

Supplementary Information

Development, Biological Evaluation, and Molecular Modelling of Some Benzene-sulfonamide Derivatives as Protein Tyrosine Phosphatase-1B Inhibitors for Managing Diabetes Mellitus and Associated Metabolic Disorders

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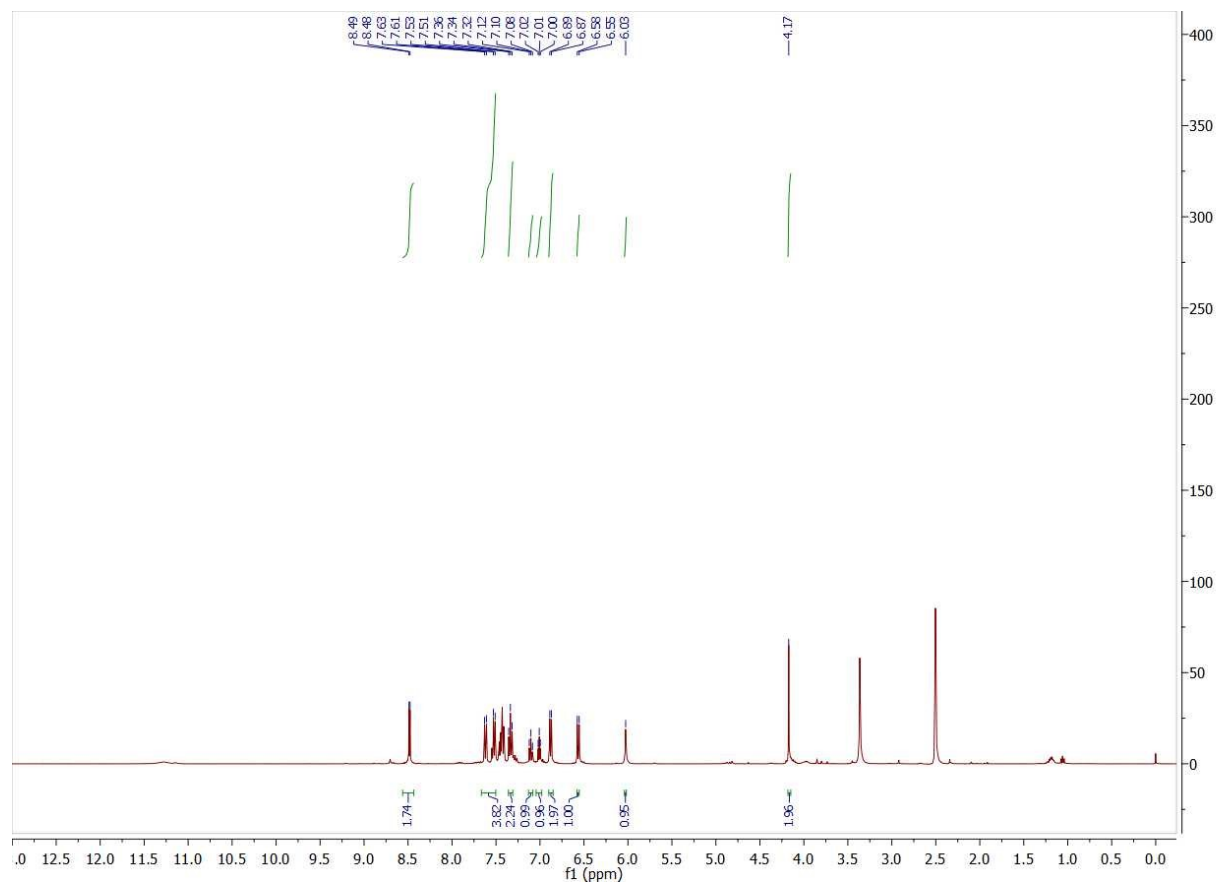


Fig. S1. ¹H-NMR of compound 3a

Supplementary Information

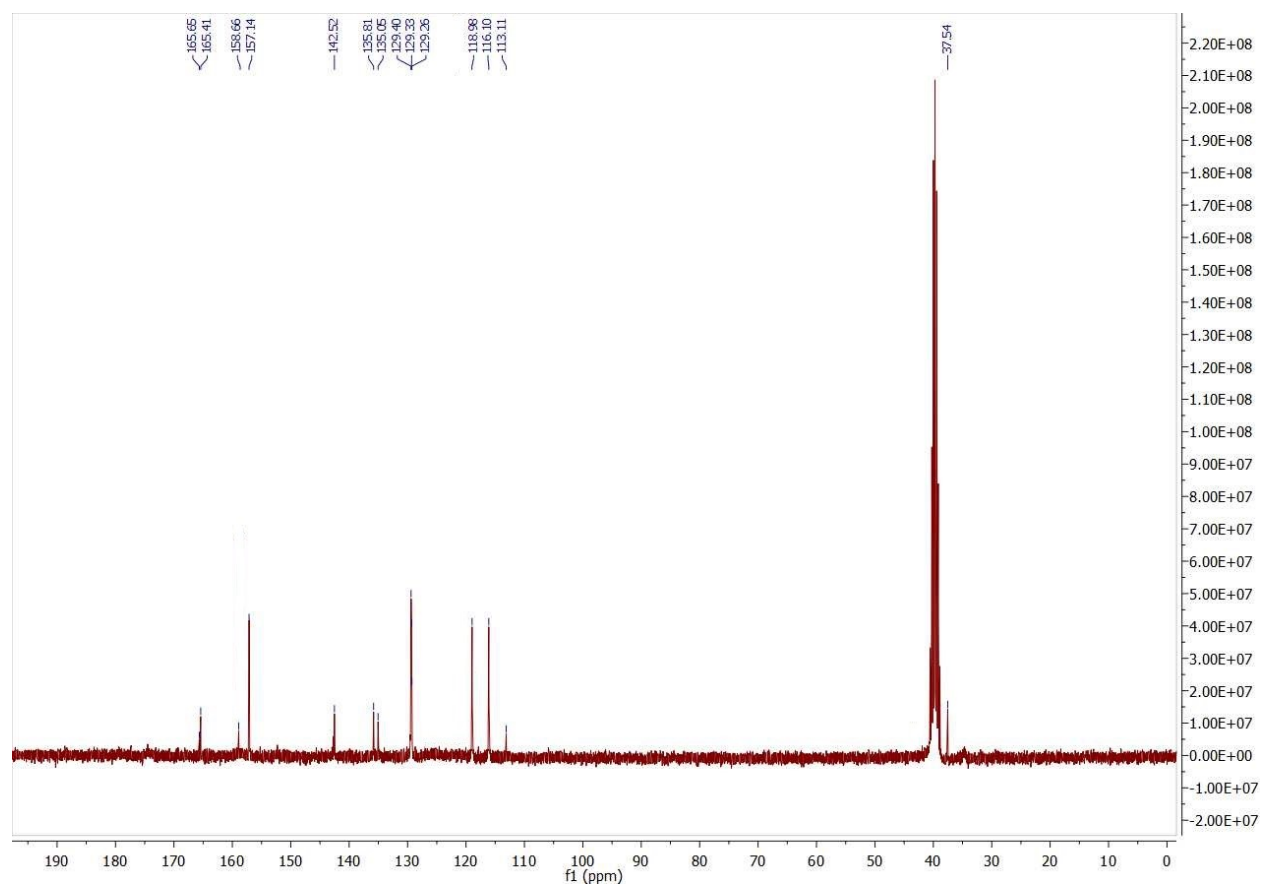


Fig. S2. ^{13}C -NMR of compound 3a

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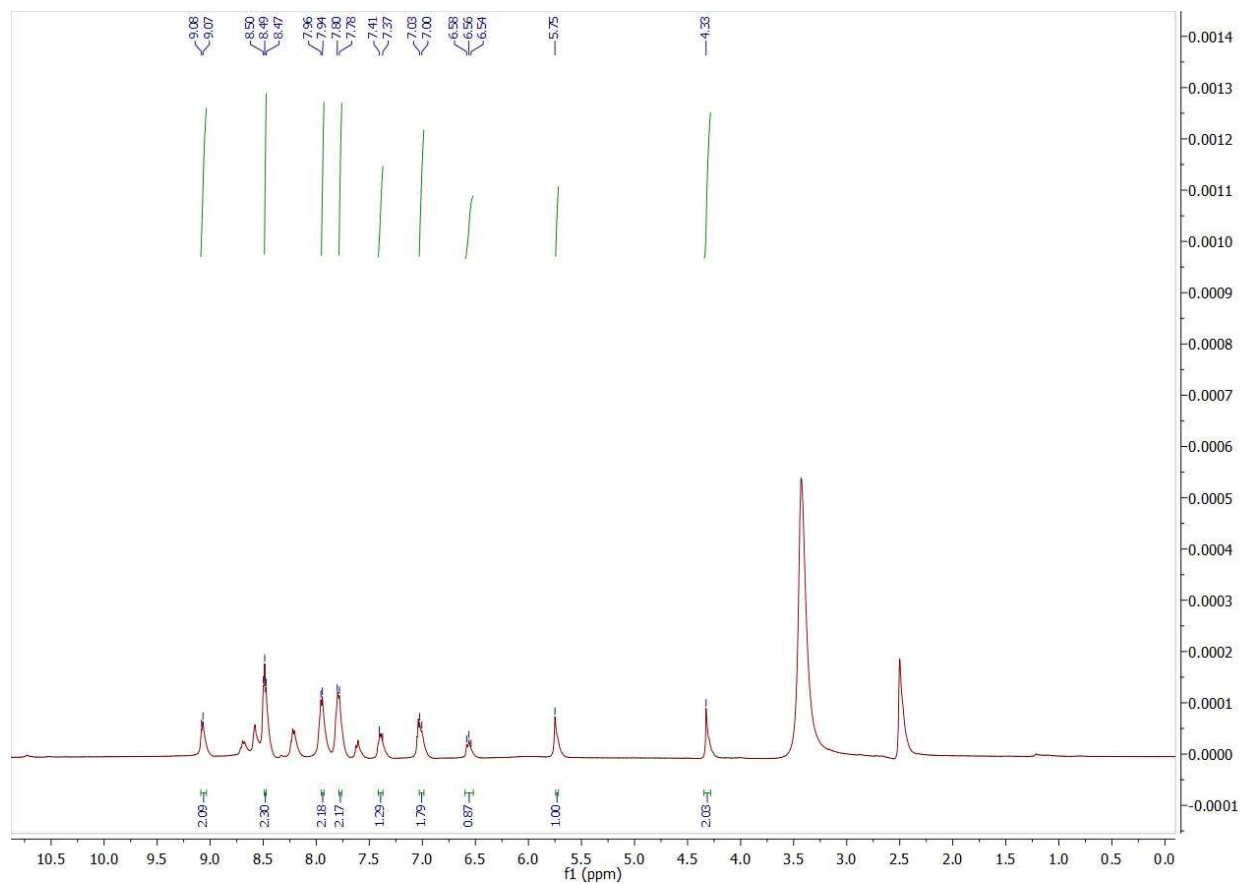


Fig. S3. ¹H-NMR of compound 3b

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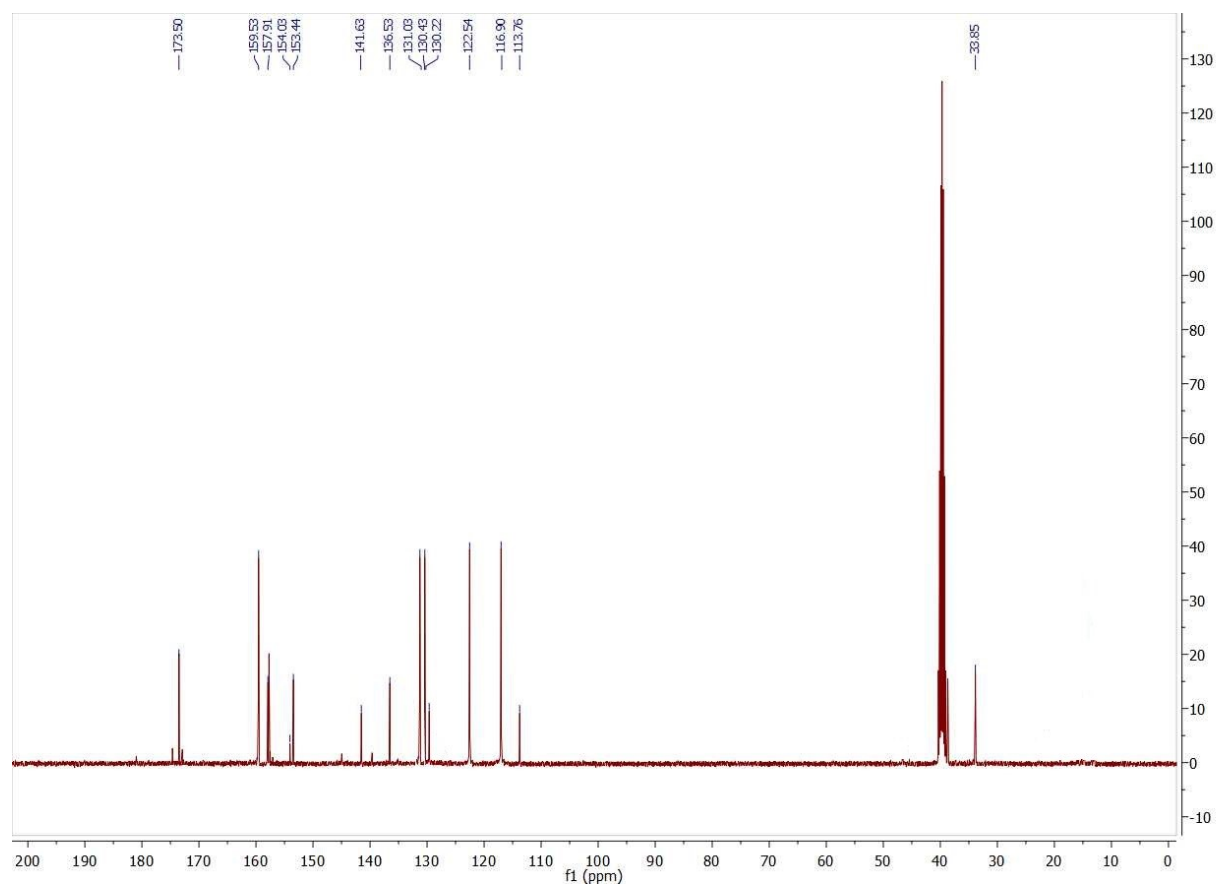


Fig. S4. ^{13}C -NMR of compound 3b

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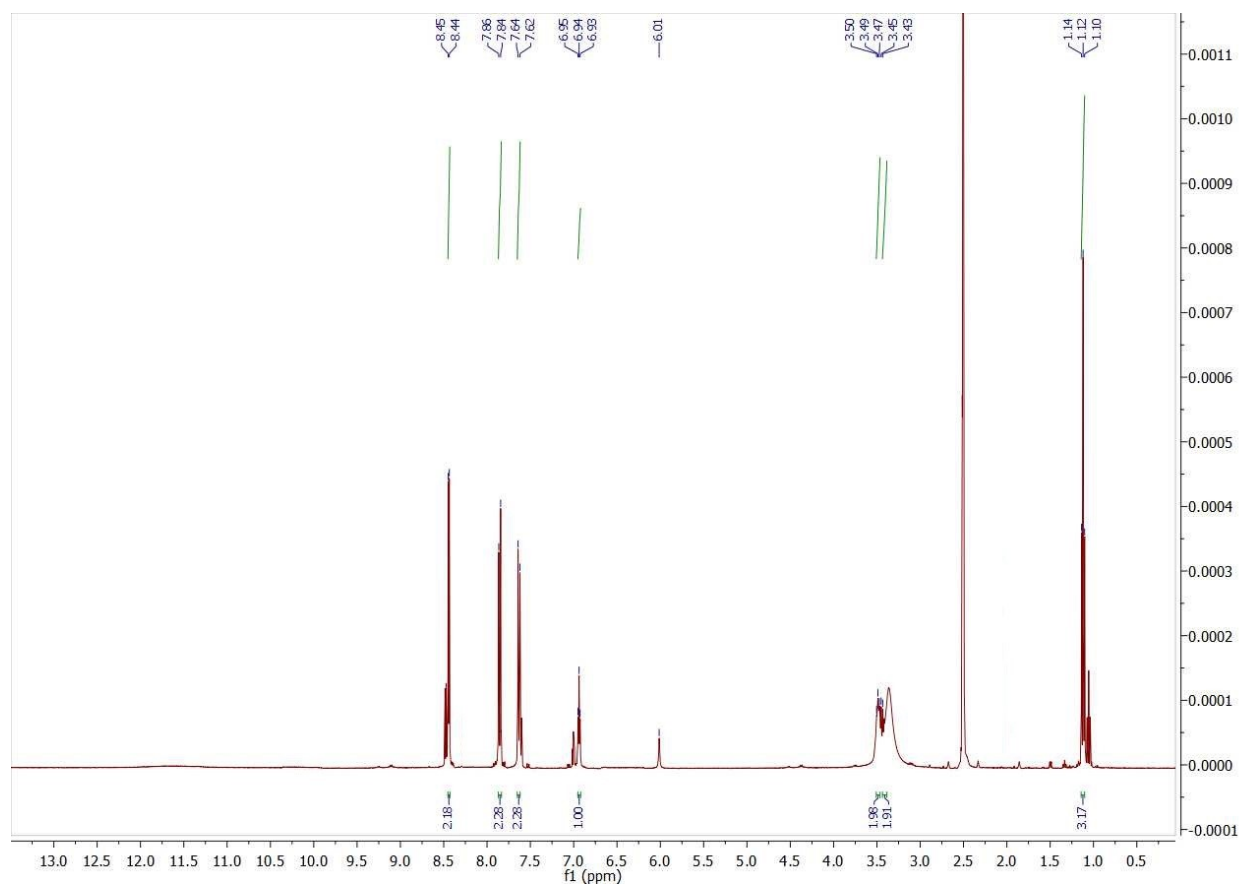


Fig. S5. ¹H-NMR of compound 3c

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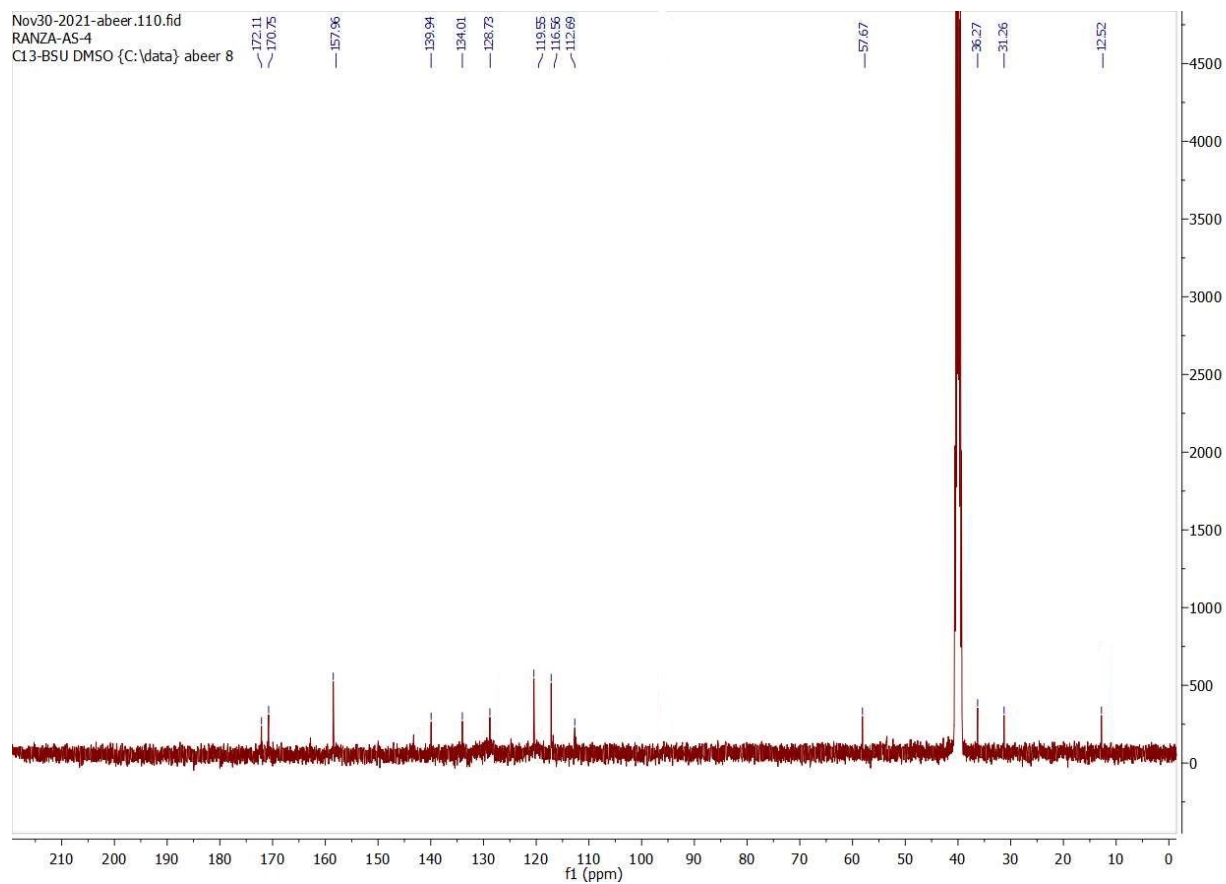


Fig. S6. ^{13}C -NMR of compound **3c**

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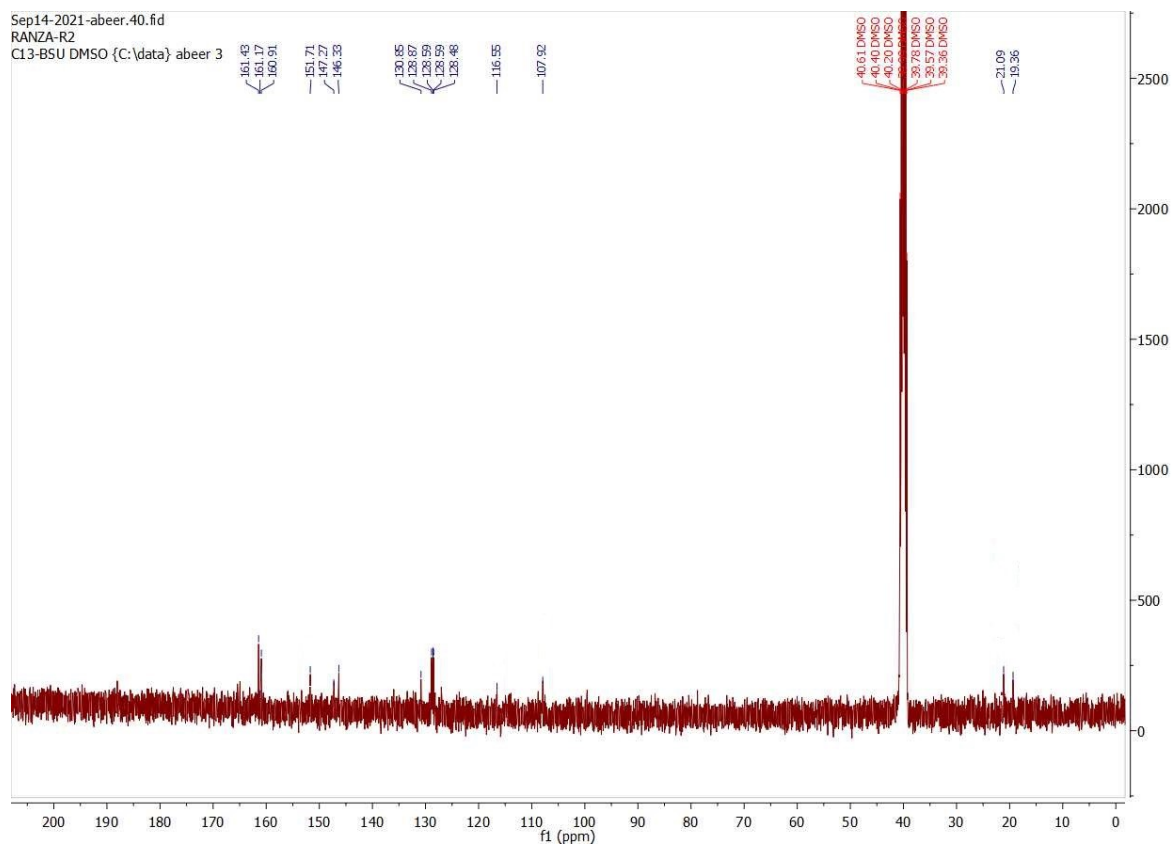


Fig. S8. ^{13}C -NMR of compound 4a

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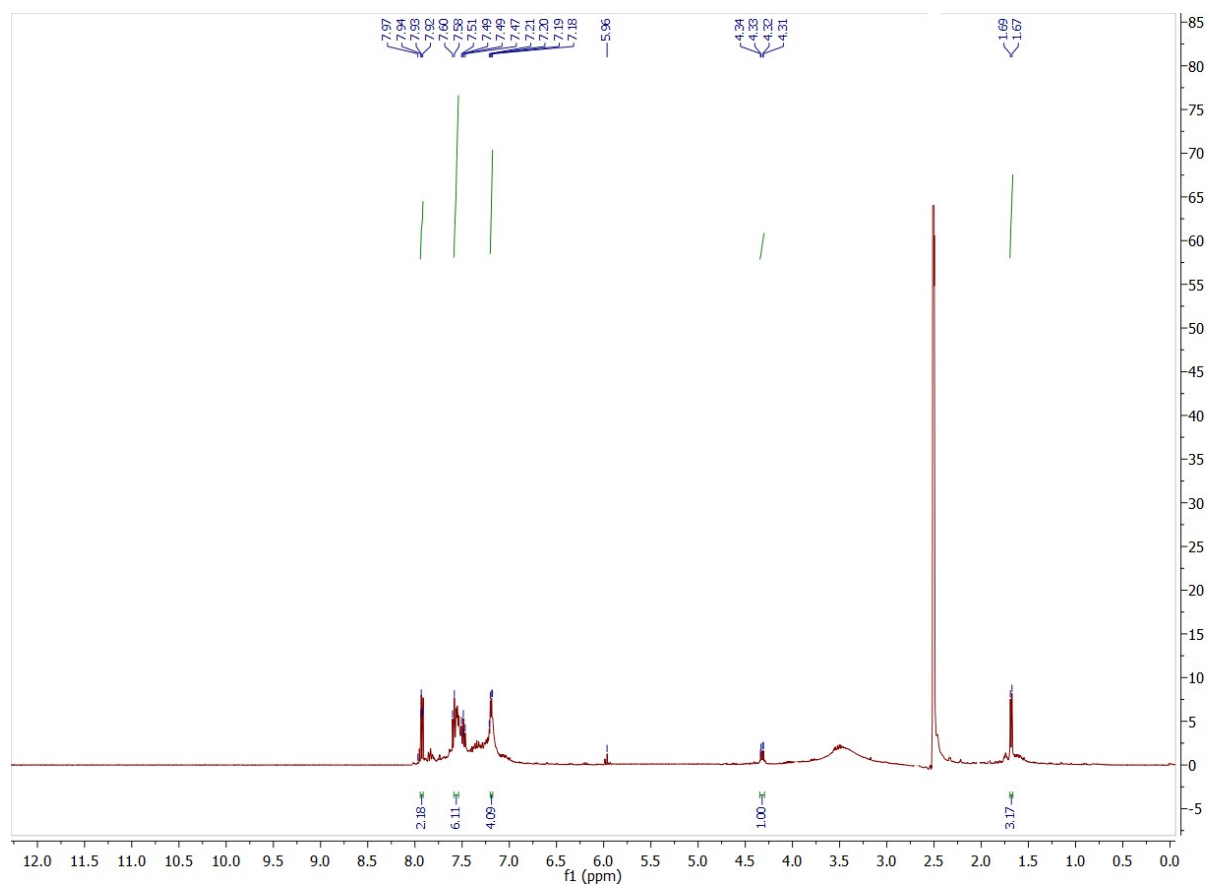


Fig. S9. $^1\text{H-NMR}$ of compound **4b**

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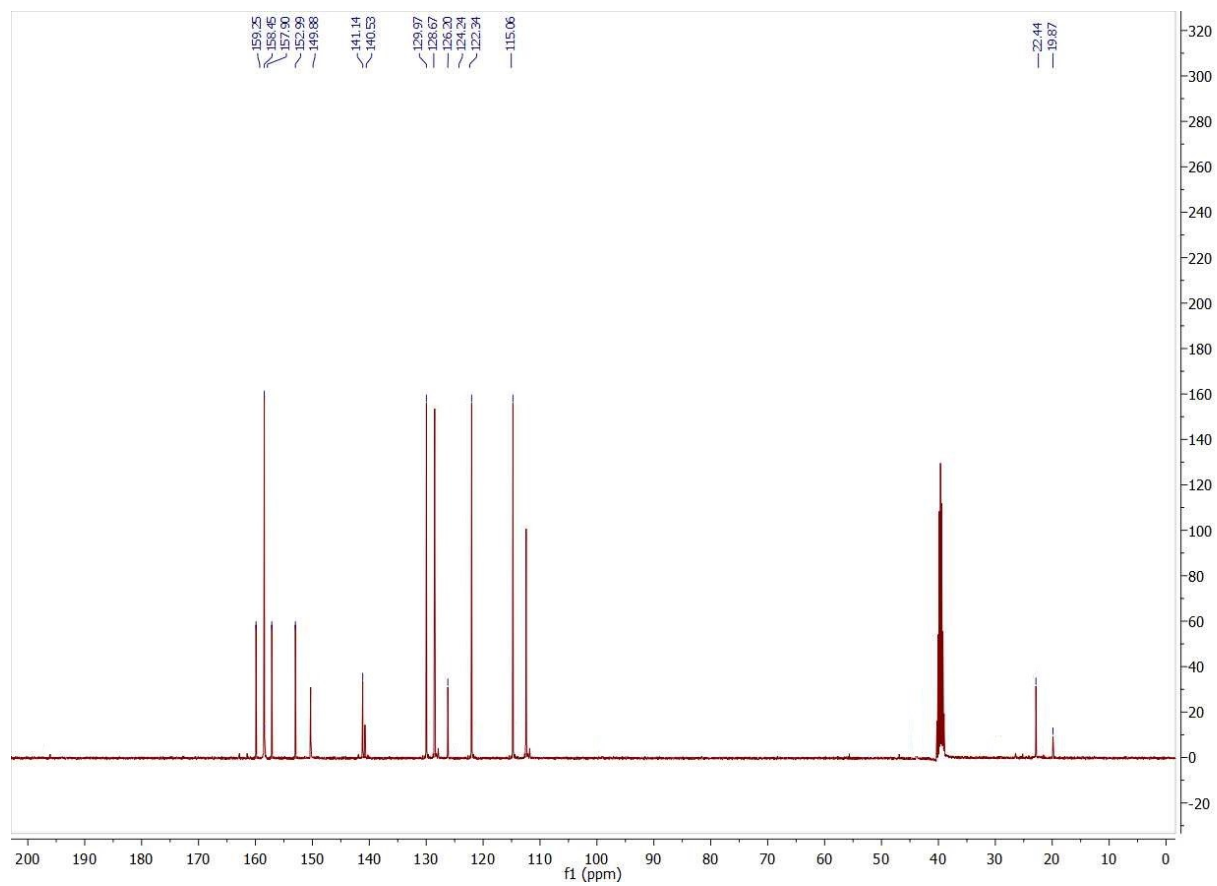


Fig. S10. ^{13}C -NMR of compound 4b

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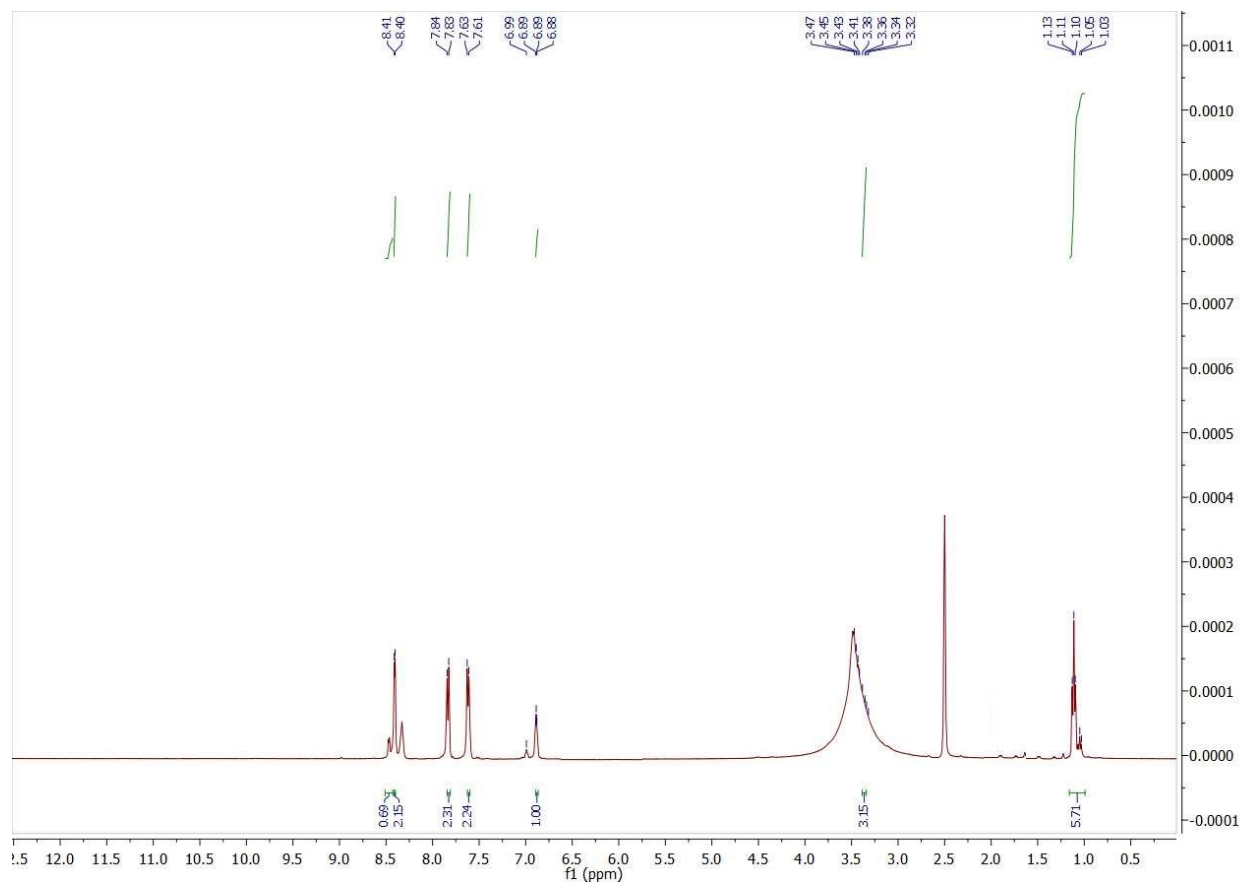


Fig. S11. ¹H-NMR of compound 4c

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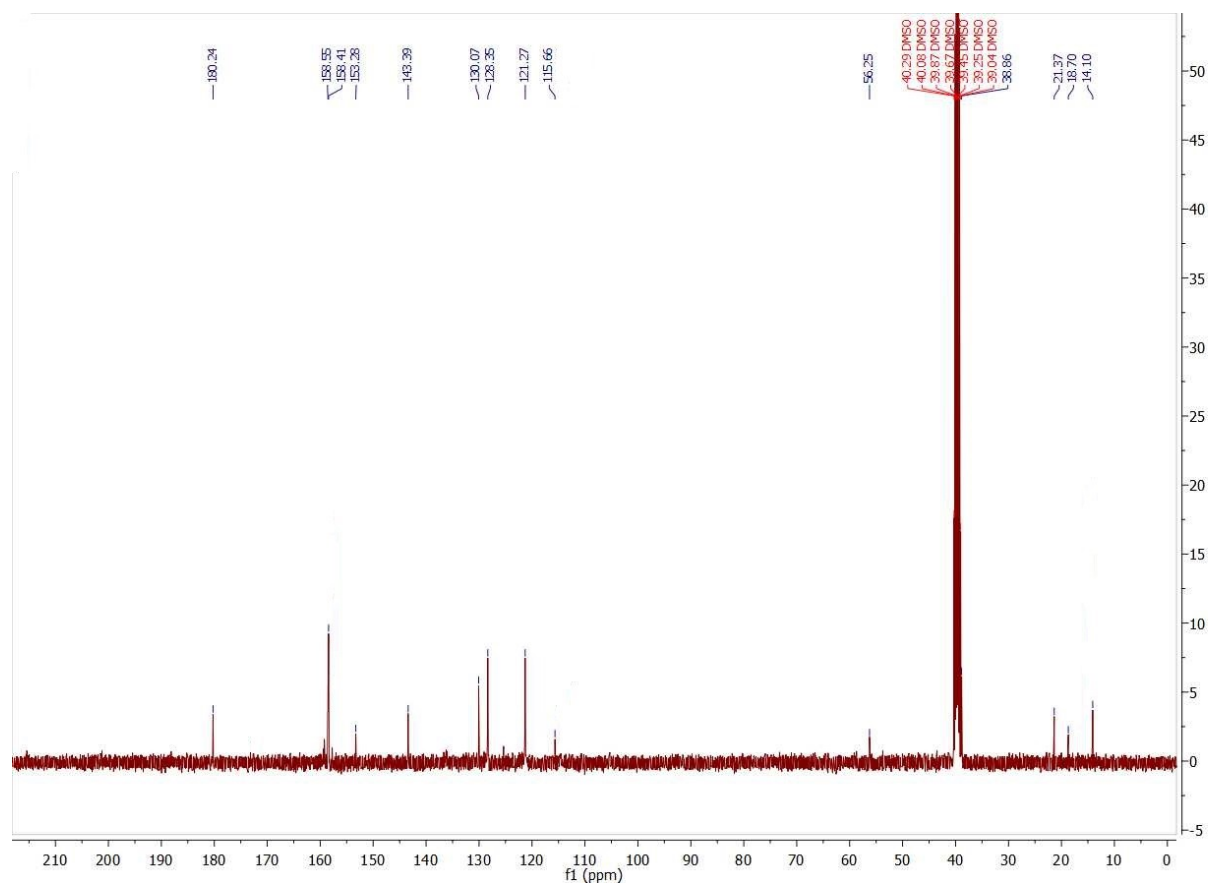


Fig. S12. ^{13}C -NMR of compound 4c

Supplementary Information

Sample code	4SD	5SD	6SD	7SD	30SD	31SD
Paper code	3a	3b	4a	4b	3c	4c



Requester Data:

Name: Dr. Naggall

Sample Data:

Eleven samples had been submitted for elemental analysis.

Analysis Report:

Sample Code	C%	H%	N%	S%
30 SD	47.46	4.31	18.79	16.77
49 B	68.71	7.32	24.75	-
6 B	67.49	5.99	22.74	-
30 B	62.46	4.69	32.83	-
42 B	68.56	5.75	9.43	11.20
25 SD	56.63	3.64	13.52	7.67
55 B	65.19	5.27	13.66	-
33 B	69.18	4.65	20.54	-
19 B	68.71	5.32	15.72	7.07
40 B	55.36	3.88	8.49	9.41
12 B	81.56	4.74	14.51	-

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M. S2

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Fig.S13. Elemental analysis of target compounds 3a-c and 4a-c

Sample code	4SD	5SD	6SD	7SD	30SD	31SD
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Supplementary Information

Paper code	3a	3b	4a	4b	3c	4c
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Requester Data:
Name: Dr. Naggatt

Sample Data:
Eleven samples had been submitted for elemental analysis.

Analysis Report:

Sample Code	C%	H%	N%	S%
21 SD	58.56	5.34	18.64	7.17
10 SD	61.81	4.22	14.70	13.20
8 B	51.64	3.52	18.68	-
29 SD	51.33	3.49	15.09	8.60
17 SD	49.57	4.37	19.14	8.81
31 SD	49.38	4.69	17.56	16.55
7 B	58.72	3.99	21.81	-
36 B	54.54	3.62	8.75	9.66
8 SD	54.34	3.91	15.65	14.52
13 SD	55.72	3.97	17.32	7.84
47 B	66.35	3.71	19.55	-

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Fig.S14. Elemental analysis of target compounds 3a-c and 4a-c

Supplementary Information

Sample code	4SD	5SD	6SD	7SD	30SD	31SD
Paper code	3a	3b	4a	4b	3c	4c



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Requester Data:
Name: Dr. Naggatt

Sample Data:
Twelve samples had been submitted for elemental analysis.


Analysis Report:

Sample Code	C%	H%	N%	S%
6 SD	54.82	3.39	16.07	14.76
15 SD	53.29	3.38	16.15	15.11
57 B	60.82	4.91	12.54	14.57
30 SD	47.46	4.06	18.39	16.57
18 B	64.72	5.63	17.65	8.27
27 SD	56.62	4.02	18.59	8.61
39 B	68.34	5.09	9.71	11.43
22 SD	56.52	4.46	22.31	8.54
11 SD	63.64	4.16	14.73	6.92
43 B	61.41	4.52	13.72	10.47
11 B	72.62	3.92	12.68	-
12 SD	53.51	3.86	16.37	15.25

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Fig.S15. Elemental analysis of target compounds 3a-c and 4a-c

Supplementary Information

Sample code	4SD	5SD	6SD	7SD	30SD	31SD
Paper code	3a	3b	4a	4b	3c	4c



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Requester Data:

Name: Dr. Naggatt

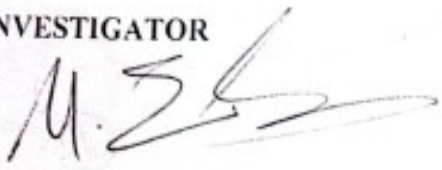
Sample Data:

Twelve samples had been submitted for elemental analysis.


Analysis Report:

Sample Code	C%	H%	N%	S%
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BB	77.46	4.45	13.81	-
19 SD	43.62	3.39	31.41	8.64
34 SD	56.34	16.44	16.44	-
10 B	76.82	4.33	19.38	-
50 B	58.48	3.96	13.45	15.79
20 CD	82.51	5.97	21.28	8.40
48 B	72.64	5.26	15.83	-
32 B	70.60	4.85	19.52	-
34 CD	47.42	4.30	18.52	16.79
14 B	64.40	3.39	11.52	-
56 B	58.67	4.24	13.48	15.57

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Fig.S16. Elemental analysis of target compounds 3a-c and 4a-c

Supplementary Information

Sample code	4SD	5SD	6SD	7SD	30SD	31SD
Paper code	3a	3b	4a	4b	3c	4c



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Requester Data:

Name: Dr. Naggatt

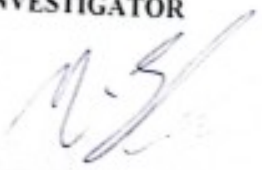
Sample Data:

Eleven samples had been submitted for elemental analysis.


Analysis Report:

Sample Code	C%	H%	N%	S%
28 SD	50.73	2.55	19.70	9.02
16 SD	55.75	3.67	17.13	7.79
26 SD	75.02	3.41	16.48	7.59
4 SD	68.76	4.53	26.57	-
5 SD	55.52	3.31	17.38	7.64
33 SD	57.32	4.42	16.03	14.34
24 SD	44.43	3.35	20.19	18.02
4 SD	53.28	3.58	16.71	15.22
41 SD B	61.51	4.52	13.67	10.66
31 SD B	62.62	3.81	22.63	-
7 SD	56.38	4.16	16.79	7.71

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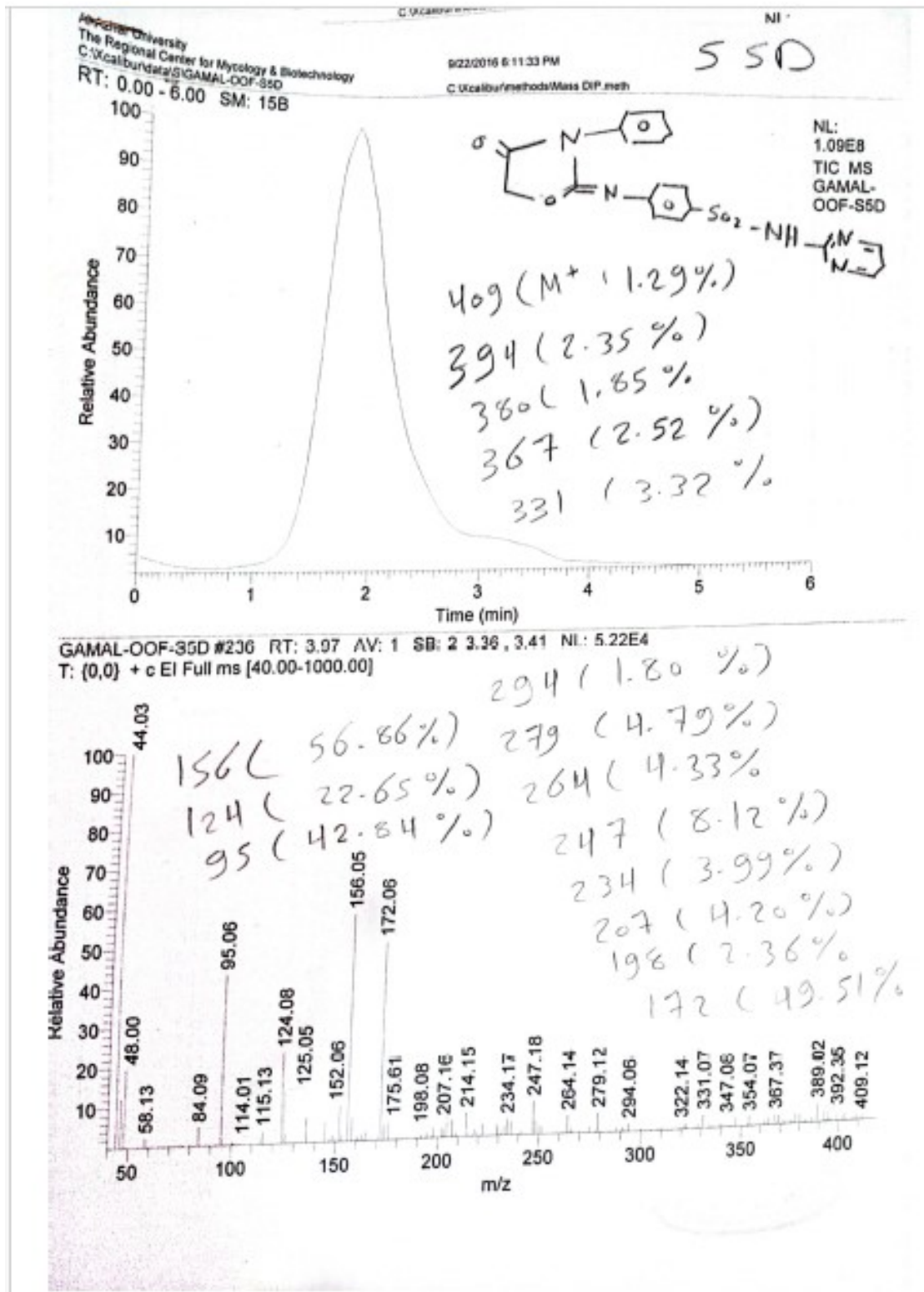
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Fig.17 Elemental analysis of target compounds 3a-c and 4a-c

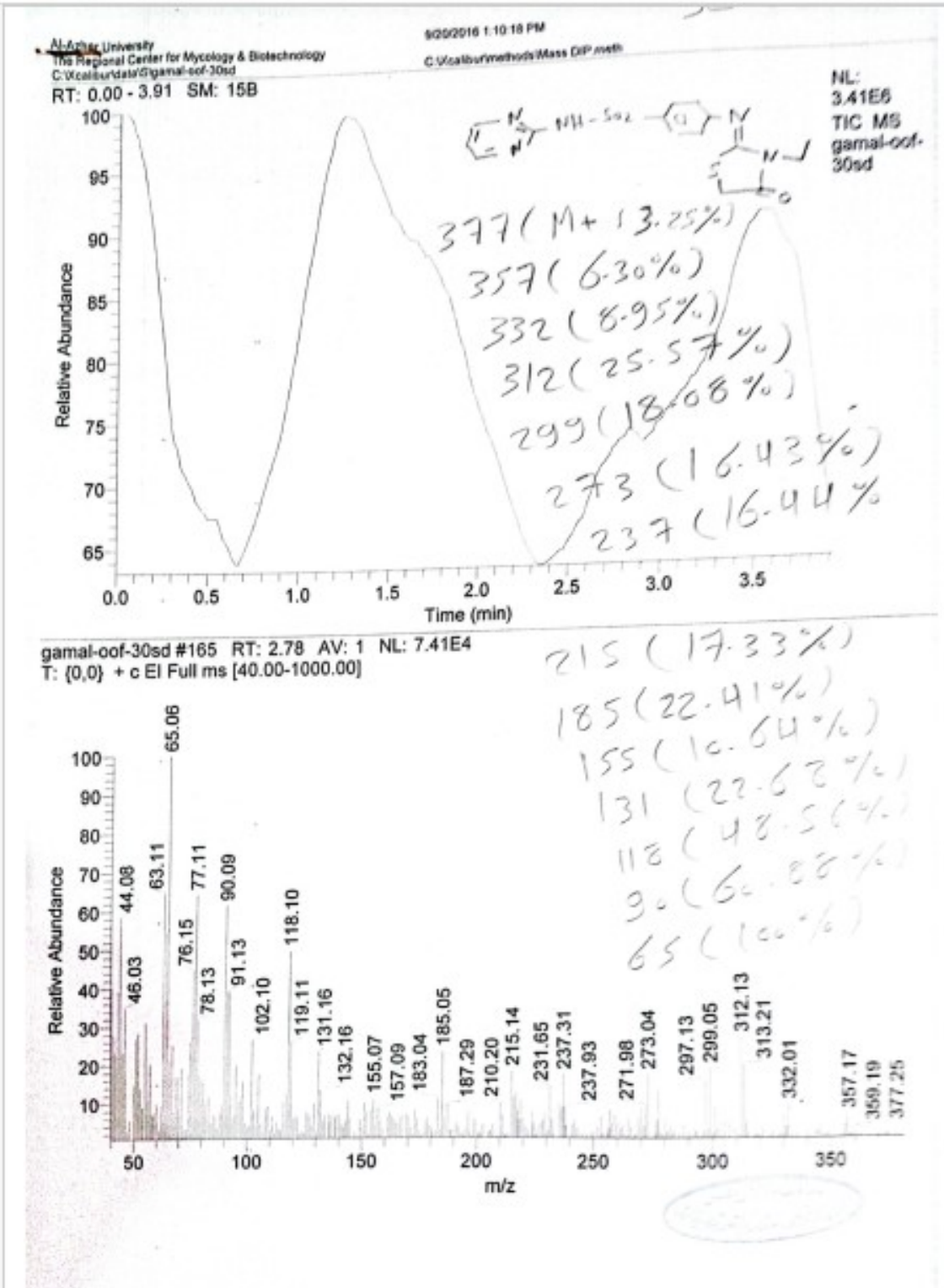
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Figure S18. Mass spectrum of compound 3b



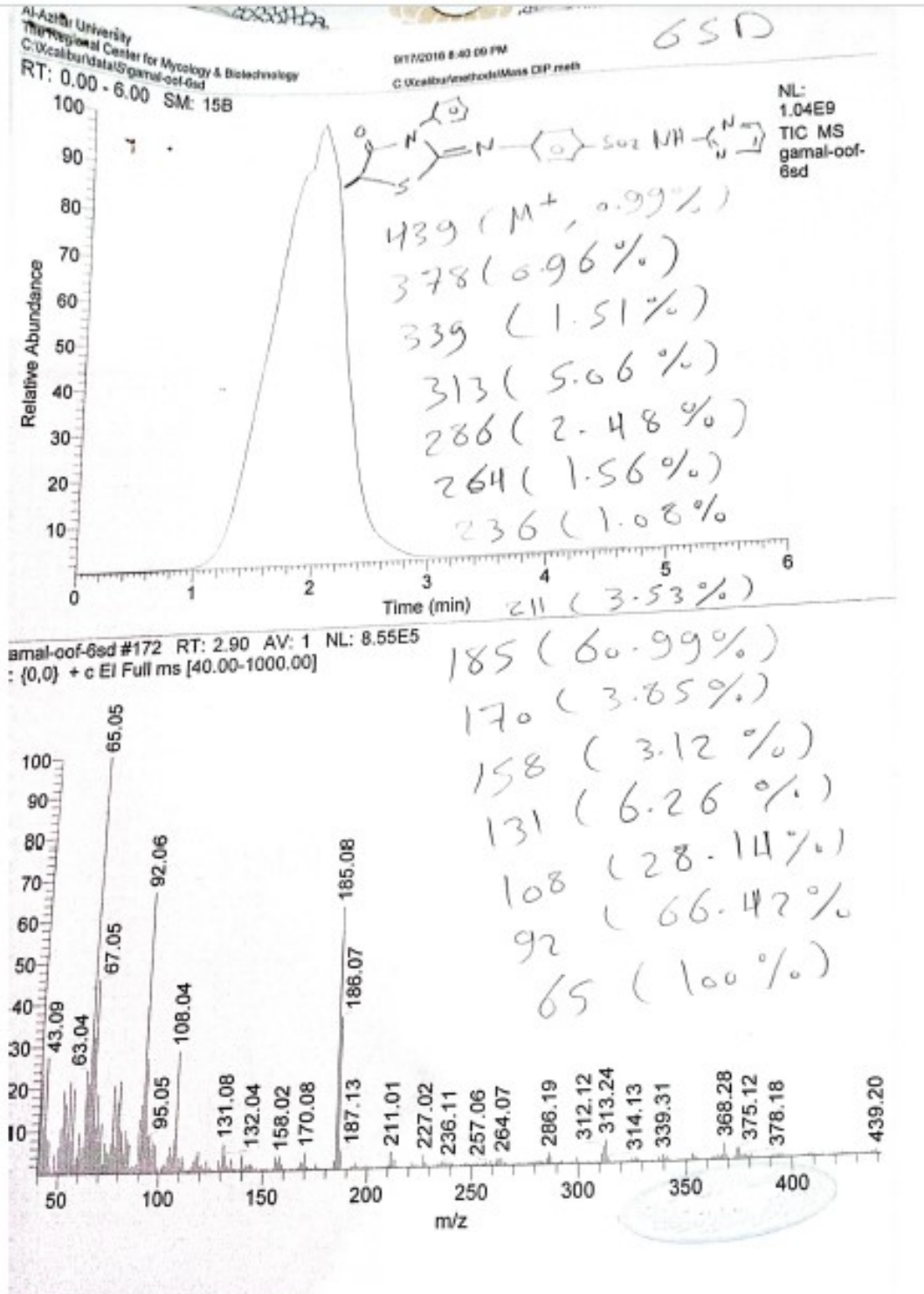
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Figure S19. Mass spectrum of compound 3c



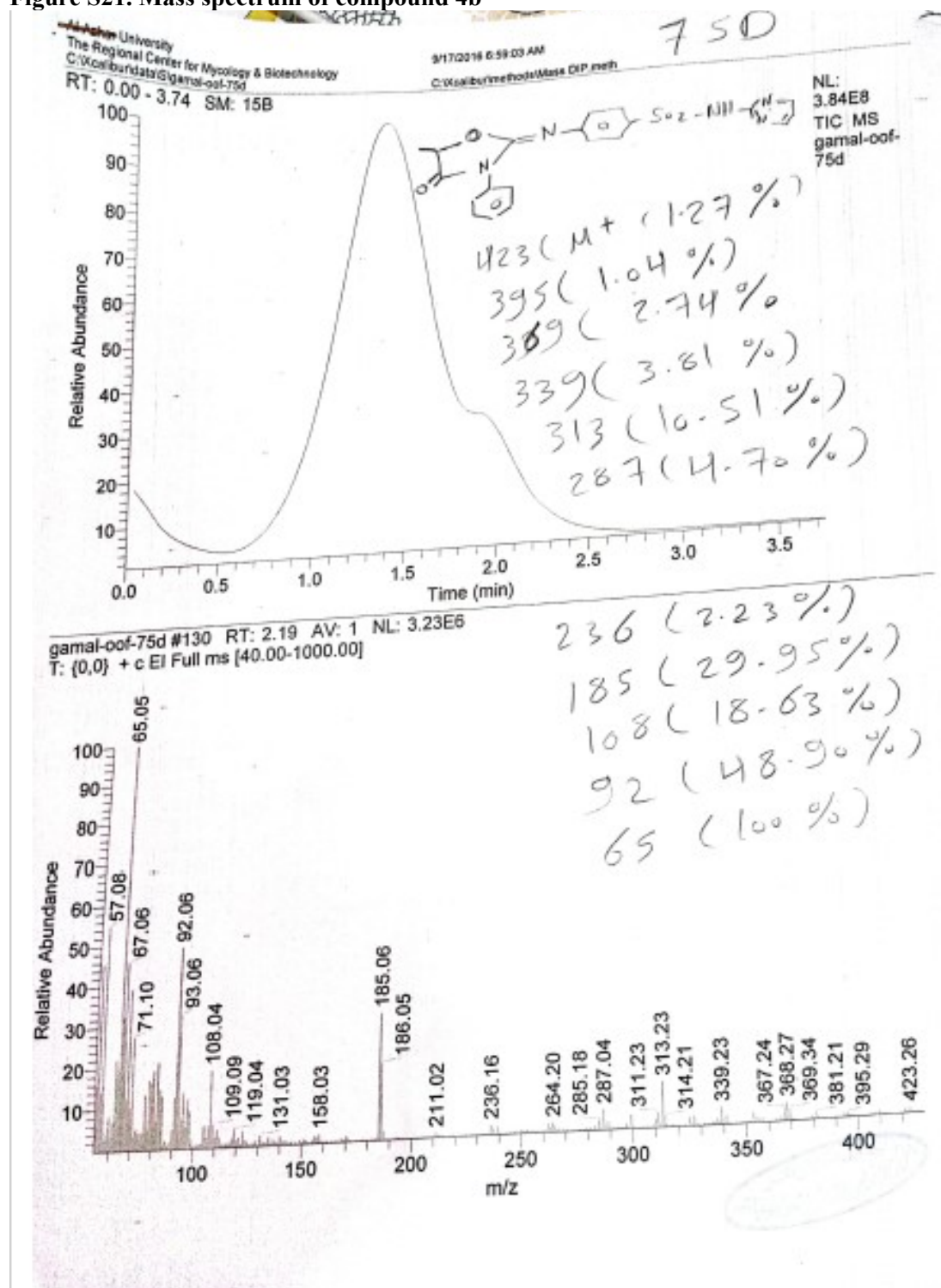
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Figure S20. Mass spectrum of compound 4a



Supplementary Information

Figure S21. Mass spectrum of compound 4b



Supplementary Information

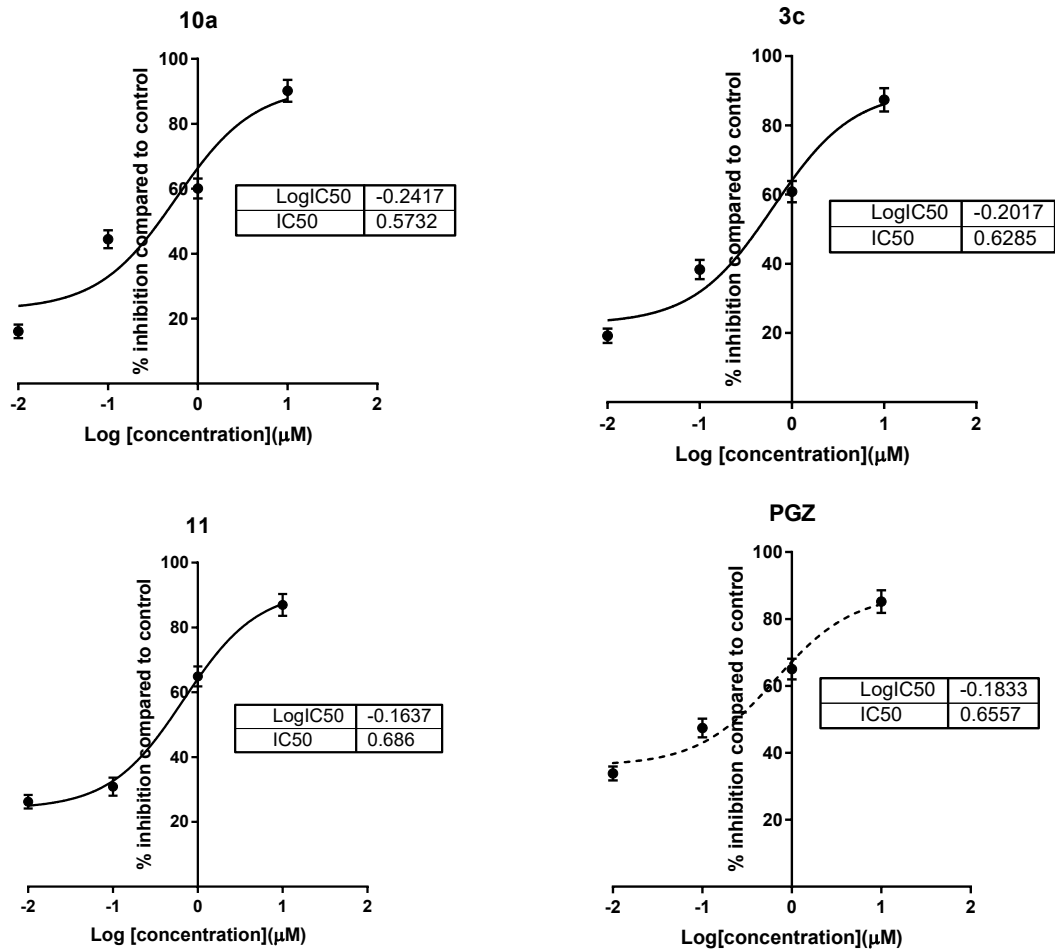
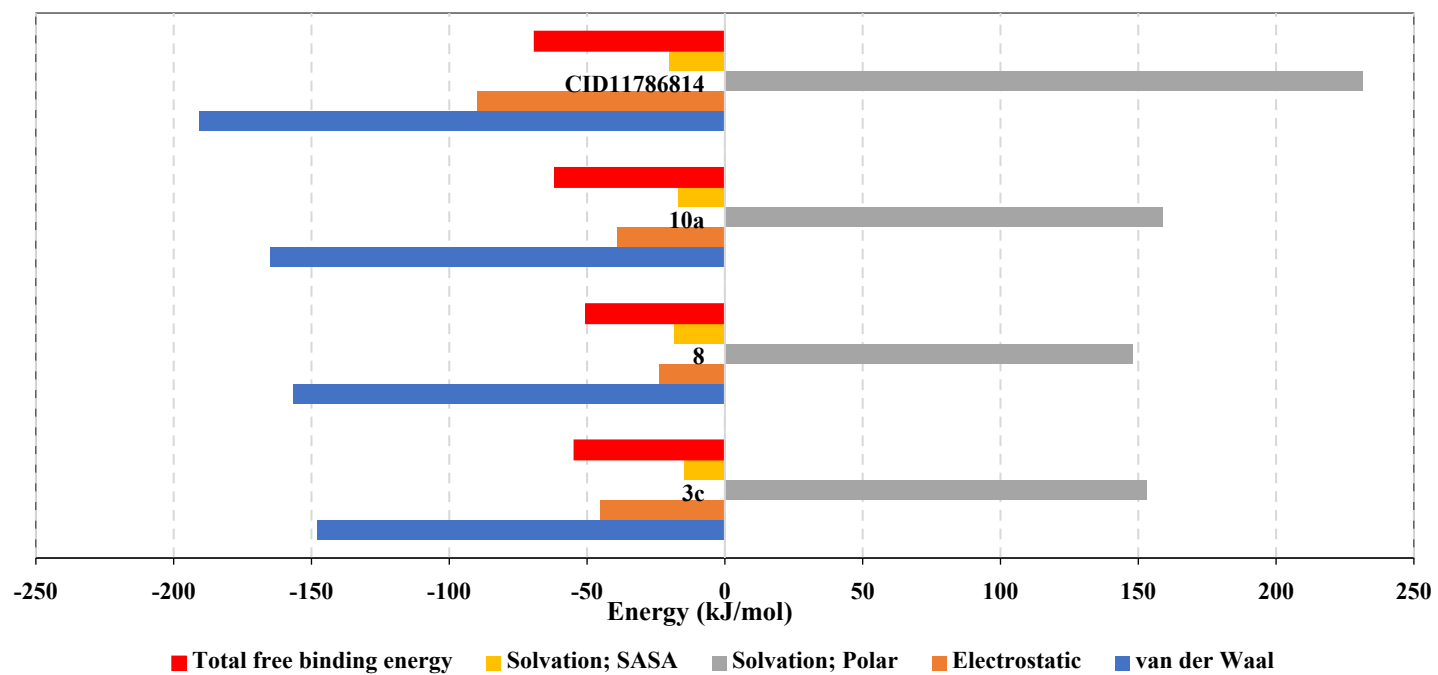


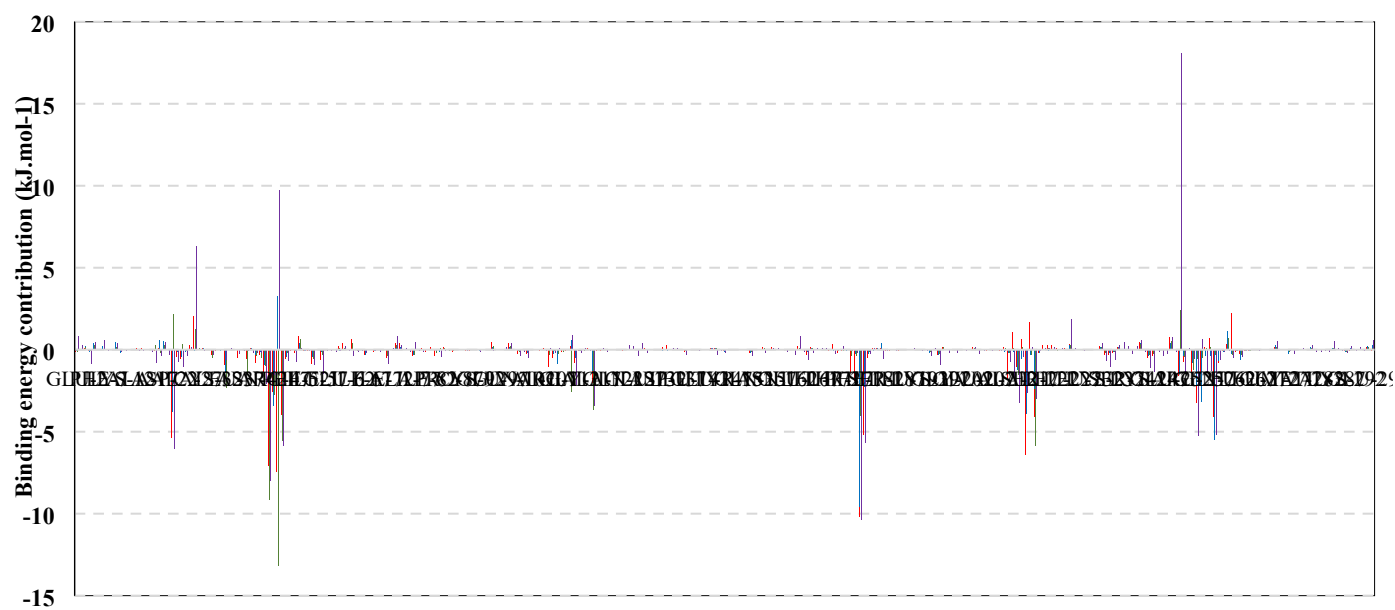
Figure S22. Dose-response curve for the PTB1B protein inhibition at the serial concentrations of 0.01-10 μM compared to pioglitazone (PGZ).

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(A)



(B)



Supplementary Information

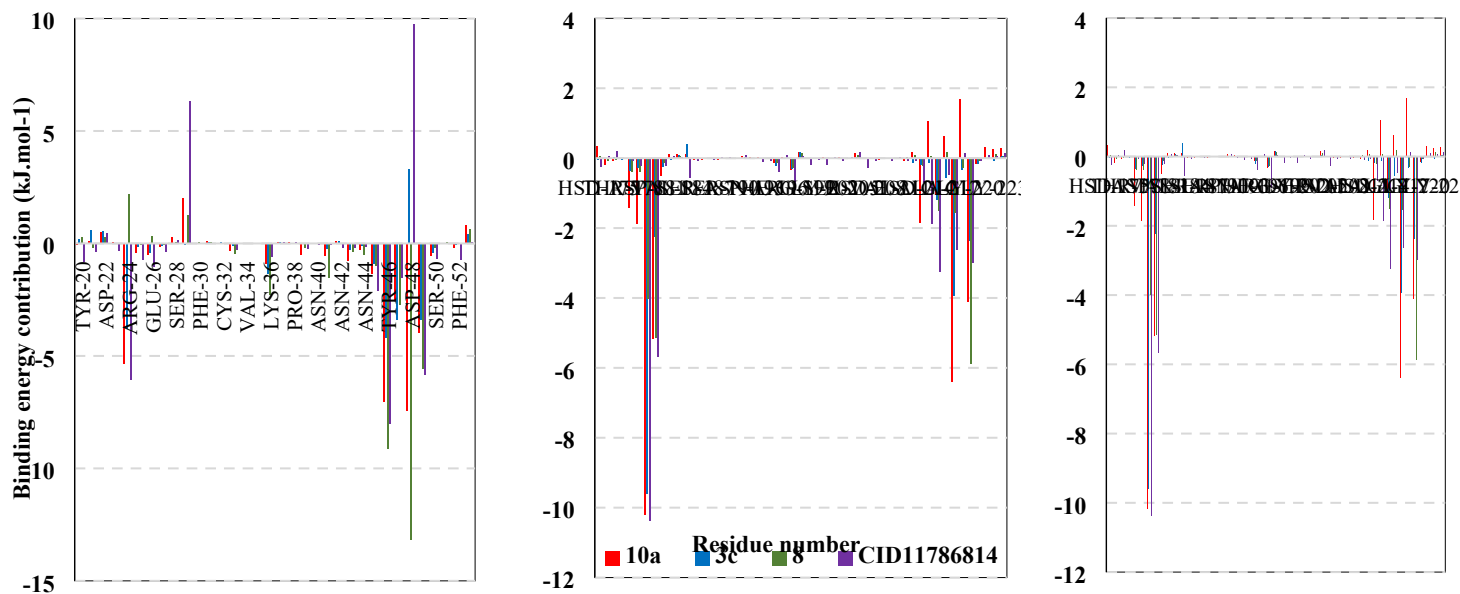


Figure S23. Binding-free energy of compound/PTP1B complexes as per MM_PBSA calculations. (A) Total binding-free energies and constituting terms. (B) Residue-wise energy contributions; Lower panels are expanded views of upper panel illustrating PTP1B's secondary structural loop residue ranges; partial Tyr-P cleft/PTR-loop (left), WPD/P-loop (middle), and Tyr-P/Q-loop (right).

	Size (d.nm):	% Intensity:	St Dev (d.n...)
Z-Average (d.nm): 135.2	Peak 1: 170.9	100.0	92.19
PdI: 0.181	Peak 2: 0.000	0.0	0.000
Intercept: 0.957	Peak 3: 0.000	0.0	0.000
Result quality: Good			

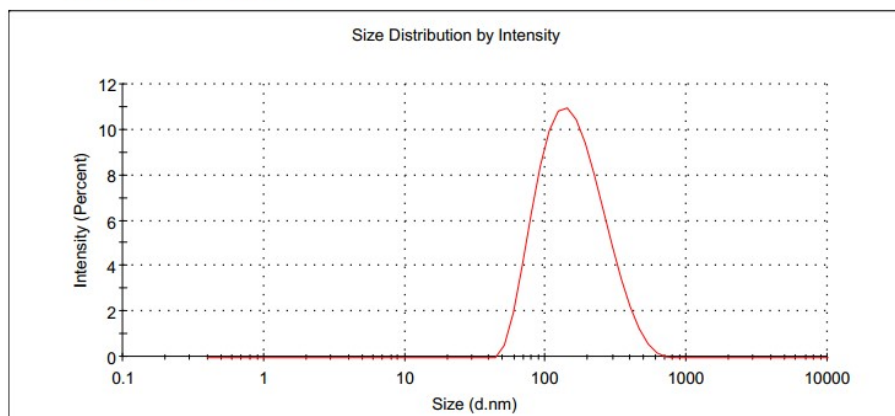


Figure S24. Chart of particle size and polydispersity index of the nano dispersion

Supplementary Information

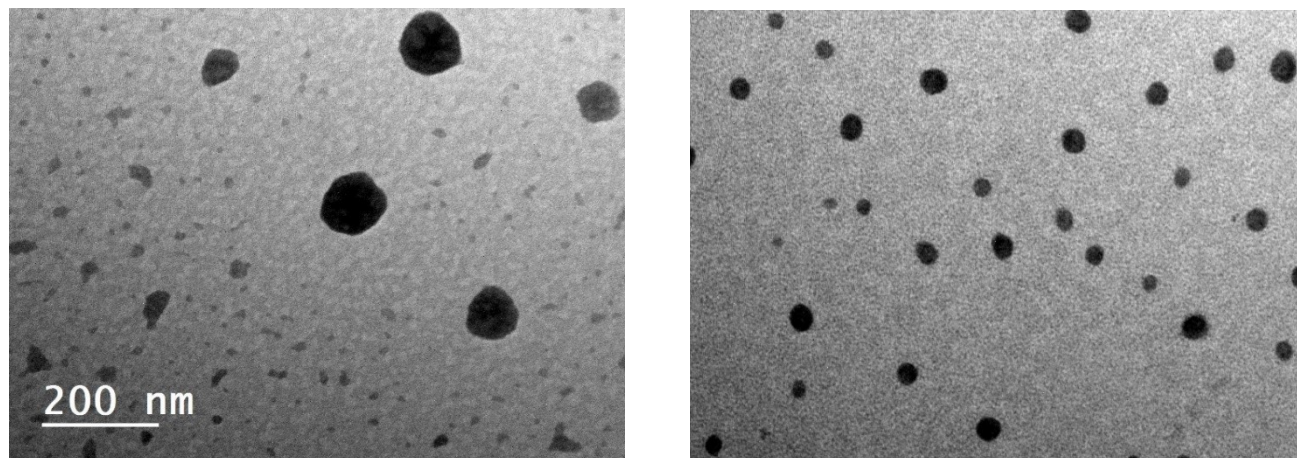


Figure S25. TEM imaging of the dispersion, showing on the left the size range suggested, on the right a wider display of the particle shape and uniformity.

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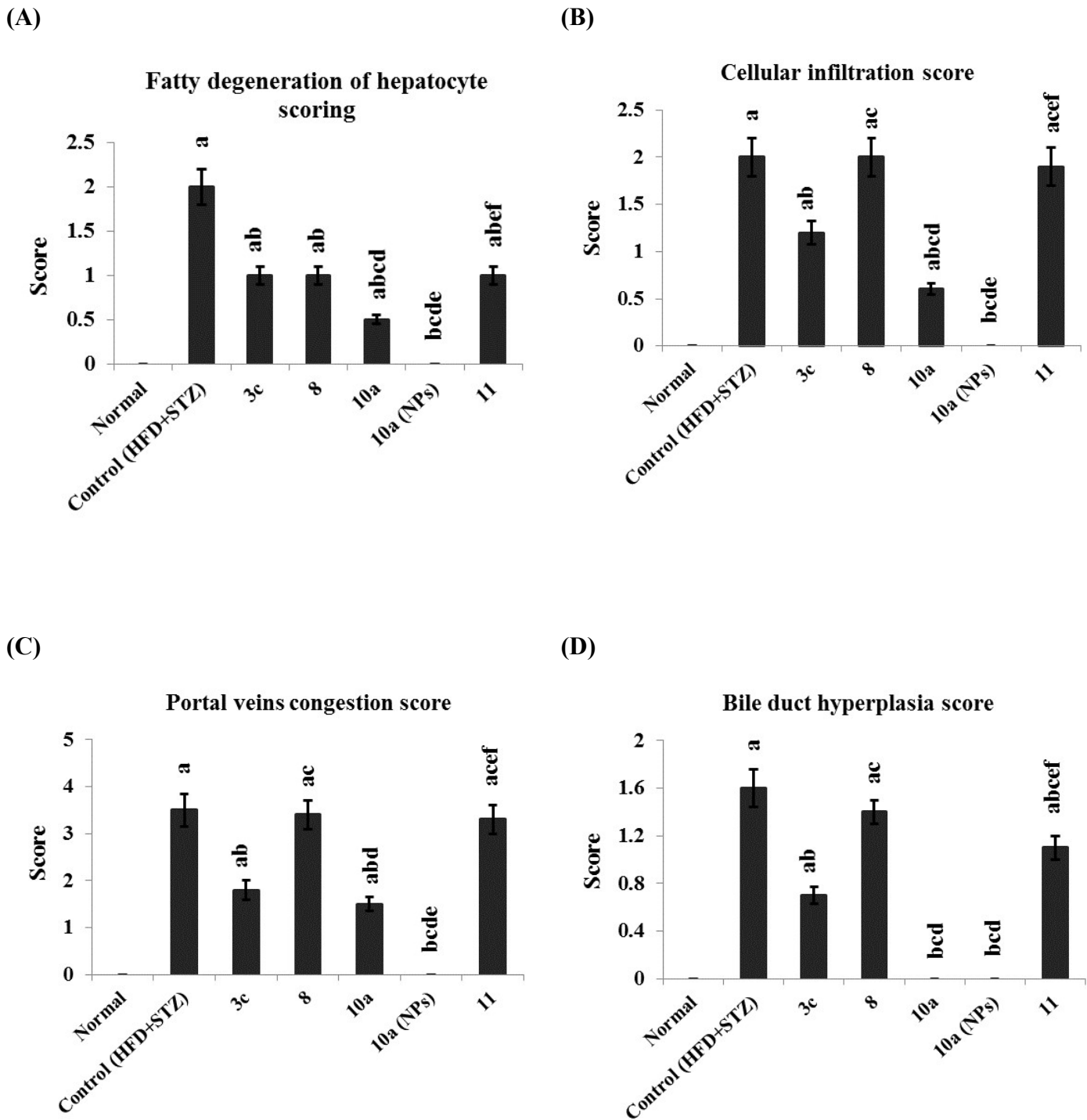


Figure S26. The microscopic damage score for liver of all experimental groups. A) fatty degeneration of hepatocytes scoring, B) cellular infiltration scoring, C) portal veins congestion scoring and D) bile duct hyperplasia scoring. Data are expressed as mean \pm SD and analyzed using one-way ANOVA followed by Bonferroni's post hoc test (n = 6-8). ^a significantly different at $p < 0.05$ vs normal, ^b vs control (HFD+STZ), ^c vs 3c, ^d vs 8, ^e vs 10a, ^f vs 10a (NPs).

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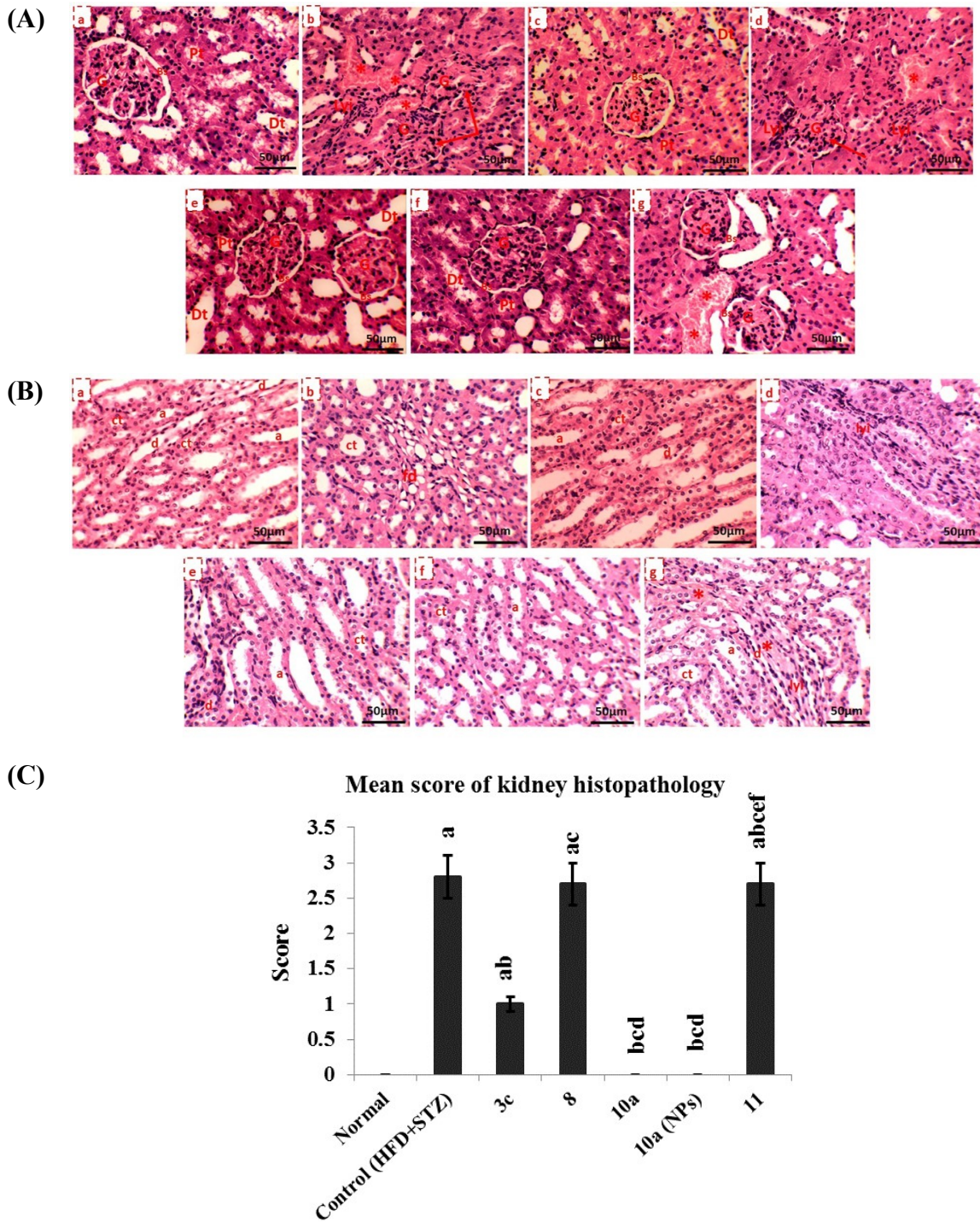


Figure S27. Results of kidney tissue histopathological examination. (A) area of renal cortex and (B) area of renal medulla of different experimental group showing a) Normal group with typical renal cortex and medulla structure, b) HFD+STZ-control group showed hypertrophy of glomerulus, infiltration of inflammatory cells and hemorrhage while the medullary region showed signs of tubular fatty changes, c) 3c-treated group showed completely restored renal cortical and medullary architecture with no evidence of histopathological changes, d) 8-treated group showed hypertrophy of glomerulus, infiltration of

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inflammatory cells and hemorrhage while the medullary region showed signs of cellular infiltration, e) **10a**-traeted group showed completely restored renal cortical and medullary architecture with no evidence of histopathological changes, f) **10a** (NPs)-treated group showed completely restored renal cortical and medullary architecture with no evidence of histopathological changes, g) **11**-treated group showed hypertrophy of glomerulus, infiltration of inflammatory cells and hemorrhage while the medullary region showed signs of infiltration of inflammatory cells and hemorrhage. (G) glomerulus, (Bs) Bouman space, (Pt) proximal tubules, (Dt) distal tubules, (Ct) collecting tubules, (a) thick segment of Henle loop, (d) thin segment of Henle loop, (*) hemorrhage, (arrow) hypertrophy of glomerulus, (Lyi) infiltration of inflammatory cells, (fd) fatty degeneration. (C) Histopathology scoring of kidney cortical damage for all experimental groups. Data are expressed as mean \pm SD and analyzed using one-way ANOVA followed by Bonferroni's post hoc test (n = 6-8). ^a significantly different at $p < 0.05$ vs normal, ^b vs control (HFD+STZ), ^c vs **3c**, ^d vs **8**, ^e vs **10a**, ^f vs **10a** (NPs).

Supplementary Information

Table S1. Combining two different oils with surfactants were also investigated in as shown:

Olive oil	Oleic acid	Tween 80	Tween 20
30 %	30 %	20 %	20 %
30%	30 %	40 %	
30 %	30%		40 %

Table S2. Primer sequences used in the present study.

	Primer Sequences	Annealing Temp.	Accession NO.
Leptin	Forward: 5`-GACATTTACACACGCAGTC-3` Reverse: 5`-GAGGAGGTCTCGCAGGTT-3`	57°C	NM_013076.3
Adiponectin	Forward: 5`-AATCCTGCCCAGTCATGAAG-3` Reverse: 5`-CATCTCCTGGGTCACCCTTA-3`	56°C	NM_144744.3
GAPDH	Forward: 5`-ATGACTCTACCCACGGCAAG-3` Reverse: 5`-GATCTCGCTCCTGGAAGATG-3`	56°C	NM_017008.4

Table S3. The effect of the synthesized compounds on the markers of liver and kidney functions in the experimental rats.

	ALT (IU/L)	AST (IU/L)	Serum creatinine (mg/dL)	Serum urea (mg/dL)
Normal	22 ± 2	64 ± 7	0.4 ± 0.03	22 ± 3
Control (HFD+STZ)	73 ± 8 ^a	223 ± 25 ^a	0.6 ± 0.09 ^a	58 ± 6 ^a
Compound 3c	34 ± 4 ^{ab}	99 ± 10 ^{ab}	0.5 ± 0.05	35 ± 4 ^{ab}
Compound 8	41 ± 5 ^{ab}	128 ± 14 ^{abc}	0.5 ± 0.06	46 ± 5 ^{abc}
Compound 10a	34 ± 3 ^{ab}	99 ± 9 ^{abd}	0.5 ± 0.04	31 ± 3 ^{abd}
Compound 10a (NPs)	25 ± 3 ^{bcde}	96 ± 9 ^{abd}	0.4 ± 0.04 ^b	23 ± 3 ^{bcde}
Compound 11	34 ± 4 ^{abf}	104 ± 11 ^{abd}	0.5 ± 0.05	37 ± 4 ^{abdf}

Data are expressed as mean ± SD and analyzed using one-way ANOVA followed by Bonferroni's post hoc test (n = 6-8). ^a significantly different at $p < 0.05$ vs normal, ^b vs control (HFD+STZ), ^c vs **3c**, ^d vs **8**, ^e vs **10a**, ^f vs **10a** (NPs). NPs = nanoparticles; ALT = alanine aminotransferase; AST = aspartate aminotransferase.