INTERNATIONAL JOURNAL OF PHARMACY AND ANALYTICAL RESEARCH

ISSN:2320-2831

IJPAR |Vol.7 | Issue 2 | Apr- Jun- 2018

Journal Home page: www.ijpar.com

Research article *Open Access*

Synthesis and Biological evaluation of some new Heterocyclic compounds

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ABSTRACT

2-pyrazolines **(B1PY1-B10PY10)** derivatives were prepared by treating chalcones **(B1-B15)** with phenyl hydrazine in presence of pyridine and ethanol. All the synthesized compounds were depicted by means of IR, 1HNMR spectral data and microanalyses. The prepared compounds were studied for analgesic effect, some of them were found to have significant activity, when compared to standard drugs.

Keywords: Pyrazolines, Analgesic activity.

INTRODUCTION

Derivatives of Pyrazoline consist of an interesting class of compounds with various pharmacological activities like anti-inflammatory, analgesic, antidepressant, antimicrobial, antitubercular and antimalarial activities [1-5]. Many of the compounds are therapeutically useful such as phenylbutazone, oxyphenbutazone, celecoxib, belonging to pyrazoles exhibited antipyretic, anti-inflammatory and analgesic properties [6]. Among various pyrazoline derivatives, 2-pyrazolines seem to be the most frequently studied pyrazoline type of compounds. Ratna Deep et al, demonstrated analgesic activity of 3,2-(4,5- dihydro-5-(4-morphilinophenyl)-1H-pyarazol-3-yl)phenols [7] by earlier studies. Suresh et al, reported a novel series of 5-substituted aryl-3-(3-coumarinyl)-1-phenyl-2-pyrazolines as novel anti-inflammatory and analgesic agents [8]. Manna et al, reported analgesic and antipyretic activity of some new N-acetyl-Δ 2 -pyrazolines and dihydrothienocoumarines [9]. The reaction of an α, β-unsaturated ketone with phenylhydrazine became a generally used, simple and convenient procedure for the synthesis of pyrazolines [10]. In view of these observations and in continuation of our research programme on the synthesis of chalcones and their derivatives [11], we report here the synthesis of some new pyrazoline derivatives which have been found to possess an interesting profile of analgesic activity.

Synthetic methods for the synthesis of pyrazoline derivatives **(B1PY1-B10PY10)** are

summarized in **Scheme 1**. Chalcones were synthesized by the reacting 3-acetyl-2,5-dimethylthiophene and various substituted aromatic and heterocyclic aldehydes (II) in presence of aq. KOH and ethanol. Pyrazolines were obtained in good yields by reacting chalcones **(B1-B15)** with phenylhydrazine in hot pyridine. The structures of the various synthesized compounds were assigned on the basis of elemental analyses, IR and ^{1}H NMR spectral data. These compounds were also screened for their antimicrobial activity and anti-inflammatory activity.

MATERIAL AND METHODS

All the chemicals used in the synthesis were obtained from standard commercial sources. Melting points were determined on an open capillary melting point apparatus and are uncorrected. 1H NMR spectra were recorded in CDCl3 on Bruker WM 400 MHz spectrometer with TMS as internal standard. Infrared spectra were recorded (KBr) on a Perkin-Elmer AC-1 spectrophotometer. Micro analyses were performed on Carlo Erba E– 1108 element analyzer and were within the ± 0.4% of the theoretical values. Reaction completion was identified by TLC using silica gel for TLC (Merck). All the chalcones have been purified by column chromatography performed on silica gel columns (100-200 mesh, Merck).

General procedure for the synthesis of chalcones of 3-acetyl-2,5-dimethylthiophene (B_1-B_{15})

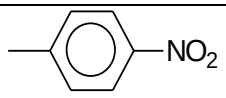
Equimolar quantities (0.005 mol) of 3-acetyl-2,5-dimethylthiophene**(I)** and respective aldehydes**(II)** were mixed and dissolved in the minimum amount of alcohol. To this, aqueous potassium hydroxide solution (50 %, 7.5 mL) was added slowly and mixed occasionally for 24 hrs, at room temperature. Completion of the reaction was identified by TLC using silica gel-G. After completion of the reaction, the mixture was poured onto crushed ice, acidified if necessary with dilute hydrochloric acid, and the solid that separated was isolated by filtration, dried and purified by column chromatography on silica gel (100- 200 mesh, Merck), with a mixture of ethyl acetate and hexane as the mobile phase [12,13].

General Procedure for the synthesis of 2-pyrazolines

The chalcones were condensed with phenylhydrazine in absolute ethanol in the presence of pyridine at reflux temperature (2 to 6 hr). The solvent was completely evaporated and the residue was poured into ice cold water, which resulted in the formation of the corresponding 2-pyrazolines. Reaction completion was established by TLC using silica gel - G. After completion of the reaction, the reaction mixture was poured into crushed ice with constant stirring. The separated solid was filtered and dried. It was purified by column chromatography on silica gel, using ethyl acetate and hexane mixture as the mobile phase. After purification, the 2-pyrazolines were obtained as light or bright coloured powders.

Anti-inflammatory activity

The Carrageenan-induced rat paw oedema method was adopted for the evaluation of **anti-inflammatory** activity of the test compounds. The results clearly revealed the potential anti-inflammatory activity of all these 2-pyrazolines when compared with the standard drug aceclofenac, but not at an identical dose level. The results of the analgesic activity of ibuprofen and the compounds tested are shown in Table3.

Compound	Ar	Molecular Formula	Relative Molecular Mass(RMM)	Melting Point (°C)	Yield %	(% Calc.) C	H	N	(% found) C	H	N
B_1PY_1		$C_{21}H_{19}N_3O_2S$	377	135	78	66.84	5.03	11.14	66.82	5.01	11.12

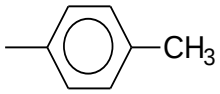
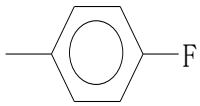
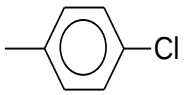
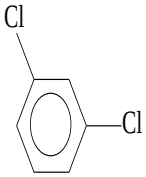
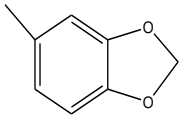
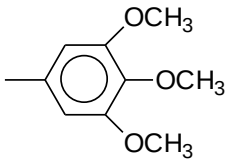
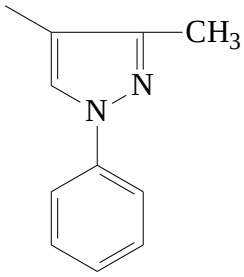
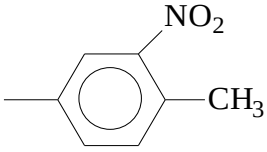
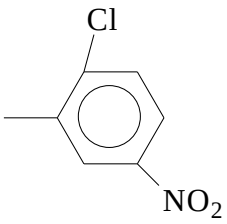
B_2PY_2		$C_{22}H_{22}N_2S$	346	124	75	76.30	6.35	8.09	76.29	6.33	8.07
B_3PY_3		$C_{21}H_{19}FN_2S$	350	135	74	72.00	5.42	8.00	72.02	5.40	8.02
B_4PY_4		$C_{21}H_{19}ClN_2S$	366	150	72	68.85	5.19	7.65	68.83	5.17	7.63
B_5PY_5		$C_{21}H_{18}Cl_2N_2S$	400	128	82	63.00	4.50	7.00	63.02	4.48	7.02
B_6PY_6		$C_{22}H_{20}N_2O_2S$	376	138	75	70.21	5.31	7.44	70.22	5.29	7.42
B_7PY_7		$C_{24}H_{26}N_2O_3S$	422	144	79	68.24	6.16	6.63	68.22	6.14	6.61
B_8PY_8		$C_{25}H_{25}N_4S$	413	141	81	72.63	6.05	13.55	72.61	6.03	13.52
B_9PY_9		$C_{22}H_{21}N_3O_2S$	391	129	78	67.51	5.37	10.74	67.49	5.35	10.72
$B_{10}PY_{10}$		$C_{21}H_{18}ClN_3O_2S$	411	151	74	61.31	4.37	10.21	61.29	4.35	10.19

Table 2: Physical characterization data of prepared compound (B_1PY_1- $B_{10}PY_{10}$)

Compound	IR spectral data	1 H NMR spectral data Chemical shift (δ) in ppm
B_1PY_1	1598 (C=N), 1533 (N=O, asymmetric), 1342 (N=O, symmetric), 1504 (C=C), 1153 (C-N) and 691 (C-S)	3.13 (1H, dd, H_A), 3.85 (1H, dd, H_B), 5.30 (1H, dd, H_X), 2.28 and 2.53 (each 3H, s, 2x Ar-CH_3) and 6.95-8.19 (10H, Ar-H).
B_2PY_2	1596 (C=N), 1502 (C=O), 1148 (C-N) and 688 (C-S)	3.10 (1H, dd, H_A), 3.85 (1H, dd, H_B), 5.32 (1H, dd, H_X), 2.28, 2.56 and 2.75 (each 3H, s, 3x Ar-CH_3) and 6.68-7.57 (10H, Ar-H).
B_3PY_3	1591 (C=N), 1502 (C=C), 1152 (C-N), 858 (C-F) and 684 (C-S)	3.10 (1H, dd, H_A), 3.75 (1H, dd, H_B), 5.10 (1H, dd, H_X), 2.40 and 2.70 (each 3H, s, 2x Ar-CH_3) and 6.52-7.25 (10H, Ar-H).
B_4PY_4	1583 (C=N), 1503 (C=C), 1153 (C-N), 834 (C-Cl) and 649 (C-S)	3.10 (1H, dd, H_A), 3.76 (1H, dd, H_B), 5.10 (1H, dd, H_X), 2.40 and 2.70 (each 3H, s, 2x Ar-CH_3) and 6.58-7.40 (10H, Ar-H).
B_5PY_5	1594 (C=N), 1504 (C=C), 1148 (C-N), 836 (C-Cl) and 656 (C-S)	3.10 (1H, dd, H_A), 3.90 (1H, dd, H_B), 5.58 (1H, dd, H_X), 2.28 and 2.55 (each 3H, s, 2x Ar-CH_3) and 6.50-7.60 (9H, Ar-H).
B_6PY_6	1596 (C=N), 1499 (C=C), 1251 (C-O-C), 1112 (C-N) and 689 (C-S)	3.10 (1H, dd, H_A), 3.75 (1H, dd, H_B), 5.16 (1H, dd, H_X), 5.95 (2H, s, O-CH_2-O) and 6.70-7.40 (9H, Ar-H).
B_7PY_7	1598 (C=N), 1502 (C=C), 1165 (-O-CH_3), 1142 (C-N) and 684 (C-S)	3.10 (1H, dd, H_A), 3.71 (1H, dd, H_B), 5.15 (1H, dd, H_X), 3.85 (6H, s, 2x O-CH_3), 3.81 (3H, s, -OCH_3) and 6.30-7.60 (8H, Ar-H).
B_8PY_6	1578 (C=N), 15202 (C=C), 1138 (C-N) and 650 (C-S)	3.12 (1H, dd, H_A), 3.75 (1H, dd, H_B), 5.15 (1H, dd, H_X), 2.31, 2.40 and 2.70 (each 3H, s, 3x Ar-CH_3) and 6.80-7.40 (12H, Ar-H).
B_9PY_9	1598 (C=N), 1529 (C=C), 1110 (C-N) and 1063 (C-O-C)	3.11 (1H, dd, H_A), 3.83 (1H, dd, H_B), 5.20 (1H, dd, H_X), 2.52, 2.59 and 2.72 (each 3H, s, 3x Ar-CH_3) and 6.58-7.40 (10H, Ar-H).
$B_{10}PY_{10}$	1595 (C=N), 1553 (N=O, asymmetric), 1333 (N=O, symmetric),1500 (C=C), 1172 (C-N) and 688 (C-S)	3.12 (1H, dd, H_A), 3.76 (1H, dd, H_B), 5.50 (1H, dd, H_X), 2.30 and 2.50 (each 3H, s, 2x Ar-CH_3) and 6.55-7.50 (9H, Ar-H).

Table 3: Anti-inflammatory activity of 2-pyrazolines (B_1PY_1-$B_{10}PY_{10}$)

Compound	Ar	Percent inhibition ± SEM at various time intervals					
		0.5 h	1.0 h	2.0 h	3.0 h	4.0 h	6.0 h
B_1PY_1	4″-nitrophenyl	25 ± 1	40 ± 1	60 ± 1	71 ± 2	80 ± 2	90 ± 2
B_2PY_2	4″-methylphenyl	23 ± 2	38 ± 2	58 ± 1	69 ± 2	77 ± 1	87 ± 2
B_3PY_3	4″-fluorophenyl	28 ± 1	44 ± 1	66 ± 2	78 ± 2	85 ± 2	96 ± 2
B_4PY_4	4″-chlorophenyl	27 ± 2	41 ± 1*	64 ± 1	73 ± 2	81 ± 2	94 ± 2
B_5PY_5	2″,4″-dichlorophenyl	29 ± 1*	45 ± 1	67 ± 1	80 ± 2	95 ± 2	98 ± 2
B_6PY_6	3″,4″-methylenedioxyphenyl	22 ± 1	35 ± 1*	56 ± 1	65 ± 1	74 ± 2	85 ± 2
B_7PY_7	3″,4″,5″-trimethoxyphenyl	20 ± 2	27 ± 1	50 ± 1	60 ± 2*	65 ± 2	80 ± 2

B_8PY_8	3″-methyl-1″-phenyl-pyrazolyl	21 ± 1	32 ± 1	55 ± 1	62 ± 2*	70 ± 1*	82 ± 2
B_9PY_9	3″-nitro-4″-methylphenyl	24 ± 1	39 ± 1	59 ± 1	70 ± 2	79 ± 2*	89 ± 2
$B_{10}PY_{10}$	2″-chloro-5″-nitrophenyl	26 ± 1	42 ± 2	62 ± 1	74 ± 2	81 ± 2*	95 ± 2
Aceclofenac		35 ± 2	48 ± 1	70 ± 2	84 ± 1	98 ± 2.52*	99 ± 2

All values are represented as means (n=6). *P<0.01 compared to reference standard aceclofenac. Student's t-test. **Dosage:** Aceclofenac-2 mg/kg and test compounds-10 mg/kg body weight of rat.

RESULTS AND DISCUSSION

The title compound 1-Phenyl-3-(2',5'-dimethylthiophen-3'-yl)-5-(4″-nitrophenyl)2pyrazoline**(B1PY1B10PY10).** Of all the compounds tested, compound **B_5PY_5** having the dichloro substitution on the aromatic ring at position 5 of the 2-pyrazoline ring showed maximum activity and this is followed by compounds having a 4-fluorophenyl, 2-chloro-5-nitrophenyl, 4-chlorophenyl, 4-nitrophenyl and 3-nitro-4-methylphenyl moieties. The results once again demonstrated the necessity of halogen substituents and nitro substituents on the aromatic ring, as they enhanced the activity. It is interesting to note that the observed anti-inflammatory activity of 2-pyrazolines is more than that observed in the case of chalcones and pyrimidines.

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