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# Synthesis and Biological Evaluation of Novel Series of 1-(4, 5-Dihydropyrazolyl) - Indoles

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**ABSTRACT**

*Non steroidal anti-inflammatory agents continue to be one of the most widely used groups of therapeutic agents. They are used for the treatment of inflammation including pain releasing, antipyretic and rheumatoid arthritis. However, almost all the NSAIDs under clinical usage are highly acidic in nature and suffer from a common drawback of gastrointestinal toxicity.The paper reports the synthesis and pharmacological screening of various derivatives of 1-(4, 5-dihydropyrazolyl)-indoles viz 1-(1-phenyl-5-substitutedphenyl-4,5-dihydro-1H-pyrazol-3-yl)-2-substitutedphenyl-1H-indole (4a-4l). These compounds (4a-4l) were synthesized by cyclization of chalcones of indole viz (E)-3-substitutedphenyl-1-(2-substitutedphenyl-1H-indol-1-yl) prop-2-en-1-one with phenyl hydrazine in presence of base NaOH. The structures of these synthesized compounds were supported by FT IR, $^1$H NMR and elemental analysis. These compounds were tested in vivo for their analgesic, anti-inflammatory and ulcerogenic activities. All these compounds tested (4a-4l) showed good analgesic and anti-inflammatory activities. Six compounds (4c, 4g, 4i, 4j, 4k, 4l) out of twelve compounds showed anti-inflammatory and analgesic activity comparable to the standard drug indomethacin with very less ulcerogenic action. The compounds 2-(4-chlorophenyl)-1-(5-(4-methoxyphenyl)-1-phenyl-4,5-dihydro-1H-pyrazol-3-yl)-1H-indole (4g) and 4-(3-(2-(4-methoxyphenyl)-1H-indol-1-yl)-1-phenyl-4,5-dihydro-1H-pyrazol-5-yl)-N,N-dimethylaniline (4l) showed good anti inflammatory as well as analgesic activity with less ulcerations. Pyrazolines having methoxy and dimethylamino group substituted at para position of phenyl ring at position-5 found to be more active than others, indicating that the presence of these functional groups may be helpful in more efficient binding with the receptors. The presence of methoxy group at para position of 2-phenyl ring on indole nucleus seems to be important for good anti inflammatory action.*

**Keywords**: Anti-inflammatory activity, Analgesic activity, Indole derivatives, Pyrazoline, Ulcerogenic action

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## INTRODUCTION

Inflammation is the result of concerted participation of a large number of vasoactive, chemotactic and proliferative factors at different stages of infections. The NSAIDs are popular in reducing the acute and chronic inflammation as they have no abuse liability [1, 2]. Present NSAIDs have common side effects like gastric and peptic ulceration, acute renal failure, hypersensitivity reaction when administered in large dose or in long term therapy [3,4,5,6]. The search for newer non-steroidal anti-inflammatory agents is the only way to fortify against these adverse effects. The discovery of Indomethacin as a successful agent for clinical treatment of inflammatory disorders has led to the exploration of indole moiety to obtain better anti-inflammatory agents. Various indole derivatives have been reported to possess promising biological activities including analgesic, antipyretic[7], antifungal[8], anti-

inflammatory[9,10,11], anthelmintic[12], cardiovascular[13], anticonvulsant [14,15] antimicrobial [16,17] and selective COX-2 inhibitory activities[18,19,20,21]. The efficient synthesis of novel substituted indole derivative compounds still represents the highly pursued target. The substitution of heterocyclic moiety at the 1- position of indole ring markedly influences its anti inflammatory activity[22].

The area of design and synthesis of novel NSAIDs is being explored for drugs with better efficacy and safety profile. Diarylheterocycle class of compounds has been investigated extensively as COX-2 inhibitors. In contrast, relatively few reports document structural modifications of the existing NSAIDs into better drugs. Thus we decide to explore indole nucleus of indomethacin (NSAID) for structural modifications in order to produce potential anti inflammatory agents[23].

Pyrazoline derivatives have also been reported to possess potent analgesic and anti inflammatory activity [24,25,26]. This prompted us to synthesize hybrid analogues of two pharmacophores viz. indole and pyrazoline in the hope to achieve safer and better NSAIDs having combined biological activities as anti-inflammatory and analgesic activity with the lower incidences of GI side effects. In the present research work, various derivatives of 1-(4, 5-dihydropyrazolyl) indoles are successfully synthesized and screened for their analgesic, anti-inflammatory and ulcerogenic activities.

## MATERIALS AND METHODS

### Animals

The anti-inflammatory and ulcerogenic activity of newly synthesized compounds (4a-4l) was carried out on Wistar rats (150-200 g) and analgesic activity was carried on albino mice (25-30 g) of either sex. These animals were reared with robust health by providing pellet diet and water *ad libitum* in the animal house under standard environmental conditions of temperature, relative humidity and dark/light cycle. After randomization into various groups and before initiation of experiment, the rats were acclimatized for one week. The animal experiments were previously approved by Institutional Animal Ethical Committee (IAEC) and followed CPCSEA requirements.

### Materials

All the reagents and solvents used in synthesis were of laboratory grade. All the solvents were dried and distilled before use. Animals were procured from institute animal house. The melting points were determined in open capillary on Veego (model:-VMP-D) electronic apparatus and are uncorrected. The IR spectra of synthesized compounds were recorded on Shimadzu 8400-S FT-IR Spectrophotometer using potassium bromide. The $^1$H NMR were recorded in $CDCl_3$ or DMSO-$d_6$ using NMR Varian-Mercury 300 MHz spectrometer and chemical shifts are reported as parts per million (ppm) using tetramethylsilane (TMS) as an internal standard. To monitor the reactions and to establish the identity and purity of reactants and products, thin layer chromatography (TLC) was performed on microscopic glass slides (2 x 7.5 cm) coated with silica gel-G (Merck), using benzene-methanol and chloroform-methanol as the solvent systems and the spots were visualized by exposure to iodine vapour or spraying dilute sulfuric acid.

***Synthesis of 2-(4-substitutedphenyl) indole (1a-1c)***

Synthesis of 2-(4-substitutedphenyl) indole (1a-1c) was carried out by reported procedure of Fischer Indole synthesis [27].

***Synthesis of 1-(2-(4-substitutedphenyl)-1H-indol-1-yl) ethanone (2a-2c)***

Synthesis of 1-(2-(4-substitutedphenyl)-1H-indol-1-yl) ethanone (2a-2c) was carried out by acetylation reaction.

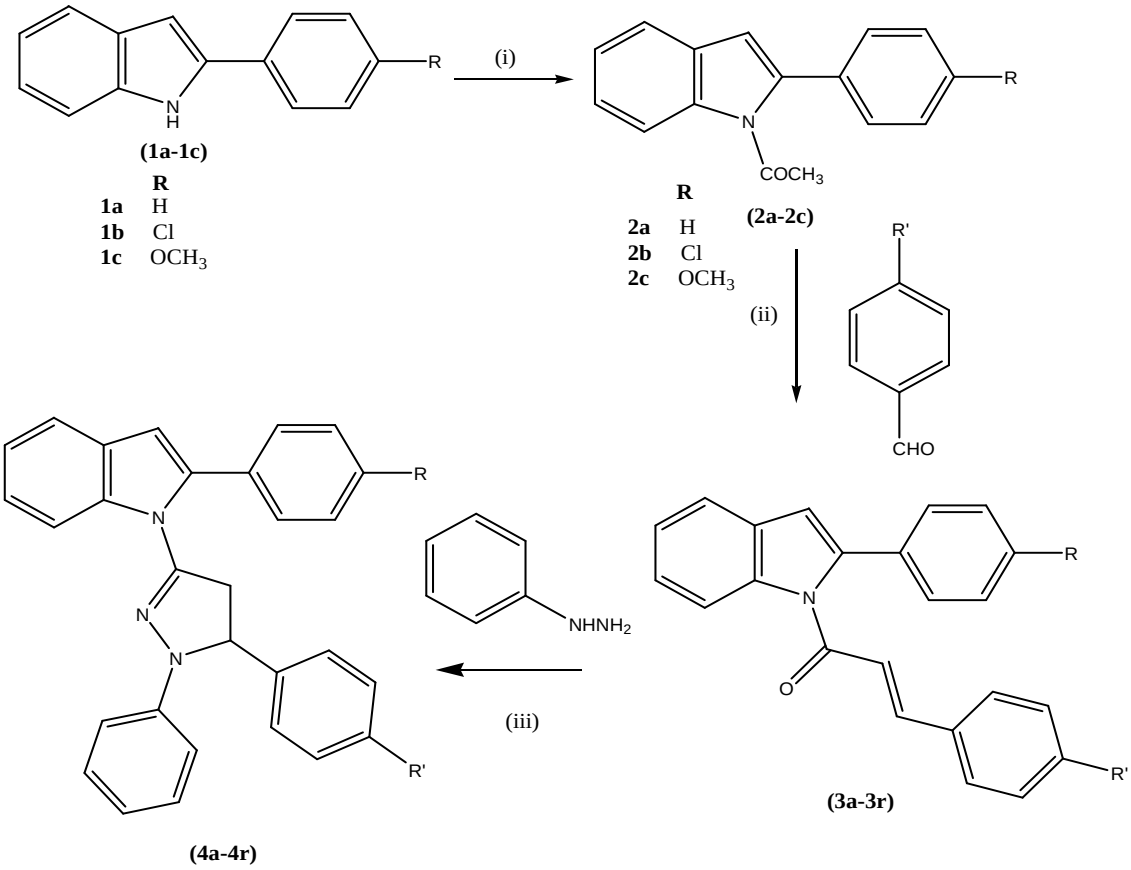
***Synthesis of (E)-3-substitutedphenyl-1-(2-substitutedphenyl-1H-indol-1-yl) prop-2-en-1-one (3a-3l)***

0.01mole of 1-(2-(4-substitutedphenyl)-1H-indol-1-yl) ethanone, 0.015 mole of 4-substituted aldehydes and 0.015 mole of piperidine were mixed into 20 mL ethylene glycol. The solution was refluxed at 160-180$^0$C for 4-5 h. The solution was cooled; solid was filtered and washed with ethanol. The spectral analysis of the synthesized compounds is as follows:

*(3a) (E)-3-Phenyl-1-(2-phenyl-1H-indol-1-yl) prop-2-en-1-one*

IR (cm$^{-1}$ , KBr): 3086 (Ar-C-H str), 2986, 1712(-C=O str), 1654 (Aliph-C=C str),1565,1435, 741; $^1$H NMR (DMSO-$d_6$): δ 6.26 (d, J=7Hz, 1H,=CH-Ar), 7.11-8.14 (m, 15H, Ar), 8.02 (d, J=7Hz, 1H-COCH=)

**Figure 1: Scheme of Synthesis**




| Code | R | R' | Code | R | R' |
|---|---|---|---|---|---|
| **4a** | H | H | | | |
| **4b** | H | Cl | **4j** | $OCH_3$ | Cl |
| **4c** | H | $OCH_3$ | **4k** | $OCH_3$ | $OCH_3$ |
| **4d** | H | $N(CH_3)_2$ | **4l** | $OCH_3$ | $N(CH_3)_2$ |
| **4e** | Cl | H | | | |
| **4f** | Cl | Cl | | | |
| **4g** | Cl | $OCH_3$ | | | |
| **4h** | Cl | $N(CH_3)_2$ | | | |
| **4i** | $OCH_3$ | H | | | |

Scheme: Reagent and condition: (i) acetic anhydride, anhydrous sodium acetate; (ii) absolute ethanol, NaOH, reflux; (iii) ethanol, reflux

*(3b) (E)-3-(4-Chlorophenyl)-1-(2-phenyl-1H-indol-1-yl)prop-2-en-1-one*
IR ($cm^{-1}$ , KBr): 3011 (Ar C-H str), 2879,1723 (-C=O str), 1658 (Aliph-C=C str),1534,1420, 736; $^1$H NMR (DMSO-$d_6$): δ 6.14 (d, J=6 Hz, 1H =CH-Ar), 7.15-8.20 (m, 14H, aromatic), 8.01 (d, J=10Hz, 1H-COCH=)

*(3c) (E)-3-(4-Methoxyphenyl)-1-(2-phenyl-1H-indol-1-yl)prop-2-en-1-one*
IR ($cm^{-1}$ , KBr): 3014 (Ar C-H str), 2955, 1728 (-C=O str), 1662 (Aliph-C=C str),1549,1421,1243,773; $^1$H NMR (DMSO-$d_6$): δ 3.65 (s, 3H, -$OCH_3$), 6.16 (d, J=11 Hz, 1H =CH-Ar), 7.10-7.97 (m, 14H, aromatic), 8.02 (d, J=10 Hz, 1H-COCH=)

*(3d) (E)-3-(4-(Dimethylamino)phenyl)-1-(2-phenyl-1H-indol-1-yl)prop-2-en-1-one*
IR ($cm^{-1}$ , KBr): 3011 (Ar C-H str), 2951, 1726 (-C=O str), 1651 (Aliph-C=C str),1552,1438,1332, 786; $^1$H NMR (DMSO-$d_6$): δ 3.01 (s, 6H, $-CH_3$), 6.29 (d, J=12 Hz, 1H =CH-Ar), 7.01-7.98 (m, 14H, aromatic), 8.01 (d, J=9 Hz, 1H-COCH=)

*(3e) (E)-1-(2-(4-Chlorophenyl)-1H-indol-1-yl)-3-phenylprop-2-en-1-one*
IR ($cm^{-1}$ , KBr): 3018 (Ar C-H str), 2861, 1742 (-C=O str), 1659 (Aliph-C=C str),1522,1441, 743; $^1$H NMR (DMSO-$d_6$): δ 6.48 (d, J=10 Hz, 1H,=CH-Ar), 7.10-8.11 (m, 14H, Ar), 8.12 (d, J=9 Hz, 1H-COCH=)

*(3f) (E)-3-(4-Chlorophenyl)-1-(2-(4-chlorophenyl)-1H-indol-1-yl)prop-2-en-1-one*
IR ($cm^{-1}$ , KBr): 3020 (Ar C-H str), 2863, 1724 (-C=O str), 1652 (Aliph-C=C str),1550,1445, 761; $^1$H NMR (DMSO-$d_6$): δ 6.32 (d, J=8 Hz, 1H =CH-Ar), 7.06-8.12 (m, 13H, aromatic), 8.04 (d, J=10 Hz, 1H-COCH=)

*(3g) (E)-1-(2-(4-Chlorophenyl)-1H-indol-1-yl)-3-(4-methoxyphenyl)prop-2-en-1-one*
IR ($cm^{-1}$ , KBr): 3026 (Ar C-H str), 2902, 1725 (-C=O str), 1665 (Aliph-C=C str),1548,1426, 1251,788; $^1$H NMR (DMSO-$d_6$): δ 3.65 (s, 3H, $-OCH_3$),6.31 (d, J=10 Hz, 1H =CH-Ar), 7.06-7.98 (m, 13H, aromatic), 8.09 (d, J=13 Hz, 1H-COCH=)

*(3h) (E)-1-(2-(4-Chlorophenyl)-1H-indol-1-yl)-3-(4-(dimethylamino)phenyl)prop-2-en-1-one*
IR ($cm^{-1}$ , KBr): 3015 (Ar C-H str), 2961, 1743(-C=O str), 1649 (Aliph-C=C str), 1431,1359, 781; $^1$H NMR (DMSO-$d_6$): δ 3.04 (s, 6H, $-CH_3$), 6.30 (d, J=11 Hz, 1H =CH-Ar), 7.01-7.98 (m, 13H, aromatic), 8.06 (d, J=9 Hz, 1H-COCH=)

*(3i) (E)-1-(2-(4-Methoxyphenyl)-1H-indol-1-yl)-3-phenylprop-2-en-1-one*
IR ($cm^{-1}$ , KBr): 3012 (Ar C-H str), 2952, 1723(-C=O str), 1646 (Aliph-C=C str),1562,1438, 1248, 768; $^1$H NMR (DMSO-$d_6$): δ 3.52 (s, 3H, $-OCH_3$), 6.35 (d, J=9 Hz, 1H =CH-Ar), 7.02-8.16 (m, 14H, aromatic), 8.03 (d, J=8 Hz, 1H-COCH=)

*(3j) (E)-3-(4-Chlorophenyl)-1-(2-(4-methoxyphenyl)-1H-indol-1-yl)prop-2-en-1-one*
IR ($cm^{-1}$ , KBr): 3014 (Ar C-H str), 2840, 1732(-C=O str), 1659 (Aliph-C=C str),1538,1426, 1244, 756; $^1$H NMR (DMSO-$d_6$): δ 3.55 (s, 3H, $-OCH_3$), 6.28 (d, J=10 Hz, 1H =CH-Ar), 7.11-8.21 (m, 13H, aromatic), 8.10 (d, J=7 Hz, 1H-COCH=)

*(3k) (E)-3-(4-Methoxyphenyl)-1-(2-(4-methoxyphenyl)-1H-indol-1-yl)prop-2-en-1-one*
IR ($cm^{-1}$ , KBr): 3022 (Ar C-H str), 2950, 1722(-C=O str), 1649 (Aliph-C=C str),1542,1433, 1247, 756; $^1$H NMR (DMSO-$d_6$): δ 3.68 (s, 6H, $-OCH_3$), 6.22 (d, J=11 Hz, 1H =CH-Ar), 7.03-8.19 (m, 13H, aromatic), 8.01 (d, J=9 Hz, 1H-COCH=)

*(3l) (E)-3-(4-(Dimethylamino) phenyl)-1-(2-(4-methoxyphenyl)-1H-indol-1-yl) prop-2-en-1-one*
IR ($cm^{-1}$ , KBr): 3025 (Ar C-H str), 2941, 1734 (-C=O str), 1662 (Aliph-C=C str),1557,1428, 1249, 782; $^1$H NMR (DMSO-$d_6$): δ 3.60 (s, 3H, $-OCH_3$), 6.32 (d, J=10 Hz, 1H =CH-Ar), 6.98-7.97 (m, 13H, aromatic), 8.03 (d, J=8 Hz, 1H-COCH=)

***Synthesis of 2-(4-substitutedphenyl)-3-(5-(4-substitutedphenyl)-1-phenyl-4, 5-dihydro-1H-pyrazol-3-yl)-1H-indole (4a-4l)***
A mixture of 0.01 moles of chalcones (3a-3l), 0.02 moles of phenyl hydrazine and 2-3 drops of glacial acetic acid in absolute alcohol (50 mL) was refluxed for 6-7 h. The reaction mixture was concentrated in vacuuo and the solid obtained was filtered and recrystallized from ethanol. The spectral analysis of the synthesized compounds is as follows:

***(4a)*** *1-(1, 5-Diphenyl-4, 5-dihydro-1H-pyrazol-3-yl)-2-phenyl-1H-indole*
IR ($cm^{-1}$ , KBr): 3045 (Ar C-H str ), 2987 (Ali C-H str), 1618(C=C str), 1588(C=N str), 1470,1351 (Ar C-N str), 1062 (-C-O str), 746 ; $^1$H NMR (DMSO-$d_6$): δ 4.082 - 4.120 (dd, J=5, 4.2 Hz, 1H, $CH_2$ pyraz), 4.390 - 4.418 (dd, J=8, 4 Hz 1H, CH pyraz) 4.602- 4.640 (dd, J=2, 8.2 Hz 1H, $CH_2$ pyraz),6.588 - 8.166 (m, 20H, ar); Elemental (CHN) Analysis: Anal. Calcd for $C_{29}H_{23}N_3$ C, 84.23; H, 5.61; N, 10.16 Found: C, 84.27; H, 5.60; N, 10.13

***(4b)*** *1-(5-(4-Chlorophenyl)-1-phenyl-4,5-dihydro-1H-pyrazol-3-yl)-2-phenyl-1H-indole*
IR ($cm^{-1}$ , KBr): 3037 (Ar C-H str ), 2980 (Ali C-H str), 1599 (C=C str), 1570 (C=N str), 1475 , 1354 ( Ar C-N str), 1071 (-C-O str), 748 , 712 (C-Cl str); $^1$H NMR (DMSO-$d_6$ δ 4.084 - 4.122 (dd, J= 5,7.1Hz, 1H, $CH_2$ pyraz), 4.390 - 4.418 (dd,J= 3.2,6 Hz, 1H, CH pyraz) 4.602 - 4.640 (dd,J= 6.4, 3 Hz, 1H, $CH_2$ pyraz),6.590 - 8.170 (m, 19H, ar); Elemental Analysis: Anal. Calcd for $C_{29}H_{22}ClN_3$ C, 77.76; H, 4.95; N, 9.38 Found: C, 77.77; H, 4.92; N, 9.39

***(4c)*** *1-(5-(4-Methoxyphenyl)-1-phenyl-4,5-dihydro-1H-pyrazol-3-yl)-2-phenyl-1H-indole*
IR ($cm^{-1}$ , KBr): 3048,(Ar C-H str ), 2995(Ali C-H str),1610(C=C str),, 1572(C=N str),1468 1340( Ar C-N str), 1074(-C-O str), 765; $^1$H NMR (DMSO-$d_6$): δ 3.84 (s, 3H, -$OCH_3$) , 4.086 - 4.124 (dd, J= 8, 2.3 Hz, 1H, $CH_2$ pyraz), 4.390 - 4.418 (dd,J= 4, 2.2 Hz, 1H, CH pyraz) 4.602- 4.640 (dd, J= 7, 6.3 Hz, 1H, $CH_2$ pyraz), 6.586 – 8.158 (m, 19H, ar); Elemental Analysis: Anal. Calcd for $C_{30}H_{25}N_3O$ C, 81.24; H, 5.68; N, 9.47 Found: C, 81.26; H, 5.67; N, 9.45

***(4d)*** *N,N-Dimethyl-4-(1-phenyl-3-(2-phenyl-1H-indol-1-yl)-4,5-dihydro-1H-pyrazol-5-yl)aniline*
IR ($cm^{-1}$ , KBr): 3038,(Ar C-H str ) ,2968 (Ali C-H str), 1625(C=C str), 1584(C=N str), 1459, 1344,( Ar C-N str), 1082(-C-O str), 742; $^1$H NMR (DMSO-$d_6$): δ 3.012 (s, 6H, -$CH_3$), 4.086 - 4.126 (dd, J= 4, 2.3 Hz, 1H, $CH_2$ pyraz), 4.390 -4.420 (dd, J= 6, 4.3 Hz,, 1H, CH pyraz) 4.606- 4.640 (dd, J= 6, 3.4 Hz, 1H, $CH_2$ pyraz), 6.594 -8.170 (m, 19H, ar); Elemental Analysis: Anal. Calcd for $C_{31}H_{28}N_4$ C, 81.55; H, 6.18; N, 12.27 Found: C, 81.56; H, 6.16; N, 12.28

***(4e)*** *2-(4-Chlorophenyl)-1-(1,5-diphenyl-4,5-dihydro-1H-pyrazol-3-yl)-1H-indole*
IR ($cm^{-1}$ , KBr): 3036 (Ar C-H str ), 2979 (Ali C-H str), 1585 (C=C str), 1573 (C=N str), 1465 , 1356 ( Ar C-N str), 1081 (-C-O str), 764 , 698 (C-Cl str); $^1$H NMR (DMSO-$d_6$): δ 4.085 - 4.122 (dd, J= 4, 5.4 Hz, 1H, $CH_2$ pyraz), 4.392- 4.418 (dd, J= 8, 3.6 Hz, 1H, CH pyraz) 4.604 -4.641 (dd, J= 6, 2.2 Hz, 1H, $CH_2$ pyraz), 6.590-8.162 (m, 19H, ar); Elemental Analysis: Anal. Calcd for $C_{29}H_{22}ClN_3$ C, 77.76; H, 4.95; N, 9.38 Found: C, 77.74; H, 4.96; N, 9.40

***(4f)*** *2-(4-Chlorophenyl)-1-(5-(4-chlorophenyl)-1-phenyl-4,5-dihydro-1H-pyrazol-3-yl)-1H-indole*
IR ($cm^{-1}$ , KBr): 3016 (Ar C-H str ), 2972 (Ali C-H str), 1592 (C=C str), 1555 (C=N str), 1472 , 1368 ( Ar C-N str), 1078 (-C-O str), 748 , 696 (C-Cl str); $^1$H NMR (DMSO-$d_6$): δ 4.088 - 4.120 (dd, J= 8, 6.2 Hz, 1H, $CH_2$ pyraz), 4.388 - 4.420 (dd, J= 5, 2.7 Hz, 1H, CH pyraz) 4.605 - 4.643 (dd, J= 6.6, 2 Hz, 1H, $CH_2$ pyraz), 6.592- 8.163 (m, 18H, ar); Elemental Analysis: Anal. Calcd for $C_{29}H_{21}Cl_2N_3$ C, 72.20; H, 4.39; N, 8.71 Found: C, 72.22; H, 4.41; N, 8.69

***(4g)*** *2-(4-Chlorophenyl)-1-(5-(4-methoxyphenyl)-1-phenyl-4,5-dihydro-1H-pyrazol-3-yl)-1H-indole*
IR ($cm^{-1}$ , KBr): 3027 (Ar C-H str ), 2985 (Ali C-H str), 1590 (C=C str), 1560 (C=N str), 1485 , 1352 ( Ar C-N str), 1070 (-C-O str), 745 , 687 (C-Cl str); $^1$H NMR (DMSO-$d_6$): δ 3.69 (s, 3H, -$OCH_3$) , 4.084 - 4.122 (dd J= 4, 7.2 Hz 1H, $CH_2$ pyraz), 4.390-4.418 (dd, J= 7, 2 Hz,1H, CH pyraz) 4.602- 4.640 (dd, J= 9.1, 4 Hz 1H, $CH_2$ pyraz), 6.584 - 8.165 (m, 19H, ar); Elemental Analysis: Anal. Calcd for $C_{30}H_{24}ClN_3O$ C, 75.38; H, 5.06; N, 8.79; Found: C, 75.41; H, 5.09; N, 8.76

***(4h)*** *4-(3-(2-(4-Chlorophenyl)-1H-indol-1-yl)-1-phenyl-4,5-dihydro-1H-pyrazol-5-yl)-N,N-dimethylaniline*
IR ($cm^{-1}$ , KBr): 3045,(Ar C-H str ),2982(Ali C-H str), 1608(C=C str), 1578(C=N str), 1470, 1347( Ar C-N str), 1082(-C-O str), 758, 704(C-Cl str); $^1$H NMR (DMSO-$d_6$): δ 3.010 (s, 6H, -$CH_3$), 4.086 - 4.121 (dd, J= 5, 1.2 Hz 1H, $CH_2$ pyraz), 4.390 - 4.416 (dd J= 4.5, 6 Hz, 1H, CH pyraz) 4.606- 4.640 (dd, J= 5, 1.2 Hz J=6, 9 Hz, 1H, $CH_2$ pyraz), 6.601 - 8.178 (m, 18H, ar); Elemental Analysis: Anal. Calcd for $C_{31}H_{27}ClN_4$ C, 75.83; H, 5.54; N, 11.41 Found : C, 75.85; H, 5.55; N, 11.44

***(4i)*** *1-(1,5-Diphenyl-4,5-dihydro-1H-pyrazol-3-yl)-2-(4-methoxyphenyl)-1H-indole*
IR ($cm^{-1}$ , KBr): 3050 (Ar C-H str ), 2990 (Ali C-H str), 1615(C=C str), 1595(C=N str), 1477, 1355( Ar C-N str), 1055(-C-O str) ,748; $^1$H NMR (DMSO-$d_6$): δ 3.82 (s, 3H, -$OCH_3$) , 4.084 - 4.122 (dd, J= 6.2,2 Hz, 1H, $CH_2$ pyraz), 4.390- 4.418 (dd, J= 6, 4.3 Hz, 1H, CH pyraz) 4.602 -4.640 (dd, J= 3, 2.6 Hz J=6, 9 Hz, 1H, $CH_2$ pyraz), 6.598 - 8.168 (m, 19H, ar); Elemental Analysis: Anal. Calcd for $C_{30}H_{25}N_3O$ C, 81.24; H, 5.68; N, 9.47 Found C, 81.26; H, 5.66; N, 9.51

***(4j)*** *1-(5-(4-Chlorophenyl)-1-phenyl-4,5-dihydro-1H-pyrazol-3-yl)-2-(4-methoxyphenyl)-1H-indole*
IR ($cm^{-1}$ , KBr): 3024 (Ar C-H str ), 2990 (Ali C-H str), 1595 (C=C str), 1574 (C=N str), 1481 , 1362 ( Ar C-N str), 1083 (-C-O str), 756 , 711 (C-Cl str); $^1$H NMR (DMSO-$d_6$): δ 3.84 (s, 3H, -$OCH_3$) , 4.084 - 4.124 (dd, J=4, 6.2 Hz 1H, $CH_2$ pyraz), 4.388 - 4.416 (dd, J= 8.4, 6 Hz 1H, CH pyraz) 4.602 - 4.640 (dd, J= 2, 6 Hz,1H, $CH_2$ pyraz), 6.596 - 8.170 (m, 18H, ar); Elemental Analysis: Anal. Calcd for $C_{30}H_{24}ClN_3O$ C, 75.38; H, 5.06; Cl, 7.42; N, 8.79; O, 3.35 Found: C, 75.39; H, 5.02; N, 8.80

***(4k)*** *2-(4-Methoxyphenyl)-1-(5-(4-methoxyphenyl)-1-phenyl-4,5-dihydro-1H-pyrazol-3-yl)-1H-indole*
IR ($cm^{-1}$ , KBr):, 3049 (Ar C-H str ),2985(Ali C-H str),1621(C=C str), 1592 (C=N str),1478 1350( Ar C-N str), 1054(-C-O str), 745; $^1$H NMR (DMSO-$d_6$): δ 3.69(s, 3H, -$OCH_3$), 3.82 (s, 3H, -$OCH_3$) , 4.084 - 4.122 (dd J= 7.4, 4 Hz 1H, $CH_2$ pyraz), 4.390 - 4.418 (dd, J= 6, 5.4 Hz 1H, CH pyraz) 4.602 - 4.640 (dd, J=6, 9 Hz, 1H, $CH_2$ pyraz), 6.602- 8.168 (m, 18H, ar); Elemental Analysis: Anal. Calcd for $C_{31}H_{27}N_3O_2$ C, 78.62; H, 5.75; N, 8.87; O, 6.76 Found: C, 78.61; H, 5.74; N, 8.89

***(4l)*** *4-(3-(2-(4-Methoxyphenyl)-1H-indol-1-yl)-1-phenyl-4,5-dihydro-1H-pyrazol-5-yl)-N,N-dimethylaniline*
IR ($cm^{-1}$ , KBr): 3030 (Ar C-H str ),2960 (Ali C-H str), 1615(C=C str), 1591(C=N str), 1465, 1348( Ar C-N str), 1062(-C-O str), 742; $^1$H NMR (DMSO-$d_6$)δ 3.015 (s, 6H, -$CH_3$), 3.82 (s, 3H, -$OCH_3$) , 4.084 - 4.122 (dd J= 4, 2.2 Hz 1H, $CH_2$ pyraz), 4.390 - 4.418 (dd, J= 3.4, 2 Hz 1H, CH pyraz) 4.602 - 4.640 (dd, J=5, 8.2 Hz, 1H, $CH_2$ pyraz), 6.598 - 8.168 (m, 18H, ar); Elemental Analysis: Anal. Calcd for $C_{32}H_{30}N_4O$ C, 78.98; H, 6.21; N, 11.51; O, 3.29 Found: C, 78.96; H, 6.23; N, 11.54

**Physical evaluation of the synthesized compounds**
Physical evaluation of the synthesized compounds viz. molecular weight, melting point, $R_f$ value, percentage yield were carried out. (**Table 1**)

**Table 1 Physical data of the newly synthesized 1-(4, 5-dihydropyrazolyl) indole derivatives (4a-4l)**

| Compd | R | R' | Molecular Formula | Molecular Weight | MP ($^0$C) | Rf values | Yield (%) |
|---|---|---|---|---|---|---|---|
| **4a** | -H | -H | $C_{29}H_{23}N_3$ | 413.51 | 172-174 | 0.61 | 64.33 |
| **4b** | -H | 4-Cl | $C_{29}H_{22}ClN_3$ | 447.96 | 184-187 | 0.69 | 64.23 |
| **4c** | -H | 4-$OCH_3$ | $C_{30}H_{25}N_3O$ | 443.54 | 178-182 | 0.65 | 63.73 |
| **4d** | -H | 4-N($CH_3$)$_2$ | $C_{31}H_{28}N_4$ | 456.58 | 189-192 | 0.72 | 69.19 |
| **4e** | -Cl | -H | $C_{29}H_{22}ClN_3$ | 447.96 | 170-172 | 0.74 | 63.94 |
| **4f** | -Cl | 4-Cl | $C_{29}H_{21}Cl_2N_3$ | 482.40 | 198-200 | 0.57 | 58.22 |
| **4g** | -Cl | 4-$OCH_3$ | $C_{30}H_{24}ClN_3O$ | 477.98 | 176-178 | 0.66 | 73.21 |
| **4h** | -Cl | 4-N($CH_3$)$_2$ | $C_{31}H_{27}ClN_4$ | 491.03 | 188-190 | 0.77 | 58.64 |
| **4i** | -$OCH_3$ | -H | $C_{30}H_{25}N_3O$ | 443.54 | 179-181 | 0.63 | 59.48 |
| **4j** | -$OCH_3$ | 4-Cl | $C_{30}H_{24}ClN_3$ | 477.98 | 166-168 | 0.61 | 50.51 |
| **4k** | -$OCH_3$ | 4-$OCH_3$ | $C_{31}H_{27}N_3O_2$ | 473.56 | 168-171 | 0.57 | 65.58 |
| **4l** | -$OCH_3$ | 4-N($CH_3$)$_2$ | $C_{32}H_{30}N_4O$ | 486.61 | 161-163 | 0.76 | 64.33 |

**Biological Activity [28]**
***Anti-inflammatory activity***
The anti-inflammatory activity was evaluated using carrageenan induced paw edema on Wistar rats by Winter *et al*.[29] method, using indomethacin as reference compound. Wistar rats were divided into groups of six animals each. Group 1 served as control group without using drug, group 2 received indomethacin 10 mg/kg and other groups received test drugs in dose equivalent to indomethacin. The drugs were prepared as homogenous suspensions in saline (0.9 % NaCl) and were administered orally to animals. One hour after administration of drugs, each rat received a sun planter injection of 0.1 ml of 1 % carrageenan solution in its left paw. The measurement of the hind paw volume was carried out using Plethysmometer before any treatment (Vo) and in any interval (Vt) after the administration of the drugs. All the results are expressed as mean ± SEM. Statistical evaluation was performed using analysis of variance followed by t-test for subgroup comparison. (**Table 2**)

**Table 2 Anti-inflammatory effects of the newly synthesized 1-(4, 5-dihydropyrazolyl) indole derivatives in carrageenan induced rat's edema**

| Compound | Dose | Percentage inhibition (mean± SEM) | |
|---|---|---|---|
| | | 2h | 3h |
| **4a** | 20 mg/kg | 51.92 ± 2.82 | 62.73 ± 3.12** |
| **4b** | 20 mg/kg | 53.97 ± 3.04 | 64.66 ± 2.44 * |
| **4c** | 20 mg/kg | 59.32 ± 1.68 | 71.36 ± 1.93** |
| **4d** | 20 mg/kg | 60.41± 2.16 | 68.33 ± 2.10** |
| **4e** | 20 mg/kg | 48.31 ± 1.67 | 55.94 ± 1.44* |
| **4f** | 20 mg/kg | 52.22 ± 2.49 | 64.69 ± 2.98** |
| **4g** | 20 mg/kg | 76.33 ± 1.64 | 86.33 ± 2.18** |
| **4h** | 20 mg/kg | 56.78 ± 1.28 | 66.31 ± 1.52** |
| **4i** | 20 mg/kg | 59.63 ± 1.71 | 74.14 ± 2.06** |
| **4j** | 20 mg/kg | 61.82 ± 2.24 | 70.34 ± 1.78** |
| **4k** | 20 mg/kg | 63.28 ± 1.60 | 74.28 ± 2.14** |
| **4l** | 20 mg/kg | 64.77 ± 1.05 | 75.18 ± 3.34** |
| **Control** | - | | |
| **Indomethacin** | 10 mg/kg | 83.12 ± 1.24 | 91.88 ± 1.36 |

*a) Data are analyzed by one way ANOVA followed by Dunnett's test.*
*b) ** Values are significant at P<0.01*
*c) * Values are less significant at P<0.01*

***Analgesic activity***

The anti-inflammatory activity was evaluated using acetic acid induced writhing in albino mice by Seigmund *et al*.[30] method. The 0.6 % v/v solution of acetic acid was used as writhing inducing agents. The test compounds were administered orally 1 h prior to acetic acid injection. Mice were divided into groups of six animals each. Group 1 served as control group without using drug, group 2 received indomethacin 10 mg/kg and other groups received test drugs in dose equivalent to the indomethacin. All the drugs were prepared as homogenous suspensions in saline (0.9 % NaCl) and were administered orally to animals. Acetic acid was administered intraperitonially. The number of writhings were counted for 20 min in control, standard and test compounds and compared. Analgesic activity was measured as percent decrease in writhings in comparison to control. All the results are expressed as mean ± SEM. Statistical evaluation was performed using analysis of variance followed by t-test for subgroup comparison. (**Table 3**)

**Table 3 Analgesic effects of newly synthesized 1-(4, 5-dihydropyrazolyl) indole derivatives in acetic acid induced writhing in rats**

| Compound | Dose | Analgesic activity | |
|---|---|---|---|
| | | Number of writhings (mean ± SEM) | % Protection |
| **4a** | 20 mg/kg | 18.26 ± 0.66 | 44.05* |
| **4b** | 20 mg/kg | 19.21 ± 0.37 | 41.14* |
| **4c** | 20 mg/kg | 14.50 ± 0.76 | 55.57** |
| **4d** | 20 mg/kg | 11.83± 0.61 | 63.75** |
| **4e** | 20 mg/kg | 15.33 ± 0.66 | 53.03* |
| **4f** | 20 mg/kg | 13.16 ± 0.47 | 59.69** |
| **4g** | 20 mg/kg | 7.16 ± 0.30 | 78.06** |
| **4h** | 20 mg/kg | 10.46 ± 0.43 | 67.95** |
| **4i** | 20 mg/kg | 10.17 ± 0.47 | 68.84** |
| **4j** | 20 mg/kg | 16.56 ± 0.42 | 49.26* |
| **4k** | 20 mg/kg | 12.83 ± 0.87 | 60.69** |
| **4l** | 20 mg/kg | 10.0 ± 0.85 | 69.36** |
| **Control** | - | 32.64 ± 0.58 | - |
| **Indomethacin** | 10 mg/kg | 6.880 ± 0.46 | 78.92 |

*a) Data are analyzed by one way ANOVA followed by Dunnett's test.*
*b) ** Values are significant at P<0.01*
*c) * Values are less significant at P<0.01*

***Acute ulcerogenesis***

The ulcerogenic activity was evaluated by Cioli *et al*.[31] method. The studies were carried out on healthy Wistar rats at a dose two times the anti inflammatory dose. The animals were divided into different groups of six each. Group 1 served as control and received vehicle only, group 2 received standard drug indomethacin 60 mg/kg and other groups were administered test compounds in dose molecularly equivalent to 60 mg/kg of indomethacin. The animals were fasted 6 hrs before giving a single dose of each of vehicle, standard and test compounds respectively

and sacrificed 14 h later when food and water was given. The gastric mucosa of the rats was examined by means of magnifier. For each stomach the severity of mucosal damage was assessed according to the following scoring system: 0 - no lesions of upto five punctiform lesions; 1 - more than five punctiform lesions; 2 - one to five small ulcers; 3 - more than five small ulcers of one large ulcer; 4 – more than one large ulcer. The mean score of each treated group minus the mean score of the control group was considered as the 'severity index' of gastric damage (level of significance p< 0.001). (**Table 4**)

**Table 4 Ulcerogenic activity1-(4, 5-dihydropyrazolyl) indole derivatives observed on gastric mucosa of rats**

| Compound | Dose | Ulcerogenic activity (S. I.) |
|---|---|---|
| **4a** | 60 mg/kg | 1.40 ± 0.26* |
| **4b** | 60 mg/kg | 1.63 ± 0.34* |
| **4c** | 60 mg/kg | 1.03 ± 0.26** |
| **4d** | 60 mg/kg | 1.12 ± 0.21** |
| **4e** | 60 mg/kg | 1.98 ± 0.33** |
| **4f** | 60 mg/kg | 1.89 ± 0.19** |
| **4g** | 60 mg/kg | 0.96 ± 0.30** |
| **4h** | 60 mg/kg | 1.01 ± 0.44** |
| **4i** | 60 mg/kg | 1.61 ± 0.28** |
| **4j** | 60 mg/kg | 1.54 ± 0.42* |
| **4k** | 60 mg/kg | 0.91 ± 0.40** |
| **4l** | 60 mg/kg | 1.02 ± 0.22** |
| **Control** | - | - |
| **Indomethacin** | 60 mg/kg | 2.16 ± 0.33** |

*a) Data are analyzed by one way ANOVA followed by Dunnett's test.*
*b) ** Values are significant at P<0.01*
*c) * Values are less significant at P<0.01*

## RESULTS AND DISCUSSION

The synthesis of the target compounds (4a-4l) is outlined in scheme 1. The required 2-phenyl indoles (1a-1c) were prepared by condensing phenyl hydrazine with substituted acetophenones in presence of polyphosphoric acid by following Fischer Indole method. The 1-acetylindoles (2a-2c) of the corresponding 2-phenyl indoles (1a-1c) were prepared by adding to it acetic anhydride and anhydrous sodium acetate and refluxing the mixture for 5 h. The 1-acetylindoles compounds (2a-2c) were further treated with different *para*substituted aldehydes to obtain chalcones (3a-3r) by following Claisen-Schimdt reaction. The treatment of chalcones with phenyl hydrazine in presence of strong base resulted in the cyclization of α, β-unsaturated ketone into the title compounds (4a-4l) in 50-73% yield. The purity of the compounds was checked by TLC in Benzene: methanol (8:2) or Chloroform: Methanol (7:3). The structures of the all the compounds were assigned on the basis of $^1$H NMR, IR spectral data and elemental analysis.

**Anti inflammatory activity**

The anti inflammatory activity of compounds was carried out at an equimolar oral dose relative to 10 mg/kg of indomethacin. The percent edema inhibition relative to control was measured after 2 h and 3 h of the treatment. The inhibition of swelling in carrageenan induced edema in rat paw brought about by oral administration of the drug is shown in table 2. The percentage of swelling by the drugs was calculated using eq. (1)

Inhibition % = {[ (Vt- Vo) control-(Vt-Vo) treated]/ (Vt- Vo) control}x100 ---------- (1)

(Vt and Vo relates to the average volume in the hind paw of the rats (n=6) before any treatment and after anti-inflammatory agent treatment, respectively).

All the synthesized compounds tested for anti-inflammatory activity showed inhibition of edema ranging from 55.94 to 86.33%. Compounds (4c, 4g, 4i, 4j, 4k, 4l) showed very good anti-inflammatory activity. 2-(4-chlorophenyl)-1-(5-(4-methoxyphenyl)-1-phenyl-4,5-dihydro-1H-pyrazol-3-yl)-1H-indole (4g) (86.33%) and 4-(3-(2-(4-methoxyphenyl)-1H-indol-1-yl)-1-phenyl-4,5-dihydro-1H-pyrazol-5-yl)-N,N-dimethylaniline (4l) (75.18%) were equipotent to indomethacin (91.88%) in inhibiting the paw edema in rats. Compounds 2-(4-methoxyphenyl)-1-(5-(4-methoxyphenyl)-1-phenyl-4,5-dihydro-1H-pyrazol-3-yl)-1H-indole (4k) 1-(1,5-diphenyl-4,5-dihydro-1H-pyrazol-3-yl)-2-(4-methoxyphenyl)-1H-indole (4j) showed anti-inflammatory activity 74.28 % and 74.14 % respectively compared to the standard drug. Compounds 4c, and 4g showed inhibition in edema equivalent to 70% of inhibition

by indomethacin. Pyrazolines having substituted phenyl ring at $5^{th}$ position were in general more active than unsubstituted ones, indicating that the presence of functional group may be helpful in orienting the molecule in active site. Pyrazolines having methoxy and dimethylamino group substituted at para position of phenyl ring at position-5 found to be more active than others, indicating that the presence of these functional groups may be helpful in more efficient binding with the receptors. The presence of methoxy group at para position of 2-phenyl ring on indole nucleus seems to be important for good anti inflammatory action. The statistical significance testing using one way analysis of variance showed that the anti inflammatory activity of indomethacin and all the newly synthesized compounds were effective in comparison with the control group ($p<0.01$).

**Analgesic activity**

Compounds (4a-4l) were further tested for analgesic activity at the same dose as used for anti-inflammatory activity. The percent protection in mice brought about by administration of the drugs is shown in Table 3. The compounds tested showed analgesic activity in the range of 41.14 to 78.06%. The percent protection was calculated using Eq (2).

Protection (%) = 100-[number of writhing in test/ number of writhing in control x 100] ----------(2)

Compounds 4g and 4l showed 78.06 and 69.36% of protection respectively against acetic acid induced writhing compared to 78.92 % protection with indomethacin. The analgesic effect was observed in the compounds in the similar way to anti-inflammatory effects. The compounds with 4-methoxyphenyl and 4-dimethylaminophenyl ring at $5^{th}$ position of pyrazoline ring were in good in analgesic effect compared to other substitutions.

**Acute ulcerogenesis**

The compounds were screened further for their gastric irritation activity. The ulcerogenic effect of indomethacin and newly synthesized compounds were studied at 60 mg/kg in rats. It was observed that the ulcerogenic effect of the test compounds (4a-4l) was appreciably less than indomethacin. Less number of ulcers was observed in animals treated with test compounds compared with the animals treated with indomethacin. The tested compounds showed severity index ranging from 0.91 to 1.98 whereas the standard drug indomethacin showed high severity index of 2.16 (table 4 ). The compounds 4c,4g, 4h, 4k and 4l showed severity index of 1.03, 0.96, 1.01, 0.91 and 1.02 respectively which is less than that of indomethacin. These findings suggest that the newly synthesized compounds will produce less gastric irritation and may be considered as safer drugs for treating inflammatory conditions.

All the above observations indicate that the compounds having indole nucleus with substituted phenyl ring at 2-position and substituted pyrazoline ring at 1-position are safer analgesic and anti-inflammatory agents which is supported by their less ulcerogenic effect. Future scope for this study includes in vitro COX-2 assay and study of quantitative structure activity relationship to derive an equation.

## CONCLUSION

Various derivatives of 4, 5-dihydropyrazolyl indoles were successfully synthesized and screened for their analgesic, anti-inflammatory and ulcerogenic activities. Some of the synthesized compounds were safe with their analgesic and anti-inflammatory activities comparable to indomethacin. The tested compounds were good in analgesic and anti-inflammatory activities and less irritant to gastric mucosa as indicated by severity index. The results obtained support our hypothesis that chemical hybridization of indole nucleus and pyrazoline ring at appropriate position lead to afford the compounds with good analgesic and anti-inflammatory activities with lesser gastric irritation.

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