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Antitumor, Analgesic, and Anti-inflammatory Activities of Synthesized Pyrazolines

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ABSTRACT

Nitrogen heterocyclic compounds such as pyrazolines have been found to possess a broad spectrum of biological activities such as anticancer, antitubercular, anti-inflammatory, analgesic, and antidepressant activities. Pyrazoline derivatives IV, V (a–e) have been synthesized from the intermediate chalcones III (a–h) by cyclizing with phenyl hydrazine and hydrazine hydrate. The structures of these compounds were confirmed by IR, NMR, and mass spectroscopy. Biological studies of the synthesized compounds showed promising antitumor, analgesic, and anti-inflammatory activities. The compounds were tested for their *in vitro* antitumor activity against EAC tumor cell lines. Compounds IVa and IVb showed the highest cytotoxicity of 80% at a 200 μg/mL concentration. Among the tested compounds, IVa and Vd seem to be more effective analgesic agents. Compounds IVc, IVd, and Ve are found to be the most effective anti-inflammatory agents. Thus the results show that synthesized compounds possess antitumor, analgesic, and anti-inflammatory activity. It was observed that the test compounds with electron withdrawing groups (halogens) on the aromatic ring favors antitumor, analgesic, and anti-inflammatory activity.

Key words: Analgesic, anti-inflammatory activity, antitumor, chalcones, pyrazolines

INTRODUCTION

Recently, different authors worldwide have reported antitumor, antiproliferative, or anticancer potential of thiophene,[1] and pyrazoline derivatives.[2] This gave us immense confidence to carry out work on pyrazoline which possesses antitubercular,[3] antidepressant,[4] anticonvulsant,[4] antitumor,[5] anti-inflammatory,[6] analgesic,[6] and anticancer[7] activities. Pain directly related to cancer or caused by treatments for cancer is a highly prevalent clinical problem. Therefore, analgesics and anti-inflammatory drugs are prescribed simultaneously along with cancer chemotherapeutics, in normal practice. Due to great potential of both the moieties, synthesis of pyrazoline bearing thiophene [IVa–d, Va–d] was carried out to evaluate antitumor, anti-inflammatory, and analgesic potential.

Pyrazolines are synthesized from the intermediate chalcones by the condensation of 2-acetyl thiophene with substituted benzaldehydes. Chalcones are of great interest as compounds exhibiting antimalarial,[8] anticancer,[9] antioxidant,[9] analgesic,[10] and anti-inflammatory[10] activities.

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The drug development program has employed testing in a few well characterized transplantable animal tumor systems. Simple *in vitro* assays shorten the testing program. Here the method is tryphan blue exclusion and the tumor cell lines are Ehrlich Ascites Carcinoma (EAC).[11]

MATERIALS AND METHODS

Melting points were determined by the capillary method and were uncorrected. The IR spectra are recorded by using a Shimadzu Perkin Ekmer 8201 PC IR Spectrometer and using a thin film on potassium bromide pellets techniques and frequencies are expressed in cm^{-1}. The PMR spectra were recorded on a Bruker Avance II 400 NMR spectrometer. All spectra were obtained in $CDCl_3$ and Dimethyl sulphoxide (DMSO). Chemical shift values are reported as values in ppm relative to TMS (δ=0) as an internal standard. The FAB mass spectra were recorded on a JEOL SX-102/DA-6000 Mass spectrometer using Argon/Xenon (6 kV, 10 Ma) as the FAB gas. All the animal experiments were approved by institutional animal ethical committee (IAEC).

General procedure for synthesis of chalcones

A mixture of 2-acetyl thiophene (0.01 mol) and substituted benzaldehydes (0.01 mol) in ethanol (20 ml) were stirred together for 24 h, in the presence of 20% NaOH (4 ml). The mixture was poured into crushed ice and acidified with 5% HCl. The product (substituted chalcones) obtained was filtered, washed with water, and re-crystallized from suitable solvents [Table 1].

3-(4-Fluorophenyl)-1-(thiophen-2-yl) prop-2-en-1-one
IR (KBr, cm^{-1}): 1648.9 (CO), 1596.4 (aliphatic C=C), 3067.7 (C–H), 1516 (aromatic C=C), 1216.2 (C–F); ^{1}H NMR (δ ppm): 7.79 (d, 1H,=CH), 7.18 (d, 1H,=CH), 7.52–7.87 (m, 7H, Ar-H); Mass (m/z): 232.

3-(4-Chlorophenyl)-1-(thiophen-2-yl)prop-2-en-1-one
IR (KBr cm^{-1}): 1672.8 (CO) group, 1611.3 (aliphatic C=C), 2924.1 (C–H), 1533.7 (aromatic C=C), 765.3 (C–Cl); ^{1}H NMR (δ ppm): 6.97–6.99 (d, 1H,=CH), 6.71–6.72 (d, 1H,=CH), 7.53–7.89 (m, 7H, Ar–H); Mass (m/z): 248.

3-(4-Methylphenyl)-1-(thiophen-2-yl) prop-2-en-1-one
IR (KBr cm^{-1}): 1683.5 (CO), 1609.7 (aliphatic C=C), 2987.3 (C-H), 1523.5 (aromatic C=C), 765.3 (C–Cl); ^{1}H NMR (δ ppm): 7.12–7.14 (d, 1H,=CH), 7.17–7.19 (d, 1H,=CH), 7.51–7.899 (m, 7H, Ar–H); Mass (m/z): 228.

Table 1: Physical data of substituted chalcone derivatives

Chalcones	R	Molecular formula	MP (°C)	% Yield
IV	4-Cl	$C_{13}H_9ClOS$	80–82	78
IVb	4-F	$C_{13}H_9FOS$	83–85	75
IVc	4-OH	$C_{13}H_{10}O_2S$	104–106	62
IVd	4-N$(CH_3)_2$	$C_{15}H_{15}NOS$	87–89	68
Va	4-CH_3	$C_{14}H_{12}OS$	96–98	77
Vb	3-OH	$C_{13}H_{10}O_2S$	88–90	68
Vc	3-Cl	$C_{13}H_9ClOS$	92–95	63
Vd	3-NO_2	$C_{13}H_9NO_3S$	111–112	68

General procedure for synthesis of pyrazolines

A mixture of substituted chalcones (0.01 mol) in 20 ml of ethanol and phenyl hydrazine, hydrazine hydrate (0.01 mol) were added and refluxed for 5–8 h and 16–20 h, respectively, in the presence of few drops of pyridine as catalyst. After the completion of the reaction, the reaction mixture was poured into 250 ml of ice cold water. The solid separated is filtered and washed with cold water. The separated compound is recrystallized by using methanol/ethyl acetate. Ethyl acetate: acetone (9:1) is the solvent system for TLC [Table 2].

5-(4-Fluorophenyl)-1-phenyl-3-(thiophen-2-yl)-4,5-dihydro-1H-pyrazole
IR (KBr cm^{-1}): 3431 (C–H), 1646.8 (C=N), 1324.3 (C–N), 1594.7 (C=C), 1224.9 (C–F); ^{1}H NMR (δ ppm): 3.064–3.124 (dd, 1H, Ha), 3.786–3.859 (dd, 1H, Hb), 5.213–5.261 (dd, 1H, Hc), 6.76–7.31 (m, 12H, Ar–H); Mass (m/z): 322.

5-(4-Chlorophenyl)-1-phenyl-3-(thiophen-2-yl)-4, 5-dihydro-1H-pyrazole
IR (KBr cm^{-1}): 3039.6 (C–H), 1635.6 (C=N), 1336.7 (C–N), 1522.5 (C=C), 703.8 (C–Cl); ^{1}H NMR (δ ppm): 3.049–3.109 (dd, 1H, Ha), 3.779–3.852 (dd, 1H, Hb), 5.190–5.239 (dd, 1H, Hc), 6.769–7.308 (m, 12H, Ar–H); Mass (m/z): (M^+) 338, (M^++2) 340.

5-(4-Fluorophenyl)-3-(thiophen-2-yl)-4,5-dihydro-1H-pyrazole
IR (KBr cm^{-1}): 3239.2 (C–H), 1546.3 (C=N), 1499.33

Table 2: Physical data of the synthesized pyrazolines

Pyrazolines	R	Molecular formula	MP (°C)	% Yield
IV	4-Cl	$C_{19}H_{15}ClN_2S$	153–155	69
IVb	4-F	$C_{19}H_{15}FN_2S$	158–160	71
IVc	4-CH_3	$C_{20}H_{18}N_2S$	106–108	55
IVd	3-NO_2	$C_{19}H_{15}N_3O_2S$	175–177	49
Va	p-Cl	$C_{13}H_{11}ClN_2S$	171–174	68
Vb	*p*-F	$C_{13}H_{11}FN_2S$	159–161	65
Vc	*p*-CH_3	$C_{14}H_{14}N_2S$	88–90	43
Vd	*m*-NO_2	$C_{13}H_{11}N_3O_2S$	145–147	51