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Original Article

Synthesis of novel indole based scaffolds holding pyrazole ring as anti-inflammatory and antioxidant agents

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ABSTRACT

Aim: To synthesize substituted indole based scaffolds having pyrazole ring and evaluate for their anti-inflammatory activity and antioxidant.

Method: The structures of newly synthesized compounds were elucidated by spectroscopic methods such as IR, ¹H NMR, ¹³C NMR, mass, ¹H NMR spectra and elemental analysis. Antioxidant assays like 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging, 2,2-azino bis (3-ethylbenzothiazoline-6-sulfonic acid) (ABTS⁺) radical ion decolorization assay and lipid peroxidation activity (LPO) were performed. Anti-inflammatory activity was studied using linoleic acid as substrate and lipoxidase enzyme.

Results: Among the synthesized analogues compound 7d revealed broad-spectrum of antioxidant activity and on the other hand compound 7c exhibits a promising anti-inflammatory activity.

Conclusion: The achieved results prove that the distinctive compounds could serve as promising lead candidates and also for acclimatization and investigation to construct more active analogues.

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The structural diversity and biological importance of nitrogen containing heterocycles have made them attractive targets for synthesis over many years. Indole derivatives are biologically important chemicals with a wide range of therapeutic properties antifungal,¹ antiviral,² antimalarial,³ have been reported to be associated with the indolic nucleus. Several pyrazoline, pyrrolidine and pyrazole derivatives were potent dual 5-LOX and COX inhibitors.⁴

Even though many biological studies have been carried out on substituted indole analogues, the antioxidant and anti-

inflammatory activities on them bearing pyrazole ring were not explored. Prompted by all these observations and also in continuation of our laboratory work^{5–8} on reaction of indole derivatives, a simple strategy has been planned to synthesize several indole derivatives possessing pyrazoline moiety in their structure with the hope getting compounds with more potent antioxidant and anti-inflammatory agents.

In the present investigation, the synthesis of the title compounds was achieved from the simple synthetic route (Scheme 1). The yields of the synthesized compounds

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(7a–n) are presented in Table 1. The intermediates involved for the synthesis of target compounds (7a–n) were 1H-indole-2-carbohydrazide (6) and substituted chalcones (3a–n). Initially, 1H-indole-2-carbohydrazide (6) was prepared by esterification of 1H-indole-2-carboxylic acid (4) afforded ethyl indole-2-carboxylate ester (5) which upon addition of hydrazine hydrate to compound (5) afforded the compound (6). On the other side, various substituted chalcones (3a–n) were prepared by the Claisen–Schmidt condensation of acetophenones and substituted aldehydes (2a–g).⁹ Finally, both the intermediates (6) and (3a–n) were reacted by refluxing in the presence of catalytic amounts of glacial acetic acid to obtain target compounds (7a–n) (Scheme 1).

1. Chemistry

1.1. Synthesis of ethyl indole-2-carboxylate ester (5)

To the mixture of 1H-indole-2-carboxylic acid (1 mM) in DCM and ethanol is added with the addition of Conc. H₂SO₄ and refluxed for 3 h to get ethyl indole-2-carboxylate ester (5) in good yield, m.p: 122–125 °C.

1.2. Synthesis of 1H-indole-2-carbohydrazide (6)

The mixture of hydrazine hydrate (15 mL) and ethyl indole-2-carboxylate ester (1 mM) was stirred at 0–5 °C for 30 min. The reaction is being monitored by TLC (hexane:ethyl acetate 4:6). Further, the reaction mixture was refluxed for 4 h to give 1H-indole-2-carbohydrazide as a pale yellow colored shining product, m.p: 138–141 °C.

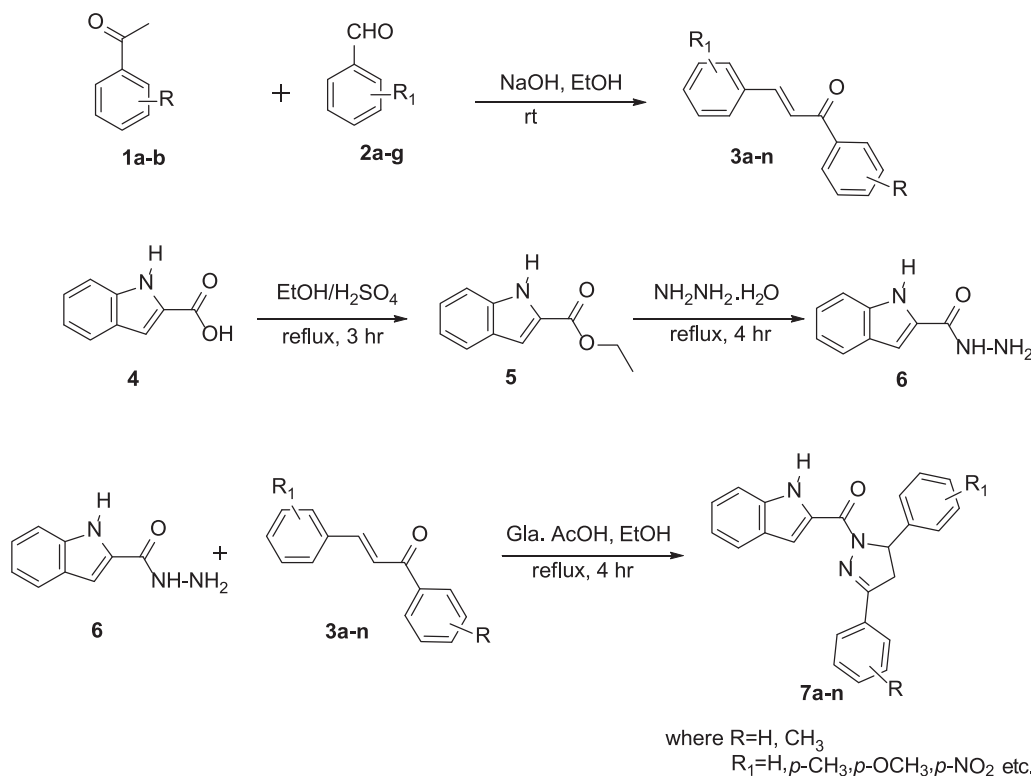
1.3. General procedure for the synthesis of 1H-indol-2-yl (4,5-dihydro-3,5-substituted diphenylpyrazol-1-yl) methanones (7a–n)

The solution of substituted chalcones (3a–n) (1 mM) and 1H-indole-2-carbohydrazide (6) (1 mM) and was refluxed in the presence of glacial acetic acid in catalytic amounts for 4 h. The reaction is being monitored by TLC using hexane:ethyl acetate (4:6). After the completion of the reaction, the mixture was quenched with cold water and extracted with diethyl ether. The extract was washed with distilled water and with brine solution. Finally, dried under reduced pressure.

(3,5-diphenyl-4,5-dihydro-1H-pyrazol-1-yl)(1H-indol-2-yl)methanone 7a. Yellowish, m.p: 168–170 °C; IR ν_{\max} (cm⁻¹): 3338, 2985, 2857, 1688, 1642, 1263, 747, 700; ¹H NMR (400 MHz, DMSO-d₆) δ (ppm): 11.87 (s, 1H, NH), 7.85 (d, 1H), 7.81 (m, 2H), 7.58 (d, 1H), 7.53 (m, 3H), 7.44 (d, 1H), 7.40 (d, 2H), 7.25 (d, 2H), 7.24 (m, 1H), 7.10 (t, 1H), 6.99 (t, 1H), 5.69 (m, 1H), 3.76 (d, 1H), 3.19 (d, 1H); ¹³C NMR (100 MHz, DMSO-d₆) δ (ppm): 168.2, 151.3, 139.4, 130.8, 129.6, 128.5, 128.2, 126.7, 126.4, 121.5, 120.6, 119.6, 114.9, 111.1, 64.6, 42.2; MS (EI): *m/z* 366.44 (M+1)⁺. Anal. calcd. for C₂₄H₁₉N₃O: C, 78.88; H, 5.24; N 11.50; O 4.38. Found: C, 78.89; H, 5.26, N, 11.52, O, 4.36.

(5-(4-hydroxyphenyl)-3-phenyl-4,5-dihydro-1H-pyrazol-1-yl)(1H-indol-2-yl)methanone 7b. Light black, Yield: 78%; m.p: 172–174 °C; IR ν_{\max} (cm⁻¹): ¹H NMR (400 MHz, DMSO-d₆) δ (ppm): 5.32 (s, 1H, –OH); ¹³C NMR (100 MHz, DMSO-d₆) δ (ppm): MS (EI): *m/z* 382.47 (M+1)⁺. Anal. calcd. for C₂₄H₁₉N₃O₂: C, 75.57; H, 5.02; N, 11.02; O, 8.39. Found: C, 75.55; H, 5.05; N, 11.04; O, 8.37.

(1H-indol-2-yl)(5-(4-methoxyphenyl)-3-phenyl-4,5-dihydro-1H-pyrazol-1-yl)methanone 7c. Blackish, m.p: 183–185 °C; IR



Scheme 1 – Protocol for the synthesis of 1H-indol-2-yl (4,5-dihydro-3,5-substituted diphenylpyrazol-1-yl) methanones (7a–n).

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