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Synthesis, Characterisation and Analgesic Evaluation of Some Pyrazolone Derivatives

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ABSTRACT

The objective of the present study was taken with a desire to prepare and evaluate the derivatives for analgesic activity confirming with spectral data. An analgesic (also known as a painkiller) is any member of the group of drugs used to relieve pain (achieve analgesia). 3-Methyl-4-substituted benzylidine pyrazol-5-ones (1-5) were synthesized by the condensation of 3-methyl-pyrazol-5-one with substituted aromatic aldehydes. Their structures have been elucidated from IR, H^1NMR and Mass spectroscopy. All the synthesized compounds were evaluated for their analgesic activity by in-vivo methods. Among the synthesized derivatives SPCB and SPCT were found to have good analgesic activity whereas compounds SPNB and SPAT were found to have moderate analgesic activity. All the experimental data are found to be significant activity.

Keywords: Pyrazolones, Aromatic aldehydes, Analgesic activity.

INTRODUCTION

The main purpose of the present study is to synthesize different derivatives with pyrazolone as basic heterocyclic nucleus condensed with aromatic aldehydes and screening for their analgesic activity. Pyrazolone is a five membered lactam ring and is a derivative of pyrazole that has additional keto group. Analgesic drugs act in various ways on the peripheral and central nervous systems. They are distinct from anesthetics, which reversibly eliminate sensation. In choosing analgesics, the severity and response to other medication determines the choice of agent; the analgesic choice is also determined by the type of pain. Aspirin and NSAID's provide analgesia by blocking chemicals (prostaglandins) that sensitize the peripheral pain receptors to send a pain signal to the central nervous system (CNS). These drugs have anti-inflammatory, analgesic, and antipyretic actions. The anti-inflammatory and analgesic actions are both CNS and peripheral nervous system (PNS) effects, whereas the antipyretic actions are CNS effects.

Pyrazolones are important class of heterocyclic compounds that occur in many drugs and is a non-steroidal anti-inflammatory agent used in the treatment of arthritis and other musculoskeletal and joint disorders.

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Pyrazolones are biologically important group of compounds having different activities like antibacterial, antifungal, anti-inflammatory, antidiabetic, analgesic, antipyretic, immunosuppressive agents, hypoglycemic, antiviral, antineoplastic activity and other biological activities. This literature has encouraged dealing on pyrazolones. (Mariappan *et al*., 2010), (Harikumaran *et al*., 2008).

MATERIALS AND METHODS

All the chemicals were of synthetic grade and are procured from S. D. Fine Chemicals Ltd., Jiangsu Huani International Trade Pvt. Ltd., Sisco Research Laboratory Pvt. Ltd., Finar Chemicals Ltd. and Nice Chemicals Pvt. Ltd. Melting points were determined in open capillary tubes and are uncorrected. The IR spectra were recorded on ThermoNicoleNexus 670 Spectrometer using KBr disc. The ^{1}H NMR spectra were obtained on a Bruker DRX-600 MHz spectrometer in $CDCl_3$ using TMS as internal standard and chemical shifts are expressed in ∂ scale.

Experimental

Step-1: Synthesis of 3-methyl pyrazol-5-one (III)

Ethyl acetoacetate (0.5 mol) was taken in a 250 mL conical flask and stirred magnetically during slow drop wise of a solution of (0.5 mol) hydrazine hydrate in 40 mL absolute ethanol. The temperature of the reaction

mixture was increased during reaction so that temperature was regulated around 60°C. A crystalline deposit was separated after stirring for 1h at 60°C. The reaction mixture was cooled in an ice bath to complete the crystallization. After standing for completion of crystallization, it was filtered and the residue was recrystallized from cold alcohol. (Mariappan *et al*., 2010), (Desai *et al*., 2008).

***Step- II: Synthesis of 3-methyl pyrazol-5-one derivatives* (I-V)**

Pyrazolone (0.01 mol) was taken in a 100 mL round bottomed flask, and then 50 mL of freshly prepared 20% sodium hydroxide alcoholic solution was poured into it. The mixture was stirred with magnetic stirrer for 30 min. Substituted aromatic and aliphatic aldehyde (0.01 mol) was added to the reaction mixture and kept under stirring for 8 h. The reaction mixture was transferred into crushed ice and neutralized with dilute hydrochloric acid to precipitate the product. Residue was filtered, dried and recrystallized from ethanol. Similarly, other compounds were prepared with some change in refluxing time and reaction workup was done according to the literature. All the Physico-chemical details are shown in Table.1. (Mariappan *et al*., 2010), (Goudgoan *et al*., 2008).

SCHEME

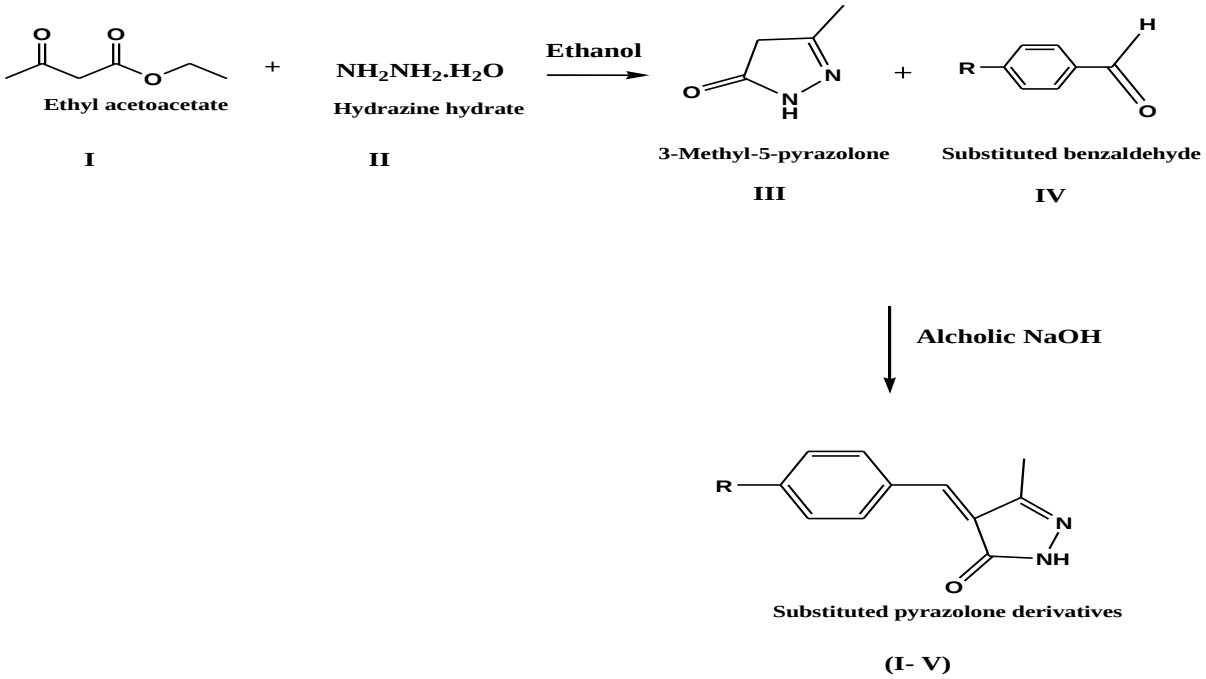

Table.1 Physico-Chemical data of synthesized compounds

Compounds	Mol. Formula	R'	Mol.Wt (gm)	% yield	M.P (°C)	R_f value (cm)
SPAT (I)	$C_{12}H_{12}N_2O$	H_3CO	106	95	140-160	0.67
SPBT (II)	$C_{10}H_{10}N_2O$	CH	92	92	160-180	0.45
SPCT (III)	$C_{14}H_{12}N_2O_2$	$C_6H_5HC=CH$	118	93	120-140	0.87
SPCB (IV)	$C_{10}H_9N_2OCl$	p-Cl	126	91	40-60	0.63
SPNB (V)	$C_{10}H_9N_3O_3$	m-NO_2	114	94	120	0.91

*Solvent system: Ethanol: Acetone: Chloroform (3:30:70)

Table.2 Analgesic activities of synthesized compounds determined by Tail Immersion Method on mice

Compound	Dose (mg/kg)	Percent analgesic activity Reaction time Mean ± SD (in seconds)			
		0 min	30 min	60 min	120 min
SPAT (I)	10	5±0.894	5±0.5764	5.83±1.472	5.5±1.049
SPBT (II)	10	4±0.894*	5.5±1.049**	4.66±1.366	5.66±1.633***
SPCT (III)	10	5.83±2.137*	6.5±1.643**	7.33±1.211	7.33±1.862
SPCB (IV)	10	4.5±1.049	4.166±1.472***	5.5±1.049**	7.83±1.69***
SPNB (V)	10	4.66±1.63	4.33±1.211	6±1.414	5.6±1.36
Standard	10	4.83±1.169	5.6±0.816	5.3±0.816	5.8±0.752
Control	-	1.46 ± 0.7	2.27 ± 0.9	3.02 ± 0.5	2.09 ± 0.67

*All the values are expressed as mean ± SD (n=6). The ***indicates P value is <0.0001, considered extremely significant; the **indicates P value is <0.001, considered significant. Standard : Diclofenac Sodium

PHARMACOLOGICAL EVALUATION

ANALGESIC EVALUATION

Animals

Albino mice weighing 200-250 gm, supplied by M/s: B.N. Ghosh & Co., Kolkatta, India, were placed in cages with wire-net floors in a controlled room temperature 29° c, Relative humidity 60-70% and provided with food and water ad libitum. The animals were deprived of food for 24 hrs before experimentation but allowed free access to tap water throughout. All studies were carried out by using six rats in each group.

Hot plate latency assay in Mice

Experiments were carried out according to method described by Adzu et al., 2001. Mice that showed nociceptive responses within 20 S when placed on hot plate maintained at 55± 0.5 ° C were selected and grouped in to seven groups of (n=6). Group 1 was treated with saline groups 2 to 6 received 200 mg/kg p.o resp., while group 7 received 100 mg/kg of acetyl salicylic acid (standard drug) p.o., each mice was placed singly on the hot plate and the latency to exhibit thermal stimulus were determined at 0 h, 0.5h, 1h and 2 h before and after the treatment. Licking of paws and jumping were the parameters evaluated. Sixty seconds was taken as the cut-off time to avoid mouse tissue damage. Analgesic activity was expressed as mean percent maximal effect calculated as %MPE = Post drug latency-Pre drug latency/cut off time pre drug latency (Uramaru *et al*., 2010).

Tail immersion method

Mice (20-25g) are held in position in a suitable restrainer with the tail protruding out. The tail up to 5cm is dipped in a beaker of water at 55 degrees. The time taken to withdraw the tail out of water is taken as reaction time. Then Diclofenac (10mg/Kg) is injected and the reaction time was noted. The percentage increase in reaction time at each interval is calculated and reports are shown in Table.2 (Gokulan *et al*., 2010).

RESULTS AND DISCUSSION

Spectral data of 4-(2-(4-methoxy phenyl)ethylidene)-3-methyl-1*H*-pyrazol-5(4*H*)-one (I)

I.R data* (cm^{-1}):** 2930 (Ar), 1605 (C=O), 1249 (CH_3O). ***H^1 NMR(∂) **:** 1.94 (3H,S,-CH_3), 2.4 (3H,S, CH_3O), 6.87(1H,S,=CH-Ar), 7-7.8 (4H,M,Ar-H),8.6 (1H,S,NH). ***Mass spectra*:** 106 M^+

Spectral data of 4-(2-(3-methyl-5-oxo-1*H*-pyrazol-4(5*H*)-ylidene)ethyl) phenyl) acryladehyde (III)

I.R data* (cm^{-1}):** 3196 (Ar), 1518 (C=O), 1595.39 (C=C). ***H^1 NMR(∂) **:** 1.94 (3H,S,-CH_3), 2.4 (3H,S, CH_3O), 7.1-7.5 (4H,M,Ar-H),8.1 (1H,S,NH). ***Mass spectra*:** 118 M^+

Spectral data of 4-(2-(4-chlorophenyl)ethylidene)-3-methyl-1*H*-pyrazol-5(4*H*)-one (IV)

I.R data* (cm^{-1}):** 2838 (Ar-Cl), 1648 (C=O), 2557 (NH). ***H^1 NMR(∂) **:** 1.94 (3H,S,-CH_3), 5.3 (1H,S,=CH-Ar), 7-7.8 (4H,M,Ar-H)8.6 (1H,S,NH). ***Mass spectra*:** 126.5 M^+

CONCLUSION

The present study has been taken up to investigate possible analgesic effects of pyrazolone derivatives. Some pyrazolone derivatives were reported to possess some degree of analgesic activity. A total of 5 derivatives were prepared and the structure of these compounds has been confirmed by the IR, NMR, Mass spectra and also supported by physical data. The synthesis of pyrazolone (IV) was carried out in step-I and Step-II. All the compounds were screened for analgesic activity using diclofenac sodium as the standard. The synthesized derivatives were characterized and identified on the basis of physical and spectral data. The derivatives were tested for analgesic potential using tail flick method and tail immersion method. SPAT, SPBT, SPCT, SPCB and SPNB derivatives were found to have good analgesic activity. Among all the pyrazolone derivatives SPCB and SPCT have shown good analgesic activity compared to other derivatives. SPAT and SPNB have shown moderate analgesic activity and SPBT has shown less analgesic activity.

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