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Research Article

Novel Synthesis of Functionally Substituted Pyrazole and Biological Evaluation

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ABSTRACT

In the present work, a series of some new substituted 3, 5 dimethyl pyrazole **(4a-c)**, 3-methyl pyrazol-5-one derivatives **(5a-c),** 3-Methyl- 1-(substituted phenyl) pyrazol-5-ones **(7a-b)** and 2, 3-dimethyl-1- (substituted phenyl) pyrazol-5-one **(8a-b)** has been synthesized. All the synthesized compounds were characterized by physical, chemical, analytical and spectral data. The newly synthesized compounds were screened for anti-inflammatory activity. The biological in vivo evaluation of these compounds in experimental models (carrageenan-induced oedema) proved the presence of anti-inflammatory activity.

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INTRODUCTION

Among the wide variety of heterocycles that have been explored for developing pharmaceutically important molecules. The pyrazole nucleus has found considerable attention due to outstanding biological activities as antipyretic, analgesic [1], anti-inflammatory [2], antianxiety [3,4] as well as its good antibacterial and antifungal properties [5-7]. Encouraged by these observations, we have synthesized some new pyrazole derivatives in the hope of obtaining potential anti-inflammatory agents and analgesic agents.

Substituted 1-Benzoyl-3, 5-dimethyl pyrazole **(4)** was synthesized by treatment of substituted phenyl carbamide**(3)** and acetyl acetone and substituted 1-Benzoyl-3-methyl pyrazol-5-one**(5)** was synthesized by the condensation of substituted phenyl carbamide**(3)** and ethylacetoacetate. **(Scheme-1)**

2, 3-dimethyl-1- (substituted phenyl) pyrazol-5-one **(8)** was synthesized by the reaction of 3-methyl-(1-substituted phenyl) - pyrazol-5-one **(7)** with dimethyl sulphate **(Scheme-2)**

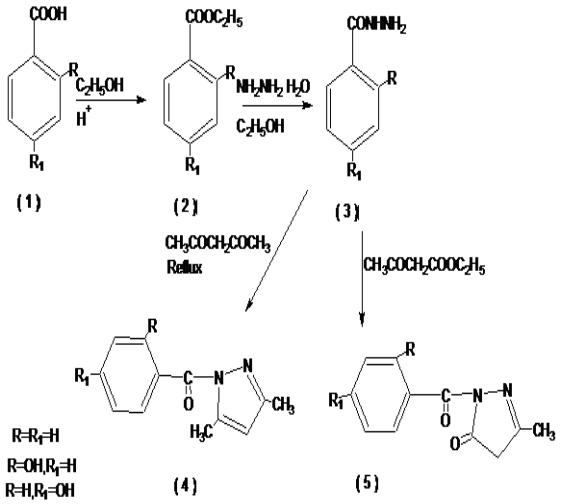
Anti-inflammatory activity

The anti-inflammatory activity of newly synthesised ten compounds in pyrazole (4a-c, 5a-c, 7a-b and 8a-b) series were carried out by the method of Winter et al[8] carrageenan induced rat paw edema method in Wistar albino rats. The anti-inflammatory activity of the newly synthesized compounds was compared, using indomethacin as standard drug. The synthesized compounds were suspended in 2% Tween 80. Percentage reduction in paw edema at 4 hr in comparison to the control is given in **Table-1**.

EXPERIMENTAL

The melting points were determined in open capillary tubes and are uncorrected. The purity of the compounds was checked by thin layer chromatography on silica gel G coated plates using iodines as the visualizing agent. IR spectra were scanned on Shimadzu IR spectrophotometer using KBr disc and expressed in cm^{-1}. ^1H NMR spectra were recorded in DMSO on BRUKER (300MHz) spectrometer using TMS as an internal standard (chemical shifts in δ, ppm).

The elemental analysis for C, H, and N were in a agreement with the calculated values (C±0.4, H, N)



Scheme: 1

(1) Synthesis of Substituted 1-Benzoyl-3, 5-dimethyl pyrazole (4a-c):

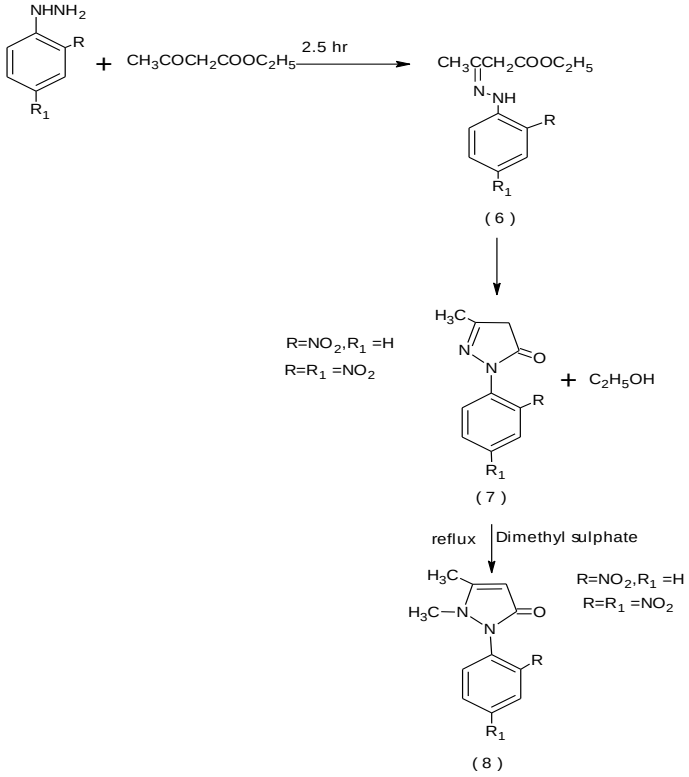
A mixture of substituted phenyl carbamide (1.3g, 10.0 mmol) and acetyl acetone (1g, 10.0 mmol) was refluxed in methanol (25 ml), containing concentrated hydrochloric acid (1 ml) for 12 hours on a water bath. The resulting solution was then concentrated and cooled at room temperature. The solid thus separated was washed with methanol and recrystallized with ethanol.

1-Benzoyl-3, 5-dimethyl pyrazole (4a)

Yield-54.9 %, m.p. 176-178°C, IR (KBr) ν cm^{-1} : 3116.75 (aromatic C-H stretching), 2941.24 (asymmetric (CH_3) (C-H stretching), 2883.38 (symmetric (CH_3) (C-H) stretching, 1670.24 (C=O stretching), 1598.86 (C=N stretching), 1446.51 (C=C stretching) and 842.83 (C-N stretching)

^{1}H-NMR ($CDCl_3$): δ ppm 2.42 (s, 6H, CH_3), 6.15 (s, 1H CH-pyrazole), 7.44-7.48 (m, 2H, $H_{3,5}$ 1-benzoyl), 7.57 (m, 1H, H_4 1-benzoyl), 8.02-8.04 (d, 2H, $H_{2,6}$ 1-benzoyl).

Calcd for $C_{12}H_{12}N_2O$: C, 72.0; H, 6.0; N, 14.0. Found: C, 69.97; H, 5.98; N, 13.97.



Scheme: 2

1-(2-Hydroxy benzoyl)-3, 5-dimethyl pyrazole (4b)

Yield-54 %, m.p. 188-190°C. IR (KBr) ν cm^{-1} : 3595 (O-H stretching), 3392 (aromaticC-H stretching), 2941.24 (asymmetric (CH_3) (C-H stretching), 2885.31(symmetric (CH_3)(C-H) stretching, 1718.46 (CO-N-CO), 1683.74 (C=O stretching), 1598.88 (C=N stretching), 1446.51, 1469.66, 1494.73, 1521.73 (C=C ring stretching) and 1232, 1188.07 (C-O stretching)

^{1}H-NMR ($CDCl_3$): δ ppm 2.49 (s, 6H, CH_3), 6.08 (s, 1H CH- pyrazole), 6.87-6.96 (m, 2H, $H_{4,5}$ 2-hydroxy benzoyl), 7.41-7.43 (d, 1H, H_6 2-hydroxy benzoyl), 10.93 (s, 1H, OH).

Calcd for $C_{11}H_{10}N_2O_3$: C, 66.67; H, 5.56; N, 12.96. Found: C, 66.64; H, 5.54; N, 12.97.

1-(4-Hydroxy benzoyl)-3, 5-dimethyl pyrazole (4c)

Yield-60.8 %, m.p. 182-184°C, IR (KBr) ν cm^{-1} : 3609 (O-H stretching), 3304.43,3040 (aromatic C-H stretching), 2960 (asymmetric (CH_3) (C-H stretching), 1679.64 (C=O stretching), 1587 (C=N stretching),1431 (C=C stretching) and 1190 (C-O stretching)

Table: 1: Characterization data and anti inflammatory activity of synthesized compounds

Comp.	R	R_1	R_f value	Anti-inflammatory (%inhibition±SEM)
Control				-
Indomethacine				61.50±1.19*
4a	H	H	0.90	-
4b	OH	H	0.86	49.06±1.08*
4c	H	OH	0.67	56.51±1.14*
5a	H	H	0.56	-
5b	OH	H	0.78	31.25±1.10
5c	H	OH	0.89	53.12±1.44*
7a	NO_2	H	0.67	74.21±1.32
7b	H	NO_2	0.76	76.25±2.98*
8a	NO_2	H	0.81	44.37±1.51*
8b	H	NO_2	0.89	17.80±1.00

Anti-inflammatory activity of the test compounds was compared w.r.t control

*P< 0.01; Data were analyzed by *Dunnett's test* for n=6

^{1}H-NMR ($CDCl_3$): δ ppm 2.17 (s, 3H, CH_3), 2.49 (s, 3H, CH_3), 6.06 (s, 1H CH- pyrazole), 6.84-6.88(d, 2H, $H_{2,6}$ 1-benzoyl), 7.86-7.89 (d, 2H, $H_{3,5}$ 1-benzoyl), 9.63 (s, 1H, CHO).

Calcd for $C_{12}H_{12}N_2O_2$: C, 66.67; H, 5.56; N, 13.0. Found: C, 66.64; H, 5.54; N, 12.97.

(1) Synthesis of Substituted 1-Benzoyl-3-methyl pyrazol-5-one (5a-c)

A mixture of substituted phenyl carbamide (1.3 g, 10.0 mmol) and ethyl acetoacetate (0.13 g, 10.0 mmol) was refluxed in methanol (25 ml), containing 1.0 ml of concentrated hydrochloric acid for 10 hours on a water bath. The resulting solution was then concentrated and cooled at room temperature. The solid thus separated was washed with methanol, dried and recrystallized with acetone.

1-Benzoyl-3-methyl pyrazol-5-one (5a)

Yield-51.0 %, m.p. 128-130°C, IR (KBr) ν cm^{-1} : 3033 (aromatic C-H stretching), 2941 (asymmetric (CH_3) (C-H stretching), 2883 (symmetric (CH_3) (C-H) stretching, 1670 (C=O stretching), 1598 (C=N stretching), 1431 (C=C stretching) and 842 (C-N stretching)

^{1}H-NMR (DMSO): δ ppm 2.57 (s, 3H, CH_3), 5.26 (s, 2H CH_2-pyrazole), 6.84-6.87 (m, 3H, $H_{3,4,5}$ 1-benzoyl), 7.85-7.88 (d, 2H, $H_{2,6}$ 1-benzoyl)

Calcd for $C_{11}H_{10}N_2O_2$: C, 65.34; H, 4.95; N, 13.86. Found: C, 65.30; H, 4.92; N, 13.84.

1-(2-Hydroxy benzoyl)-3-methyl pyrazol-5-one (5b)

Yield-52.1 %, m.p. 128-130°C, IR (KBr) ν cm^{-1} : 3608, (O-H stretching), 3024 (aromatic C-H stretching), 2933 (asymmetric (CH_3) (C-H stretching), 1608(C=O stretching), 1550, 1488 (C=N stretching), 1436, 1448, 1458 (C=C ring stretching) and 1240 (C-O stretching)

^{1}H-NMR (DMSO): δ ppm 2.49 (s, 3H, CH_3), 5.47 (s, 2H CH_2-pyrazole), 6.87-6.96 (m, 2H, $H_{4,5}$ 2-hydroxybenzoyl), 7.41-7.43 (d, 1H, H_6 2-hydroxy benzoyl), 7.98-8.00 (d, 1H, H_3 2-hydroxy benzoyl), 10.34 (s,1H,OH)

Calcd for $C_{11}H_{10}N_2O_3$: C, 60.56; H, 4.59; N, 12.84. Found: C, 60.52; H, 4.56; N, 12.80.

1-(4-Hydroxy benzoyl)-3-methyl pyrazol-5-one (5c)

Yield-51.0 %, m.p. 128-130°C. IR (KBr) ν cm^{-1} : 3610 (O-H stretching), 3053.11 (aromatic C-H stretching), 3006.82 (C-H stretching of CH_3), 1718.46 (CO-N-CO), 1668.31(C=O stretching), 1631.67 (C=N stretching), 1579.59, 1535.23, 1487.01, 1434.94 (C=C stretching), 1238.21 (C-O stretching) and 869.84 (C-N stretching).

^{1}H-NMR (DMSO): δ ppm 2.57 (s, 3H, CH_3), 5.47 (s, 2H CH_2-pyrazole), 7.43-7.47 (d, 2H, $H_{2,6}$ 1-benzoyl), 7.96-8.01 (d, 2H, $H_{3,5}$ 1-benzoyl), 10.34 (s ,1H, OH)

Calcd for $C_{11}H_{10}N_2O_3$: C, 60.56; H, 4.59; N, 12.84. Found: C, 60.59;

H, 4.58; N, 12.81

(3) 3-Methyl- 1-(substituted phenyl) pyrazol-5-ones (7a-b)

Ethyl acetoacetate (3.10 g, 6.52 mmol) and 1.0 g (6.52 mmol) of substituted phenyl hydrazine were mixed together in a evaporating dish. The mixture was heated on a boiling water bath in a fume cupboard for 2.5 hours and stirred

from time to time with a glass rod. The heavy reddish syrup was allowed to cool, 10.0 ml of ether was added and the mixture was stirred vigorously. The syrup, which was insoluble in ether, was solidified with in 15 minutes. The solid was filtered at pump and washed thoroughly with ether to remove coloured impurities. Recrystallised from equal volume of ethanol and water.

3-Methyl- 1-(4-nitro phenyl) pyrazol-5-ones (7a)

Yield-52.63 %, m.p. 82-84°C. IR (KBr) ν cm^{-1} : 3516 (N-H stretching), 3316.(aromatic C-H stretching), 2977 (C-H stretching of CH_3), 1713 (C=O stretching), 1596(C=C stretching), 1495 (asymmetric ($ArNO_2$) $(N=O)_2$ stretching), 1394 (symmetric ($ArNO_2$) $(N=O)_2$ stretching) and 838 (C-N stretching)

^{1}H-NMR ($CDCl_3$): δ ppm 3.10 (s, 3H, CH_3), 5.28 (s, 1H, CH), 7.04-7.07 (d, 2H, $H_{2,6}$ 1-nitrophenyl), 8.12-8.14 (d, 2H, $H_{3,5}$ 1-nitrophenyl), 10.29(s, broad, 1H, NH)

Calcd for $C_{10}H_9N_3O_3$: C, 54.79; H, 4.10; N, 19.17. Found: C, 54.75; H, 4.07; N, 19.14.

3-Methyl- 1-(2, 4-dinitro phenyl) - pyrazol-5-one (7b)

Yield-42.12 %, m.p. 66-68°C. IR (KBr) ν cm^{-1} : 3309 (N-H stretching), 3100(C-H stretching), 2977 (C-H stretching of CH_3), 1725 (C=O stretching),1698, 1594(C=C stretching), 1512 (asymmetric ($ArNO_2$) $(N=O)_2$ stretching), 1423 (symmetric ($ArNO_2$) $(N=O)_2$ stretching) and 833 (C-N stretching)

^{1}H-NMR ($CDCl_3$): δ ppm 1.29 (s, 3H, CH_3), 5.26 (s, 1H, CH), 8.12-8.14 (d, 2H, $H_{5,6}$ 2,4-dinitrophenyl), 8.52 (s, 1H, H_3, 2,4-dinitrophenyl), 10.29 (s,broad,1H, NH)

Calcd for $C_{10}H_8N_4O_5$: C, 45.45; H, 3.03; N, 21.21. Found: C, 45.42; H, 3.06; N, 21.18.

(4) 2, 3-Dimethyl- 1-substituted phenyl - pyrazol-5-one (8a-b)

In a 50 ml (three necked) flask, equipped with a dropping funnel, a sealed stirrer unit and double surface condenser was set up in a fume cupboard. A solution of 0.5 g of sodium hydroxide in small volume of water was placed in solution of 1.40 g (5.73 mmol) of 3-methyl-1-substituted phenyl- pyrazol-5-one(7) in 1.0 ml of methanol. The mixture was warmed on a water bath and 0.72 g (0.54 ml, 5.73 mmol) of dimethyl sulphate was added. The mixture was refluxed for 1 hour and allowed to cool, with continuous stirring. Methanol was distilled off, hot water was added to the residue, filtered from impurities, 2, 3-dimethyl-1-substituted phenyl-pyrazol-5-one was extracted with benzene and solvent was evaporated. The crude product was recrystallised from benzene.

2, 3-Dimethyl- 1-(4-nitro phenyl) - pyrazol-5-one (8a)

Yield-59.73 %, m.p. 224-226°C, IR (KBr) ν cm^{-1} : 3467(C-H stretching), 2977(C-H stretching of CH_3), 1636 (C=O stretch)ing),1498 (C=C stretching), 1447 (asymmetric ($ArNO_2$) $(N=O)_2$ stretching), 1322(symmetric ($ArNO_2$) $(N=O)_2$ stretching) and 849 (C-N stretching)

^{1}H-NMR (DMSO): δ ppm 1.27 (s, 3H, CH_3), 2.01 (s, 3H, CH_3), 3.39 (s, 1H, CH), 7.04-7.07(d, 2H, $H_{2,6}$ 1-nitrophenyl), 8.12-8.14 (d, 2H, $H_{3,5}$ 1-nitrophenyl)

Calcd for $C_{11}H_{11}N_3O_3$: C, 56.65; H, 4.72; N, 18.03. Found: C, 56.63; H, 4.70; N, 18.06.

2, 3-Dimethyl- 1-(2, 4-dinitro phenyl) - pyrazol-5-one (8b)

Yield-40 %, m.p. 240-242°C, IR (KBr) ν $cm^{-1:}$ 3100(C-H stretching), 2977 (C-H stretching of CH_3), 1725 (C=O stretching), 1594(C=C stretching), 1512 (asymmetric ($ArNO_2$) $(N=O)_2$ stretching), 1423 (symmetric ($ArNO_2$) $(N=O)_2$ stretching) and 833 (C-N stretching)

^{1}H-NMR (DMSO): δ ppm 1.31(s, 3H, CH_3), 2.57(s, 3H, CH_3), 5.26(s, 1H, CH), 8.12-8.14(d, 2H, $H_{5,6}$ 2,4-dinitrophenyl), 8.52(s, 1H, H_3 2,4-dinitrophenyl)

Calcd for $C_{10}H_8N_4O_5$: C, 47.48; H, 3.60;N, 20.14 . Found: C, 47.45; H, 3.62; N, 20.11.

STATISTICAL ANALYSIS

Data were analyzed by one–way ANOVA followed by Dunnett's t-test using computerized Graph Pad Instat version 3.05 (Graph Pad software, U.S.A.).

RESULTS

Biological results are reported in Table 1 which also records the effects of the standard drug included for comparison, Series of compound are prepared in this study exhibited significant pharmacological properties in different biological models. The general pattern of pharmacological activity encountered in this synthesized compounds was seen mainly in their effect on pain perception and local inflamation. Considerable variation of these effects were seen with each structural change, varying from agents that had less activity to those with high potency, and significant changes in potency resulted even from minor change in chemical structure as shown in Table 1.

DISCUSSION

The purpose of the present study was to examine whether molecular modification might result in detection of new potential anti-inflammatory drugs. A series of compounds were prepared and assayed in a variety of biological test for anti-inflammatory. The data reported in Table 1 shows that effect of variation in chemical structure on activity was rather unpredictable. Seldom did a particular structural modification lead to uniform alteration in activity in all tests. However some point of interest did emerge and a few generalizations can be made. The substitution which appeared to be most important for high order of activity in the greatest number of test was the p-nitro group. The introduction of Para nitro and p-hydroxy group in the moiety of the pyrazole, analogs 7a and 7b produce compounds with potent anti-inflamatory.

CONCLUSION

A new series of some new substituted 3, 5 dimethyl pyrazole **(4a-c)**, 3-methyl pyrazol-5-one derivatives **(5a-c),** 3-Methyl- 1-(substituted phenyl) pyrazol-5-ones **(7a-b)** and 2, 3-dimethyl-1- (substituted phenyl) pyrazol-5-one **(8a-b)** has been synthesized and characterized through elemental and spectral analysis. A number of agents caused marked reduction of the carrageenan induced edema of the rat foot, however, with exception of compounds 7a (R = p-Nitro). In this test also only analogs with a p-nitro phenyl group in R_1 (7b) showed equal to that exhibited by the standard paracetamol .Compounds 7a, 7b in addition to being the most potent agents of this series against rat-foot inflammation.

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