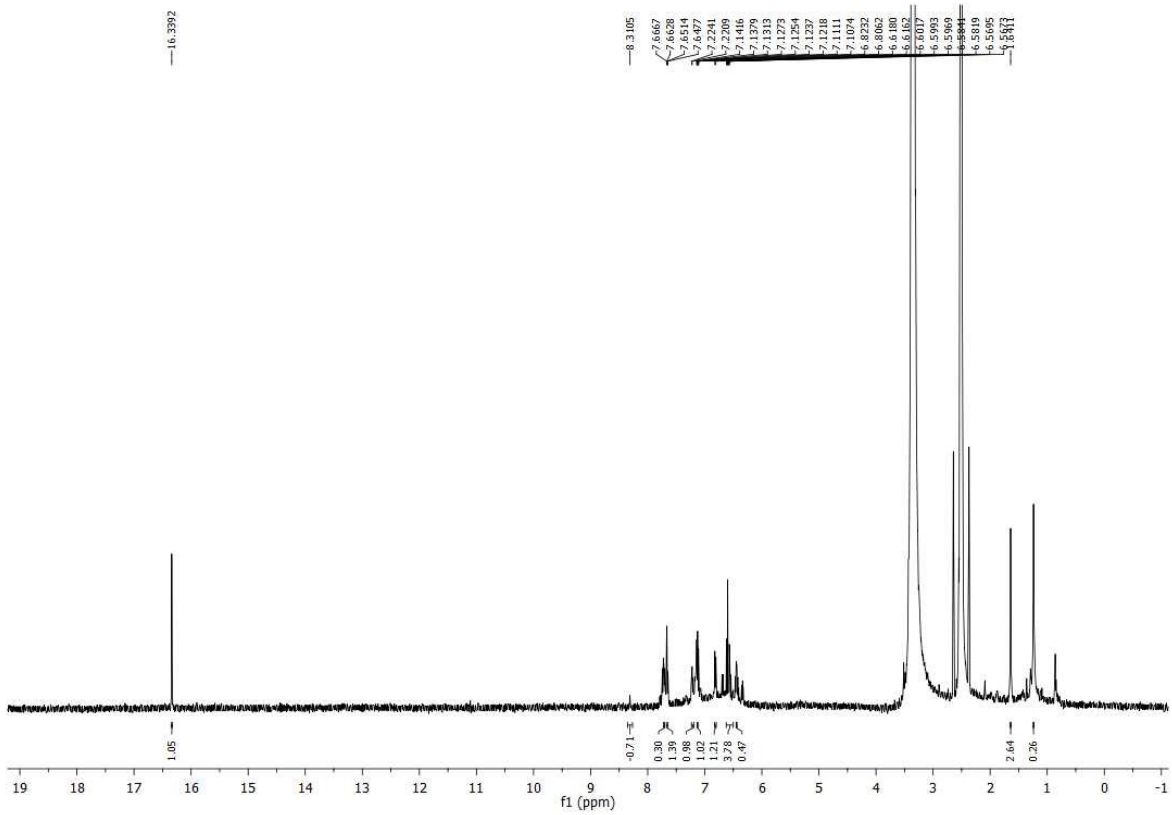

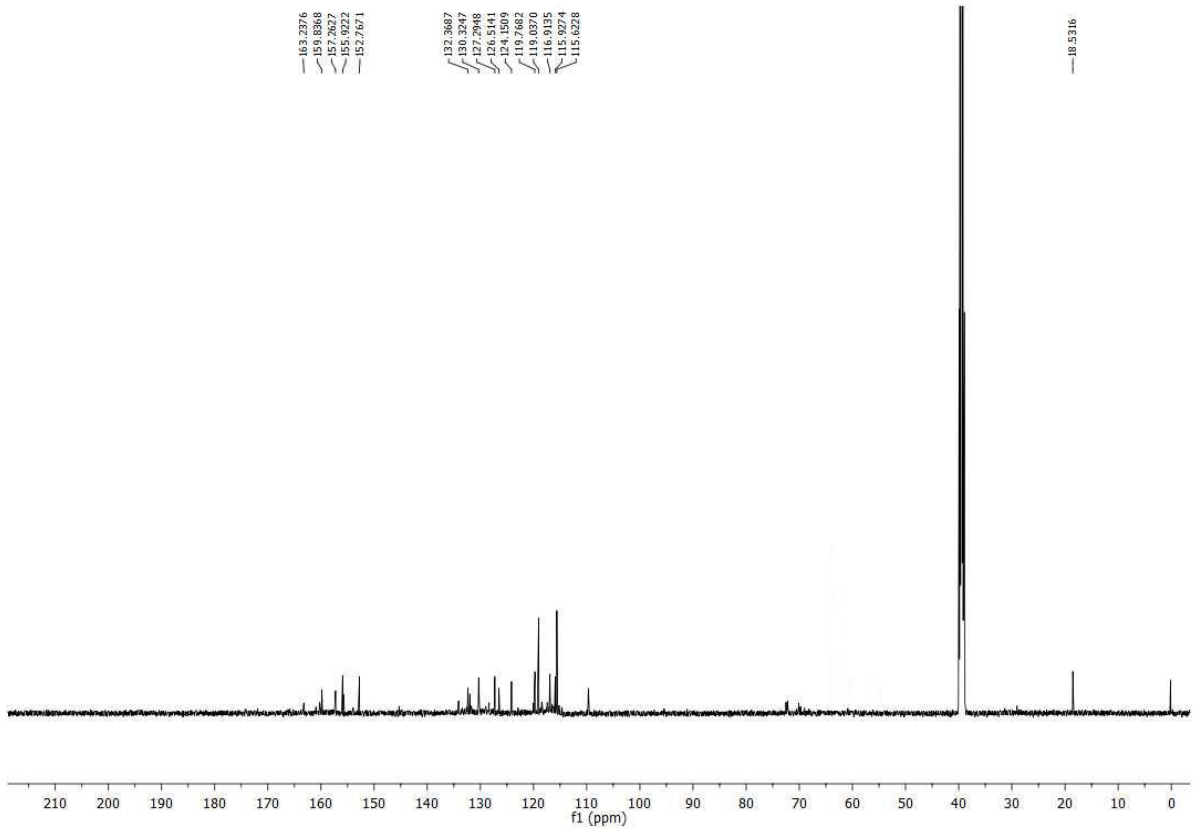

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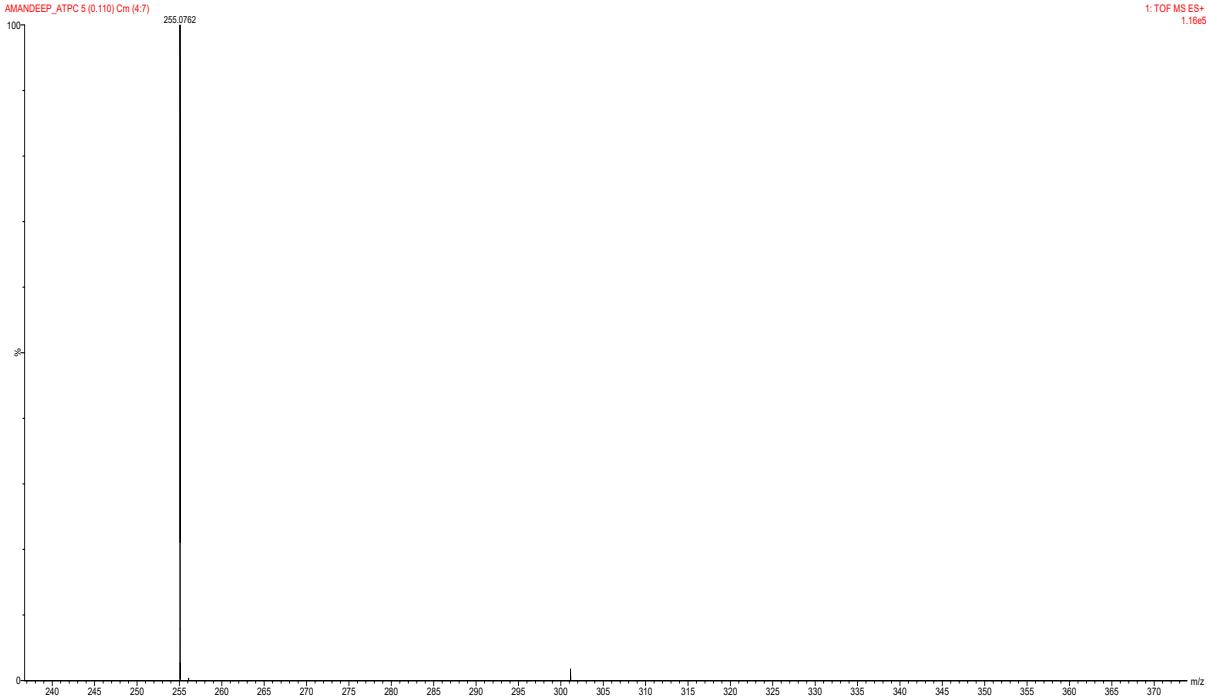

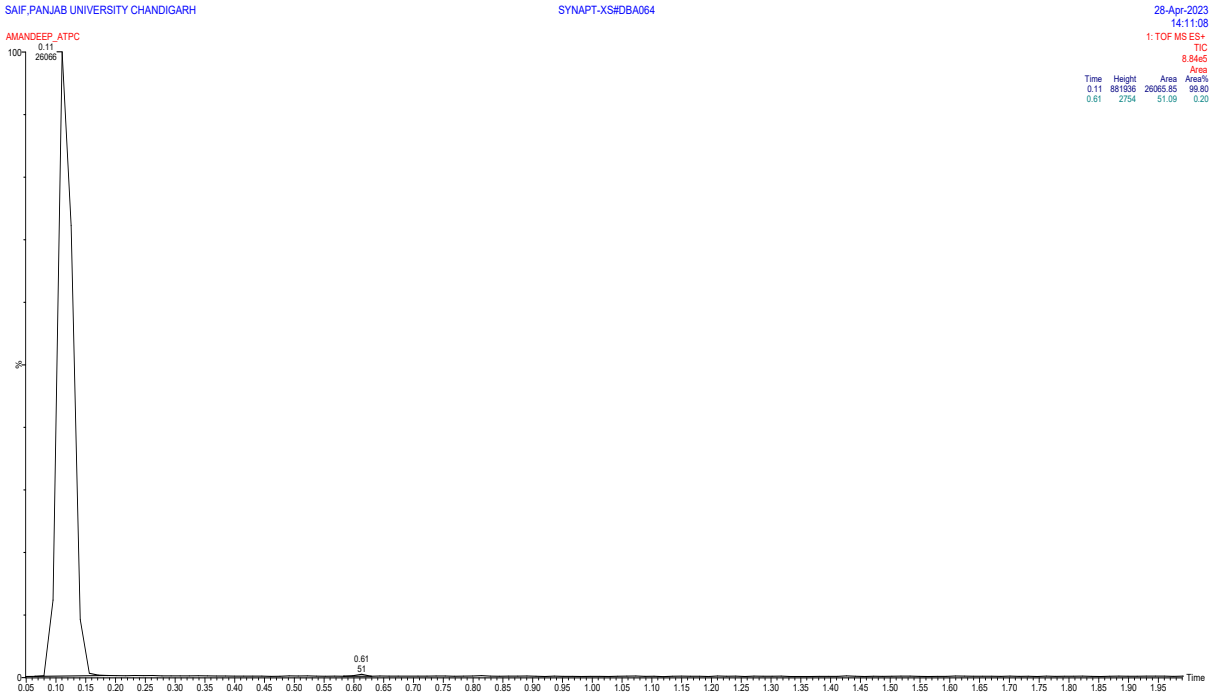

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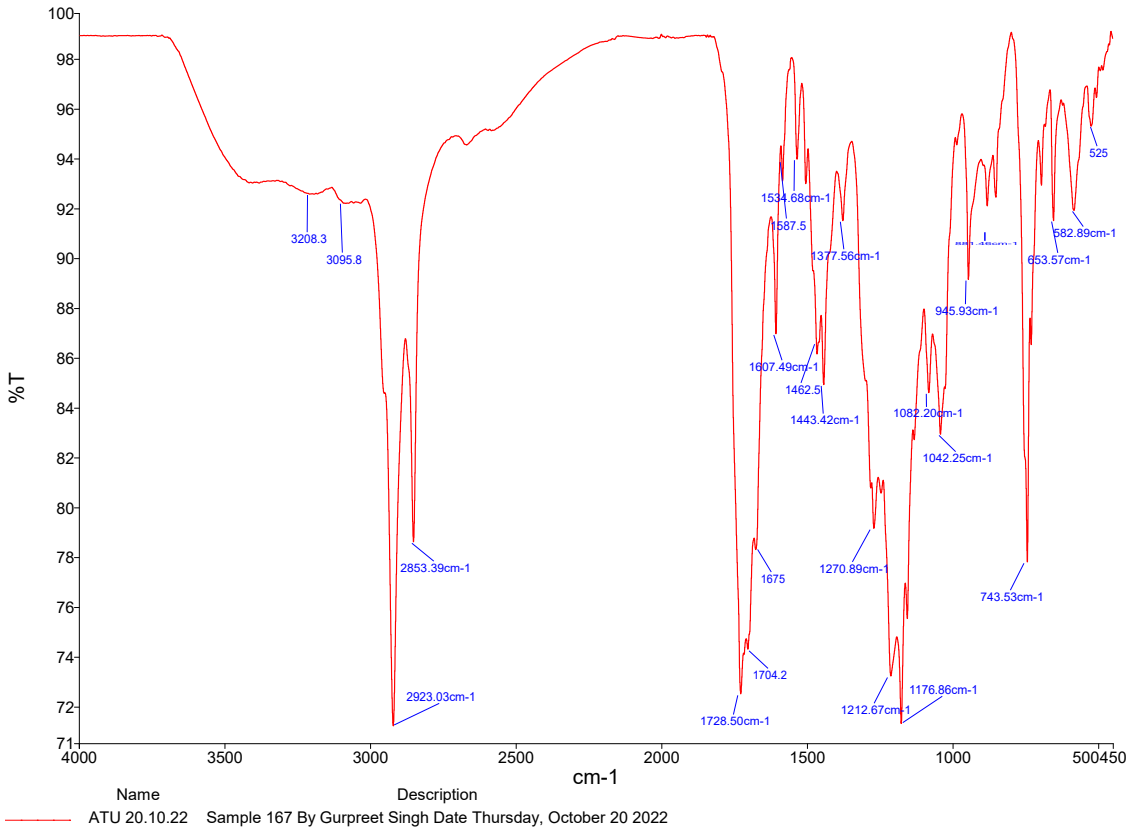

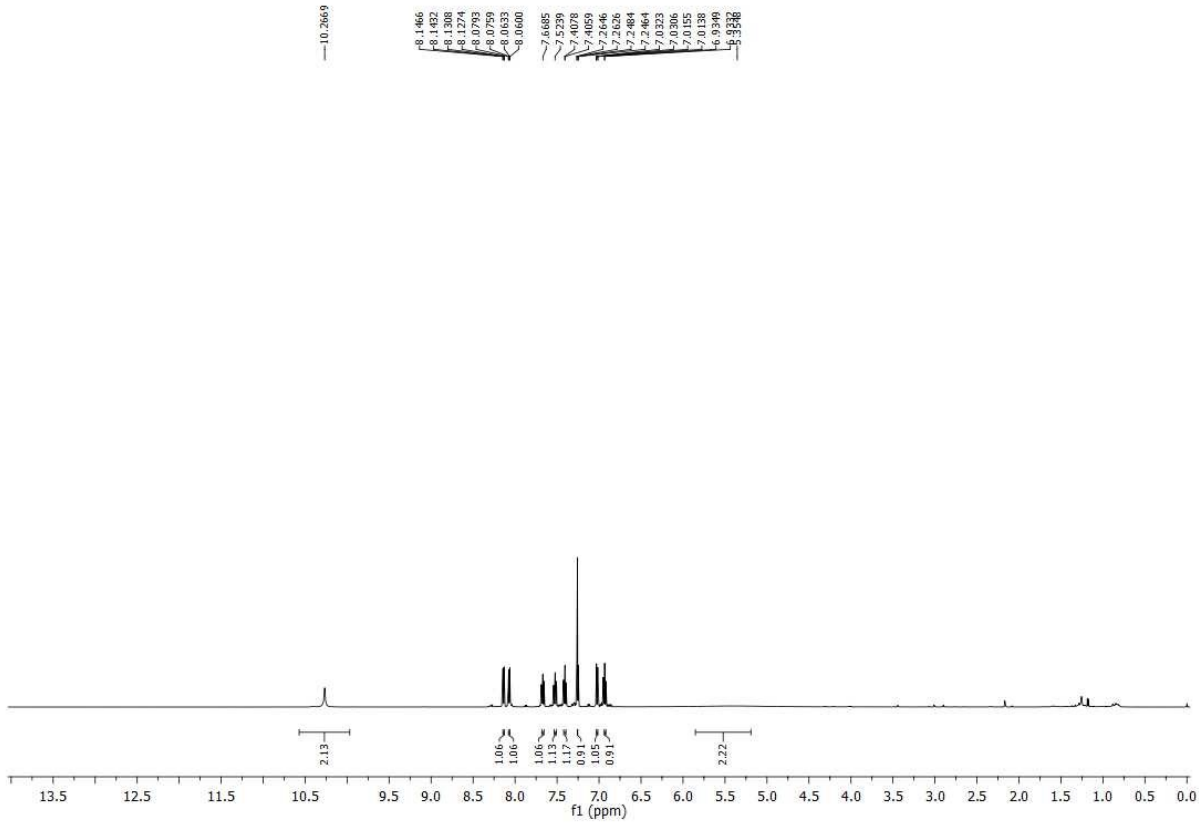
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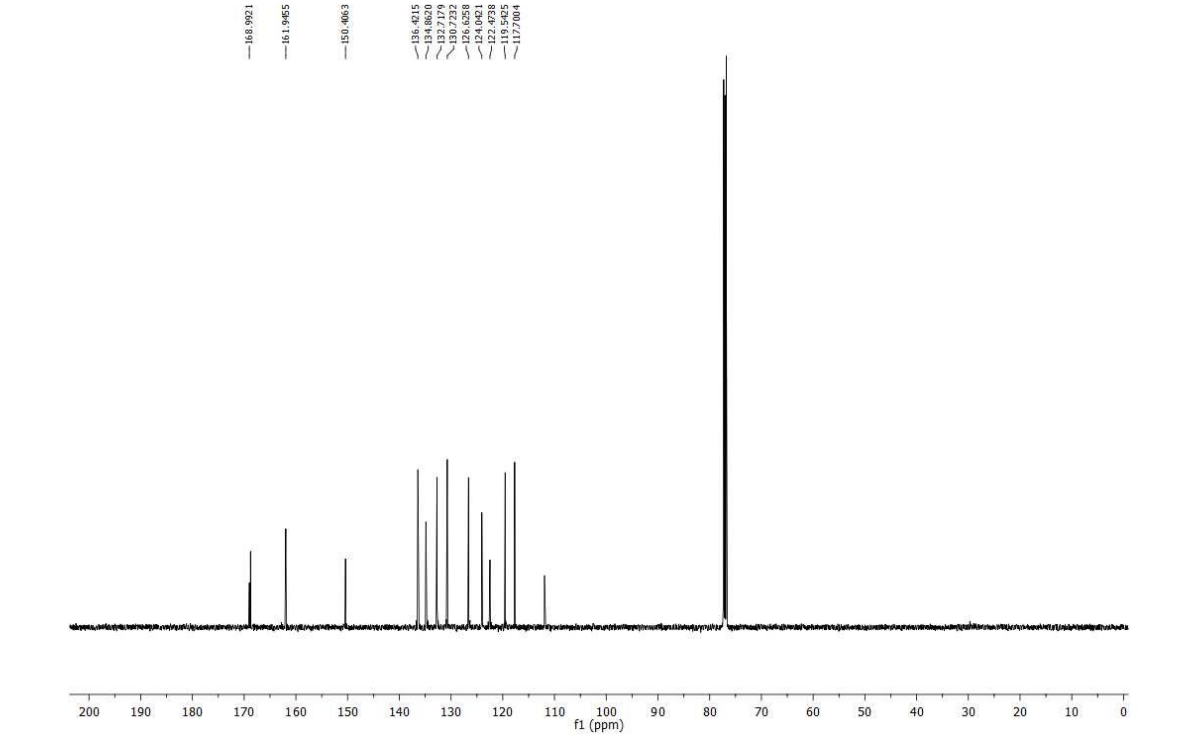
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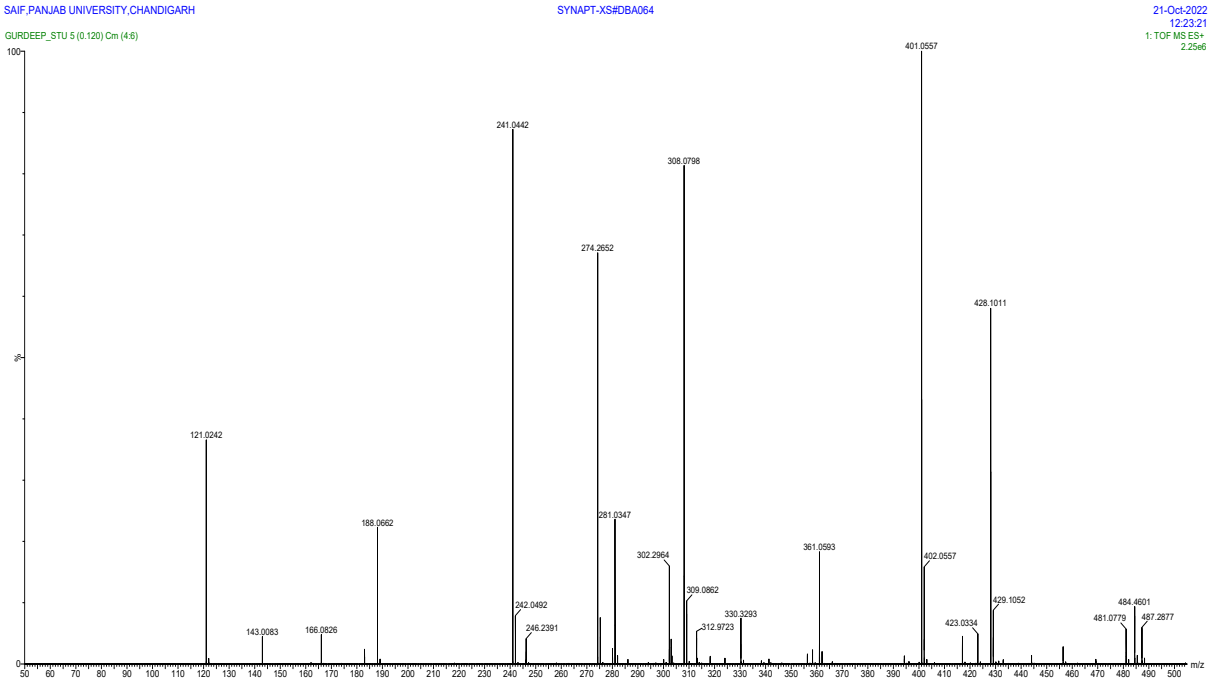
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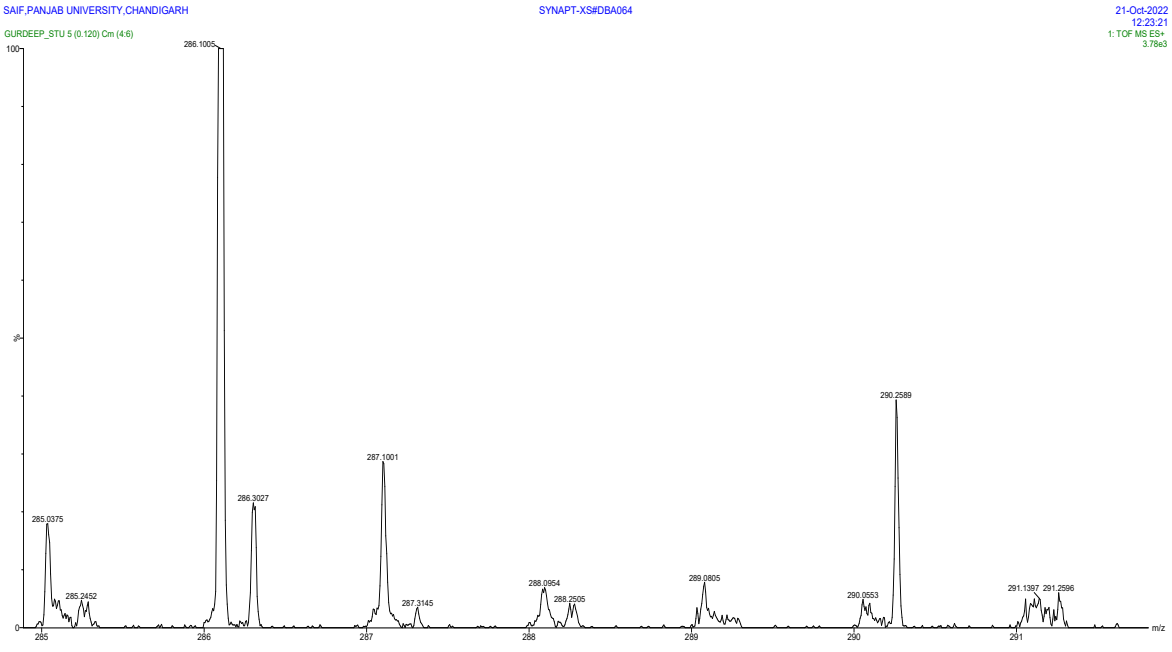
%
m/z


SAIF,PANJAB UNIVERSITY,CHANDIGARH
SYNAPT-XS#DBA064
21-Oct-2022
12:23:21
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1: TOF MS ES+
3.78e3
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290.2589
287.1001
286.3027
285.0375
288.0954
289.0805
291.1397
291.2596
285.2452
287.3145
288.2505
290.0553
%
m/z

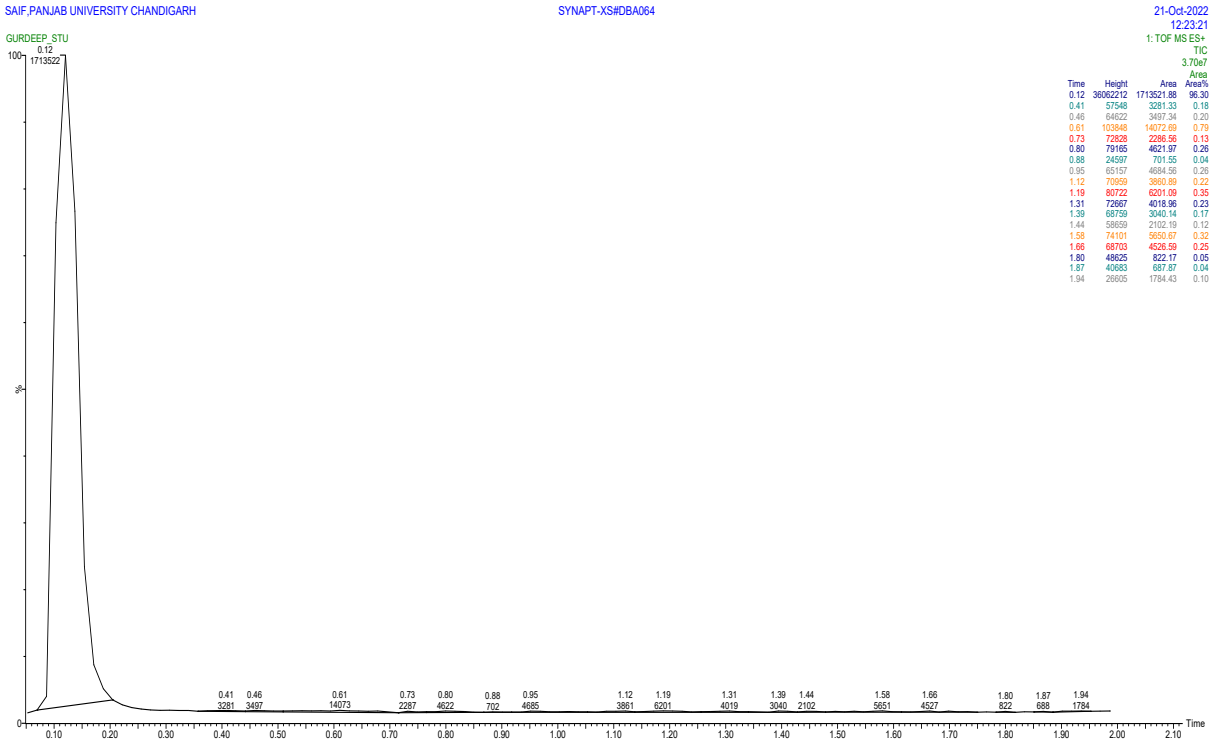
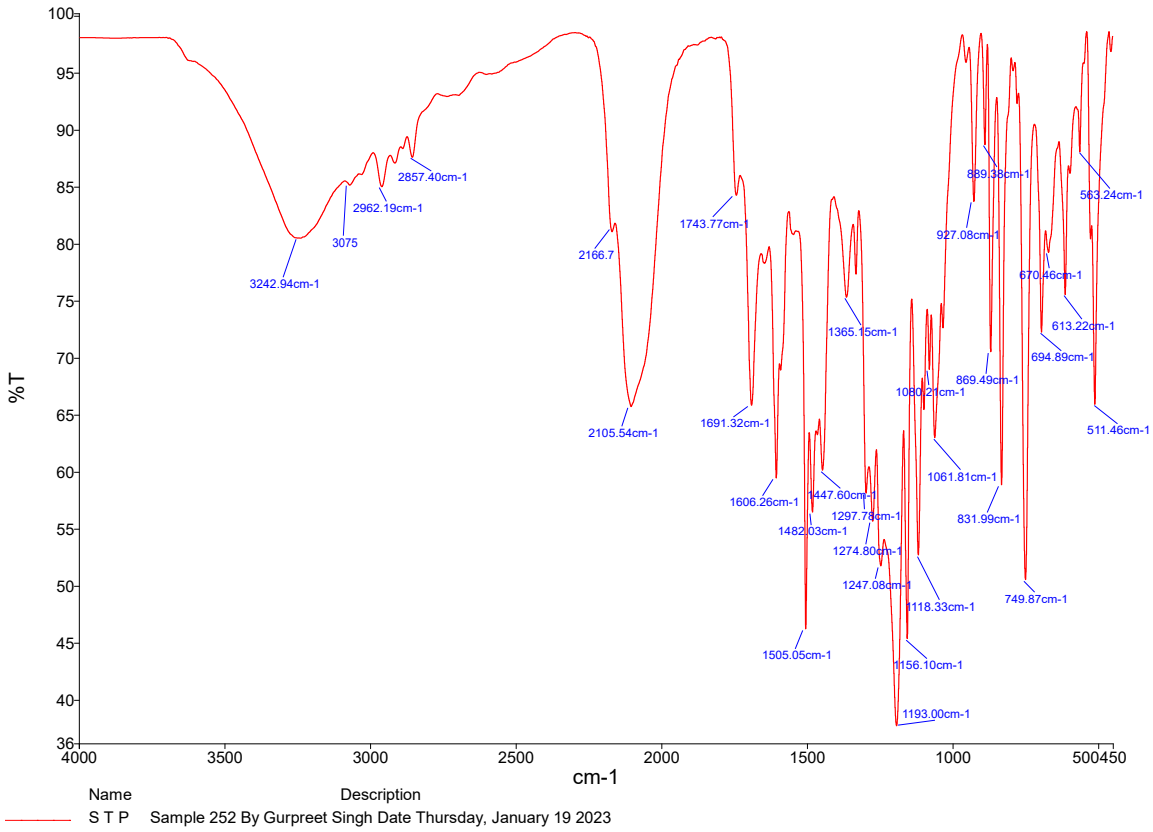
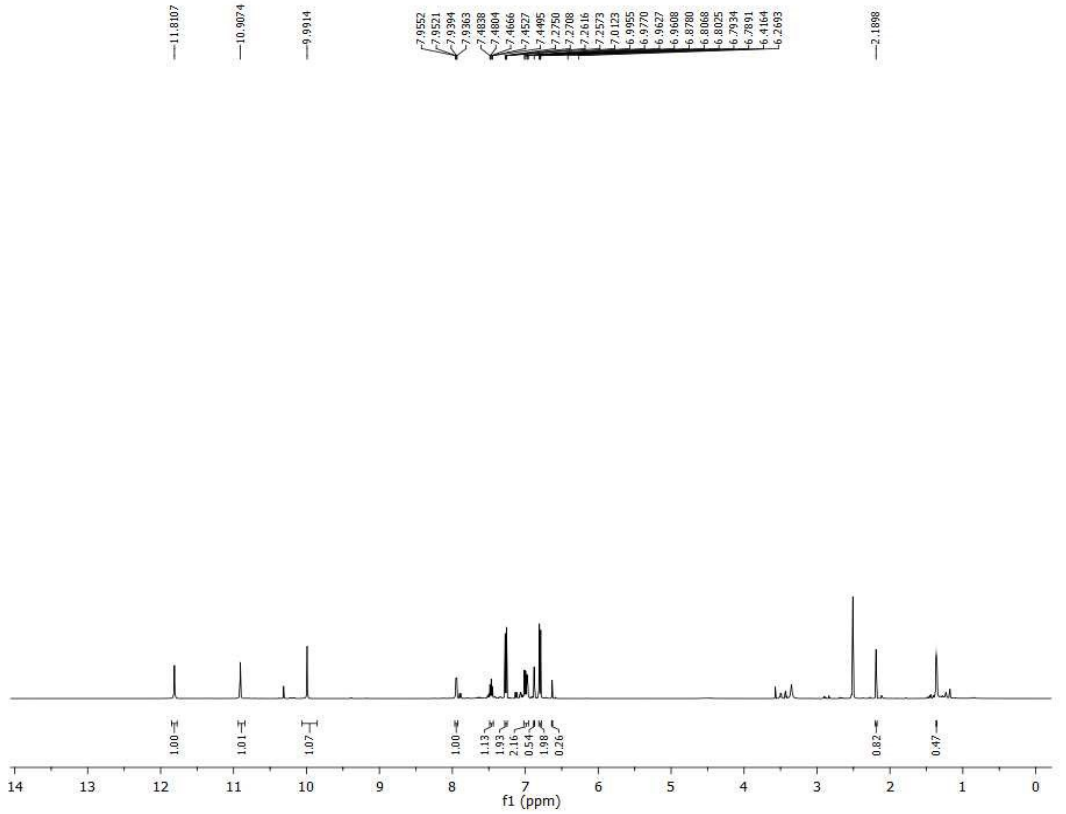
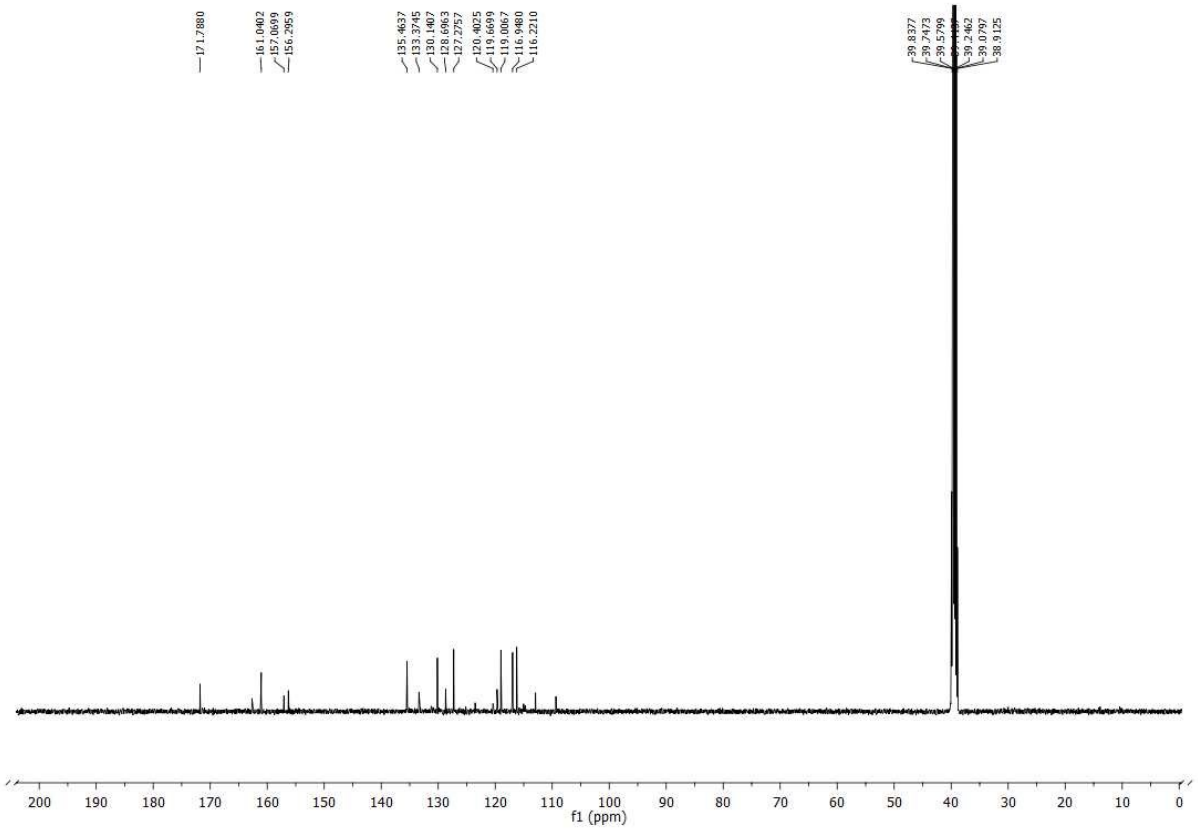


Figure S6. IR, ^{1}H-NMR, ^{13}C-NMR, and HRMS spectra of Compound 7.




11.8107
10.9074
9.9914
7.9552
7.9521
7.9394
7.9363
7.4838
7.4804
7.4666
7.4527
7.4495
7.2750
7.2708
7.2616
7.2573
7.0123
6.9955
6.9770
6.9627
6.9608
6.8780
6.8068
6.8025
6.7934
6.7891
6.4164
6.2693
2.1898
1.00
1.01
1.07
1.00
1.13
1.93
2.16
0.54
1.98
0.26
0.82
0.47
f1 (ppm)


171.7880
161.0402
157.0699
156.2959
135.4637
133.3745
130.1407
128.6963
127.2757
120.4025
119.6699
119.0067
116.9460
116.2210
39.8377
39.7473
39.5799
39.4121
39.2462
39.0797
38.9125
f1 (ppm)

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SYNAPT-XS#DBA064

11-Jul-2022
12:59:04

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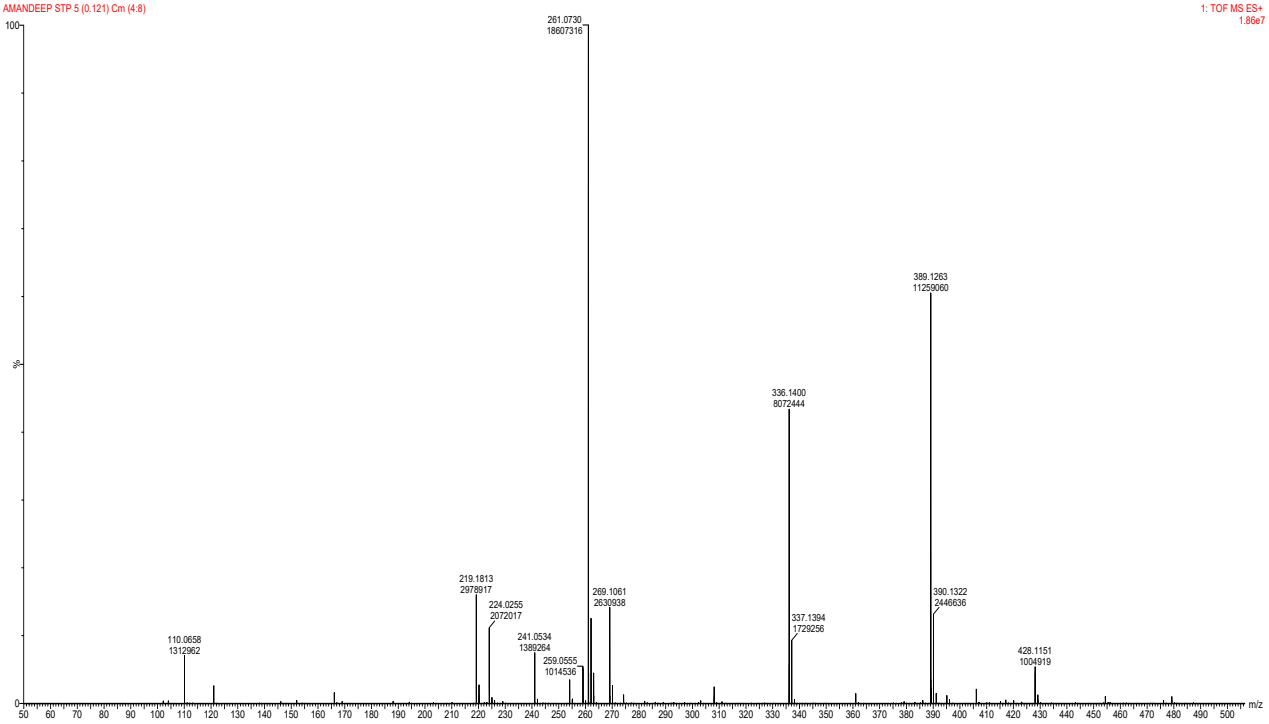

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SYNAPT-XS#DBA064

11-Jul-2022
12:59:04

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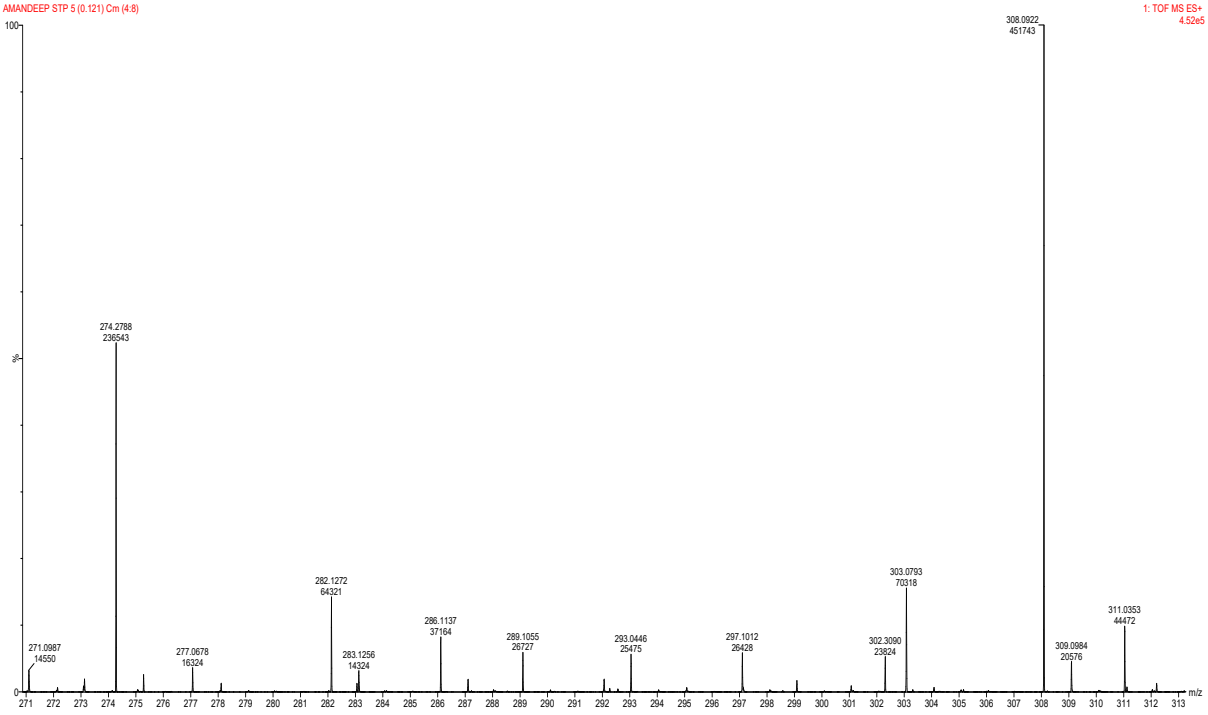


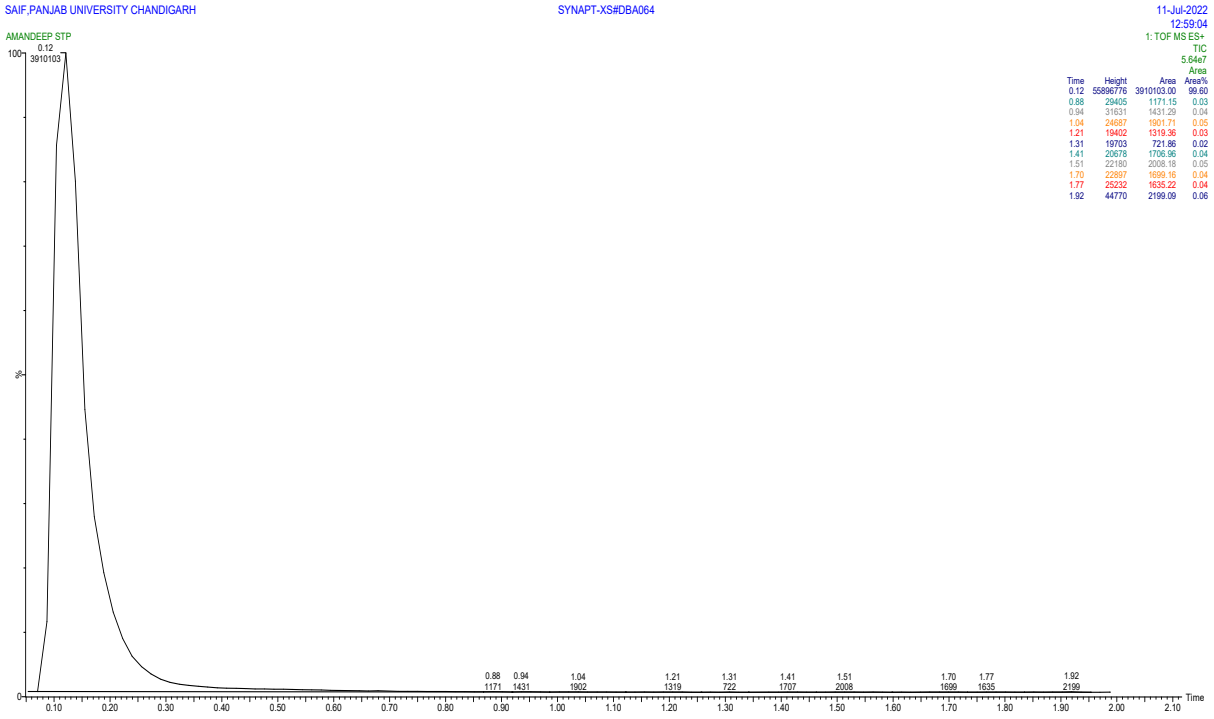
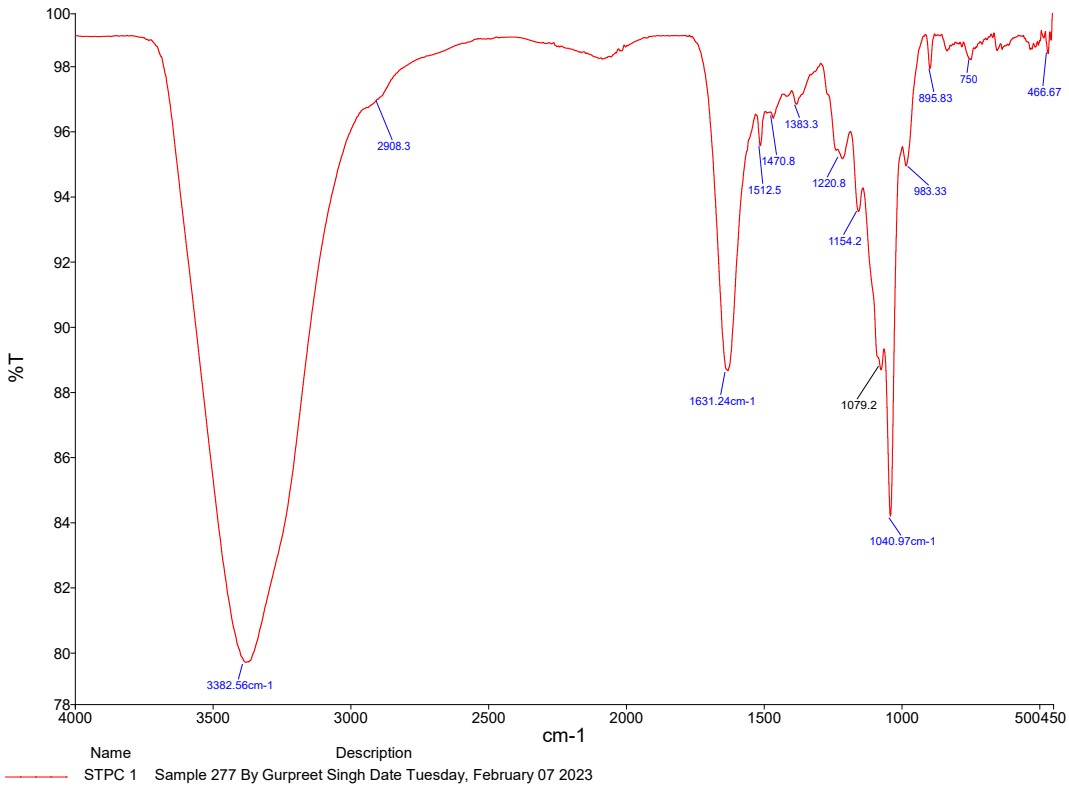
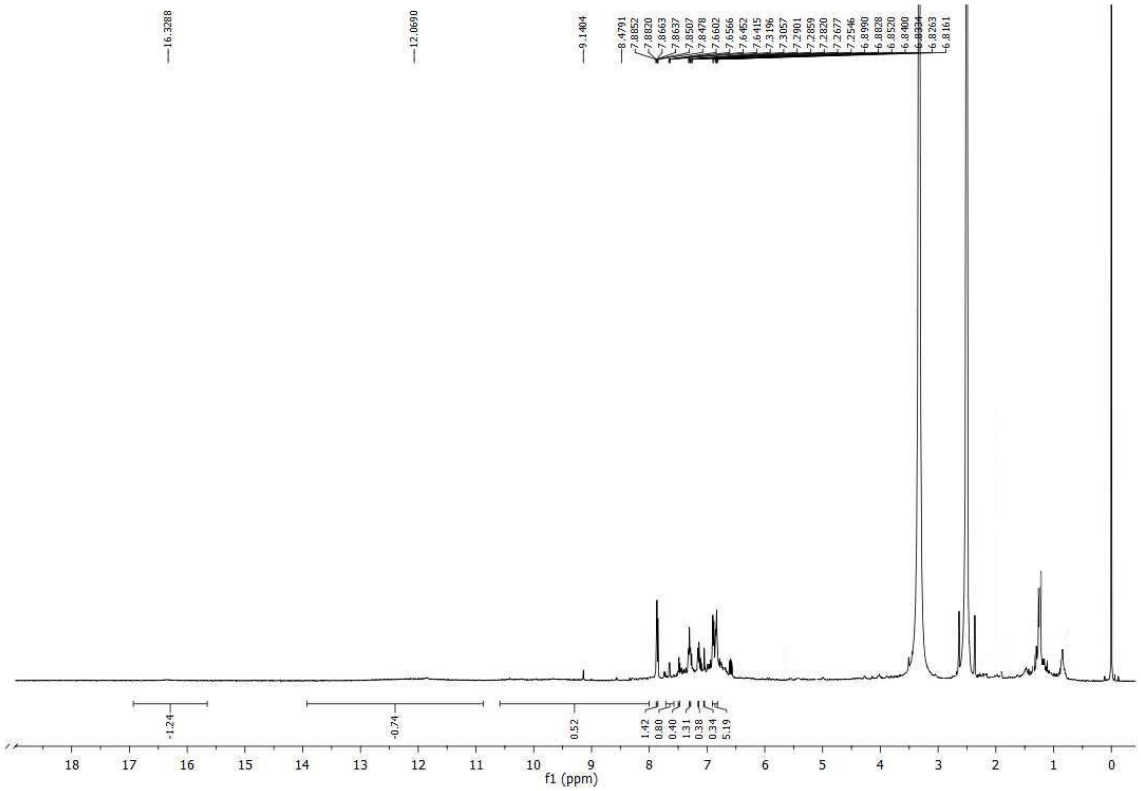


Figure S7. IR, ^{1}H-NMR, ^{13}C-NMR, and HRMS spectra of Compound 8

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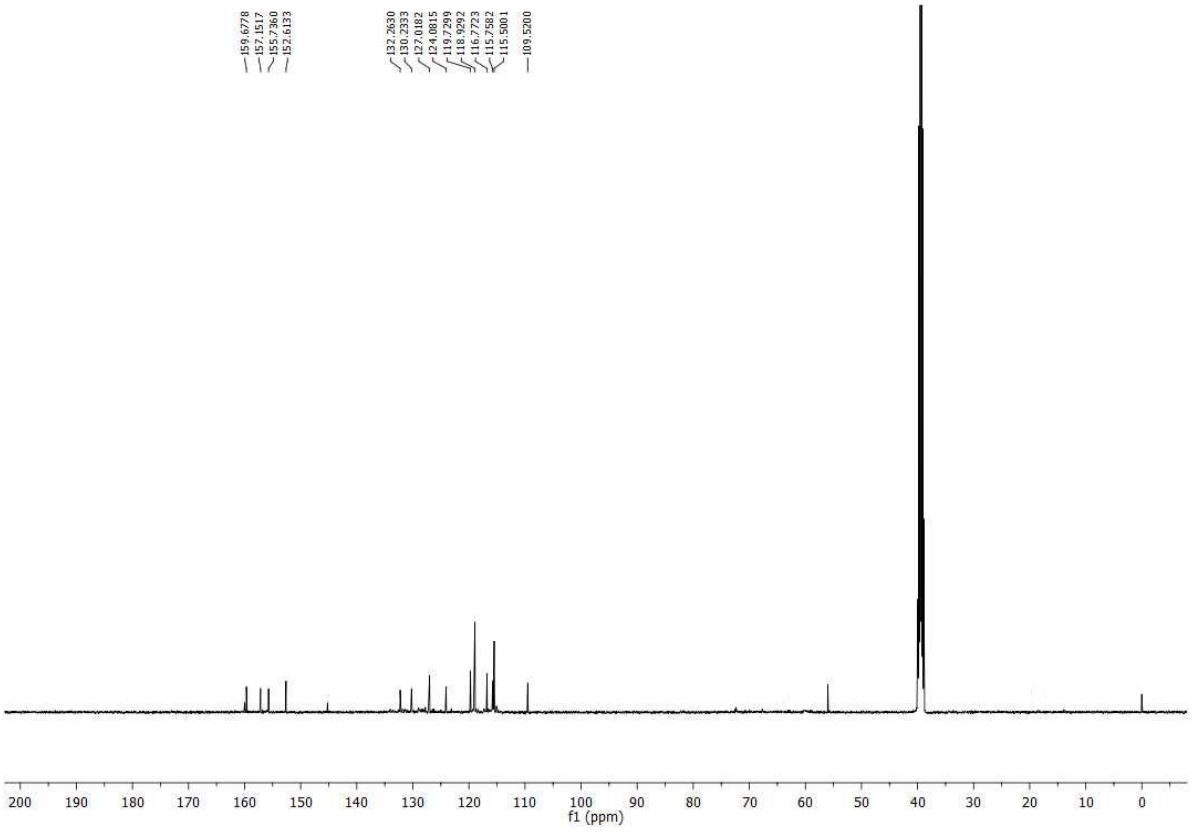
12.0690
9.1404
8.4791
7.8852
7.8820
7.8663
7.8637
7.8507
7.8478
7.8402
7.6566
7.6452
7.6415
7.3196
7.3057
7.2901
7.2859
7.2820
7.2677
7.2546
6.8990
6.8828
6.8520
6.8400
6.8334
6.8263
6.8161
1.24
0.74
0.52
1.42
0.80
0.40
1.31
0.38
0.34
5.19
f1 (ppm)


159.6778
157.1517
155.7360
152.6133
132.2630
130.2353
127.0182
124.0815
119.7299
118.9292
116.7723
115.7582
115.5001
109.5200
f1 (ppm)

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SYNAPT-XS#DBA064

04-Jul-2023
12:05:40

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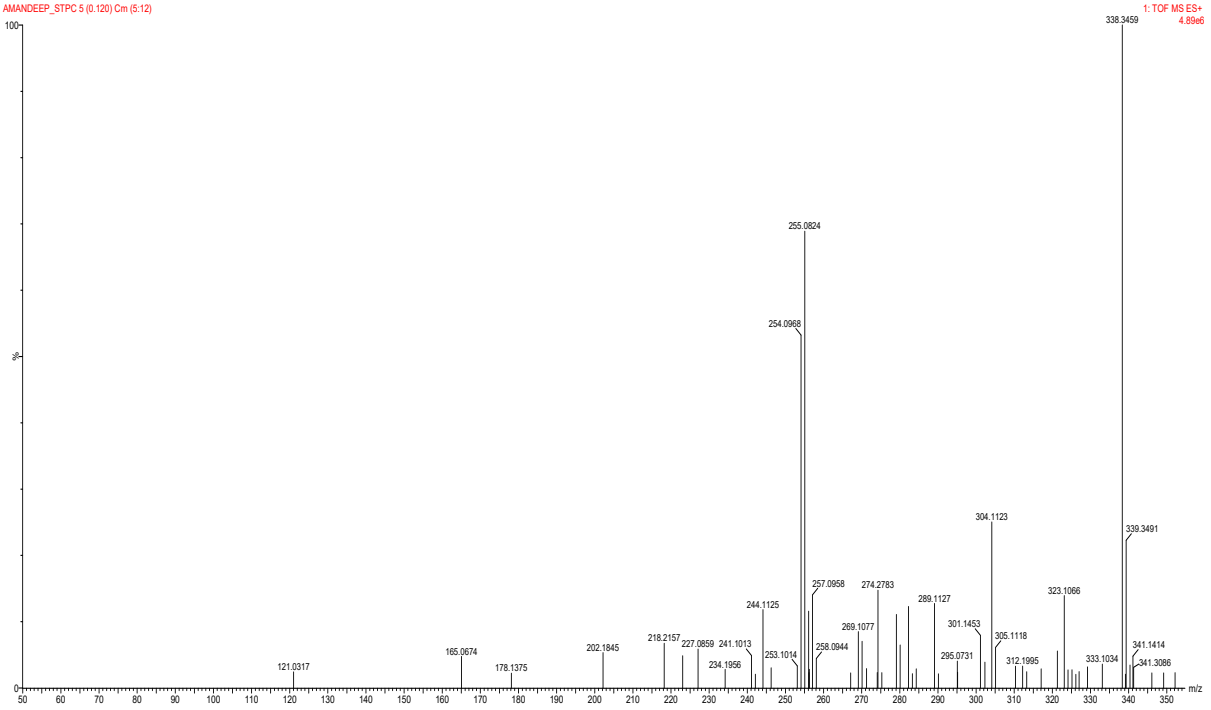
4.89e6



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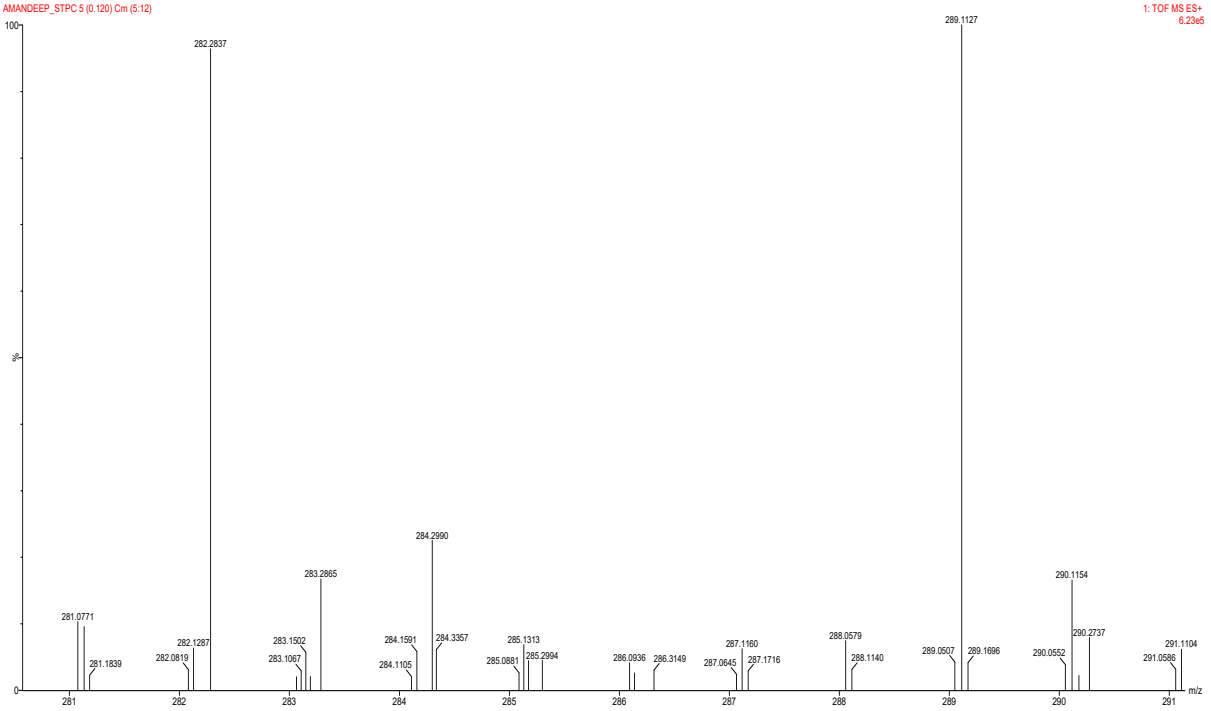
SYNAPT-XS#DBA064

04-Jul-2023
12:05:40

AMANDEEP_STPC 5 (0.120) Cm (5:12)

1: TOF MS ES+
6.23e5



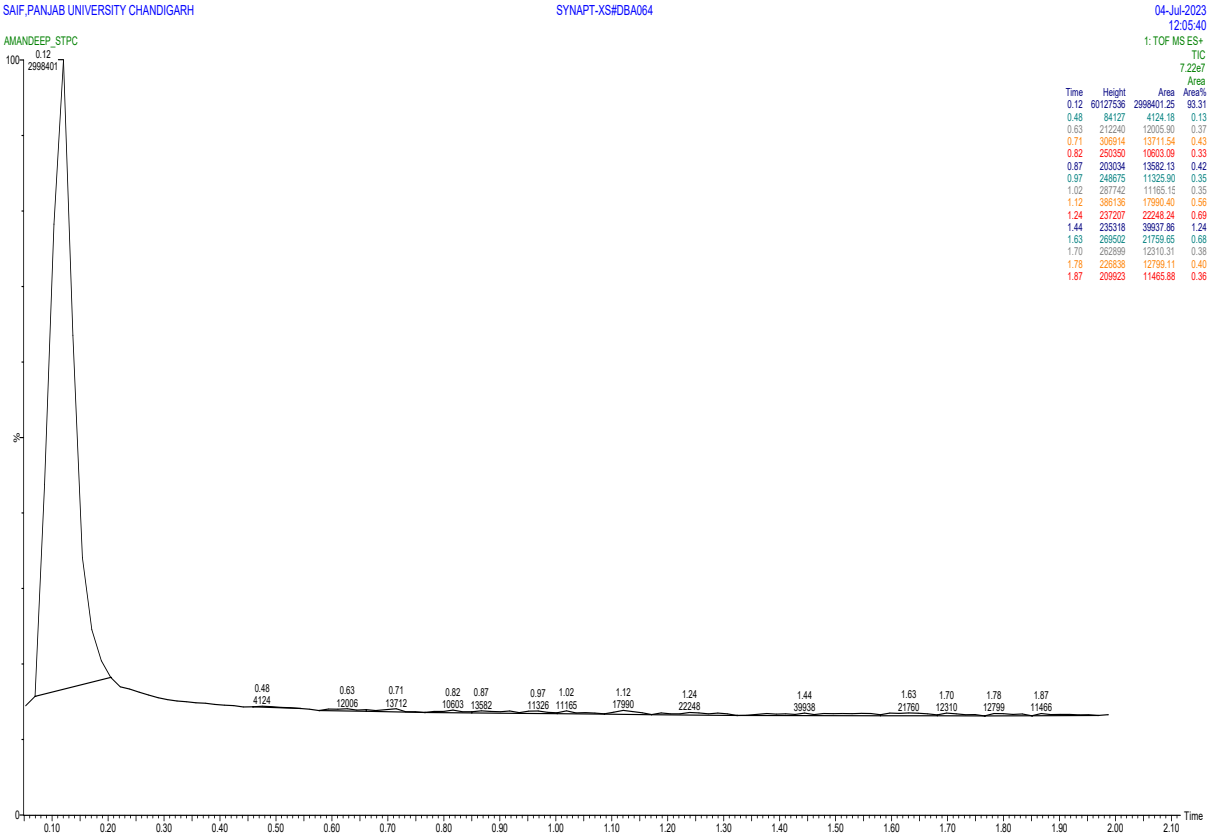
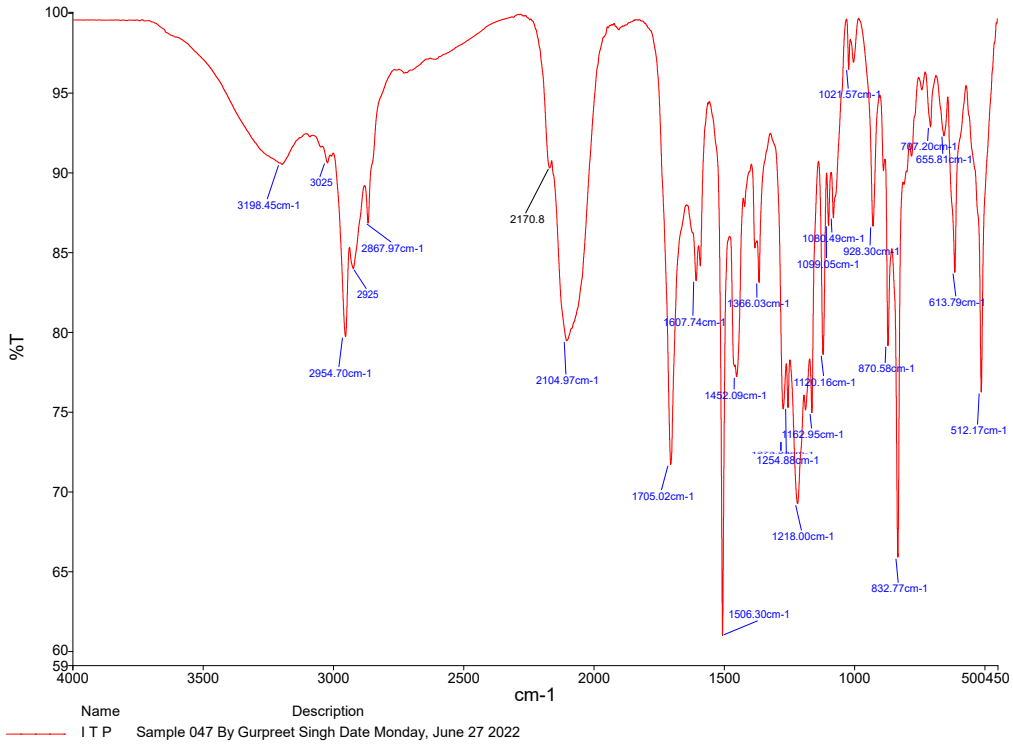
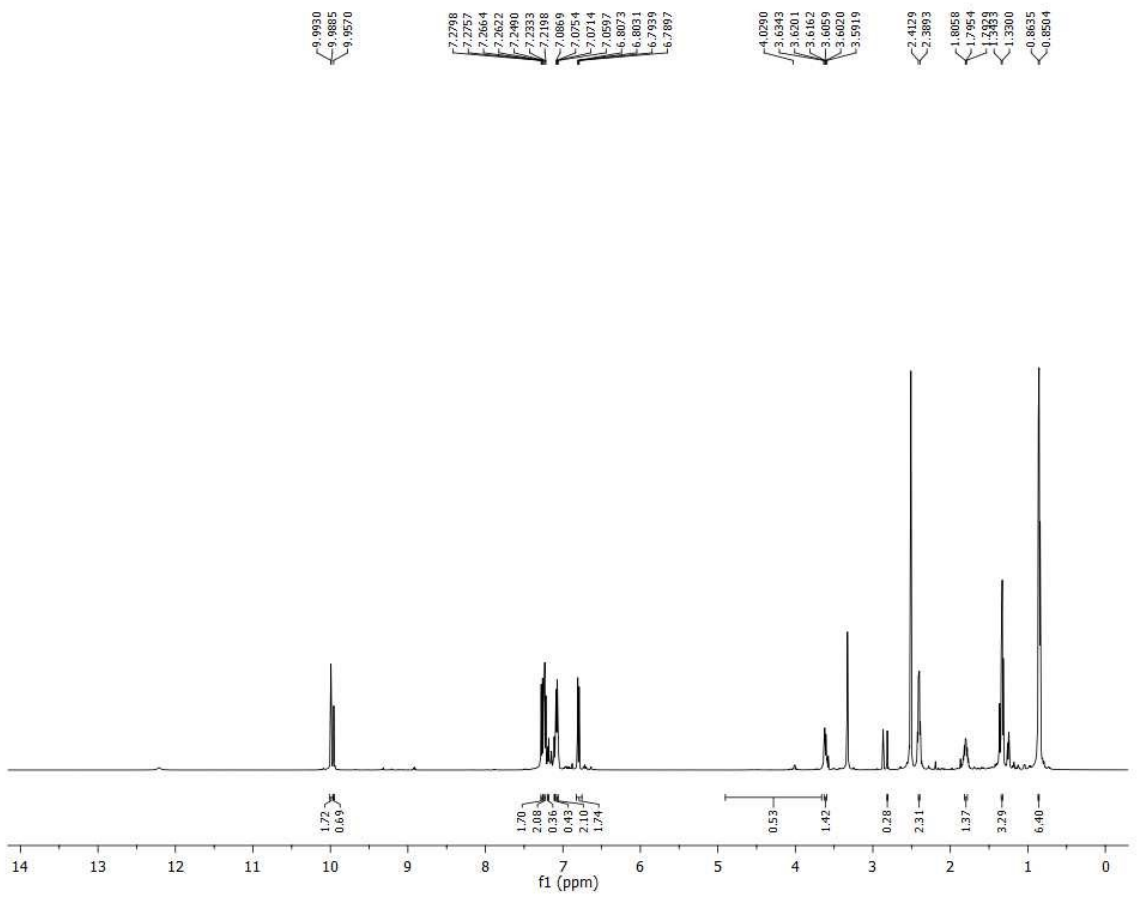
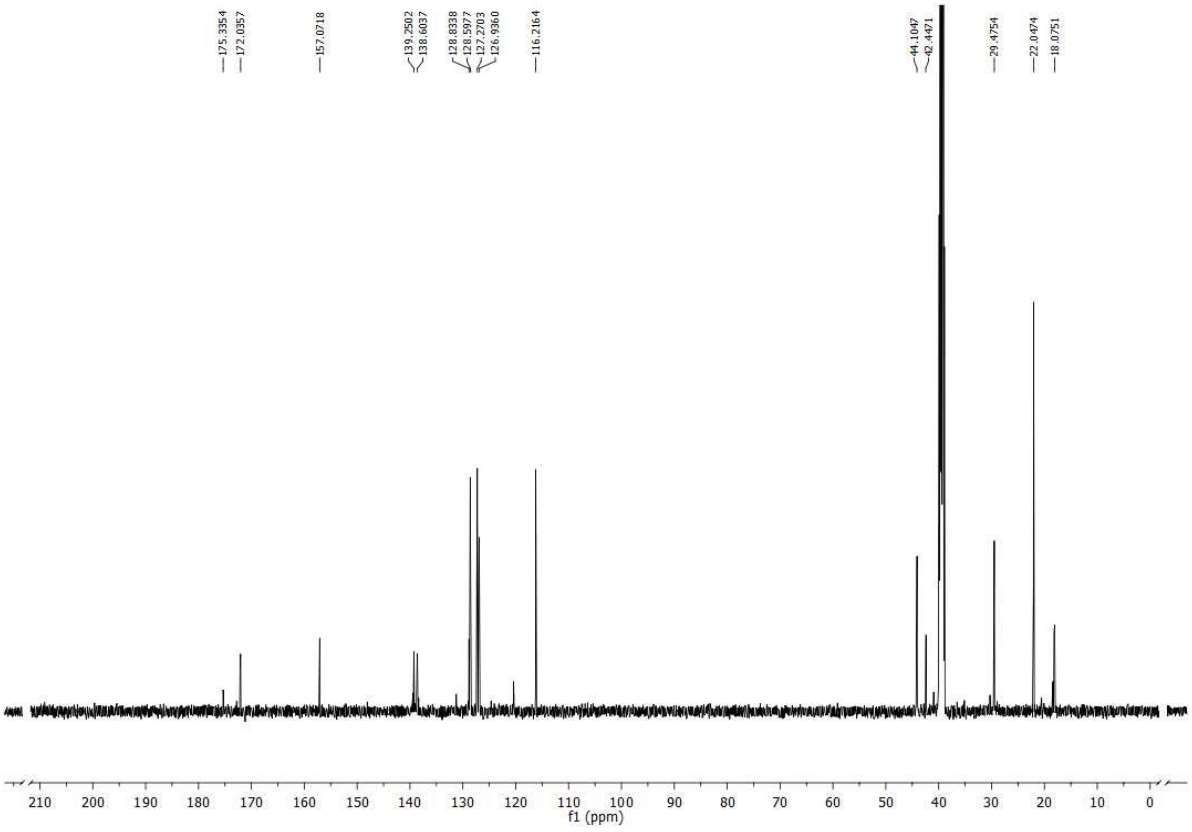


Figure S8. IR, ^{1}H-NMR, ^{13}C-NMR and HRMS spectra of Compound 11.




9.9930
9.9885
9.9570
7.2798
7.2757
7.2664
7.2622
7.2490
7.2333
7.2198
7.0869
7.0754
7.0714
7.0597
6.8073
6.8031
6.7939
6.7897
4.0290
3.6343
3.6201
3.6162
3.6059
3.6020
3.5919
2.4129
2.3893
1.8058
1.7954
1.7933
1.3493
1.3300
0.8635
0.8504
1.72
0.69
1.70
2.08
0.36
0.43
2.10
1.74
0.53
1.42
0.28
2.31
1.37
3.29
6.40
14 13 12 11 10 9 8 7 6 5 4 3 2 1 0
f1 (ppm)


175.3354
172.0357
157.0718
139.2502
138.6037
128.8338
128.5977
127.2703
126.9360
116.2164
44.1047
42.4471
29.4754
22.0474
18.0751
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

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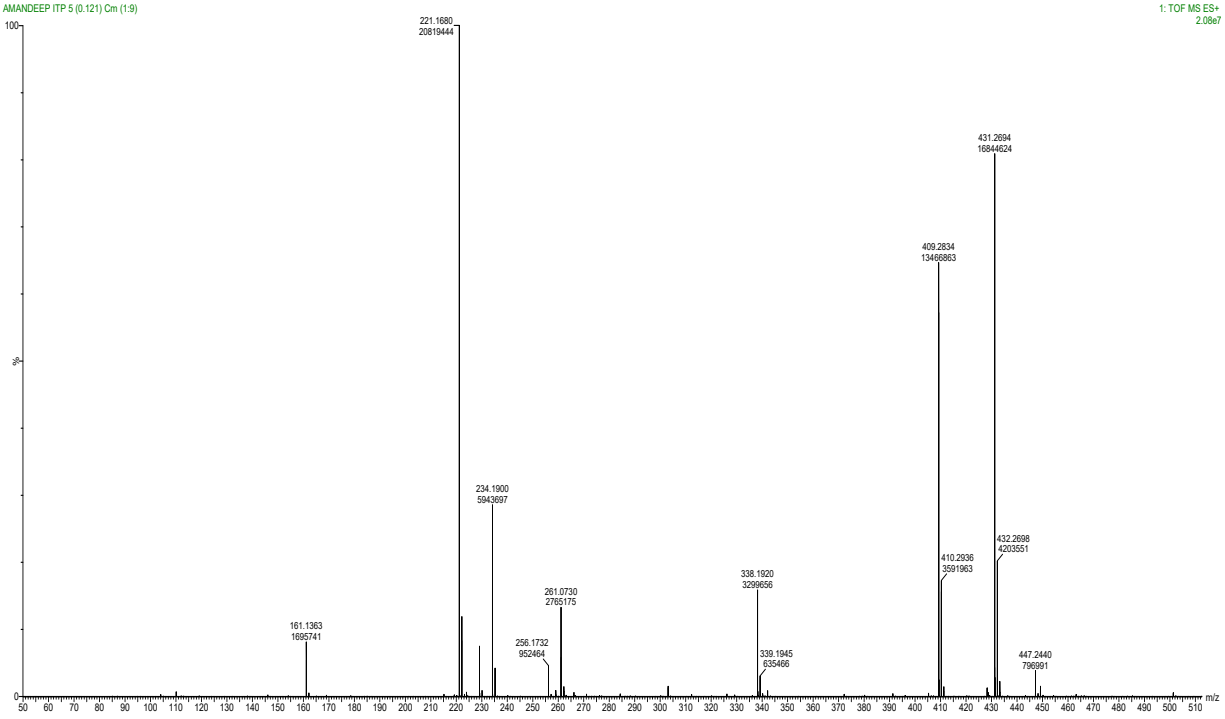
SYNAPT-XS#DBA064

11-Jul-2022
13:01:44

AMANDEEP ITP 5 (0.121) Cm (1:9)

1: TOF MS ES+
2.06e7



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SYNAPT-XS#DBA064

11-Jul-2022
13:01:44

AMANDEEP ITP

1: TOF MS ES+
TIC
5.55e7

Time	Height	Area	Area%
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1.31	33741	5826.76	0.13
1.53	9052	310.06	0.01
1.63	79994	3405.74	0.08
1.73	25505	943.22	0.02
1.80	31197	1471.44	0.03
1.85	28352	1689.33	0.04

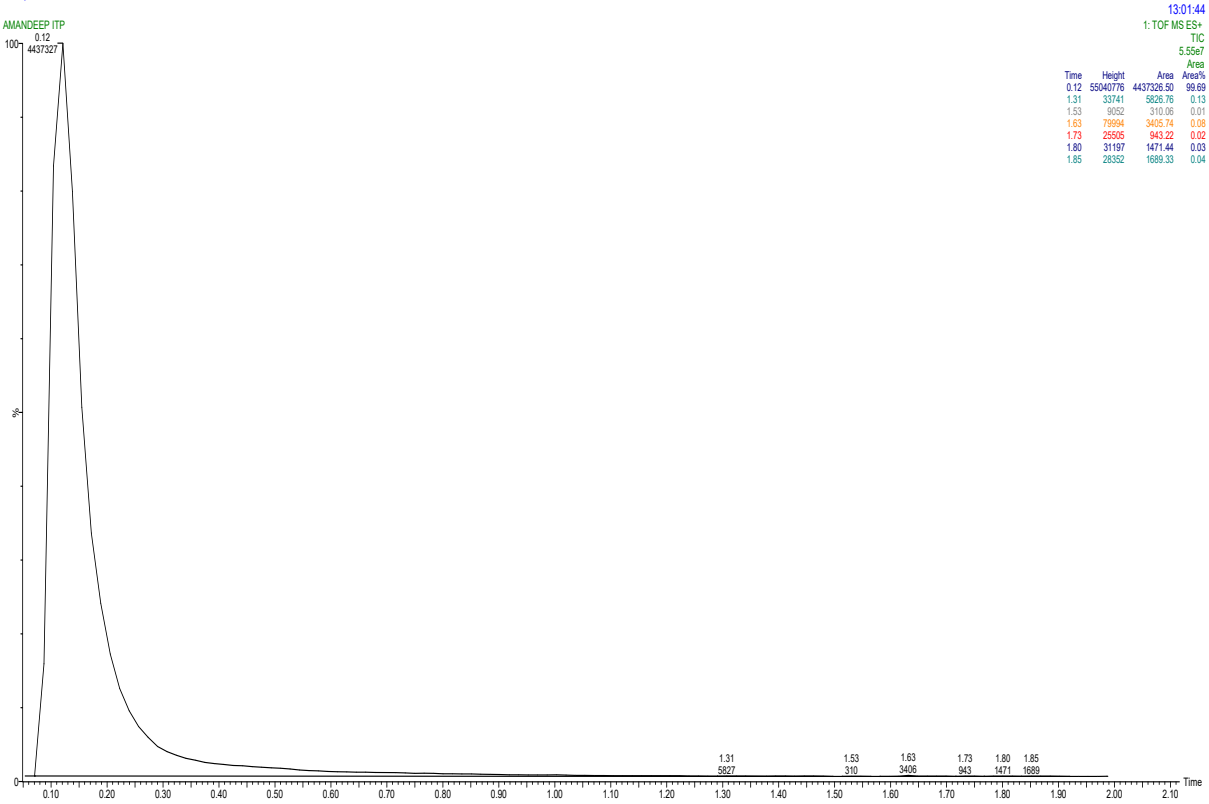
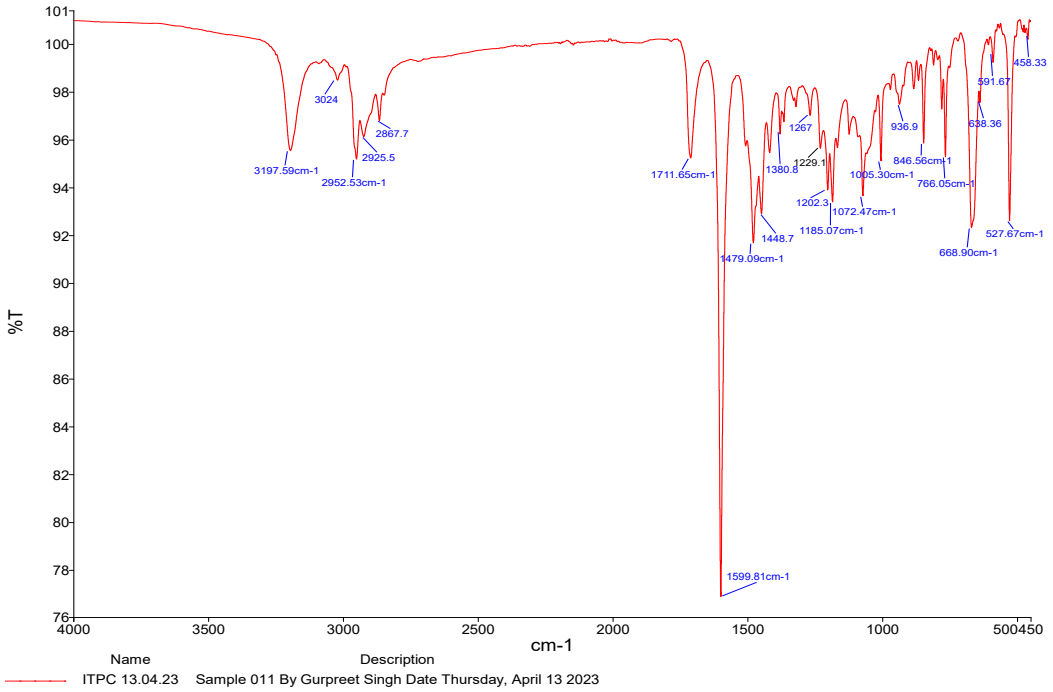
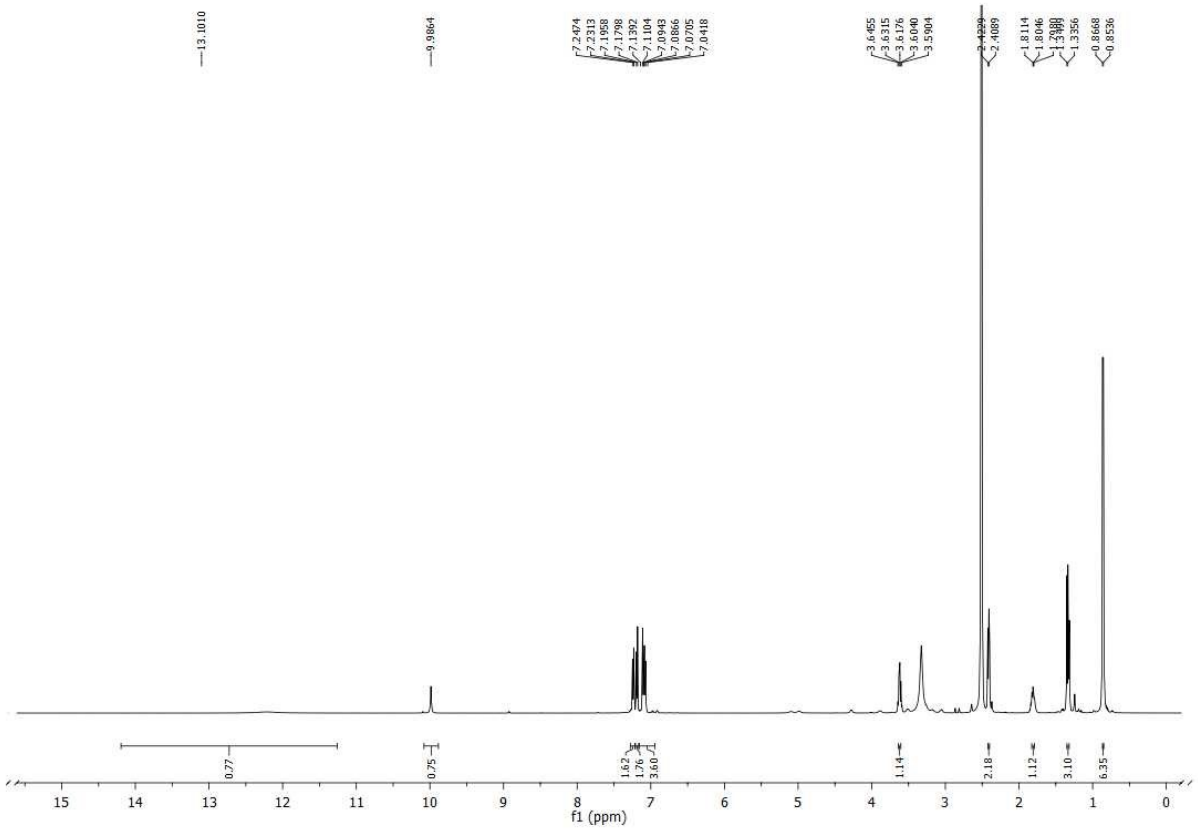
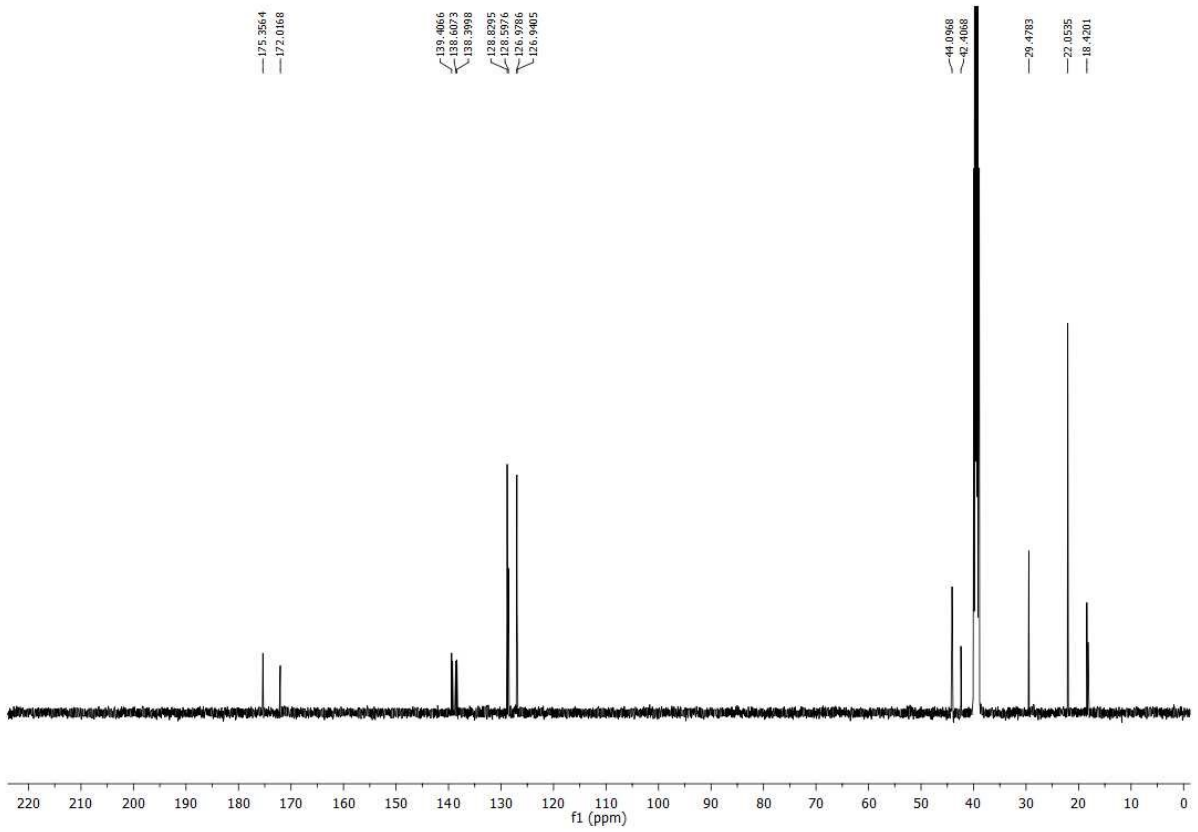
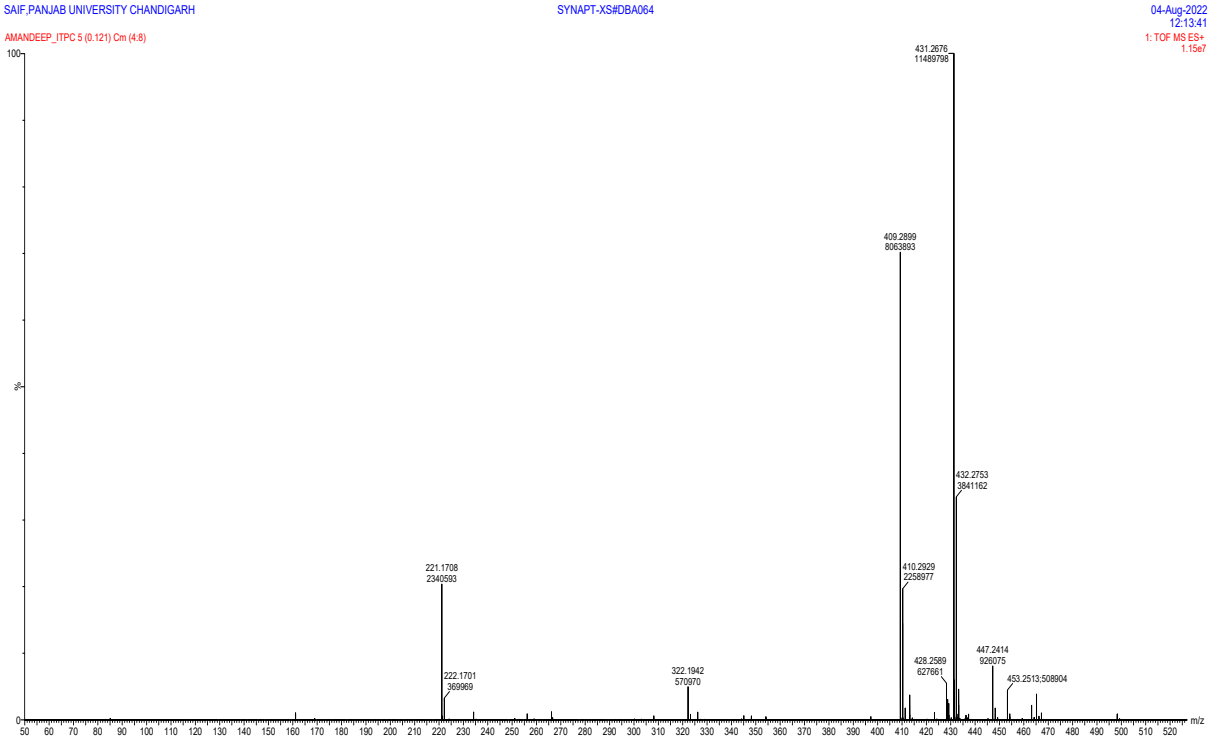


Figure S9. IR, ^{1}H-NMR, ^{13}C-NMR and HRMS spectra of Compound 12






175.3564
172.0168
139.4066
138.6073
138.3998
128.8295
128.5976
126.9786
126.9465
44.0968
42.4068
29.4783
22.0535
18.4201
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


SAIF,PANJAB UNIVERSITY CHANDIGARH
SYNAPT-XS#DBA064
04-Aug-2022
12:13:41
AMANDEEP_ITPC 5 (0.121) Cm (4:8)
1: TOF MS ES+
1.15e7
100
%
0
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11489798
409.2899
8063893
432.2753
3841162
410.2929
2258977
221.1708
2340593
222.1701
369969
322.1942
570970
428.2589
627661
447.2414
926075
453.2513;508904
50 60 70 80 90 100 110 120 130 140 150 160 170 180 190 200 210 220 230 240 250 260 270 280 290 300 310 320 330 340 350 360 370 380 390 400 410 420 430 440 450 460 470 480 490 500 510 520
m/z

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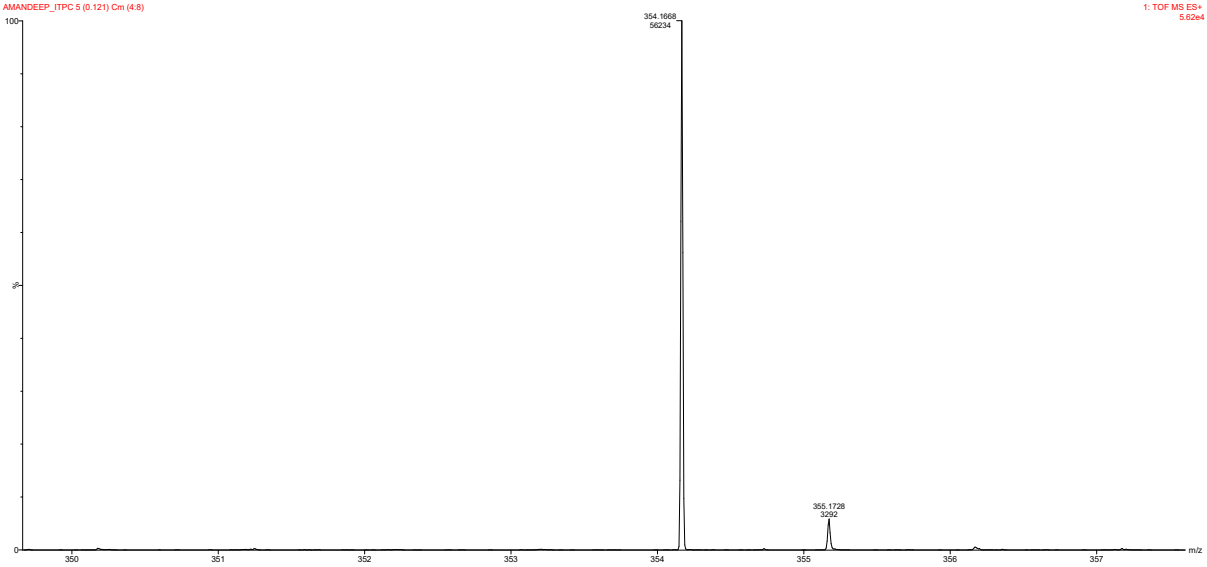
SYNAPT-XS#DBA064

04-Aug-2022
12:13:41

AMANDEEP_ITPC 5 (0.121) Cm (4:8)

1: TOF MS ES+
5.62e4



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SYNAPT-XS#DBA064

04-Aug-2022
12:13:41

AMANDEEP_ITPC

1: TOF MS ES+
TIC
5.39e7

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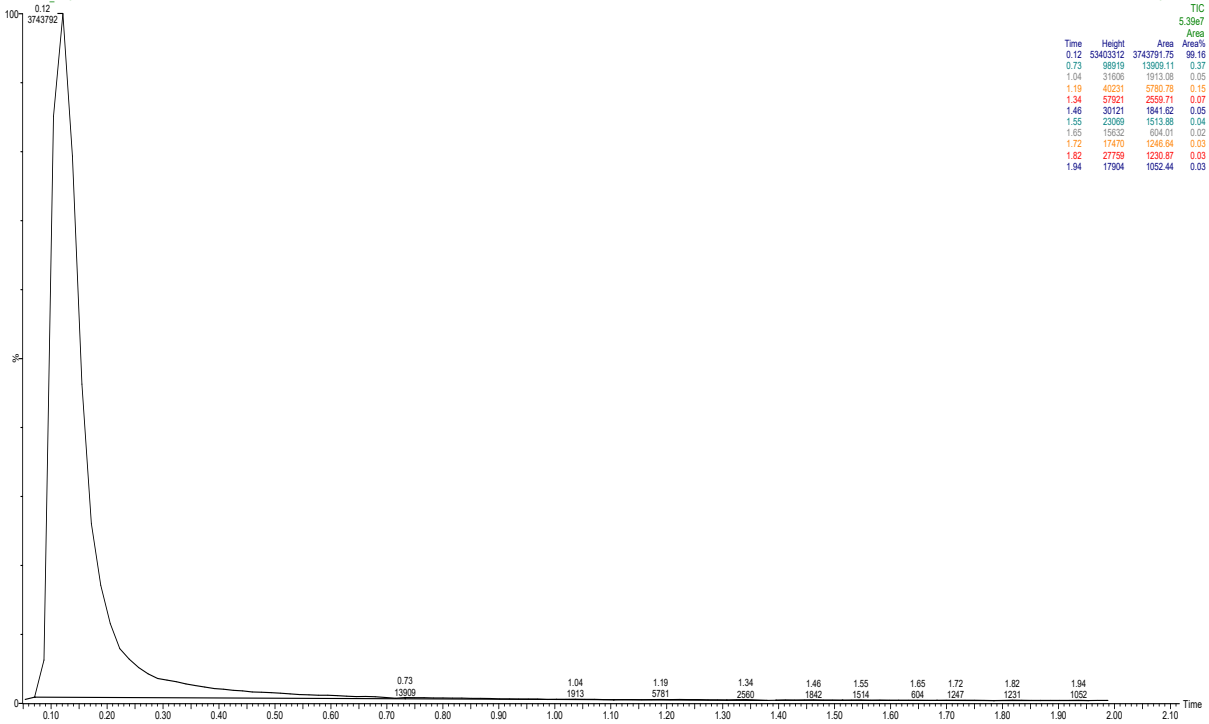
1.04	31606	1913.08	0.05
1.19	40231	5780.78	0.15
1.34	57921	2559.71	0.07
1.46	30121	1841.62	0.05
1.55	23069	1513.88	0.04
1.65	15632	604.01	0.02
1.72	17470	1246.64	0.03
1.82	27759	1230.87	0.03
1.94	17904	1052.44	0.03



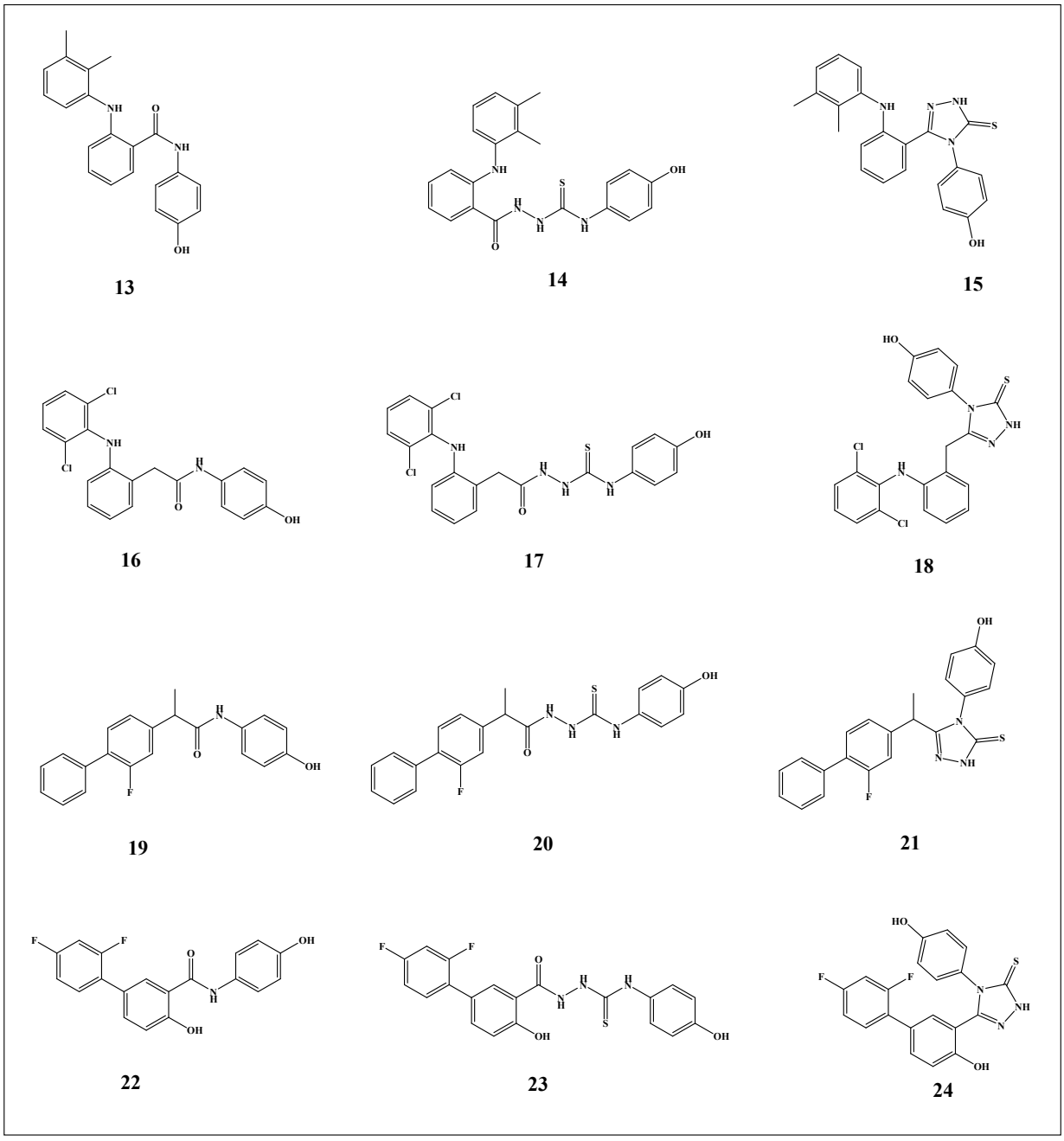


Figure S10. List of compounds with inappropriate ADMET profile.

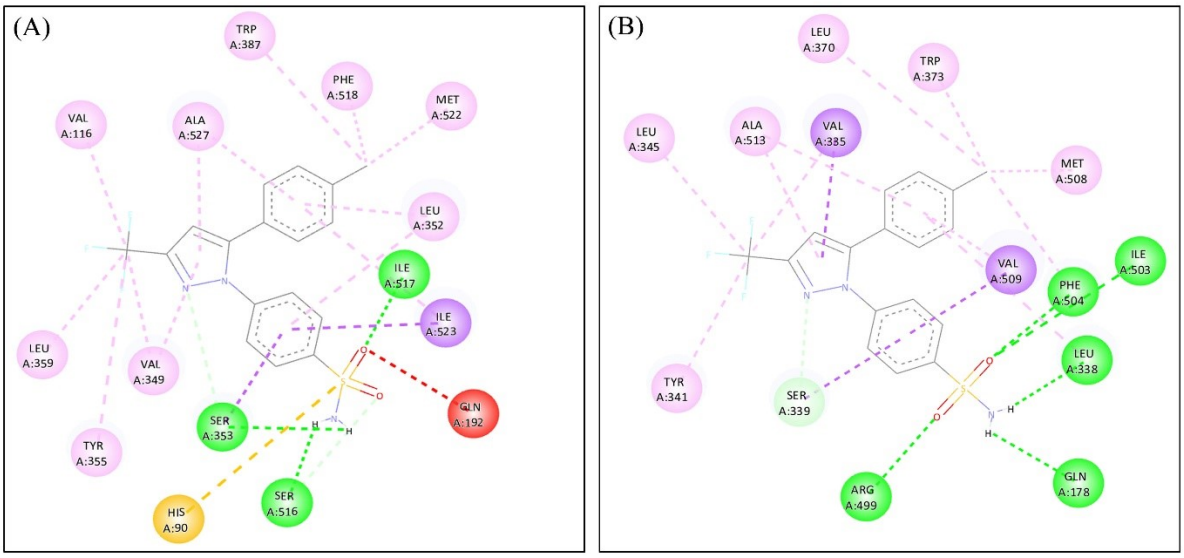


Figure S11. 2D diagram showing the redocked poses of celecoxib in the binding pocket of COX-1 and COX-2.

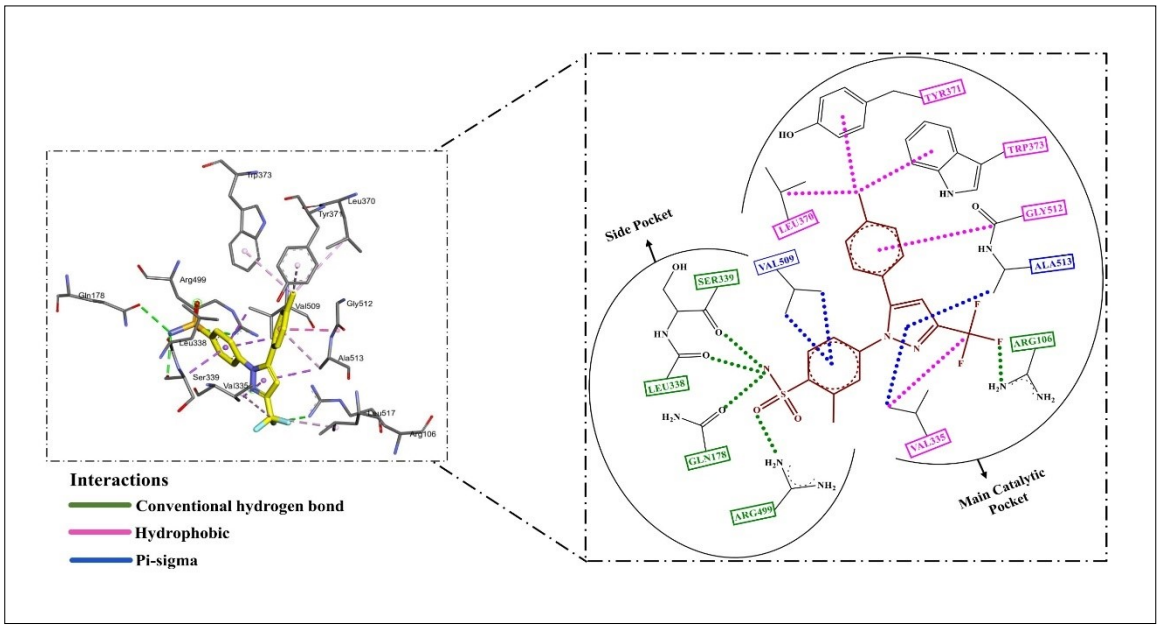


Figure S12. Orientation of celecoxib within the side pocket and main catalytic pocket of COX-2

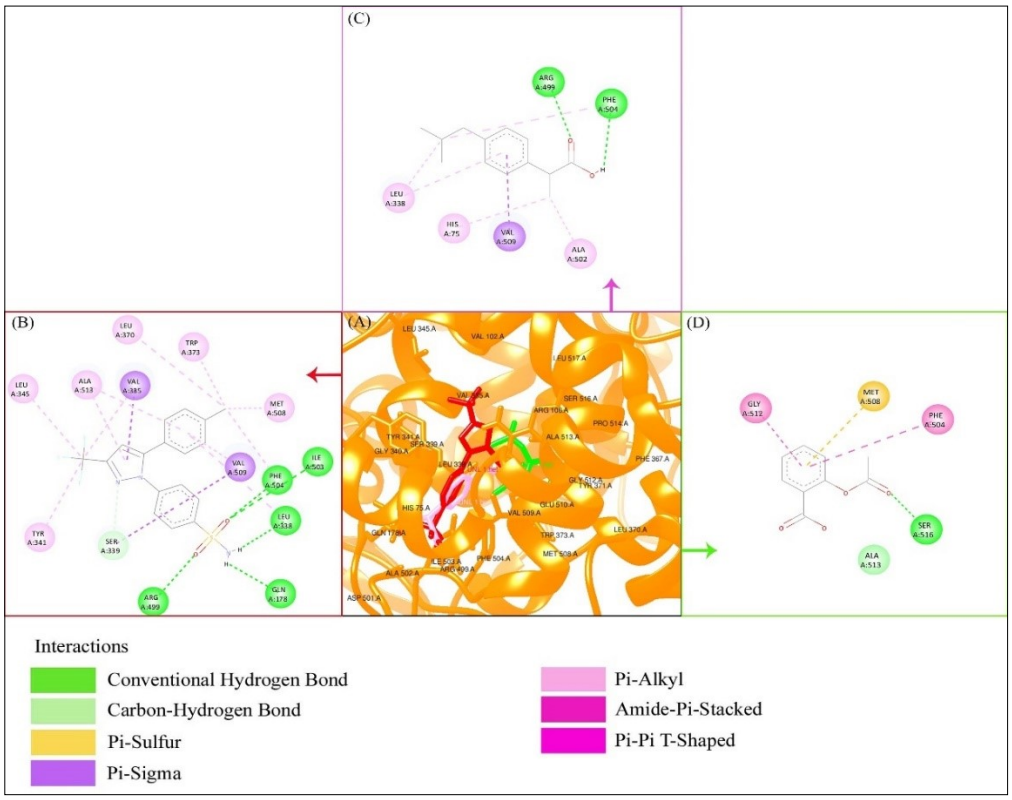


Figure S13. (A) 3D diagram showing penetration of celecoxib (red), aspirin (green) and ibuprofen (pink) in the side pocket of COX-2. 2D representations of predicted binding modes of celecoxib (B), ibuprofen (C) and aspirin (D).

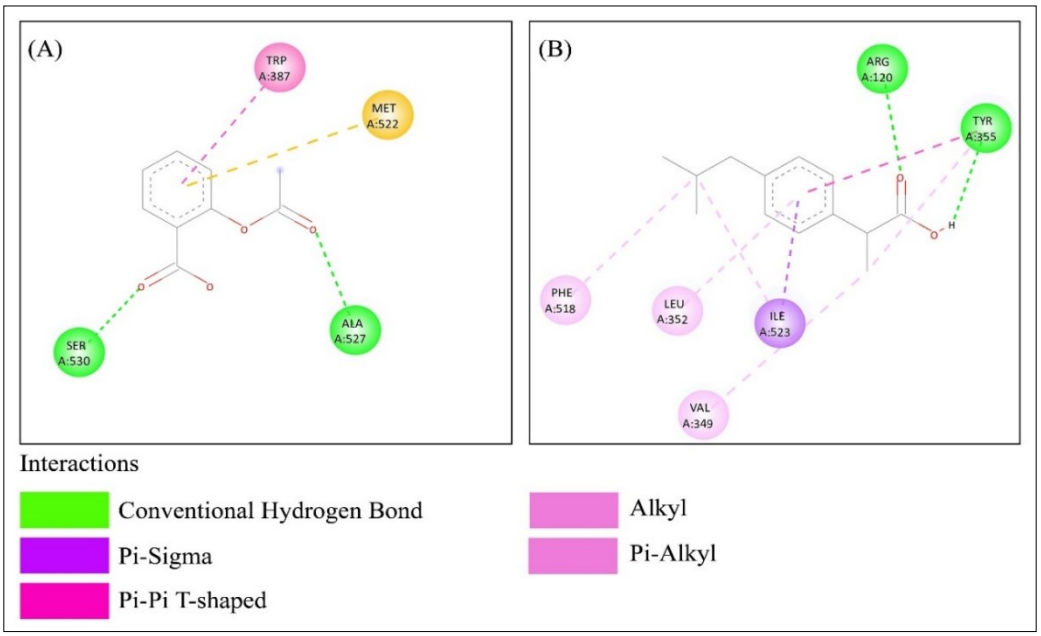


Figure S14. 2D interaction diagrams of aspirin and ibuprofen with the key residues of COX-1 binding pocket.

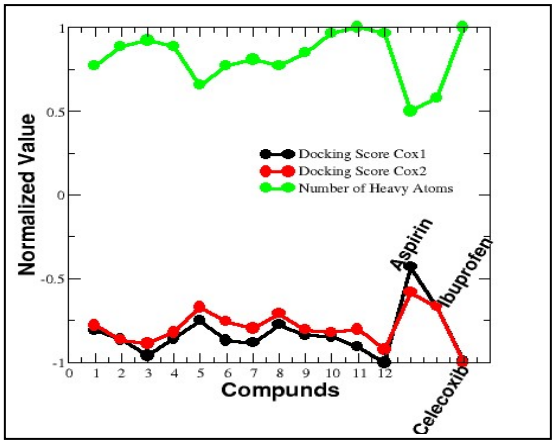


Figure S15. Correlation of Normalized Docking Score and number of heavy atoms

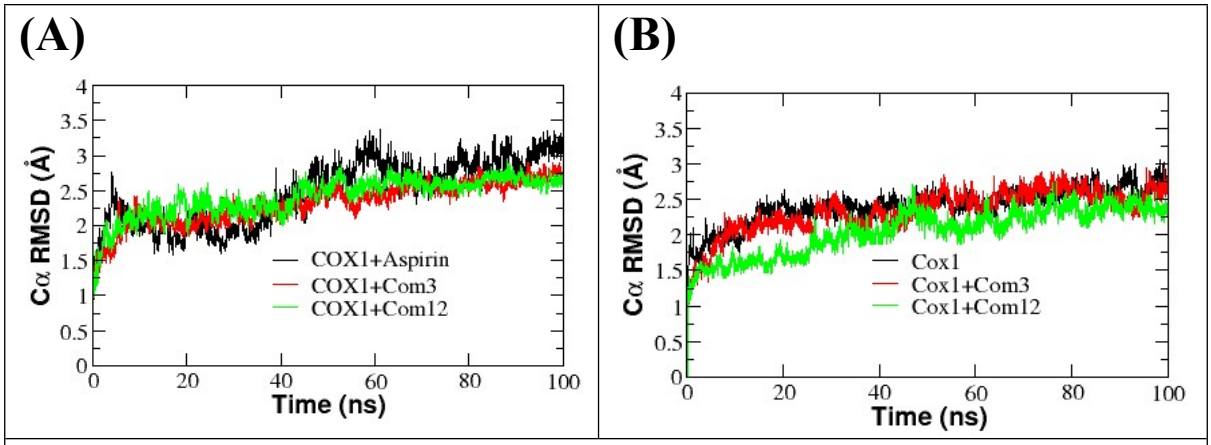


Figure S16. RMSD plots of compounds 3, 12, and aspirin with COX-1 during the 2nd (A) and 3rd (B) replica Simulation

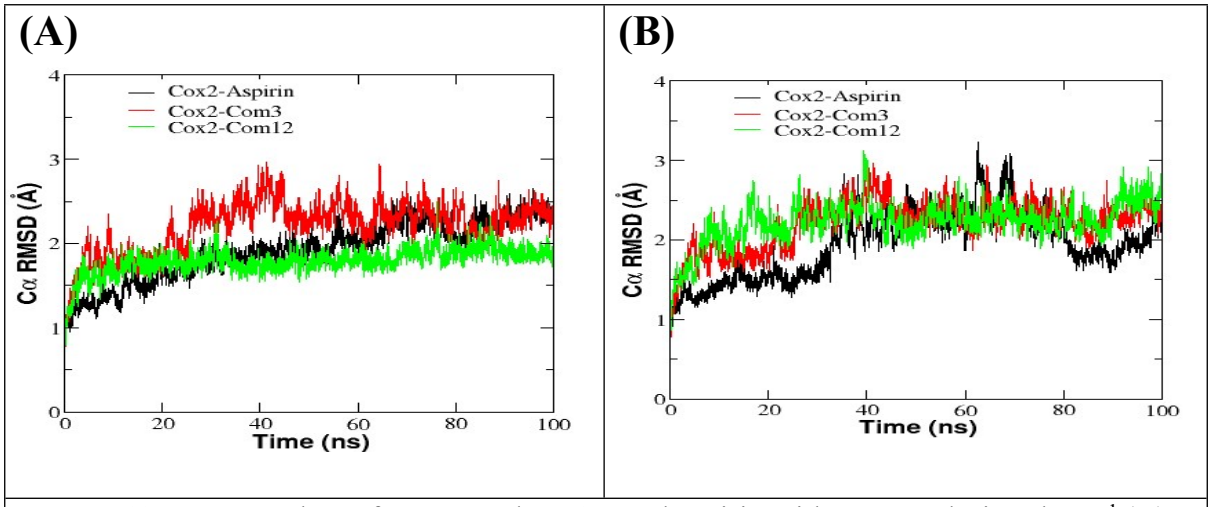


Figure S17. RMSD plots of compounds 3, 12, and aspirin with COX-2 during the 2nd (A) and 3rd (B) replica Simulation.

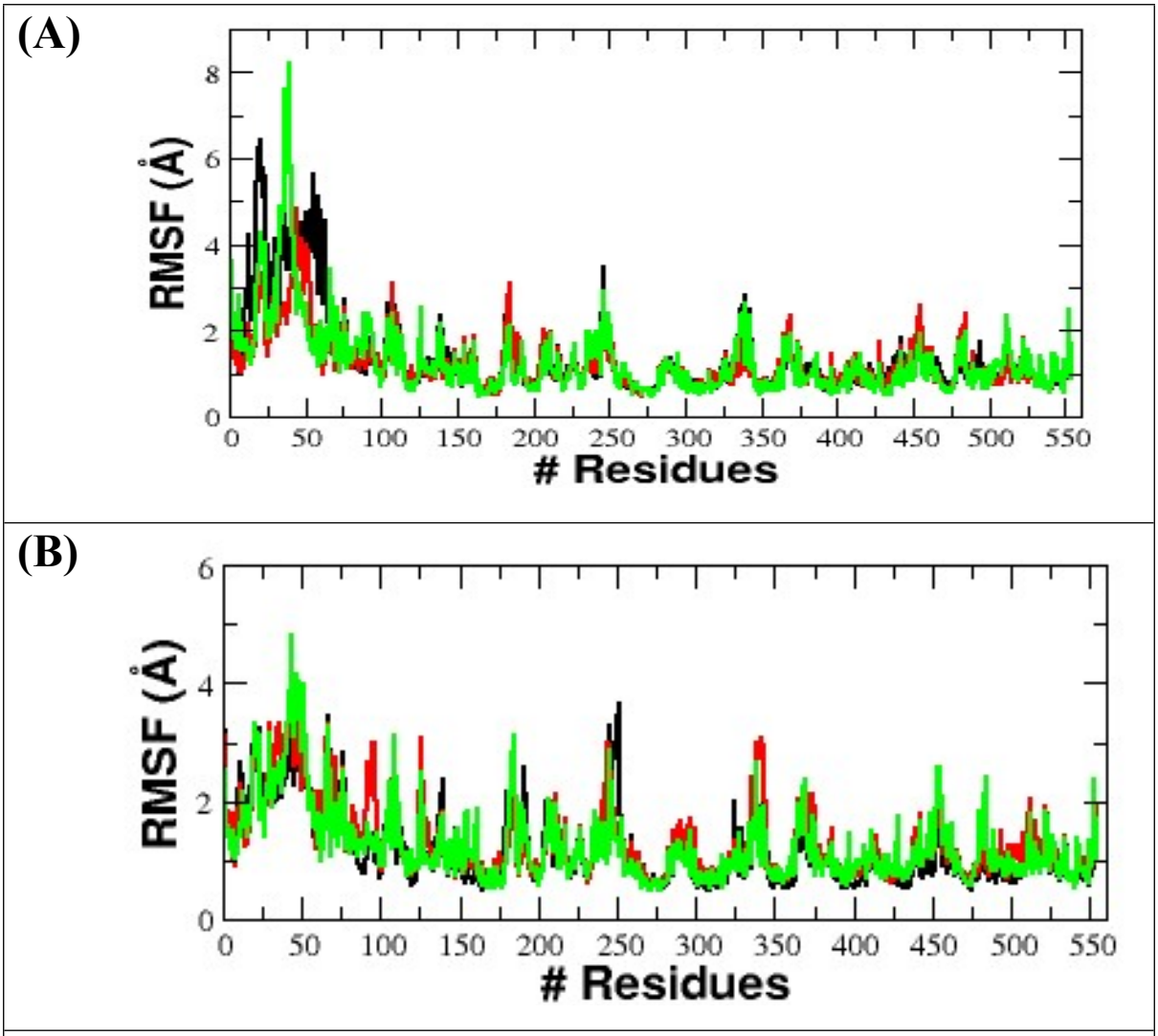


Figure S18. RMSF plots of compounds 3 (red), 12 (green), and aspirin (black) with COX-1 during the 2nd (A) and 3rd (B) replica Simulation

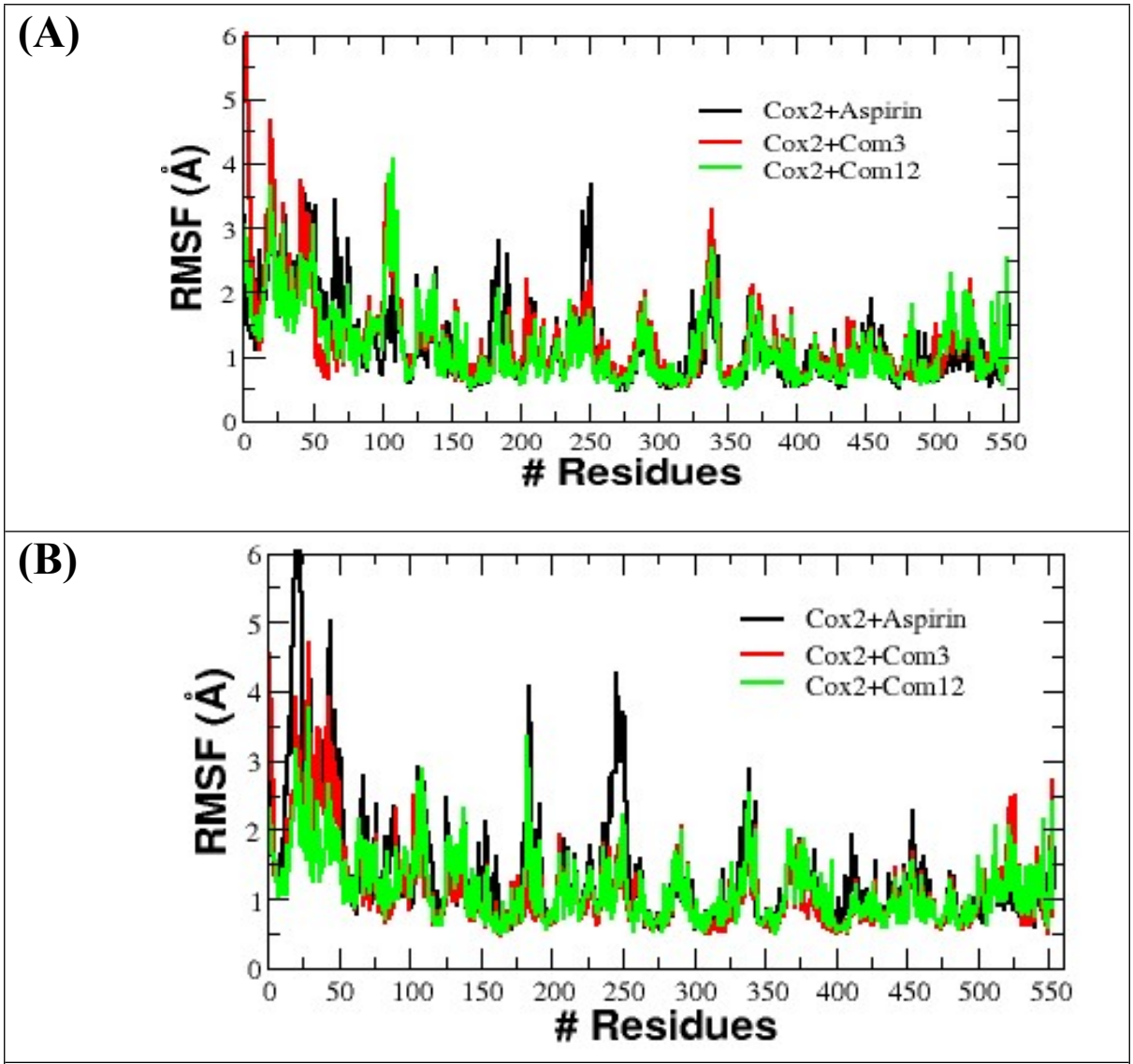


Figure S19. RMSF plots of compounds 3 (red), 12 (green), and aspirin (black) with COX-2 during the 2nd (A) and 3rd (B) replica Simulation.

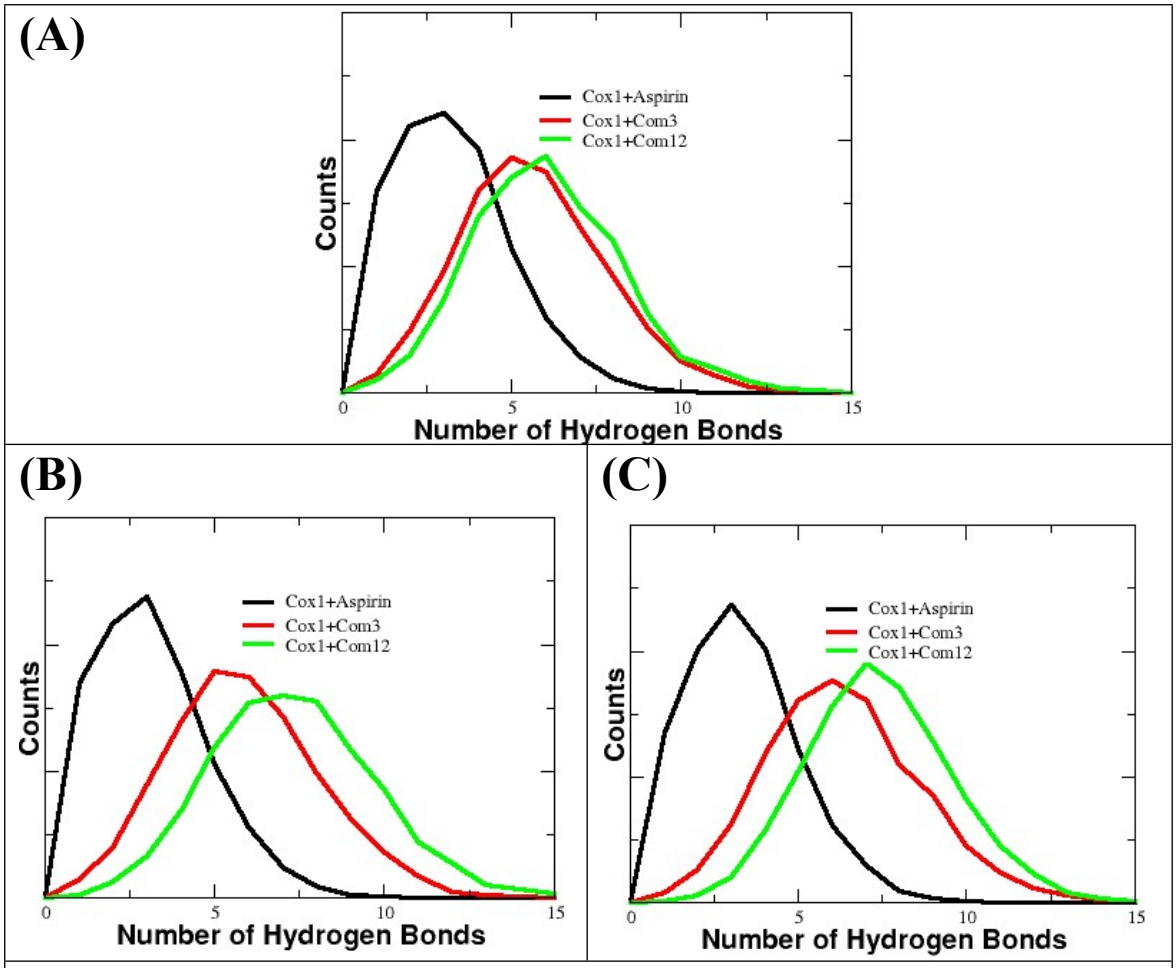


Figure S20. The hydrogen bonding population graph between inhibitors and COX-1 in three replica of 100 ns Simulations (A-C).

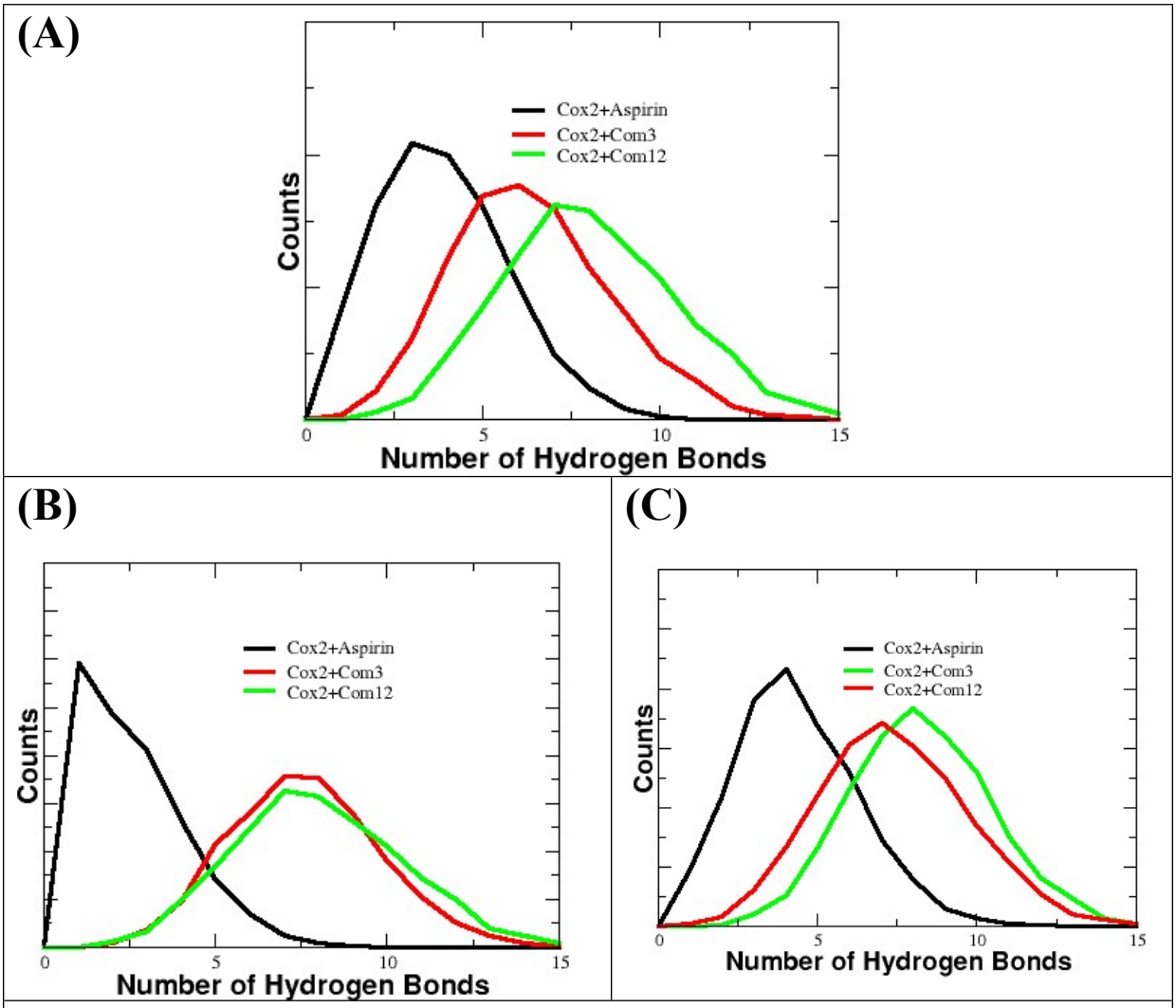


Figure S21: The hydrogen bonding population graph between inhibitors and COX-2 in three replicas of 100 ns Simulations (A-C)

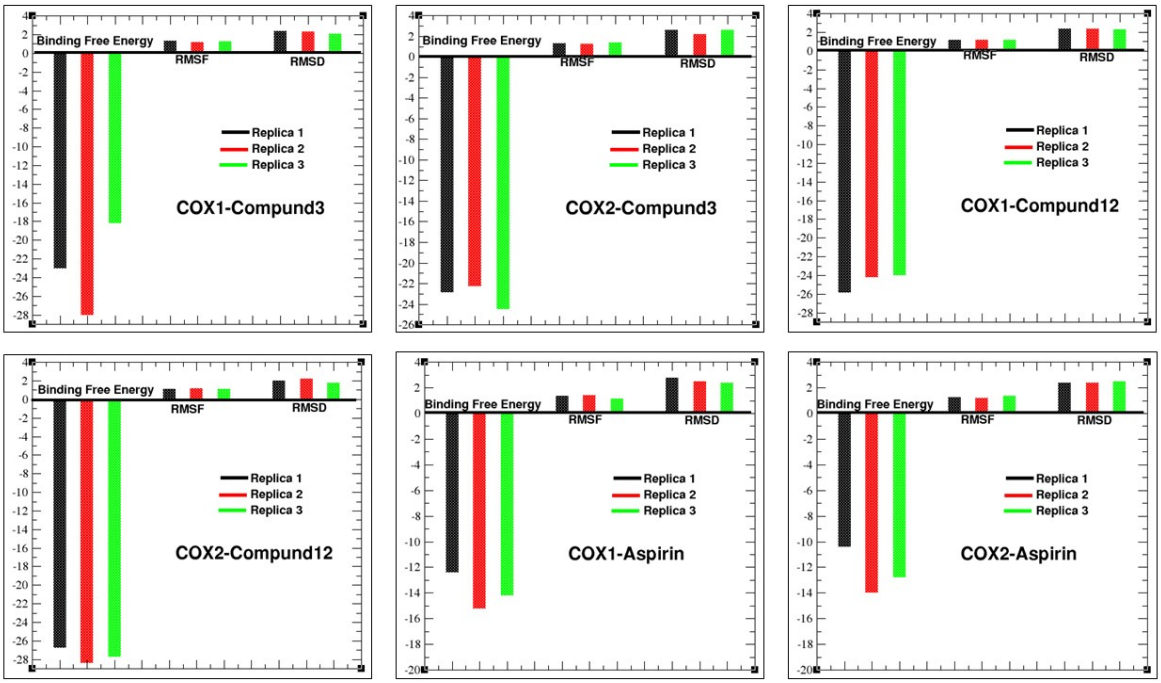


Figure S22. Cumulative diagram of RMSD, RMSF, and binding-free energy of compounds 3, 12, and aspirin with COX-1 and COX-2 during three replica simulations

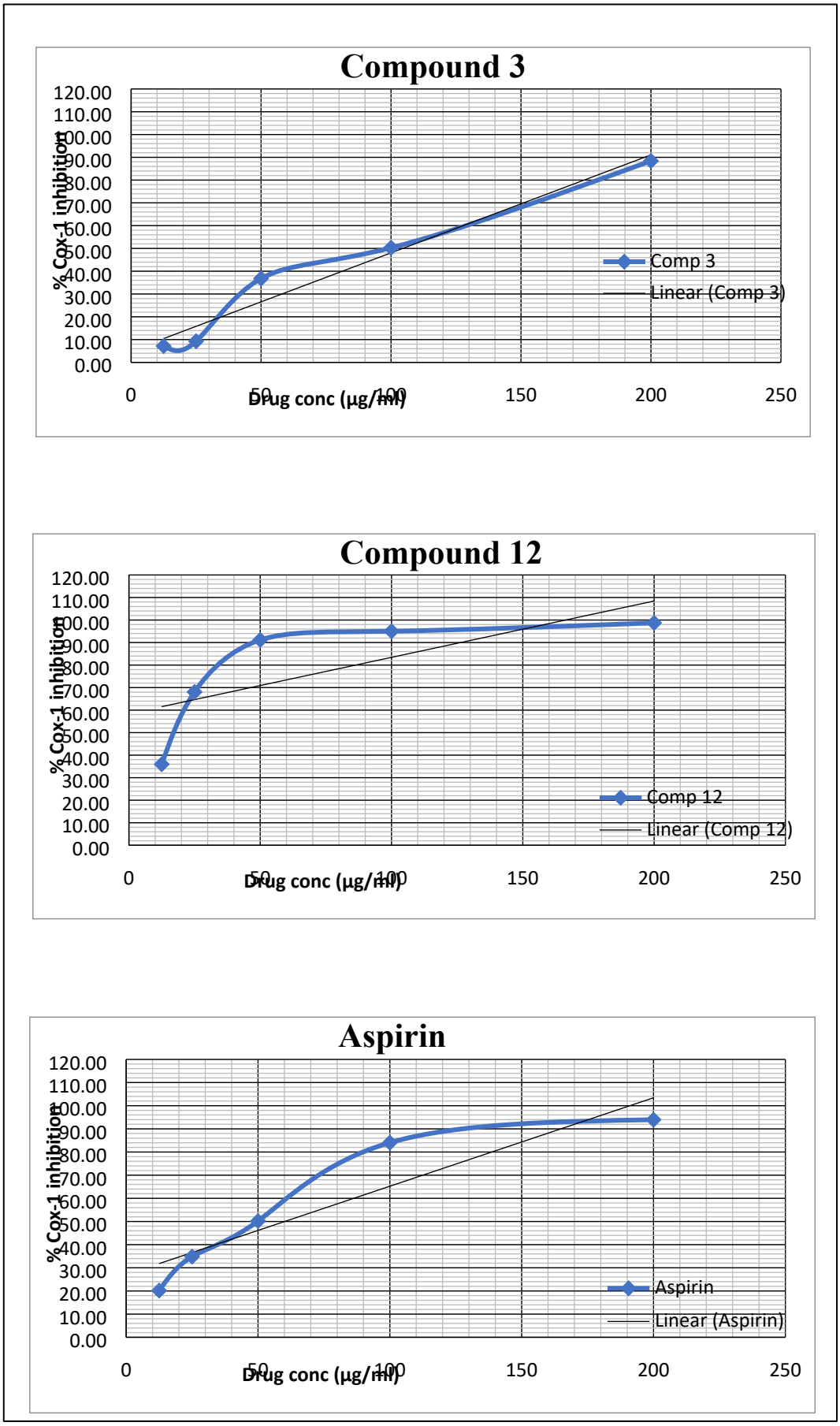


Figure S23. Data for the calculation of IC50 value of compounds 3, 12, and aspirin with COX-1 enzyme.

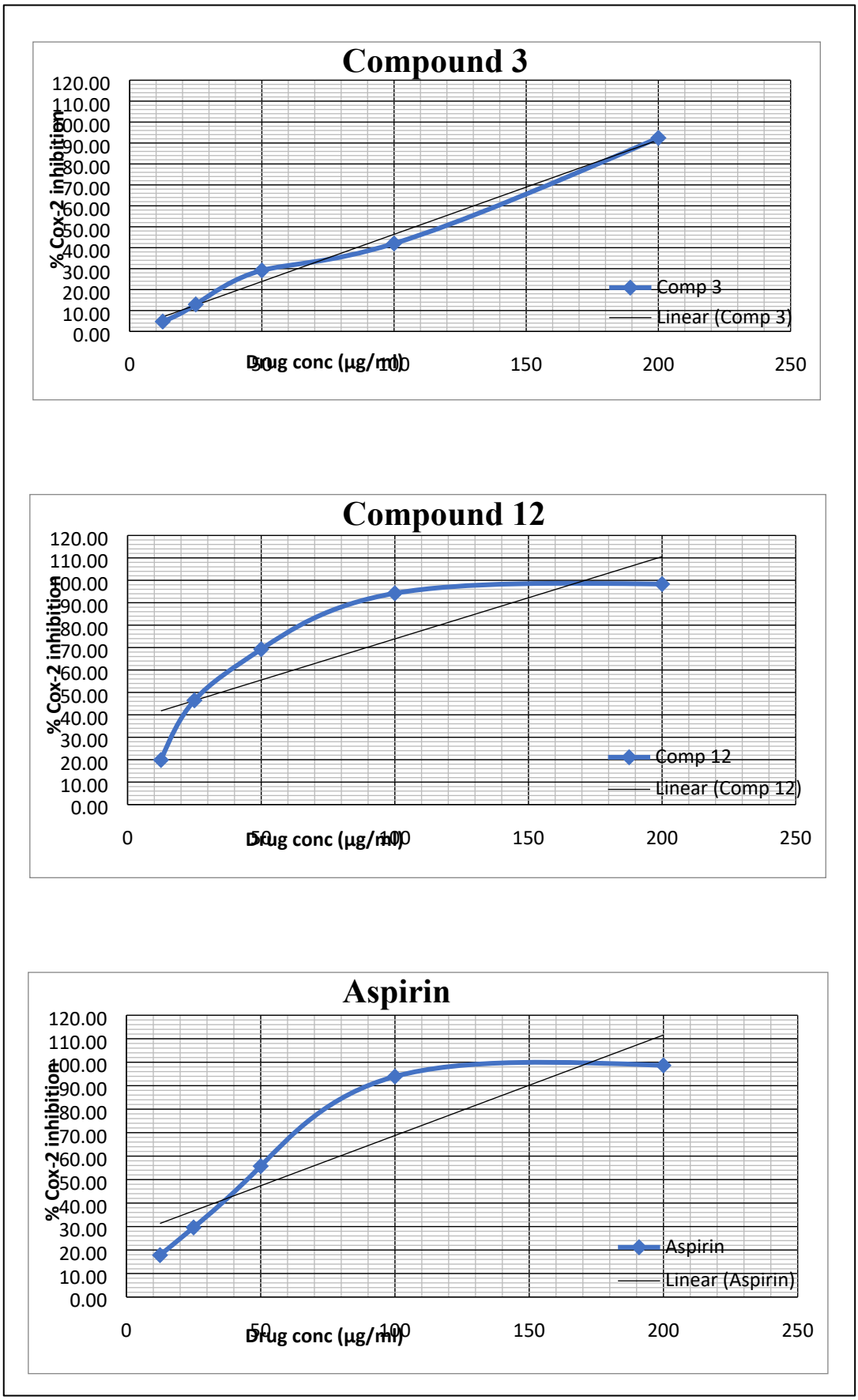


Figure S24. Data for the calculation of IC_{50} value of compounds 3, 12, and aspirin with COX-2 enzyme.

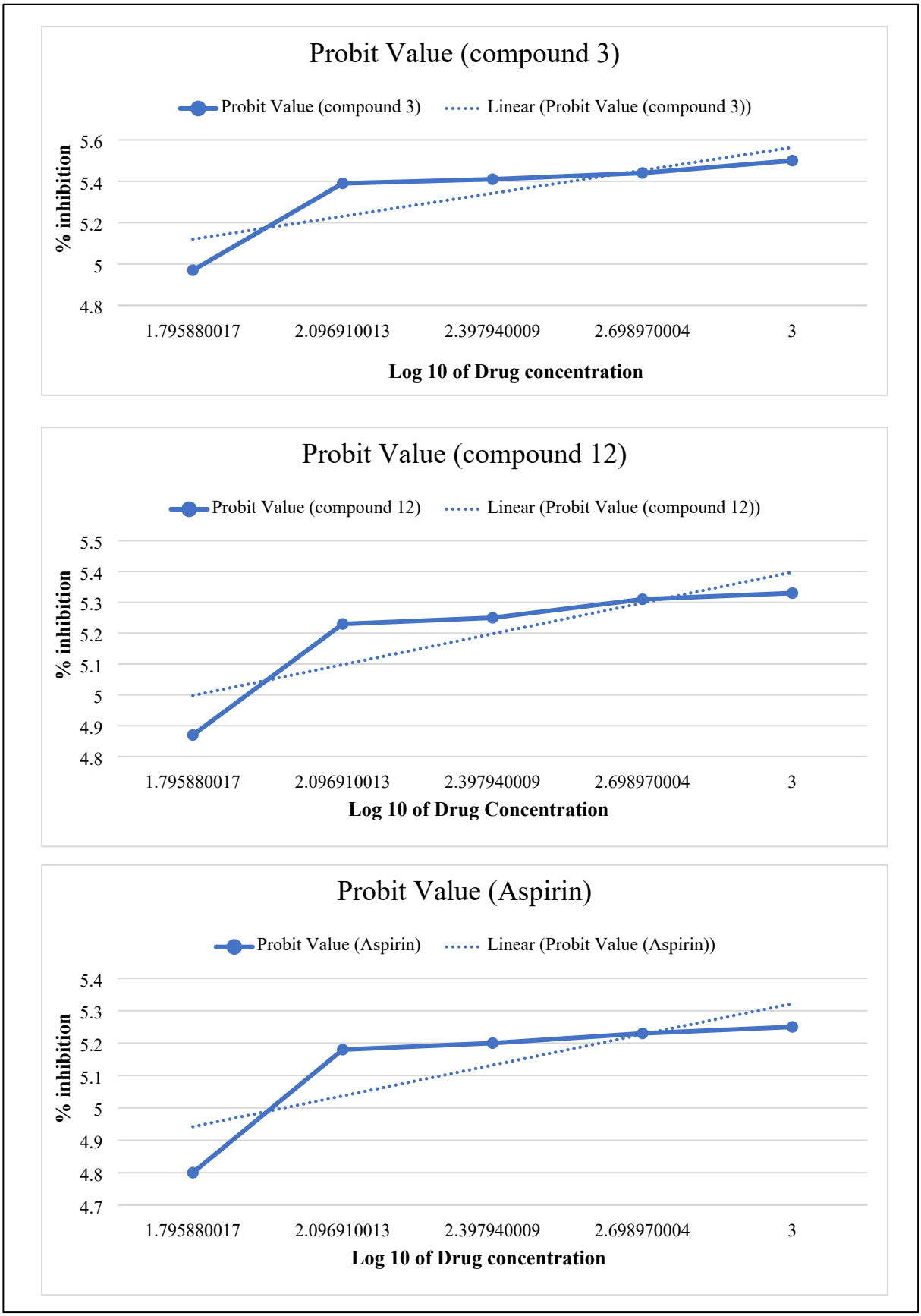
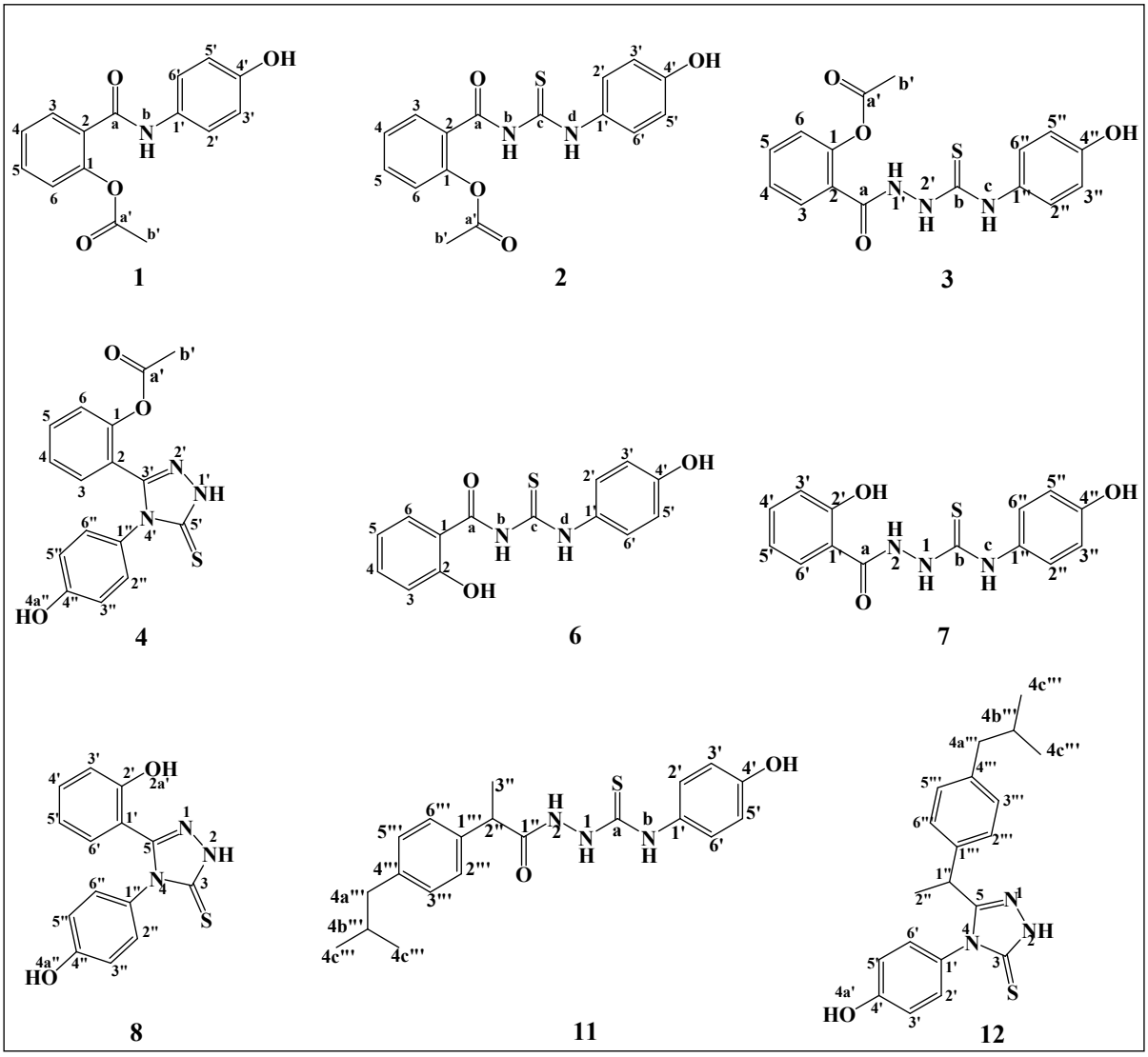


Figure S25. Data for the calculation of IC50 value of compounds 3, 12, and aspirin for the antiplatelet activity.



Note- The compound numbering and IUPAC nomenclature have been assigned using ChemDraw Professional 15.0 software.

Figure S26. Structures of newly synthesized compounds with numbering.

Table S1. ADMET features of compounds other than those selected for synthesis

Compounds	MW	% ABS	TPSA (Å²)	LogP	LogS	GI	P-gp	BBB	Lipinski's rule	LD_{50} (mg/kg)	Toxicity class	Drug Score
13	332.40	87.83	61.36	4.28	-7.66	High	No	Yes	Followed	936.83	3	0.67
14	406.50	68.45	117.51	4.12	-7.86	High	No	No	Followed	1052.13	3	1.83
15	388.49	75.20	97.96	4.49	-7.88	High	No	No	Followed	969.18	3	2.00
16	387.46	87.83	61.36	4.49	-8.48	High	No	No	Violated	1119.46	3	1.03
17	461.36	68.45	117.51	4.33	-8.66	Low	No	No	Followed	1230.41	3	2.02
18	443.35	75.20	97.96	5.01	-8.69	Low	No	No	Violated	1269.85	3	2.24
19	335.37	91.98	49.33	4.38	-7.54	High	Yes	Yes	Violated	560.44	3	1.51
20	409.48	72.60	105.48	4.09	-7.74	High	No	No	Followed	1393.92	3	2.01
21	391.46	29.64	85.93	4.90	-7.77	High	Yes	No	Violated	939.09	3	1.05
22	341.31	85.00	69.56	4.09	-6.81	High	No	No	Followed	881.35	3	-0.59
23	415.41	65.63	125.71	3.83	-7.00	Low	No	No	Followed	1378.75	3	0.54
24	397.40	72.21	106.16	4.36	-7.03	Low	No	No	Followed	1553.25	3	0.52

Table S2. Predicted physicochemical, medicinal, excretion and toxicological parameters from SwissADME, Osiris DataWarrior and ADMETlab tools

Compounds				Excretion		Toxicity Prediction			
	HBA	HBD	PAINS	$T_{1/2}$ (h)	CL ml/min/kg	Tumorigenic	Reproductive effective	Skin Sensitization	Mutagenic
1	4	2	0 alert	0.897	1.725	🟢	🟢	🟢	🟢
2	4	3	0 alert	0.892	1.072	🟢	🟡	🟢	🟢
3	4	4	0 alert	0.827	1.131	🟢	🟡	🟢	🟢
4	4	2	0 alert	1.285	1.480	🟢	🟡	🟢	🟡
5	3	3	0 alert	0.967	1.803	🟢	🟢	🟢	🟢
6	3	4	0 alert	0.962	1.006	🟢	🟡	🟢	🟢
7	3	5	0 alert	0.929	1.190	🟢	🟡	🟢	🟢
8	3	3	0 alert	1.391	1.550	🟢	🟡	🟢	🟡
9	2	2	0 alert	1.672	2.218	🟢	🟢	🟢	🟢
10	2	3	0 alert	1.742	1.958	🟢	🟡	🟢	🟢
11	2	4	0 alert	1.672	1.722	🟢	🟡	🟢	🟢
12	2	2	0 alert	1.946	1.707	🟢	🟡	🟢	🟡
Aspirin	4	1	0 alert	0.895	2.004	🟡	🟡	🟢	🟡
Ibuprofen	2	1	0 alert	0.801	0.536	🟢	🟡	🟢	🟡
Celecoxib	7	1	0 alert	1.872	0.618	🟢	🟢	🟢	🟢

Note: - HBA: hydrogen bond acceptor, HBD: hydrogen bond donor, PAINS- pan assay interference compounds, $T_{1/2}$: half-life time, CL: clearance rate

🔴 Toxic, 🟡 slightly toxic, 🟢 safe

Table S3. Interactions of compounds 3,12, aspirin, ibuprofen, and celecoxib with COX-1 from Discovery Studio Visualizer

Compounds	Name	Distance	Category	Type
3	A:PHE518:HN - :UNK1:O1	2.9562	Hydrogen Bond	Conventional Hydrogen Bond
	A:SER530:HG - :UNK1:O3	1.97968	Hydrogen Bond	Conventional Hydrogen Bond
	:UNK1:H6 - :UNK1:O2	1.7416	Hydrogen Bond	Conventional Hydrogen Bond
	:UNK1:S1 - :UNK1:O2	3.76464	Hydrogen Bond	Conventional Hydrogen Bond
	:UNK1:H1 - A:GLN192:OE1	1.96565	Hydrogen Bond	Conventional Hydrogen Bond
	A:ILE523:CA - :UNK1:O4	2.90951	Hydrogen Bond	Carbon Hydrogen Bond
	A:ILE523:CD1 - :UNK1	3.77496	Hydrophobic	Pi-Sigma
	A:MET522:SD - :UNK1	5.99659	Other	Pi-Sulfur
	A:TRP387 - :UNK1	5.32366	Hydrophobic	Pi-Pi T-shaped
	A:GLY526:C,O;ALA527:N - :UNK1	3.67493	Hydrophobic	Amide-Pi Stacked
	:UNK1 - A:LEU352	5.45511	Hydrophobic	Pi-Alkyl
12	:UNK1:H21 - A:MET522:O	1.80044	Hydrogen Bond	Conventional Hydrogen Bond
	A:ILE523:CA - :UNK1:N2	3.71604	Hydrogen Bond	Carbon Hydrogen Bond
	A:ILE523:CG2 - :UNK1	3.70587	Hydrophobic	Pi-Sigma
	:UNK1:S1 - A:TRP387	5.56252	Other	Pi-Sulfur
	:UNK1:S1 - A:TRP387	4.59253	Other	Pi-Sulfur
	A:TRP387 - :UNK1	5.97936	Hydrophobic	Pi-Pi T-shaped
	A:ALA527 - :UNK1:C17	3.53854	Hydrophobic	Alkyl
	:UNK1:C17 - A:VAL349	4.6748	Hydrophobic	Alkyl

	:UNK1:C12 - A:ILE523	4.61523	Hydrophobic	Alkyl
	:UNK1 - A:LEU352	5.44247	Hydrophobic	Pi-Alkyl
	:UNK1 - A:LEU352	4.56172	Hydrophobic	Pi-Alkyl
	:UNK1 - A:VAL349	5.13873	Hydrophobic	Pi-Alkyl
Aspirin	A:ALA527:HN - :UNL1:O	2.78627	Hydrogen Bond	Conventional Hydrogen Bond
	A:SER530:HG - :UNL1:O	1.99733	Hydrogen Bond	Conventional Hydrogen Bond
	A:MET522:SD - :UNL1	5.78959	Other	Pi-Sulfur
	A:TRP387 - :UNL1	5.057	Hydrophobic	Pi-Pi T-shaped
Ibuprofen	A:ARG120:HE - :UNL1:O	2.87362	Hydrogen Bond	Conventional Hydrogen Bond
	A:ARG120:HH21 - :UNL1:O	2.40037	Hydrogen Bond	Conventional Hydrogen Bond
	:UNL1:H - A:TYR355:OH	2.14108	Hydrogen Bond	Conventional Hydrogen Bond
	A:ILE523:CG2 - :UNL1	3.52442	Hydrophobic	Pi-Sigma
	A:TYR355 - :UNL1	5.05626	Hydrophobic	Pi-Pi T-shaped
	:UNL1:C - A:VAL349	5.32998	Hydrophobic	Alkyl
	:UNL1:C - A:ILE523	4.05527	Hydrophobic	Alkyl
	A:TYR355 - :UNL1:C	4.12718	Hydrophobic	Pi-Alkyl
	A:PHE518 - :UNL1:C	4.73574	Hydrophobic	Pi-Alkyl
	:UNL1 - A:LEU352	5.2533	Hydrophobic	Pi-Alkyl
Celecoxib	A:ILE517:HN - :UNL1:O	2.15627	Hydrogen Bond	Conventional Hydrogen Bond
	:UNL1:H - A:SER353:O	2.40538	Hydrogen Bond	Conventional Hydrogen Bond
	:UNL1:H - A:SER516:OG	2.119	Hydrogen Bond	Conventional Hydrogen Bond

	A:SER353:CB - :UNL1:N	3.37675	Hydrogen Bond	Carbon Hydrogen Bond
	A:SER516:CB - :UNL1:O	3.17226	Hydrogen Bond	Carbon Hydrogen Bond
	A:SER353:CA - :UNL1	3.30624	Hydrophobic	Pi-Sigma
	A:ILE523:CG2 - :UNL1	3.69443	Hydrophobic	Pi-Sigma
	:UNL1:S - A:HIS90	5.55944	Other	Pi-Sulfur
	:UNL1:C - A:MET522	4.54335	Hydrophobic	Alkyl
	:UNL1:C - A:VAL116	4.85726	Hydrophobic	Alkyl
	:UNL1:C - A:VAL349	5.47623	Hydrophobic	Alkyl
	:UNL1:C - A:LEU359	5.0707	Hydrophobic	Alkyl
	A:TYR355 - :UNL1:C	5.22082	Hydrophobic	Pi-Alkyl
	A:TRP387 - :UNL1:C	4.77939	Hydrophobic	Pi-Alkyl
	A:PHE518 - :UNL1:C	4.52176	Hydrophobic	Pi-Alkyl
	:UNL1 - A:VAL349	5.13022	Hydrophobic	Pi-Alkyl
	:UNL1 - A:ALA527	4.22688	Hydrophobic	Pi-Alkyl
	:UNL1 - A:LEU352	5.04157	Hydrophobic	Pi-Alkyl
	:UNL1 - A:ILE523	5.23641	Hydrophobic	Pi-Alkyl
	:UNL1 - A:ALA527	4.49751	Hydrophobic	Pi-Alkyl
	:UNL1 - A:LEU352	5.25538	Hydrophobic	Pi-Alkyl

Table S4. Interactions of compounds 3,12, aspirin, ibuprofen, and celecoxib with COX-2 from Discovery Studio Visualizer

Compounds	Name	Distance	Category	Type
3	A:PHE504:HN - :UNK1:O1	2.74021	Hydrogen Bond	Conventional Hydrogen Bond
	A:SER516:HG - :UNK1:O3	1.95556	Hydrogen Bond	Conventional Hydrogen Bond
	:UNK1:H6 - A:VAL509:O	2.42338	Hydrogen Bond	Conventional Hydrogen Bond
	:UNK1:H1 - A:GLN178:OE1	2.02181	Hydrogen Bond	Conventional Hydrogen Bond
	:UNK1:H1 - A:LEU338:O	2.59717	Hydrogen Bond	Conventional Hydrogen Bond
	A:VAL509:CG2 - :UNK1	3.60279	Hydrophobic	Pi-Sigma
	A:MET508:SD - :UNK1	5.0845	Other	Pi-Sulfur
	A:TYR371 - :UNK1	5.89196	Hydrophobic	Pi-Pi T-shaped
	A:GLY512:C,O;ALA513:N - :UNK1	4.07177	Hydrophobic	Amide-Pi Stacked
12	A:VAL509:CA - :UNK1:N2	2.91897	Hydrogen Bond	Carbon Hydrogen Bond
	A:VAL509:CG2 - :UNK1	3.92178	Hydrophobic	Pi-Sigma
	:UNK1:C14 - A:HIS75	3.78461	Hydrophobic	Pi-Sigma
	A:MET508:SD - :UNK1	5.24332	Other	Pi-Sulfur
	:UNK1:S1 - A:TRP373	5.06532	Other	Pi-Sulfur
	:UNK1:S1 - A:TRP373	4.47975	Other	Pi-Sulfur
	A:TRP373 - :UNK1	5.73736	Hydrophobic	Pi-Pi T-shaped
	A:GLY512:C,O;ALA513:N - :UNK1	4.50941	Hydrophobic	Amide-Pi Stacked
		3.32681	Hydrophobic	Alkyl

	A:ALA502 - :UNK1:C12	3.39136	Hydrophobic	Alkyl
	A:ALA513 - :UNK1:C17	4.46524	Hydrophobic	Alkyl
	:UNK1:C17 - A:VAL509	4.52228	Hydrophobic	Alkyl
	:UNK1:C12 - A:ARG499	5.08708	Hydrophobic	Alkyl
	:UNK1:C12 - A:VAL509	4.60226	Hydrophobic	Pi-Alkyl
	A:HIS75 - :UNK1:C12	4.78394	Hydrophobic	Pi-Alkyl
	:UNK1 - A:VAL509	4.89884	Hydrophobic	Pi-Alkyl
	:UNK1 - A:LEU338	5.21132	Hydrophobic	Pi-Alkyl
	:UNK1 - A:VAL335	5.41693	Hydrophobic	Pi-Alkyl
	:UNK1 - A:LEU338			
Aspirin	A:SER516:HG - :UNL1:O	1.90095	Hydrogen Bond	Conventional Hydrogen Bond
	A:MET508:SD - :UNL1	5.38311	Other	Pi-Sulfur
	A:PHE504 - :UNL1	5.68346	Hydrophobic	Pi-Pi Stacked
	A:GLY512:C,O;ALA513:N - :UNL1	3.79773	Hydrophobic	Amide-Pi Stacked
Ibuprofen	A:ARG499:HH12 - :UNL1:O	2.06873	Hydrogen Bond	Conventional Hydrogen Bond
	:UNL1:H - A:PHE504:O	2.15225	Hydrogen Bond	Conventional Hydrogen Bond
	A:VAL509:CG2 - :UNL1	3.73666	Hydrophobic	Pi-Sigma
	A:ALA502 - :UNL1:C	3.42614	Hydrophobic	Alkyl
	:UNL1:C - A:LEU338	4.33802	Hydrophobic	Alkyl
	A:HIS75 - :UNL1:C	4.81816	Hydrophobic	Pi-Alkyl
	A:PHE504 - :UNL1:C	4.78367	Hydrophobic	Pi-Alkyl

	:UNL1 - A:LEU338	5.05159	Hydrophobic	Pi-Alkyl
Celecoxib	A:ARG499:HH12 - :UNL1:O	2.64895	Hydrogen Bond	Conventional Hydrogen Bond
	A:ILE503:HN - :UNL1:O	3.04467	Hydrogen Bond	Conventional Hydrogen Bond
	A:PHE504:HN - :UNL1:O	2.18854	Hydrogen Bond	Conventional Hydrogen Bond
	:UNL1:H - A:LEU338:O	2.09329	Hydrogen Bond	Conventional Hydrogen Bond
	:UNL1:H - A:GLN178:OE1	2.11807	Hydrogen Bond	Conventional Hydrogen Bond
	A:SER339:CB - :UNL1:N	3.41	Hydrogen Bond	Carbon Hydrogen Bond
	A:VAL335:CG1 - :UNL1	3.76658	Hydrophobic	Pi-Sigma
	A:SER339:CA - :UNL1	3.51185	Hydrophobic	Pi-Sigma
	A:VAL509:CG1 - :UNL1	3.96631	Hydrophobic	Pi-Sigma
	A:VAL509:CG2 - :UNL1	3.77583	Hydrophobic	Pi-Sigma
	:UNL1:C - A:LEU370	5.14177	Hydrophobic	Alkyl
	:UNL1:C - A:MET508	4.32464	Hydrophobic	Alkyl
	:UNL1:C - A:VAL335	4.68521	Hydrophobic	Alkyl
	:UNL1:C - A:LEU345	4.98995	Hydrophobic	Alkyl
	A:TYR341 - :UNL1:C	5.14782	Hydrophobic	Pi-Alkyl
	A:TRP373 - :UNL1:C	5.28007	Hydrophobic	Pi-Alkyl
	A:TRP373 - :UNL1:C	4.50065	Hydrophobic	Pi-Alkyl
	A:PHE504 - :UNL1:C	4.45339	Hydrophobic	Pi-Alkyl
	:UNL1 - A:ALA513	4.33015	Hydrophobic	Pi-Alkyl
	:UNL1 - A:LEU338	5.37761	Hydrophobic	Pi-Alkyl

	:UNL1 - A:VAL509	4.96206	Hydrophobic	Pi-Alkyl
	:UNL1 - A:ALA513	4.84037	Hydrophobic	Pi-Alkyl

Table S5. Average RMSD analysis of compounds 3, 12, and aspirin with COX-1 and COX-2 isozymes during the three replicas

S. No.	Complexes	RMSD Analysis			Average RMSD (Å)
		Replica 1 (Å) ± SD	Replica 2 (Å) ± SD	Replica 3 (Å) ± SD	
1	Compound 12_COX-1	2.37± 0.272	2.40± 0.22	2.33± 0.21	2.37
2	Compound 12_COX-2	2.00± 0.207	2.22± 0.407	1.80± 0.307	2.01
3	Compound 3_COX-1	2.36±0.14	2.33±0.24	2.05± 0.264	2.24
4	Compound 3_COX-2	2.6.±0.197	2.20±0.197	2.61±0.97	2.46
5	Aspirin_COX-1	2.75± 0.40	2.47±0.21	2.41± 0.25	2.55
6	Aspirin_COX-2	2.37± 0.359	2.39±0.388	2.49± 0.388	2.41

Table S6. Average RMSF analysis of compounds 3, 12, and aspirin with COX-1 and COX-2 isozymes during the three replicas

S. No.	Complexes	RMSF Analysis			Average RMSF (Å)
		Replica 1 (Å) ± SD	Replica 2 (Å) ± SD	Replica 3 (Å) ± SD	
1	Compound 12_COX-1	1.20± 0.11	1.19± 0.02	1.22± 0.10	1.20
2	Compound 12_COX-2	1.10± 0.15	1.15± 0.07	1.12± 0.07	1.13
3	Compound 3_COX-1	1.30±0.14	1.17±0.10	1.23± 0.09	1.24
4	Compound 3_COX-2	1.3 ±0.09	1.27±0.09	1.40±0.10	1.32
5	Aspirin_COX-1	1.36± 0.1	1.40±0.10	1.20± 0.06	1.33
6	Aspirin_COX-2	1.23± 0.08	1.20±0.08	1.35± 0.08	1.27

Table S7. Binding free energy components of *COX-1* and Aspirin

Energy Component	COX-1-aspirin		
	Replica 1 (Å) ± SD	Replica 2 (Å) ± SD	Replica 3 (Å) ± SD
ΔE_{VDW}	-28.89	-30.60	-28.92
ΔE_{ELEC}	-7.28	-4.92	-6.25
ΔEPB	26.21	22.71	23.47
ΔEPB_{np}	-2.47	-2.43	-2.49
ΔE_{Disper}	0.00	0.00	0.00
ΔG	-12.4±1.1	-15.24	-14.20

Binding free energy (ΔG) of *COX-1* and ligand complex was calculated from the 100 ns

simulation. The molecular-mechanical energy calculations were performed using MM/PBSA analysis. ΔE_{ELEC}, ΔE_{VDW}, $\Delta EPB_{np,}$ and ΔEPB_{solv} are referred to as the electrostatic, Vander Waals, polar, the non-polar contribution to the solvation energy and the electrostatic contribution to the solvation energy, respectively.

Table S8. Binding free energy components of *COX-1,* and Compound 3

Energy Component	COX-1-Compound 3		
	Replica 1 (Å) ± SD	Replica 2 (Å) ± SD	Replica 3 (Å) ± SD
ΔE_{VDW}	-.03	-47.84	-49.03
ΔE_{ELEC}	-33.78	-41.70	-17.084
ΔEPB	59.19	64.99	52.72
ΔEPB_{np}	-4.48	-4.22	-4.22
ΔE_{Disper}	0.00	0.00	0.00
ΔG	-22.89±1.7	-28.0±1.7	-18.21±1.43

Binding free energy (ΔG) of *COX-1 protein* and ligand complex was calculated from the 100 ns simulation. The molecular-mechanical energy calculations were performed using MM/PBSA analysis. ΔE_{ELEC}, ΔE_{VDW}, $\Delta EPB_{np,}$ and ΔEPB_{solv} are referred to as the electrostatic, Vander Waals, polar, the non-polar contribution to the solvation energy, and the electrostatic contribution to the solvation energy, respectively.

Table S9. Binding free energy components of *COX-1* and Compound 12

Energy Component	COX-1-Compound12		
	Replica 1 (Å) ± SD	Replica 2 (Å) ± SD	Replica 3 (Å) ± SD
ΔE_{VDW}	-48.73	-48.57	-48.73
ΔE_{ELEC}	-11.19	-14.96	-11.19
ΔEPB	40.48	44.01	40.48
ΔEPB_{np}	-4.64	-4.7061	-4.64
ΔE_{Disper}	0.00	0.00	0.00
ΔG	-25.86±0.25	-24.22±1.4	-24.01±1.5

Binding free energy (ΔG) of *COX-1 protein* and ligand complex was calculated from the 100 ns simulation. The molecular-mechanical energy calculations were performed using MM/PBSA analysis. ΔE_{ELEC}, ΔE_{VDW}, $\Delta EPB_{np,}$ and ΔEPB_{solv} are referred to as the electrostatic, Vander Waals, polar, the non-polar contribution to the solvation energy, and the electrostatic contribution to the solvation energy, respectively.

Table S10. Binding free energy components of *COX-2* and Aspirin

Energy Component	COX-2-Aspirin		
	Replica 1 (Å) ± SD	Replica 2 (Å) ± SD	Replica 3 (Å) ± SD
ΔE_{VDW}	-29.19	-26.84	-290.3
ΔE_{ELEC}	-9.18	-19.42	-2.084
ΔEPB	30.12	33.98	20.82
ΔEPB_{np}	-2.48	-2.35	-2.52
ΔE_{Disper}	0.00	0.00	0.00
ΔG	-10.4±1.2	-14.0±0.85	-12.81±1.33

Binding free energy (ΔG) of *COX-2 protein* and ligand complex was calculated from the 100

ns simulation. The molecular-mechanical energy calculations were performed using MM/PBSA analysis. ΔE_{ELEC}, ΔE_{VDW}, ΔEPB_{np} and ΔEPB_{solv} are referred to as the electrostatic, Vander Waals, polar, the non-polar contribution to the solvation energy, and the electrostatic contribution to the solvation energy, respectively.

Table S11. Binding free energy components of *COX-2* and Compound 3

Energy Component	COX-2-Compound 3		
	Replica 1 (Å) ± SD	Replica 2 (Å) ± SD	Replica 3 (Å) ± SD
ΔE_{VDW}	-43.32	-45.34	-43.89
ΔE_{ELEC}	-24.04	-32.81	-29.86
ΔEPB	48.46	59.61	53.19
ΔEPB_{np}	-3.95	-3.78	-3.90
ΔE_{Disper}	0.00	0.00	0.00
ΔG	-22.86±1.4	-22.30±2.5	-24.51±0.59

Binding free energy (ΔG) of *COX-2 protein* and ligand complex was calculated from the 100 ns simulation. The molecular-mechanical energy calculations were performed using MM/PBSA analysis. ΔE_{ELEC}, ΔE_{VDW}, $\Delta EPB_{np,}$ and ΔEPB_{solv} are referred to as the electrostatic, Vander Waals, polar, the non-polar contribution to the solvation energy, and the electrostatic contribution to the solvation energy, respectively.

Table S12. Binding free energy components of *COX-2* and Compound 12

Energy Component	COX-2-Compound12		
	Replica 1 (Å) ± SD	Replica 2 (Å) ± SD	Replica 3 (Å) ± SD
ΔE_{VDW}	-48.35	-50.90	-48.21
ΔE_{ELEC}	-14.51	-10.33	-11.64
ΔEPB	40.57	37.46	36.53
ΔEPB_{np}	-4.45	-4.50	-4.41
ΔE_{Disper}	0.00	0.00	0.00
ΔG	-26.76±0.95	-28.40±1.28	-27.73±0.55

Binding free energy (ΔG) of *COX-2 protein* and ligand complex was calculated from the 100 ns simulation. The molecular-mechanical energy calculations were performed using MM/PBSA analysis. ΔE_{ELEC}, ΔE_{VDW}, $\Delta EPB_{np,}$ and ΔEPB_{solv} are referred to as the electrostatic, Vander Waals, polar, the non-polar contribution to the solvation energy, and the electrostatic contribution to the solvation energy, respectively.

Table S13. Average Binding free energy (kcal/mol) and Docking Energy of Com3, Com12, and Aspirin with COX-1/COX-2 enzyme

	Aspirin_COX-2	Aspirin-COX-1	Com3-COX-2	Com3-COX-1	Com12-COX-2	Com12-COX-1
ΔG	-19.1±2.2	-20.2±2.1	-31.6±1.9	-31.23±1.8	-36.2±2.4	-35.0±2.3
Docking Energy	-6.40	-4.42	-9.73	-9.80	-10.11	-10.23

Binding free energy (ΔG) of *COX-2/COX-1* protein and ligand complex was calculated from the 100 ns simulation. The molecular-mechanical energy calculations were performed using MM/GBSA in Amber18. and docking energies in Kcal/mol (Pre MD simulations).

Table S14. The percentage inhibition of compounds 3, 12, and aspirin against COX-1 and COX-2 enzymes at specific concentrations.

Compounds	Conc. (µg/mL)	% COX-1 inhibition ± SD	% COX-2 inhibition ± SD
3	12.5	7.15±1.59	4.74±0.57
	25	9.26±1.63	12.94±0.84
	50	36.80±0.65	29.16±0.38
	100	50.30±1.14	42.01±0.91
	200	88.41±0.27	92.44±0.39
12	12.5	35.97±0.76	19.86±4.26
	25	68.06±0.87	46.46±0.83
	50	91.17±0.35	69.26±0.27
	100	95.04±0.13	94.21±0.17
	200	98.74±0.08	98.32±0.14
Aspirin	12.5	20.18±1.34	17.81±0.99
	25	34.83±0.71	29.61±0.38
	50	50.21±1.10	55.74±0.95
	100	84.04±1.23	93.92±0.23
	200	93.95±0.14	98.65±0.15

Note: - SD: standard deviation

Table S15. Percentage inhibition of compounds 3, 12 and aspirin on AA-induced platelet aggregation at specific concentrations

S. no.	Concentration (µg/mL)	% inhibition		
		Compound 3± SD	Compound 12± SD	Aspirin± SD
1	62.5	49.48±0.71	45.39±0.97	41.78±0.93
2	125	65.59±0.27	59.81±0.54	56.99±0.27
3	250	66.53±0.54	60.42±0.27	57.93±0.27
4	500	66.99±0.54	61.69±0.71	58.87±0.27
5	1000	68.73±0.71	62.77±0.58	60.09±0.46

Note: - SD: standard deviation

SMILES

Table S16. SMILEs for compounds given in the manuscript

Compounds	SMILES
1	OC1=CC=C(NC(C2=CC=CC=C2OC(C)=O)=O)C=C1
2	O=C(NC(NC1=CC=C(O)C=C1)=S)C2=C(OC(C)=O)C=CC=C2
3	OC1=CC=C(NC(NNC(C2=C(OC(C)=O)C=CC=C2)=O)=S)C=C1
4	S=C1N(C2=CC=C(O)C=C2)C(C3=C(OC(C)=O)C=CC=C3)=NN1
5	OC1=CC=CC=C1C(NC2=CC=C(O)C=C2)=O
6	O=C(NC(NC1=CC=C(O)C=C1)=S)C2=CC=CC=C2O
7	OC1=CC=C(NC(NNC(C2=CC=CC=C2O)=O)=S)C=C1
8	OC1=C(C(N2C3=CC=C(O)C=C3)=NNC2=S)C=CC=C1
9	CC(C(NC1=CC=C(O)C=C1)=O)C2=CC=C(CC(C)C)C=C2
10	CC(C(NC(NC1=CC=C(O)C=C1)=S)=O)C2=CC=C(CC(C)C)C=C2
11	OC1=CC=C(NC(NNC(C(C2=CC=C(CC(C)C)C=C2)C)=O)=S)C=C1
12	CC(C)CC1=CC=C(C(C(N2C3=CC=C(O)C=C3)=NNC2=S)C)C=C1
Aspirin	CC(=O)OC1=CC=CC=C1C(=O)O
Ibuprofen	CC(C)CC1=CC=C(C=C1)C(C)C(=O)O
Celecoxib	CC1=CC=C(C=C1)C2=CC(=NN2C3=CC=C(C=C3)S(=O)(=O)N)C(F)(F)F