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Original article

Synthesis and bioactivities of some new 1*H*-pyrazole derivatives containing an aryl sulfonate moiety

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ABSTRACT

A new series of 1*H*-pyrazole derivatives **5a–j** bearing an aryl sulfonate moiety have been synthesized by a one-pot cyclo-condensation reaction of 2-(3-(dimethylamino)acryloyl)phenyl-4-methyl benzene sulfonates **4a–e** and hydrazine hydrate or phenyl hydrazine in ethanol under reflux conditions. Some of the newly synthesized compounds were screened for their anti-inflammatory activity. All synthesized compounds were screened against Gram positive and Gram negative bacterial and fungal strains. The compound **5b** was found to be a potent anti-inflammatory agent while the majority of the compounds were found to be active against microbial strains.

1. Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are an important class of bioactive heterocycles and commonly prescribed medication worldwide, especially for the treatment of inflammation, pain and fever [1,2]. The drugs such as salicin, aspirin and indomethacin are well-known anti-inflammatory medicines and also showed a variety of other bioactivities. The poor gastrointestinal tolerability of this class of drugs led to the development of selective agents known as COX-2 inhibitors [3]. The pyrazole derivatives have been identified as selective COX-2 inhibitors that were associated with cardiovascular toxicity [4]. Thus, design and synthesis of novel COX-2 inhibitors with enhanced safety profile is still a necessity and challenge for the pharmaceutical industry.

The pyrazole derivatives play important roles in the development of pesticides and medicines and are found to exhibit a wide range of interesting bioactivities such as anti-inflammatory [5], anti-viral [6], anti-tumor [7], anti-depressant, anti-convulsant [8], antimicrobial [9] and anti-cancer activity [10]. In addition, some pyrazole derivatives are widely used as fungicides, antiviral agents, analgesic agents, insecticides and herbicides [11].

It has been observed that compounds containing aromatic sulfonate or sulfonamide moieties possess strong acaricidal [12] as well as insecticidal [13] activities. In addition, they are endowed with variety of biological activities like papillomavirus microbicidal [14], anti-human immunodeficiency virus-1 [15], antineoplastic [16], and anticancer activity [17]. Recently, Habib *et al.* [18] described the synthesis of pyrazole and imidazolone derivatives containing aryl sulfonate moiety with their antimicrobial activity.

In continuation of our research work directed towards the development of simple and efficient synthesis of biologically active heterocyclic compounds, herein we report the synthesis of novel 2-(1*H*-pyrazol-5-yl)phenyl-4-methylbenzene sulfonates and 2-(1-phenyl-1*H*-pyrazol-5-yl)phenyl-4-methylbenzene sulfonates from enaminones under reflux conditions in ethanol and their anti-inflammatory and anti-microbial activities.

2. Experimental

Melting points were performed in open capillary tubes and were uncorrected. IR spectra were recorded in KBr pellets on a 250 MHz spectrometer and ^{1}H NMR spectra in DMSO-d_6 on PerkinElmer 200 MHz spectrometer using TMS as an internal standard and chemical shifts in ppm. ^{13}C NMR spectra were recorded on Avance 50 MHz spectrometer in $CDCl_3$.

3. Results and discussion

The synthesis of intermediates **4a–e** [19] and targeted title compounds **5a–j** [20] was achieved through the useful and efficient synthetic route outlined in Scheme 1. Initially, the substrates **1b–c** was prepared according to the literature

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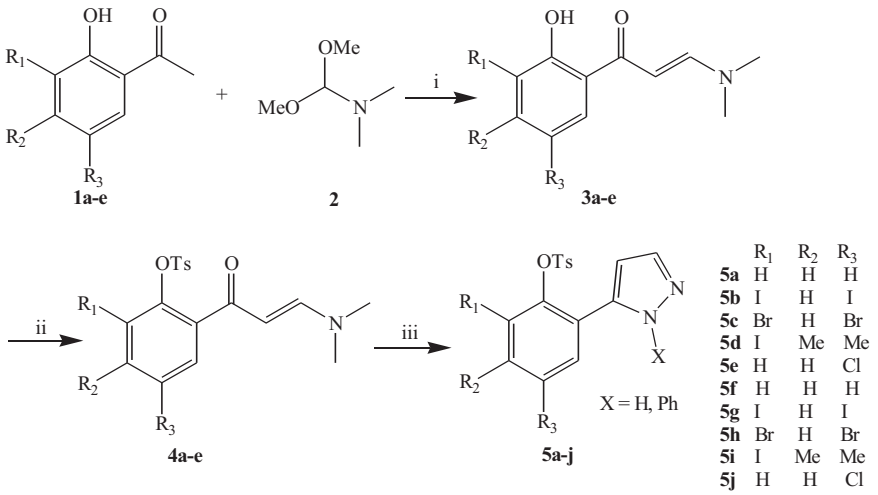

	R_1	R_2	R_3
5a	H	H	H
5b	I	H	I
5c	Br	H	Br
5d	I	Me	Me
5e	H	H	Cl
5f	H	H	H
5g	I	H	I
5h	Br	H	Br
5i	I	Me	Me
5j	H	H	Cl

Scheme 1. Reaction conditions: (i) toluene, MW 9–10 min; (ii) *p*-toluene sulfonyl chloride, K_2CO_3, grind 7–8 min; (iii) EtOH/AcOH, $NH_2{\cdot}NH_2$ or Ph-$NHNH_2$, reflux, 6–7 h.

procedures [21]. The intermediates **3a–e** were prepared in excellent yields (80%–90%) by the reaction of 2-hydroxy acetophenones **1a–e** with *N,N*-dimethyl formamide dimethyl acetal (DMF-DMA) **2** in toluene as a solvent (5 mL) under microwave irradiation at 110–120 °C [22]. The same reaction under reflux conditions occurred in moderate yields (60%–65%). The enaminone **3a** reacted with *p*-toluene sulfonyl chloride in the presence of a catalytic amount of anhydrous potassium carbonate under solvent free conditions using mortar and pestle technique produced 2-(3-(dimethylamino)acryloyl)phenyl-4-methylbenzene sulfonate **4a** in moderate to good yields (90%) in 7–8 min. The production of the desired products **4a–e** was confirmed by the absence of ferric chloride test for phenolic OH group and thin layer chromatography. The appearance of characteristic absorption bands in IR spectrum for compound **4a** at 2962, 1710, 1532, 1312 cm^{-1} corresponding to the presence of C–H_{str}, C=O_{str}, C=C_{str} and SO_{3str}, respectively, implied the existence of these functional groups in the molecule. ^1H NMR spectrum of **4a**, the peaks at δ 2.37, 2.51, 7.40 and δ 7.01–7.82 are assigned to the CH_3, N–CH_3, –CH=CH and Ar–H protons, respectively. The observed peaks at δ 21.3, 45.2, 91.8 and δ 151.3, 188.4 were assigned to the CH_3, N–CH_3, C=C, and C=O in the ^{13}C NMR spectrum.

To identify the suitable solvent and other optimal reaction conditions for the synthesis of pyrazole derivative **5a**, we performed the reaction of 2-(3-(dimethylamino)acryloyl)phenyl-4-methylbenzene sulfonates with hydrazine hydrate or phenyl hydrazine in polar solvents such as ethanol, water, methanol and non-polar solvents such as toluene and benzene. The desired product was obtained in lower yields with longer reaction time for all solvents used. The reaction carried out in ethanol under reflux conditions gave unexpected yield of product even with prolonged refluxing. The reaction was also attempted under microwave irradiation in ethanol at different temperatures but the reaction was unable to proceed. The optimized reaction conditions were achieved when the reaction was performed in ethanol with 5–6 drops of glacial acetic acid under reflux conditions and good yield of titled derivatives was obtained. Under these optimized reaction conditions, the titled compounds **5a–j** were prepared in excellent yields (85%–90%) by the reaction of 2-(3-(dimethylamino)acryloyl)phenyl-4-methylbenzene sulfonates with hydrazine hydrate or phenyl hydrazine (Scheme 1). The synthesized compounds were purified by column chromatography eluting with *n*-hexane: ethyl acetate (8:2) mixture and characterized by various spectroscopic techniques and elemental analysis [23].

Anti-inflammatory activity data (Table 1) revealed that, most of the tested compounds exhibited good anti-inflammatory effects on the paw volumes of treated animals. It is worth noting that, minor changes in the aromatic ring by halogen substitutions profoundly influenced the activity. Among the tested compounds, **5b** showed highest reduction in edema volume compared to the standard drug indomethacin. Similarly, all the synthesized pyrazole derivatives were screened for their antimicrobial activity using ampicillin and norcadine as standard drugs by the agar cup plate method as reported in Indian Pharmacopoeia [24]. Antimicrobial activity data (Table 2) revealed that the majority of the compounds were active against both Gram-positive and Gram-negative bacteria and fungal

Table 1
Anti-inflammatory activity of pyrazole derivatives.

Group (*n*)	Substance	Dose (mg/kg)	Difference in paw edema volume after							
			1 h		2 h		4 h		6 h	
			Mean ± SEM	% REV	Mean ± SEM	% REV	Mean ± SEM	% REV	Mean ± SEM	% REV
1	Control	0.1 mL	4.94 ± 0.219	–	4.63[a] ± 0.210	–	4.93 ± 0.446	–	4.73 ± 0.262	–
2	Standard	10	4.56[a] ± 0.256	7.69	4.16 ± 0.171	10.15	4.29 ± 0.231	12.98	3.96[a] ± 0.182	16.27
3	**5b**	50	4.57 ± 0.158	7.48	4.27[b] ± 0.092	7.77	4.42 ± 0.134	10.34	4.11 ± 0.145	13.10
4	**5c**	50	4.72[b] ± 0.217	4.45	4.36[b] ± 0.228	5.83	4.51[b] ± 0.415	8.51	4.20[a] ± 0.236	11.20
5	**5d**	50	4.63[b] ± 0.210	6.27	4.30[a] ± 0.232	7.12	4.46[c] ± 0.445	9.53	4.13[b] ± 0.266	12.68
6	**5e**	50	4.94[b] ± 0.213	0.00	4.47[b] ± 0.224	3.45	4.71[c] ± 0.445	4.46	4.37[b] ± 0.256	7.61
7	**5f**	50	4.94 ± 0.011	0.00	4.54 ± 0.087	1.94	4.69[b] ± 0.405	4.86	4.41[a] ± 0.242	6.76

n: six albino rats in each group; REV: reduction in edema volume; SEM: standard error of the mean; Standard: indomethacin drug.
[a] Significance level: $p < 0.05$ compared with respective control.
[b] Significance level: $p < 0.01$ compared with respective control.
[c] Significance level: $p < 0.001$ compared with respective control.