Ultrasound-assisted ring opening of epoxides in HFIP: THF: Synthesis, characterization, computational studies and molecular docking of novel 2-hydroxy dithiocarbamates

Amit Patel, Ashish K. Tewari*

*E-mail: ashishtewarichem@gmail.com ; amitp123ok@gmail.com

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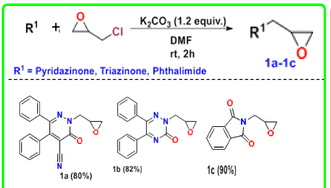
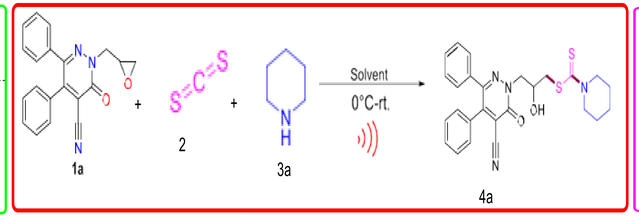
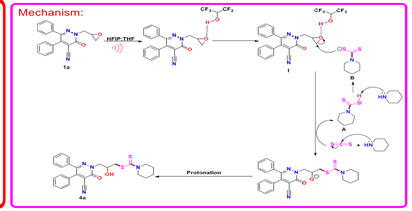
Abstract: Under the influence of ultrasonic irradiation, pyridazinone, triazinone, or phthalimide containing 2-hydroxy dithiocarbamates, a biologically relevant novel organo-sulfur compound, was synthesized. Detailed characterization, computational, and molecular docking studies are being investigated. Molecular interactions were studied using 3D Hirshfeld surfaces and corresponding 2D fingerprint plots. Theoretical (DFT) studies on the molecular structure, HOMO, LUMO, and quantum chemical descriptors were performed at the B3LYP/ 6–311++G(d,p) level of theory. At the same time, the interaction energy was computed using the B3LYP/6–31G (d,p) level of theory. The FMO study revealed that molecules 4a and 4p in the gas phase have 3.545 eV and 3.263 eV HOMO-LUMO energy gaps, respectively, and they are hence kinetically stable. Quantum chemical calculations confirm the electrophilic character of compounds 4a and 4p, as the molecule is stable and highly electrophilic. The interactions of 2-hydroxy dithiocarbamate derivatives (4a-4t) with the ligand-binding site of the target COX-2 (cyclooxygenase-2) enzyme were investigated using in-silico molecular docking experiments. Compared to the standard medicine celecoxib, the results showed that most synthesized derivatives had better glide scores and interaction. The docking study of all the synthesized compounds revealed that compounds 4a, 4e, and 4o interact well with the COX-2 enzyme as anti-inflammatory drugs.

❖ **Keywords:** Dithiocarbamates
Hirshfeld surface analysis HOMO-LUMO
Molecular docking
Interactions energy calculations
Quantum chemical descriptor



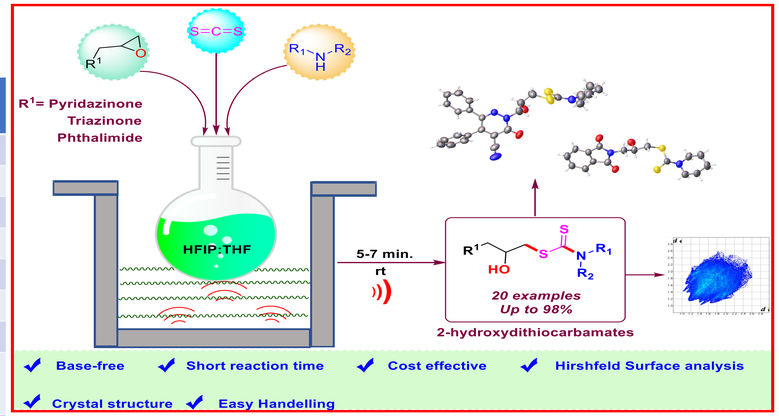
Scheme 1. Synthesis of epoxide derivatives (1a-1c).





Optimization of the reaction conditions[a] for the synthesis of 2-hydroxy dithiocarbamates

Entry	Promoter	Solvent	Time	Yield (%)
1.	-	DCM	2	50
2.	-	DCE	3	48
3.	-	CH3CN	3	45
4.	-	DMF	1.5	65
5.	-	THF	1	70
6.	-	EtOH	2	60
7.	-	MeOH	2.5	56
8.	TFE (1.0 equiv.)	THF	25(min.)	88
9.	HFIP (1.0 equiv.)	THF	15(min.)	90
10.	HFIP (1.2 equiv.)	THF	5-7(min.)	96
11.	HFIP (1.2 equiv.)	DMF	30(min.)	82
12.	HFIP	-	20(min.)	92



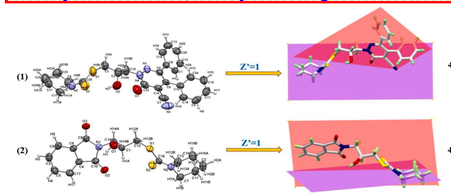


Fig.1 ORTEP diagram and dihedral angles of **(1)** compound **4a**, and **(2) 4p** with thermal ellipsoid plot shown at 50 % probability level.

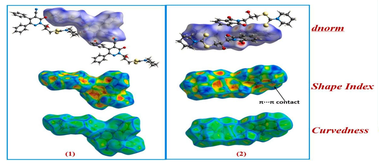


Fig.2 (1) and (2) represent the Hirshfeld surfaces mapped over dnorm, Shape Index, and Curvedness for compounds **4a** and **4p**, respectively.

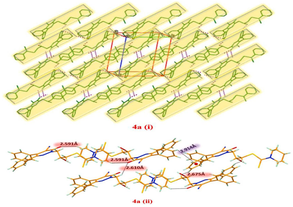


Fig.6 Crystal packing diagram of compound **4a** with unit cell outlines and showing important C–H···O, and C–H···π intermolecular interactions.

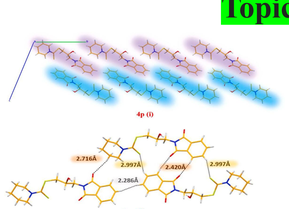


Fig.7 Crystal packing diagram of compound **4p** showing important C–H···O, and C–H···S intermolecular interactions.

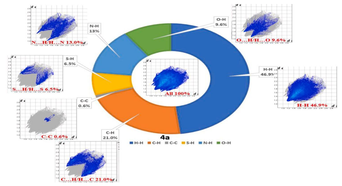


Fig.4 2D fingerprint plot of compound **4a** with percentage contribution of various intermolecular interactions obtained from decomposed fingerprint plots of compound **4a**.

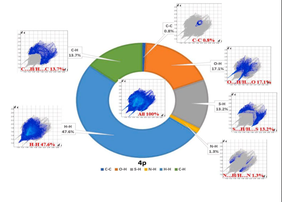


Fig.5 2D fingerprint plot of compound **4p** with percentage contribution of various intermolecular interactions obtained from decomposed fingerprint plots of compound **4p**.

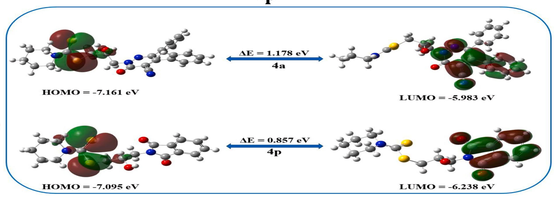


Fig. 3 FMO (HOMO-LUMO) energies and the density distributions of molecular orbitals of compound **4a** and **4p**, calculated at B3LYP/6–311++*G*(dp) level in the gas phase.

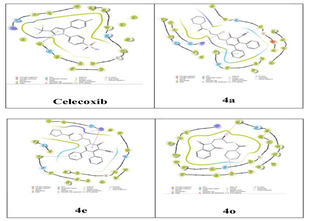


Fig.8 The 2D interactions of Celecoxib and best three compounds **4a, 4e**, and **4o** with COX-2 enzyme (PDB: 4M11).

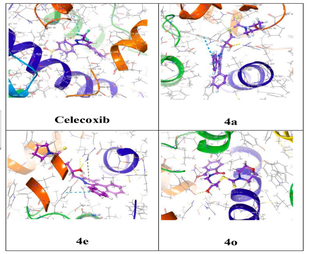


Fig.9 The 3D interactions of Celecoxib and best three compounds **4a, 4e**, and **4o** with COX-2 enzyme (PDB: 4M11). The ligands are shown in the purple colour stick model and the enzyme in the grey colour thin stick model inside the pocket. The standard drug and compounds show interaction with amino acid residues of the enzyme.

Conclusion: In conclusion, a convenient, selective, and environmentally friendly methodology was developed for the synthesis of various biologically relevant novel pyridazinone, triazinone, and phthalimide-containing 2-hydroxy dithiocarbamates in HFIP: THF under the influence of ultrasound irradiation, and their characterization, computational, and molecular docking studies are being investigated. Spectral studies such as ^{1}H NMR, ^{13}C NMR, and single crystal X-ray examinations were done to analyze the structures of the generated compounds. The intermolecular interactions of 2-hydroxy dithiocarbamates were thoroughly investigated using single crystal and Hirshfeld surface analysis. DFT simulations are used in the computational analysis to optimize the structure and find the interaction energies and HOMO-LUMO energy gap. The Hirshfeld surface investigation revealed the proportionate percentage contributions of intermolecular interactions such as C–H···O, C–H···S, C–H···N, C–H···π, and H···H. Fingerprint plots, which depict all of the intermolecular interactions within the crystal, allow for a far more thorough investigation and are hence ideal for analyzing crystal packing. The FMO analysis found that molecules **4a** and **4p** in the gas phase had 3.545 eV and 3.263 eV HOMO-LUMO energy gaps, respectively, and are hence kinetically stable. Quantum chemical descriptors indicate that compounds **4a** and **4p** are stable, with electrophilicity indexes (ω) of 5.615 eV and 5.113 eV, respectively. Molecular docking experiments were used to study the interactions of 2-hydroxy dithiocarbamate derivatives (**4a-4t**) with the ligand-binding site of the target COX-2 (cyclooxygenase-2) enzyme. The results showed that most of the synthesized derivatives exhibited good glide scores and interaction when compared to the standard drug celecoxib. In practically all compounds, the hydroxy group (-OH) in the linker part that constitutes dithiocarbamate is necessary for H-bond interaction

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