

Review Article

Indole as a Core Anti-Inflammatory Agent- A Mini Review

K. Hemalatha^a, G. Madhumitha^{*a}, Selvaraj Mohana Roopan^b^aOrganic Chemistry Division, School of Advanced Sciences, VIT University, Vellore – 632 014, Tamil Nadu, India.^bChemistry Research Laboratory, Organic Chemistry Division, School of Advanced Sciences, VIT University, Vellore – 632 014, Tamil Nadu, India. Tel.: 91-416 220 2352, Fax: 91-416 224 3092.**Abstract**

Indole is a privileged heterocyclic nucleus set up in diverse natural products, endogenous molecules and medicinal agents. Even though it has diversified actions, the role of indole in anti-inflammatory therapy is of prime interest which is prominently shown in the drug molecule Indomethacin. The efficacy of the indomethacin and tenidap is primarily due to the inhibition of the cyclooxygenase (COX) enzyme activity. The adverse reactions of most of the NSAIDs (Non Steroidal Anti-

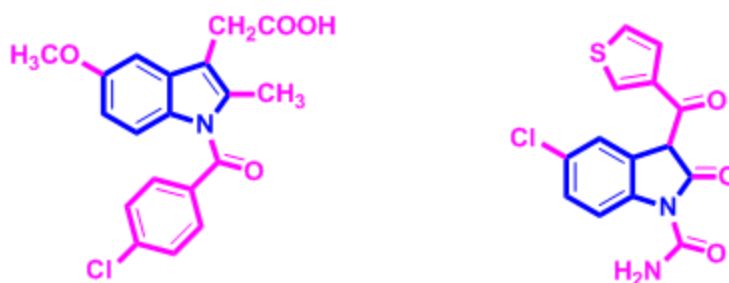
inflammatory Drugs) are due to the irritating moiety present in the molecule or due to the decreased production of cytoprotective prostaglandins. In this review, the various structural modifications of indole have been studied to enlist the improvement in the therapeutic profile of the nucleus.

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Keywords: Indole, NSAIDS, Anti-inflammatory, Cyclooxygenase**Introduction**

NSAIDs are the most frequently prescribed drug for the treatment of pain and inflammation. It is a complex process involving various endogenous substances. The mediation of the endogenous prostaglandin is responsible for both the therapeutic and adverse reactions. NSAIDs includes diverse category of functional groups and Indomethacin and Tenidap (**Figure 1**) having indole nucleus are among the most widely used drug. The inhibition of cyclooxygenase enzyme has to be concerned with paramount care. COX-1, the house keeping enzyme and COX-2 enzyme expressed principally in the inflammatory cells has to be selectively inhibited. Even though indomethacin is a selective inhibitor of COX-1 enzyme, the changes in the core indole motif can change the selectivity towards the COX-2 enzyme [1]. Indole is an attention-grabbing molecule and the current review discusses the effect of alterations made at various positions of indole over the anti-inflammatory activity.

**Figure 1** Chemical structure of Indomethacin and Tenidap

Indole and its Anti-Inflammatory Activity

The selectivity of cyclooxygenase enzyme was estimated by altering the substituent at N-1 and C-3 positions of the indole ring. The results explored that all the compounds showed potent in-vitro inhibition against COX-2 enzyme than COX-1 enzyme. The compound 1-benzoyl-3-[(4-trifluoromethylphenylimino)methyl]indole (**Figure 2**) exhibited significant COX-2 inhibition and selectivity (COX-1 $IC_{50} > 100 \mu\text{M}$, COX-2 $IC_{50} = 0.32 \mu\text{M}$) in the in-vitro determination using enzyme immune assay kit. Also it was supported by the energy of intermolecular interactions ($E_{\text{intermolecular}} = -12.50$) calculated in the docking of compounds against COX-1/COX-2 active site [2].



Figure 2 Significant COX-2 inhibitory compound

The anti-inflammatory activity of various isatin semicarbazide derivatives were evaluated by carrageenan-induced paw edema test in rats. The compound (**Figure 3**) containing trifluoro methyl substituent displayed significant anti-inflammatory activity at the dose of 10 and 20 mg/kg and one-third of ulcer index compared to the reference drug diclofenac and aspirin. It was concluded that the electron-withdrawing nature and the increased lipophilicity of the substituent may be the reason for the potent activity compared to that of the other substituent [3].

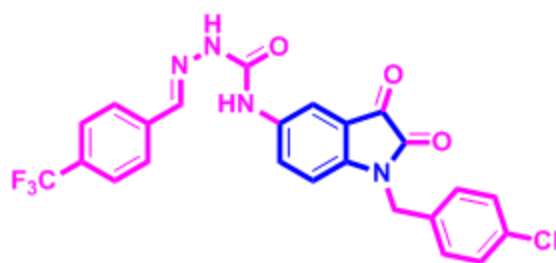


Figure 3 Chemical structure of Anti- inflammatory compound

Indole substituted in the 3rd position with various chalcones, pyrazolines and azo-compounds were evaluated for their anti-inflammatory activity. The compound (**Figure 4**) showed a maximum of 47% anti-inflammatory activity among the compounds obtained in the various three stages. It also exhibited less ulcerogenic liability than the standard drug, phenylbutazone and approximate lethal dose (ALD₅₀) at the maximum dose of 2000 mg/kg p.o. The comparative activity can be explained in such a way that pyrazolines are more active than chalcones and azo-compounds (Pyrazolines > Azo-compounds > Chalcones) [4].

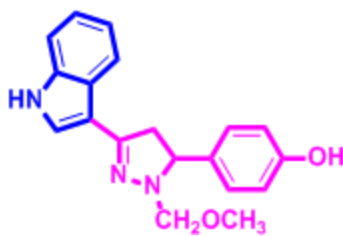


Figure 4 Maximum potency of anti- inflammatory compound

Indole library containing two types of substitution pattern were explored for the COX inhibition using the grouping of NMR, molecular modeling, and biological screening. One type containing substitution at the N-1, C-3, C-5 and another at C-2, C-3 and C5 position of indole ring. The most potent compound (**Figure 5**) exhibited selectivity towards COX-2 inhibition at 50 μ M. It attained the selectivity towards the COX-2 enzyme because of the correct Y shape orientation of the molecule in the active site which was similar to that of the known selective inhibitor SC-558 [5].

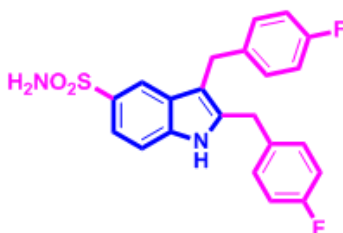


Figure 5 COX-2 inhibitory compound

A Series of novel 1,3,4-oxadiazole and 1,2,4-triazole moieties substituted in the indole ring at C-3 position was evaluated for anti-inflammatory activity. Even though all the compounds exhibited remarkable activity, the compound (**Figure 6**) was superior to the other compounds [6].

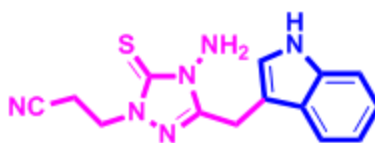


Figure 6 Chemical structure of 1,2,4-triazole hybrid indole

The consequence of varying 4-octyl residue and bioisosteric replacement of carboxylic acid in 1-[3-(4-octylphenoxy)-2-oxopropyl]indole-5-carboxylic acid (**Figure 7**), a dual inhibitor of cPLA₂ α (cytosolic phospholipase A₂ α) and FAAH (fatty acid amide hydrolase) was studied. Both these enzymes are responsible for increasing arachidonic acid, a key substance involved in inflammation. Most of the compounds are active against both the enzymes and it was concluded that an effective anti-inflammatory agent can be produced by dual inhibition of enzymes instead of selective inhibitors [7].

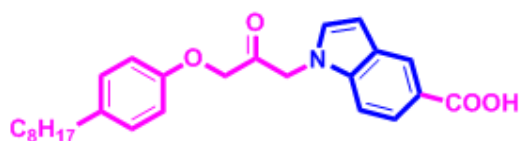


Figure 7 Structure of dual inhibitory cPLA₂ α and FAAH

Indole derivatives containing substituted pyrimidines in the C-3 position were reported with potent anti-inflammatory activity and less ulcerogenic index. In specific the substituent's such as hydroxyl and amino groups (**Figure 8**) on the pyrimidine ring have superior activity since it can form hydrogen bond with the receptor and efficient binding can be achieved [8].

[2-[[4-substituted)-pyridin-2yl]carbonyl]-(6 or 5-substituted)-1H-indol-3-yl]acetic acid analogues were synthesized. All the compounds showed selectivity towards COX-2 than the COX-1 enzyme. The compound (**Figure 9**) demonstrated potent activity for COX-2 enzyme in the human whole blood assay, human cell based assay and edema suppression effect in carrageenan-induced peripheral inflammation model on the paw of rats [9].

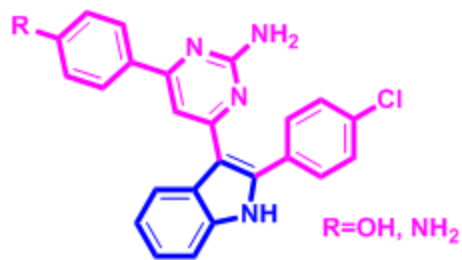


Figure 8 Potent pyrimidone analogue

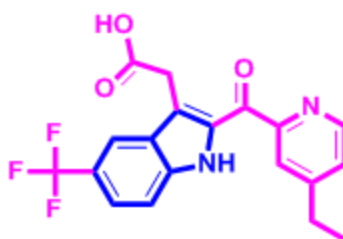


Figure 9 Compound selective towards COX-2 than the COX-1 enzyme

The gastro toxicity exerted by the direct contact of the acidic drug such as indomethacin was rectified by the ester prodrug formation. The prodrug compound (**Figure 10**) reported low ulcer index and exhibited comparable anti-inflammatory activity with that of the standard drug indomethacin. The prodrugs are more lipophilic than indomethacin which was confirmed in octanol-buffer partition coefficient system. Also the metabolic stability of the prodrug was proved by the rat liver chromosomes and rat plasma assay [10].

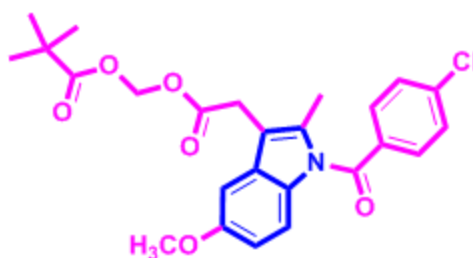


Figure 10 Chemical structure of low ulcer index compound

Pyrano(2,3-*c*)pyrazole nucleus substituted at the 3rd position of indole moiety (**Figure 11**) were reported with remarkable anti-inflammatory activity and the presence of halogen atom influenced the activity than the other compounds [11].

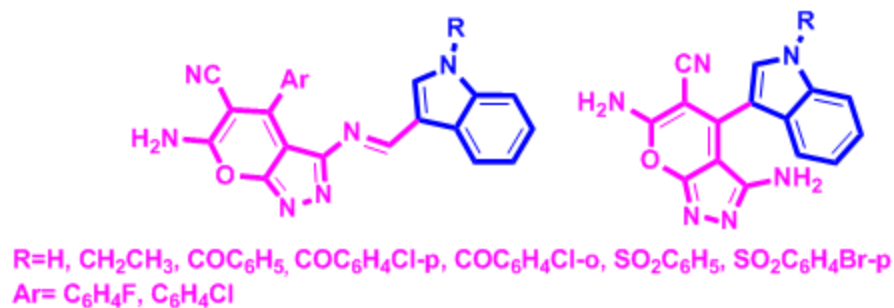


Figure 11 Pyrano[2,3-*c*]pyrazole analogues

The effect of nitro group over the anti-inflammatory activity was investigated and it was found that the compound (**Figure 12**) containing 6-nitro group and the chloro phenyl moiety exhibited significant anti-inflammatory activity at the dose of 5 mg/kg.

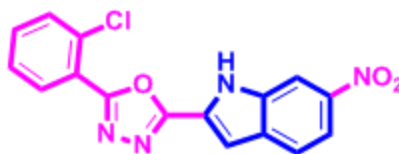


Figure 12 Chemical structure of anti- inflammatory compound

Conclusions

The uniqueness of the indole nucleus has to be understood clearly and it has to be modified accordingly. The necessity for this review arises because of the potency of the indole containing NSAIDs. The extensive analysis of indole provides a scope for the invention of effectual agent in the future drug discovery.

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References

- [1] Mitchell J A, Larkin S, Williams T J (1995) Cyclooxygenase-2: Regulation and relevance in inflammation. *Biochem Pharmacol* 50:1535-1542.
- [2] Kaur J, Bhardwaj A, Huang Z, Knaus E E (2012) N-1 and C-3 substituted indole Schiff bases as selective COX-2 inhibitors: Synthesis and biological evaluation. *Bioorg Med Chem Lett* 22:2154-2159.
- [3] Prakash C R, Raja S, Saravanan G (2012) Design and synthesis of 4-(1-(4-chlorobenzyl)-2,3-dioxindolin-5-yl)-1-(4-substituted/unsubstituted benzylidene) semicarbazide: Novel agents with analgesic, anti-inflammatory and ulcerogenic properties. *Chinese Chem Lett*, **2012**, 23, 541-544.
- [4] Rani P, Srivastava V K, Kumar A (2004) Synthesis and antiinflammatory activity of heterocyclic indole derivatives. *Eur J Med Chem* 39, 449-452.
- [5] Estevao M S, Carvalho L C R, Freitas M, Gomes A, Viegas A, Manso J, Erhardt S, Fernandes E, Cabrita E J, Marques M M B (2012) Indole based cyclooxygenase inhibitors: Synthesis, biological evaluation, docking and NMR screening. *Eur J Med Chem* 54:823-833.

- [6] Gadegoni H, Manda S (2013) Synthesis and screening of some novel substituted indoles contained 1,3,4-oxadiazole and 1,2,4-triazole moiety. *Chinese Chem Lett* 24:127-130.
- [7] Zahov S, Drews A, Hess M, Elfringhoff A S, Lehr M (2011) 1-(3-Biaryloxy-2-oxopropyl)indole-5-carboxylic Acids and related compounds as dual inhibitors of human cytosolic phospholipase A₂α and fatty acid amide hydrolase. *Chemmedchem* 6:544-549.
- [8] Chavan R S, More H N, Bhosale A V (2011) Synthesis, characterization and evaluation of analgesic and anti-inflammatory activities of some novel indoles. *Trop J Pharm Res* 10:463-473.
- [9] Hayashi S, Sumi Y, Ueno N, Murase A, Takada J (2011) Discovery of a novel COX-2 inhibitor as an orally potent anti-pyretic and anti-inflammatory drug: Design, synthesis, and structure–activity relationship. *Biochem Pharmacol* 82, 755-768.
- [10] Bandgar B P, Sarangdhar R J, Viswakarma S, Ahamed F A (2011) Synthesis and biological evaluation of orally active prodrugs of Indomethacin. *J Med Chem* 54:1191-1201.
- [11] Mandour A H, El-Sawy E R, Ebaid M S, Hassan S M (2012) Synthesis and potential biological activity of some novel 3-[(N-substituted indol-3-yl)methyleneamino]-6-amino-4-aryl-pyrano(2,3-c)pyrazole-5-carbonitriles and 3,6-diamino-4-(N-substituted indol-3-yl)pyrano(2,3-c)pyrazole-5 carbonitriles. *Acta Pharm* 62:15-30.
- [12] Narayana B, Ashalatha B V, Vijaya Raj K K, Fernandes J, Sarojini B K (2005) Synthesis of some new biologically active 1,3,4-oxadiazolyl nitroindoles and a modified Fischer indole synthesis of ethyl nitro indole-2-carboxylates. *Bioorg Med Chem* 13:4638-4644.

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