SUPPORTING INFORMATION

Journal of Chemical Information and Modeling

Design, Synthesis and Molecular Modeling Studies of Novel Coumarin Carboxamide Derivatives as eEF-2K Inhibitors

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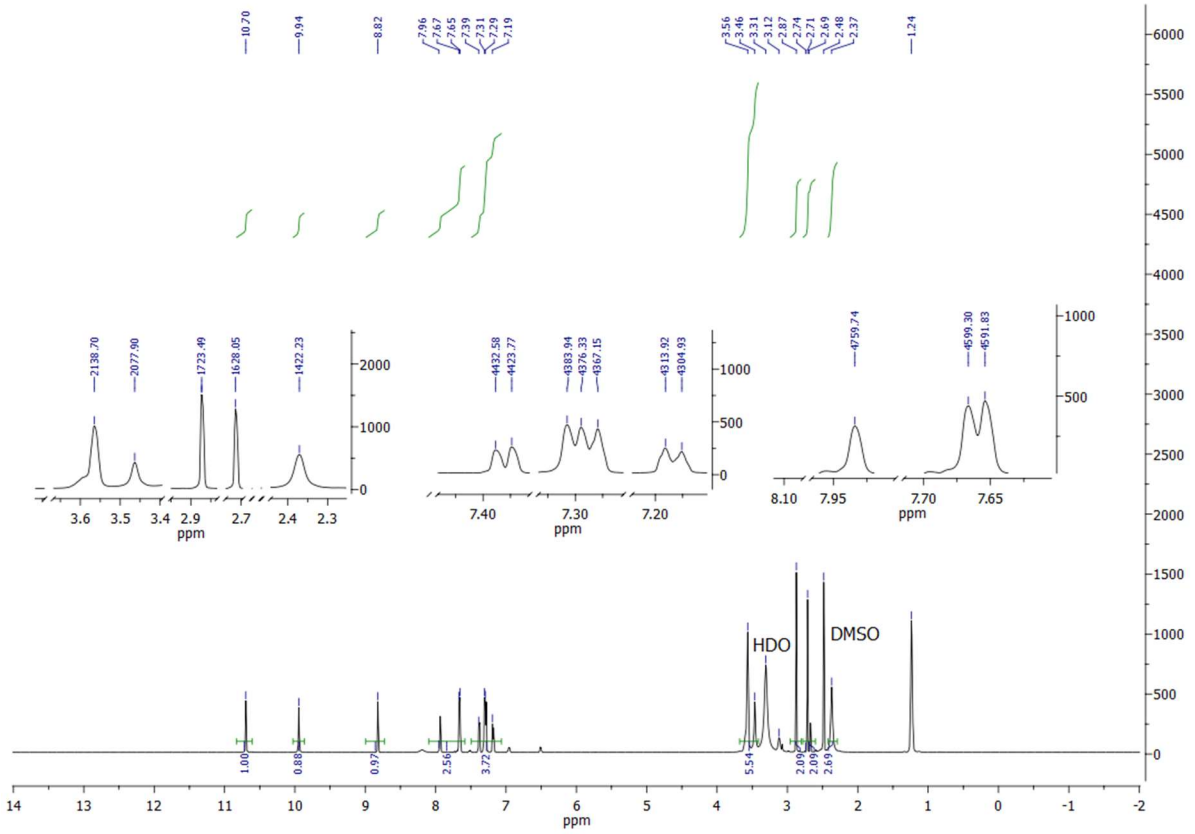
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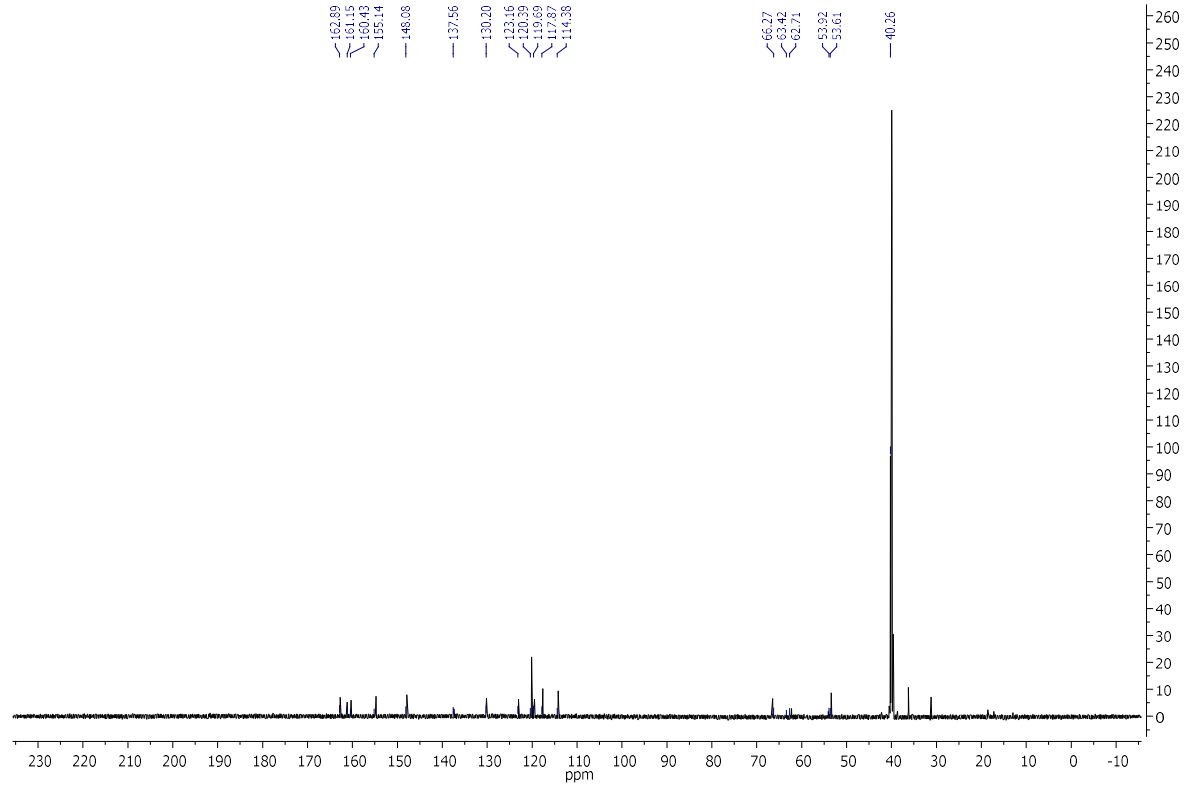
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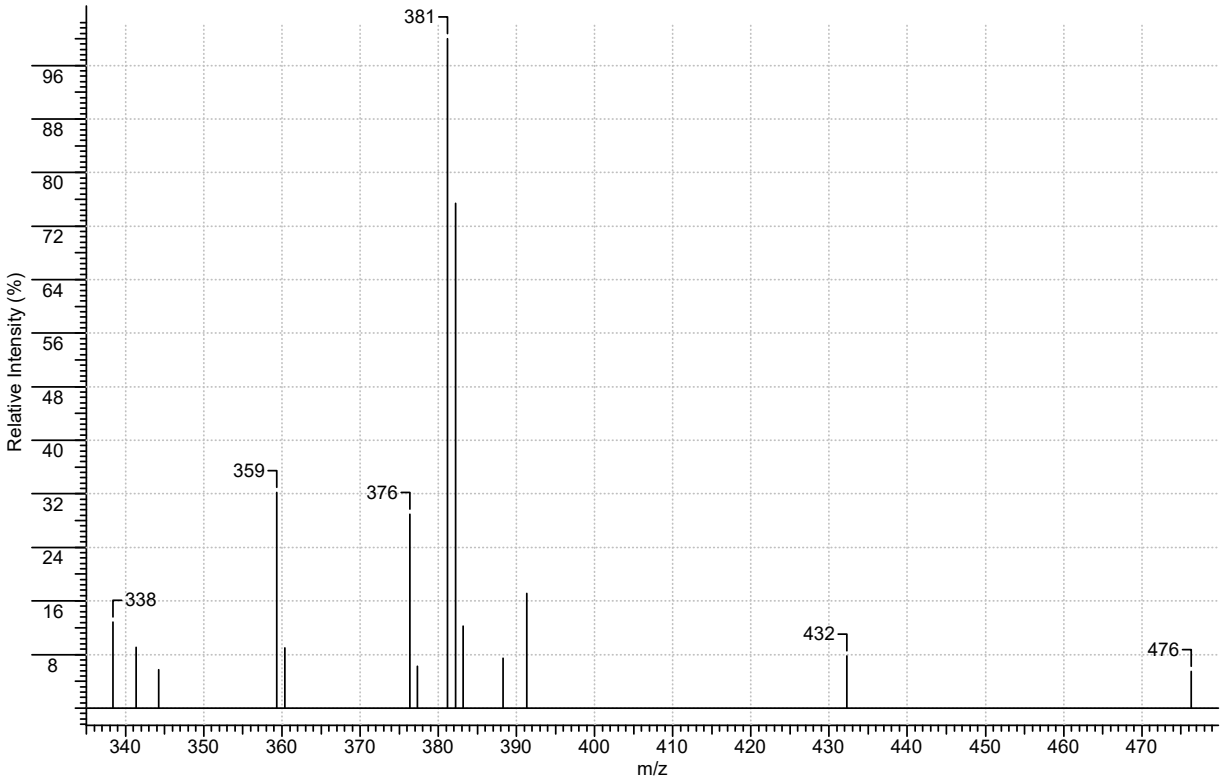
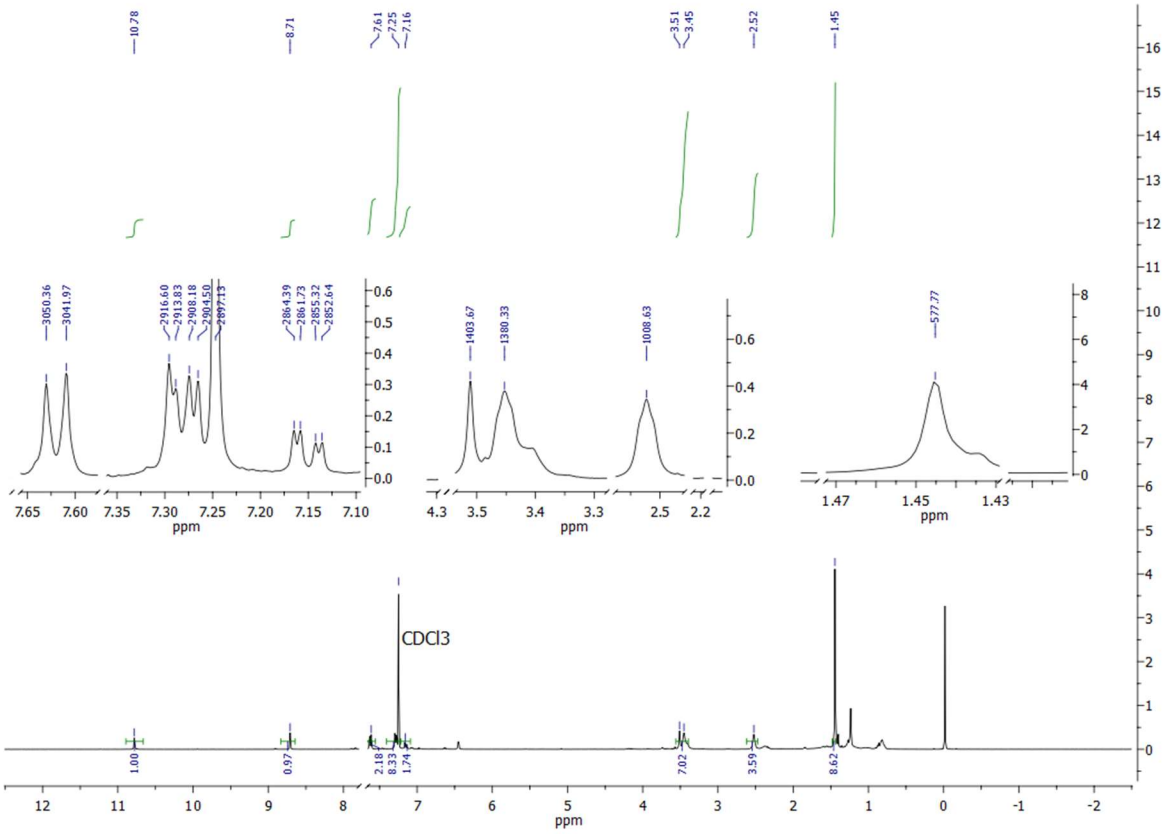


Figure S1. ^{1}H NMR, ^{13}C NMR and LC-MS/MS spectra of compound **A1**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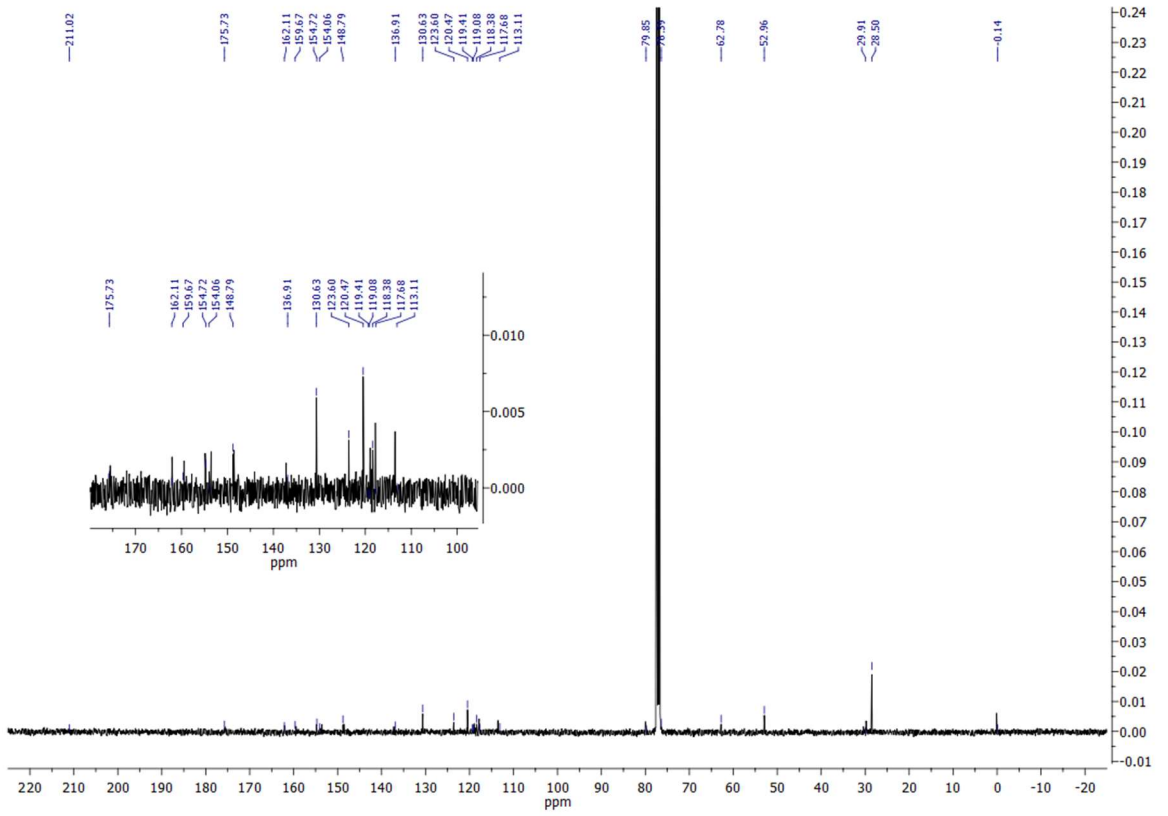
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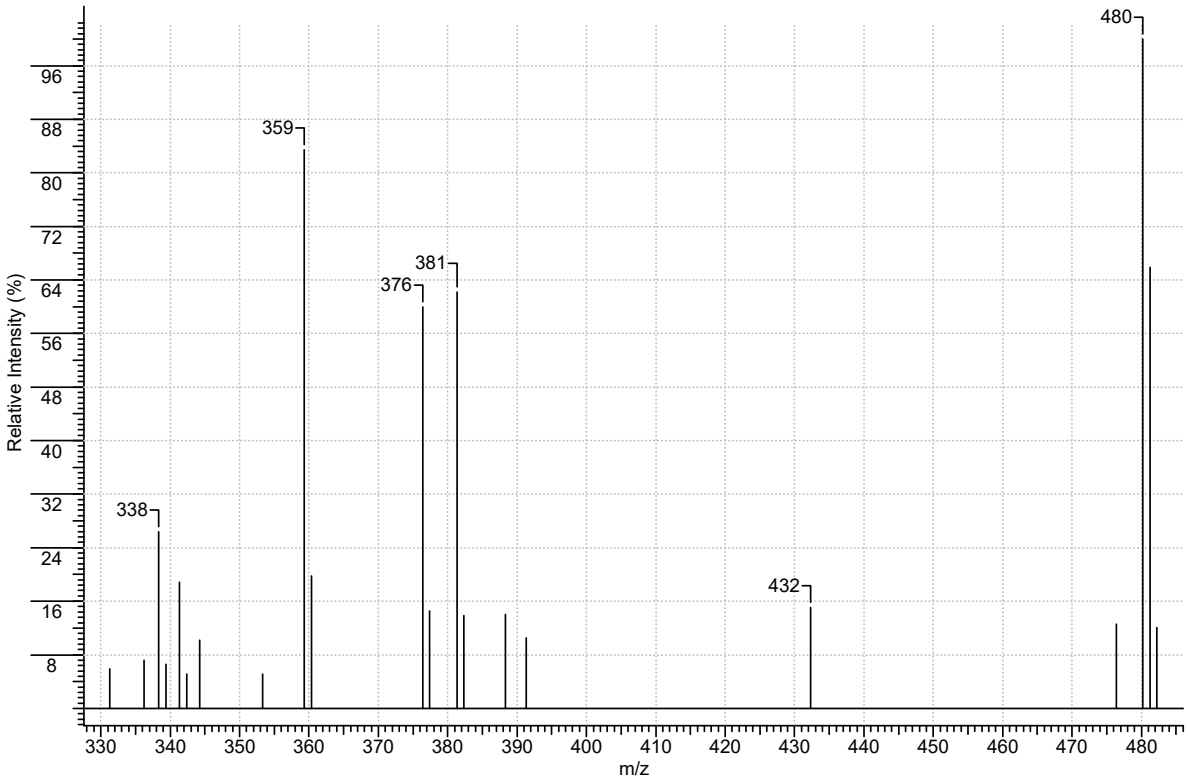
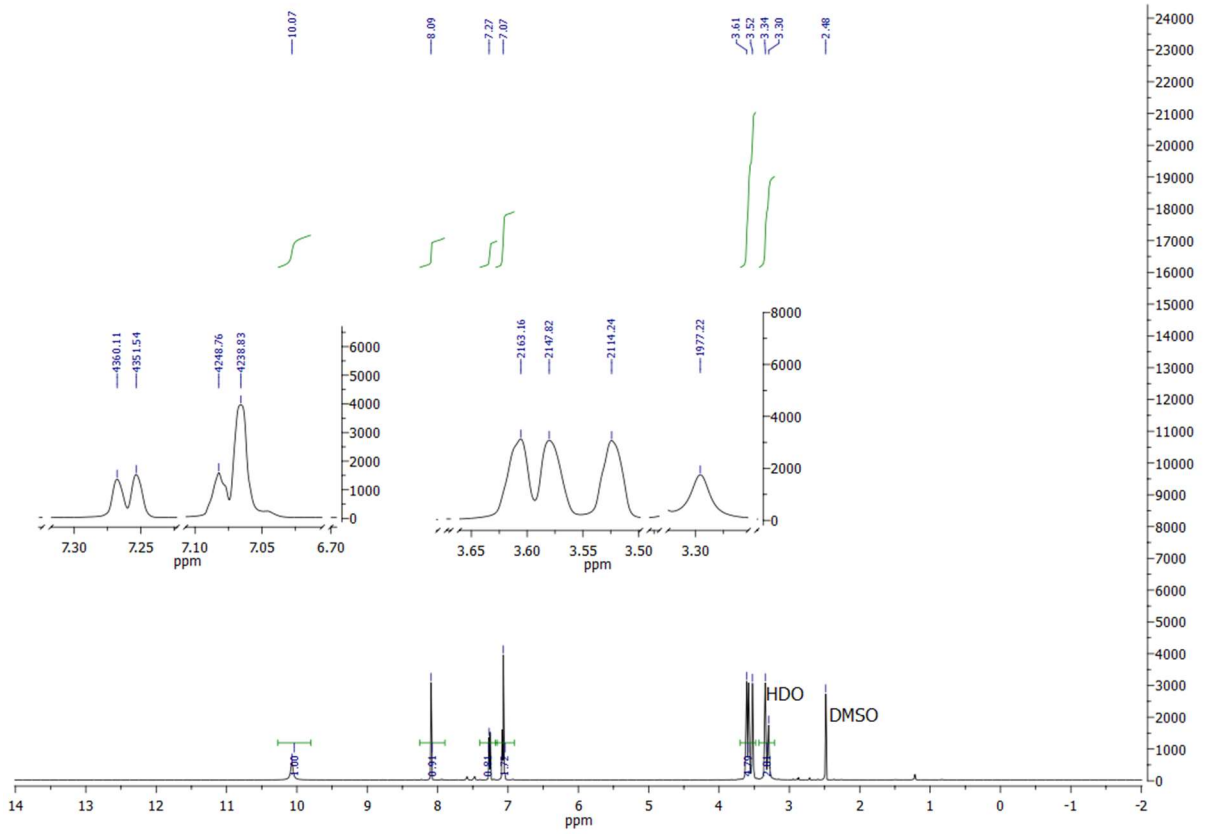


Figure S2. ^{1}H NMR, ^{13}C NMR and LC-MS/MS spectra of compound **A2**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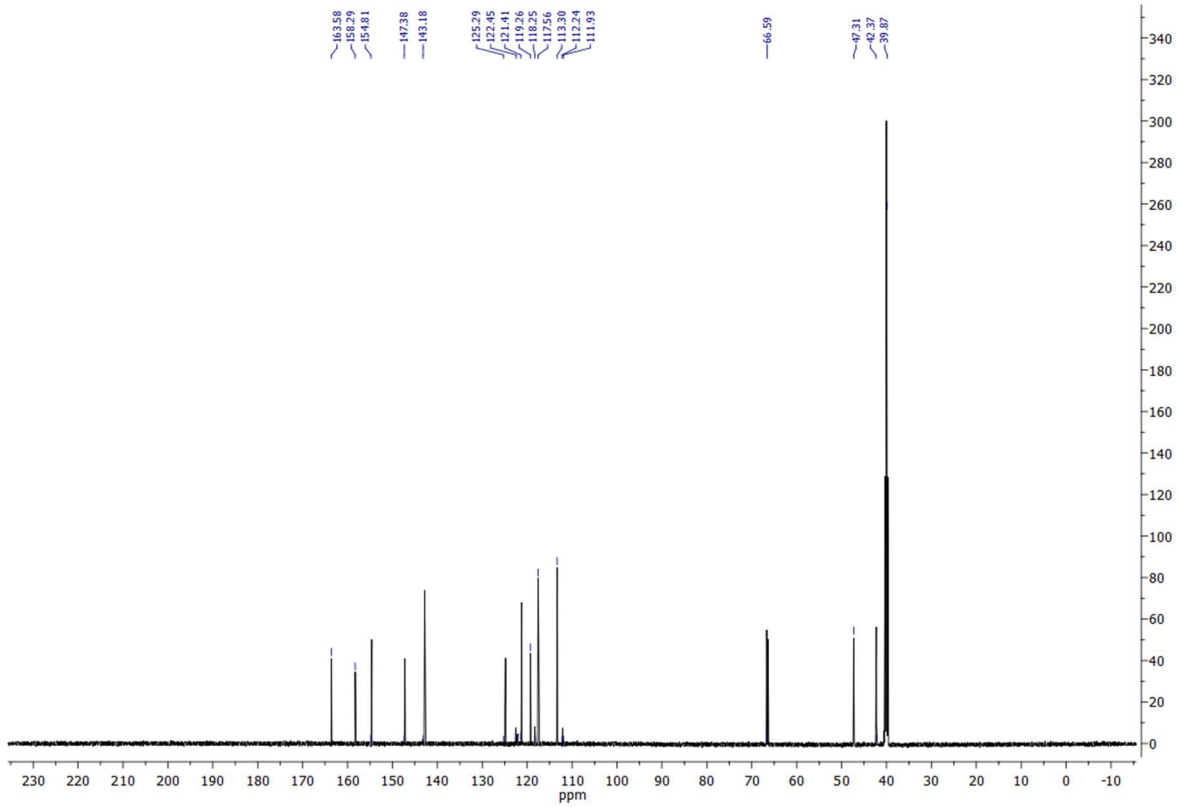
DMSO
ppm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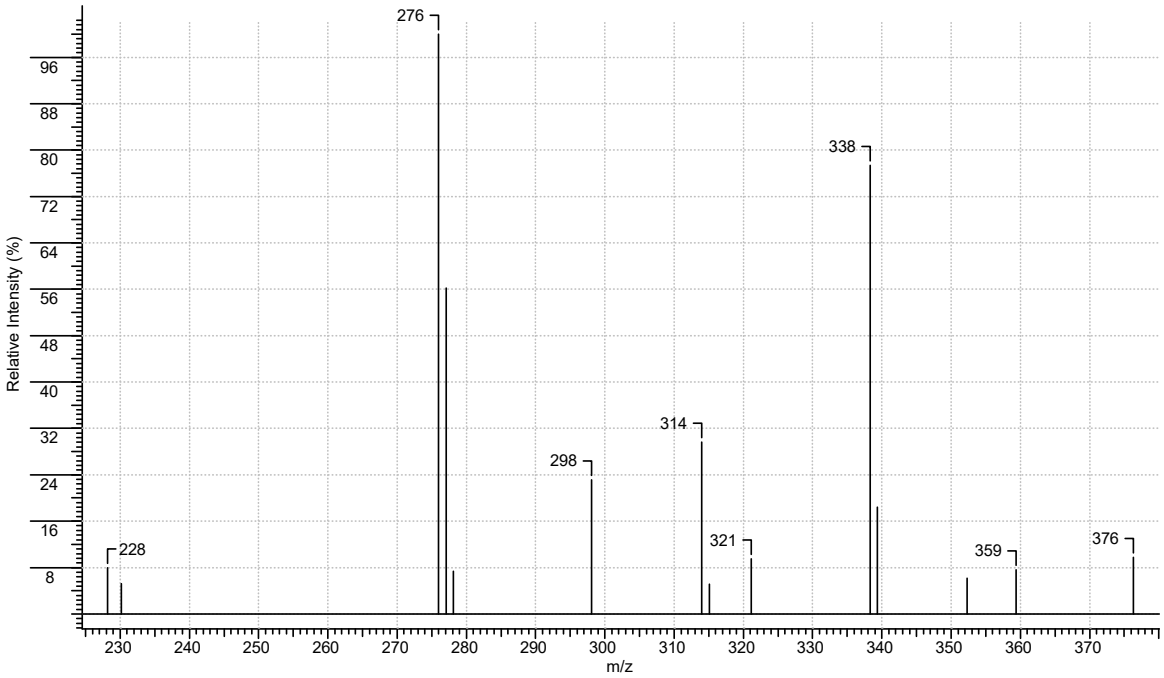
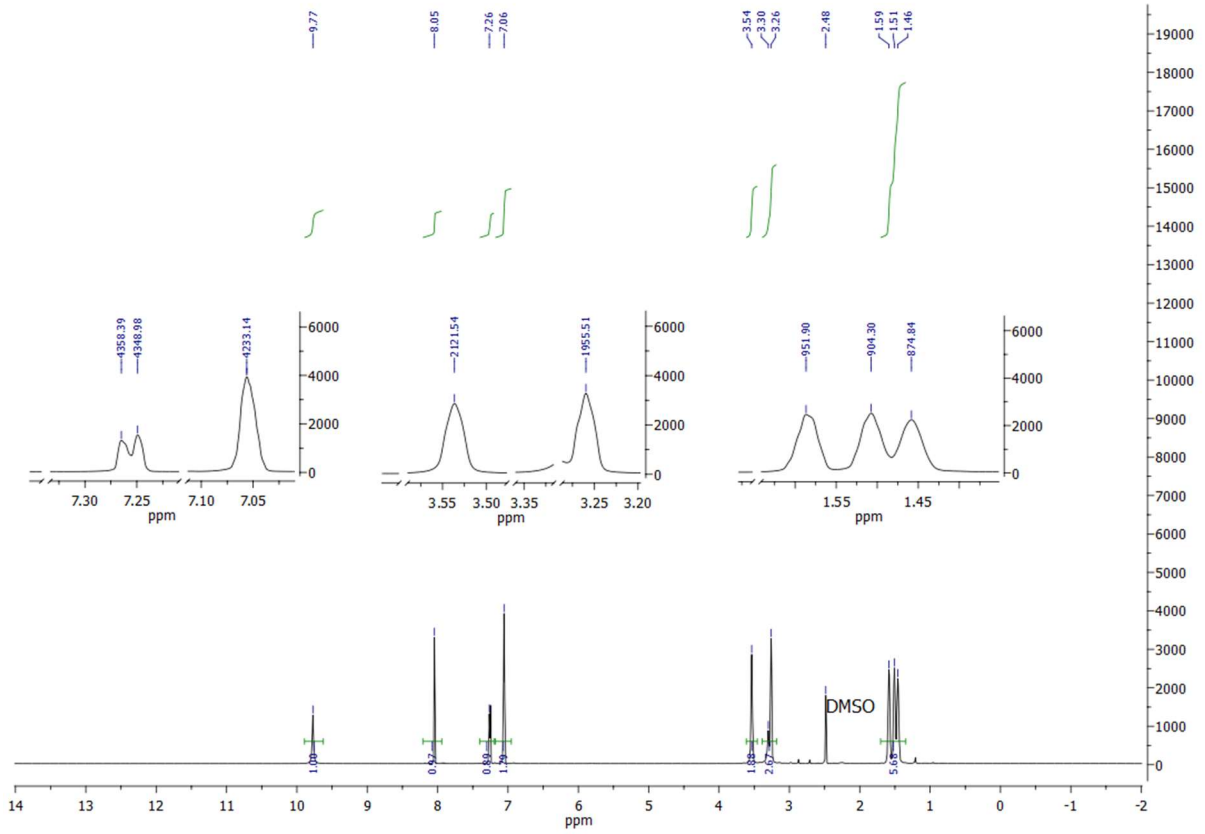


Figure S3. ^{1}H NMR, ^{13}C NMR and LC-MS/MS spectra of compound **B1**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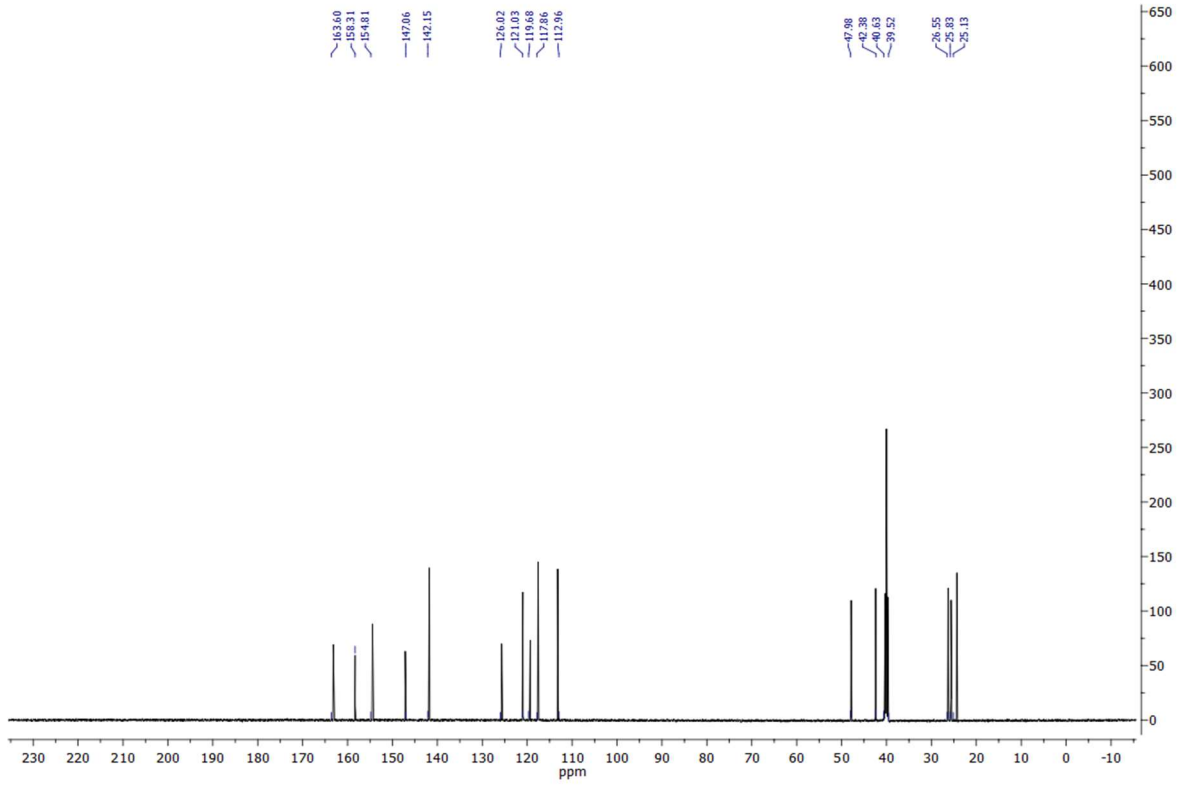
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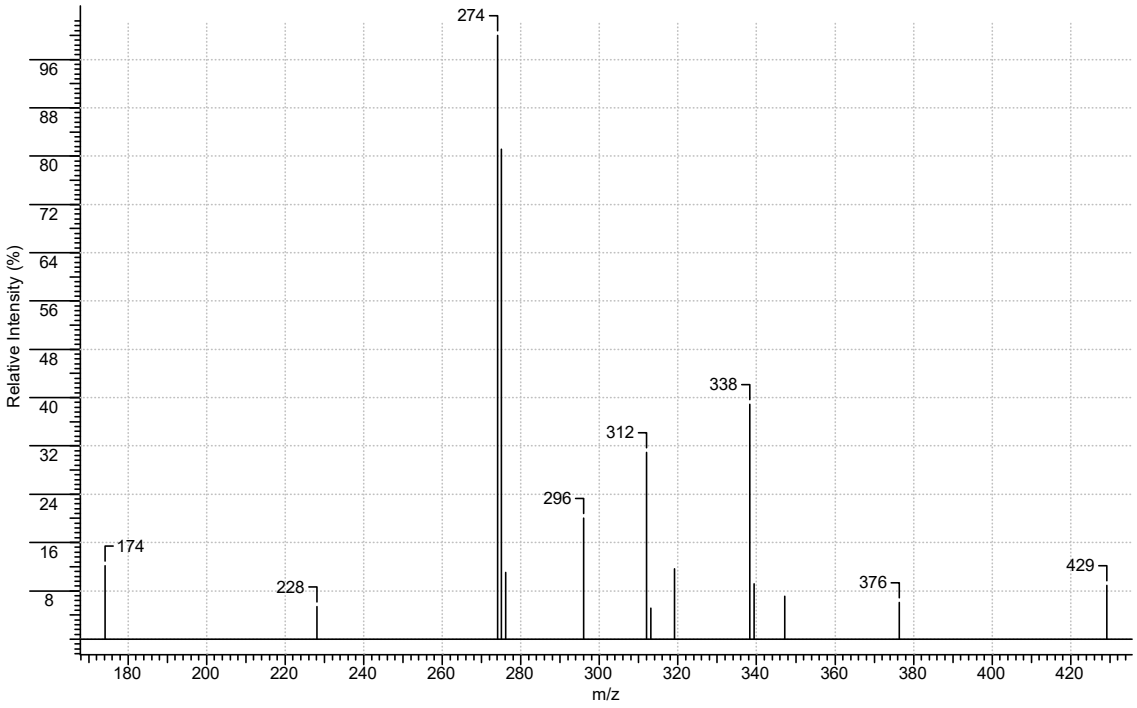
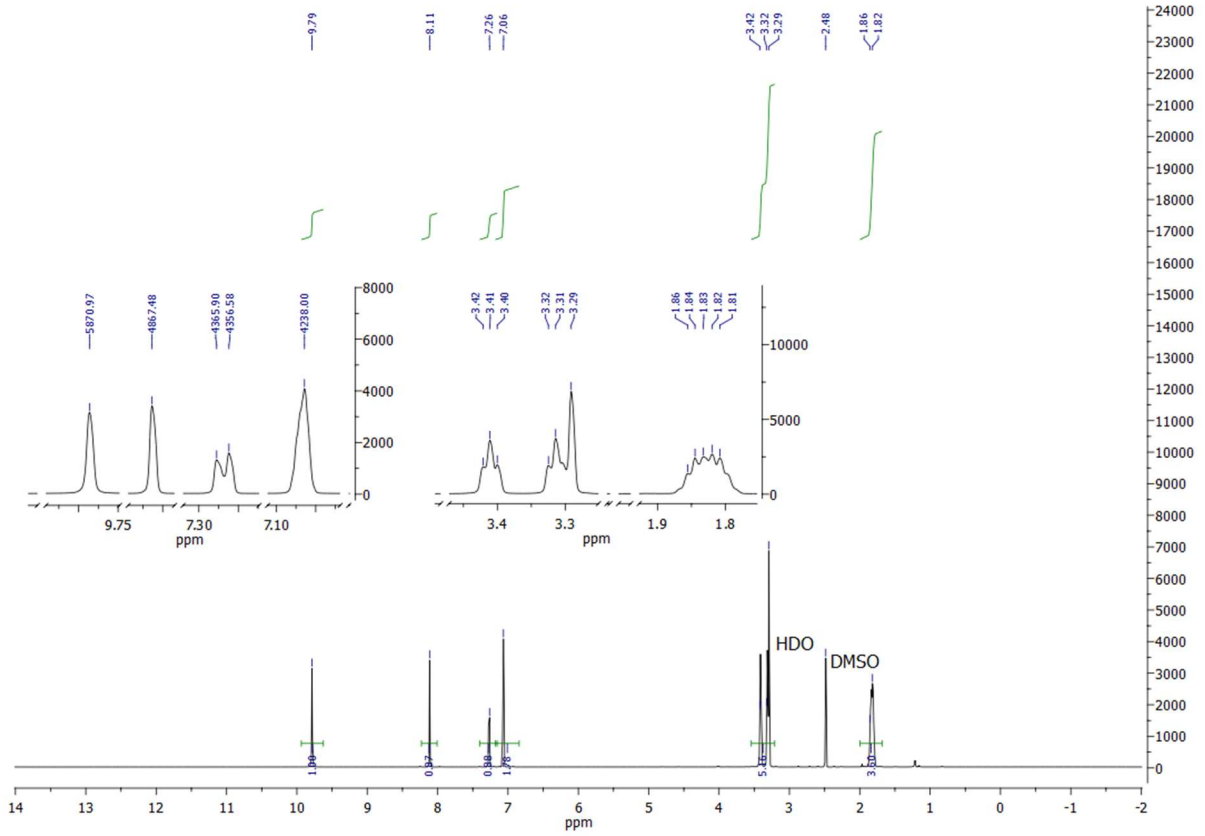


Figure S4. ^{1}H NMR, ^{13}C NMR and LC-MS/MS spectra of compound **B2**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DMSO
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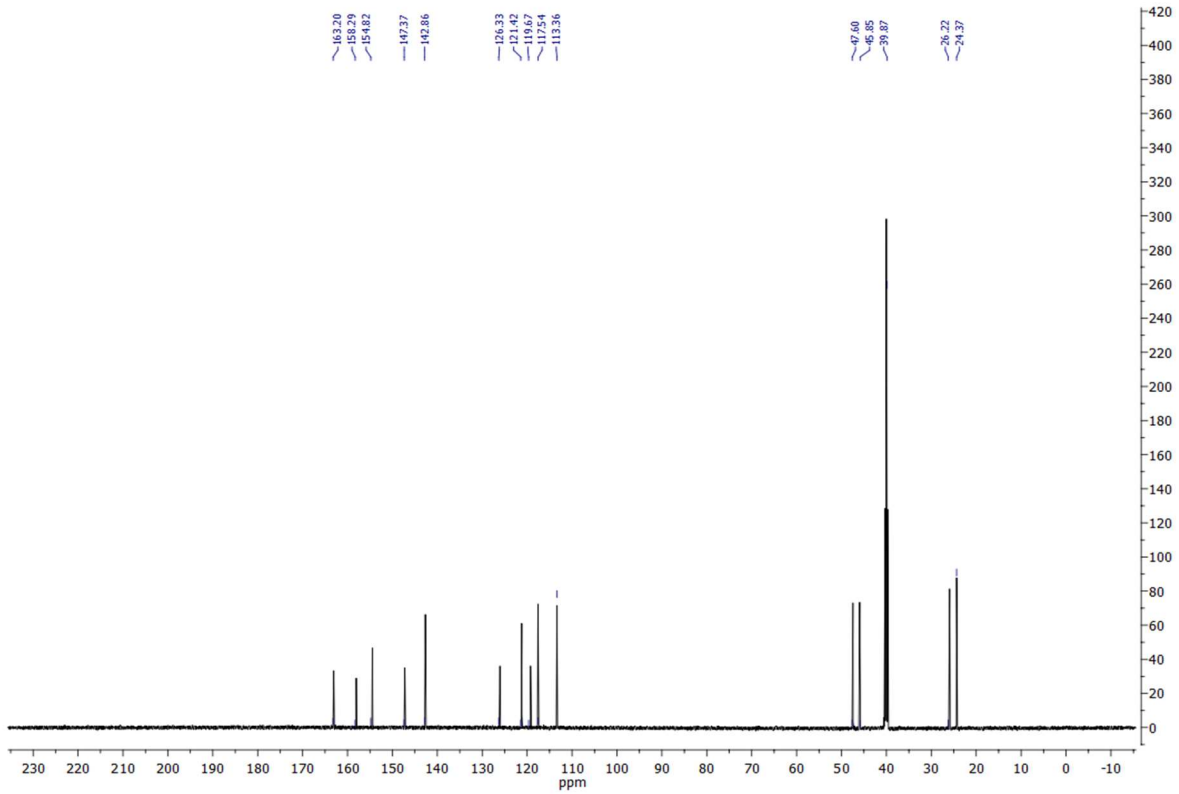
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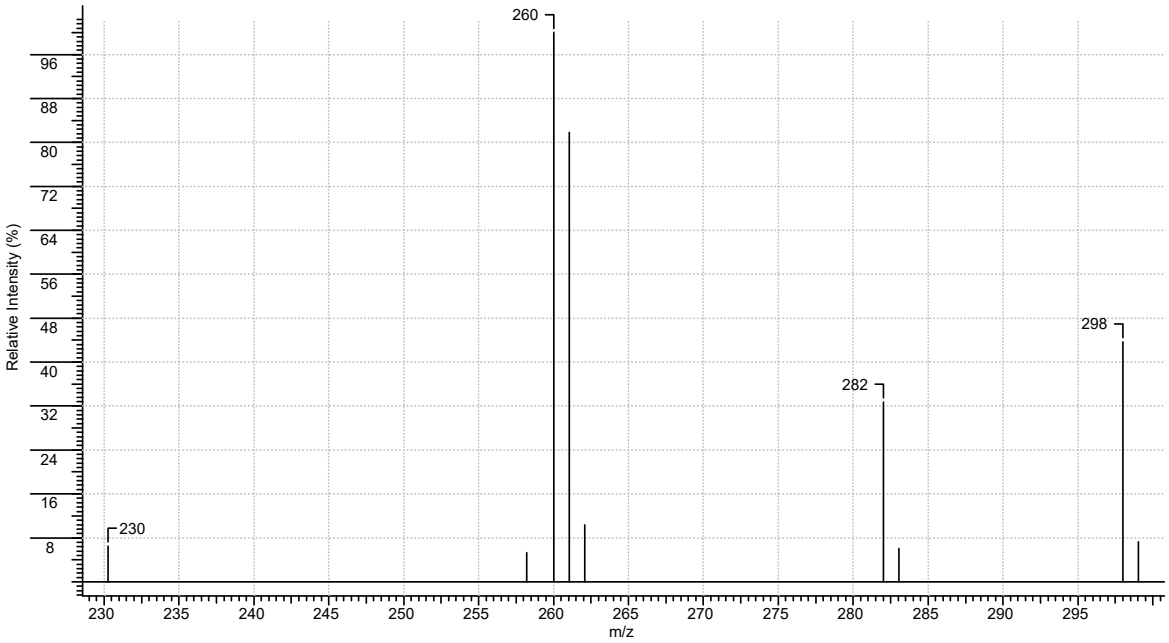
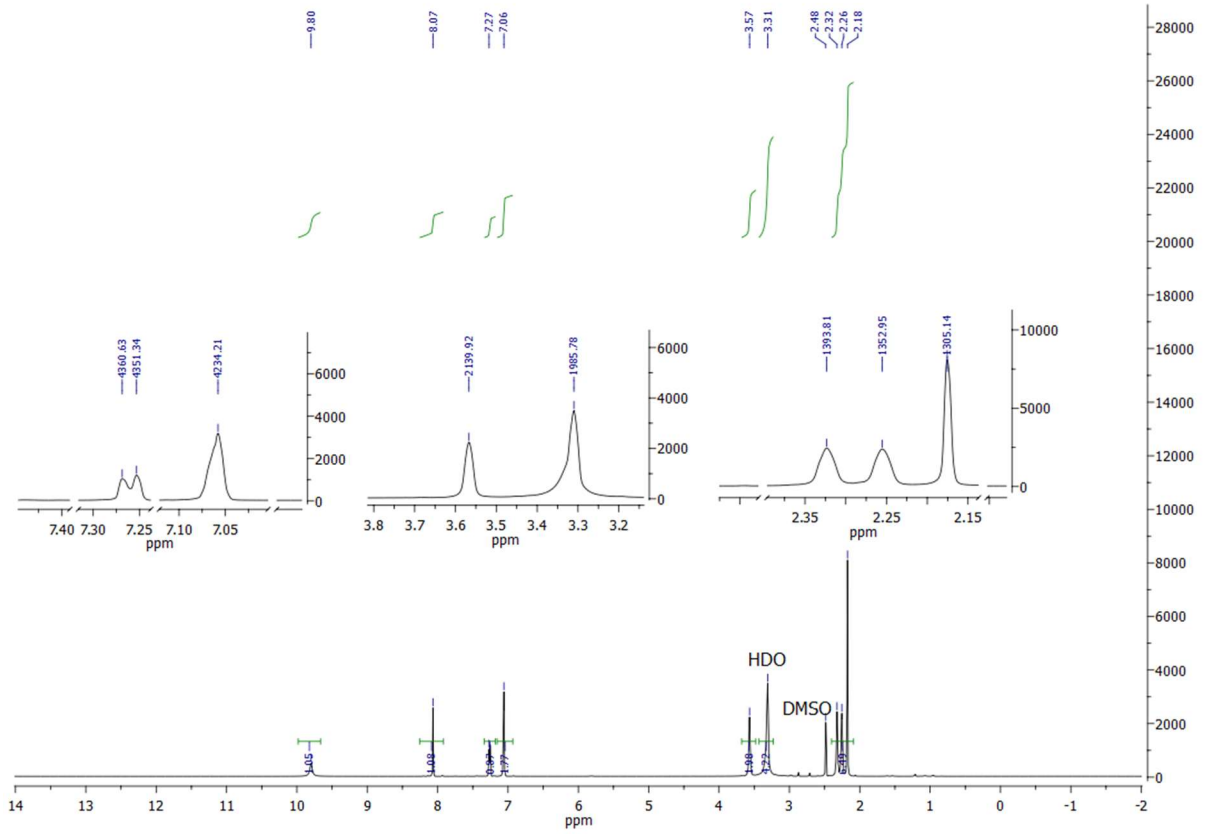


Figure S5. ^{1}H NMR, ^{13}C NMR and LC-MS/MS spectra of compound **B3**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DMSO
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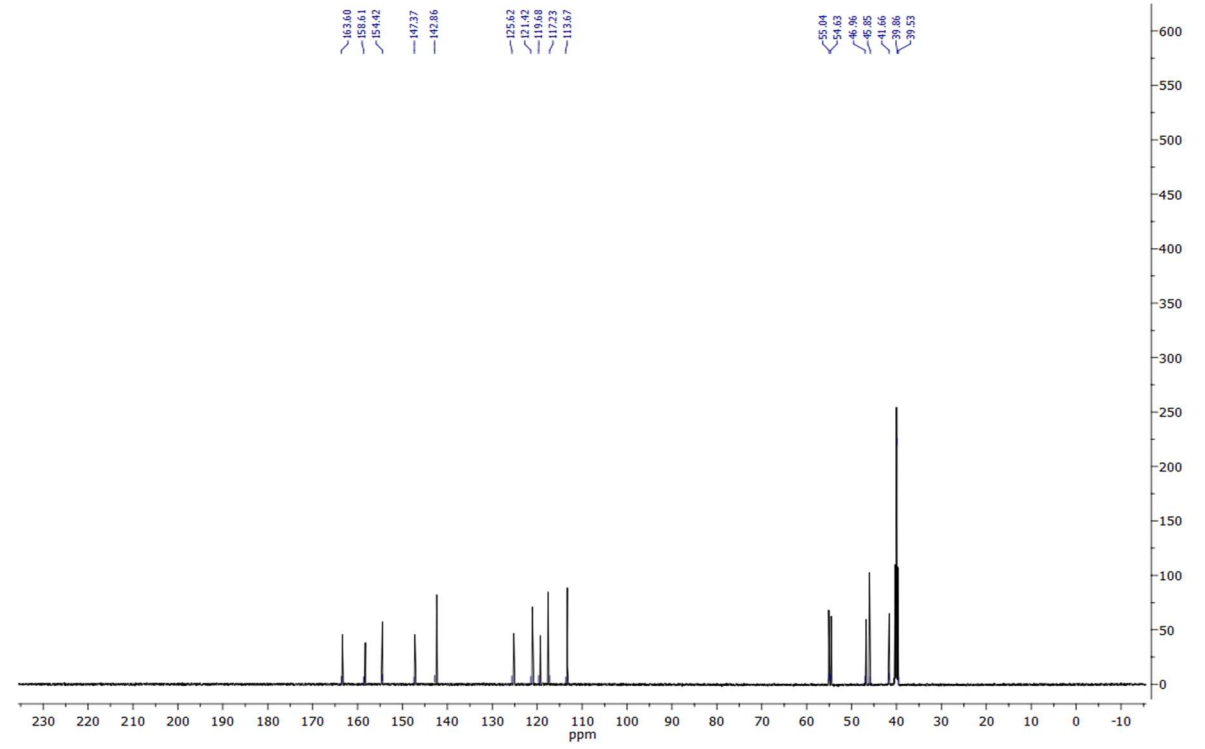
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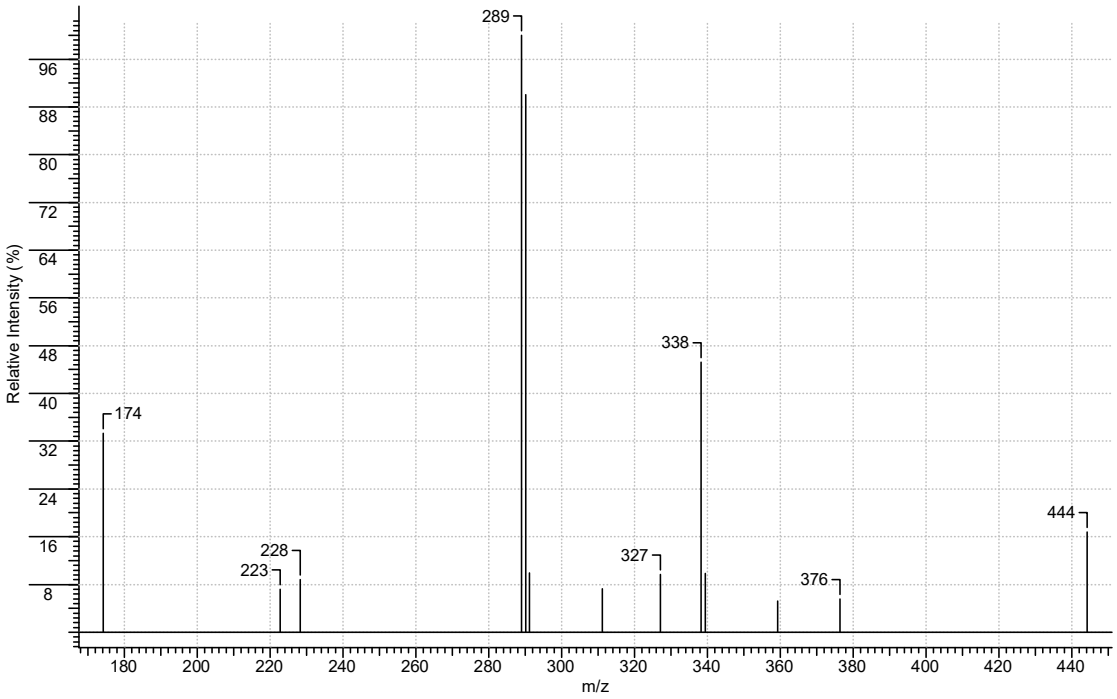

Figure S6. ^{1}H NMR, ^{13}C NMR and LC-MS/MS spectra of compound **B4**

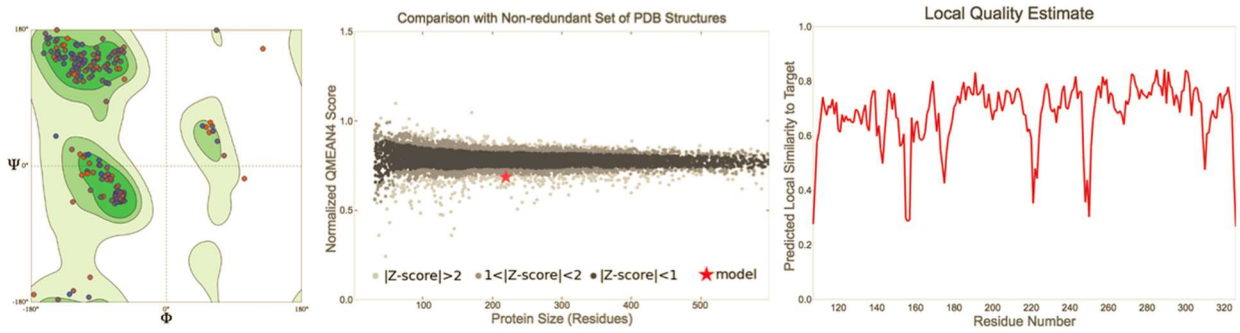

Figure S7. Quality assessment results of homology modeling

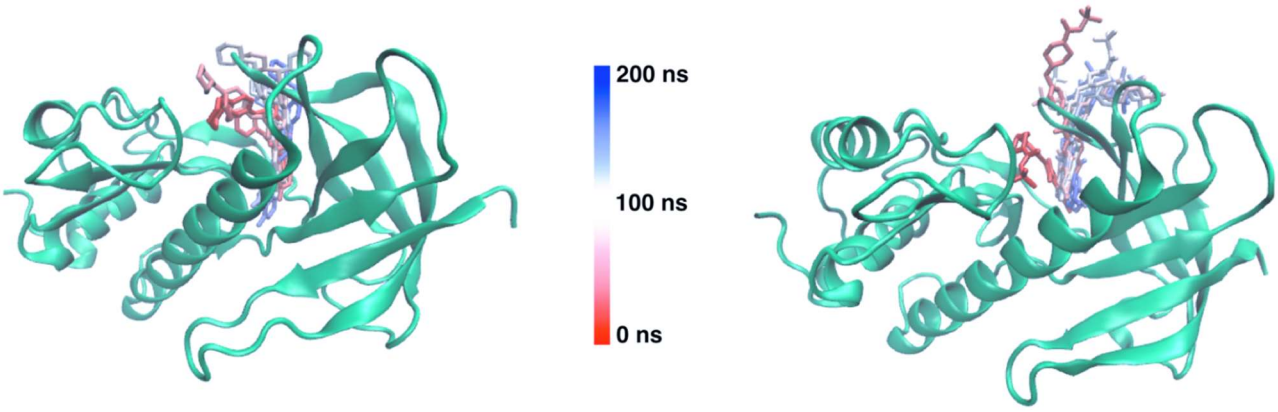

Figure S8. Conformational changes of **A1** and **A2** at the binding pocket of target structure throughout MD simulations. (Initial pose (top-docking pose from QPLD) was shown by red color)

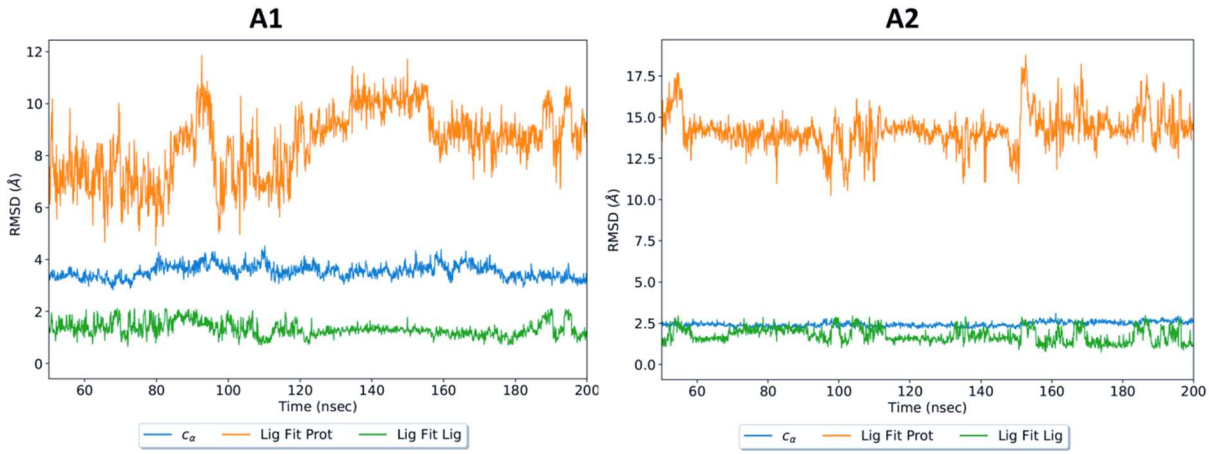

Figure S9. Protein and ligand RMSDs throughout the MD simulations. (Last 150 ns region were represented for clarity). LigFitProt and LigFitLig RMSD plots represent translational and rotational motions of ligands. (left, **A1**; right, **A2**)

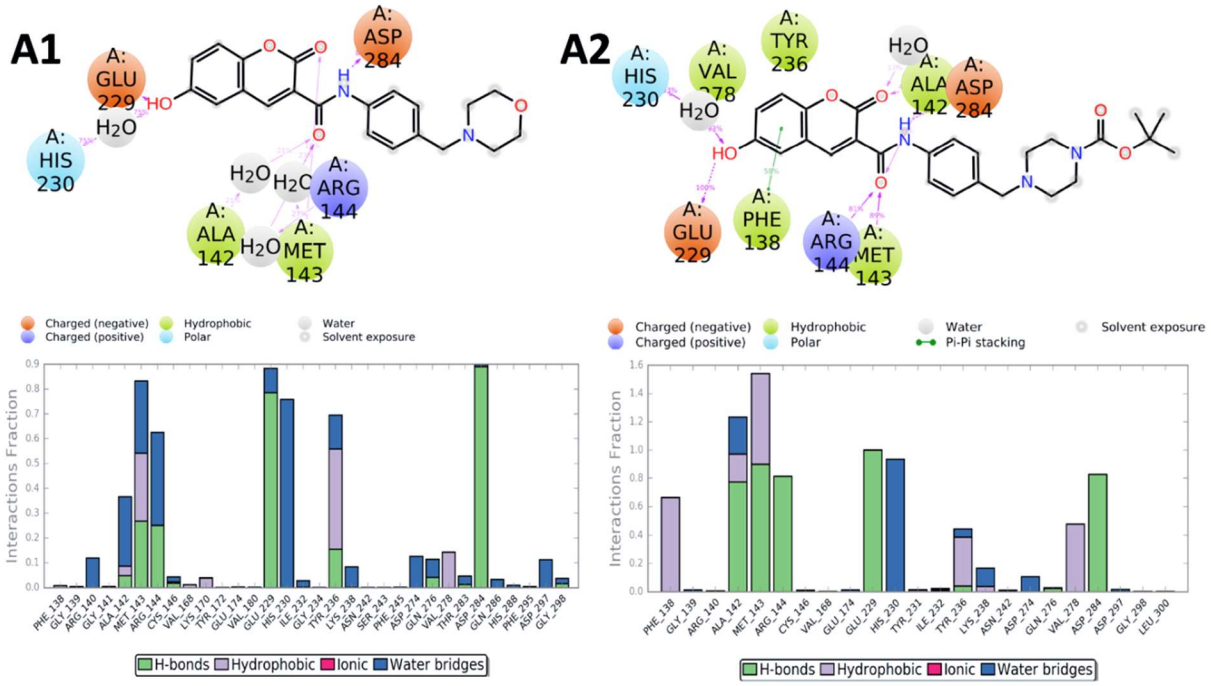

Figure S10. **(top)** Interaction fractions of **A1** (left) and **A2** (with binding pocket residues for the MD simulations initiated by the IFD docking poses. Bar charts show H-bonds (green), hydrophobic interactions (purple), ionic interactions (red), and water bridges (blue). **(bottom)** A schematic of detailed ligand atom interactions with the protein residues. Interactions that occur more than 15.0% of the simulation time, are shown.

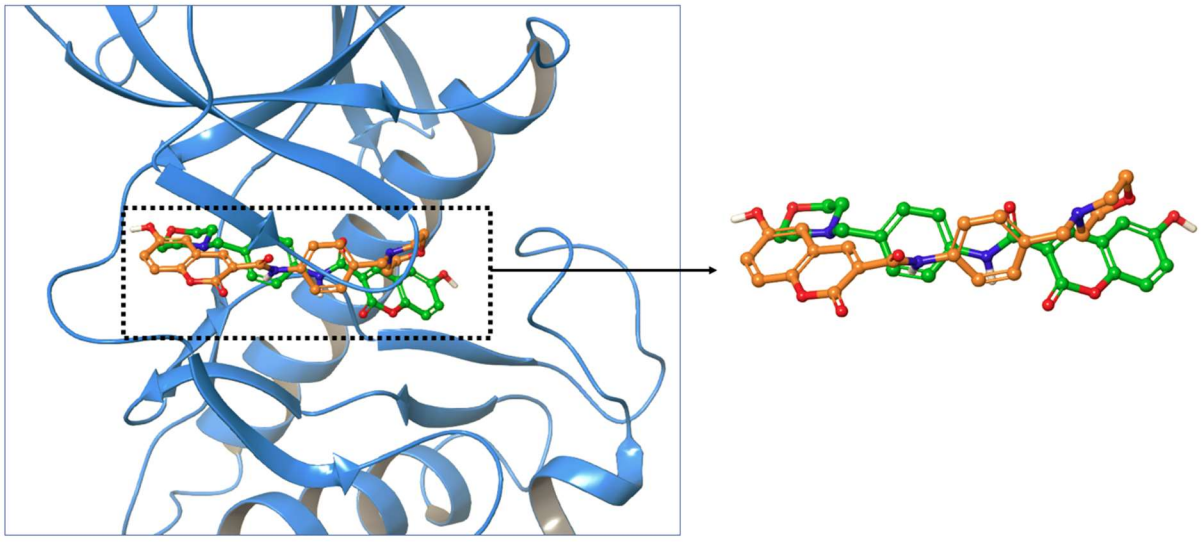

Figure S11. Superimposition of top-docking poses of compound **A1** at the eEF-2K using IFD (pink-colored carbons) and QPLD (green-colored carbons). It can be seen that their orientations at the binding pocket are exactly opposite to each other (and isoenergetic).

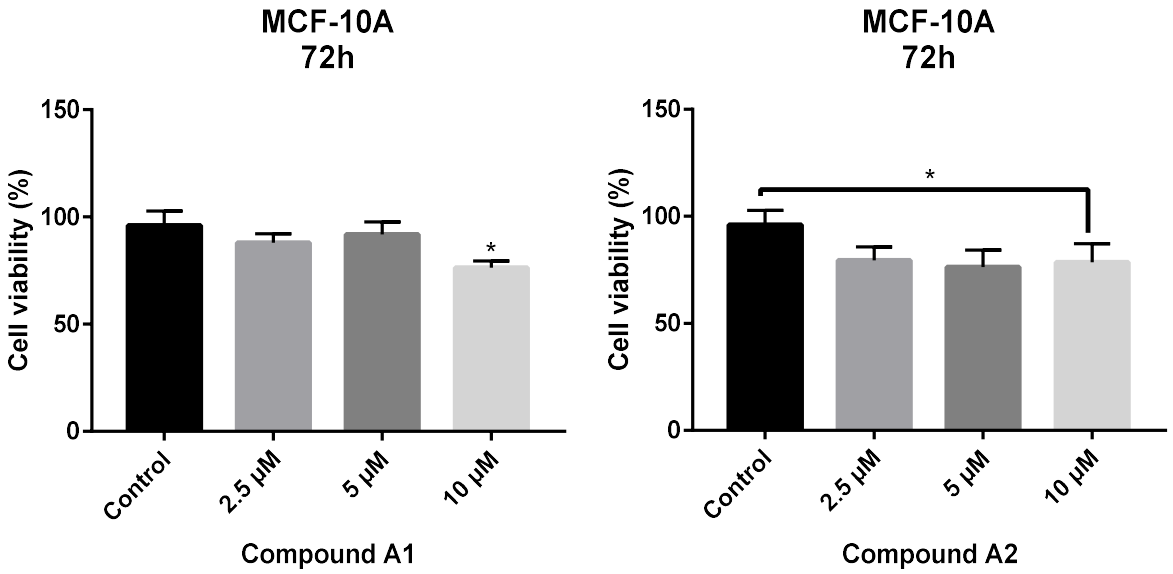

Figure S12. The cell viability of compounds **A1** and **A2** on mammary epithelial cell lines, MCF-10A.

Table S1. Prediction of the Therapeutic Activity and Toxicity Values for the Synthesized Compounds Using MetaCore/MetaDrug

Therapeutic Activity	A1	A2	B1	B2	B3	B4
Cancer [a]	0.45	0.55	0.19	0.19	0.19	0.16

Toxicity Property	A1	A2
AMES [1]	0.60	0.30
Anemia [2]	0.30	0.33
Carcinogenicity [3]	0.06	0.04
Carcinogenicity Mouse Female [4]	0.14	0.09
Carcinogenicity Mouse Male [5]	0.10	0.02
Carcinogenicity Rat Female [6]	0.03	0.04
Carcinogenicity Rat Male [7]	0.05	0.02
Cardiotoxicity [8]	0.18	0.22
Cytotoxicity Model, -log GI50 (M) [9]	5.07	3.61
Epididymis Toxicity [10]	0.05	0.22
Genotoxicity [11]	0.22	0.08
Hepatotoxicity [12]	0.11	0.23
Kidney Necrosis [13]	0.21	0.21
Kidney Weight Gain [14]	0.15	0.22
Liver Cholestasis [15]	0.36	0.26
Liver Lipid Accumulation [16]	0.42	0.37
Liver Necrosis [17]	0.55	0.20
Liver Weight Gain[18]	0.25	0.06
MRTD [19]	0.22	-0.99
Nasal Pathology [20]	0.16	0.43
Nephron Injury [21]	0.32	0.04
Nephrotoxicity [22]	0.25	0.23
Neurotoxicity [23]	0.63	0.41
Pulmonary Toxicity [24]	0.07	0.07
SkinSens, EC3 [25]	38.90	42.50
Testicular Toxicity [26]	0.14	0.27

1. Potential to be mutagenic (AMES positive), range from 0 to 1. A value of 1 is AMES positive (mutagenic), and a value of 0 is AMES negative (non-mutagenic). Cutoff is 0.5. Values close to zero are preferable. The AMES assay is based upon the reversion of mutations in the histidine operon in the bacterium Salmonella enterica sv Typhimurium.
2. Potential for causing anemia. Cutoff is 0.5. Values higher than 0.5 indicate potentially toxic compounds. Training set consists of chemicals and drugs causing anemia in vivo. Model organisms: human. Model description: Training set N=324, Test set N=51, Sensitivity= 0.82, Specificity=0.90, Accuracy=0.86, MCC=0.72.
3. Potential for inducing carcinogenicity in rats and mice. Cutoff is 0.5. Values higher than 0.5 indicate potentially toxic compounds. Training set consists of chemicals and drugs causing carcinogenicity in vivo. Model organisms: mouse, rat. Model description: Training set N=1210, Test set N=185, Sensitivity= 0.96, Specificity=0.90, Accuracy=0.93, MCC=0.86.
4. Potential for inducing carcinogenicity in female mice. Cutoff is 0.5. Values higher than 0.5 indicate potentially toxic compounds. Training set consists of chemicals and drugs causing carcinogenicity in vivo. Model organisms: female mice. Model description: Training set N=640, Test set N=94, Sensitivity= 0.90, Specificity=0.93, Accuracy=0.92, MCC=0.83.
5. Potential for inducing carcinogenicity in male mice. Cutoff is 0.5. Values higher than 0.5 indicate potentially toxic compounds. Training set consists of chemicals and drugs causing carcinogenicity in vivo. Model organisms: mouse male. Model description: Training set N=584, Test set N=93, Sensitivity= 0.91, Specificity=0.88, Accuracy=0.89, MCC=0.78.
6. Potential for inducing carcinogenicity in female rats. Cutoff is 0.5. Values higher than 0.5 indicate potentially toxic compounds. Training set consists of chemicals and drugs causing carcinogenicity in vivo. Model organisms: female rat. Model description: Training set N=667, Test set N=120, Sensitivity= 0.90, Specificity=0.96, Accuracy=0.93, MCC=0.86.
7. Potential for inducing carcinogenicity in male rats. Cutoff is 0.5. Values higher than 0.5 indicate potentially toxic compounds. Training set consists of chemicals and drugs causing carcinogenicity in vivo. Model organisms: male rat. Model description: Training set N=715, Test set N=117, Sensitivity= 0.92, Specificity=0.88, Accuracy=0.90, MCC=0.79.
8. Potential for inducing cardiotoxicity. Cutoff is 0.5. Values higher than 0.5 indicate potentially toxic compounds. Training set consists of chemicals and drugs causing cardiotoxicity in vivo. Model organisms: mouse, rat, human. Model description: Training set N=143, Test set N=30, Sensitivity= 0.80, Specificity=1.00, Accuracy=0.90, MCC=0.82.
9. Growth inhibition of MCF7 cell line (human caucasian breast adenocarcinoma), pGI50. Cutoff is 6. Values from 6 to 8 correspond to a

toxic metabolite, values less than 6 are preferable, values less than 3 are more preferable and less toxic. Model description: N=1474, R2=0.9, RMSE=0.05.

10. Potential for inducing epididymis toxicity. Training set consists of chemicals and drugs causing epididymis toxicity in vivo. Model organisms: mouse, rat, human. Cutoff is 0.5. Values higher than 0.5 indicate potentially toxic compounds. Model description: Training set N=252, Test set N=42, Sensitivity= 0.90, Specificity=0.86, Accuracy=0.88, MCC=0.76.

11. Potential for inducing genotoxicity. Cutoff is 0.5. Values higher than 0.5 indicate potentially toxic compounds. Training set consists of chemicals and drugs causing genotoxicity in vivo. Model organisms: mouse, rat. Model description: Training set N=372, Test set N=86, Sensitivity= 0.75, Specificity=0.84, Accuracy=0.79, MCC=0.59.

12. Potential for inducing hepatotoxicity. Cutoff is 0.5. Values higher than 0.5 indicate potentially toxic compounds. Training set consists of chemicals and drugs causing hepatotoxicity in vivo. Model organisms: mouse, rat, human. Model description: Training set N=1380, Test set N=231, Sensitivity= 0.73, Specificity=0.88, Accuracy=0.81, MCC=0.62.

13. Potential for inducing kidney necrosis. Cutoff is 0.5. Values higher than 0.5 indicate potentially toxic compounds. Training set consists of chemicals and drugs causing renal necrosis in vivo. Model organisms: mouse, rat, human. Model description: Training set N=221, Test set N=42, Sensitivity= 0.96, Specificity=1.00, Accuracy=0.98, MCC=0.95.

14. Potential for inducing kidney weight gain. Cutoff is 0.5. The values higher than 0.5 indicate potentially toxic compounds. Training set consists of chemicals and drugs causing kidney weight gain in vivo. Model organisms: mouse, rat. Model description: Training set N=240, Test set N=49, Sensitivity= 0.95, Specificity=1.00, Accuracy=0.98, MCC=0.96.

15. Potential for inducing liver cholestasis. Cutoff is 0.5. Values higher than 0.5 indicate potentially toxic compounds. Training set consists of chemicals and drugs causing cholestasis in vivo. Model organisms: mouse, rat, human. Model description: Training set N=218, Test set N=35, Sensitivity= 0.79, Specificity=0.67, Accuracy=0.74, MCC=0.46.

16. Potential for inducing liver lipid accumulation. Cutoff is 0.5. Values higher than 0.5 indicate potentially toxic compounds. Training set consists of chemicals and drugs causing lipid accumulation in vivo. Model organisms: mouse, rat, human. Model description: Training set N=172, Test set N=28, Sensitivity= 0.80, Specificity=0.85, Accuracy=0.82, MCC=0.64.

17. Potential for inducing liver necrosis. Cutoff is 0.5. Values higher than 0.5 indicate potentially toxic compounds. Training set consists of chemicals and drugs causing hepatic necrosis in vivo. Model organisms: mouse, rat, human. Model description: Training set N=300, Test set N=57, Sensitivity= 0.91, Specificity=0.91, Accuracy=0.91, MCC=0.82.

18. Potential for inducing liver weight gain. Cutoff is 0.5. Values higher than 0.5 indicate potential liver weight-changing compounds. Training set consists of chemicals and drugs causing liver weight gain in vivo. Model organisms: mouse, rat. Model description: Training set N=292, Test set N=52, Sensitivity= 1.00, Specificity=1.00, Accuracy=1.00, MCC=1.00.

19. Maximum Recommended Therapeutic Dose, log mg/kg-bm/day, range is from -5 to 3. Cutoff is 0.5. Chemicals with high log MRTDs can be classified as mildly toxic compounds, chemicals with low log MRTDs as highly toxic compounds. Model description: N=1209, R2= 0.86, RMSE=0.42.

20. Potential for causing nasal pathology. Training set consists of chemicals and drugs causing nasal pathology in vivo. Model organisms: mouse, rat, human. Cutoff is 0.5. Values higher than 0.5 indicate potentially toxic compounds. Model description: Training set N=246, Test set N=47, Sensitivity= 1.00, Specificity=0.93, Accuracy=0.96, MCC=0.92.

21. Potential for inducing nephron injury. Cutoff is 0.5. Values higher than 0.5 indicate potentially toxic compounds. Training set consists of chemicals and drugs causing nephron injury in vivo. Model organisms: mouse, rat, human. Model description: Training set N=598, Test set N=109, Sensitivity= 0.91, Specificity=1.00, Accuracy=0.96, MCC=0.93.

22. Potential for inducing nephrotoxicity. Cutoff is 0.5. Values higher than 0.5 indicate potentially toxic compounds. Training set consists of chemicals and drugs causing nephrotoxicity in vivo. Model organisms: mouse, rat, human. Model description: Training set N=847, Test set N=154, Sensitivity= 0.90, Specificity=0.84, Accuracy=0.87, MCC=0.74.

23. Potential for inducing neurotoxicity. Training set consists of chemicals and drugs causing neurotoxicity in vivo. Model organisms: mouse, rat, human. Cutoff is 0.5. Values higher than 0.5 indicate potentially toxic compounds. Model description: Training set N=175, Test set N=34, Sensitivity= 0.94, Specificity=0.94, Accuracy=0.94, MCC=0.88.

24. Potential for inducing pulmonary toxicity. Training set consists of chemicals and drugs causing pulmonary toxicity in vivo. Model organisms: mouse, rat, human. Cutoff is 0.5. Values higher than 0.5 indicate potentially toxic compounds. Model description: Training set N=482, Test set N=87, Sensitivity= 0.89, Specificity=0.88, Accuracy=0.89, MCC=0.77.

25. Skin sensitization potential expressed as effective concentration 3, EC3 %. Values higher than 10 indicate weak and moderate sensitizers. Model description: N=89, R2=0.67, RMSE=22.56.

26. It consists of chemicals and drugs causing testicular toxicity in vivo. Model organisms: mouse, rat, human. Cutoff is 0.5. Values higher than 0.5 indicate potentially toxic compounds. Model description: Training set N=439, Test set N=88, Sensitivity= 0.81, Specificity=0.85, Accuracy=0.83, MCC=0.66.

a. Potential activity against cancer. Cutoff is 0.5. Values higher than 0.5 indicate potentially active compounds. Training set consists of approved drugs. Model description: Training set N=886, Test set N=167, Sensitivity= 0.89, Specificity=0.83, Accuracy=0.86, MCC=0.72.