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Microwave-Assisted Synthesis and Pharmacological Activity of Pyrazolyl Benzofuran Deravatives

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Abstract Microwave-assisted Organic Reaction Enhancement (MORE) has emerged as a new 'lead' in organic synthesis. During the studies we observed that microwave –assisted organic synthesis requires 2-4 min. of time whereas the conventional ones takes 4-6 hrs and often with poor yields. Hence, with an objective of reducing the reaction time, application of microwave technique has proved to be advantageous in case of synthesis of new benzofuran derivatives. The structures of synthesized derivatives emerged is confirmed by their IR, NMR and Mass spectra. The representative compounds synthesized with this route is further screened for anti-bacterial, analgesic, anti-inflammatory and ulcerogenic studies. In this study we have observed that the benzofuran derivatives are less ulcerogenic compared to phenyl butazone. The structural comparisons have revealed that the chloro substitution will increase the ulcerogenic toxicity.

Keywords Analgesic, anti-inflammatory, antimicrobial, microwave-assisted synthesis, pyrazolyl benzofuran, ulcerogenic toxicity

1. Introduction

In the recent years, microwave-assisted organic reactions have emerged as a new 'lead' in modern organic synthesis technology[1-5]. Important advantage of this technique is highly accelerated rate of the reaction with improved quality and quantity of the product. The technique offers simple, clean, fast, efficient, and economical and environment friendly method for the synthesis of number of organic molecules. Moreover, the technique is considered as an important 'green chemistry' approach because of its eco-friendly nature[6-9]. Conventional methods of organic synthesis usually need longer heating time, elaborate and tedious apparatus set up, resulting in higher cost of production. Excessive use of solvents/ reagents leads to environmental pollution Efforts are being made to establish the green chemical transformations and to develop several new effective microwave-induced methods for the synthesis of organic compounds[10-12]. The energy used in microwave irradiation is same as that of thermal energy. The advantage in application of this method is its completion in short duration and operational simplicity. The use of single frequency microwave oven for this is well established in MORE(Carroet al) (Microwave Induced Organic Reaction Enhancement) chemistry. The experiments like determination of saponification value, loss on drying could be performed within minutes[13,14].

Pyrazolobenzofurans which carried off only synthetic interest, initially, are now finding greater importance as biologically active molecules[15]. Some of these compounds are reported to possess bactericidal, anti-viral and anti-cancer activity[16,17]. Annulation of pyrazole ring system on benzofuran nucleus has resulted in compounds possessing analgesic and anticonvulsant activities[18]. In view of these findings, we focused our interest on benzofuran coupled with pyrazole for our research program. The carbonyl hydrazide is used for the development of pyrazole ring system (as quoted in literature for having best functionality). The synthetic strategy that involves the modification of carbonyl hydrazide group located on the furan moiety of benzofuran nucleus in to the desired pyrazole ring system. 3- methoxy-2-carbohydrazide has chosen for this investigation. The reaction on condensation of benzofuran-2-carbonylhydrazide with different acetones and chloroacetones and further treated with DMF and $POCl_3$ under microwave irradiation. Benzofuran-2-carbonyl hydrazine and pyrazoles are biologically active, synthetically useful and important heterocyclic compounds[19,20]. In

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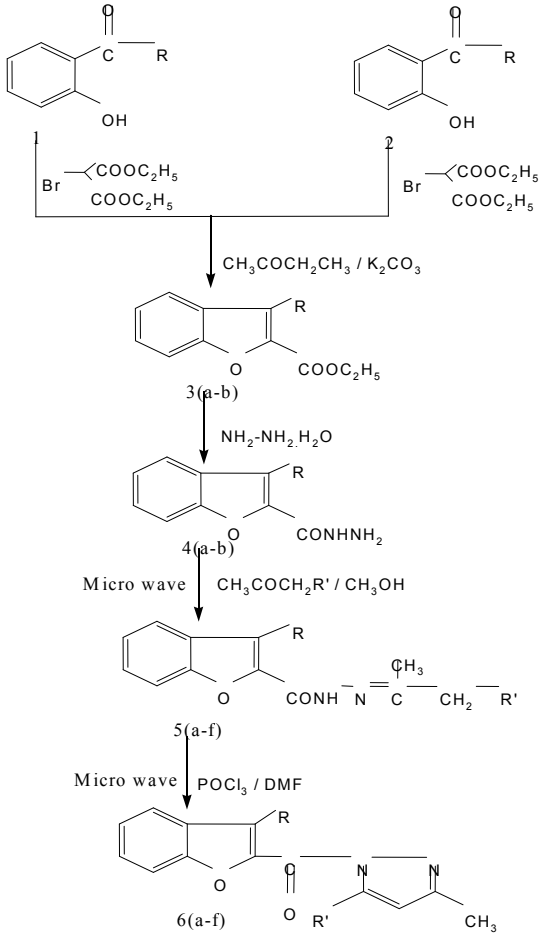
view of this, we report here the microwave assisted synthesis of pyrazolyl benzofurans and screened for different pharmacological activities.

2. Materials and Methods



Scheme 1. Microwave mediated synthesis of different pyrazolyl benzofuran derivatives from Benzofuran-2-carbohydrazide

All the chemicals used for the synthesis are of AR grade and obtained from Qualigens fine Chemicals and carragenin 1% (in normal saline) solution prepared from the gift samples obtained from R&D section of Micro labs Ltd, Bangalore. Samsung, 450MHz single frequency instrument is used for the microwave-assisted synthesis of pyrazolyl benzofuran derivatives. Melting points are in degree centigrade. These were determined in open capillary tubes and are uncorrected. The synthesized compounds were purified, recrystalized and subjected to FTIR measurements carried on a Perkin-Elmer Spectrum-One instrument at a resolution of 4 cm−1 in KBr pellets. PMR spectra were recorded using 90MHz FX – 909 JEOL spectrophotometers using TMS as internal standard and the solvent used is CDCl3. Mass spectra were recorded on Finnigan-Mat 1020 (EI, 70 ev). Micro-organisms sub cultures were procured from the Department of Microbiology, Gulbarga University Gulbarga (pure cultures were obtained from IMTECH, Chandigarh).

Synthesis of 3-ethylsubstitutedbenzofuran-2-carbohydraz ide 4(a-b)

Benzofuran-2-carbohydrazide was prepared initially by dimethylmalonate (0.01mol) and 2-carboxybenzofuran (0.01mol) (Scheme) with hydrazine hydrate (5ml, 99%) in ethanol (30ml). The mixture was magnetically stirred at room temperature for 12 hrs. IR OF 4a: 3341, 3160 NHNH2 and 1667 C=O cm-1. 1H NMR OF 4a: δ 6.5-7.4(m,ArH),8.2(s,NH2),2.4(s, NH). Mass spectrum of 4a: m/z=176. IR OF 4b: 3313, 3220 NHNH2 and 1627 C=O cm-1. 1H NMR of 4b: δ 6.0-7.1 (m, ArH), 8.0 (s,NH2), 2.2 (s, NH), 3.7 (s, -CH2). Mass spectrum of 4b: m/z=206.

General procedure for synthesis of N`-(3-substitutedprop ylen-2-ylidene)-3-substituted benzofuran-2-carbohydrazide 5 (a-f)

A mixture of benzofuran-2-carbazide (0.01mol) and acetophenone (0.01mol) with few drops of glacial acetic acid was taken in 100ml conical flask capped with funnel. The flask was incubated in a microwave at 100watts for 2 min 30 sec. The reaction mixture is cooled; the solid thus separated was filtered and recrystalized using methanol. IR of 5a: 3341, 3160 NHNH2 and 1667 C=O cm-1. 1H NMR 5a: δ 6.5-7.4(m,ArH),8.2(s,NH2),2.4(s, NH). Mass spectrum of 5a: m/z=176. IR of 5b: 3313, 3220 NHNH2 and 1627 C=O cm-1. 1H NMR of 5b: δ 6.0-7.1 (m, ArH), 8.0 (s,NH2), 2.2 (s, NH), 3.7 (s, -CH2). Mass spectrum of of 5b: m/z=206. IR of 5c: 3160 NH2 and 1657 C=O cm-1. 1H NMR of 5c: δ 6.5-7.5 (m, ArH), 7.8 (s, NH), 1.4 (s, NH), 2.6 (s, CH2). Mass spectrum of 5c: m/z 328, 329. IR 5d: 3160 NH2 and 1657 C=O cm-1. 1H NMR 5d: δ 6.5-7.5 (m, ArH), 7.8 (s, NH), 1.4 (s, NH), 2.6 (s, CH2). Mass spectrum of 5d: m/z 260. IR of 5e: 3160 NH2 and 1657 C=O cm-1. 1H NMR of 5e: δ 6.5-7.5 (m, ArH), 7.8 (s, NH), 1.4 (s, NH), 2.6 (s, CH2). Mass spectrum of 5e: m/z 322.IR of 5f: 3160 NH2 and 1657 C=O cm-1. 1H NMR of 5f: δ 6.5-7.5 (m, ArH), 7.8 (s, NH), 1.4 (s, NH), 2.6 (s, CH2). Mass spectrum of 5f: m/z 358, 359.

General procedure for synthesis of (3-substituted-5substit uted-1H-pyrazol-1-yl)(3-substituted benzofu ran-2-yl)metha none 6(a-f)

To the Vilsmeier – Hack complex, prepared from DMF (10ml) and POCl3 (0.012mol) in a conical flask at 0oC the hydrazone (0.01mol) was added and capped with funnel. The reaction mixture was irradiated in microwave oven at 100 watts for 3 minutes. The reaction mixture quenched by pouring on to the crushed ice. The product which is separated on neutralization with NaHCO3 was filtered, washed with water and recrystalized with methanol. The 4-chloro derivative is prepared similarly and their characterization data is recorded. IR 6a: 3160 NH2 and 1657 C=O cm-1. 1H NMR 6a: δ 6.5-7.5 (m, ArH), 7.8 (s, NH), 1.4 (s, NH), 2.6 (s, CH2). Mass spectrum 6a: m/z 240. IR 6b: 3160 NH2 and 1657 C=O cm-1. 1H NMR 6b: δ 6.5-7.5 (m, ArH), 7.8 (s, NH), 1.4 (s, NH), 2.6 (s, CH2). Mass spectrum 6b: m/z 302. IR 6c: 3160 NH2 and 1657 C=O cm-1. 1H NMR 6c: δ 6.5-7.5 (m, ArH), 7.8 (s, NH), 1.4 (s, NH), 2.6 (s, CH2). Mass spectrum 6c: m/z 336, 337. IR 6d: 3160 NH2 and 1657 C=O cm-1. 1H NMR 6d: δ 6.5-7.5 (m, ArH), 7.8 (s, NH), 1.4 (s, NH), 2.6 (s, CH2).

Mass spectrum 6d: m/z 271. IR 6e: 3160 NH2 and 1657 C=O cm-1. 1H NMR 6e: δ 6.5-7.5 (m, ArH), 7.8 (s, NH), 1.4 (s, NH), 2.6 (s, CH2). Mass spectrum 6e: m/z 333. IR 6f: 3160 NH2 and 1657 C=O cm-1. 1H NMR 6f: δ 6.5-7.5 (m, ArH), 7.8 (s, NH), 1.4 (s, NH), 2.6 (s, CH2). Mass spectrum 6f: m/z 336, 337.

In vitro studies

Antibacterial activity

In vitro antibacterial activities of the representative derivatives of benzofuran, 6b, 6c, 6e and 6f compounds were analyzed against two gram-positive and two gram negative bacteria, by broth dilution method as per the national standards[21,22]. The microorganisms were revived by inoculating in broth media and grown at 37 ℃ for 18 hrs, harvested by centrifugation, and then washed several times with fresh deionised water. Stock solutions of the series of compounds were prepared in DMSO. Potato Dextrose Agar (PDA) media was used. The compound used was in a concentration of 1, 5, 10 and 25 µg per 0.1ml. All the plates were incubated at 37 ℃ for 48 h and the minimum inhibitory concentration of the respective compounds against the representative micro-organism was determined.

Antifungal activity

The stock cultures of Candida albicans, Aspergillus fumigatus were revived by inoculating in broth media and incubating at 27℃ for 48 hrs. Potato Dextrose Agar media was used. The compound used was in a concentration of 1, 5, 10 and 25 µg per 0.1ml. All the plates were incubated at 37 ℃ for 48 h and the minimum inhibitory concentration of the respective compounds against the representative micro-organism was determined.

In vivo Studies

The animals were procured from the animal house of M.R. Medical College, were kept at ambient temperature, and had free access to water and diet. The animal experiments were carried in accordance with the guidelines of Institutional Animal Ethics Committee.

Anti-inflammatory Activity

Anti-inflammatory Activity is determined by the rat hind paw method according to[22]. Albino rats of either sex weighing 175 to 185 gm were selected and divided into six each and fasted for 24 hrs prior to experiment with water ad libitum. The edema was induced by injecting 1% caragenin into the plantar surface of the hind paw of rats. The first group was given the acacia suspension (control) and the other group was administered with Phenylbutazone as a standard (50mg/kg I.P.). The animals of group 3 to 6 were given 4 representative analogues of pyrazolyl benzofuran at a dose of 200mg/kg. The reaction time of each rat was recorded at the interval of 0, ½ h, 1h, 2h, 4h and 6h of time interval. The paw edema was measured by plethysmograph. Mean volume in the paw is measured and the percentage inhibition was calculated using following formula.

Table 1. Physical constants and elemental analyses of the compounds 4 (a-b), 5(a-f) and 6(a-f) compounds

Comp No.	R	R'	Yield %	M.P. oC	Mol.Formula (Mol Wt)	Microanalysis % calc & found		
						C	H	N
4a	H	-	62	163-165	$C_9H_8N_2O_2$	61.36	4.58	15.86
					(176)	61.30	4.53	15.86
4b	OCH_3	-	60	110-112	$C_{10}H_{10}N_2O_3$	58.25	4.89	13.59
					(206)	58.20	4.82	13.55
5a	H	CH_3	74	200-202	$C_{13}H_{14}N_2O_2$	67.81	6.13	12.17
					(230)	67.80	6.10	12.80
5b	H	C_6H_5	71	200-202	$C_{18}H_{16}N_2O_2$	73.95	5.52	9.58
					(292)	73.90	5.48	9.55
5c	H	C_6H_4Cl (p)	66	200-202	$C_{18}H_{15}N_2O_2Cl$	66.16	4.63	8.57
					(326)	66.10	4.60	8.55
5d	OCH_3	CH_3	78	200-202	$C_{18}H_{15}N_2O_2$	64.6	6.20	10.76
					(291)	64.55	6.15	10.75
5e	OCH_3	C_6H_5	70	200-202	$C_{14}H_{16}N_2O_3$	70.79	5.63	8.69
					(260)	70.71	5.60	8.65
5f	OCH_3	C_6H_5	81	200-202	$C_{19}H_{18}N_2O_3$	63.96	4.80	7.85
					(322)	63.90	4.75	7.80
6a	H	CH_3	81	200-202	$C_{19}H_{17}N_2O_3$	69.99	5.03	11.66
					(321)	69.95	5.00	11.64
6b	H	C_6H_5	63	200-202	$C_{19}H_{14}N_2O_2$	75.48	4.67	9.27
					(302)	75.40	4.65	9.25
6c	H	C_6H_4Cl (p)	65	200-202	$C_{19}H_{13}N_2O_2Cl$	67.76	3.89	8.32
					(336)	67.71	3.85	8.30
6d	OCH_3	CH_3	88	200-202	$C_{15}H_{14}N_2O_3$	66.66	5.22	10.36
					(270)	66.60	5.20	10.33
6e	OCH_3	C_6H_5	86	200-202	$C_{20}H_{16}N_2O_3$	72.28	4.85	8.43
					(332)	72.20	4.80	8.40
6f	OCH_3	C_6H_4Cl (p)	81	200-202	$C_{20}H_{15}N_2O_3Cl$	65.49	4.12	7.64
					(367)	65.45	4.08	7.62

Percentage inhibition = 100 – (1-VT/VC)

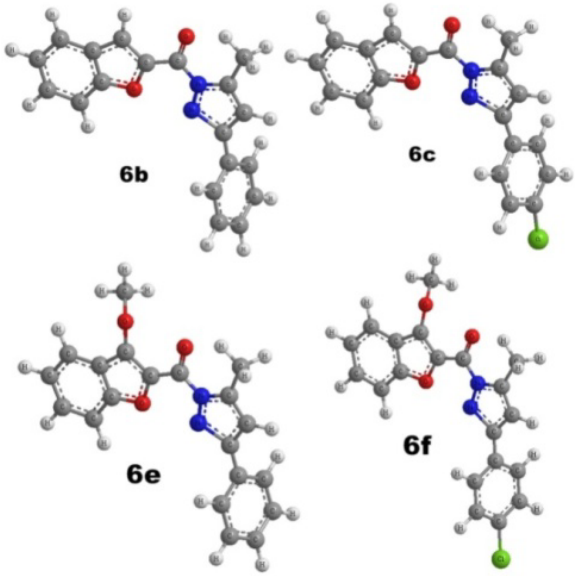
Whereas VC = Edema volume in control

VT = Edema volume in test / standard compound

Analgesic activity

Eddy's hot plate method is adopted[23]. Preliminary experiments were conducted to select the rat which showed a reaction time of 2 to 4 seconds. The results of analgesic screening are summarized in Table. The cut-off point of 10 sec was strictly practiced to avoid any damage to the paws.

Acute ulcerogenesis



The procedure is followed as per given in[24]. Albino rats (175-185 g) were divided into different groups consisting of six animals in each group. Ulcerogenic activity evaluated after the administration of test compounds or Phenyl butazone at the dose of 50 mg/kg. Control rats received administration of vehicle (suspension of 2% acacia). Food but not water was removed 24 h before administration of the test compounds. After the drug treatment, the rats were fed normal diet for 17 h and then sacrificed. The stomach was removed and opened along the greater curvature, washed with distilled water and opened along the greater curvature, washed with distilled water and cleaned gently by dipping in saline. The gastric mucosa of the rats was examined using 10X microscope. The lesions were checked, counted and categorized into perforated (greater than 2mm in diameter), average (1-2 mm) and small (less than 1 mm). For each stomach the severity of mucosal damage was assessed according to the following scoring system. The mean score of each treated group minus the mean score of the control group was considered as the 'ulcer index' of gastric damage. The score on the performance of the respective compounds based upon their ulcerative response i.e., more the score less the ulcerogenic response.

3. Results and Discussions

The derivative obtained from pyrazolylbenzofuran basic nucleus in two step synthesis, their structures was confirmed by IR, 1HNMR and Mass spectra. For brevity only 4 synthesized derivatives which have shown satisfactory in-vitro and in-vivo biological activities were reported.

In vitro activity

Anti-bacterial & anti-fungal activity

In the series, representative compounds 6b, 6c, 6e and 6f analyzed is shown in table 2. The compound 6f is highly active against all the gram-positive bacteria and gram negative bacteria, the compound 6c were active against B. subtilis. It is interesting to note that the compounds which were substituted with chloro at 4th position of pyrazolyl ring, displayed notable antibacterial activity.

In anti-fungal analysis, compound 6f has shown satisfactory activity against Candida albicans and moderate activity against *Aspergillus fumigatus*. All other compounds (6b, 6cand 6e) did not indicate any positive sign in this experiment.

In vivo activity

Anti- inflammatory activity & Analgesic activity

The pharmacological screening of the tested compounds showed anti-inflammatory activity ranging from 38.33 to 78.11% (Table 3), whereas the standard drug phenylbutazone showed 79.5% inhibition after 4 h. The anti-inflammatory activity of pyrazolylbenzofuran derivatives synthesized using microwave exposure of compound 6b, 6c, 6e and 6f ranged from 52.5 to 74.5%. The compounds 6c and 6f which are chloro substituted showed higher activity than the standard drug phenylbutazone, whereas in the compound 6b, the anti-inflammatory activity decreased. Also, it was observed that the compound 6e showed activity ranging from 48.1 to 66.63%, which is nearly equivalent to the standard drug phenylbutazone. It is clear from Table that the presence of 3-methoxy group and further chloro substitution at 4th position increases the anti-inflammatory activity.

All the four compounds have anti-inflammatory activity than those of the standard were further tested for their analgesic activity at a dose of 50 mg kg–1 phenylbutazone (Table. 1). Compounds showed analgesic activity ranging from 58.4 to 72.7%, whereas the standard drug ibuprofen showed 69.5% inhibition. The results followed the path equal to that of analgesic activity as the chloro substitution even in this case enhanced the analgesic activity, however with a degree of variation.

Ulcerogenic activity

It is noted that though the antimicrobial, analgesic and anti-inflammatory activities increased with chloro substitutions on pyrazolyl ring system the ulcerogenicity profile is also slightly increased (Table 4). The toxicity profile is almost negligible on comparison with standard drug phenylbutazone. The compounds 6b and 6e which had shown moderate analgesic and anti-inflammatory activity had shown nil GI perforations.

Table 2. Anti-microbial data of 6b, 6c, 6e and 6f

=Anti-bacterial activity					Anti-fungal Activity		
Minimum inhibitory concentration (MIC, µg/mL)							
	Gram +ve		Gram -ve				
	B.subtilis	*S.aureus*	*P.aerosenosa*	*K.aerogenes*		*C.albicans*	*A.fumigatus*
6b	75	50	---	50	6b	75	---
6c	25	50	75	50	6c	50	---
6e	75	75	---	50	6e	75	---
6f	25	25	75	25	6f	25	75
Streptomycin	5	10	2.5	5	Amphoterisin B	5	2.5

Microorganisms: Bacillus subtilis MTCC 441; Staphylococcus aureus MTCC 96; Pseudomonas aeruginosa MTCC 741; Klebsiella aerogenes MTCC 39
(---) no inhibition zone

Candida albicans ATCC 19231; Aspergillus fumigatus HIC 6094

Gr	Compd.	Admn. mg/Kg	Analgesic activity						Anti-inflammatory Activity on carrageenan induced rat paw edema					
			Mean response in Hour & % of Inhibition						% of Inhibition in Hour					
			0 hr	½ hr	1hr	2hr	4hr	6hr	0 hr	½ hr	1hr	2hr	4hr	6hr
I	Control	-	0.2 ± 0.05 ---	0.33 ± 0.04 ---	0.37 ± 0.06 ---	0.34 ± 0.06 ---	0.35 ± 0.06 ---	0.26 ± 0.07 ---	---	---	---	---	---	---
II	Phenyl butazone	50	0.20 ± 0.05 (39%)	0.13 ± 0.04 (58%)	0.16 ± 0.01 (56%)	0.17± 0.03 (35%)	0.16 ± 0.02 (55%)	0.15 ± 0.01 (58%)	46.65	50.01	56.12	58.22	62.66	61.01
III	6b	200	0.15 ± 0.01 (54%)	0.15 ± 0.01 (54%)	0.11 ± 0.03 (70%)	0.13 ± 0.03 (60%)	0.12 ± 0.03 (65%)	0.12± 0.03 (65%)	38.3	41.17	44.43	46.42	49.34	48.14
IV	6c	200	0.13 ± 0.02 (63%)	0.14 ± 0.02 (57%)	0.13 ± 0.03 (65%)	0.16 ± 0.02 (55%)	0.12 ± .02* (65%)	0.13 ± 0.03 (62%)	52.5	62.06	64.03	65.58	66.63	64.86
V	6e	200	0.09 ± 0.04 (57%)	0.10 ± 0.03 (62%)	0.12 ± 0.03 (65%)	0.11± 0.02* (53%)	0.13 ± 0.02 (65%)	0.11 ± 0.04 (50%)	48.61	57.41	59.25	60.65	61.05	60.34
VI	6f	200	0.08 ± 0.06	0.11 ± 0.03	0.09 ± 0.01	0.06 ± 0.01	0.50 ± .01*	0.06 ± 0.01	55.3	66.66	69.55	72.35	74.46	74.01

scoring of Gastric Ulcers					
Compound Dose mg/ kg.					
Ulcerogenic response	**score**	**compound**	**Dose**	**Ulcer index ± S.D**	**Score**
Ulcers less than 1 mm	100				
Ulcers less than 1-2 mm	90	**Control**		---	---
Ulcers less than 2-3 mm	80	**Phenyl Butazone**	50	1.85± 0.04	50
Ulcers less than 3-4 mm	70	**6b**	200	nil	100**
Ulcers less than 4-5 mm	50	**6c**	200	0.58±0.03	80*
Ulcers less than 5 mm	25	**6e**	200	nil	100**
Perforated lesions	0	**6f**	200	0.35±0..02	90*

All the test and the standard compounds were suspended in 2% of acacia solution and administered orally as 0.3 ml/dose
Higher the score safer the drug * moderate safety ** Better safety

4. Conclusions

Meaningful, safe and economical synthesis of pyrazolyl benzofuran derivatives are synthesized with microwave-assisted green chemical technology. The high yield and the better pharmacological activity and considerable in-vivo tolaratability encourages for the further research in the same line. In the developed series of derivatives, from the structural activity relationship infers that with the chloro substitution to the pyrazolylbenzofuran derivatives enhances the biological activity but with the slight increase in ulcerogicity profile. However it is negligible when compared to the commercially available standard drug, phenylbutazone.

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