Supplementary Material

(2R, 4S, 5S) 1-(4-(4-(((7-chloroquinolin-4-yl)amino)methyl)-1H-1,2,3-triazol-1-yl)-5-(hydroxymethyl)tetrahydrofuran-2-yl)-5-methylpyrimidine-2,4(1H,3H)-dione

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† These authors contributed equally to this work.

Contents

NMR spectrometry

Figure S1. 1H NMR spectrum (DMSO-*d*6, 600 MHz) of compound **3**.

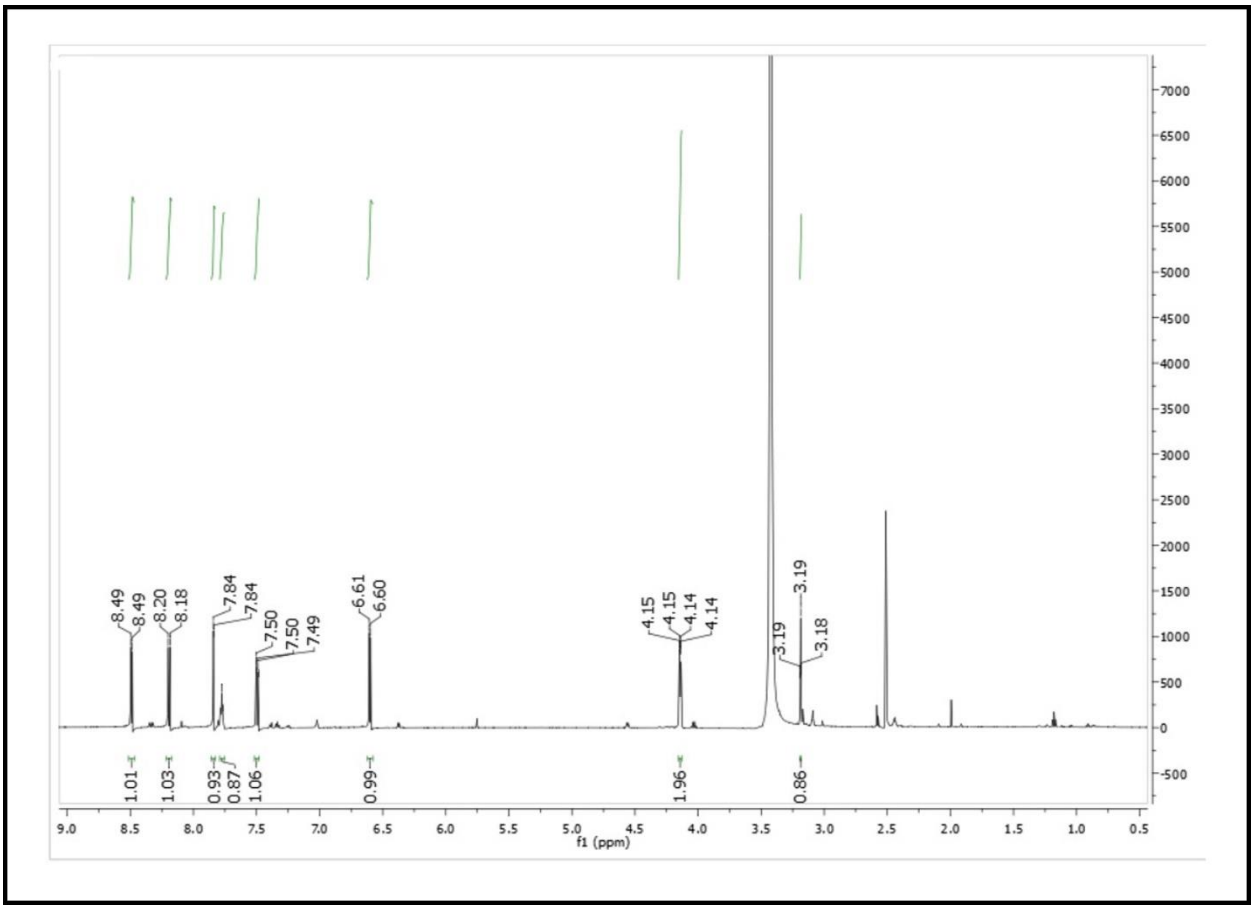


Figure S2. ^{13}C NMR spectrum (DMSO-*d*6, 150 MHz) of compound **3**.

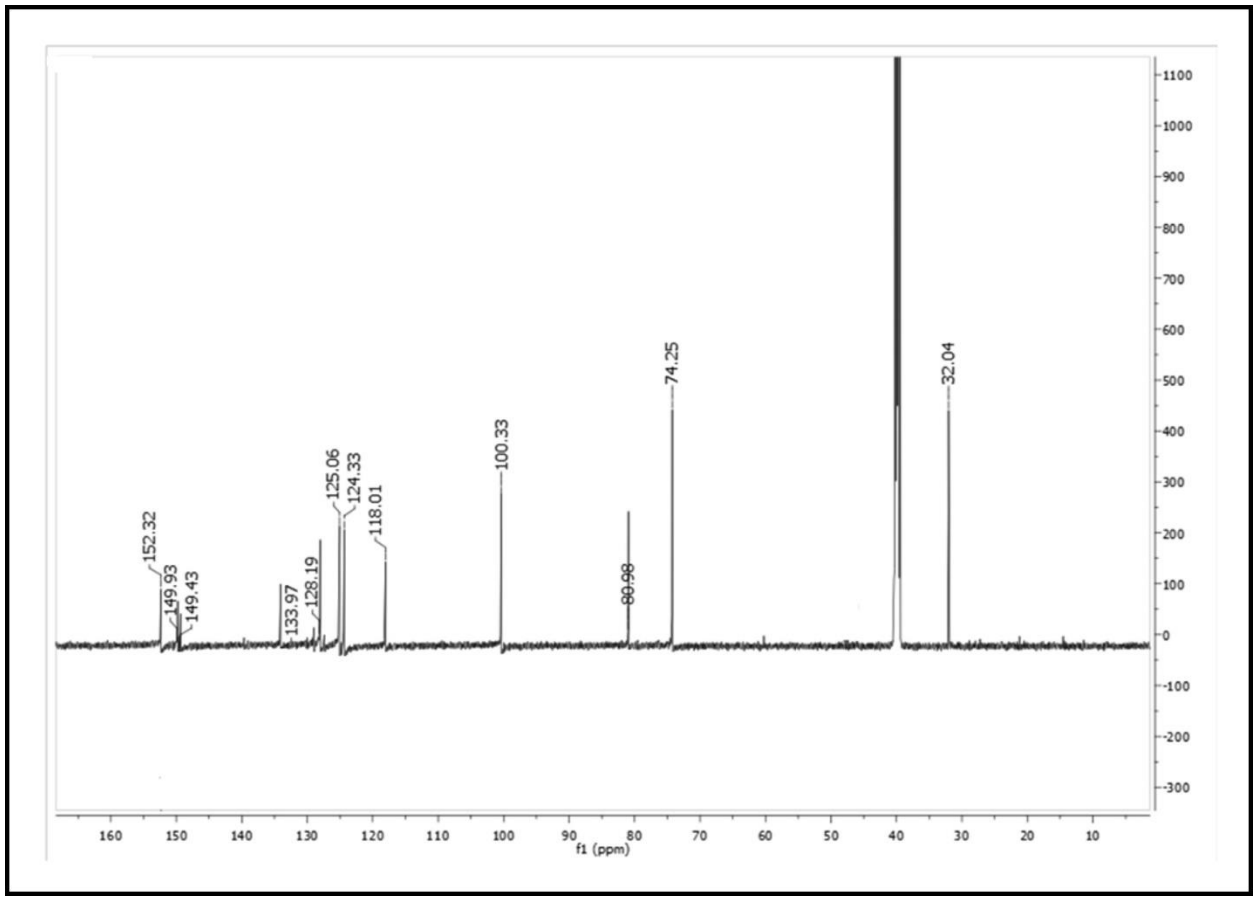
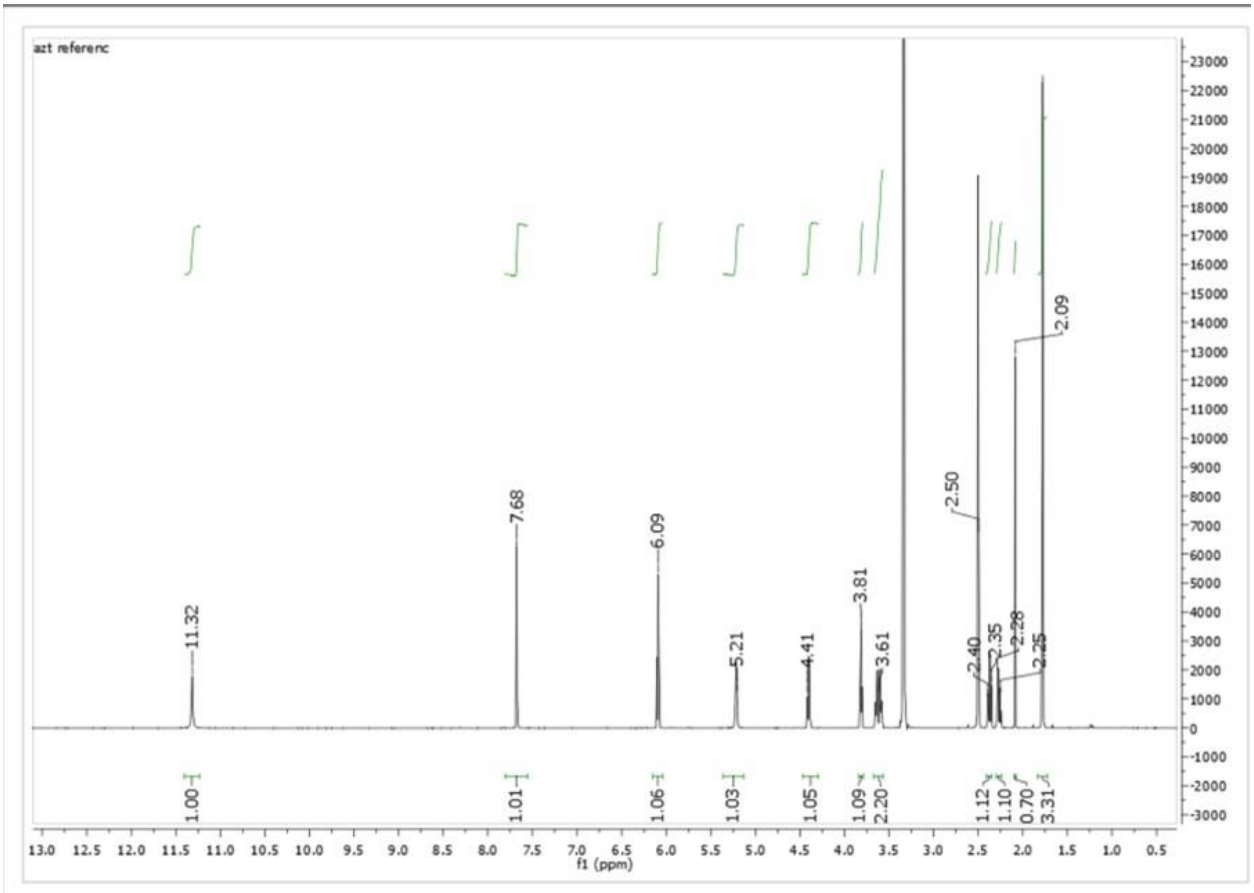
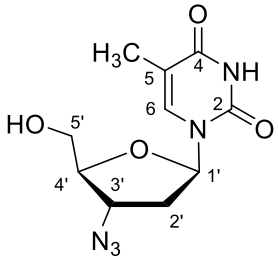


Figure S3. ^{1}H NMR spectrum (DMSO-*d*6, 600 MHz) of compound **1** (AZT).



1H NMR (300 MHz DMSO-d6) δ 1.78 (s, 3H, CH3), 2.25-2.40 (m, 2H, H-2'), 3.61 (m, 2H, H-5'), 3.81 (dd, 1H, J = 4.0, 8.5Hz, H-4'), 4.41 (dd, 1H, J = 5.2, 12.0 Hz, H-3'), 5.21 (bs, 1H, exchangeable, OH), 6.09 (t, 1H, J = 6.4 Hz, H-1'), 7.68 (s, 1H, H-6), 11.32 (bs, 1H, NH).



1.

Figure S3a. An expanded view of ^{1}H NMR spectrum (DMSO-*d*6, 600 MHz) of compound **1**.

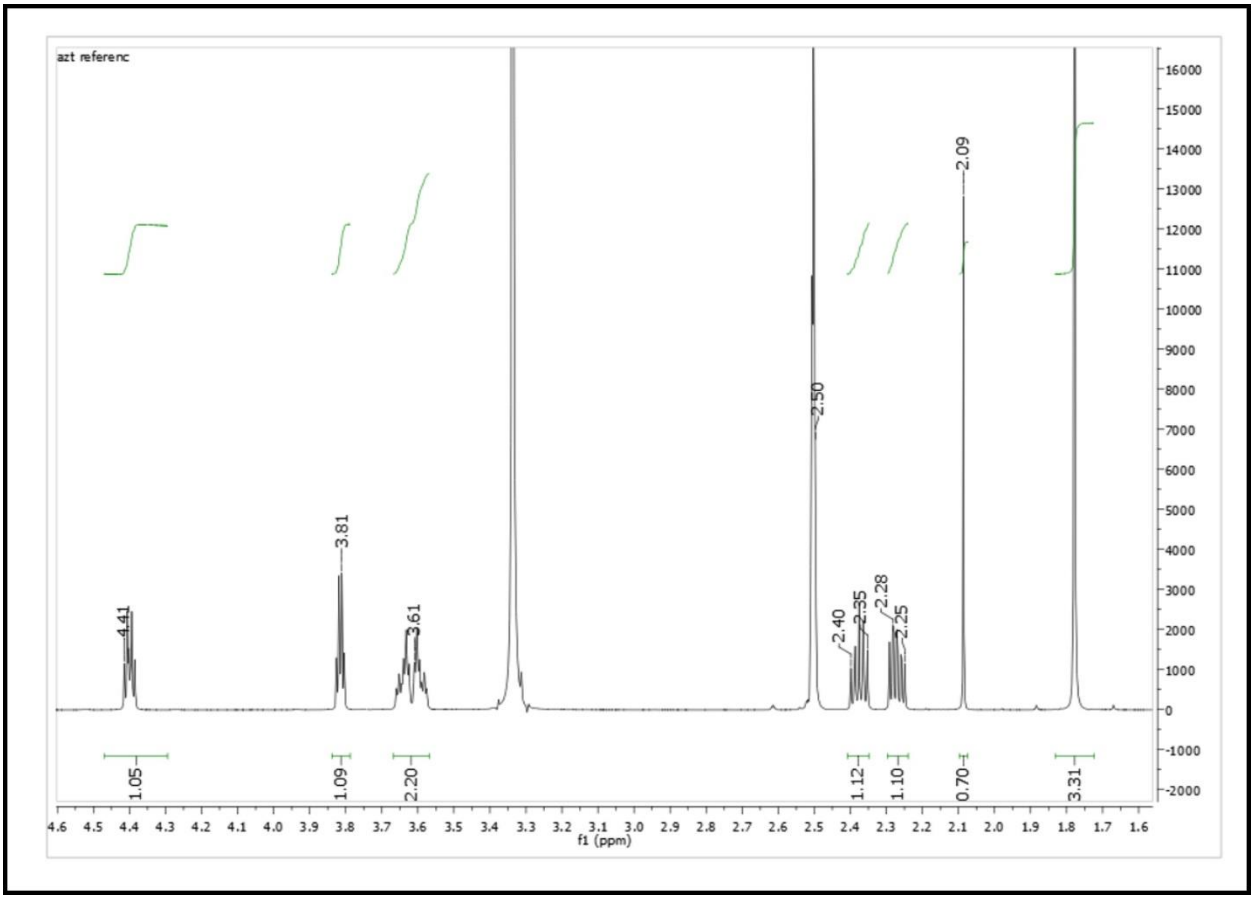


Figure S4. DEPT 90 spectrum (DMSO-*d*6, 150 MHz) of compound **1**.

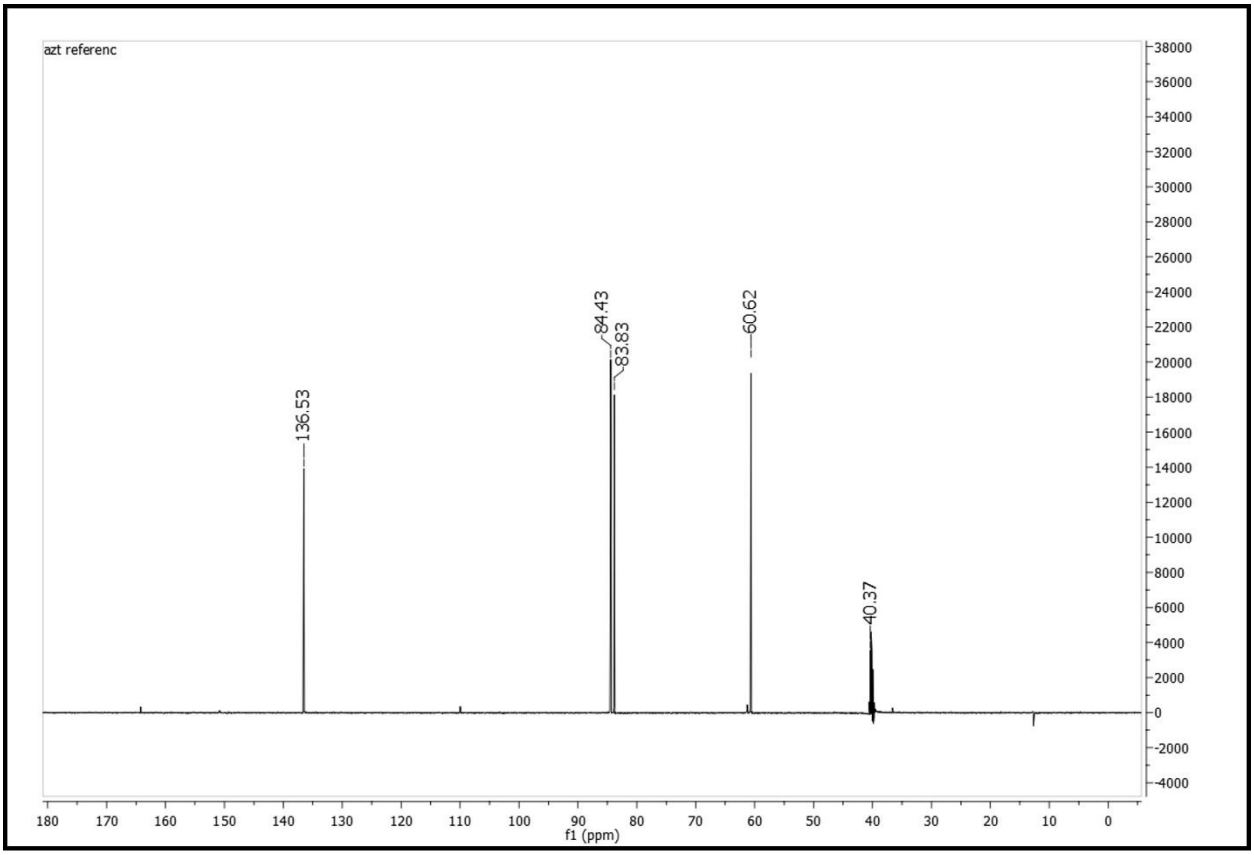


Figure S5. ^{1}H NMR spectrum (DMSO-*d*6, 600 MHz) of compound **4**.

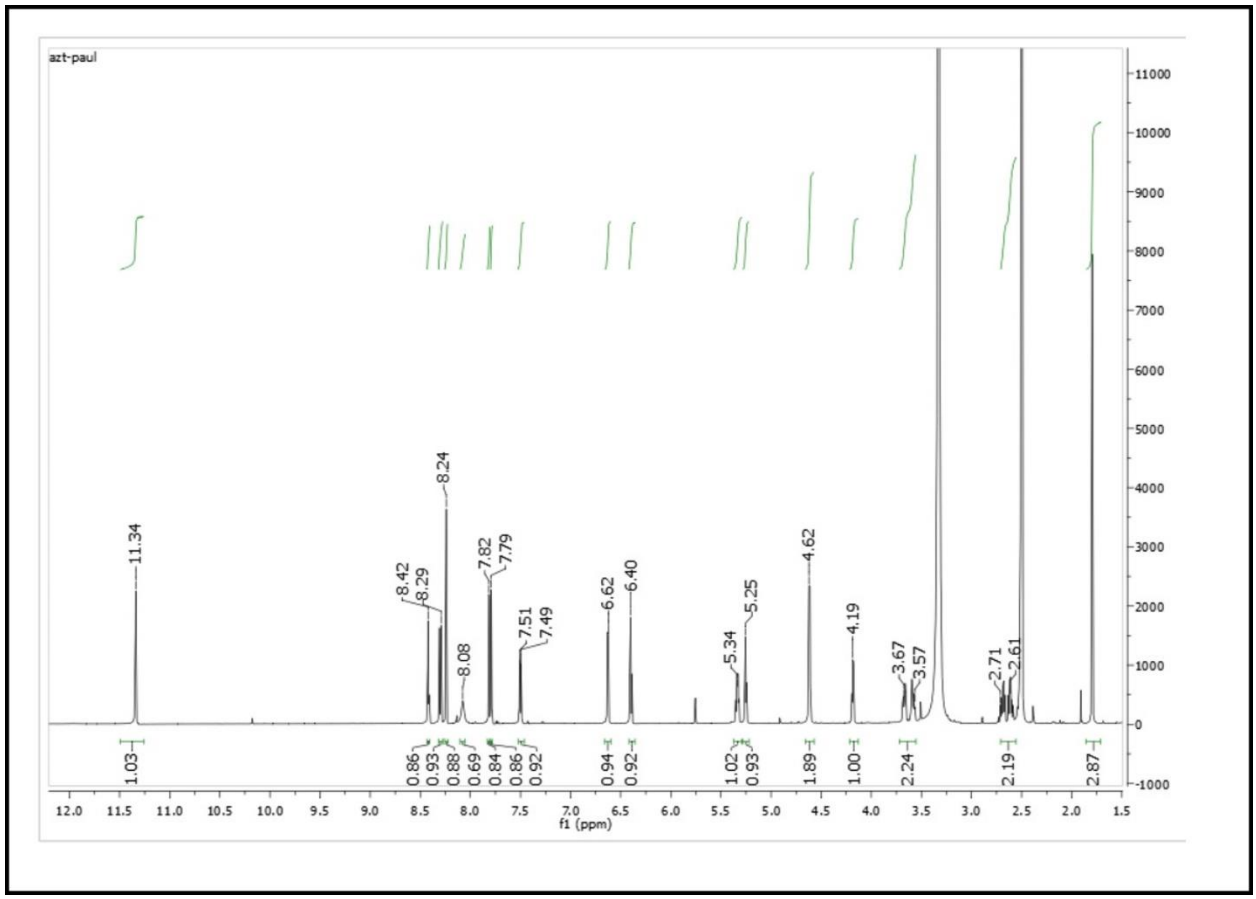


Figure S6. ^{13}C NMR spectrum (DMSO-*d*6, 600 MHz) of compound **4**.

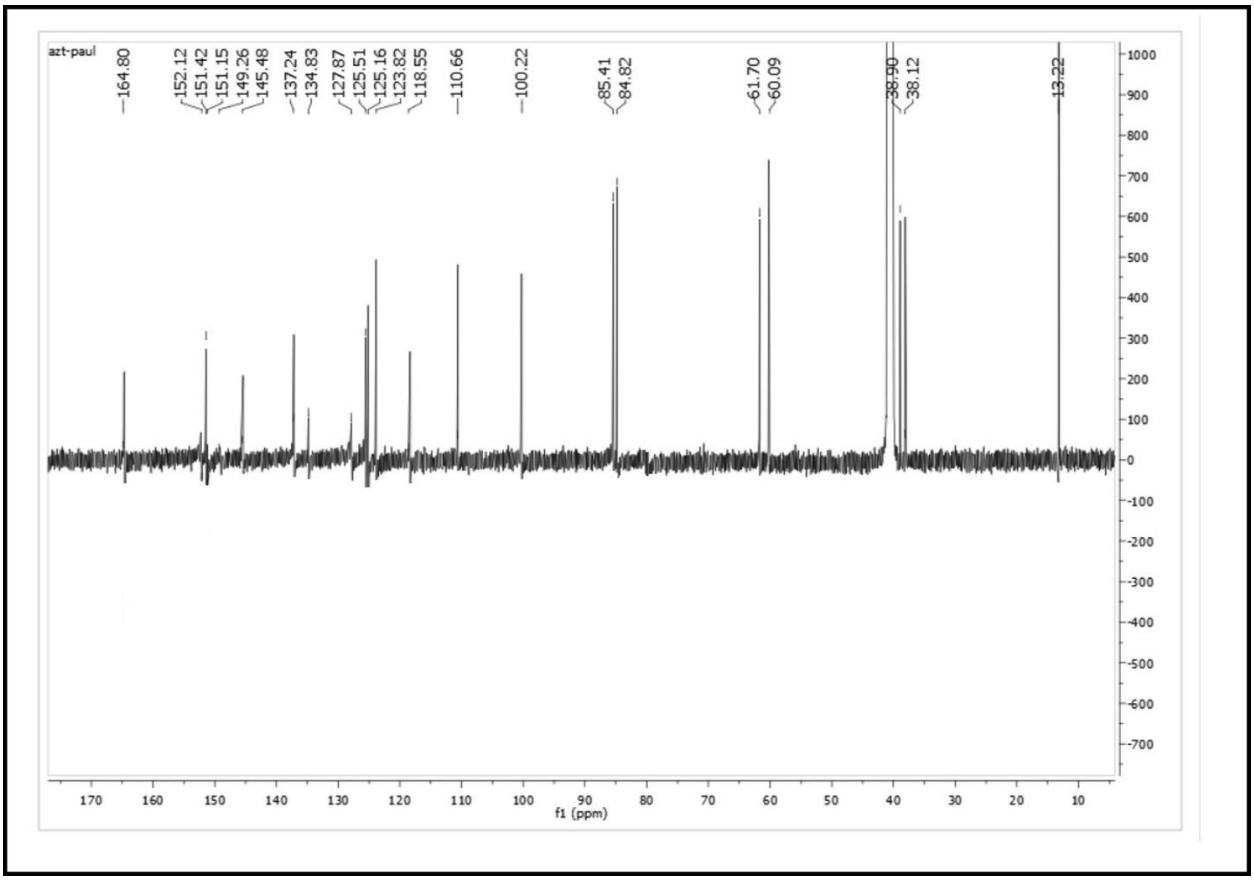


Figure S7. HSQC spectrum (DMSO-*d*6, 600 MHz) of compound **4**.

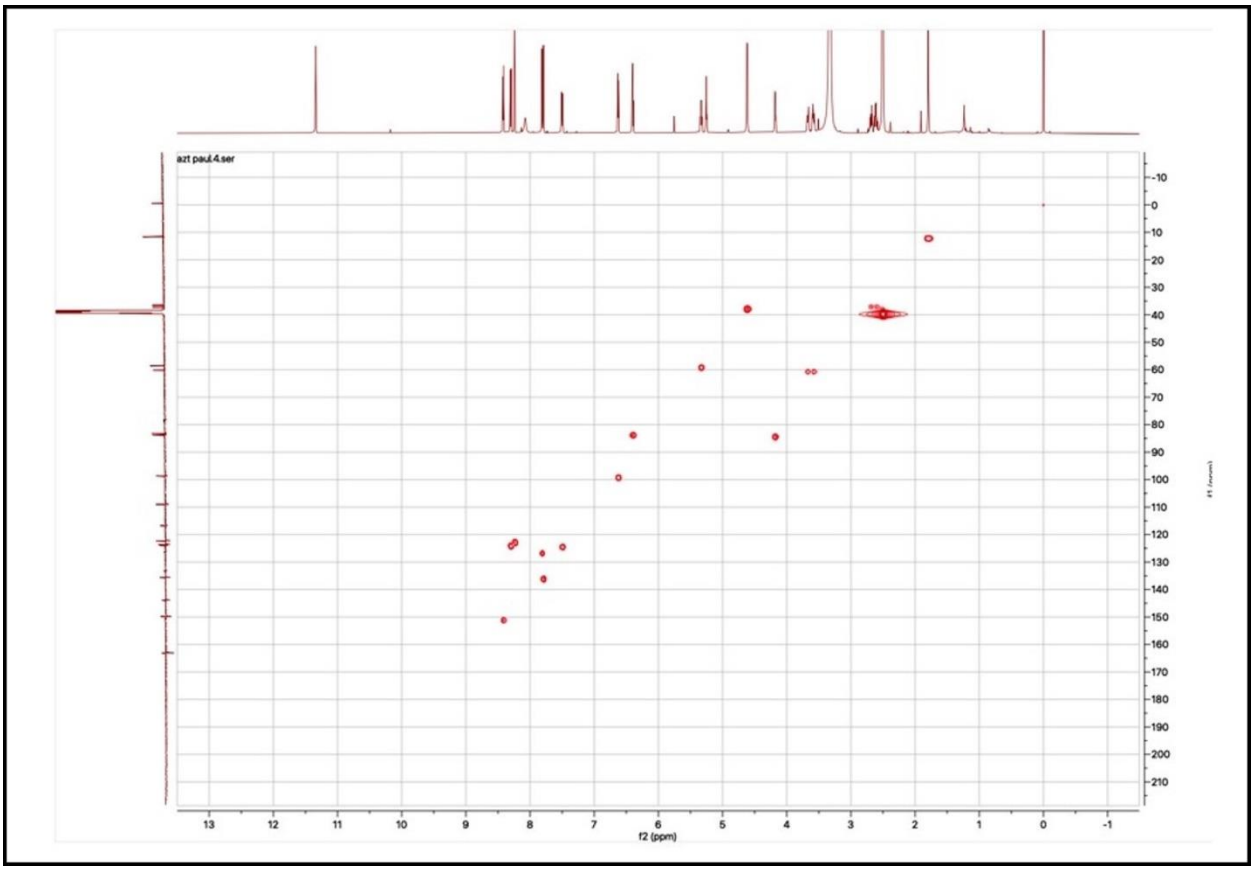


Figure S7a. An expanded view of HSQC spectrum (DMSO-*d*6, 600 MHz) of compound **4**.

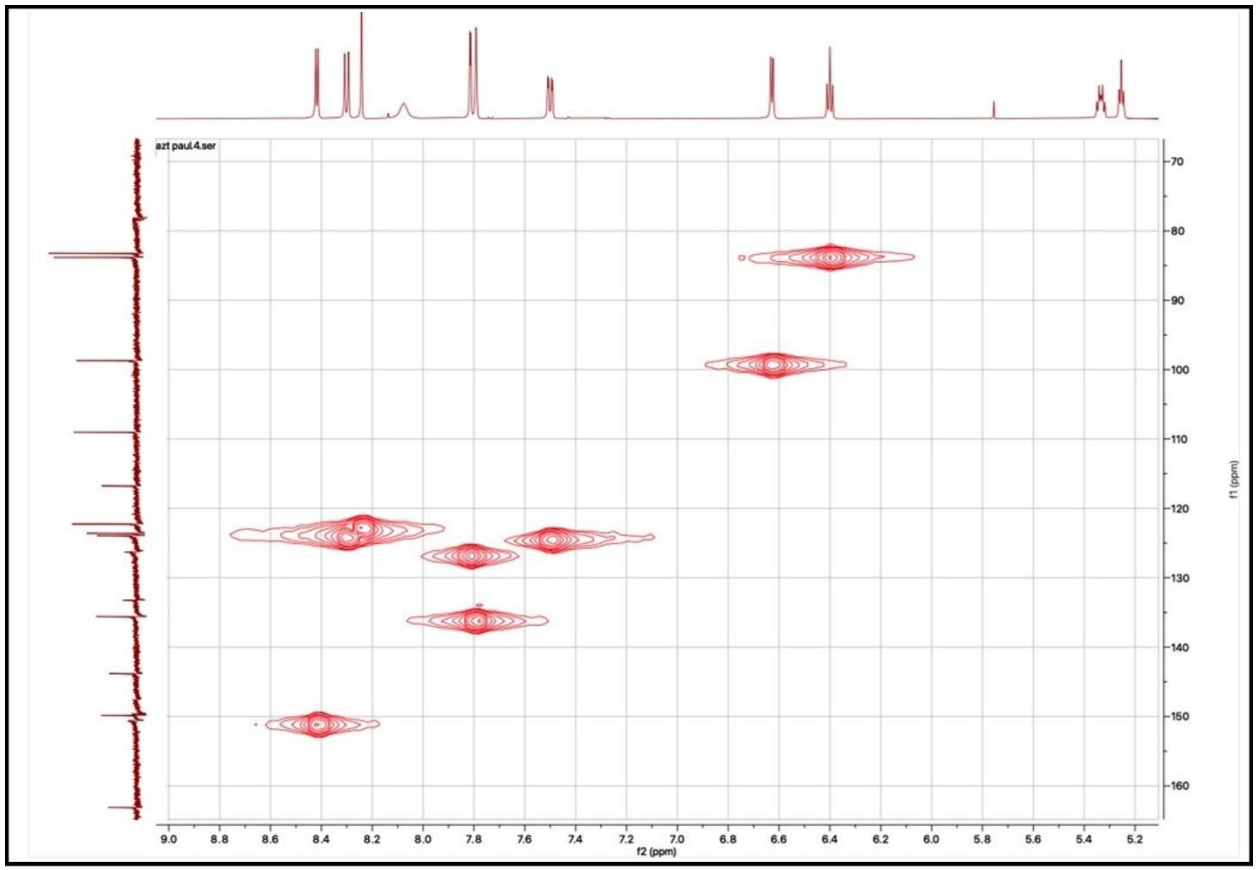


Figure S8. ^{1}H - ^{1}H -COSY spectrum (DMSO-*d*6, 600 MHz) of compound **4**.

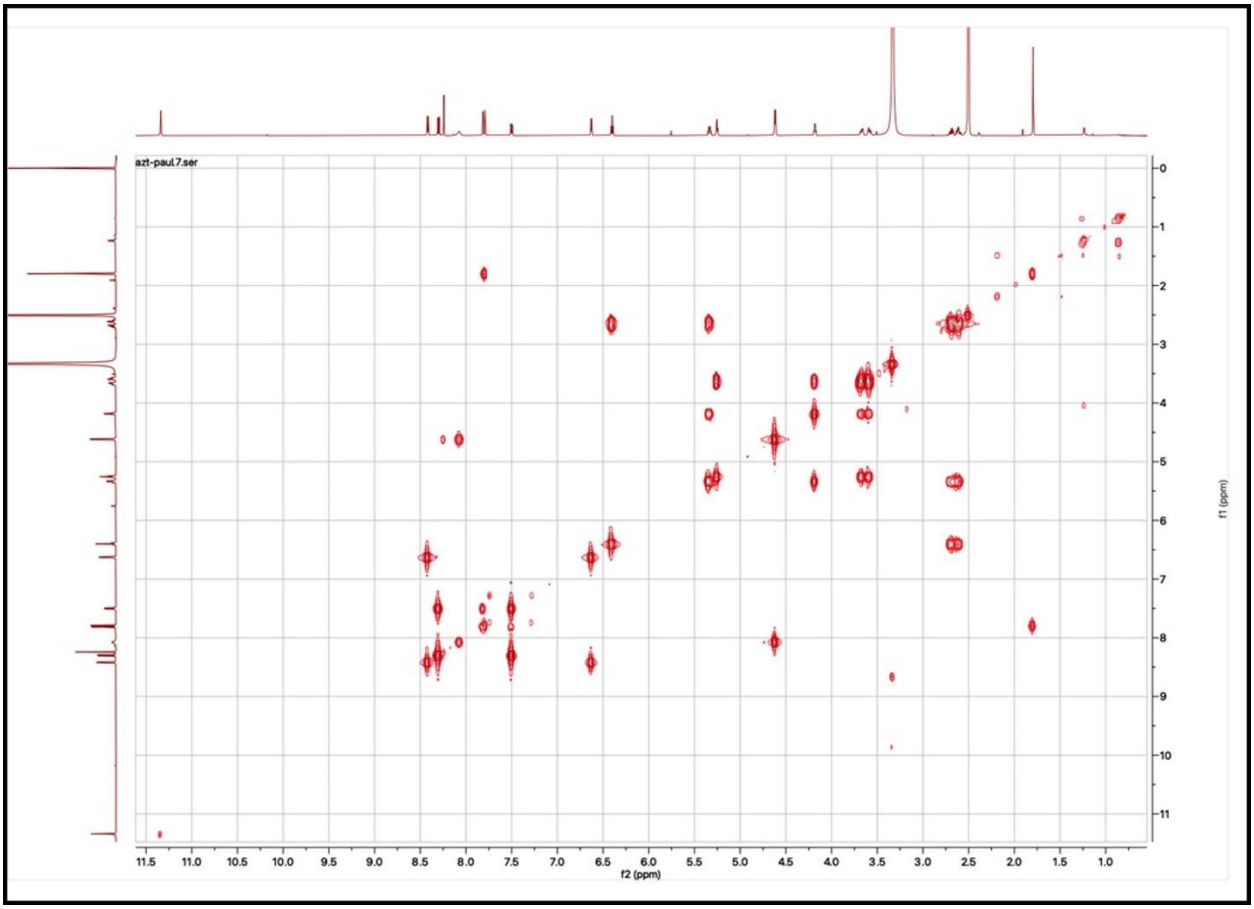


Figure S8a. An expanded view of ^{1}H - ^{1}H -COSY spectrum (DMSO-*d*6, 600 MHz) of compound **4**.

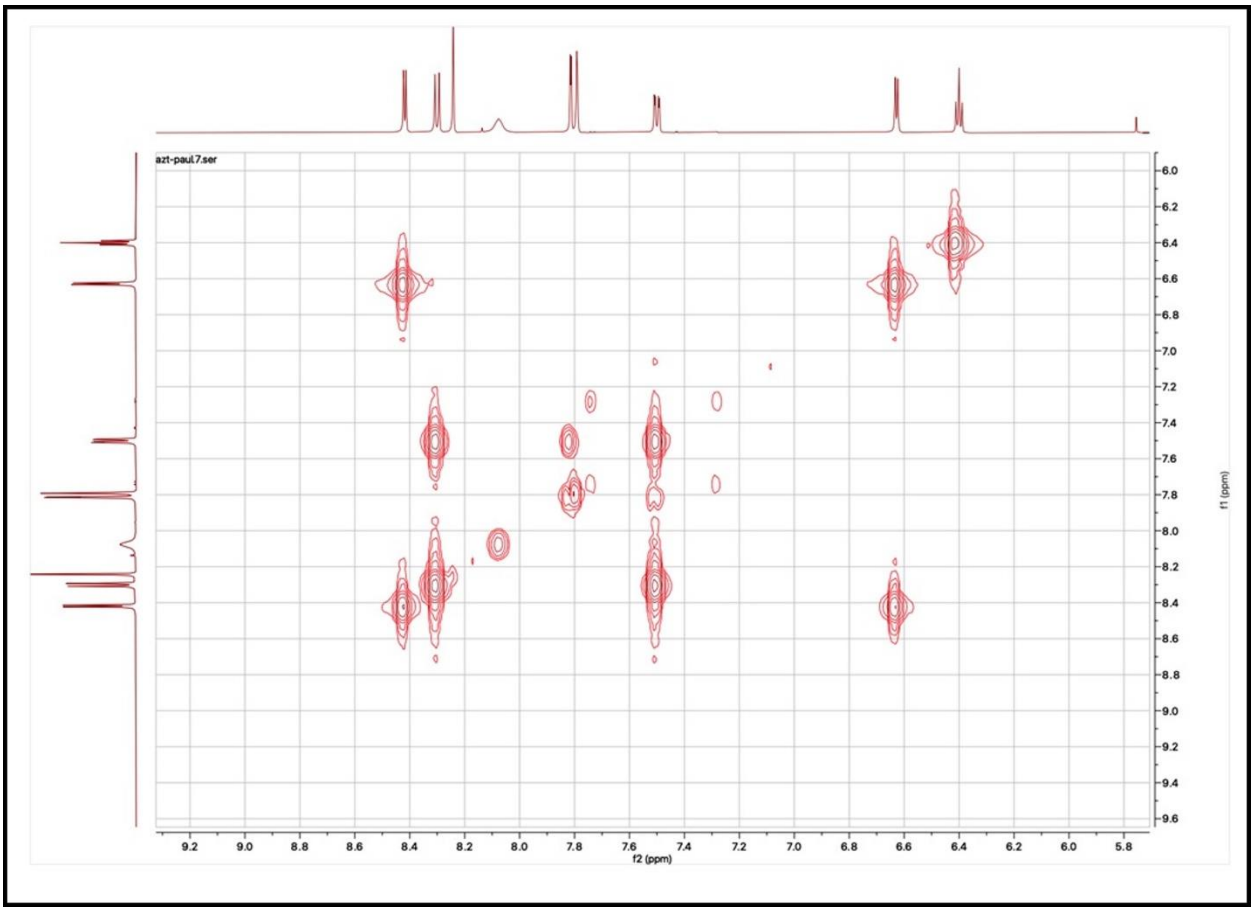
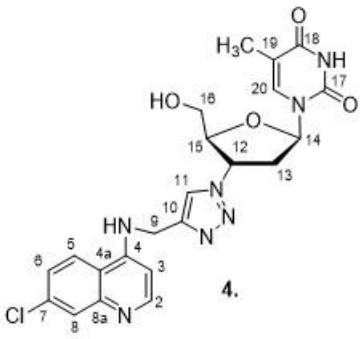


Table S1. ^{1}H and ^{13}C-nuclear magnetic spectroscopy (NMR) chemical shifts and the structure of **4**.

^{1}H Chemical Shift	^{13}C Chemical Shift	**Assignment**
1.78	13.2	Me
2.61-2.71	38.1	13 (2H)
3.57-3.67	61.7	16 (2H)
4.19	85.4	15
4.62	38.9	9(2H)
5.25	--	OH
5.33	60.1	12
6.40	84.8	14
6.62	100.2	3
--	110.5	19
--	118.0	4a
7.49	125.1	6
7.79	137.2	20
7.82	127.8	8
---	134.8	7
8.08	--	NH
8.24	123.8	11
8.29	125.5	5
--	145.4	10
--	149.2	8a
--	151.1	4
8.42	152.1	2
--	151,4	17
11.3	--	NH_{amide}
--	164.6	18



4.

Figure S9. DEPT-135 spectrum (DMSO-*d*6, 600 MHz) of compound **4**.

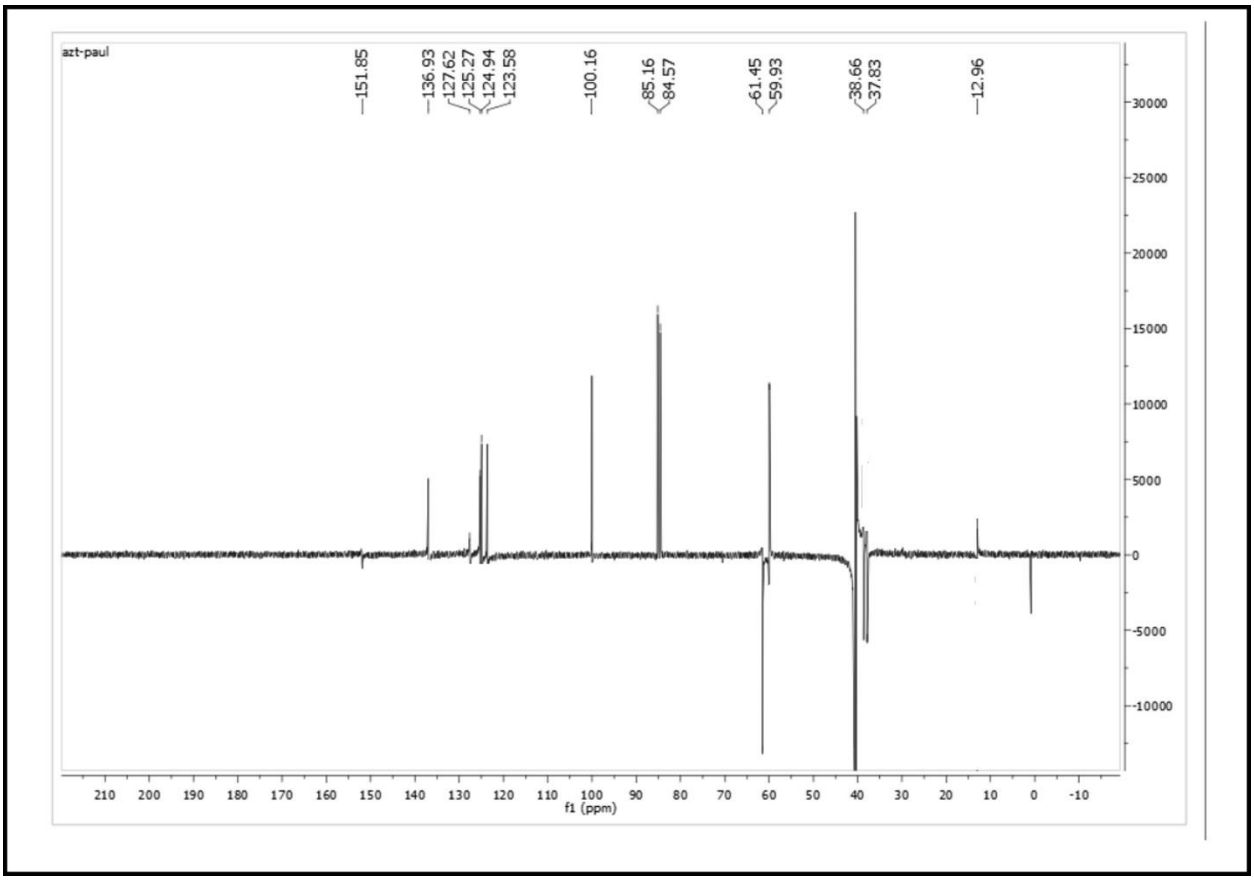


Figure S10. DEPT-90 spectrum (DMSO-*d*6, 600 MHz) of compound **4**

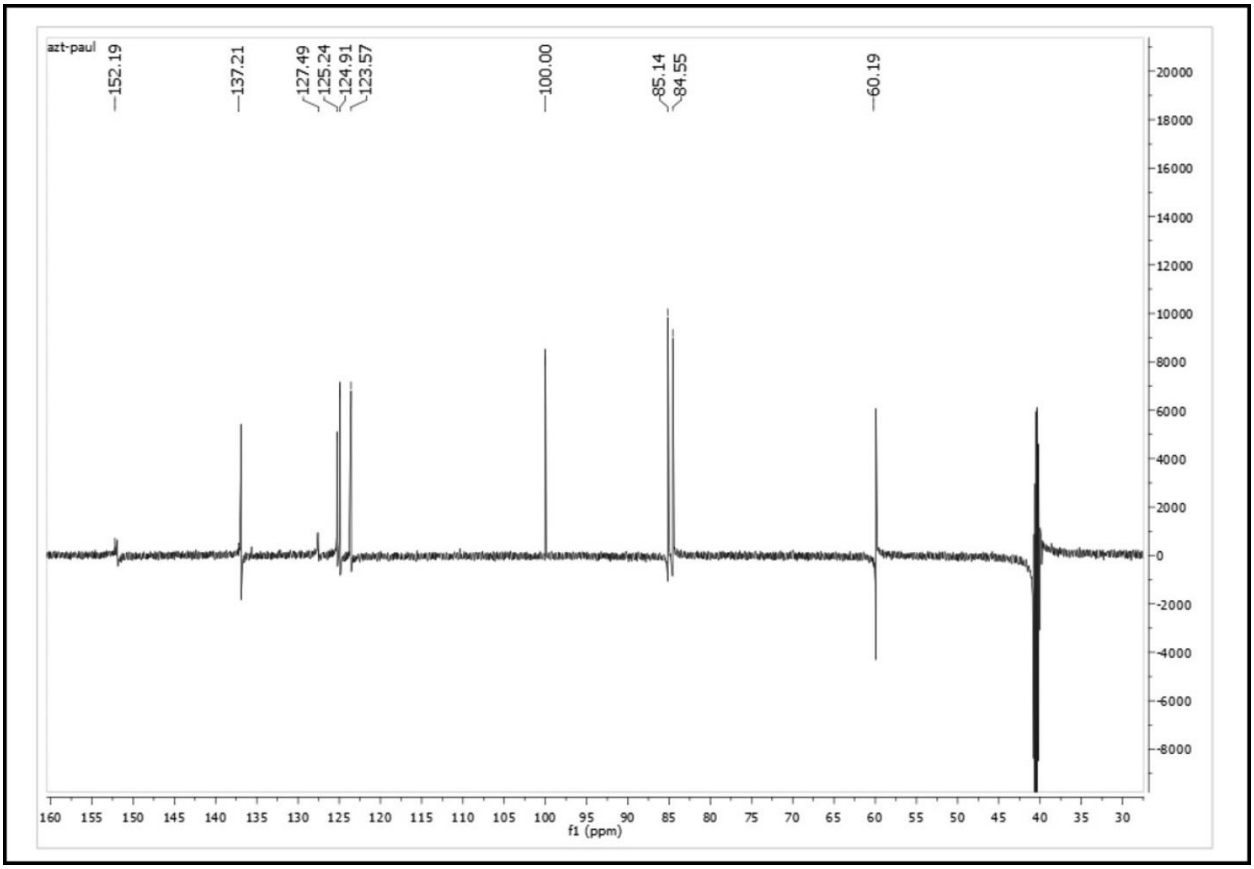


Figure S11. DEPT- 45 spectrum (DMSO-*d*6, 600 MHz) of compound 4

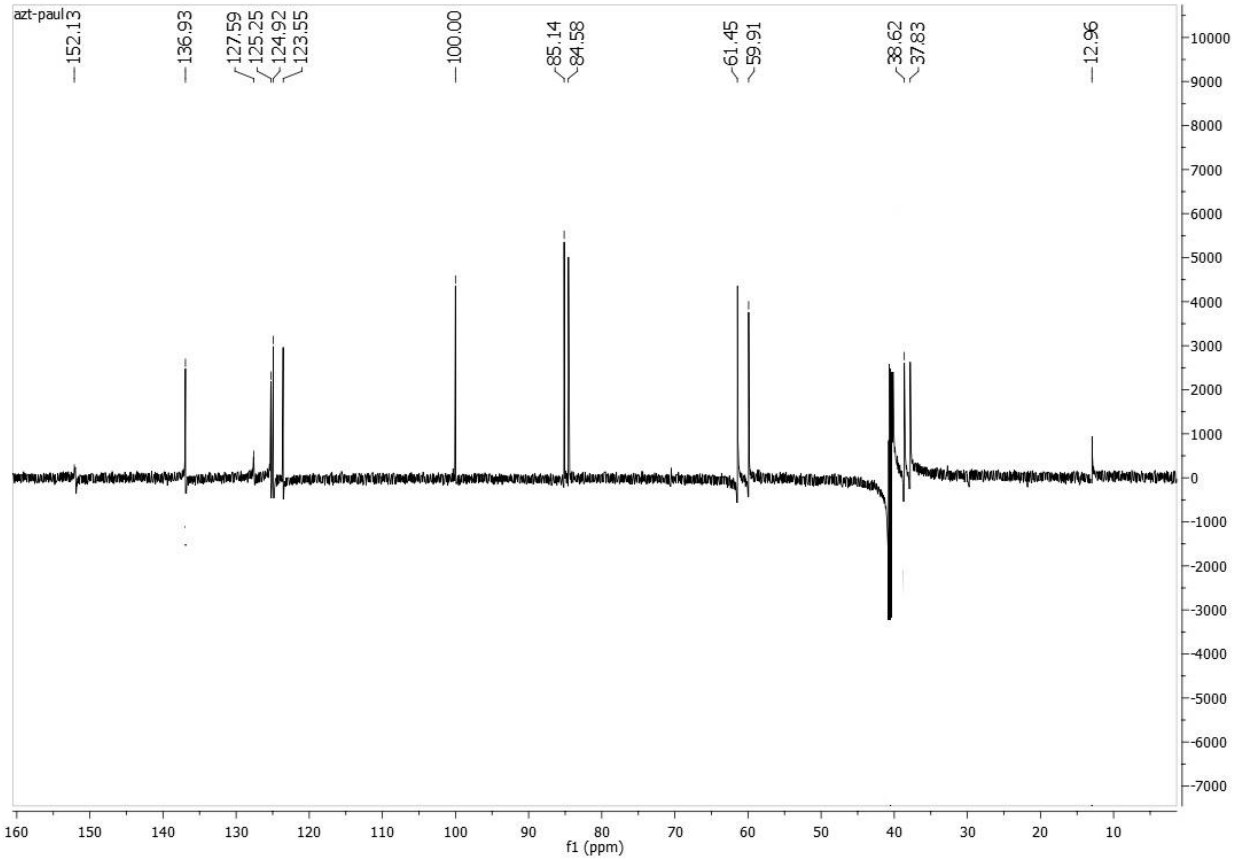


Figure S12. HMBC spectrum (DMSO-*d*6, 600 MHz) of compound **4**

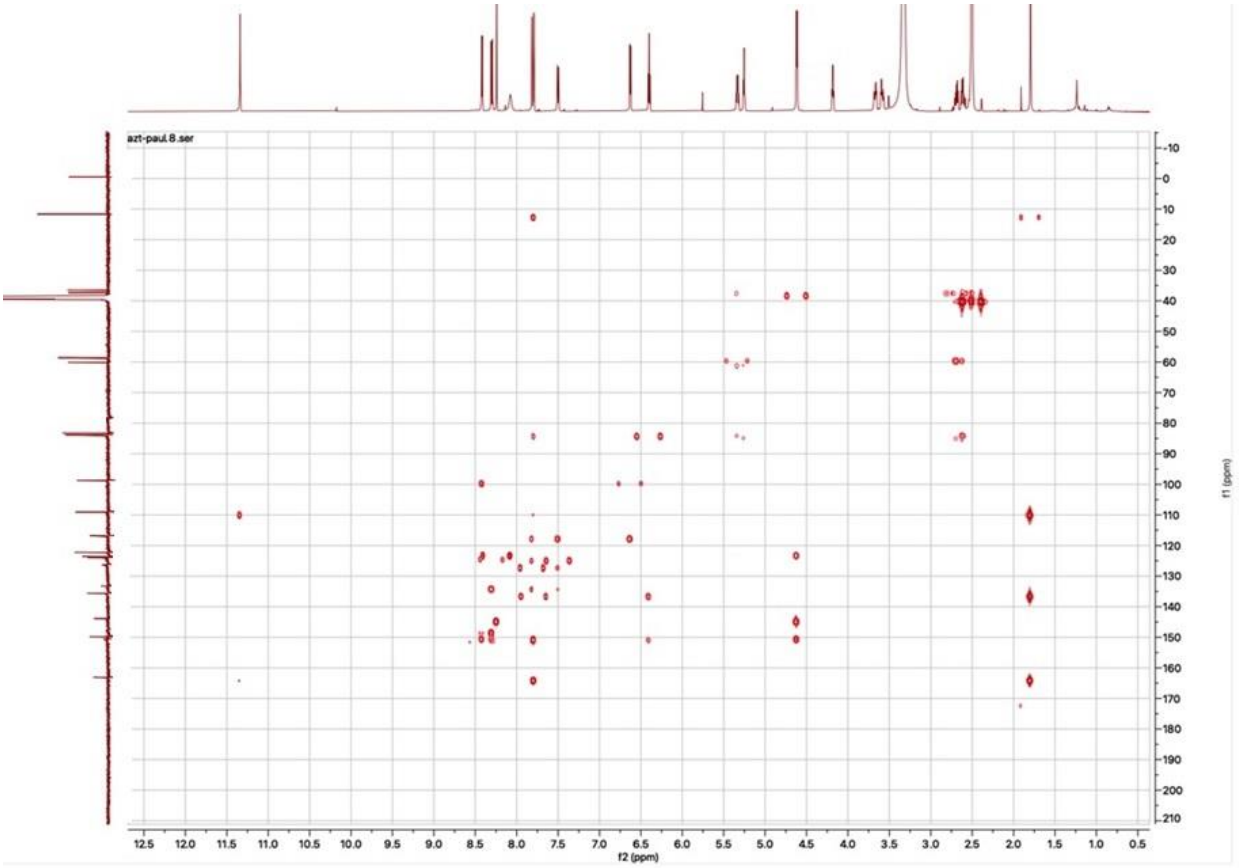
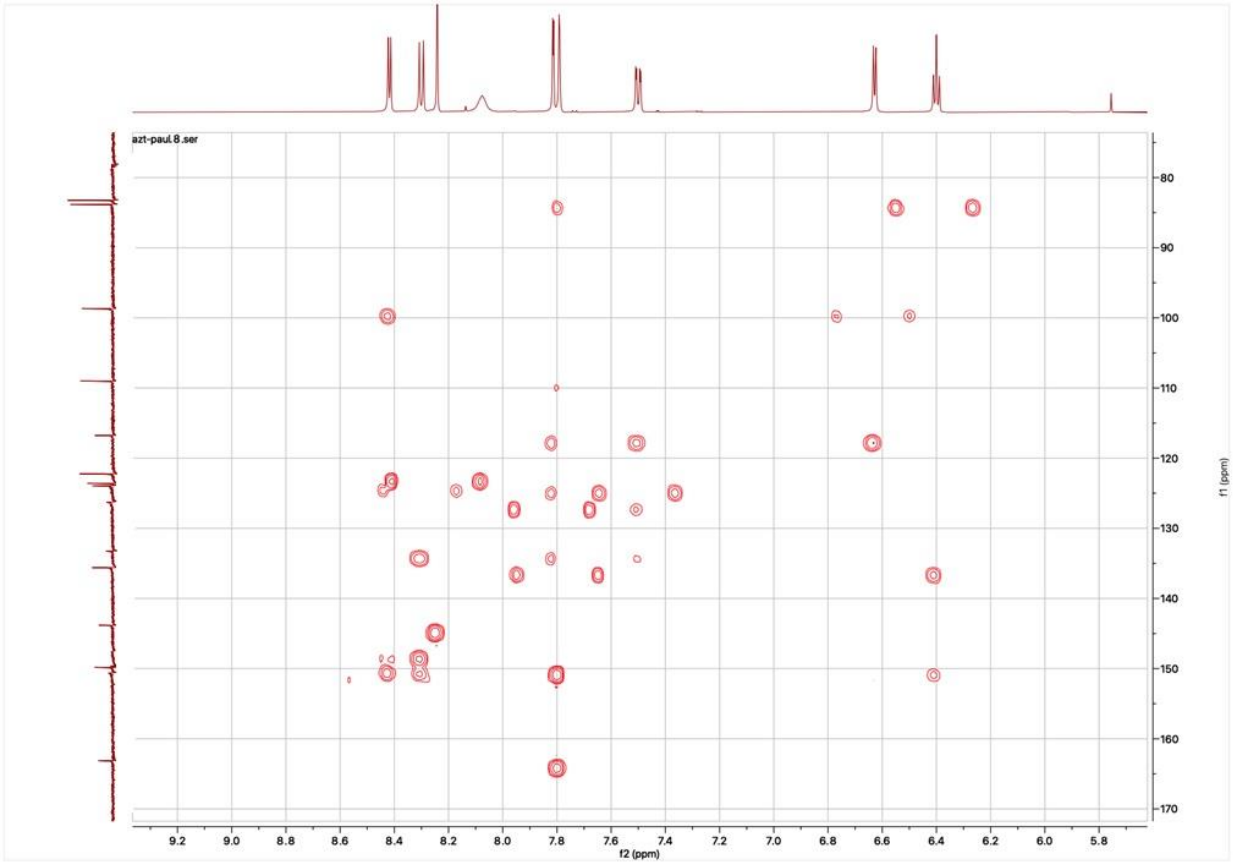


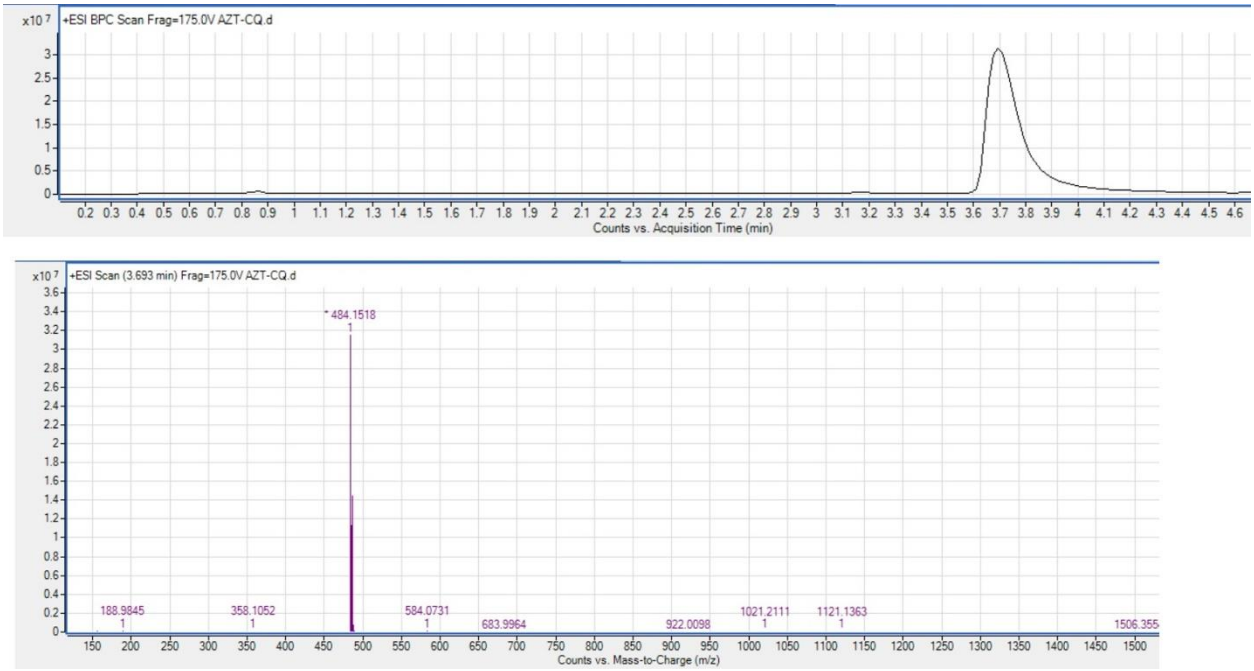
Figure S12a. An expanded view of HMBC spectrum (DMSO-*d*6, 600 MHz) of compound **4**.



(i) C-18 (δ164 ppm) due to its connectivities with H-20, Me.
(ii) C-10 (δ145.4 ppm) due to its connectivities with H-11, H-9
(iii) C-7 (δ134.8 ppm) due to its connectivities with H-5, H-8and H-6
(iv) C-4a (δ118 ppm) due to its connectivities with H-8, H-6 and H-3.
(v) C-19 (δ110 ppm) due to its connectivities with Me, H-20 and NH
(vi) C -8a (δ110 ppm) due to its connectivities with H-8
(vii) C -4 (δ151.1 ppm) due to its connectivities with H-3

Mass spectrometry

Figure S13. Mass spectrum and UPLC-ESI chromatogram (254 nm) of compound **4**



The spectrum was recorded in positive ionization mode (ESI). Analysis was performed using a solvent mixture containing acetonitrile/water at a flow rate of 0.5 mL/min. The mobile phase was isocratic (water + 0.01% TFA; CH_3CN).

UV-VIS spectroscopy

Figure 14a. UV spectrum of compound **4** in acetone (range 200-450nm in acetone)

λ_{max}= 270 and 340 nm

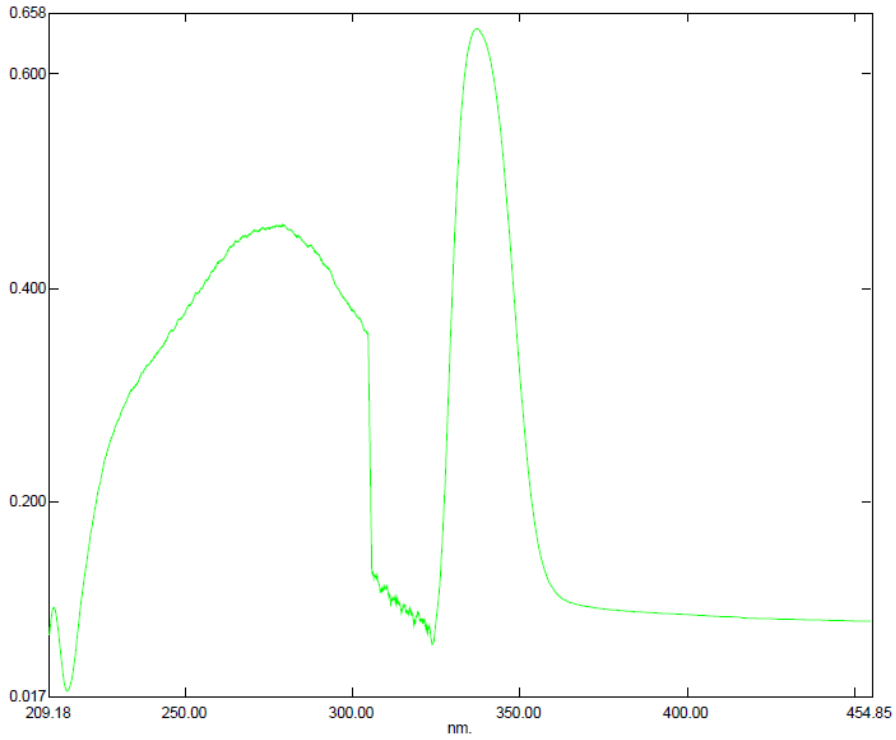
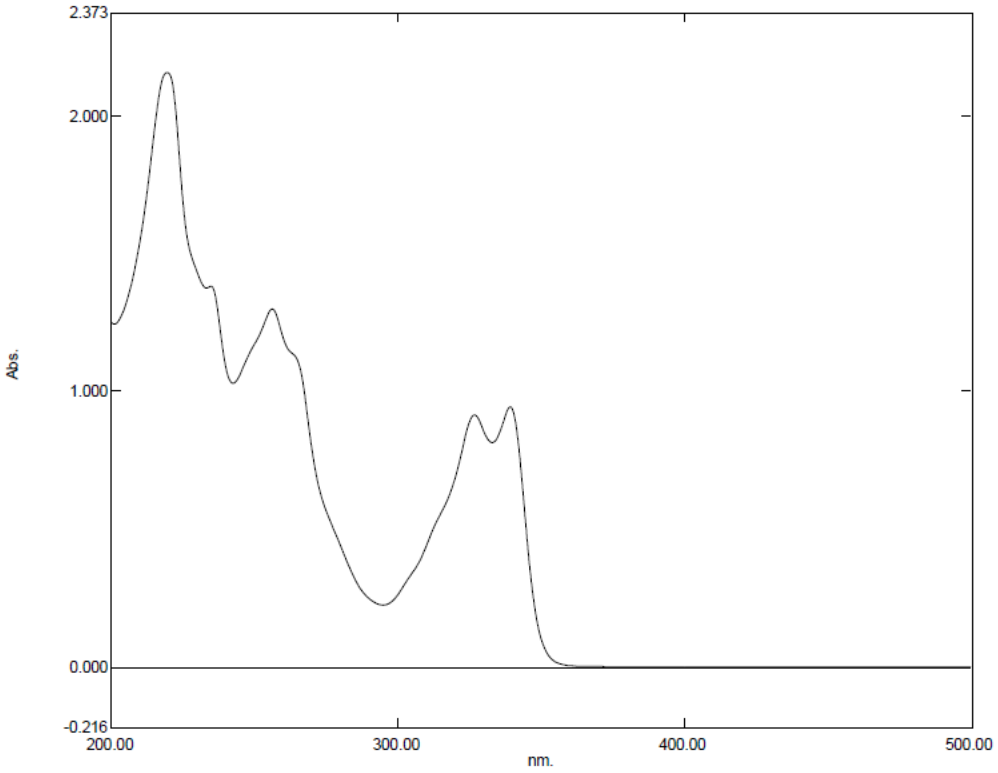


Figure 14b. UV spectrum of compound **4** in water (range 200-450nm in acetone)

λ_{max} = 256, 323 and 339 nm



IR spectroscopy

Figure S15a. FT-IR spectrum of compound **4**.

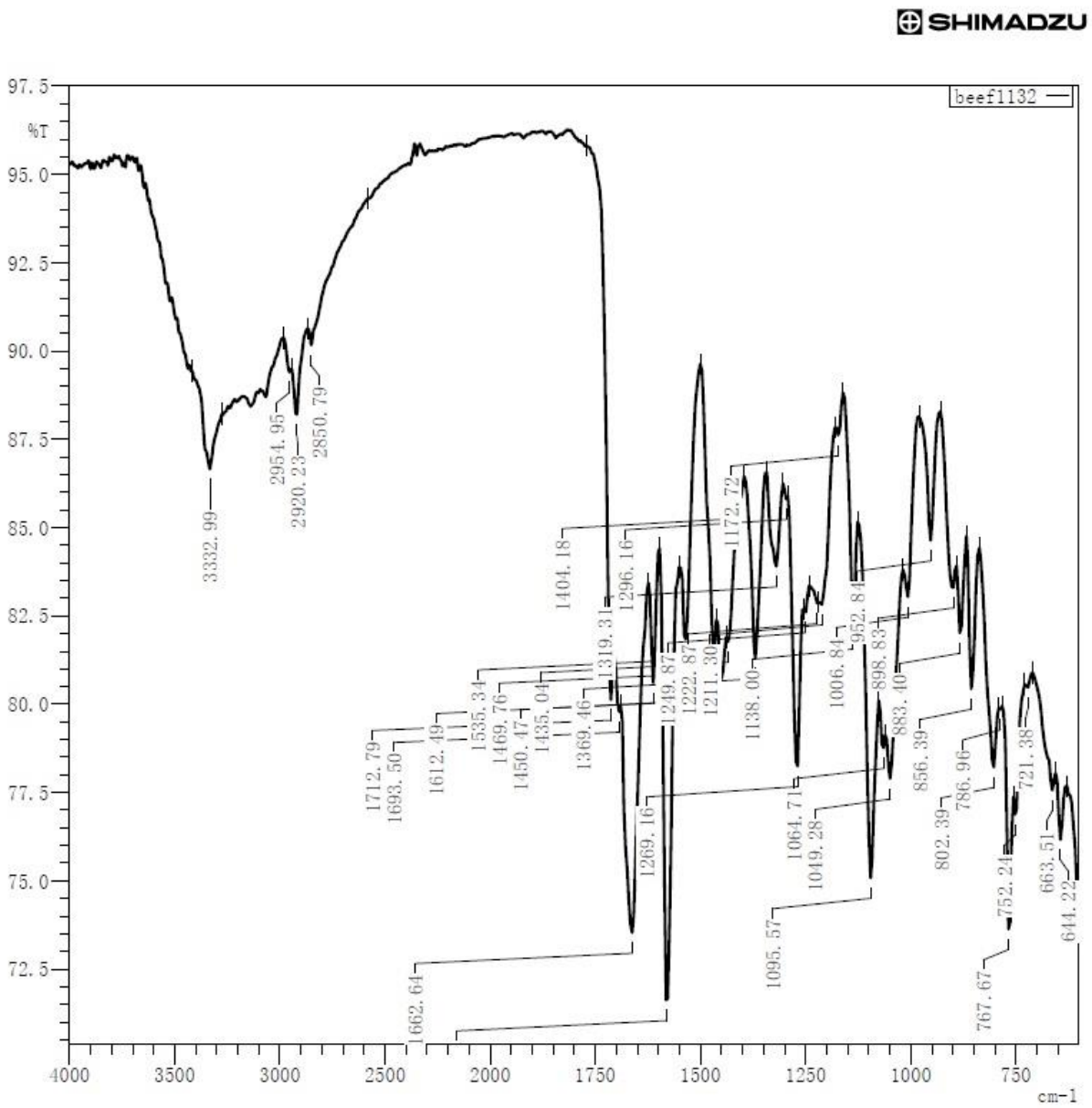


Figure S15b. FT-IR spectrum of compound **1**.

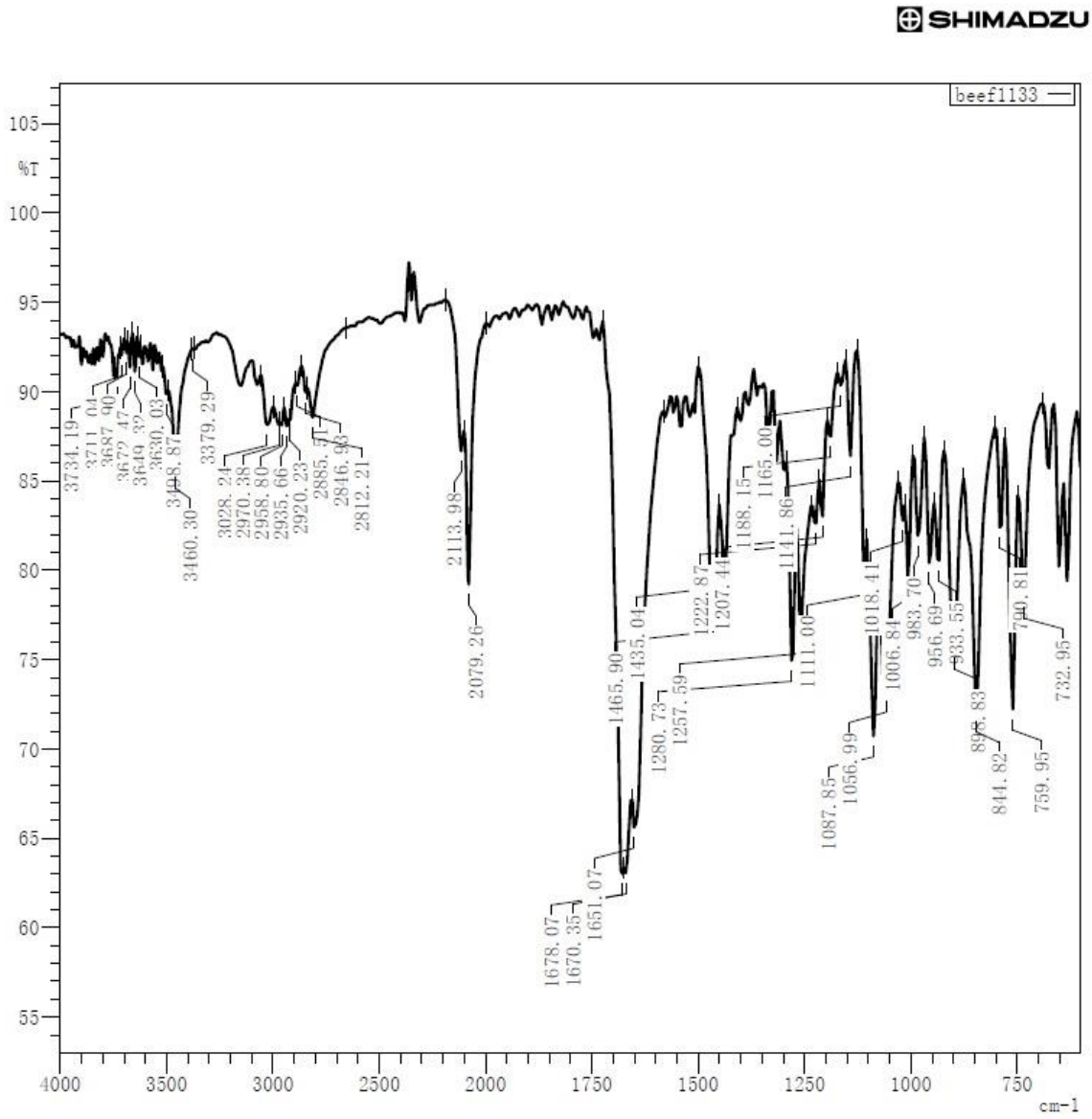


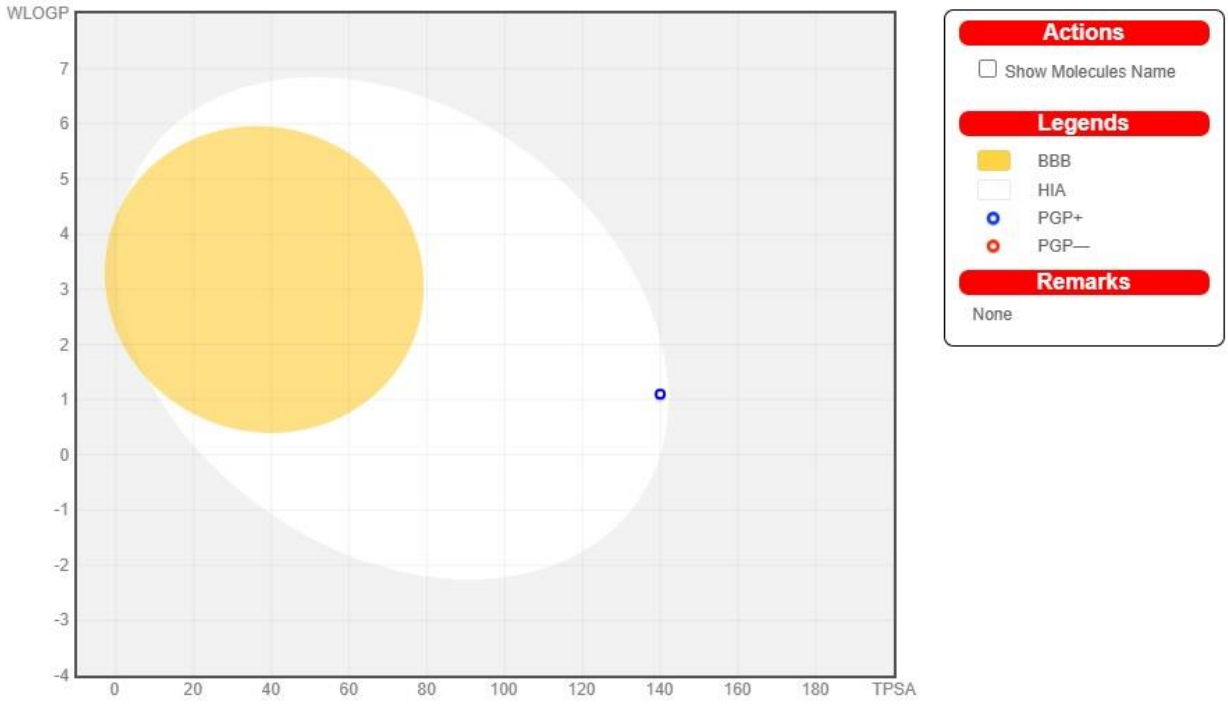
Table S2. Physicochemical properties of compound **1** and **4** calculated by SwissADME

Compound	MW	HBA	HBD	tPSA	nRtB
1	267.2	7	2	134.07	3
4	483.9	7	3	139.95	6

MW: Molecular weight. nRtB: Number of rotatable bond. HBA: Number of hydrogen-bond acceptor. HBD: Number of hydrogen-bond donor. tPSA: topological polar surface area [2].

Figure S16. BOILED-Egg graph resuming the predicted properties for the compound **4**.

The overall predicted pharmacokinetic properties were resumed in the BOILED-Egg graph [3] as reported in Figure S16. The white area indicated the molecules with high probability to be absorbed by the GI tract, while the yellow area indicated the molecules with high probability to passively permeate through the blood-brain barrier. The blue dot represented the molecule which was predicted to be effluated by P-glycoprotein.



References

1. Adasme, M.F.; Linnemann, K.L.; Bolz, S.N.; Kaiser, F.; Salentin, S.; Haupt, V.J.; Schroeder, M. PLIP 2021: Expanding the Scope of the Protein–Ligand Interaction Profiler to DNA and RNA. *Nucleic Acids Research* **2021**, *49*, W530–W534, doi:10.1093/nar/gkab294.
2. Daina, A.; Michielin, O.; Zoete, V. SwissADME: A Free Web Tool to Evaluate Pharmacokinetics, Drug-Likeness and Medicinal Chemistry Friendliness of Small Molecules. *Sci Rep* **2017**, *7*, 42717, doi:10.1038/srep42717.
3. Daina, A.; Zoete, V. A BOILED-Egg To Predict Gastrointestinal Absorption and Brain Penetration of Small Molecules. *ChemMedChem* **2016**, *11*, 1117–1121, doi:10.1002/cmdc.201600182.