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Microwave assisted Synthesis and Evaluation of Novel 3-methyl-1,4-dihydropyrazol-5-one derivatives as Anti-inflammatory agents.

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ABSTRACT

*Derivatives of 3-methyl-1,4-dihydropyrazol-5-one**(1a)**, 3-methyl-1-phenyl-1,4-dihydropyrazol-5-one**(1b)** and 3-methyl-1-(2,4 dinitrophenyl)-1,4-dihydropyrazol-5-one**(1c)** were synthesized by condensation reactions from Ethylacetoacetate with different Hydrazides then these were subjected to Mannich reaction with organic acids in presence of Formaldehyde to produce different derivatives of Pyrazolone. Novel nine compounds were characterized by IR, ^{1}H NMR ^{13}C-NMR, MS and CHN analysis. Evaluation of Anti-inflammatory activity was carried out on all synthesized the compounds. Out of A1-A3, B1-B3 and C1-C3 compound A1, B2 and C1 found to have potent Anti-inflammatory activity compare to standard Diclofenac Sodium.*

Key words: Microwave, 3-methyl-1,4-dihydropyrazol-5-one derivatives, Anti-inflammatory agents

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INTRODUCTION

1,4-dihydropyrazol-5-one is a five membered Lactam ring with two nitrogen atoms with ketone group. It is known from many decades and the investigations in this field have intensified due to its applications in most diverse areas like dyestuff, synthesis of drugs & polymer as it gives out new nitrogen compounds and supplement to other ring systems.[1]

The use of microwave energy to active organic reactions has taken a new dimension. In the last few years, Microwave-Induced Organic Enhancement(MORE) chemistry has gained popularity as a non-conventional technique for rapid organic synthesis and a large number of reactions has have been tried by researchers proving the synthetic utility of MORE chemistry in organic synthesis. It is called as a Eco-chemistry, because it is easy and eco-friendly.[2-4] Some biologically active Azetidinones have been synthesized by Microwave oven method and screened for antimicrobial activity.[5] Under the work of "Green Chemistry" we have designed and synthesized the Novel 3-methyl-1,4-dihydropyrazol-5-one derivatives as Anti-inflammatory agents.

Anti-inflammatory activity[6]

Acute anti-inflammatory method: Carrageenan induced rat hind paw edema. Oedema was produced using type IV lambada Carrageenan from sigma laboratories. Foot volumes were measured in a plethysmograph by water displacement. The instrument was calibrated before performing the experiment using standard calibrated probe number and standard drug Diclofenac Sodium.

MATERIALS AND METHODS

Melting points were determined in open capillary method and are uncorrected. Purity of the compound was checked on Silica gel TLC plates. IR spectra were recorded on Bruker Alpha FT-IR spectrophotometer using Nujol/KBr disc method. ^{1}H NMR spectra were recorded on Bruker AMX-400, with $CDCl_3$ as solvent and TMS as internal standard. Mass spectra were obtained on a Kratas MS-25. Combustion analyses were found to be within the limits of permissible errors.

General procedure for the Preparation of 3-methyl-1,4-dihydro-pyrazol-5-ones, (1a-1c)[7]

Ethylacetoacetate(3.84mmol, 0.49ml) was taken in a around bottomed flask and hydrazine hydrate(3.84mmol, 0.38gm) and its derivatives were added to the flask dropwise with constant stirring at room temperature in Microwave Oven whereupon a vigorous reaction set in. A precipitate was formed quickly. As the reaction was exothermic, the reaction mixture was allowed to cool at room temperature. The resulting precipitate was collected by filtration. The crude product (1.5 g) was purified by recrystalization by ethanol. The products were identified by spectroscopic techniques.

Table 1: Some Physical data of synthesized compounds

Compound	Melting point ^{0}C	% yield	Rf value (PE:EA-1:2)	Color
1 a	223	80	0.32	White
1 b	187	78	0.52	Pale Yellow
1 c	81	88	0.74	Yellow
A 1	131	76	0.41	White
A 2	85	72	0.29	Pale Yellow
A 3	134	75	0.35	Yellow
B 1	120	86	0.65	Light Yellow
B 2	145	84	0.62	Yellow
B 3	131	78	0.52	Yellow
C 1	162	85	0.68	Dark Yellow
C 2	155	80	0.45	Dark Yellow
C 3	168	83	0.53	Dark Yellow

Table No: 2: Anti-inflammatory activity of Synthesized compound

Comp	Mean paw oedema volume ± SE					% inhibition at 4th hr
	0 hour	1 hour	2 hour	3 hour	4 hour	
Ctrl.	0.975±0.025	1.475±0.025	1.650±0.028	1.775±0.025	1.842±0.012	
Std.	**0.975±0.025**	**1.225±0.025****	**1.325±0.025****	**1.350±0.028****	**1.275±0.025****	**44.47**
A_1	**1.000±0.021**	**1.350±0.028**	**1.425±0.045****	**1.500±0.040****	**1.425±0.047****	**40.26**
A_2	0.975±0.025	1.400±0.041	1.490±0.025*	1.420±0.025**	1.364±0.028**	35.04
A_3	0.975±0.025	1.350±0.028	1.500±0.040*	1.600±0.0**	1.370±0.025*	34.45
B_1	0.978±0.025	1.400±0.041	1.480±0.025*	1.410±0.025**	1.354±0.028**	34.04
B_2	**1.060±0.025**	**1.375±0.025**	**1.435±0.028****	**1.440±0.025****	**1.320±0.040****	**39.54**
B_3	1.020±0.021	1.350±0.028	1.425±0.045**	1.500±0.040**	1.450±0.047**	38.26
C_1	**1.020±0.021**	**1.380±0.028**	**1.450±0.045****	**1.550±0.040****	**1.525±0.047****	**40.36**
C_2	1.000±0.021	1.350±0.028	1.425±0.045**	1.500±0.040**	1.425±0.047**	40.26
C_3	0.975±0.025	1.370±0.028	1.500±0.040*	1.600±0.0**	1.370±0.025*	34.45

*One way ANOYA followed by Dunnett's 't' test **P<0.01*

Compounds A_2, A_4, B_1, B_2, and B_4 have shown significant anti-inflammatory activity. Diclofenac sodium was used as a standard drug.

RESULTS AND DISCUSSION

The nine new derivatives of Pyrazolone were synthesized. The synthesized compounds were subjected to anti-inflammatory activities. Compound with 50 mcg/ml & 100mcg/ml concentration were subjected to screening. The compounds **A1, B2** and **C1** have shown promising anti-inflammatory activity. The compounds were incorporated with p-amino salicylic acid p-amino benzoic acid and Cinnamic acid hence enhanced anti-inflammatory activity was found in these compounds. With still further molecular modification & manupulation these compounds are expected to be promising therapeutic agents in future.

Table 3:The resulting spectroscopic data for synthesized compounds:

Compound-1a: IR (Nujol): 3480 (νN-H); 2980, 2880 (νC-H aliphatic); 2700 (νO-H enolic); 1680 (νC=O lactam); 1615 (νC=N); 1580 (νC=C aromatic); 1515 (δN- -1 1H) cm ; H-NMR (DMSO-d6): δ 5.2 (s, 1H, =CH); 2.1 (s, 3H, CH3); 10.0 (s, 1H, NH); 10.5 (s, 1H, OH); 13C-NMR (DMSO-d): δ 11.4 (CH), 89.23 (C-4);63 139.82 (C-3); 161.42 (=C-OH); MS: m/z (% of rel.intensities): 98 (M+, 100), 97(17), 81(1.0), 73(1.0), 67(18).
Compound-1b: IR (Nujol): 2980, 2880 (νC-H aliphatic); 2700 (νO-H enolic); 1697.7 (νC=O lactam); 1489.2, 1541.3 (νC=N); 1616.5, 1558.8 (νC=C aromatic); 1311.5 (νC-N); 773.5 (δC-H) cm-1; 1H-NMR (CDCl3): δ 11.45 (br, s, 1H, OH); 5.36 (s, 1H, =CH); 2.1 (s, 3H,CH3); 7.43 (dd, 2H, Jm=1.1Hz, Jo=8.0Hz); 7.71 (dd, 2H, Jo=7.4Hz, Jm= 1.1Hz); 7.52 (dd, 1H, Jm=2.0Hz,Jo=7.2Hz); 13C-NMR (CDCl3): δ 14.60 (CH3), 178.3(=C-OH); 45.10 (CH2); 132.1 (N=C); 147.0 (aromaticC-1); 132.01 (aromatic C-2/6); 142.30 (aromatic C-3/5); 130 (aromatic C-4).
Compound-1c: IR (KBr): 3116 (νC-H aromatic); 2925 (νC-H saturated); 1728 (νC=O lactam); 1620 (νC=N); 1597, 1473 ((νC=C aromatic); 1410, 1518 ((νN=O nitro group); 1340 (νC-N); 1026 (νC-O); 1455, 1378 (δC-H);1357 (νN-N) cm-1; 1H-NMR (DMSO-d6): δ10.85 (br, s, 1H, OH); 3.61 (s, 2H, CH2); 2.19 (s, 3H, CH3); 8.92 (d, H, Jm=3.2Hz); 8.43 (dd, 1H, Jo=5.3Hz, Jm=2.5Hz);7.86 (dd, 1H, Jo=7.6Hz); 13C-NMR (CDCl3): δ 16.525 (CH3), 169.45 (=C-OH); 61.03 (CH2); 153.54 (N=C);116.30 (aromatic C-6); 123.31 (aromatic C-1); 129.81 (aromatic C-2); 130.54 (aromatic C-4); 137.52 (aromatic C-5); 144.88 (aromatic C-3). MS: m/z (% of rel. intensities): 264 (M+), 137 (18%), 219 (28%), 173 (6%), 145 (8%), 131 (6%), 104 (14%), 77 (32%),51 (8%); Elemental analysis: Clalc. for [C10H8N4O5]: C (46.48%), H (4.276%), N (18.43%). Found: C(46.41%), H (4.241%), N (18.36%).
Compound-A1: IR (Nujol): 3353 (νN-H); 2880 (νC-Haliphatic); 1723 (νC=O lactam); 1620 (νC=N); 1300 (νC- -1 1N); 1515 (δN-H); 1357 (νN-N) cm ; H-NMR (DMSO-d6): δ 12.0 (s, 1H, NH); 2.1 (s, 3H, CH3); 13C-NMR (DMSO-d): δ 11.4 (CH), 89.23 (C-4);63 139.82 (C-3); 161.42 (=C-OH); MS: m/z (% of rel.intensities): 98 (M+, 100), 97(17), 81(1.0), 73(1.0), 67(18). MS: m/z (% of rel. intensities): 254, 256, 258 (M, M+2, M+4,10:20:10); 177/175 (100); 98 (3.0); 94 (2.0).
Compound-A2: IR (Nujol): 3353 (νN-H); 2880 (νC-Haliphatic); 1723 (νC=O lactam); 1620 (νC=N); 1300 (νC- -1 1N); 1515 (δN-H); 1357 (νN-N) cm ; H-NMR (DMSO-d6): δ 12.0 (s, 1H, NH); 2.1 (s, 3H, CH3); 13C-NMR (CDCl3): δ 14.60 (CH3), 178.3(=C-OH); 45.10 (CH2); 132.1 (N=C); 147.0 (aromaticC-1); 132.01 (aromatic C-2/6); 142.30 (aromatic C-3/5); 130 (aromatic C-4). MS: m/z (% of rel. intensities): 254, 256, 258 (M, M+2, M+4,10:20:10); 178/179 (100); 98 (3.0); 94 (2.0).
Compound-A3: IR (Nujol): 3353 (νN-H); 2880 (νC-Haliphatic); 1723 (νC=O lactam); 1620 (νC=N); 1300 (νC- -1 1N); 1515 (δN-H); 1357 (νN-N) cm ; H-NMR (DMSO-d6): δ 12.0 (s, 1H, NH); 2.1 (s, 3H, CH3); 13C-NMR (CDCl3): δ 16.525 (CH3), 169.45 (=C-OH); 61.03 (CH2); 153.54 (N=C);116.30 (aromatic C-6); 123.31 (aromatic C-1); 129.81 (aromatic C-2); 130.54 (aromatic C-4); 137.52 (aromatic C-5); 144.88 (aromatic C-3). MS: m/z (% of rel. intensities): 254, 256, 258 (M, M+2, M+4,10:20:10); 197/195 (100); 98 (3.0); 94 (2.0).
Compound-B1: IR (Nujol): 3094 (νC-H aromatic); 2916 (νC-H aliphatic); 1738 (νC=O lactam); 1574 (νC=N); 1616.5, 1558.8 (νC=C aromatic); 1279 (νC-N);773.5 (δC-H p-substituted benzene ring); 650 (νC-Br); cm-1; 1H-NMR (DMSO-d6): δ 2.3 (s, 3H, CH3); 8.15(d, 1H, Jm=2.26Hz); 7.77 (dd, 1H, Jo=8.54Hz,Jm=2.26Hz); 7.52 (d, 1H, Jo=8.54Hz). MS: m/z (% of rel. intensities): 486, 488, 490, 492, 494 (M+, M+2,M+4, M+6, M+8, 1:4:6:4:1); 408, 410, 412, 414 (M+-Br, 1:3:3:1); 488(100%); 329(20%); 289(5%);263(50%); 235(65%); 182(5%); 154(18%); 117(5%);75(20%).
Compound-B2: IR (KBr): 3118 (νC-H aromatic); 2927 (νC-H saturated); 1714 (νC=O lactam); 1612 (νC=N);1593, 1498 ((νC=C aromatic); 1427, 1548 ((νN=O nitro group); 1338 (νC-N); 1026 (νC-O); 1455, 1315 (δC-H);1357 (νN-N); 1H-NMR (CDCl3): δ1.55 (s, 3H, CH3); 8.71 (d, H, Jm=2.5Hz); 8.30 (dd,1H, Jo=8.7Hz, Jm=2.5Hz); 8.01 (d, 1H, Jo=8.07Hz);13C-NMR(CDCl): δ 14.28 (CH), 190.20 (C=O); 187.11 (N=C); 120.97 (aromatic C-6);121.02 (aromatic C-1); 128.08 (aromatic C-2); 136.56 (aromatic C-4); 147.31 (aromatic C-5); 150.08 (aromatic C-3). MS: m/z (% of rel. intensities): 420,422, 424 (M+, M+2, M+4, 1:2:1); 281,283 (1:1, 1.5%); 246, 248 (1:1, 100%); 167 (3.99%), 156 (53.8%), 154 (23.7%), 75 (93.41%); Elemental analysis: C (28346%), H (1.43%), N (13.28%).Found: C (28.45%), H (1.46%), N (13.26%).
Compound-B3: IR (KBr): 3118 (νC-H aromatic); 2927,νC-H saturated); 1714 (νC=O lactam); 1612 (νC=N);1593, 1498 ((νC=C aromatic); 1427, 1548 ((νN=O nitro group); 1338 (νC-N); 1026 (νC-O); 1455, 1315 (δC-H);1357 (νN-N); 742 (νC-Br); cm-1; 1H-NMR (CDCl3): δ1.55 (s, 3H, CH3); 8.71 (d, H, Jm=2.5Hz); 8.30 (dd,1H, Jo=8.7Hz, Jm=2.5Hz); 8.01 (d, 1H, Jo=8.07Hz);13C-NMR (CDCl): δ 14.28 (CH), 190.20 (C=O);33 187.11 (N=C); 120.97 (aromatic C-6);121.02 (aromatic C-1); 128.08 (aromatic C-2); 136.56 (aromatic C-4); 147.31 (aromatic C-5); 150.08 (aromatic C-3). MS: m/z (% of rel. intensities): 420, 422, 424 (M+, M+2, M+4, 1:2:1); 281,283 (1:1, 1.5%); 246, 248 (1:1, 100%); 167 (3.99%), 156 (53.8%), 154(23.7%), 75 (93.41%); Elemental analysis: C (28346%), H (1.43%), N (13.28%).Found: C (28.45%), H (1.46%), N (13.26%).
Compound-C1: IR (KBr): 3118 (νC-H aromatic); 1593, 1498 ((νC=C aromatic); 1427, 1548 ((νN=O nitrogroup); 1338 (νC-N); 742 (νC-Br); cm-1; 1H-NMR(CDCl3): δ 8.84 (d, H, Jm=2.39Hz); 8.38 (dd, 1H,Jo=8.7Hz, Jm=2.39Hz); 8.21 (d, 1H, Jo=8.79Hz).13C-NMR (CDCl3): δ 16.525 (CH3), 169.45 (=C-OH); 61.03 (CH2); 153.54 (N=C);116.30 (aromatic C-6); 123.31 (aromatic C-1); 129.81 (aromatic C-2); 130.54 (aromatic C-4); 137.52 (aromatic C-5); 144.88 (aromatic C-3) MS: m/z (% of rel. intensities): 246/248 (M+/ M+2,11%/10%); 216/218 (5%); 200/202 (3.60%, 3.27%);170/172 (4.64%, 3.80%); 167 (3.02%); 154/156(6.2%, 7.32%); 134 (100%); 120(2.95%); 91(6.76%); 90(3.29%); 75 (15.02%); 74 (3.84%).
Compound-C2: IR (KBr): 3030 (νC-H aromatic); 2926 (νC-H saturated); 1684 (νC=O lactam); 1620 (νC=N);1549, 1498 ((νC=C aromatic); 1376, 1538 ((νN=O nitro group); 1318 (νC-N); 1445, 1315 (δC-H); 744 (νC-Br);cm-1; 1H-NMR (CDCl3): δ 2.44 (s, 2H, CH2); 8.84 (d,1H, Jm=2.79Hz); 8.379 (dd, 1H, Jo=8.79Hz, Jm=2.79Hz); 8.20 (d, 1H, Jo=8.79Hz). 13C-NMR (CDCl3): δ 16.525 (CH3), 169.45 (=C-OH); 61.03 (CH2); 153.54 (N=C);116.30 (aromatic C-6); 123.31 (aromatic C-1); 129.81 (aromatic C-2); 130.54 (aromatic C-4); 137.52 (aromatic C-5); 144.88 (aromatic C-3). MS: m/z (% of rel. intensities): 498/500/502/504(M+, M+2, M+4, M+6, 29.24%); 458/460/462/464(59.76%); 418/420/422(8.92%); 338/340(8.53%); 292/298/296/298 (100%); 277/279 (64.88%); 264/266/268/270(11.81%); 251/253/255 (30.84%); 184/186/188 (12.63%); 183 (52.0%); 105 (17.23%); 93 (17.07%).
Compound-C3: IR (Nujol): 2960, 2873 (νC-H aliphatic); 1708.5 (νC=O ketone); 1756.02 (νC=O ester); 1455, 1358 (δC-H); 1015 (νC-O); 742 (νC-Br); cm-1; 1H-NMR (CDCl3): δ 2.85 (s, 3H); 1.36 (t, 3H, J=6.89Hz);4.82 (q, 2H, J=6.82Hz). 13C-NMR (CDCl3): δ 16.525 (CH3), 169.45 (=C-OH); 61.03 (CH2); 153.54 (N=C); 116.30 (aromatic C-6); 123.31 (aromatic C-1); 129.81 (aromatic C-2); 130.54 (aromatic C-4); 137.52 (aromatic C-5); 144.88 (aromatic C-3). MS:m/z(%ofrel.intensities): 498/500/502/504(M+, M+2M+4, M+6, 29.24%); 458/460/462/464(59.76%); 418/420/422(8.92%); 338/340(8.53%); 292/298/296/298(100%); 277/279(64.88%); 264/266/268/270 (11.81%); 251/253/255(30.84%); 184/186/188 (12.63%); 183 (52.0%); 105 (17.23%); 93 (17.07%).

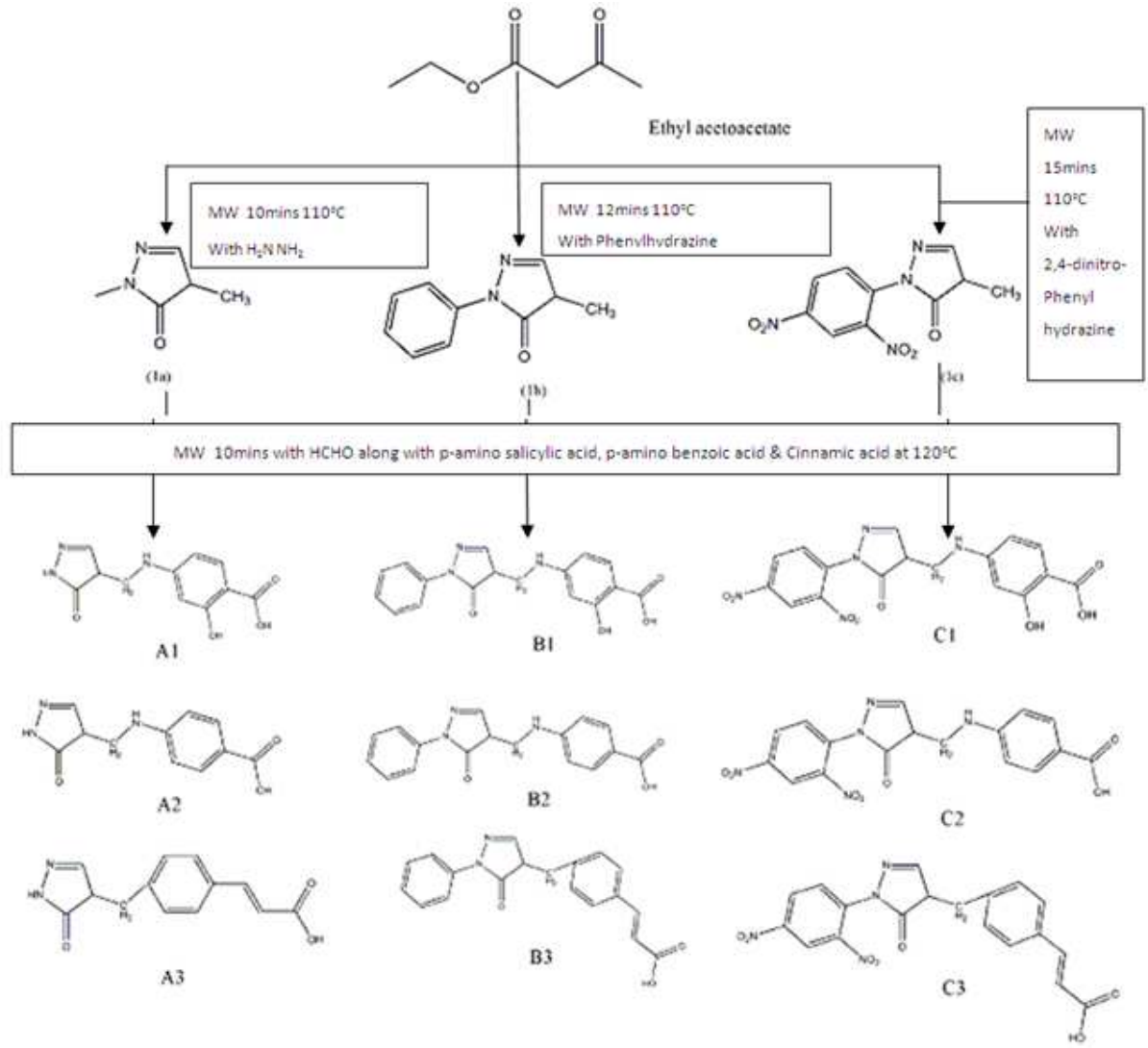

Fig.1 Scheme of synthesis of derivatives

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