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Synthesis and anti-inflammatory activity of some pyrazolone derivatives

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ABSTRACT

Pyrazolone is a ketone derivative of pyrazole having anti inflammatory, analgesic, antipyretic effect. Pyrazolone is a five- membered lactam ring compound contacting two nitrogen and ketone in the same molecule. Pyrazolones are well established in literature as important biologically active heterocyclic compounds. Pyrazolone in the class of nonsteroidal anti inflammatory agents used in the treatment of arthritis and other musculoskeletal and joint disorder. The objective of present study was, to synthesize the pyrazolone derivatives and to evaluate for their anti-inflammatory activity.

Method

In the present work, a series of some pyrazolone derivatives (2a-j) were synthesized, characterized by TLC, Melting point determination, IR, NMR and Mass spectra and evaluated for their anti-inflammatory activity by *invitro* using inhibition of albumin denaturation technique method.

Result & Conclusion

2a,2b,2d, Compounds showed significant anti-inflammatory activity as compared to other drug. Aspirin used as a standard drug.

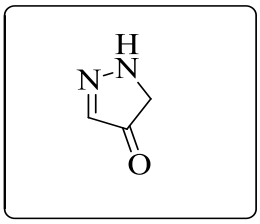
Keywords: Pyrazolone, Anti-inflammatory, 3-Methyl-1[(pyridine-4yl)carbonyl]-4,5-dihydro-1H-pyrazol-5-one.

INTRODUCTION

Introduction to Pyrazolone Ring [1, 2, 3]

Pyrazolone is a five- membered lactam ring compound contacting two nitrogen and ketone in the same molecule. Lactam structure is an active nucleus in pharmacological activity. Pyrazolone is an active moiety as a pharmaceutical ingredient, especially in the class of nonsteroidal anti inflammatory agents used in the treatment of arthritis and other musculoskeletal and joint disorder.

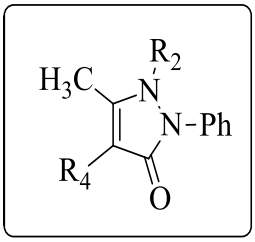
Pyrazolone is a ketone derivative of pyrazole having anti inflammatory, analgesic, antipyretic effect.



Pyrazolone includes two types

5 -pyrazolone derivative

This include antipyrine, aminopyrine,

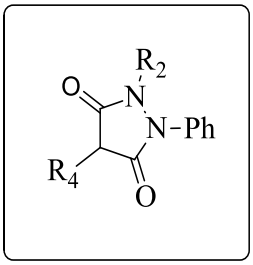


Compound	R_2	R_4
Antipyrine	CH_3	H
Aminopyrine	CH_3	$N(CH_3)_2$

These drugs are now replaced by relatively more effective and safer drugs
Main side effects: fatal agranulocytosis

3, 5- pyrazolidinedione derivative

It is a powerful anti inflammatory agent with analgesic and antipyretic properties. It is metabolized in the body into Oxyphenbutazone and Sulphinpyrazone.



Compound	R_2	R_4
Phenylbutazone	C_6H_5	n- C_4H_9
Oxyphenbutazone	P-OHC_6H_5	n-C_4H_9

Introduction to Inflammation

Definition

Inflammation is a reaction of living vascularised tissue to an injury example a boil, an acute appendicitis. Inflammation serves to destroy, dilute or wall of injurious agents. It closely intertwined with the process of repair that means regeneration. [4]

Inflammation is part of the body's natural defense system. It is a process whereby the body's cells & natural chemicals protect us from physical damage & infection from foreign substances such

as bacteria & viruses. White blood cells or leukocytes are the body's major infection fighting cells. The primary objective of inflammation is to isolate, localized & eradicate foreign substances & repair damaged tissues. From the literature survey, in recent years pyrazolone derivatives have attracted considerable interest because of their therapeutic and pharmacological properties. Several of them have been found to exhibit a wide spectrum of biological actions like anti-inflammatory, ulcerogenic, antibacterial, diuretic, analgesic, antiviral, antifungal, antimycobacterial activity etc. So it has been planned to synthesize a novel series of some pyrazolone derivatives and to check their anti-inflammatory activity [5]

Introduction to anti inflammatory drugs

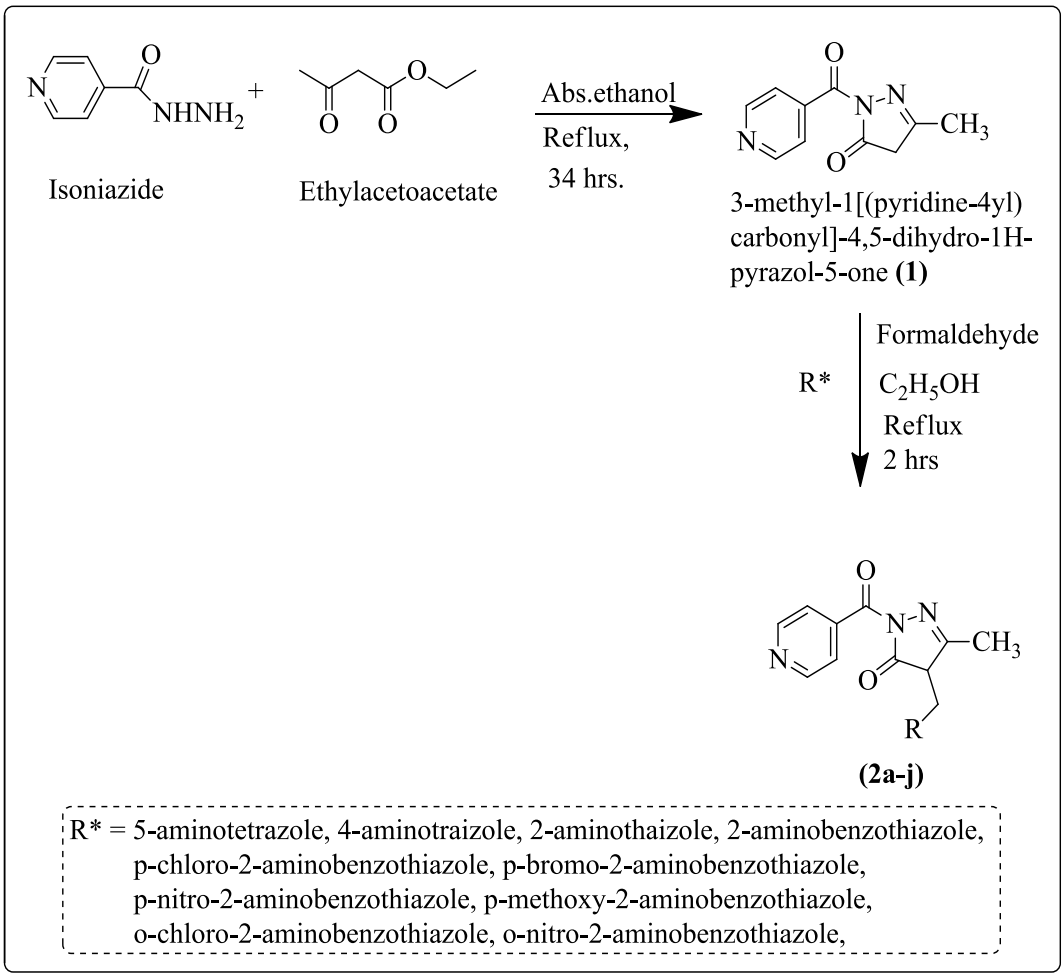
Pain is associated with any kind of health problem and for the management of pain; there is an urgent need of safer anti-inflammatory drugs. Pyrazolone derivatives possessing anti-inflammatory and analgesic activities have been reported in the literature. Non steroidal anti inflammatory drugs (NSAIDs) are the most widely prescribed drugs worldwide, this are used in various inflammatory disease including rheumatoid and osteoarthritis. However, there therapeutic use is often limited by common side effects such as gastro intestinal hemorrhage and ulceration in spite of many NSAIDs available in market, there is still need to develop new drugs that have potent anti inflammatory activity with minimum side effects [6, 7]

In particular some of pyrazolone derivatives were in depth investigated as nonsteroidal anti-inflammatory drugs (NSAIDs). The mechanism of action of this class of compounds is linked to the nonselective or selective inhibition of two cyclooxygenase isoforms, namely COX-1 and COX-2. While COX-1 is a constitutive enzyme and is necessary for the proper function of the kidney and stomach through the synthesis of prostaglandins, COX-2 is an inducible form of the enzyme that mediates the inflammatory processes. The selective inhibition of COX-2 avoids the presence of gastrointestinal and renal side effects associated with the inhibition of the production of prostaglandins by COX-1. Thus, COX-2 is a validated molecular target whose selective inhibition is sought in the development of anti-inflammatory therapies [8, 9]

Many in vitro assays, each based on a specific biochemical or cellular mechanism have been developed for the initial screening of the anti-inflammatory compounds. A number of anti-inflammatory drugs are known to inhibit the denaturation of proteins as an in vitro screening model for anti-inflammatory compounds. The synthesized compounds are screened for anti-inflammatory activity by using inhibition of albumin denaturation technique which was studied according to Muzushima and Kabayashi with slight modification [10, 11]

MATERIALS AND METHODS

General scheme



Chemicals and reagents

The chemicals and reagents **(Table 5.1)** used in the project work were of AR and LR grade, procured from s.d.fine Chem. Ltd., National Chemicals, E.Meark Chemicals, Ranbaxy fine chemicals, Finar reagents. The chemicals were used without further purification. The purity of the compounds was checked by TLC, was run on silica gel.

Synthesis of 3-methyl-1[(pyridine-4yl)carbonyl]-4,5-dihydro-1H-pyrazol-5-one(1)

A mixture of isoniazide 6.85 g (0.01 mol) and ethylacetoacetate 6.35 ml (0.01 mol) was taken in abs. ethanol (150 ml) and refluxed for 34 hrs. Excess of solvent was distilled off and the resultant residue was poured on crushed ice to obtained the yellow long needle shaped crystals of 3-methyl-1[(pyridine-4yl)carbonyl]-4,5-dihydro-1H-pyrazol-5-one.[12]

General Procedure for synthesis of 3-Methyl-1H Pyrazolone Derivative (2a-2e)

A mixture of 1.09 g (0.005 mole) of 3-methyl-1[(pyridine-4yl)carbonyl]-4,5-dihydro-1H-pyrazol-5-one, 5 ml of formaldehyde and 0.68 g (0.005 mole) of 5-aminotetrazole was refluxed with 25 ml of 95% ethanol for 2 hr. the resultant mixture was concentrated. The resultant solid mass dried and purified by recrystallization from ethanol. [13]

Table 1: Physical Parameters of synthesized Compounds

Sr.No	Product code	Molecular formula	Molecular weight(g/mol)	R_f value	% yield
1	2a	$C_{12}H_{12}N_8O_2$	300.11	0.62	70
2	2b	$C_{13}H_{13}N_7O_2$	299.29	0.60	72
3	2c	$C_{14}H_{15}N_5O_2S$	317.37	0.61	65
4	2d	$C_{18}H_{15}N_5O_2S$	365.41	0.69	70
5	2e	$C_{18}H_{14}ClN_5O_2S$	399.85	0.70	72

Table 2: Melting Point of Synthesized Compounds

Sr.No	Product code	IUPAC Name	Melting Point
1	2a	3-methyl-1-[(pyridine-4-yl) carbonyl]-4[(5H-1,2,3,4-tetrazol- 5- yl amino) methyl]-4,5-dihyro-1-H-pyrazol-5-one	250-252
2	2b	3-methyl-1-[(pyridine-4-yl)carbonyl]-4[(4H-1,2,4 triazol-4-yl amino)methyl]-4,5-dihyro-1-H-pyrazol-5-one	210-214
3	2c	4-[(4, 5-dihydro-1, 3-thiazol-2-yl amino) methyl]-3-methyl-1-[(pyridine -4-yl) carbonyl]-4, 5-dihydro-1H-pyrazol-5-one	236-238
4	2d	4-[(1, 3-benzothiazol-2yl amino) methyl]-3-methyl-1-[(pyridine-4-yl) carbonyl] -4, 5-dihydro-1H-pyrazol-5-one	246-248
5	2e	4-{[(6-chloro-1,3-benzothiazol-2-yl)amino]methyl}-3-methyl-1-[(pyridine-4-yl)carbonyl]-4,5-dihydro-1H-pyrazol-5-one	242-244

Anti-inflammatory activity

Method for studying anti-inflammatory activity [14, 15, 16]

The synthesized compounds were screened for anti-inflammatory activity by using inhibition of albumin denaturation technique which was studied according to Mizushima and Kobayashi with slight modification. The standard drug and test compounds were dissolved in minimum quantity of dimethyl formamide (DMF) and diluted with phosphate buffer (0.2 M, pH 7.4). Final concentration of DMF in all solution was less than 2.5%. Test solution (1ml) containing different concentrations of drug was mixed with 1 ml of 1mM albumin solution in phosphate buffer and incubated at 27°± 1° C in incubator for 15 min. pH of the reaction mixture was adjusted using small amount of 1N HCl. Denaturation was induced by keeping the reaction mixture at 60° ± 1° C in water bath for 10 min.

After cooling, the turbidity was measured at 660 nm (UV-Visible Spectrophotometer). Percentage of inhibition of denaturation was calculated from control where no drug was added. Each experiment was done in triplicate and average is taken. The Aspirin was used as standard drug.

The percentage inhibition of denaturation was calculated from control where no synthesized compounds were added and compared against standard (Aspirin). The percentage inhibition of denaturation was calculated by using following formula

% inhibition = $(Abs_{control} - Abs_{sample})$ X 100/ $Abs_{control}$

RESULTS AND DISCUSSION

IR Spectra

The IR spectra of compound **(2a, 2b, 2c, 2d)** shows peaks of Ar-H stretching in the range of 3150-3050 cm^{-1}, NH_2 stretching at 3500-3100 cm^{-1} and C=O stretching at 1725-1705 cm^{-1}, The IR spectra of compound **(2c)** shows peaks of Ar-Cl

stretching in the range of 785-540,The IR spectra of compound **(2d)** shows peaks of Ar-Br stretching at <667, The IR spectra of compound **(2d)**shows peaks of NO_2 stretching at 1350, The IR spectra of compound **(2b)** shows peaks of C-O stretching in the range of 1300-1000.

Mass Spectra

The mass spectra of compounds **(2a, 2b, 2c, 2d)** show molecular ion peaks (M+1) at 301.1(2a), 299.1(2b), 317.0(2c), 366.1(2d) with respect to their molecular weight.

^{1}H-NMR Spectra

The ^{1}H NMR spectra of compound **(2a)** shows singlet peak at 1.94, triplet peck at 2.7, one doublet peck at 2.6, double doublet peak at 3.0,7.8,8.89, The ^{1}H NMR spectra of compound **(2b)** shows singlet peak at 1.94, 8.29, triplet peck at 2.0, 2.7 and double doublet peck at 3.1, 7.8, 8.89 and The ^{1}H NMR spectra of compound **(2c)** shows singlet peak at 1.94, two triplet peck at 2.7, 4.0,two doublet peak at 8.01, 1.18 and double doublet peck at 3.5, 7.5, 7.8, 8.89.

Table 6.1 Anti-inflammatory activity

Sr.No.	Compounds	% Inhibition of Denaturation		
		Blank	Concentration	
			100 mic.gm/ml	200mic.gm/ml
1	2a	0	20.29±1.33	64.12±1.12
2	2b	0	20.60±0.68	62.65±2.15
3	2c	0	19.60±0.68	53.82±1.33
4	2d	0	22.12±1.10	69.15±0.64
5	2e	0	19.84±0.60	54.80±0.97
6	Aspirin	0	22.79±0.67	75.89±0.56

Among the compounds tested 2a, 2b, 2d, showed significant anti-inflammatory activity as compared to other drug. Aspirin used as a standard drug.

CONCLUSION

The main aim is to synthesis and evaluation of anti-inflammatory activity of some pyrazolone derivatives. We synthesized ten pyrazolone derivatives. All the derivatives are novel. The *in vitro* anti-inflammatory activity of all the pyrazolone derivatives were evaluated by inhibition of albumin Denaturation technique. Out of ten synthesized compounds, the 2a, 2b, 2d, showed anti-inflammatory activity better than rest of the other compounds by using Aspirin as a standard drug.

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