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HETEROCYCLIC COMPOUNDS WITH ANTI-INFLAMMATORY PROPERTY: A MINI REVIEW

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ABSTRACT

Heterocyclic rings are ubiquitous structural feature of many anti-inflammatory compounds. Non steroidal anti-inflammatory drugs (NSAIDs) are the most widely used medicines for the relief of pain and inflammation. These drugs have enormous side effects, particularly in the gastrointestinal tract and kidneys. Various approaches have been used for obtaining safer anti-inflammatory drugs. In this review, we have summarized the anti-inflammatory activity of various heterocyclic rings such as pyrazine, pyrimidine. acridine, thiazole, pyridazinone, pyrido imidazole, imidazolo quinoline, pyrazoline, quinoline, pyrrole, furan, diazole and imidazo thiadiazole, using various scientific websites like PubMed, Google Scholar, ScienceDirect etc.

KEYWORDS: Heterocyclic compound, Anti-inflammatory activity, NSAIDs, Gastric ulceration.

INTRODUCTION

Figure-1: Points of inflammation & 7 points of pain.

Anti-inflammatory drug is a term referring to the substances that used for treatment of inflammations, pain, arthritis, etc. The most common anti-inflammatory drugs are aspirin, ibuprofen and naproxen and this type of drugs are called Non-steroidal Anti-inflammatory Drug (NSAIDs)[1] and this term recognizes these drugs from steroids.[2] The mechanism of actions of these drugs includes inhibiting the activity of cyclooxygenase (COX) enzymes resulting in the prevention of prostaglandins (PGs) Synthesis, which are the cause of inflammation.[1] Prostaglandins are released at the site of inflammation when leukocytes are attracted to the inflamed or injured area. All mammalian cells except red blood cells can produce the prostaglandins and when injured the injured cells release large amount of these substances. cyclooxygenase is the enzyme which is responsible for converting arachidonic acid to prostaglandin. This enzyme has two types such as COX1 and COX2. In contrast to COX-1, COX-2 expression is usually minimal, but when activated, COX-2 regulates prostaglandin production primarily within the inflammatory cell.[3] Inhibition of COX-1 turns some of its important functions such as the repair and maintenance of stomach lining which results in varying degrees of gastric ulceration and acute renal failure.[4-7] These observations emerged the need for newer anti-infammatory NSAIDs without gastric toxicity.[8-12]

Heterocyclic compounds are the largest family of organic compounds. In search of safer anti-inflammatory drugs, different types of heterocyclic compounds have been synthesized and screened for the anti-inflammatory and pain reducing activity. In this review, we mainly focused on the anti-inflammatory activities of heterocyclic compounds, like pyrimidine, pyridine, thiazole, imidazole, oxazole, pyrazole and pyrole, acridine with their reduced side effect compared to the traditional NSAIDs.[13]

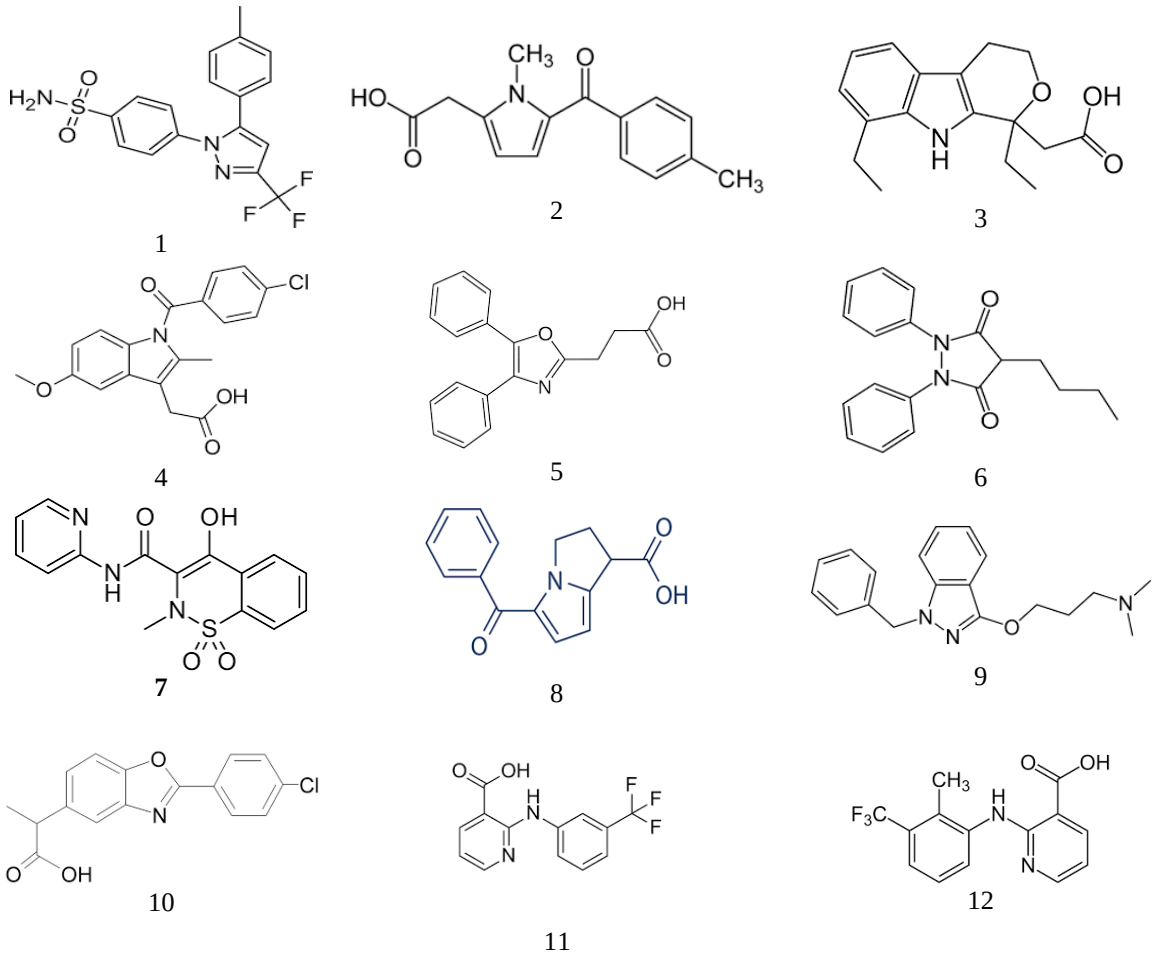

Figure-2: Marketed anti-inflammatory drugs containing heterocyclic ring: (1) Celecoxib (2) Tolmetin (3) Etodolac (4) Indomethacin (5) Oxaprozin (6) Phenylbutazone (7) Piroxicam (8) Ketorolac (9) Benzydamine (10) Benoxaprofen (11) Niflumic acid (12) Flunixin.

DIFFERENT HETEROCYCLIC MOIETIES WITH ANTI-INFLAMMATORY ACTIVITIES

1. Pyrazine Derivatives: Pyrazines are very important class of heterocyclic compounds and have attracted the attention of many eminent scientists. Synthesis and anti-infammatory activity of a number of pyrazolopyrazine derivatives have been reported by the scientist.[14,15] The mechanism of actions of these drugs includes inhibiting the activity of cyclooxygenase (COX) enzymes. The activity of these enzymes is the metabolism of

arachidonic acid. Isoenzymes of cyclooxygenase may be the target of these drugs.[16] A European patent[17] described elaborately the synthesis of a pyrazine derivative which is useful in preventing and/or treating peptic ulcer. These compounds were used in the stress-induced and pylorus ligation of ulcer tests in rats.

2. Pyrimidine Derivatives: A series of [4, 6-diaryl-2-thioxo-1, 2,3,4-tetrahydropyrimidine-5-yl]acetic acids were synthesized and evaluated against anti-inflammatory activity. These compounds exhibited moderate antiinflammatory activity[18] on screening *in-vivo* as compared to standard drug diclofenac. Pyrimidinedione derivative is useful as an anti-inflammatory agent and has been synthesized in nine steps.[19] Lee et al[20] synthesized the pyrimidine derivative and their pharmaceutically accepted non toxic salts also. It is claimed that these compounds possessed a fabulous inhibitory activity against the gastric acid secretion from stomach.[21] A number of condensed pyrimidine derivatives viz bicyclic compound, tetracyclic compound and pentacycic derivative have been synthesized and screened for anti-inflammatory activity. Many compounds at 100mg/kg p.o. have shown interesting anti-inflammatory activity which is summarize.[22]

3. Pyridazinone Derivatives: A lot of 3(2*H*)-pyridazinone derivatives have been reported as analgesic and anti-inflammatory agents without gastrointestinal side effect.[23] This compound was shown to be more effective in analgesic and anti-inflammatory activities and less potent in toxicity than aminopyrine and phenylbutazone. Several pyridazinone derivatives in which possible active sites of these compounds were eliminated and changes were prepared, Researchers are careful from the therapeutic index that the compound, was found to be more superior to tiaramide, mepirizole, benzydamine, phenylbutazone.[24]

4. Acridine Derivatives: Acridinyl 9-thioacetic acids and their derivatives have been synthesized by Gaidukevich et al.[25] and screened them for anti-inflammatory, analgesic and antihypoxia activities. Majority of these compounds have shown anti-inflammatory activity equal to that of the indomethacin. The analgesic activities of these compounds are 1.2 to 1.4-fold higher than that of analgin. The 9, 10-dihydro-9-oxo-2-acridine alkanoic acids have been synthesized and screened for anti-inflammatory activity by the rat hind paw carrageenan-induced edema assay.[26] The above mentioned few examples demonstrate that acridine derivatives posseses some interesting anti-infammatory activity.

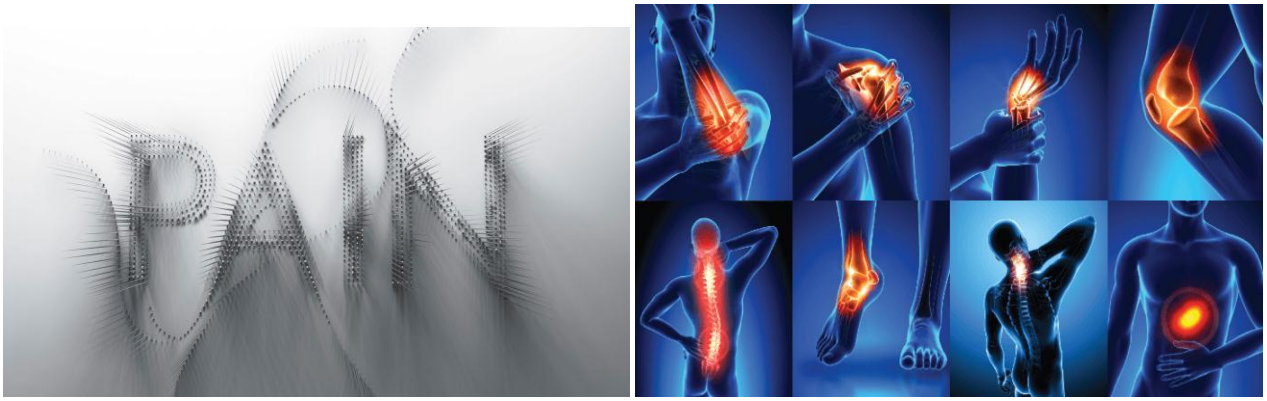

Figure-3: Pain; the most unwanted physiological feelings.

5. Pyrido Imidazole Derivatives: Various types of heterocyclic compounds in this section we will be reported in brief, different types of compounds possessing anti inflammatory activity. Synthesis of mercaptopyridoimidazole derivatives possessing anti-inflammatory activity have been reported in the literature.[27,28] The activity of the newly synthesized compounds compared with indomethacin as a reference compound was measured before and 4h after carrageenan injection. Percentage of the edema inhibition was calculated as regards with saline control group and potency was calculated as regards percentage of the change of indomethacin and tested compounds.[29] The standard drug Ibuprofen was used as for anti-inflammatory activity; and the compounds synthesized have shown the maximum anti-inflammatory activity when compared with control. The active compounds could be taken as lead for the structural and molecular modification was thought of in future.

6. Pyrimidine and Pyrazine Derivatives: Different NSAIDs such as sodium salicylate, sulindac, ibuprofen and flurbiprofen cause anti-inflammatory and antiproliferative effects independent of cyclooxygenase activity and does not cause prostaglandin synthesis inhibition. These effects are mediated through inhibition of certain transcription factors such as AP-1 and NF-kB. The effects of respective NSAIDs are probably exerted predominantly through changing of the activity of cellular kinases such as IKK, Erk, P38MAPK or CdkS. These effects are not apparently shown by all NSAIDs because indomethacin failed to inhibit NF-kB and AP-1 activation as well as Erk and Cdk activity. Sodium salicylate or aspirin do not affect pPARr however

indomethacin was able to activate the pPARr. The NSAIDs acting in cyclooxygenase independent mechanisms may be of specifc use in individual patients because additional effects may either enhance the eficacy or reduce the toxicity of the respective compounds. DiGirolama et al. studied the effect of NSAIDs on lipoxygenase and cyclooxygenase activities on human colon segments from patients with neoplasia.[30] Pyrimidine carboxamides and pyrazine carboxamides which are inhibitors of transcription factors (i.e NFK*B* and AP-1) and cytokines and have utility as anti-infammatory agents in general, have been synthesized by Suto et al.[31] The 4-benzyl-2-phenyl pyrimidine derivatives which are useful in the treatment of phospholipase A2 (PLA2) mediated disease have been synthesized and disclosed in an international patent.[32] A number of thiazolopyrimidines as modulators of chemokine receptor activity were synthesized by Austin et al.[33] Some of these compounds showed inhibition of interleukin-1 and thus useful as anti-inflammatory agents. Wachter et al.[34,35] synthesized 2-substituted imidazoles which is useful in the treatment of inflammatory diseases.

7. Thiadiazole Derivatives: Synthesis of 1,3,4-thiadiazole systems containing Pyrazoles and Pyrroles make good yields. 1,3,4-thiadiazol-2-yl-acrylamide is the key intermediate in the formation of these heterocyclic compounds.[36] All the synthesized compounds have been investigated for their anti-inflammatory activity, accordingly this novel class of new 1,3,4-thiadiazole derivatives reported from our laboratory, emerge as a valuable lead series with great potential to be used as anti-inflammatory agents and as promising candidates for further effective evaluation.[36-38]

8. Imidazolo Quinoline Derivatives: Some imidazolo quinoline derivatives were synthesized and evaluated for their anti-inflammatory and ulcerogenicity index using carageenan induced rat paw edema and pyloric ligation methods. The percent protection was measured and the activity was compared with standard drug ibuprofen. The results of anti-inflammatory screening studies are reported. The physicochemical properties of the imidazoloquinolines, which were the subject of these biological studies in this report. The imidazoloquinolines made of imidazoline and quinoline through Ethylene Bridge. All the structures were confirmed on the basis of physical and spectral studies i.e Mass spectroscopy and elemental analysis.[39-41]

9. Pyrazoline Derivatives: Various derivatives of 1,2 pyrazolines from Chalcones achieve the promising and selective inhibition as far as anti-inflammatory activity is concerned. The synthesized 1,2 pyrazoline derivatives resemble with some of the COX-II inhibitory agents like celecoxib and rofecoxib The Anti-inflammatory screening was performed by carrageenan induced paw oedema method by using water displacement plethysmography. As a result, the screened compounds have shown good Anti-inflammatory activity.[42] Pyrazoline nucleus when linked with different substituents like alkyl, aromatic, heterocyclic rings and many other groups at different positions on the ring shows considerable to more effective anti-inflammatory activity.[43] A further modification in its main nucleus provides more efficient derivatives with more potent therapeutic efficacy.[44,45]

10. Pyrrole Derivatives: A novel class of pyrrole derivatives were synthesized which consisted of a small appendage fragment (carbaldehyde, oxime, nitrile) on the central core. The compound was found most effective *in-vivo* and exhibited a significant profile when compared to the already marketed reference compounds. This compound was more efficient and potent in inducing a percentage of writhes reduction in comparison to the marketed drug, celecoxib.[46-48] All the compounds proved to inhibit J774 COX-2 activity *in-vitro*, and this inhibitory effect is reasonably involved in their analgesic and anti-inflammatory activities detected *in-vivo*. These results, even referred to only one example of each class of synthesized compounds, indicate that nitrile derivatives show a better selectivity towards COX-2 than the other two classes of derivatives.

11. Quinoline Derivatives: The present study reveals that compound exhibited better anti-inflammatory activity than other tested compounds. A structural activity resealtionship (SAR) study reveals that 2-fluoro benzyl and 4-methyl phenyl sulphonamide moieties are responsible for the observed anti-inflammatory activity and considered to be the pharamcophoric groups. The dihydroquinoline structure exists in a large number of natural products and biologically active molecules.[49] Particularly, many of these naturally occurring 1,2-dihydroquinolines and their synthetic analogs are important precursors for the synthesis of natural products and pharmaceuticals. Therefore, the development of new and efficient synthetic routes for the preparation of dihydroquinoline analogs is of importance to both organic synthetic and medicinal chemistry.[50,51] At the inflammatory site, the release of chemical mediators, which cause edema as a result of extravasations of fluid and proteins from the local microvasculature and accumulation of polymorphonuclear leukocytes resulted in acute inflammation. Carrageenan model is conventional, sensitive, and accepted for screening of newer anti-inflammatory agents as it induces inflammation resulting from a complex of diverse mediators.

12. Furan Derivatives: Furanone and its derivatives have been reported to have anti-inflammatory activity.[52] In view of these observations and as a part of an ongoing research program on development of newer anti-inflammatory and analgesic agents, the synthesis and pharmacological activities of a series of 2(3*H*)-furanones fused with the quinoline moiety are reported herein.[53,54] 5-Hydroxy methyl furfural (5-HMF) showed *in-vivo*

anti-inflammatory effects, suggesting that the compound might represent a potential therapeutic option for the treatment of inflammation processes. Related to inflammatory process, it was shown that crude Maillard reaction products or their fractions have anti-inflammatory activities on Caco cells and 5-HMF was identified as one of components of those fractions.[55] Present study aims to examine the effects of 5-HMF on topical inflammatory model. The molecular structures of 5-HMF was generated and optimized. The TPA model of ear inflammation is useful for screening prospective topical anti-inflammatory compounds that act at variety of levels.[56] The maximal anti-inflammatory activity (inhibition of 32.5%) was obtained at dose of 0.3 mg/ear of 5-HMF. this work reveals, for the first time, that 5-HMF has *in-vivo* anti-inflammatory effects, suggesting that the compound might represent a potential therapeutic option for the treatment of inflammatory processes.[57]

13. Diazoles: 1,2-diazole is a heterocyclic compound having varied biological activity and still of great scientific now a days. The present diazoles were synthesized because of its good biological activity. Compounds including a 1,2-diazole nucleus and N-substituted derivatives are having various biological activity.[58] Pharmacological study was carried out to test anti-inflammatory the activity of sulfa/substituted 1,2-diazoles. The main aim of the present investigation was to evaluate the claimed anti-inflammatory activity of sulfa/substituted 1, 2-diazoles.[59] Percent of the oedema inhibition was calculated as regards saline control group and potency was calculated as regards percentage of the change of indomethacin and tested compounds.

14. Imidazo Thiadiazole Derivatives: In order to synthesize new anti-inflammatory and analgesic compounds with a safer profile of side effects, a new compound known as 2,6-diaryl-imidazo[2,1-b][1,3,4]thiadiazole derivatives were synthesized and evaluated *in-vivo* for their anti-inflammatory and analgesic activities in carrageenan-induced rat paw edema. The compounds not showed ulcerogenic activity.[60,61]

Molecular docking studies were carried out to investigate the theoretical bond interactions between the compounds and target, the cyclooxygenases (COX-1/COX-2). The compound exhibited a higher inhibition of COX-2 compared to diclofenac. The compounds have a higher affinity to COX-2, than COX-1. The compounds presented a higher affinity to COX-2, referred to diclofenac. The analysis of the binding pattern showed that some amino acid residues are important in the formation of the hydrogen bond with the synthetic molecules.[62,63]

CONCLUSION

The plethora of research elucidated in this review furnishes the anti-inflammatory activity of different heterocyclic derivatives with less ulcerogenicity. Further modification of these derivatives may provide more potent and less toxic anti-inflammatory molecules. This review collected information about various heterocyclic nucleuses, substituted with different type of groups, having anti-inflammatory properties and also discussed their ulcer index. Huge efforts are needed to bring less ulcerogenic anti-inflammatory heterocyclic molecules in the market.

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