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Synthesis of new indole congeners as promising anti-inflammatory agents

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ABSTRACT

Substituted thiadiazolyl indoles and pyrazolyl indoles were synthesized as mentioned in scheme. Moreover these compounds also evaluated for their anti-inflammatory and analgesic activities. Compound **5e,** i.e., N-(5-((lH-indol-3-yl)methyl)-l,3,4-thiadiazol-2-yl)-3-(2,4-dichlorophenyl) acryl amide and **6e**, i.e. ,l-(3-((5-((lH-indol-3-yl)methyl)-l,3,4-thiadiazol-2-yl)-3-(2,4-dichlorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)ethanone, were found to be most active compounds of this series, which exhibits 42.44 & 48.80% anti-inflammatory activity while, 40.13 & 44.64 % analgesic activity. The structures of all the newly synthesized compounds were characterized by analytical data, IR, ^{1}H-NMR and Mass spectrometry.

Key words: Thiadiazolyl indole; Pyrazolyl indole; Anti-inflammatory & Analgesic Activities.

INTRODUCTION

Treatment of inflammation with steroids (i.e., glucocorticoids) is associated with side effects leading, at times, to liver, heart and kidney[1]. Presently, Non-Steroidal anti-inflammatory drugs (NSAIDs) are preferred for the treatment of pain, acute and chronic inflammation, different types of arthritis.

The discovery of indomethacin[2] as a successful drug for the clinical treatment of anti-inflammatory disorders has led to the exploration of indole moiety to obtain better anti-inflammatory agents. Indole, the potent basic Pharmacodynamic nucleus has been reported to possess a wide variety of biological properties viz., anti- inflammatory[3-13], anti-microbial[14-15], anti-bacterial[16-18] and cardiovascular[19] furthermore, substitution of heterocyclic moiety at 3rd – position markedly influenced the anti-inflammatory activity[5]. Moreover, thiadiazole[20-24] and Pyrazoline[25-26] derivatives have also been reported to possess Promising anti-inflammatory activities. In the light of the above report and also in continuation of our experimental work on chemoselective reaction of indole derivatives, a new drug strategy has been planned to synthesize several new indole derivatives possessing thiadiazole and Pyrazoline moieties with the hope to possess better anti-inflammatory and analgesic activities. All the compounds have been screened for their anti-inflammatory, analgesic, alcerogenic and toxicity activities.

EXPERIMENTAL

The melting points were determined in open capillaries with the help of thermonic melting

point apparatus and are uncorrected. The purity of all newly synthesized compounds was routinely checked by thin layer chromatography on silica Gel-G coated plates, eluent was a mixture of methanol-benzene in 2:8 proportion. The structure of these compounds was elucidated by IR, ^{1}H-NMR, Mass and elemental analysis. The IR (KBr) spectra were recorded on perkin-Elmer spectrum RX-1 spectrometer, ν_{max}. in Cm^{-1}. The ^{1}H-NMR' spectra were recorded by Brucker AC-300 FT instrument using $CDCl_3$ as solvent. Chemical shift values were recorded as (d) in ppm. Tetramethyl Silane (TMS) was used as internal reference standard. Elemental analysis were performed on Perkin-Elmer 2400 elemental analyzer and results were found within the ± 0.4% of theoretical values. Mass spectra were determined on a VG 70-S instrument. The Physical and analytical data of compounds are given in table-I and table-II.

General procedure for the synthesis of ethyl-2-(1H-indol-3-yl)acetate (1)

Ethyl chloroacetate (0.1 mole) and anhydrous K_2CO_3 (3.5 gm.) were added to the solution of indole (0.1 mole) in methanol (50 ml). The reaction mixture was refluxed for 8 h. Cooled and the excess of solvent was removed. The solid thus obtained were washed with water and recrystallized from ethanol to furnish compound (1).physical and analytical data are presented in Table 1

Ethyl-2-(1H-indole-3-yl)acetate(1)

Solvent of recrystallisation Ethanol; yield; 75 %, m.p.; 45°C; IR (KBr) $\nu_{max.}$ in cm^{-1} ; 3155 (N-H), 3010 (C-H aromatic) 2935 (C-H aliphatic). 1735 (C=O), 1570 (C—C of aromatic ring), ^{1}H-NMR ($CDCl_3$) d in ppm.; 8.25 (S, 1H, NH of indole ring exchangeable with D_2O), 7.58 – 7.35 (m, 5H, Ar-H), 6.72 (S, 2H, CH_2 attached to indole ring), 4.24 (q, 2H, -$COOCH_2CH_3$), 1.48 (t, 3H, - $COOCH_2CH_3$); MS ;m/z 203$[M]^+$ for $C_{12}H_{13}O_2N$.

General procedure for the synthesis of 2-(2-(1H-indol-3-yl) acetyl) hydrazine carbothioamide (2)

To a solution of Ethyl-2-(1H-indol-3-yl) acetate (0.075 mole) and thiosemicarbazide (0.075 mole) in methanol (50 ml.) were refluxed for about 8 h., concentrated, cooled, poured onto crushed ice, filtered and recrystallized from ethanol-water to give compound (2).

2-(2-(1H-indol-3-yl) acetyl) hydrazine carbothioamide (2)

Solvent of recrystallisation;Ethanol-water; yield : 70%; m.p.; 235°C; IR (KBr) $\nu_{max.}$ in cm^{-1} : 3165 (N-H), 3030 (C-H aromatic) 2935 (C-H aliphatic), 1725 (C=O), 1509 (C—C of aromatic ring), 1185 (C=S) ^{1}H-NMR ($CDCl_3$), d in ppm. : 8.36 (S, 1H, NH of indole ring exchangeable with D_2O), 7.90 (m, 4H, $NHNHCSNH_2$, exchangeable with D_2O), 7.55-7.30 (m, 5H, Ar-H), 6.80 (S, 2H, CH_2 attached to indole ring), MS : $[M]^+$ at m/z 248 for $C_{11}H_{12}ON_4S$

General procedure for the synthesis of 5-((1H-indol-3-yl) methyl)-1,3,4-thiadiazol-2-amine (3)

A mixture of 2-(2-(1H-indol-3-yl) acetyl) hydrazine carbothioamide (2) (0.05 mole) and concentrated H_2SO_4 (25 ml.) was kept overnight at room temperature. Then, the reaction mixture was poured into ice-cold water and neutralized with liquid ammonia and filtered. The product obtained was washed with water and recrystallized from ethanol to get Compound (3).

5-((1H-indol-3-yl) methyl)-1,3,4-thiadiazol-2-amine (3)

Solvent of recrystallisation;Ethanol; yield ; 70% m.p.; 244°C ; IR (KBr) $\nu_{max.}$ in cm^{-1} : 3345 (NH_2), 3150 (N-H), 3025 (C-H aromatic) 2930 (C-H aliphatic). 1590 (C=N), 1575 (C—C of aromatic ring), 1220(C-N), 1045 (N-N), 735 (C-S-C), ^{1}H-NMR ($CDCl_3$) d in ppm. : 8.32 (S, 1H, NH of indole ring exchangeable with D_2O), 7.55-7.35 (m, 5H, Ar-H), 6.80 (S, 2H, CH_2 attarched to indole ring), 5.71 (brs, 2H, NH_2, exchangeable with D_2O) MS ; $[M]^+$ at m/z 230 for $C_{11}H_{10}N_4S$

General procedure for the synthesis of N-(5-((1H-indol-3-yl)-3-yl)methyl)-1,3,4,-thiadiazol-2-yl) acetamide (4)

A solution of acetyl chloride (0.02 mole) and dry chloroform (50 ml.) was added drop wise at 0–5°C temperature to the vigorously stirred solution of 5-((1H-indol-3-yl) methyl)-1,3,4-thiadiazol-2-amine (0.02 mole) in dry chloroform (50 ml.). The reaction mixture further stirred with the help of mechanical stirrer for 3h. at room temperature, and then refluxed for 5h. on water both. The excess of solvent was distilled off, cooled and

poured onto crushed ice. The resulting mixture was filtered to afford solid product, washed with petroleum ether (55-60°) and recrystallized from ethanol-water to yield compound (4).

N-(5-((1H-indol-3-yl)-3-yl)methyl)-1,3,4,-thiadiazol-2-yl) acetamide (4) Solvent of recrystallisation;Ethanol-water; yield ; 75% m.p.; 260°C; IR (KBr) $\nu_{max.}$ in cm^{-1} : 3140 (N-H), 3020 (C-H aromatic), 2920 (C-H aliphatic), 1720 (C=O), 1592 (C=N), 1550 (C—C of aromatic ring), 1228 (C-N), 1040 (N-N), 730 C-S-C) ^{1}H-NMR ($CDCl_3$) δ in ppm. : 8.40 (brs, 1H, NHCO exchangeable with D_2O), 8.12 (S, H, NH of indole ring exchangeable with D_2O), 7.64-7.41 (m, 5H, Ar-H), 6.99 (S, 2H, CH_2 attached to indole ring), 2.50 (S, 3H, $COCH_3$); MS : $[M]^+$ at m/z 272 for $C_{13}H_{12}ON_4S$

General procedure for the synthesis of N-(5-((1H-indol-3-yl) methyl)-1,3,4-thiadiazol-2-y)-3-(substituted phenyl) arcylamide (5a-5j)

To the solution of compound N-(5-((1H-indole-3-yl)-1,3,4-thiadiazol-2-yl) acetamide mole), in methanol (50 ml.), substituted benzaldehyde (0.01 mole) was added in the presence of 10% NaOH solution. The reaction mixture was heated under reflux for 8h. The excess of solvent distilled off, cooled, filtered and the residue was thoroughly washed with cold water and recrystallized from ethanol-water to give compound (5a). OtherN-(5-((1H-indol-3-yl)methyl)-1,3,4-thiadiazol-2-y)3(dimethylamio) phenyl) arcylamide (5b-5j) were prepared in the similar manner. Their Physical and analytical data are given in Table 1.

N-(5-((1H-indol-3-yl) methyl)-1,3,4-thiadiazol-2-y)-3-(2-N,N-dimethylamino) phenyl) arcylamide (5a)

Solvent of recrystallisation; Ethanol-water; yield ; 65% m.p.; 220°C;IR (KBr) $\nu_{max.}$ in cm^{-1} : 3170 (N-H), 3055 (C-H aromatic), 2932 (C-H aliphatic), 1715 (C=O), 1612 (C=N), 1550 (C—C of aromatic ring), 1055 (N-N), 1225 (C-N), 745 (C-S-C) ^{1}H-NMR ($CDCl_3$) δ in ppm. : 9.21 (d, 1H,=CH-Ar), 8.43 (brs, 1H, NHCO, exchangeable with D_2O), 8.25 (S, 1H, NH of indole ring exchangeable with D_2O), 7.64-7.22 (m, 9H, Ar-H), 6.80 (S, 2H, CH_2, attached to indole ring), 6.35 (d, 1H,-COCH=), 2.20 (S, 6H, $N(CH_3)_2$); MS : $[M]^+$ at m/z 403 for $C_{25}H_{21}N_5OS$.

N-(5-((1H-indol-3-yl) methyl)-1,3,4-thiadiazol-2-y)-3-(4-N,N-dimethyl amino) phenyl) arcylamide (5b)

Solvent of recrystallisation ;Ethanol; yield ; 60% m.p.; 220°C; IR (KBr) $\nu_{max.}$ in cm^{-1}3195 (N-H), 3060 (C-H aromatic), 2940 (C-H aliphatic), 1725 (C=O), 1640 (C=N), 1550 (C—C of aromatic ring), 1230(C-N), 1140 (C-S-C), 1060 (N-N), 1315 $[N(CH_3)_2]$ ^{1}H-NMR ($CDCl_3$) δ in ppm. 9.20 (d, 1H,=CH-Ar), 8.50 (brs, 2H, NHCO, exchangeable with D_2O), 8.24 (S, 1H, NH of indol, exchangeable with D_2O), 7.73-7.25 (m, 9H, Ar-H), 6.86 (S, 2H, CH_2 attached to indole nucleus), 6.42 (d, 1H, COCH=), 2.20 [S, 6H, $N(CH_3)_2$];); MS : $[M]^+$ at m/z 403 for $C_{25}H_{21}N_5OS$.

N-(5-((1H-indol-3-yl) methyl)-1,3,4-thiadiazol-2-y)-3-(2-chloro phenyl) arcylamide (5c)

Solvent of recrystallisation;Methanol; yield ; 52% m.p.; 246°C**;** IR (KBr) $\nu_{max.}$ in cm^{-1}3186 (N-H), 3050 (C-H aromatic), 2930 (C-H aliphatic), 1710 (C=O), 1630 (C=N), 1545 (C—C of aromatic ring), 1225 (C-N), 1050 (N-N), 732 (C-S-C) 8.95 (d, 1H, = CH-Ar), 8.20 (brs, 2H, NHCO, exchangeable with D_2O), 8.12 (S, IH, NH of indol, exchangeable with D_2O), 7.60-7.18 (m, 9H, Ar-H), 6.68(S, 2H, CH_2 attached to indole nucleus), 6.28 (d, 1H, COCH =); MS:$[M]^+$ at m/z 394 for $C_{20}H_{15}ClN_4OS$.

N-(5-((1H-indol-3-yl)methyl)-1,3,4-thiadiazol-2-y)-3-(4-chloro phenyl) arcylamide (5d)

Solvent of recrystallisation;Methanol; yield ; 58% m.p.; 252°C; IR (KBr) $\nu_{max.}$ in cm^{-1}3190 (N-H), 3055(C-Haromatic), 2935 (C-H aliphatic), 1715 (C=O), 1625 (C=N), 1540 (C—C of aromatic ring), 1220 (C-N), 1055 (N-N), 735 (C-S-C)9.02 (d, 1H, = CH-Ar), 8.23 (brs, 2H, NHCO, exchangeable with D_2O), 8.16 (S, IH, NH of indol, exchangeable with D_2O), 7.65-7.20 (m, 9H, Ar-H), 6.69 (S, 2H, CH_2-- attached to indole nucleus), 6.31 (d, 1H, COCH=); MS:$[M]^+$ at m/z 394 for $C_{20}H_{15}ClN_4OS$

N-(5-((1H-indol-3-yl) methyl)-1,3,4-thiadiazol-2-y)-3-(2,4-dichloro phenyl) arcylamide (5e)

Solvent of recrystallisation;Acetone; yield ; 66% m.p.; 262°C**;** IR (KBr) $\nu_{max.}$ in cm^{-1} 3160 (N-H), 3040 (C-H aromatic), 2925 (C-H aliphatic), 1705 (C=0), 1610 (C=N), 1525 (C—C) of aromatic ring), 1210 (C-N), 1030 (N-N), 725 (C-S-C) 8.86 (d, 1H, = CH-Ar), 8.23 (brs, 2H, NHCO, exchangeable with

D_2O), 8.05 (S, IH, NH of indol, exchangeable with D_2O), 7.53-7.15 (m, 8H, Ar-H), 6.64 (S, 2H, CH_{2-} attached to indole nucleus), 6.21 (d, 1H, COCH=); MS:$[M]^+$ at m/z 429 for $C_{20}H_{14}Cl_2N_4OS$.

N-(5-((1H-indol-3-yl) methyl)-1,3,4-thiadiazol-2-y)-3-(2-bromo phenyl) arcylamide (5f)

Solvent of recrystallisation;Methanol; yield ; 71% m.p.; 274°C**;** IR (KBr) $\nu_{max.}$ in cm^{-1}3175 (N-H), 3050 (C-H aromatic), 2932 (C-H aliphatic), 1715 (C=O), 1635 (C=N), 1535 (C—C) of aromatic ring), 1225 (C-N), 1055 (N-N), 730 (C-S-C) 9.06 (d, 1H, = CH-Ar), 8.37 (brs, 2H, NHCO, exchangeable with D_2O), 8.17 (S, IH, NH of indol, exchangeable with D_2O), 7.63-7.20 (m, 9H, Ar-H), 6.78 (S, 2H, CH_{2-} attached to indole nucleus), 6.32 (d, 1H, COCH=); MS:$[M]^+$ at m/z 439 for $C_{20}H_{15}BrN_4OS$.

N-(5-((1H-indol-3-yl) methyl)-1,3,4-thiadiazol-2-y)-3-(4-bromo phenyl) arcylamide (5g)

Solvent of recrystallisation;DMF-water; yield ; 55% m.p.; 265°C; IR (KBr) $\nu_{max.}$ in cm^{-1}3180 (N-H), 3052 (C-H aromatic), 2935 (C-H aliphatic), 1715 (C=O), 1630 (C=N), 1535 (C—C) of aromatic ring), 1220 (C-N), 1045 (N-N), 735 (C-S-C) 9.04 (d, 1H, = CH-Ar), 8.39 (brs, 2H, NHCO, exchangeable with D_2O), 8.18 (S, IH, NH of indol, exchangeable with D_2O), 7.65-7.21 (m, 9H, Ar-H), 6.80 (S, 2H, CH_{2-} attached to indole nucleus), 6.35 (d, 1H, COCH=); MS:$[M]^+$ at m/z 439 for $C_{20}H_{15}BrN_4OS$.

N-(5-((1H-indol-3-yl) methyl)-1,3,4-thiadiazol-2-y)-3-(2,4-dibromophenyl) arcylamide (5h)

Solvent of recrystallisation;Ethanol-water; yield ; 62% m.p.; 278°C; IR (KBr) $\nu_{max.}$ in cm^{-1}3170 (N-H), 3045 (C-H aromatic), 2930 (C-H aliphatic), 1708 (C=O), 1620 (C=N), 1530 (C—C) of aromatic ring), 1215 (C-N), 1040 (N-N), 740 (C-S-C) 8.95 (d, 1H, = CH-Ar), 8.31 (brs, 2H, NHCO, exchangeable with D_2O), 8.12 (S, IH, NH of indol, exchangeable with D_2O), 7.62-7.20 (m, 8H, Ar-H), 6.75 (S, 2H, CH_{2-} attached to indole nucleus), 6.30 (d, 1H, COCH=); MS:$[M]^+$ at m/z 518 for $C_{20}H_{14}Br_2N_4OS$.

N-(5-((1H-indol-3-yl) methyl)-1,3,4-thiadiazol-2-y)-3-(2-methoxy phenyl) arcylamide (5i)

Solvent of recrystallisation;Methanol; yield ; 55% m.p.; 241°C**;** IR (KBr) $\nu_{max.}$ in cm^{-1} 3185 (N-H), 3050 (C-H aromatic), 2940 (C-H aliphatic), 1720 (C=O), 1635 (C=N), 1548 (C.....C) of aromatic ring), 1225 (C-N), 1050 (N-N), 760 (C-S-C). 9.08 (d, 1H, = CH-Ar), 8.41 (brs, 2H, NHCO, exchangeable with D_2O), 8.20 (S, IH, NH of indol, exchangeable with D_2O), 7.68-7.22 (m, 9H, Ar-H), 6.81 (S, 2H, CH_{2-} attached to indole nucleus), 6.36 (d, 1H, COCH=),3.40 (S, 3H, OCH_3) ; MS:$[M]^+$ at m/z 390 for $C_{21}H_{18}N_4O_2S$.

N-(5-((1H-indol-3-yl) methyl)-1,3,4-thiadiazol-2-y)-3-(4-methoxy phenyl) arcylamide (5j)

Solvent of recrystallisation;Methanol; yield ; 61% m.p.; 232°C; IR (KBr) $\nu_{max.}$ in cm^{-1} 3188 (N-H), 3048 (C-H aromatic), 2935 (C-H aliphatic), 1724 (C=O), 1632 (C=N), 1545 (C—C) of aromatic ring), 1228 (C-N), 1055 (N-N), 755 (C-S-C). 9.10 (d, 1H, = CH-Ar), 8.43 (brs, 2H, NHCO, exchangeable with D_2O), 8.19 (S, IH, NH of indol, exchangeable with D_2O), 7.70-7.22 (m, 9H, Ar-H), 6.82 (S, 2H, CH_{2-} attached to indole nucleus), 6.38 (d, 1H, COCH=) 3.44 (S, 3H, -OCH_3) ; MS:$[M]^+$ at m/z 390 for $C_{21}H_{18}N_4O_2S$.

General procedure for the synthesis of 1-(3-(5-((1H-indol-3-yl)-1,3,4-thiadiazol-2-ylamino)-5-(2-(substituted phenyl)-4,5-dihydro1H-Pyra zol-1-yl) ethanone (6a-6j)

Hydrazine hydrate (99%, 0.04 mole) was added to a solution of compound N-(5-((1H-indol-3-yl) methyl)-1,3,4-thiadiazol-2-yl)-3-(2-(dimethylamino) phenyl) acrylamide (0.02 mole) in ethanol (50 ml.) in the presence of few drops of glacial acetic acid. This reaction mixture was refluxed for 8h. distilled off, cooled and poured onto crushed ice. The separated solid was filtered, washed with water and recrystallized from acetone-petroleum ether to yield compound (6a). Other 1-(3-(5-((1H-indol-3-yl) methyl)-1,3,4-thiadiazol-2-ylamino)-5-(Substituted Phenyl)-4,5-dihydro-1H-Pyrazol-1-yl) ethanone (6b-6j) were prepared in the similar manner. Their Physical and analytical data are given in table 2.

1-(3-(5-((1H-indol-3-yl)-1,3,4-thiadiazol-2-ylamino)-5-(2-N,N-dimethylamino)phenyl)-4,5-dihydro1H-Pyrazol-1-yl) ethanone (6a)

Solvent of recrystallisation;Acetone-petroleum ether; yield ; 55% m.p.; 232°C; IR (KBr) $\nu_{max.}$ in cm^{-1} : 3145 (N-H), 3050 (C-H aromatic), 2930 (C-H aliphatic), 1720 (C=O), 1620 (C=N), 1562 (C—C of aromatic ring), 1230 (C-N), 1050 (N-N), 745

(C-S-C) ^{1}H-NMR ($CDCl_3$) d in ppm. : 8.25 (S, 1H, NH of indole ring exchangeable with D_2O), 7.64-7.20 (m, 9H, Ar-H) 6.90 (S, 2H, CH_2 attached to indole ring), 6.54 (t, 1H, CH-Ar of Pyrazoline ring), 5.75 (brs, 1H, NH exchangeable with D_2O), 5.30 (d, 2H, CH_2 of Pyrazoline ring), 2.55 (S, 3H, $COCH_3$), 2.12 (S, 6H, $N(CH_3)_2$).
MS : $[M]^+$ at m/z 459 for $C_{24}H_{25}N_7OS$.

1-(3-(5-((1H-indol-3-yl)-1,3,4-thiadiazol-2-ylamino)-5-(4-N,N-dimethylamino)phenyl)-4,5-dihydro1H-Pyrazol-1-yl) ethanone (6b)

Solvent of recrystallisation;Acetone; yield ; 55% m.p.; 230°C**;** IR (KBr) $\nu_{max.}$ in cm^{-1} 3160 (N-H), 3045 (C-H aromatic), 2925 (C-H aliphatic), 1725 (C=O), 1635 (C=N), 1560 (C—C of aromatic ring), 1240 (C-N), 1060 (N-N), 745 (C-S-C), 1325 [$N(CH_3)_2$] 8.25 (S, 1H, NH of indol, exchangeable with D_2O), 7.75-7.28 (m, 9H, Ar-H), 6.90 (S, 2H, CH_2 attached to indole nucleus), 6.64 (t, 1H, CH-Ar of Pyrzoline ring), 5.70 (brs, 1H, NH, exchangeable with D_2O), 5.30 (d, 2H, CH_2 of Pyrazoline ring), 2.50 (S, 3H, $COCH_3$), 2.24 [S, 6H, $N(CH_3)_2$]; MS : $[M]^+$ at m/z 459 for $C_{24}H_{25}N_7OS$.

1-(3-(5-((1H-indol-3-yl)-1,3,4-thiadiazol-2-ylamino)-5-(2-chloro **phenyl)-4,5-dihydro1H-Pyrazol-1-yl) ethanone (6c)**

Solvent of recrystallisation;Ethanol; yield ; 46% m.p.; 257°C; IR (KBr) $\nu_{max.}$ in cm^{-1} 3135 (N-H), 3025 (C-H aromatic), 2915 (C-H aliphatic), 1715 (C=O), 1620 (C=N), 1530 (C—C of aromatic ring), 1220 (C-N), 1035 (N-N), 725 (C-S-C). 8.11 (S, 1H, NH of indol, exchangeable with D_2O), 7.60-7.13 (m, 9H, Ar-H), 6.79 (S, 2H, CH_2 attached to indole nucleus), 6.56 (t, 1H, CH-Ar of Pyrzoline ring), 5.55 (brs, 1H, NH, exchangeable with D_2O), 5.14 (d, 2H, CH_2 of Pyrazoline ring), 2.36 (S, 3H, $COCH_3$), MS : $[M]^+$ at m/z 450 for $C_{22}H_{19}ClN_6OS$.

1-(3-(5-((1H-indol-3-yl)-1,3,4-thiadiazol-2-ylamino)-5-(4-chloro **phenyl)-4,5-dihydro1H-Pyrazol-1-yl) ethanone (6d)**

Solvent of recrystallisation;Ethanol; yield ; 54% m.p.; 268°C; IR (KBr) $\nu_{max.}$ in cm^{-1}3140 (N-H), 3030 (C-H aromatic), 2920 (C-H aliphatic), 1720 (C=O), 1627 (C=N), 1535 (C—C of aromatic ring), 1225 (C-N), 1030 (N-N), 720 (C-S-C) 8.15 (S, 1H, NH of indol, exchangeable with D_2O), 7.62-7.15 (m, 9H, Ar-H), 6.81 (S, 2H, CH_2 attached to indole nucleus), 6.59 (t, 1H, CH-Ar of Pyrzoline ring), 5.57 (brs, 1H, NH, exchangeable with D_2O), 5.17 (d, 2H, CH_2 of Pyrazoline ring), 2.39 (S, 3H, $COCH_3$); MS : $[M]^+$ at m/z 450 for $C_{22}H_{19}ClN_6OS$.

1-(3-(5-((1H-indol-3-yl)-1,3,4-thiadiazol-2-ylamino)-5-(2,4-dichlorophenyl)-4,5-dihydro1H-Pyrazol-1-yl) ethanone (6e)

Solvent of recrystallisation;Methanol; yield ; 60% m.p.; 279°C; IR (KBr) $\nu_{max.}$ in cm^{-1}**;**3130 (N-H), 3020 (C-H aromatic), 2910 (C-H aliphatic), 1710 (C=O), 1615 (C=N), 1525 (C—C of aromatic ring), 1215 (C-N), 1025 (N-N), 710 (C-S-C) 7.95 (S, 1H, NH of indol, exchangeable with D_2O), 7.52-7.10 (m, 8H, Ar-H), 6.75 (S, 2H, CH_2 attached to indole nucleus), 6.52 (t, 1H, CH-Ar of Pyrzoline ring), 5.48 (brs, 1H, NH, exchangeable with D_2O), 5.08 (d, 2H, CH_2 of Pyrazoline ring), 2.29 (S, 3H, $COCH_3$); MS : $[M]^+$ at m/z 485 for $C_{22}H_{18}Cl_2N_6OS$.

1-(3-(5-((1H-indol-3-yl)-1,3,4-thiadiazol-2-ylamino)-5-(2-bromo **phenyl)-4,5-dihydro1H-Pyrazol-1-yl) ethanone (6f) :**

Solvent of recrystallisation;DMF-water; yield ; 63% m.p.; 291°C; IR (KBr) $\nu_{max.}$ in cm^{-1} 3145 (N-H), 3035 (C-H aromatic), 2925 (C-H aliphatic), 1722 (C=O), 1628 (C=N), 1540 (C.....C of aromatic ring), 1222 (C-N), 1045 (N-N), 730 (C-S-C) 8.15 (S, 1H, NH of indol, exchangeable with D_2O), 7.64-7.18 (m, 9H, Ar-H), 6.82 (S, 2H, CH_2 attached to indole nucleus), 6.60 (t, 1H, CH-Ar of Pyrzoline ring), 5.58 (brs, 1H, NH, exchangeable with D_2O), 5.16 (d, 2H, CH_2 of Pyrazoline ring), 2.38 (S, 3H, $COCH_3$); MS : $[M]^+$ at m/z 495 for $C_{22}H_{19}BrN_6OS$.

1-(3-(5-((1H-indol-3-yl)-1,3,4-thiadiazol-2-ylamino)-5-(4-bromo **phenyl)-4,5-dihydro1H-Pyrazol-1-yl) ethanone (6g)**

Solvent of recrystallisation;Acetone; yield ; 50% m.p.; 283°C; IR (KBr) $\nu_{max.}$ in cm^{-1} 3150 (N-H), 3038 (C-H aromatic), 2920 (C-H aliphatic), 1725 (C=O), 1625 (C=N), 1545 (C—C of aromatic ring), 1230 (C-N), 1040 (N-N), 735 (C-S-C) 8.18 (S, 1H, NH of indol, exchangeable with D_2O), 7.65-7.20 (m, 9H, Ar-H), 6.85 (S, 2H, CH_2 attached to indole nucleus), 6.61 (t, 1H, CH-Ar of Pyrzoline ring), 5.60 (brs, 1H, NH, exchangeable with D_2O), 5.19 (d, 2H, CH_2 of Pyrazoline ring), 2.41 (S, 3H, $COCH_3$)); MS : $[M]^+$ at m/z 495 for $C_{22}H_{19}BrN_6OS$.

1-(3-(5-((1H-indol-3-yl)-1,3,4-thiadiazol-2-ylamino)-5-(2,4-dibromo **phenyl)-4,5-dihydro1H-Pyrazol-1-yl) ethanone (6h)**

Solvent of recrystallisation;Acetic acid; yield ; 53% m.p.; 301°C; IR (KBr) $\nu_{max.}$ in cm^{-1} 3135 (N-H), 3030 (C-H aromatic), 2915 (C-H aliphatic), 1715 (C=O), 1620 (C=N), 1530 (C—C of aromatic ring), 1218 (C-N), 1030 (N-N), 720 (C-S-C) 8.08 (S, 1H, NH of indol, exchangeable with D_2O), 7.58-7.16 (m, 8H, Ar-H), 6.78 (S, 2H, CH_2 attached to indole nucleus), 6.55 (t, 1H, CH-Ar of Pyrzoline ring), 5.53 (brs,1H, NH, exchangeable withD_2O), 5.12 (d, 2H, CH_2 of Pyrazoline ring), 2.33 (S, 3H, $COCH_3$) MS : $[M]^+$ at m/z 574 for $C_{22}H_{18}Br_2N_6OS$

1-(3-(5-((1H-indol-3-yl)-1,3,4-thiadiazol-2-ylamino)-5-(2-methoxy **phenyl)-4,5-dihydro1H-Pyrazol-1-yl) ethanone (6i)**

Solvent of recrystallisation;Ethanol; yield ; 47% m.p.; 221°C; IR (KBr) $\nu_{max.}$ in cm^{-1} 3155 (N-H), 3040 (C-H aromatic), 2922 (C-H aliphatic), 1724 (C=O), 1630 (C=N), 1550 (C—C of aromatic ring), 1232 (C-N), 1055 (N-N), 740 (C-S-C). 8.20 (S, 1H, NH of indol, exchangeable with D_2O), 7.68-7.20 (m, 9H, Ar-H), 6.88 (S, 2H, CH_2 attached to indole nucleus), 6.62 (t, 1H, CH-Ar of Pyrzoline ring), 5.62 (brs, 1H, NH, exchangeable with D_2O), 5.21 (d, 2H, CH_2 of Pyrazoline ring), 3.38 (S, 3H, OCH_3), 2.43 (S, 3H, $COCH_3$); MS:$[M]^+$ at m/z 446 for $C_{23}H_{22}N_6O_2S$.

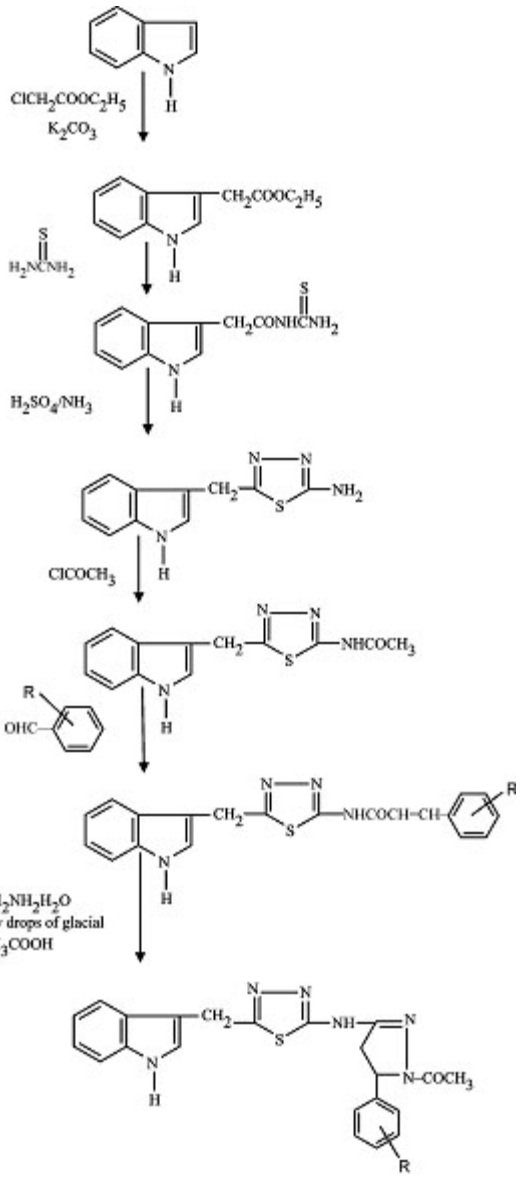
1-(3-(5-((1H-indol-3-yl)-1,3,4-thiadiazol-2-ylamino)-5-(4-methoxy phenyl)-4,5-dihydro1H-Pyrazol-1-yl) ethanone (6j)

Solvent of recrystallisation;Ethanol; yield ; 60% m.p.; 205°C; IR (KBr) $\nu_{max.}$ in cm^{-1} 3150 (N-H), 3042 (C-H aromatic), 2930 (C-H aliphatic), 1720 (C=O), 1630 (C=N), 1555 (C—C of aromatic ring), 1235 (C-N), 1050 (N-N), 743 (C-S-C). 8.21 (S, 1H, NH of indol, exchangeable with D_2O), 7.70-7.22 (m, 9H, Ar-H), 6.86 (S, 2H, CH_2 attached to indole nucleus), 6.60 (t, 1H, CH-Ar of Pyrzoline ring), 5.65 (brs, 1H, NH, exchangeable with D_2O), 5.24 (d, 2H, CH_2 of Pyrazoline ring), 3.34 (S, 3H, -OCH_3), 2.42 (S, 3H, $COCH_3$); MS:$[M]^+$ at m/z 446 for $C_{23}H_{22}N_6O_2S$

RESULTS AND DISCUSSION

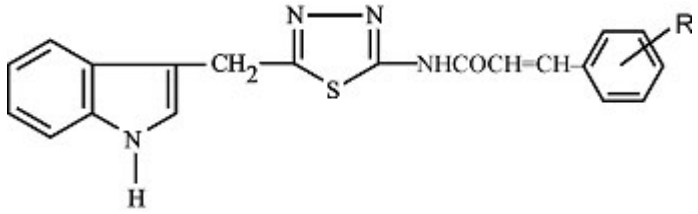
All the newly synthesized compound of this series were screened for their anti-inflammatory, analgesic and ulcerogenic activities at a dose of 50 mg/kg p.o. The result of anti-inflammatory and analgesic activities of all the compounds are statistically significant (Table 5).

Out of 20 compounds, only three compounds 5e, 6e and 6h were found to possess more potent anti-inflammatory activity in comparison to phenyl butazone. Compound 5e, which was substituted with chloro group at 2nd & 4th position of



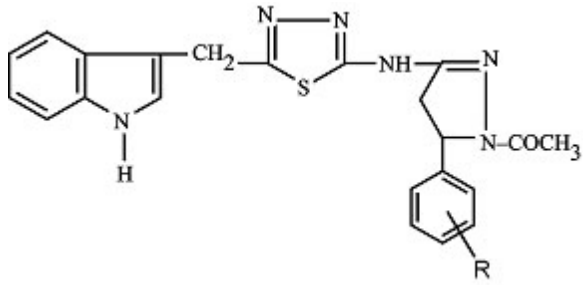
Scheme 1.

Table 1: N-(5-((1H-indol-3-yl) methyl)-1, 3, 4-thiadiazol-2-yl)-3-(Substituted Phenyl) acrylamide (5b-5j)



Comp. No.	R	Recrystallisation Solvent	Molecular Formula	Elemental Analyses (%)					
				C %		H %		N %	
				Calcd.	Found	Calcd.	Found	Calcd.	Found
5a	2-$N(CH_3)_2$	Ethanol	$C_{25}H_{21}N_5OS$	65.49	65.65	05.25	05.30	17.36	17.20
5b	4-$N(CH_3)_2$	Ethanol	$C_{25}H_{21}N_5OS$	65.49	65.65	05.25	05.30	17.36	17.20
5c	2-Cl	Methanol	$C_{20}H_{15}ClN_4OS$	60.83	60.55	03.83	03.90	14.19	14.35
5d	4-Cl	Methanol	$C_{20}H_{15}ClN_4OS$	60.83	60.60	03.83	03.92	14.19	14.10
5e	2,4-Cl_2	Acetone	$C_{20}H_{14}Cl_2N_4OS$	55.95	55.78	03.29	03.35	13.05	13.20
5f	2-Br	Methanol	$C_{20}H_{15}BrN_4OS$	54.68	54.50	03.44	03.50	12.75	12.90
5g	4-Br	DMF	$C_{20}H_{15}BrN_4OS$	54.68	54.52	03.44	03.40	12.75	12.60
5h	2,4-Br_2	Ethanol	$C_{20}H_{14}Br_2N_4OS$	46.35	46.50	02.72	02.80	10.81	10.60
5i	2-OCH_3	Methanol	$C_{21}H_{18}N_4O_2S$	64.60	64.86	04.65	04.60	14.35	14.42
5j	4-OCH_3	Methanol	$C_{21}H_{18}N_4O_2S$	64.60	64.90	04.65	04.69	14.35	14.20

Table 2: 1-(3-(5-((1H-indol-3-yl) methyl)-1, 3, 4-thiadiazol-2-ylamino)-5-(Substituted Phenyl)-4,5-dihydro-1H-Pyrazol-1-yl) ethanone (6b-6j)



Comp. No.	R	Recrystallisation Solvent	Molecular Formula	Elemental Analysis (%)					
				C %		H %		N %	
				Calcd.	Found	Calcd.	Found	Calcd.	Found
6a	2-$N(CH_3)_2$	Acetone	$C_{24}H_{25}N_7OS$	62.72	62.90	5.48	5.40	21.33	21.20
6b	4-$N(CH_3)_2$	Acetone	$C_{24}H_{25}N_7OS$	62.72	62.90	5.48	5.40	21.33	21.20
6c	2-Cl	Ethanol	$C_{22}H_{19}ClN_6OS$	58.60	58.86	4.25	4.21	18.64	18.80
6d	4-Cl	Ethanol	$C_{22}H_{19}ClN_6OS$	58.60	58.81	4.25	4.20	18.64	18.80
6e	2,4-Cl_2	Methanol	$C_{22}H_{18}Cl_2N_6OS$	54.44	54.65	3.74	3.78	17.31	17.26
6f	2-Br	DMF	$C_{22}H_{19}BrN_6OS$	53.34	53.48	3.87	3.90	16.96	16.90
6g	4-Br	Acetone	$C_{22}H_{19}BrN_6OS$	53.34	53.22	3.87	3.90	16.96	17.03
6h	2,4-Br_2	Acetic Acid	$C_{22}H_{18}Br_2N_6OS$	46.01	46.20	3.16	3.20	14.63	14.55
6i	2-OCH_3	Ethanol	$C_{23}H_{22}N_6O_2S$	61.87	61.60	4.97	4.90	18.82	18.94
6j	4-OCH_3	Ethanol	$C_{23}H_{22}N_6O_2S$	61.87	61.65	4.97	4.92	18.82	18.74

Phenyl ring have shown 42.44% of inhibition of oedema. Compound 5a which possessed N,N-dimethyl at 2nd position of Phenyl ring have shown least activity i.e. 12.18%

The last step compounds (6a-6j) were characterized by the presence of Pyrazoline ring. All the compounds of this stage have shown promising degree (20.47-48.80) of anti-inflammatory activity. Compound 6e, has shown the maximum percentage of anti-inflammatory activity, i.e. 48.80% at a dose of 50 mg/kg p.o. Considering the potentiality of compounds 5e and 6e, these were studied in detail at three graded doses 25, 50 and 100 mg/kg p.o. Compound 6e exhibited better anti-inflammatory activity at all three graded doses of 25, 50 and 100 mg/kg. p.o. as compared to phenyl butazone.

The ulcerogenic liabilities of compounds 5e (165.00 mg/kg i.p.) and 6e (135.48 mg/kg i.p.) are much less than that of phenyl butazone (66.6 mg/kg i.p.). The Pyrazoline derivatives (6a-6j) showed better analgesic activity than thiadiazolyl derivatives (5a–5j). Compounds of thiadiazolyl derivatives (5a–5j) have shown moderate to good analgesic activity. Compound 5e which was substituted by cloro group at 2nd & 4th position of phenyl ring exhibited more potent (40.13%) analgesic activity at 50 mg/kg p.o.

The most active compound of this series was 6e which has shown potent analgesic activity i.e. (44.64%) at a dose of 50 mg/kg p.o. Moreover, when these compounds were tested at three graded doses 25, 50 and 100 mg/kg p.o., it was found that analgesic activity of 5e found more than phenyl butazon, while 6e exhibited better analgesic activity than phenyl butazone in this series.

Therefore, it may be concluded that

- Different substituted thiadiazolyl nucleus have shown mild to moderate anti-inflammatory and analgesic activities. Cyclization of these thiadiazolyl derivatives into their corresponding pyrazolines enhances the anti-inflammatory and analgesic properties.
- Compound, 5e and 6e having a 2, 4-dichoro phenyl group as substituents, exhibited most potent anti-inflammatory and analgesic activities. Thus the obtained biological results clearly indicate that compounds which showed maximum anti-inflammatory activity also exhibited potent analgesic activity.

Pharmacology

The experiments were performed on albino rats of Charles Foster strain of either sex of 70 to 95 days weighing 80-140 g, albino mice weighing 20-25 g. Pregnant female rats were excluded. These rats and mice were divided into different groups (control, standard and drug treated) of six animals each. The animals had access to food and water *ad libitum.* They were housed in rooms at 20-25 ºC with 12 h light/dark cycle and relative humidity 50-60%. The test compounds and reference drug were dissolved in propylene glycol. phenylbutazone, a potent anti-inflammatory compound, was used as reference drug for comparison.

Anti-inflammatory activity against carrageenan-induced rat's paw oedema

This study was done by following the procedure of Winter *et al* [29]. The rats were divided into three groups (control, drug treated, and standard, drug of six animals each. A freshly prepared suspension of carrageenan (1% in 0.9% saline). 0.05 mn was injected under the planter aponeurosis of the right hind paw of each rat. Test compounds and standard drug were administered orally to the animals of drug treated groups and the standard drug group, respectively. 1h before the carrageenan injection. The paw volume of each rat was measured before 1 and after 3 h of carrageenan treatment with the help of a plethymometer. The percent anti-inflammatory activity was calculated according to the formula given below-

$$\text{Percentage of inhibition of oedema} = (1-V_t/V_c) \times 100$$

Where, V_t and V_c are the mean increase in paw volume of rats of the treated and the control group, respectively. Results obtained were statistically analyzed.

Analgesic activity

Following the method of Berkowitz et al. [30] performed this activity. This method is based

Table 3: Anti-inflammatory, analgesic, ulcerogenic and toxicity data of compounds (5a-5J) and (6a-6J)

Comp no.	R	Anti-Inflammatory Activity		Analgesic Activity		Ulcerogenic Activity UD_{50} (mg/kg i.p.)	Acute Toxicity ALD_{50} (mg/kg p.o)
		Dose (mg./kg P.O.)	% Inhibition of oedema	Dose (mg./kg p.o.)	% Protection		
5a	2-$N(CH_3)_2$	50	12.18	50	9.82	-	> 1200
5b	4-$N(CH_3)_2$	50	15.78	50	13.35	-	> 1200
5c	2-Cl	50	20.47	50	18.16	-	> 1200
5d	4-Cl	50	25.14	50	23.47	-	> 1200
		25	29.25	25	17.48	165.00	> 1800
5e	2,4-Cl_2	50	42.44	50	40.13		
		100	68.73	100	62.78		
5f	2-Br	50	18.67	50	16.53	-	> 1200
5g	4-Br	50	20.82	50	19.65	-	> 1200
5h	2,4-Br_2	50	27.52	50	24.48	-	> 1200
5i	2-OCH_3	50	25.24	50	23.13	-	> 1200
5j	4-OCH_3	50	24.10	50	21.46	-	> 1200
6a	2-$N(CH_3)_2$	50	20.47	50	19.10	-	> 1200
6b	4-$N(CH_3)_2$	50	23.28	50	20.36	-	> 1200
6c	2-Cl	50	30.37	50	28.64	-	> 1200
6d	4-Cl	50	32.32	50	27.60	-	> 1200
		25	32.33	25	19.63	135.48	> 1800
6e	2,4-Cl_2	50	48.80	50	44.64		
		100	72.68	100	65.96		
6f	2-Br	50	27.63	50	24.54	-	> 1200
6g	4-Br	50	28.84	50	26.17	-	> 1200
6h	2,4-Br_2	50	35.87	50	31.53	-	> 1200
6i	2-OCH_3	50	30.15	50	28.38	-	> 1200
6j	4-OCH_3	50	31.85	50	29.98	-	> 1200
Control			0.0		0.0		-
		25	26.75	25	14.25	66.6	-
Phenyl butazone		50	36.50	50	32.50		
		100	64.70	100	54.58		

on the property of the test compound to antagonize the phenyl quinone-induced pain syndrome in mice. Groups of five mice were injected intraperitonely with 0.25 ml of a 0.02% solution of phenylquinone in ethanol (5%) 1 h after of oral administration of the test compound. The number of writhes induced in each mouse was counted for 5 min (between 5 and 10 min) after injection of an irritant. The analgesic effect was expressed as percent protection in comparison to control.

% protection = (1-mean no. of writhes in mice of test groups/mean number of writhes in mice of control group) x 100

Ulcerogenic activity

Ulcerogenic labilities of newly synthesized compounds was checked with method of Verma *et al* [28]. Albino rats were fasted for 24 h prior to drug administration. All animals were sacrificed 8 h after drug treatment, and their stomachs and small intestines were microscopically examined to assess the incidence of hyperemia, shedding of epithelium, Petechial and frank hemorrhages and erosion or discrete ulceration with or without perforation. The presence of any one of these criteria was considered to be an evidence of ulcerogenic activity.

Acute toxicity study

The test compounds were investigated for their acute toxicity (ALD_{50}) in albino mice, according to the method of Smith[27]. The test compounds were given orally at different dose levels in separate groups of animals. After 24 h of drug administration, percent mortality in each group was observed. ALD_{50} was calculated from the data obtained

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