An Improved Synthesis of Key Intermediate to the Formation of selected Indolin-2-ones Derivatives Incorporating Ultrasound and Deep Eutectic Solvent (DES) Blend of Techniques, for some Biological Activities and Molecular Docking Studies

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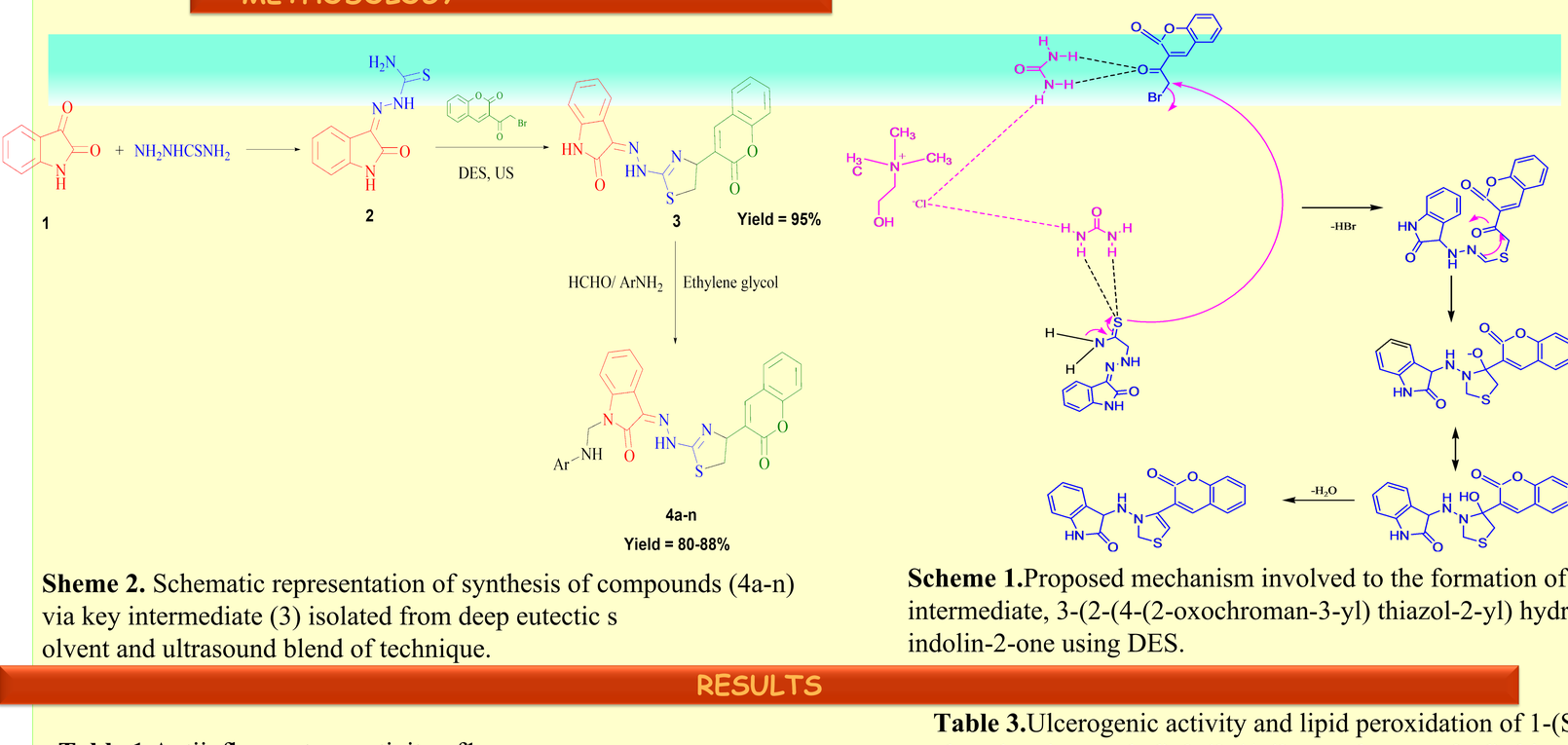
ABSTRACT

We have developed a new idea to synthesize key intermediate molecule by utilizing deep eutectic solvent (DES) and ultrasound in a multistep reaction to ensure process cost-effective. Key intermediate (3) and final compounds (4a-n) were synthesized in a higher yield of 95% and 80-88% respectively.Further, final compounds (4a-n) were assessed for their anti-inflammatory, analgesic, ulcerogenic and lipid peroxidation. The compounds 4f, 4g, 4j, 4l, and 4m showed good anti-inflammatory activity, while 4f, 4i, and 4n exhibited very good analgesic activity as compared to the standard drug. The ulcerogenicity of selected compounds was far less than the indomethacin. The ligands had also shown a good docking score (4f = -6.859 and 4 n= -7.077) as compared to control indomethacin (-6.109).State-of-art DFT theory was used to validate the lipid peroxidation mechanism of the active compoundswhich was in good agreement with the variations of BDEs and IP of the tested compounds.

Keywords: Thiazole-indole; DES; Ultrasound; anti-inflammatory; analgesic; ulcerogenic; lipid peroxidation; molecular docking; DFT

METHODOLOGY



Sheme 2. Schematic representation of synthesis of compounds (4a-n) via key intermediate (3) isolated from deep eutectic s olvent and ultrasound blend of technique.

Scheme 1. Proposed mechanism involved to the formation of key intermediate, 3-(2-(4-(2-oxochroman-3-yl) thiazol-2-yl) hydrazono) indolin-2-one using DES.

RESULTS

Table 1. Antiinflammatory activity of1-(Substituted phenyl amino methyl)-3 -(2-(4-(2-oxochroman-3-yl) thiazol-2-yl) hydrazono) indolin-2-one (4a-n).

Compound	Mean writhe ± SEM	% Analgesic Activity (Dose = 10 mgkg-1)	Potency
Indomethacin	8.55 ± 0.394	73.61 ± 0.315*	1.00
4a	17.00 ± 0.2582	47.54 ± 0.7071*	0.64
4b	24.00 ± 0.3651	25.94 ± 0.5802**	0.35
4c	13.00 ± 0.2582	59.88 ± 0.8458*	0.81
4d	18.50 ± 0.4282	42.91 ± 0.710***	0.58
4e	16.88 ± 0.222	47.91 ± 1.0049*	0.65
4f	9.93 ± 0.386	69.36 ± 0.5845*	0.94
4g	20.09 ± 0.3561	38.01 ± 1.0035**	0.51
4h	23.83 ± 0.3073	26.47 ± 0.3165*	0.35
4i	10.93 ± 0.3128	66.27 ± 1.0072*	0.90
4j	17.13 ± 0.539	47.14 ± 0.4018***	0.64
4k	29.83 ± 0.3073	7.96 ± 0.4318*	0.10
4l	17.83 ± 0.3079	44.98 ± 0.3361*	0.61
4m	21.83 ± 0.2051	32.64 ± 0.8454**	0.44
4n	10.00 ± 0.3651	69.14 ± 0.6892*	0.93

Table 2. Analgesic activity of 1-(Substituted phenyl amino methyl)-3 -(2-(4-(2-oxochroman-3-yl) thiazol-2-yl) hydrazono)indolin-2-one (4a-n).

Compound	% age inhibition of rat paw edema(Dose = 10 mgkg-1)		Potency
	2 Hour	4 Hour	
Indomethacin	66.34 ± 0.051	82.05 ± 0.08	1.00
4a	38.29 ± 0.016	5.57 ± 0.041	0.06
4b	59.29 ± 0.73*	45.81 ± 0.069	0.55
4c	59.29 ± 0.143*	30.17 ± 0.294	0.36
4d	51.92 ± 0.337	6.98 ± 0.315	0.08
4e	62.24 ± 0.080**	48.60 ± 0.090**	0.59
4f	48.377 ± 0.219*	72.42 ± 0.183*	0.88
4g	53.57 ± 0.160*	77.94 ± 0.184***	0.94
4h	35.39 ± 0.273	64.69 ± 0.245	0.78
4i	31.268 ± 0.188	63.95 ±0.218	0.77
4j	53.81 ± 0.120**	77.906 ± 0.171**	0.94
4k	38.095 ± 0.214	70.75 ± 0.165	0.86
4l	54.76 ± 0.228**	80.94 ± 0.149***	0.98
4m	53.27 ± 0.183*	78.42 ± 0.183**	0.95
4n	42.57 ± 0.213	69.58 ± 0.133	0.84

Table 3. Ulcerogenic activity and lipid peroxidation of 1-(Substituted phenyl amino methyl)-3-(2-(4-(2- oxochroman-3-yl) thiazol-2- yl) hydrazono)indolin-2-one.

Compound	Severity Index	Nanomoles of MDA content ± SEM/ 100 mg tissue
Control	0.0	3.16±0.12*
Indomethacin	4.500 ± 0.316	6.71±0.18*
4c	0.666 ± 0.105*	4.26±0.12*
4f	0.666 ± 0.105*	4.08±0.22*
4i	0.500 ± 0.129	3.89±0.17*
4n	0.833 ± 0.210*	4.81±0.13*

Table 4. BDEs (kcal/mol) of i-NH groups of the In-H synthesized derivatives and its corresponding ionization potential energies calculated at the B3P86/6-31+G(d,p) level of theory.

Compound	IP (eV)	17-NH	26-NH	Lipid peroxidation Inhibition
4c	-5.96	62.03	72.58	4.08±0.22
4f	-5.97	62.08	75.60	4.26±0.12
4i	-6.04	62.05	72.84	3.89±0.17
4n	-5.80	62.05	72.02	4.81±0.13

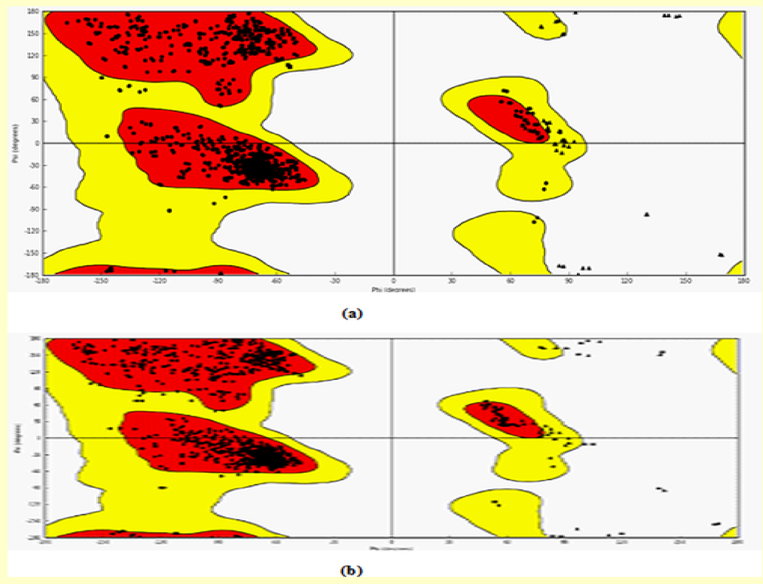


Figure2. The binding site predicted where ligand is docked in COX-2 from (a) mouse (PDB ID 3NT1) (b) human (PDB ID : 5F19).

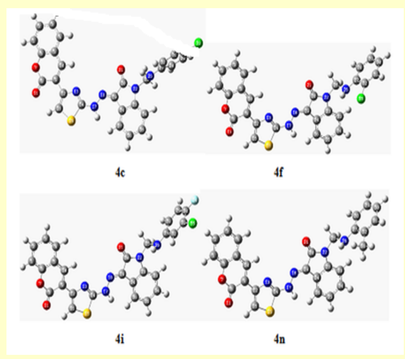


Figure 1. The optimized structure with numbering of In-H synthesized derivatives

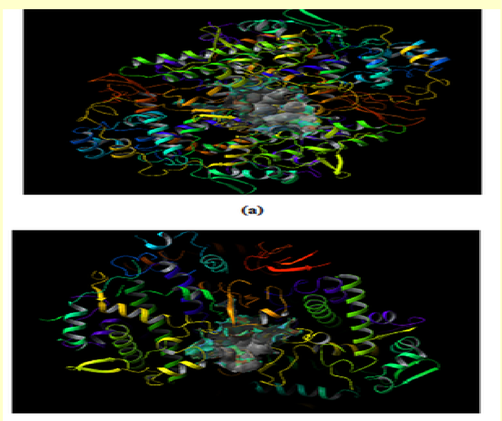


Figure3. The binding site predicted where ligand is docked in COX-2 from (a) mouse (PDB ID 3NT1) (b) human (PDB ID : 5F19)

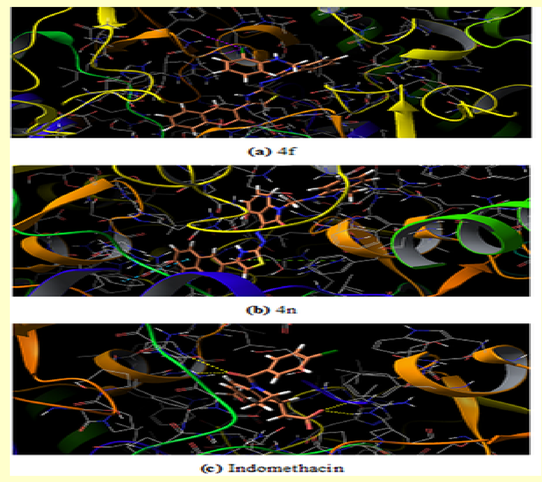


Figure 5. Docked ligand inside from the binding pocket of COX-2 from human (a) 4f (b) 4n (c) Indomethacin.

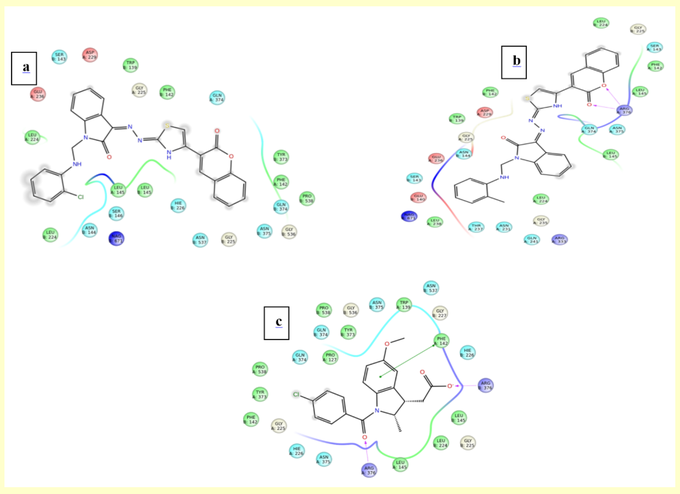


Figure6. Ligand interaction of test ligand with the target protein COX-2 from mouse (a) 4f (b) 4n (c) Indomethacin.

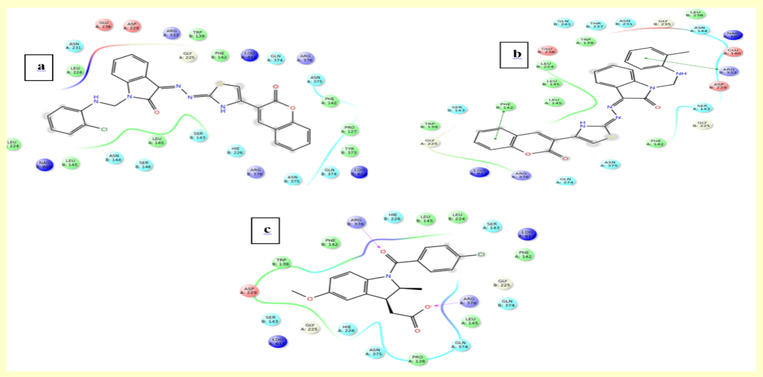


Figure 7. Ligand interaction of test ligand with the target protein COX-2 f rom human (a) 4f (b) 4n (c) Indomethacin.

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CONCLUSIONS

In conclusion, an improved synthesis of key intermediate through the combined use of deep eutectic solvent and ultrasound is a rational approach to enhance the yield of desired compounds via an economically viable and environmentally acceptable way. Further, all the final compounds (4a-n) have been evaluated as anti-inflammatory and analgesic activities. Selected compounds were further tested for ulcerogenic and lipid peroxidation potential.