REVIEW OF LITERATURE

INFLAMMATION The word inflammation was defined time to time by many workers. It has been defined as the 'reaction of irritated and damaged tissue which still retain vitality' while others proposed that "inflammation is a process which begins following a sublethal injury to tissue and ends with complete healing". The important idea at the out set is that inflammation is a process and not a state (Florey, 1970).

HISTORY OF INFLAMMATION

The study of inflammation dates back to first coherent description of the phenomenon, presented by Celsus, a Roman physician (about B.C. 30 to A.D. 38); enunciating four cardinal signs; rubor (redness), tumour (swelling), calor (heat) and dolar (pain). To these Galen added fifth sign functio loesa (loss of function), that was supported by John Hunter. Boerhaave laid much emphasis on the changed state of blood vessels, Haller and Spallanzane in 17th and 18th century established that the redness of the inflammed part was due to the passage of blood into tissues. Cohnheim in 1882 shared the view with Samnel, that the main feature of the reaction was an increased permeability of the vascular wall; a view which has been subsequently modified and extended. Metchnikoff put forward the theory of phagocytosis being the central phenomenon (Florey, 1970).

The whole phenomenon acquired a new meaning with notion of autopharmacology, introduced by Sir Henry Dale to describe the phenomenon that depend upon formation, synthesis or release of endogenous active substances, the so called mediators of physiopathological phenomenon. From a historical point of view, the histamine produced a typical flare in human skin, indistinguishable from that produced by insect bites and other irritating agents, including antigens or allergens in allergic individuals. The search for new mediators of the inflammatory reaction became a main concern. Kallidin was identified by Werle (1970) as mediator while and Ramwell and Pharris (1972) claimed that prostaglandins of E series are involved in cellular injury and inflammation. Paulus and Whitehouse (1972) mentioned some of the complements in this regard which together form approximately 10% (w/v) of human globulins.
PATHOPHYSIOLOGY

Inflammation is a manifestation of severe cellular injury leading to the inflammation which is a complex vascular, lymphatic and local tissue reaction, elicited in higher animals by the presence of viable or non-viable irritants. Normally, the tissue damaging stimulus may arise from exogenous or endogenous substances, which initiates a series of biochemical, immunological and cellular events, proceeding through apparently well regulated steps ending into physical repair and restitution of function of the "injured" tissue.

Any inflammatory reaction has three features in chronological sequence:

1. Transudative phase – dilatation of blood vessels and increased vascular permeability causing erythema and oedema at the site of irritating stimulus.
2. Exudative phase – cellular infiltration and general "mapping up" reaction.

ACUTE INFLAMMATION

Local Tissue Response To Injury

The orderly interaction between cells the microcirculation and the extracellular fluid in the maintenance of tissue homeostasis gets disrupted both anatomically and physiologically following injury. The immediate reaction is one of vasodilation, leading to an increase in the permeability of the vascular wall. Small molecules together with plasma fluid leak out of the extravascular space in increasing quantities, leading to oedema. This immediate response reaches a peak of intensity at about 30 minutes following injury and progresses to a latent phase after about 2 hours. However, within 2 to 4 hours a second wave of fluid loss occurs secondary to even more marked vascular permeability. Oedema formation becomes severe and the loss of large plasma molecules including fibrinogen leads to formation of fibrin with in the field of injury. Polymorphonuclear leucocytes also begin to flood the field, with the early formation of pus. These extracellular events following injury are accompanied by changes within the vessels.

The nature of the local tissue at the site of injury begins to change after the initial 5 hours, particularly in the quantity and type of cellular infiltrate. Specifically the polymorphonuclear leucocytes begin to decline and mononuclear cells comprise more
and more exudate. Thus, by 24 hours, the field of inflammation is composed almost entirely of monocytes. The entravascular events in acute response to injury are schematically presented in Fig. 1.

**Chemical Mediators of Inflammation**

The acute inflammation response is mediated by potent chemical substances, which have their effect chiefly on the vessels of the microcirculation. The dilatation of blood vessels and increase in permeability is the basic process underlying inflammatory response. It should again be pointed out that the response is biphasic; the initial or immediate response is short timed and lasts not more than two hours, while the second or delayed response begins after 2 hours of injury and may last up to 12 hours after the time of injury. These two distinct responses are mediated by a different group of chemicals, which are produced following a complicated chain reaction.
involving a number of precursor or substances. The important mediators are amines, Kallikrein and prostaglandins.

Amines: Amongst the diogenic amines, histamine and 5-hydroxytryptamine (serotonin) are present in the metachromatic cytoplasmic granules of the mast cells.

Mast cells are small mononuclear cells that are present in moderate number in the connective tissue, most concentrate within the outer covering (adventitia) of blood vessels and are thought to be tissue counterpart of the circulating blood basophils. These cells are quite vulnerable to injury and under a variety of stimuli. Such as mechanical trauma, chemical toxins, heat or cold or ionizing radiation undergo cytoplasmic granulation with release of their vasoactive amines. The exact mechanism by which injury induces mast cells to degranulate has not been totally resolved although the activation of surface enzymes rich in −NH₂ and −SH groups seems to be involved (Koneman, 1971).

(a) Histamine: It is the principle mediator of immediate response to injury. Furthermore, histamine liberators like trypsin, lysolecithin, snake venom and polymixin produce response similar to that of inflammation. Two separate mechanisms apparently, are involved in the release of histamine at the site of injury. The enzyme histamine decarboxylase is present in normal tissue. When damage, injured cells release the amino acid histidine, which is immediately decarboxylated by this enzyme to form histamine, This probably accounts for only a minor proportion of the histamine that is released. Of more significance is the release of histamine from mast cells. Histamine acts to increase the size of the interepithelial pores or gaps in the walls of small vessels, through which fluids and small molecules can readily leak into the extravascular fluid. The response reaches a peak by 30 minutes and subsides by 2 hours following injury. This increased permeability of vessels is mainly due to activation of the receptors.

(b) 5-Hydroxytryptamine (Serotonin 5-HT): Serotonin (5-HT) is stored in specific granules in the cell cytoplasm as in platelets, mast cells and the argentaffin cells of intestine from there it is readily liberated. Like histamine, it has been shown to be liberated during early phase of inflammation and might be responsible for vascular reaction and the oedema formation after injury. The permeability effects of 5-HT might be due to direct effects on the vascular epithelium or to the release of histamine.
The early phase of inflammation by egg white and dextran is reduced by anti 5-HT agents.

**Role of Kallikrein-Kinin system:** In the blood are precursor glycoprotein of the alpha-2-globulin fraction called kininogens. Following a stimulus or contact with glass, Hagmen factor is activated, which in turn, activates kallikrein, derived from pancreas. This kallikrein acts on kininogens and split them into bradykinin lysyl-bradykinin, methionyl-lysyl-bradykinin, and kallidin. These kinins have a similar biological action except that the methionyl lysyl derivative is more resistant to inactivation by kinase and thus has a more prolonged action *in vivo* (Koneman, 1971).

The kallikrein is acted upon by the proteolytic enzymes like trypsin and chymotrypsin, and again leads to formation of kinin. The concept of proteolytic mechanism involved in the inflammatory reaction was supported by the demonstration of anti-inflammatory activity of drugs on various protease inhibitors such as trypsin, soyabean, ovomucoid and potato.

Kallikrein is also acted upon by plasmin or fibrinolysin. Fibrinolysin is present in the blood as an inactive precursor, profibrinolysin which is converted into fibrinolysin by activation of fibrinokinase attributed kinin release to the activation of plasma kallikreinogen by plasmin system.

The kinins are responsible for the delayed acute response to injury. Bradykinin has been shown to possess all characteristics of a "chemical mediator of inflammation" such as increase in capillary permeability, pain and migration of leucocytes. Tissue injury leads to a disturbance in cell membrane resulting in activation of kinin forming protease enzyme and production of kinin.

**Prostaglandins (PGS):** Prostaglandins are formed in the body from their precursor, arachidonic acid and are considered as mediators of inflammatory response. But, there is no common agreement on the significance of prostaglandins in the inflammatory response. PGS of E type have been reported to suppress acute and chronic inflammation in normal and adrenalectomized rats, while Ramwell and Pharris (1972) have claimed them to be involved in cellular injury and inflammation. Willis (1969) demonstrated the presence of PGS in the inflammatory process and are often associated with migration of leucocytes into inflamed sites.
In rabbits, it has been shown that during phagocytosis, prostaglandins are released from leucocyte lysosome. PGE$_1$ and PGE$_2$ often induce and increase of vascular permeability in animals and flare response in humans. The increase in vascular permeability and migration of leucocytes is due to release of amines from the mast cells. When the acute phase of inflammation is over, PGS promotes granuloma formation, mediate collagen metabolism and activate mucopolysaccharide synthesis. It was reported that PGE$_2$ elicits potent anti-arthritic effects on adjuvant polyarthritis in the rat, but prostaglandins did not prove to be anti-inflammatory in acute experiments. PGE$_2$, PGA$_1$ and PGA$_2$ inhibited where as PGF$_2$ alpha increased the immunogenic release of betaglucuronidase from human leucocytes. Further, PGE, PGE$_2$, PGA$_1$, PGA$_2$ and PGF$_2$ alpha were reported to depress phagocytosis by polymorphonuclear leucocytes. Centrally administered PGF$_2$ alpha exerts anti-inflammatory while, PGE$_2$ exerts pronociceptive effect on Brewer yeast-induced acute inflammation and pain providing evidence of involvement of CNS in modulation of peripheral inflammation and pain (Hore et al., 1997).

**Other Factors**

**Cell adhesion molecules, complement factor C5a, platelet activating factor, leukotriene and cytokines:** Several classes of leukocytes play an essential role in inflammation. Although earlier ideas emphasized the promotion of migration of cells out of the microvasculature, recent studies have examined the role of endothelial cell (Fan and Dale, 1994) and of cell adhesion molecules (Kincade, 1993) including E-, P- and L- selecting, intracellular adhesion molecular (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1) and leucocyte integrins in the adhesion of leucocytes; platelets and endothelium at sites of inflammation (Cronstein and Weissmann, 1993 and Wilkinson, 1994). Activated endothelial cells play a key role in targeting circulating cells to inflammatory sites. Expression of the various adhesion molecules varies among different cell types involved in the inflammatory response: e.g. expression of E-selectin is restricted primarily to endothelial cells and it enhanced at sites of inflammation. P-selectin is expressed predominantly on platelets and on endothelial cells and is enhanced by cytokines. L-selectin in contrast is a receptor for P-selectin and L-selectin is expressed on leukocytes and is shed when these cells are activated. Cell adhesion appears to occur by recognition of cell surface glycoprotein and
carbohydrates on circulating cells by the adhesion molecules whose expression has been enhanced on resident cells. Thus, endothelial activation results in adhesion of leukocytes by their interaction with newly expressed L-selectin and P-selectin, where as endothelial expressed E-selectin interacts with sialylated Lewis X and other glycoproteins on the leukocyte surface; endothelial ICAM-1 interacts with leucocyte integrins.

The recruitment of inflammatory cells to sites of injury involves the concerted interaction of several types of soluble mediators in addition to the cell adhesion molecules outlined above. These include the complement factor Cs₈ (Salman and Higg, 1994), platelet activating factor (Page, 1994), Leukotriene B₄ (Lin et al., 1982). Several different cytokines also appear to play an essential role in orchestrating the inflammatory process, especially interleukin-1 (IL-1) (Dinarello et al., 1993) and tumor necrosis factor (TNF). Both IL-1 and TNF are derived from mono-nuclear cells and macrophages and induce expression of numerous genes to promote the synthesis of a variety of proteins that contributes to inflammatory events. IL-1 and TNF are considered principal mediators of biological responses to bacterial lipopolysaccharides (endotoxins) and may other infectious stimuli. IL-1 and TNF appear to work in concert with each other and with growth factors such as graunlocyte/macrophage colony stimulating factor. GM-GSF and other cytokines such as 1L-8 and related chemotactic cytokines (chemokines) which can promote neutrophil infiltration and activation.

IL-1 comprises two distinct pilypeptides (IL-1 α and 1L-2 β) (Handerson 1994) that bind to the same cell surface receptor and produce similar biological responses. Plasma IL-1 levels are increased in patients with certain inflammatory process, e.g. active rheumatoid arthritis. IL-1 can bind to two types of receptors, an 80 KD (Kilodaltons) IL-1 receptor typel and a 68 - KD IL-1 receptor type 2, which are present on different types of cells.

TNF, originally termed 'cachectin' because of its ability to produce a wasting syndrome is composed of two closely related proteins, Mature TNF- α and lymphotoxin (TNF β) both of which are recognised by the same cell surface receptors. These are two types of TNF receptors, 975 - KD type-I and 55 KD type -2 receptor for TNF.
IL-1 and TNF produce many of the same proinflammatory responses, which include induction of fever, sleep and anorexia, mobilization and activation of polymorphonuclear leucocytes, induction of cyclooxygenase and lipoxygenase enzyme increase in adhesion molecule expression, activation of B cells, T cells and natural killer cells and stimulation of production of other cytokines. Other actions of these agents likely contribute to the fibrosis and tissue degeneration of the chronic proliferative phase of inflammation; stimulation of fibroblast proliferation, induction of collagenase and activation of osteoblasts and osteoclasts. Both IL-1 and TNF increase expression of many types of genes, probably in part via the activation of transcription factors, such as NFKB and AP-1. Other cytokines and growth factors like IL-2, IL-6, IL-8 and GM-CSF contribute to manifestation of the inflammatory response. The concentration of many of these factors are increased in the synovia of patients with arthritis such as rheumatoid arthritis. The consideration of peptides such to as substance P, which promotes firing of pain fibres, also is increased in such sites.

According to Cunha et al. (2000) IL-1ra (Interleukin-1 receptor antagonist), released at sites of inflammation, limits inflammatory hyperalgesia. This effect is independent of (IL-1 ra induced) IL-4 and IL-10 and appears to be the result of antagonism by IL-1ra of IL-1 (β-stimulated eicosanoid production.

**Leucocytosis promoting factors and lymph node permeability factor:** Leucocyte emigration begins from 1 to 3 hours following injury by a process that is apparently mediated by a mechanism other than causing plasma leakage. From time to time different factors viz. leucocytosis promoting factors and lymph node permeability factors have been implicated in causation of increased capillary permeability in inflammation (Spector and Willoughby, 1964).

**Inhibition of adrinaline like substances:** The increase in vascular permeability in acute response may also be accentuated through the inactivation of substances such as norepinephrine and epinephrine (adreraline), which normally act as constrictors of blood vessels. This inactivation is apparently secondary to release from injury cells, of the enzyme monoamine oxidase. The loss of action of those vasoconstrictive substances leaves the vasodilator action of histamine unopposed suggested that adrenaline is pro inflammatory since it causes release of kinins by the activations of proteases. On the other hand Spector and Willoughby (1964) suggested that
adrenaline is a natural anti-inflammatory local hormone and inflammation is due to rapid inactivation of adrenaline. The anti-inflammatory effect of adrenaline arises not from a local action but from an action on the pituitary adrenal system. Adrenalectomy abolishes the anti-inflammatory activity of adrenaline. Experimental proof has been provided for adrenaline mediated cortisol release which could be responsible for the anti-inflammatory action.

**CHRONIC INFLAMMATORY REACTION**

The events that occur at the local site of injury with in the initial 24 to 48 hours appear to determine the fate of inciting agent if the inciting agent is eliminated, healing occurs. However, if the inciting agent is not handled by acute response and persists in tissues, it eventually becomes antigenic. As it persists in tissues, it may result in distinction of the cells that release proteolytic enzymes, from their disrupted lysosomes. These enzymes can act on various protein exudates and the breaking down products may become antigen leading to formation of antibodies. If the antibody can inactivate the antigen by binding with it healing ensures. As long as the antigen is present, however, the chronic inflammatory cycle continues and the local reaction may persist for years.

Lysosomal enzyme secretion occurs as a result of interaction between leucocyte or macrophage plasma membrane and immunologic reactions or stimulus. They are regulated by autonomic neurohormone, glucocorticoids, prostaglandins and cyclic nucleotides in immunologically provoked secretion of lysosomal mediators of inflammation by human leucocytes. These play an important role in the initiation of inflammation, tissue injury and connective tissue breakdown. Shen (1967) found higher levels of catalytic enzymes in inflamed tissue or serum of arthritic rats as compared to normal animal. It has been stressed that the potential destructive capacity of connective tissue is acid hydrolases and is liberated within the endogenous cellular elements of connective tissue or derived from migrating leucocytes. However, Paulous and Whitehouse (1972) have stressed the presence of potentially destructive enzymes in serum which is not the sole factor in injury, because, it was found no correlation between maximum enzyme activity and presence of tissue damage. This is further supported by the fact that in rheumatoid arthritis the catabolic activity is not the sole problem, but there is also the articular damage which may be due to adopted
leucocytes in synovial tissue. However, the catabolic enzymes degraded from connective tissue or cellular elements make a common pathway for inflammatory process.

The lysosomal enzymes of human leucocytes have the capacity to degrade intact cartilage under conditions of neutral pH and balanced ionic movements in contrast to that of rabbit or guinea pig. The presence of elevated lysosomal contents namely neutral protease, acid hydrolases, chemotactic factors, kinin generating factors, vascular permeability factors and pyrogens in synovial fluid or arthritic patient has been clearly documented.

POSSIBLE MECHANISM OF ACTION OF ANTI-INFLAMMATORY DRUGS

Inactivation of Histamime and HT: The increase in vascular permeability induced by histamine and serotomic in the early phase of inflammation is rapidly reversed by administration of anti-histamine drugs, as increased permeability is mainly due to activation of $H_1$ receptors. $H_1$ receptor blockers may be regarded as having anti-inflammatory activity. These are effective only during the immediate phase of the acute inflammatory response. Amidopyrine, phenylbutazone, oxyphenbutazone, and salicylates have anti-histaminic activity which might be related to their anti-inflammatory activity. Salicylates, phynylbutazone, amidopyrine and hydrocortisone were shown to inhibit 5-HT oedema in rats. However, indomethacin was found to be devoid of antiserotonin activity.

Inactivation of Kinins and Antiplasmins: It is possible that drugs may exert anti-inflammatory effect by antagonising kinins but specific antagonists or drugs, interfering with plasma kinins formation has not been developed. The anti-inflammatory drugs inhibit the activity of kinins only in a limited number of test systems (Erdos, 1966). The relief of pain and reduction in swelling production by aspirin results from its ability either to inactivate the kinins or to prevent the activation and/or biological action of kallikrein or kininogen (Koneman, 1971).

The anti-inflammatory activity of hydrocortisone, salicylic acid, antipyrin may be the result of plasmin inhibition in vitro, but this effect was not observed by phenacetin and aspirin. Increased fibrinolytic activity was observed in rats subjected to carrageenan induced oedema which was prevented by hydrocortisone, indomethacin, flufenamic acid, oxyphenbutazone, acetyl salicylic acid, amidopyrin, sodium
salicylate and phenacetin. No correlation could be established between the magnitude of anti-inflammatory and anti-fibrinolytic activities of these agents. On the contrary, it was observed no correlation between fibrinolytic activity and kinin release by plamin.

**Inhibition of Prostaglandins:** Non-steroidal anti-inflammatory drugs inhibit prostaglandin biosynthesis but do not influence the action of exogenous PGS on inflammatory response. Aspirin like drugs mainly inhibit microsomal prostaglandin systehtase (Lecomte et al., 1994, O'Neill et al., 1994). Indomethacin is the most potent PG synthetase inhibitor, the nature of inhibition seems to be competetive and irreversible (Flower, 1974), Corticosteroids inhibit the release of PGS by blockade of active transport of PGS through cell membrane, but their synthesis is not affected (Flower, 1974). Most currently used NSAID nonselectively inhibit the COX-1 and COX-2 isoforms or have moderate selectivity for COX -1 isoform. One exception is nabumetone which preferentially inhibits COX -2. Its anti-inflammatory effects with a lower incidence of the ulcerogenic side effects characteristic of aspirin like drugs have propelled the current efforts to design NSAIDs with greater selectivity for COX -2 versus COX-1 (Meade et al.1993; Masferrer et al., 1994; O'Neill et al., 1994).

UTP (Uridin triphosphate) - mediated COX-2 and iPLA$_2$ (Ca$^{2+}$ independent phospholipase A$_2$) potatiation and PGE2 formation contribute to the INOS (inducible nitric oxide synthase) induction and that CaMK (Calmodulin-dependent protein kinase) activation is the primary step in the UTP enhancement of COX-2 induction (Chene et al., 2000).

COX-1 may be induced in modulating the threshold for activating the micturition reflex in the normal rats and also demonstrates that inhibition of COX-2 prevents or reverses the urodynamic changes associated with bladder inflammation induced either by surgery LPS (endotoxin) or CVP (cyclophosphamide) treatm ents (Alessendro Lecci et al., 2000).

According to Gretzer et al. (2001) normal stomach lesions only develop when both COX-1 and COX$_7$2 are inhibited. In contrast, during acid callange inhibition of COX-1 renders the mucosa more vulnerable suggesting an important role of COX-1 in mucosal defense in the presence of potentially noxious agent. In this function COX-1 is supported by COX-2, in the face of pending injury. However, COX-2 cannot maintain mucosal integrity when the activity of COX-1 is suppressed.
All drugs except sodium salicylate, inhibited COX-1 and COX-2 when added directly to the test systems. Plasma from aspirin treated rats was without effect on either COX-1 or COX-2 consistent with the rapid in vivo metabolism to salicylate. Conversely, plasma from sulindac-treated rats inhibited COX-1 and COX-2 with potencies according with in vitro metabolism to sulindac sulphide. Diclofenac was COX-1/2 non selective when tested in vitro but a slightly preferential inhibitor of COX-2 when tested ex vivo. Nimesulide was confined as preferential inhibitor of COX-2 both in vitro and ex vivo. Generation and action of prostaglandins by cyclooxygenase.

**Stabilization of Lysosomes:** There are a number of bacterial or chemical toxins that are capable of causing cell damage, through disruption of lysosomal membranes. The anti-inflammatory effect of steroid hormones is supposed to be due to rendering lysosomes less permeable (Koneman, 1971), but there are conflicting reports regarding the action on these lysosomal enzymes.

**Monoamine oxidase inhibitors:** Monoamine oxidase released from the damaged cells, is capable of inactivating epinephrine. Therefore, its inhibition by a specific inhibitor drug would allow the persistence of epinephrine at the site of injury, and its vasoconstrictor action on the microcirculation would act to reduce vascular permeability and formation of tissue oedema (Koneman, 1971).

**Antibiotics:** The rationale of antibiotic therapy is to eliminate any viable agent that may be the cause of any inflammatory response, so the specific viable agent should be isolated and identified for the choice of proper antibiotic (Koneman, 1971).

**Suppression of antibody production:** Antibody formation is intimately involved in perpetuating the inflammatory response. Therefore, the suppression of antibodies is one mechanism by which chronic inflammatory cycle can be interrupted. The corticosteroid drugs have a primary action on lymph nodes reducing lymphocytic proliferation. Additionally, they block, various metabolic pathways within the lymphocytes, both in the nucleus and in the cytoplasm, by which protein synthesis (specifically antibody production) is markedly reduced. As the suppression of antibodies may improve the inflammatory response, it may not eliminate the inciting agent; the effect is palliative and not curative (Koneman, 1971).
Antimetabolites; They are finding more and more use in the treatment of chronic inflammatory diseases, where they are thought to both decrease the production of antibodies by lymphocytes and reduce the activity of hydrolytic and proteolytic enzymes that may be released by damaged cells (Koneman, 1971).

Pharmacological Modulators

The Salicylates: Despite the introduction of many new drugs, acetylsalicylic acid is still the most widely prescribed analgesic-antipyretic and anti-inflammatory agent and is the standard for the comparison and evaluation of the others. A brief description of its chemistry, mechanism of action and toxic effects is given below.

Salicylic acid (orthohydroxy benzoic acid) is so irritating that it can be used only externally, therefore, various derivatives of this acid have been synthesized for systemic use. These comprise two large classes, namely esters of salicylic acid obtained by substitution in the carboxyl group and salicylate esters of organic acids in which the carboxyl group of salicylic acid is retained and substitution is made in the hydroxyl group.

Mechanism of Action

The first enzyme in the prostaglandin synthesis is protaglandin endoperoxidase synthase or fatty acid cyclo-oxygenase. This enzyme converts arachidonic acid to the unstable intermediates PGG₂ and PGH₂. There are two form of cyclo-oxygenase, viz., cyclo-oxygenase 1 (COX -1) and cyclo-oxygenase-2 (COX -2). COX -1 is a constitutive isoform found in blood vessels, stomach and kidney; while cox-2, induced in settings of inflammation by cytokines and inflammatory mediators (Battistine, 1994). Arachidonic acid can also be converted via 12-liprogenase to 12-HPETE and 12 HETE or via the 5-lipxygenase to a variety of leukotriens.

Aspirin inhibits the cyclo-oxygenase enzyme (Lecomte et al., 1994, Masferrer et al., 1994) and prostaglandin production (Marshall et al., 1987, O'Neill et al., 1994). Aspirin covalently modifies both cox-1 and cox-2 thus resulting in irreversible inhibition of cyclooxygenase activity.

The fatal dose varies with the preparation of salicylate 10 to 30 g of sodium salicylate or aspirin has caused death (Leonards et al., 1973). The lethal dose of methyl
salicylate (oil of wintergreen sweet birch oil, guatheria oil, betula oil) is considerably less than that of sodium salicylate. As little as 4 ml. is fatal.

**Acetaminophen:** Acetaminophen (Paracetamol. N. acetyl-p-aminophenol) is the active metabolite of phenacetin. Acetaminophen has analgesic and antipyretic activity similar to aspirin but has weak anti-inflammatory activity. The failure of acetaminophen to exert anti-inflammatory activity may be attributed to the fact that acetaminophen is only a weak inhibitor of cyclo-oxygenase in the presence of high concentration of peroxidases that are found in inflammatory lesions (Marshal et al., 1987; Hanel and Lands, 1982). Further, acetaminophen does not inhibit neutrophil activation as do other NSAIDs (Abramson and Weissmann, 1989).

Nitroparacetamol (NCX-701) is a newly synthesized nitric oxide releasing derivative of paracetamol. Following i.p. administration, nitroparacetamol inhibits carrageenan induced hind paw oedema formation in rat (Swayth et al., 2000).

In recommended therapeutic doses, acetaminophen is usually well tolerated. Skin rash and other allergic reactions occur occasionally. The rash is usually erythematous or urticarial and is some time accompanied by drug fever and mucosal lesions. The most serious adverse effect of acute overdosage of acetaminophen is a dose dependent potentially fatal hepatic necrosis. Nephrotoxicity associated with chronic abuse of acetaminophen has been reported (Sandier et al., 1989).

**Indomethacin:** Indomethacin has prominent anti-inflammatory and analgesic, antipyretic properties similar to those of the salicylates. Indomethacin has analgesic properties distinct from its anti-inflammatory effect, and there is evidence for both a central and a peripheral action. Indomethacin is a potent inhibitor of the prostaglandin forming cyclo-oxygenase, it also inhibits the motility of polymorphonuclear leukocytes. It also uncouples oxidative phosphorylation at superatherapeutic concentrations and depresses the biosynthesis of mucopolysaccharides.

**The Fenamates:** These are derivatives of N-phenyl-anthranilic acid. They include mefenamic, meclofenamic, flufenamic tolfenamic and etofenamic acid. The fenarnates have anti-inflammatory, antipyretic and analgesic properties. They appear lo owe these properties primarily to their capacity to inhibit cyclo-oxygenase. The most common side effect is gastro-inestinal disturbances. A potentially serious side
effect seen in isolated cases is a haemolytic anemia, which may be of an autoimmune type.

**Ketorolac and Diclofenac:** These are structurally related hetroaryl acetic acid derivatives with different pharmacological features. Ketorolac is a potent analgesic but only a moderately effective anti-inflammatory drug. It inhibits prostaglandin biosynthesis. Ketorolac inhibits platelet aggregation and promotes gastric ulceration. The pharmacology of ketorolac has been reviewed by Buckley and Broden (1990). Side effects include somnolence, dizziness, headache, gastrointestinal pain, dyspepsia and pain at the site of injection.

Diclofenac has analgesic anti-pyretic and anti-inflammatory activities. It is an inhibitor of cyclo-oxygenase. In addition diclofenac appears to reduce intracellular concentrations of free arachidonate in leukocytes, perhaps by altering the release or uptake of the fatty acid. It produces side effects in about 20% of patients. Gastrointestinal effects are the most common; bleeding and ulceration or perforation of the intestinal wall have been observed. Elevation of hepatic aminotransferase activity in plasma occurs in 15% patients.

**Propionic Acid Derivatives:** This class includes Ibuprofen, Naproxen, Fenoprofen, Ketoprofen and Flurbiprofen. The pharmacological properties (Kantor, 1979; Todd and Clissold 1990) and pharmacodynamic properties of the propionic acid derivatives do not differ significantly. All are effective cyclo-oxygenase inhibitor. All of the agents alter platelet function and prolong bleeding time.

Gastrointestinal side effects are experienced by 5% to 15% patient. CNS side effects range from drowsiness, headache, dizziness and sweating to fatigue, depression and autotoxicity.

**Piroxicam:** It is an oxicam derivative. The pharmacological properties and therapeutic uses of piroxicam have been reviewed by Wiseman 1985 and by Lombardino and Wiseman (1987). Piroxicam is an effective anti-inflammatory agent. It is a very potent inhibitor of prostaglandin biosynthesis. Piroxicam also can inhibit activation of neutrophils even when products of cyclo-oxygenase are present. It also inhibit proteoglyconase and collagenase in cartilage (Abramson and Weisman, 1989; Lombardino and Wiseman, 1987). Gastrointestinal reactions are most common, the
incidence of peptic ulcer is less than 1%. Piroxicam can reduce the renal excretion of lithium to a clinically significant extent.

**Pyrazolon Derivatives:** This group of drugs includes phenylbutazone, oxyphenbutazone, antipyrine, aminopyrine and dipyrone. Phenylbutazone is the prototype drug. The anti-inflammatory effects of phenylbutazone are similar to those of the salicylate. It also inhibits the cyclo-oxygenase pathway. Phenylbutazone is poorly tolerated by many patients. Side effects are noted in 10 to 40% of patients. Nausea, vomiting, epigastric discomfort and skin rashes are the most common. In addition, water and electrolyte retention and edema formation occurs. More serious side effects are peptic ulcers, hemorrhage and perforation, hypersensitivity reactions.

**Other Non-steroidal Anti-inflammatory Drugs:** Apazme and nimesulidde come under this category. Apazone is an NSAID that is anti-inflammatory, analgesic and antipyretic but is only a weak inhibitor of cyclo-oxygenase. In addition apazone is a potent uricosuric agent and is particularly useful for the treatment of acute gout.

Nimesulide on the other hand, is a sulfonanilide compound and appears to be a weak inhibitor of prostaglandin synthesis. In addition, it also inhibits leukocyte function. This inhibitory effect is particularly prominent for the oxidative response of polymorphonuclear leukocytes and for mediator release by these and other classes of leukocytes.

**Antagonists of Leukotrine formation and action:** Most NSAIDs, decrease cyclo-oxygenase activity without decreasing generation of lipoxygenase produced leukotriens. Substantial evidence indicates that these later agents contribute to the inflammatory response through a variety of effects, such as on smooth muscle contractility (LTC₄, LTD₄, LTE₄), neutrophil aggregation, degranulation and chemotaxis (LTB₄). A large number of drugs have been developed that are either 5-lipoxygenase inhibitors, which block leukotriene formation or cysteinyl leukotrine receptor antagonists that block receptor function. Inhibitors of 5-lipoxygenase include docebenone, ICID2318, MK-0591, MK-886, piriprost and Zileution.

**Gold:** Gold is employed in the treatment of rheumatoid arthritis, usually it is reserved for patient with progressive disease who do not obtain satisfactory relief from therapy with NSAIDs. These are some time called disease modifying drugs which is probably a misnomer (Edmonds et al, 1993). The best hypothesis regarding the mechanism of
action of gold compounds is their capacity to inhibit the maturation and function of mononuclear phagocytes and of T cells, thereby suppressing immune responsiveness.

**Other Drugs for Rheumatoid Arthritis**: This group includes immunosuppressive agents for e.g. cyclosporine, azathioprine, methotrexate, glucocorticoids, penicillamine and hydroxychloroquine. With the exception of glucocorticoids, sulfasalazine and perhaps methotrexate, these drugs do not possess anti-inflammatory or analgesic properties. These drugs are reserved for patients who are refractory to therapeutic regimens that include rest, physiotherapy and NSAIDs.

**Drugs for Gouty Arthritis**: Colchicine is a unique anti-inflammatory agent in that it is largely effective in gouty arthritis. The anti-inflammatory effect of colchicine in acute gouty arthritis is relatively selective for this disorder. Colchicine is only occasionally effective in other types of arthritis, it is not an analgesic and does not provide relief of other types of pain.

**Nabumetone**: It is a recently developed pro-drug. It generates an active metabolic (6-MNA) which is a more potent COX-2 than COX-1 inhibitor. It possesses analgesic, antipyretic and anti-inflammatory activity; effective in the treatment of rheumatoid and osteoarthritis as well as soft tissue injury. Nabumetone has caused a low incidence of gastric erosions, ulcers and bleeding. Confirmatory data on efficacy and adverse effect profile have yet to be generated. Recently marketed in India: NABUFLAM 500 mg tab : 1 tab O.D.

Today it is estimated that more than 800 million people are suffering from one or other type of arthritis which is the most distressing and disabling syndrome. This has been called the great crippler and king of human miseries. The majority of the drugs used for the treatment are anti-inflammatory drugs. In the last 6-8 decades, a large number of synthetic derivatives viz. indoles, quinazolinones, phenothiazones, naphthalenes, thiazoles, thiazolidinones, formazans, azetidinones etc. and compounds of endogenous origin have been investigated with a view to find out a potent and safe anti-inflammatory and anti-arthritic drug which would come near enough to steroids without any deleterious side effect. The steroids such as prednisolone, methyl prednisolone betamethasone, dexamethasone etc. are although strong anti-inflammatory agents, they have equally strong and dangerous side effects. Moreover, they have the drawback of inducing rebound inflammation in chronic inflammatory
disorders upon their withdrawl. Their use for common trivial inflammatory conditions is, therefore, not desirable. The other group of anti-inflammatory drugs comprising the non-steroidal agents are a heterogenous group of compounds.

Most of which are organic acids. The treatment of inflammation is largely empirical and the drugs used currently have diverse type of mechanism of action. However the most widely accepted mechanism of action of this class of drug is inhibition of prostaglandin synthesis. Generally arachdonic acid is converted to prostaglandins in the presence of prostaglandin synthetase and cause erythema, oedema, pain, fever, vasodialation which are the typical features of inflammation.

The non-steroidal anti-inflammatory agents which act mainly by inhibiting the prostaglandin synthesis will there for subside these symptoms and also the inflammation. Indomethacin(I), sulindac (II) Ibuprofen (V), naproxen (VI), piroxicam (IX), Nabumetone etc. are prototype of such NSAIDs. Currently, a number of compounds have been synthesized and evaluated for their anti-inflammatory activity. The important compounds are detailed below-
INDOLE DERIVATIVES

The discovery of indomethacin, sulindac, indole derivatives, as potent anti-inflammatory agents, has led to the exploration of indole nucleus. Further, it has been reported that substitution of different heterocyclic or aliphatic moieties at 2-or 3-position of indole nucleus modulates the anti-inflammatory activity of such substituted indole derivatives. In the light of these observations, scientists have synthesized several indole derivatives which possess potent anti-inflammatory activity. Some of these are as given below-

2-(Indol-3-ylmethyl)-4-methylpyridine (I) was prepared by Shavel and Morrison (1968) and they reported anti-inflammatory, analgesic and antitussive activities in this newly synthesized compound.

![Image of compound I]

Nakanishi et al. (1969) have synthesized some newer indole derivatives (II), which were found to be useful as anti-inflammatory, analgesic, antihistaminic and coronary vasodilator.

![Image of compound II]

R=H, Me etc.

1-[3-(dimethylamino)propyl-3-(2-piperidinoethyl)]indole were prepared by Herbst and David (1970) (III) have been reported potent anti-inflammatory.

![Image of compound III]
Potent anti-inflammatory activity was reported in 1-substitutedbenzimidoyl- indole derivatives (IV) by Murakami et al. (1971).

\[ R^1=R^2= \text{Me, Et, etc.} \]

(IV)

Anti-inflammatory, analgesic, antipyretic activities etc. were found in 1-acyl-2-methyl-5-methoxyindole-3-acetic acids (V) Toth et al., (1972).

\[ R= 5\text{-nitro-2-furly etc.} \]

(V)

Lundt and Andersen (1973) have been synthesized some indole derivatives (VI) and promising anti-inflammatory activity.

\[ R, R_1= \text{H, } NR_2^2 = \text{NMe}_2, \text{ piperidino etc; } R^3 = 5\text{-Cl, } n=2 \]

(VI)

Houser et al. (1974) prepared some indomethacin analogs (VII) with cyclopropyl substituents and reported promising anti-inflammatory, analgesic and anti-pyretic activities in them.

\[ R= \text{H, Cl, etc.}, R^1= \text{cycloalkyl, etc, } R^2= \text{NH}_2, \text{ H, etc.} \]
\[ R^3 = \text{NHMe, CI, H, etc.} \]

\( \text{(VII)} \)

\( \alpha \)-Ethylenic ketone derivatives of (VIII) 1-phenyl-2-methyl-5-methoxyindole have been reported anti-inflammatory analgesic, antihypertensive and sedative activities by Fauran et al (1975).

\[ R = \text{Ph, 4-Cl-C}_6\text{H}_4, 4-\text{MeO-C}_6\text{H}_4 \text{ etc.} \]

\( \text{(VIII)} \)

Synthesis and anti-inflammatory, analgesic activities of pyridoindolones (IX) have been given by Coffen and Kotonak(1976).

\[ R=\text{H,2-NO}_2, 3-\text{Cl, 2-Cl etc.} \]

\( \text{(IX)} \)

Noda et al. (1978) reported potent anti-inflammatory and analgesic activities in indole acetic acid derivatives (X).

\[ R=\text{OH, Halo, F}_3\text{C, alkoxy etc.} \]

\( \text{(X)} \)

Some substituted 1,2,6,7-tetrahydroindolo (1,7-ab) (1,5) benzodiazepines (XI) were synthesized by Glamkowski and Fortunato (1980), which showed anti-inflammatory, anti-depressant and analgesic activities.
Sarpeu et al. (1980) synthesized some new indole derivatives (XII) with anti-inflammatory, analgesic and anticholinergic activities.

Verma et al. (1982) have been reported some new indolyl compounds as promising anti-inflammatory agents (XIII).

Kameyama (1982) prepared some furoindole compounds (XIV) and reported their use as anti-inflammatory and analgesic agents.

Some new thiadiazolylindole derivatives (XV) were synthesized and screened for their anti-inflammatory analgesic and anti-pyretic activities by Tandon et al. (1983). Most of these compounds showed prominent activities.
N-(indol-3-yl-glyoxyl) amino acid derivatives (XVI) were prepared by Dasittimo et al (1984) and they reported their use of anti-inflammatory and analgesic agents.

Singh et al. (1986) prepared a new series of indolythiazolidinones (XVII) as potent anti-inflammatory agents.

Garcia and Maria (1987) have synthesized 1-alkyl-8-ethyl-1,3,4,9-tetrahydropyrano (3,4-b) indole-1-acetic acids (XVIII) as anti-inflammatory and analgesic agents.
Dhaneshwer et al (1988) were synthesized N-acetyl-2-phenyl indole derivatives (XIX) as potent anti-inflammatory agents.

\[ R = N (R^1)_2 \text{Morpholino etc; } R^1 = \text{Pr, Me, CH}_2\text{Ph etc.} \]

(XIX)

3-Indole carboxamide derivatives (XX) as analgesic, inflammatory inhibitors and 5-lipoxygenase inhibitors have been reported by Nakao et al (1988).

\[ R^1=\text{H, OH, Halo etc; } R^2 = \text{H, Sub-Ph, alkyl etc; } R^3 = \text{alkyl, methyl; } R^4\text{-H, alkyl Et; } Z=\text{NHCH}_2\text{Ph} \]

(XX)

Aggarwal (1989) synthesized 1-substituted-2-oxo-3-(2-chlorophenoxy)-4-(2-aryl-indol-3-yl) azetidines (XXI) and reported them to be anti-inflammatory and CNS active agents.

\[ R = \text{H, CH}_3\text{,Cl, OMe etc., } X = 4\text{-N,N-diphenylbenzamido etc.} \]

(XXI)

Some 6H-thiazolo(3′,2′:1,2)-5-oxopyrimido [5,4-b] indole derivatives (XXII) have shown pronounced anti-inflammatory activity and no compounds showed any ulcerogenic effect Russo et al., (1990).
Some substituted indole derivatives (XXIII) as anti-inflammatory agents have been reported by El-Diwani et al (1992).

R=COOEt, COCH₂Cl

(XXIII)

Significant anti-inflammatory and analgesic activities were exhibited by indolylquinazolones and their congeners (XXIV) by Bhalla et al., (1993)

(XXIV)

Verma et al (1994) synthesized novel indole derivatives (XXV) and these derivatives and screened for their anti-inflammatory activity.

n=1-3
Substituted 3-(4-oxothiazolidin-2-aryl/alkylimino)indoles (XXVI) were prepared and screened for their anti-inflammatory and anti-convulsant activities by Bajji et al. (1994) and some of them possess promising activity.

\[ R=\text{H, CI, Me etc., } R^1=\text{Et, } C_6H_4\text{Br, } C_6H_4\text{Cl etc.} \]

Anti-inflammatory, anti-asthmatic, anti-allergic and immunomodulating activities have been reported in following indole derivative (XXVII) by Le-Baut et al. (1996).

Some 2,3-diphenylindole derivatives (XXVIII) have been synthesized and found to possess promising anti-inflammatory activity Ismail et al., (1997)

\[ R=X=\text{H etc.} \]

Amir et al (1997) have been prepared new indole and indazol derivatives (XXIX) and promising anti-inflammatory activity.
Newer 3-(Thiazol-2-ylmethyl)indoles (XXX) have been synthesized by Woods et al. (1998) as COX-2 inhibitors.

A = halo, C\textsubscript{1-6} alkyl etc., B = O\textsubscript{2}, H\textsubscript{2}; X = Br, Cl, L = 5-7 membered heteroatom containing ring such as thiazole, oxazole etc., R = Substituted aryls.

Some new 1-(2'-hydroxybenzoyl)-5-(substituted phenyl)-3-(2'methyl indolyl)-2-pyrazolines (XXXI) were prepared by Bansal et al. (1999). These compounds were screened for their anti-inflammatory, ulcerogenic activities and for acute toxicity. Some compounds showed pronounced anti-inflammatory activity with less ulcerogenic liability.

R = H, 2-OMe, N(CH\textsubscript{3})\textsubscript{2} etc.

Faull and Kettle (2000) have reported promising anti-inflammatory activity in indolecarboxylates (XXXII).
\[ X = CH_2, SO_2, R^1 = \text{substituted aryl}, R^2 = \text{COOH, COCH}_2\text{OH etc.} \]
\[ R^3 = H, \text{alkenyl, aryl etc.}, R^4 = \text{OR}^{15} \text{etc.} \]

(XXXII)

Bansal et al. (2000) synthesized some new formazanyl-thiazolyl-indoles and formazanyl-oxazolyl-indoles (XXXIII) as inflammation inhibitors. All the compounds have been shown to have good anti-inflammatory activity, but thiazoly derivatives possessed better anti-inflammatory activity than the oxazolyl derivatives.

\[ R = 2-\text{OMe}, 4-\text{OMe}, \text{Ph etc.}, R^1 = H, 2-\text{Cl etc.} \]

(XXXIII)

Sridhar et al (2001) have been prepared indole derivative (XXXIV) as potent anti-inflammatory and analgesic activities.

(XXXIV)

Sonar et al (2001) were synthesized oxadiazolylindole derivatives (XXXV) as promising anti-inflammatory activity.

(XXXV)

Sridhar and Ramesh, (2002) (XXXVII) have reported the synthesis of 3[(4-bromo phenylidene)1-amino] isatin as analgesic activity, anti-inflammatory and antipyretic activity.

\[ R=H, \text{CH}_3, \text{NO}_2, R^1=1-\text{Naphthyl, 4-bromophenyl, 4-methoxyphenyl, phenylhydrazino etc.} \]

(XXXVII)

Sharma (2002) has reported (XXXVIII) promising anti-inflammatory activity in substituted 1-(4-aminophenyl) indoles, these compounds were used in treatment of autoimmune diseases.

\[ R^1 = R^2=H, \text{CF}_3, \text{Halo CN etc., L} = \text{NHC}=\text{O, NHC}=\text{OO, NHC (S), NH C(S) NH etc.} \]

(XXXVIII)

New N-pyridinyl (methyl)-indole-2- and 3-(alkyl) corboxamides and derivatives (XXXIX) were synthesized by Breteche et al (2002) as topical inflammation inhibitors.
Synthesis and anti-inflammatory activity of some new indole derivatives (XXX) have been given by Gadaginamath et al. (2003).

\[ R^1 = R^2 = H, \text{Halo, alkyl, alkoxy etc., } R^3 = H \]

(XXXI)

Seehra et al (2003) (XXXII) synthesized indole derivative for the treatment of inflammatory conditions such as arthritis and inflammatory bowel disease.

\[ R^1 = R^6 = H, \text{halo, CF}_3, \text{alkoxy etc., } R^2 = H, \text{halo, alkyl, OH, CF}_3, \text{etc.} \]

\[ R^3 = \text{COOH, SO}_3\text{H, etc., } R^4 = H, \text{CF}_3, \text{halo, CHO etc., } R^5 = \text{alkyl, alkoxy etc.} \]

(XXXII)

Synthesis and anti-inflammatory, analgesic and COX-II inhibitory activities of indolylpyrazoline derivatives (XXXIII) have been given by Kumar et al. (2004).

\[ R = \text{CH}_3, \text{C}_6\text{H}_5 \]

(XXXIII)


\[ R = \text{SCH}_3, \text{C}_6\text{H}_5, \text{CH}_2\text{COOC}_2\text{H}_5 \]

(XXXIV)
Some novel isatinoid compounds were prepared by Kar et al (2003) (XXXXV) and reported promising anti-inflammatory and antimicrobial activities in these compounds.

\[ \text{XXXV} \]

Rani et al (2004) synthesized some heterocyclic indole derivatives (XXXXVI) and evaluated for their anti-inflammatory activity. The most active compound was 3-[1-acetyl-5-(p-hydroxyphenyl)-2-pyrazoline-3-yl] indole which should higher percent of inhibition of odema, lower ulcerogenic liability and acute toxicity than the standard drug phenylbutazone.

\[ \text{XXXVI} \]

Indolecarbamides were synthesized by Brown et al (2004) (XXXXVII) and these are useful for treating inflammatory and respiratory diseases.

\[ \text{XXXVII} \]
Biradar and Manjunath (2004) (XXXVIII) synthesized 7-phenyl-5-(2-phenylindol-3'-yl)-1,4-benzo[b] diazepines and have been screened for analgesic, anti-inflammatory and locomotor activities.

\[ R^1 = \text{Cl, Me, H}, \quad R^2 = \text{Me, Br, NH}_2, \text{NO}_2, \text{OH, H.} \]

(XXXVIII)

Narayana et al (2005) were prepared (XXXIX) some new biologically active 1,3,4-oxadiazolyl nitroindoles and a modified fisher indole synthesis of ethyl nitro indole-2-carboxytates.

(XXXIX)

Dubby et al (2006) (XXXX) have been synthesized 2-6-3-oxo-3,4-dihydro-2H-benzo (1,4-oxazin-6-carbonyl)-1H-indol-3-yl acetic acids as potential COX-2 inhibitors.

\[ R = \text{H, CH}_3, \text{C}_2\text{H}_5; \quad R^1 = \text{H, OCH}_3, \text{OC}_2\text{H}_5; \quad R^2 = \text{H, OCH}_3, \text{OC}_2\text{H}_5 \]

(XXXX)
Synthesis and biological evaluation of new-3-substituted indole derivatives (XXXXXI) as potential anti-inflammatory and analgesic activities have been reported by Mohd. Radwan et al (2007).

![Chemical Structure of XXXXII](image)

\[ R = CH_3, C_6H_5 \]  

(XXXXXI)

Sondhi et al (2007) have been reported synthesis of indole and furan derivatives (XXXXXII) possessing good anti-inflammatory and analgesic activities.

![Chemical Structure of XXXXII](image)

\[ R = H, CH_3, \text{etc.} \]  

(XXXXXII)
PYRAZOLINE & PYRAZOLE CONGERNERS

Pyrazolines and pyrazolones are the most important representatives of hydrazine in both the synthetic and theoretical respect. Compounds of these classes are widely used as photographic developers, dyes, herbicides and medicinal agents with potent analgesic and anti-inflammatory activities. The most important, from the therapeutic point of view, are phenylbutazone and oxyphenbutazone. These potent anti-inflammatory drugs have been prescribed by clinicians for the treatment of rheumatoid arthritis and other inflammatory disorder. They act by inhibiting both cyclooxygenase-1 and cyclooxygenase-2 enzymes. Moreover, other important drugs of this pharmacodynamic family are anti-pyretic like aminopyrine, pipyrone and apazone. In addition, a large number of pyrazolines have been synthesized by several scientists which are summarized below:

Blatter (1969) synthesized some new pyrazolo [3,4-c] pyridine derivatives (I) which are useful anti-inflammatory agents.

\[ R= \text{4-methylphenyl etc., } R^1= -\text{fluorophenyl, } \text{OH etc., } R^2= \text{OH etc.} \]

(I)

Swett and Ratajczyk (1970) prepared some pyrazolo derivatives (II), which were found to possess potent anti-inflammatory profile.

\[ R= \text{Me etc., } R^3= R^4= R^5= \text{H etc., } R^2= \text{Chlorophenyl etc.} \]

(II)

Promising anti-inflammatory, anti-pyretic, analgesic, hypotensive activities etc. were found in following pyrazoline derivatives (III) Laboratories D.S.A., (1971).
Potent anti-inflammatory activity has been reported in following compounds (IV) by Swett (1972).

Kamitani et al. (1973) have synthesized 3-pyrazolin-5-one derivatives (V) and these compounds exhibited anti-inflammatory activity.

10-[3,5-Diaryl-2-pyrazolin-1-yl)acetyl] phenothiazines were prepared by Jaiswal et al. (1981) and they have reported (VI) anti-inflammatory and anti-convulsant activities in these compounds.
2-(4'-Carboxymethyl-3'-methyl-5'-oxo-2'-pyrazolin-1'-yl)benzothiazoles and 2-(4'-carboxymethyl-3'-methyl-5'-oxo-2'-pyrazolin-1'-yl)-4-arylthiazoles (VII) have been reported as potent anti-inflammatory agents Sawhney et al., (1982).

![Chemical structures of compounds VII and VIII](image)

\[ R = \text{H, Cl, Br etc., } R^1 = \text{H, Cl, NO}_2, \text{ Me etc.} \]

(VII)

Joshi et al. (1983) have synthesized some fluorine containing pyrazolo [5, 1-C] [1,2,4] triazines (VIII) which showed potent anti-inflammatory and CNS depressant activities.

![Chemical structure of compound VIII](image)

\[ R = \text{Me, CF}_3, \text{ Ph etc., } R^1 = 4-\text{FC}_6\text{H}_4, 3,4-\text{F (MeO)C}_6\text{H}_3 \text{ etc.} \]

(VIII)

Tandon et al (1985) have been synthesized some pyrazolones derivatives (IX) as anti-inflammatory activity.

![Chemical structure of compound IX](image)

\[ R = \text{H, 4-Cl, 4-Br, 2-CH}_3, 4-\text{CH}_3, 2-\text{OC}_2\text{H}_5, 4-\text{OC}_2\text{H}_5 \ R^1 = \text{H, Cl etc.} \]

(IX)

Singh et al. (1984) prepared 6-fluoro-2-(3-methyl-5'-oxo-2'-pyrazolin-1'-yl)benzothiazole and its 4-substituted analogs (X). These compounds exhibited promising anti-inflammatory activity.
Kamal et al. (1985) reported potent anti-inflammatory activity in 4-aryl-2-(3'-5'-dimethylpyrazolyl) quinazolines (XI).

Promising anti-inflammatory and analgesic activity was found in following compounds (XII) which was by Vaid et al., (1986).

Synthesis and anti-inflammatory activity of some glycosidated-3-methylpyrazolin-5-(4H)-one-4-benzylidenes (XIII) have been given by Jain et al. (1988).
3-Amino- and 3-trifluoroacetylamino-4,5-dihydro-1H-pyrazoles (XIV), as anti-inflammatory agents, have been synthesized by Sawhney et al. (1989).

\[
\text{R} = \text{C}_6\text{H}_3\text{NSR}^1, \text{R}^1 = \text{H, Cl etc.}
\]

(XIV)

Synthesis of pyrazole derivatives of 4-(3H)-quinazolines as potent anti-inflammatory inhibitors, have been reported (XV) by Farghaly et al (1990).

(XV)

Indolylthiazolidinyl pyrazolines as potent anti-inflammatory agents have been reported (XVI) by Kumar et al (1990).

(XVI)

Kumar et al. (1990) reported that quinazolinylpyrazolines (XVII) possessed potent anti-inflammatory profile.

(XVII)
Synthesis and anti-inflammatory activity of 2'-phenyl steroidal [17,16-C] pyrazoles have been reported (XVIII) by Jindal and Pathak (1991).

\[
\text{R}= \text{H, CH}_2\text{CO etc.}
\]

(XVIII)

Promising anti-inflammatory and analgesic activities were found in some new 3-(pyrazol-5-yl)-1,2,3-benzotriazine-4(3H)-ones/quinazolin-4-(3H)-ones (XIX) Daidone et al., (1991).

\[
\text{R}= \text{H, Me, Ph, R}^1= \text{H, COOH, COOMe etc., X= N, CH etc.}
\]

(XIX)

Mann et al. (1992) have synthesized the N-acetyl pyrazoline derivatives (XX) and these compounds possess potent anti-inflammatory, analgesic and anti-pyretic activities.

\[
\text{R} = \text{H, 2-Cl etc., R}^1 = \text{H, 2-Cl, 3-Cl, 4-Cl, 2-Br etc.}
\]

(XX)

Potent anti-inflammatory activity was exhibited in substituted pyrazolines and pyrimidines (XXI) (Andotra et al., 1993).
Potent anti-inflammatory and analgesic activities have been reported in ethyl-1-methyl-5-[2-substituted-4-oxo-3(4H)-quinazolinyl]-H-pyrazole-4-acetates (XXII) Daidone et al., (1994).

Talley et al. (1995) have prepared pyrazolylbenzenesulphonamides and its derivatives (XXIII), which were found to be useful anti-inflammatory agents.

Freital et al. (1995) have reported anti-inflammatory and analgesic activities in 5-arylhydrazonyl-N-phenylpyrazole derivatives (XXIV).

\[ \text{R} = \text{Me, Et etc., Ar = Ph etc.} \]

(XXI)

\[ \text{R} = \text{H, Me, Et, Ph etc.} \]

(XXII)

\[ \text{R}^1 = \text{Substituted (hetero) aryls, R}^2 = \text{H, cyano, alkyl etc.} \]
\[ \text{R}^3 = \text{H, NO}_2, \text{formyl etc.}, \quad \text{R}^4 = \text{Cycloalkyl, aryl, heterocycl etc.} \]

(XXIII)

\[ \text{R} = \text{Nitropiperonal residue etc.} \]

(XXIV)
New 3-(3-Aryl-1-phenylpyrazol-5-yl)-7-substituted-2-chloroquinolines (XXV) were reported as potent anti-inflammatory agents by El-Sayed et al. (1996).

Synthesis of 1,5-diarylpyrazoles selective COX-2 inhibitors reported (XXVI) by the Bertenshaw (1996)

1,3,5-Trisubstitutedpyrazoles (XXVII) have been synthesized and used as inflammation inhibitors. Matsuo et al., (1997).

Udupi et al. (1998) have synthesized some new pyrazoline derivatives (XXVIII) as anti-inflammatory, analgesic and anti-microbial agents.
Katsuya et al. (1999) prepared 1,5-diphenylpyrazoles (XXIX) as COX-II inhibitors.

![Chemical Structure](image)

(XXIX)

Cirille et al. (2000) have reported potent anti-inflammatory activity in N-carbamoyl pyrazoloquinazolines and its analogs (XXX).

![Chemical Structure](image)

(XXX)

1-(10-Bromo-7H-indolo[2,3-c]isoquinoline-5-yl)-3-(p-methoxyphenyl)-5-(phenyl)pyrazoline (XXXI) has been found to possess significant anti-inflammatory activity Hiremath et al., (2002).

![Chemical Structure](image)

(XXXI)


![Chemical Structure](image)

R= C₆H₅, 4-CH₃OC₆H₄, 4-OHC₆H₄, N(CH₃)₂C₆H₄, etc.

(XXXII)
Potent anti-inflammatory agents were reported \((XXXIII)\) in Isoxazolinyl derivatives of anthranilic acid by Rani et al (2003).

\[
X= H, I, R= m\text{-OCH}_3, p\text{-OH} \text{ etc, } R^1 = n, o\text{-Cl, o-CH}_3;
\]

\((XXXIII)\)

Bkhit and Aziem (2004) have reported \((XXXIV)\) synthesis and biological evaluation of some pyrazole derivatives as anti-inflammatory and antimicrobial agents.

\((XXXIV)\)

Synthesis and anti-inflammatory, analgesic, ulcerogenic and lipid peroxidation activities of 3, 5-dimethylpyrazoles, 3-methyl pyrazol-5-ones and 3, 5 disubstituted pyridoxines reported \((XXXV)\) by Amir and Kumar (2005).

\[(XXXV)\]

El-Hawash (2006) et al. prepared some substituted 3-pyrazolin-5-ones and 1,2,4,5,6,7-3H-hexahydroindazol-3-ones derivatives \((XXXVI)\) which were found to possess potent anti-inflammatory, analgesic and antipyretic activities.

\((XXXVI)\)
Patten et al. (2007) have been synthesized some indole and pyrazole derivatives (XXXVII) as potent anti-inflammatory activity.

\[
\text{R} = p\text{-Cl, } p\text{-Br etc.}
\]

(XXXVII)
NAPHTHALENE DERIVATIVES

Naproxen and nabumetone, substituted naphthalene derivatives, are one of the most widely used NSAIDs other than aspirin, and have been found to possess potent anti-inflammatory activity. Heterocyclic/aliphatic functionalized systematic variations at \( \alpha \)- or \( \beta \)-position of naphthalene nucleus markedly modulate the anti-inflammatory activity. Some of the naphthalene derivatives exhibiting various biological activities especially anti-inflammatory, are given below-

Potent anti-inflammatory activity was reported in 2-(1-naphthyl) ethanols (I) by Parke (1969).

\[
\begin{align*}
\text{CHRCH}_2\text{OH} \\
\text{R}_1 \quad \text{R}_2
\end{align*}
\]

\( R = R_1 = H \text{ etc., } R_2 = \text{Ph etc.} \)

(I)

Naphthisoxazoklylalkanoic acid derivatives (II) were found to be useful as analgesic and anti-inflammatory agents by Suzuki et al. (1971).

\[
\begin{align*}
\text{CH}_2\text{COR} \\
\text{O} \quad \text{N} \\
\text{X} = \text{halogen}, \text{R= substituted aryls}
\end{align*}
\]

(II)

Harrison (1972) has prepared naphthalene derivatives and following compound (III) of this series exhibited promising anti-inflammatory activity.

\[
\begin{align*}
\text{CHMeCO}_2\text{H} \\
\text{MeO}
\end{align*}
\]

(III)

Sulkowski and Moseitti (1972) have been prepared (IV) several \( \alpha \)-aryl-3-(2-imidozolin-2-yl)-2-naphthalene methanols as showed anti-inflammatory activity.
Gautier et al. (1973) have synthesized 1-(methylsulfinyl) naphthalene derivatives (V) and these were found to be useful as analgesic and anti-inflammatory agents.

\[
\text{R} = \text{H, Me; } \text{R}^1 = \text{Ph, } p-\text{Cl}_6 \text{H}_4, 3,4-\text{Cl}_2 \text{C}_6 \text{H}_3 \text{ etc.}
\]

(IV)

Potent anti-inflammatory activity was found in 4-(and 5-) (2-thienyl)-1-naphthaleneacetic acid (VI) Kaltenbronn and Rhee, (1974).


\[
\text{R} = \text{H, 2-Me, 2-F, 2-Cl or 3-Me } \text{R}^1 = \text{N, Cl, Br or alkyl}
\]

(VII)

Potent analgesic and anti-inflammatory activity have been reported (VIII) by Moreau et al (1974) in 2-[1-amino methyl] naphthalene derivatives.
(6-Substituted-2-naphthyl) acetic acids (IX) have been synthesized and were found to possess promising anti-inflammatory activity (Fried and Harrison, 1977).

Compounds (X) has shown analgesic, anti-pyretic and anti-inflammatory activity as reported by Jurado and Duran (1978).

Saint and Marie (1979) have synthesized 1-naphthylacetic acid derivatives (XI) and reported anti-inflammatory activity without ulcerogenic potential in them.

2-(6-Methoxy-2-naphthyl) propionic acids have been prepared by Kita and Yamada (1980). Compound (XII) has been found to possess promising anti-inflammatory and analgesic activities.
Onesu et al. (1981) have reported potent anti-inflammatory, analgesic and anti-pyretic activities in 2-(carboxymethoxy)-1-naphthalenesulfonamide derivatives (XIII).

Descours et al (1984) have synthesized acyl-2- naphthalene acetic derivatives (XIV) by Fridel-Craft reaction from methyl-2-naphthalene acetate. The compounds exhibited mild to moderate analgesic, antipyretic and anti-inflammatory activities.

Nohira and Teraguchi (1986) have synthesized and reported anti-inflammatory, analgesic and anti-pyretic activities in the following compound (XV).

2–Naphthol derivatives (XVI) have shown pronounced anti-inflammatory activity by Akubue et al.,(1991).
Singh et al. (1993) reported anti-inflammatory and cardiovascular activities in \(\alpha\)-(aryl-amido-alkyl-methyl)-\(\beta\)-(diphenylimino) naphthyl ethers (XVII).

\[
\text{R = Benzamido etc., } R^1 = \text{ H, Me, Ph etc. (XVII)}
\]

Anti-inflammatory, anti-asthmatic and antiallergic activities have been reported in 3-(hydroxymethyl)-4-phenyl-7-[5-{4-(4-hydroxytetrahydropyran-4yl)-3-pyridinylmethoxy]-2-naphthalenecarboxylic acid (lactone) (XVIII) by Girard and Hamel (1994).

\[
\text{(XVIII)}
\]

Some 1-ether-and 1-thioether-2-naphthalenecarboxamides (XIX) have been found to possess prominent anti-inflammatory activity Boschelli et al., (1995).

\[
\text{R}^1 = \text{Ph, lower alkyl etc., } R^2 = \text{H, lower alkyl etc., } R^3 \text{ or } R^4 = \text{lower alkoxy} \\
R^3, R^6 = \text{H, OH, halogen. alkoxy (XIX)}
\]

Carganico et al. (1997) have synthesized following compound (XX), and found to be useful in the treatment of inflammatory and allergic diseases.

\[
\text{(XX)}
\]
Hodges (1998) reported that naphthoquinones (XXI) are useful as antibacterial and anti-inflammatory agents.

![Structure](image1)

\[ R = H, \text{alkyl}, \quad R^1 = \text{side chain contg.-COOH}, \quad R^2 = H, \text{org.substituent.} \]

(XXI)

Mohammad et al. (1999) have reported better anti-inflammatory activity in 6-methoxy-\(\alpha\)-methyl-naphthaleneacetic acid derivatives (XXII) in comparison to the reference drug, naproxen.

![Structure](image2)

\[ R^1 = H, \text{CH}_3, \text{OCH}_3 \text{ etc.} \]

(XXII)

Tjornebo (2000) have synthesized 2-[2-hydroxy-4-(pyridin-3-yl)-butoxy/ butothioxy]naphthalenes (XXIII) for modulation of inflammatory and allergic conditions.

![Structure](image3)

\[ W = O, S, m= 1-4, X= \text{ester, amide, etc.}, \quad R^1 = \text{CN, (un)substituted Ph.} \]

(XXIII)

Bansal et al (2001) have been synthesized 1-acetyl-5- substituted aryl-3- (b-aminonaphthyl)-2- pyrazolines derivatives (XXIV) as potent anti-inflammatory activity.

![Structure](image4)

(XXIV)
Ferixes et al (2001) (XXV) have been synthesized a new series of selective Cox-II inhibitors.

\[
\text{R}_1 = \text{CH}_2\text{O}, \text{R}_2=\text{H}, \text{R}_3=\text{Cl etc.}
\]

(XXV)

Significant anti-inflammatory activity has been reported in following compound (XXVI) by Sridhar and Ramesh (2002).

(XXVI)

J Damodar et al (2002) reported synthesis and anti inflammatory activity in a large numbers compounds, out of 2-hydroxy which-(P-i sobutyl phenyl) propanic acid and 2-hydroxy-2-(6-methoxy haphthyl) propanoic acid have shown promising. anti inflammatary activity. (XXVII)

(XXVII)

Sharma et al (2003) have been prepared and reported (XXVIII) anti-inflammatory activity in some novel $\alpha$-amino naphthalene derivatives.

(XXVIII)

Kongkathip et al (2005) have been prepared 2-substituted- 1-naphthole derivatives (XXIX) as Cox-I & Cox- II, inhibitors.
α-Amino naphthalene and β-amino naphthalene derivatives (XXX) have been reported as potent anti-inflammatory by Sharma et al (2006)

Ravindra et al (2006) have reported (XXXI) potent antimicrobial and anti-inflammatory activities in 1,3,4-oxadiazoles lined to naphtho [2,1-b] furan in comparison to reference drugs.

R= C₆H₅, m-ClC₆H₄, p-ClC₆H₄, p-OCH₃-C₆H₄ etc.

(XXXI)

Synthesis and pharmacological evaluation of heterocyclic-6 substituted-1,2,4, triazole [3,4-b] 1,3,4, thiadiazole derivatives (XXXII) prepared by Mohd Amir et al (2007)

Parmeshwari et al (2007) have been reported amino ethyl ester derivatives (XXXIII) of naphthalene as potent anti-inflammatory.

R= Me, H

(XXXIII)
THIADIAZINE

1,3,4-Thiadiazine derivatives (I) were found to be useful as anti-inflammatory drugs Takamizawa and Sato, (1970).

\[ R^1 = \text{H etc., } R^2 = \text{Cl, OME etc.} \]

(III)

Reddy et al (1986) (II) have synthesized 6-alkyl/aryl quinazolino-[3,2-b] [1,2,4] benzothiadiazine-13(6H) one 11, 11-dioxides as potent anti-inflammatory and analgesic activities.

\[ R = \text{CH}_3, \text{C}_2\text{H}_5, \text{C}_6\text{H}_5, \text{etc.} \]

(II)

Reddy, and Rao. 2006) have been reported (III) -5-[2-arylmino-4-(3-oxo1,4-benoxazin-6-yl thiazole acetates and 7h-[3-aryl-6-(3-oxo-1,4-benzoxazin-7-ylacetates as possible Cox-II inhibitors.

\[ R = \text{C}_6\text{H}_5, \text{4-CH}_3, \text{C}_6\text{H}_5, \text{4-ClC}_6\text{H}_4, \text{4-ClC}_6\text{H}_4 \text{etc.} \]

(III)
THIADIAZOLE CONGENERS

Cameron (1971) reported mesoionic aryl anhydro 1,2,3-thiadiazolium hydroxides (I) as oxidase inhibitors and anti-inflammatory agents.

\[
\text{R, R}^1, \text{R}^2 = \text{H, CO, MeO etc.}
\]

(I)

Some 5-aryl-2-amino-1,3,4-oxo (thia) diazoles (II) were prepared and screened for anti-inflammatory, anti-fungal and anti-pyretic activities. Amino oxadiazoles possessed better anti-inflammatory activity than the thio analogs (Mazzone et al., 1982).

\[
\text{R = substituted Ph, R}^1 = \text{H, C}_1 - \text{C}_3 \text{ alkyl or Ph}
\]

(II)

Deshmukh et al. (1984) observed mild anti-inflammatory and CNS depressant activities in following 1,3,4-thiadiazole congeners (III).

\[
\text{R} = \text{H, Cl, OMe etc., R}^1 = \text{H, Cl etc., Z = bond, CH}_2, \text{CH}_2 \text{etc.,}
\]

\[
\text{Z}^1 = \text{bond, CH}_2.
\]

(III)

Mohan et al. (1985) reported pronounced anti-inflammatory activity in 4-(2-alkyl-1,3-quinazolin-4-yloxyethyl)-2-(p-substituted phenylamino)-1,3,4-thiadiazoles (IV).

\[
\text{R} = \text{Me, C}_2\text{H}_5 \text{ etc., R}^1 = 2\text{-OMe, 4-OMe, H, etc.}
\]

(IV)
2-(Aryloxyalkyl)-5-(3,4-methylenedioxyphenyl)-5-triazolo[3,4-b]-1,3,4-thiadiazoles (V) were prepared by Prasad et al. (1986). Analgesic and anti-inflammatory activities were observed during primary screening of these compounds.

\[ R = \text{Ph, substituted Ph etc., } R^1, R^2 = \text{H, Me etc.} \]

(V)

Russo et al. (1987) have been synthesized 5H-benzothieno[3,2-d] [1,3,4]-thiadiazolo [3,2-a] pyrimidin-5-one derivatives and these were examined for analgesic, ulcerogenic and anti-inflammatory activities. All compounds showed anti-inflammatory activity, but the activity was less than that of phenylbutazone, mefenamic acid and acetylsalicylate. Compounds (VI) have shown potent anti-inflammatory activity. Compound (V, R=Et) was also possessed ulcer inhibiting activity.

\[ R = \text{SEt, SMe, Et etc.} \]

(VI)

5-(Benzothiazol-2-phenylamino)-1,3,4-thiadizole (VII) was prepared and evaluated for anti-inflammatory activity by Rani et al. (1990), and reported as potent anti-inflammatory agent.

(VII)

Sawhney and Gupta (1991) have reported (VIII) 2-(5-substituted 1,3,4-oxadiazol-2-yl)-2-(5-substituted 1,3,4-thiadiazol-2-yl) and 2-(3-mercapto-4-substituted-4H-1,2,4-triazol-5-yl) benzimidazoles as potential anti-inflammatory agents.

\[ R = \text{CH}_3, \text{C}_2\text{H}_5, \text{C}_6\text{H}_5, 4-\text{CH}_3\text{OC}_6\text{H}_5, 4-\text{ClC}_6\text{H}_4, 4-\text{NO}_2\text{C}_6\text{H}_4 \]

(VIII)
Gupta et al. (1997) (IX) were synthesized some 2 substituted phenyl-3-(3-alkyl/aryl-5,6 dihydro-5-triazolo [3,4b] [1,3,4] thiaiazol-6-yl indoles as anti-inflammatory, anti-bacterial and anti-fungal agents.

\[
\begin{align*}
\text{R} &= \text{H, MeOC}_6\text{H}_4, \text{CH}_2\text{C}_6\text{H}_5, \text{CH}_3, \text{C}_2\text{H}_5 \text{ etc. } R^1 = \text{H, CH}_3, \text{CH}_3\text{Cl} \\
\end{align*}
\]

(IX)

Amir and Shahni (1998) have prepared some new 2-(4- isobutylphenyl) propionic acid derivatives (X) as potent anti-inflammatory activity.

\[
\begin{align*}
\text{R} &= \text{CH}_3; R^1 = \text{H, p-CH}_3, \text{p-OCH}_3 \text{ X = S, R}'' = \text{NHC}_6\text{H}_5\text{R etc.} \\
\end{align*}
\]

(X)

Gupta et al. (1998) have synthesized some substituted-5-triazole [3,4-b] [1,3,4] thiaiazole derivatives (XI), a heterocyclic system containing bridged nitrogen atom. These compounds showed promising anti-inflammatory activity.

\[
\begin{align*}
\text{R} &= \text{Cl, OMe, Br etc., R} = 4-\text{OMeC}_6\text{H}_5, \text{CH}_3, \text{C}_2\text{H}_5, \text{etc.} \\
\end{align*}
\]

(XI)

Compound (XII) was prepared, and reported as cyclooxygenase-II inhibitors by Song et al. (1999).

\[
\begin{align*}
\end{align*}
\]

(XII)
1-[5’-(N\textsuperscript{9}-carbazolylmethyl)-1’,3’,4’-thiadiazol-2’-yl]-4-substitutephenyl-3-chloro-2-oxo-azetidines (XIII) have been synthesized by Srivastava et al. (1999) and these are useful as anti-inflammatory, anti-microbial, and anti-convulsant agents.

\[
\text{Ar} = \text{substituted (hetero) aryls}
\]  

(XIII)

Synthesis of new 2-chloro phenothiazinothiadiazol-2-oxoazetidines as anti-microbial and anti-inflammatory agents were reported (XIV) by Srivastava et al (2000).

\[
\text{Ar} = 2-\text{ClC}_6\text{H}_4, 3-\text{ClC}_6\text{H}_4, 2-\text{NO}_2\text{C}_6\text{H}_4, 2-\text{BrC}_6\text{H}_4, 2-\text{OCH}_3, \text{C}_6\text{H}_4 \text{etc.}
\]  

(XIV)

Synthesis of new 1,2,4-triazolo-thiadiazoles and 2-oxoazetidines as antimicrobial, anti convulsant and anti-inflammatory agents reported (XV) by the Srivastava et al (2002).

\[
\text{Ar} = 2-\text{ClC}_6\text{H}_4, 2-\text{BrC}_6\text{H}_4, 2-\text{NO}_2\text{C}_6\text{H}_4, 2-\text{OCH}_3\text{C}_6\text{H}_4 \text{etc.}
\]  

(XV)

3-Alkyl-6-aryl-1,2,4-triazolo [3,4-b]-1,3,4-thiadiazoles have been synthesized by Ghate and Sreenivasa (2002) (XVI). There new heterocycles were screened for their antibacterial, anti-fungal and anti-inflammatory activities.
\[ R^1 = \text{H, Me, Et, Pr}, \quad R^2 = 4-\text{MeOC}_6\text{H}_4, \text{C}_6\text{H}_5\text{CH etc.} \]

(XVI)

Manna et al (2005) have been reported (XVII) 5-substituted arylimino-3-(2,4-diethoxy arylimino)-1,2,4-dithiazolidines as anti fungal, antitumor and anti-inflammatory activities.

\[
\begin{align*}
\text{R} = \text{H, Cl, CH}_3, \text{OCH}_3, \text{OC}_2\text{H}_5 \\
\end{align*}
\]

(XVII)

Schenone et al (2006) have been reported (XVIII) potent anti-inflammatory activity in 1,3,4-thiadiazoles derivatives.

\[
\begin{align*}
\text{R} = \text{H, Cl, CH}_3, \text{OCH}_3, \text{OC}_2\text{H}_5 \\
\end{align*}
\]

(XVIII)

Kamotra et al (2007) prepared some 3-alkyl/aryl-6-(1-chloro-13,4-dihydonaphth-2-yl)-5,6 dihydro-\&-triazolo [3,4-b] [1,3,4] thiadiazoles and reported (XIX) promising anti-inflammatory activity.

\[
\begin{align*}
\text{R} = \text{CH}_3, \text{C}_6\text{H}_5, \text{C}_2\text{H}_5, \text{CH}_2\text{CH}_2\text{CH}_3 \text{ etc.} \\
\end{align*}
\]

(XIX)
THIAZOLIDINONES

Thiazolidinones are the derivatives of thiazolidine which belongs to an important group of heterocyclic compound. Thiazolidinones with a carbonyl group at position 2,4 or 5 have been subject of extensive study in the recent past. Furthermore, diverse biological activities like anti-inflammatory, bactericidal, fungicidal, insecticidal anti-convulsant, tuberculostatic, antithyroidal, potentiation of phenobarbital, induced sleeping time, cardiovascular etc. have been found to be associated with thiazolidinone derivatives. Several thiazolidinone derivatives have been synthesized and evaluated for their anti-inflammatory activities. Such as-

Promising anti-inflammatory activity has been found in 2-imino-4-oxo-5-thiazolidine acetic acids (I) (Kishore et al. 1970).

\[ \text{(I)} \]

Pronounced anti-inflammatory activity has been reported in 2-substituted-4-thiazolidinones (II) (Patel and Trivedi; 1977).

\[ \text{(II)} \]

Krapcho (1978) have reported the synthesis of 4-thiazolidinone derivatives (III). Some of the compounds of the series were found to possess promising anti-inflammatory activity.

\[ \text{(III)} \]

A novel series of 4-thiazolidinones (IV) have been synthesized. Some compounds of this series exhibited potent anti-inflammatory activity (Okuda; 1982).
R,R^2=H, Me; R^1=Ph, 3-or 4-pyridyl, 2-(Cl or HO) C_6H_4 etc.  

(IV)

Promising anti-inflammatory and analgesic activities have been shown in some compounds of a series of thiazolidinone derivatives. (V) (Sempuku; 1983).

R,R^1,R^2=H,Ph,H; H,2-ClC_6H_4,H; H,4-ClC_6H_4,H; H,4-pyridyl, Et; H,3-O_2NC_6H_4; H,3-pyridyl, H;H,3-O_2NC_6H_4Et; H,3-F_3CC_6H_4H etc.  

(V)

Acyl aminophenyl thiazolidine carboxylates (VI) have been synthesized and reported to possess pronounced anti-inflammatory activity. (Revesz and Petcher; 1985).

Potential anti-inflammatory activity has been reported in some thiazolidinone derivatives (VII and VIII). (Merck & Co. 1985).

R=Carboxy, alkoxy carbonyl; R^1=H,D,Me; R^2=H, alkanoyl; R^3=H,C_1-3 alkyl; R^4=C_3-7 alkyl, alkenyl etc.; R^3R^4=alkylene; Z=phenylene, 2,5-thienylene, 2,5-furylene; Z^1=alkylene, alkenylene; m=0,1; n=3,4  

(VII and VIII)
Singh et al. (1986) were synthesized newer Indolylthiazolidinones (IX) as potent anti-inflammatory activities.

\[
R = \text{C}_6\text{H}_5, 1-\text{OHC}_6\text{H}_4, 4-\text{CH}_3\text{OC}_6\text{H}_4, 3-\text{ClC}_6\text{H}_4 \text{ etc.}
\]

(T IX)

Tandon et al. (1986) have prepared a series of thiazolidinones (X) as potent anti-inflammatory and analgesic agents.

\[
\begin{align*}
\text{R} &= \text{H,Me}; \text{R}^1 = \text{H,OH,OMe}; \text{n}=0-3; \text{R}^2 = \text{Pr, C}_6\text{H}_4\text{OH}-2 \\
\text{X} &= \text{aryl-5-alkyl-4-thiazolidinones (XI)} \text{ as cyclooxygenase inhibitors and 5-lipoxygenase inhibitors have been synthesized (Walsh and Vwaydah; 1992)}.
\end{align*}
\]

\[
\begin{align*}
\text{R} &= \text{H,alkyl; W=O; R}^1 \text{=} \text{C}_1-\text{alkyl; r=}0-2; \text{X=}=(\text{CH}_2)_n\text{A, O(})\text{CH}_2\text{)nA}; \text{n=}0-3; \text{A=} \text{Ph, pyridyl; } \theta=(\text{O})_M, (\text{B})_M; \text{M=}0,1; \text{B=} \text{pyridylene phenylene}
\end{align*}
\]

(XI)

Synthesis, stereochemistry and anti-inflammatory activity in 3-3'-Bis(1,3-thiazolidin-4-one) (XII) have been reported by Vigorita et al. (1997).

\[
\begin{align*}
\text{R} &= \text{Br, CF}_3; \text{R}^1 = \text{H}; \text{R} = \text{R}^1 = \text{Cl, } \text{MeO}
\end{align*}
\]

(XII)
Mishra et al (1997) were synthesized 5-arylidene-2-aryl-3-(phenothiazino/benzotriazolo acetamidyl)-1,3-thiazolidine-4-ones as anti-inflammatory, anti-convulsant, (XIII) analgesic and antimicrobial agents

$$\text{R}_1, \text{R}_2, \text{R}_3, \text{R}_4 = \text{H/aryl/sub. aryl}$$

(XIII)

Goel et al (1999) were prepared 2-substituted-3-(4-bromo-2-carboxyphenyl)-5-methyl-4-thiazolidinones (XIV) as potential anti-inflammatory activity.

$$\text{R} = \text{H, 2-OCH}_3, \text{R-OH, 4-OCH}_3 \text{ etc.}$$

(XIV)

Preparation of 3,4-diaryl thiazolin-2-ones (XV) as anti-inflammatory agents has been reported by Sartori et al. (1999). These compounds were also reported to be used in the treatment of Cancer, neurogenerative diseases in the prevention of stroke and epilepsy and premature labour.

(XV)

Vigorita et al (2001) have been reported 3,3'(1,2-ethanediyl)-bis[2-aryl-4-thiazolidinone]chiral (XVI) as anti-inflammatory activity.
Synthesis and anti-inflammatory activity of some 2-arylamino-2-thiazolin-4-ones have been reported by Roman et al (2003) one of these derivatives (XVII) i.e. 5-[2-chloro-3-(4-nitrophenyl)-2-propenylidene]-2-[3-hydroxy amino]-2-thiazoline-ones showed anti-inflammatory activity.

Synthesis and biological activity of oxo-thiazolidines and their 5-arylidenes have been reported (XVIII) been Srivastava et al (2004).

Anti-inflammatory and anti-bacterial activities in substituted oxadiazole, triazole, thiathiazole and 4-thiazolidinone (XIX) derivatives have been reported by Mohd Amir et al (2004).

R = p-Cl, o-OCH₃, Ar = C₆H₅CONHC₆H₄ etc.
Attania et al (2005) have been reported (XX) 5-arylidene-2-imino-4-thiazolidinones as potent anti-inflammatory

![Molecule XX](image)

Jayachandran et al (2006) have been prepared (XXI) substituted benzothiazole as potent anti-inflammatory activity.

![Molecules XXI](image)

Kumar et al (2007) have been reported (XXII) 3-[4’-(p-chlorophenyl)-thiazol-2’-yl]-2-[(substituted azetidinone/thiazolidinone)-amino-methyl]-6-bromo quinazolin-4-ones as anti-inflammatory agent.

![Molecule XXII](image)

R = H, O-Cl-p-Cl, p-OCH₃, o-OCH₃, p-CH₃ etc.
AZETIDINONES

Pifferi and Testa (1970) has been reported (I) anti-inflammatory activity in azetidin-2-ones.

\[
\begin{align*}
\text{R} &= \text{R}^1 = \text{Pr}, \; \text{NR}^2 \text{R}^3 = 5 \text{ nitro-2-thienylidene amino. (I)}
\end{align*}
\]

Synthesis and anti-inflammatory activity of some 3-substituted azetidine derivatives (II) have been reported by Okutani et al. (1974).

\[
\begin{align*}
\text{R} &= \text{OH}, \; \text{R}^1 = \text{Me}_2\text{CH}, \text{PhCHMe, etc., R}^2 = \text{H. (II)}
\end{align*}
\]

Anti-inflamatory and antihypertensive activities in azetidinol derivatives (III) have been reported by Castaigne et al. (1976).

\[
\begin{align*}
\text{R} &= \text{H, CH}_2 \text{N Me}_2 \text{ etc., R}^1 = \text{R}^2 = \text{Me, Et etc., R}^3 = \text{H, AC, etc. (III)}
\end{align*}
\]

Krapacho and Turk (1978) synthesized 3, 3-dichloro-2-azetidinone derivatives (IV) as anti-inflammatory agents.

\[
\begin{align*}
\text{X= bond, CH}_2\text{-CH}_2 \text{ etc., Z= C}_2\text{,5 alkyline (CH}_2)_3, \; \text{R= alkyl, aryl etc., R}^1 = \text{dialkylamino, Me}_2\text{Netc. (IV)}
\end{align*}
\]
Bose (1981) reported (V) \( \beta \)-lactams and their intermediates as anti-inflammatory agents.

\[
\begin{align*}
\text{R} &= \text{H, acyl, etc., } R^1 = \text{H, SMe, } R^2 = \text{H, Furyl, CH: CH Ph etc.} \\
R^3 &= \text{H, Me, CH}_3\text{Ph etc.}
\end{align*}
\]

(V)

Tandon et al (1983) reported (VI) some new azetidinones as anti-inflammatory and analgesic agents.

\[
\begin{align*}
\text{R} &= \text{H, 4- Me}_3\text{N etc.}
\end{align*}
\]

(VI)

Salicylic and benzoic acid derivatives (VII) were synthesized by Singh et al (1984). These compounds exhibited promising anti-inflammatory activity.

\[
\begin{align*}
\text{X} &= \text{H, OH, R} = 2\text{-F, 2-Cl, 2-OH etc.}
\end{align*}
\]

(VII)

3,4 di phenyl-1- (arylmethyl)-2-azetidione derivatives (VIII) have been synthesized by Osaka Soda Co. (1985) as patent anti-inflammatory agents.

\[
\begin{align*}
\text{R} &= \text{halo, alkoxy etc.}
\end{align*}
\]

(VIII)
Agarwal (1989) synthesized some (IX) 1-substitued-2-oxo-3 chloro/3-(2-chlorophenoxy)-4-(2-arylinadol-3-yl)-azetidines as anti-inflammatory agents.

\[
R^1 = H, \text{Cl, } \text{CH}_3 \text{ etc.}
\]

(IX)

Kumar et al. (1990) have been synthesized (X) a series of 1-(2-carboxyphenyl)-3-chloro-4-arylazetidin-2-ones. All the compounds exhibited promising anti-inflammatory activity.

\[
R = H, 2-\text{OCH}_3, 4-\text{OCH}_3, 4-\text{N (CH}_3)_2 \text{ etc.}
\]

(X)

Potential anti-inflammatory activity in substituted azetidinones (XI) have been reported by Doherty et al (1994).

\[
M = H, \text{C}_{1-6} \text{ alkenyl etc., } R = \text{C}_{1-6} \text{ alkyl, } R^1 = \text{alkoxyalkyl etc.} \\
R^2 = R^3 = H, \text{COOH, Ph etc., } R^4 = (4N) \text{ Substituted carbonyl conty. Substituted,} \\
R^5 = R^6 = H, \text{COOH, Ph, OH etc.}
\]

(XI)
Crawley (1995) reported anti-inflammatory and antidegenerative activities in some newer N-carbamoylazetidinone derivatives (XII).

\[ X = \text{S. SO. SO}_2, \ Y = \text{H, alkyl etc., R}^1 = \text{H, OH, COOH, etc., p= 1,2.} \]

(XII)

Anti-inflammatory activity in azetidinone derivatives (XIII) have been reported by Kobayashi et al (1996).

\[ R^1 = R^2 = \text{H, alkyl, R}^3 = \text{H, alkyl etc., W = O, CONH, etc.} \]
\[ Y = \text{O, CO, bond., Z = diphenylamino etc., n= 0-6 integer, m= 0-6 integer.} \]

(XIII)

Amato et al (1997) synthesized some substituted (XIV) azetidinones as anti-inflammatory agents.

(XIV)

Some newer derivatives (XV) of 10-substituted phenothiazine have been synthesized and evaluated for their anti-inflammatory potency, ulcerogenic liability and acute toxicity by Bansal and Kumar (1999). 10-[2'-(3''-chloro-2''-oxo-4''-methoxyphenyl-1''-azetidinyl)-4-oxazolyl] phenothiazine was found to be most potent compound of this series.
Synthesis of some newer corbazolyl-thiadiazol-2-oxo-azetidines, as potential anti-inflammatory, anticonvulsant and antimicrobial agents (XVI) reported by Srivastava et al. (1999).

![Chemical Structure XVI](image)

R = NO$_2$ etc.

Bansal et al. (2000) synthesized some new substituted β-amino naphthaline derivatives (XVII) and screened them for anti-inflammatory activity.

![Chemical Structure XVII](image)

R = Furyl, 2, 4- OCH$_3$, 4-N Me$_2$ etc.

Some newer derivatives (XVIII) of substituted azetidinyl thiozolyl/oxazolyl benzidine have been synthesized and screened for their anti-inflammatory activity by Bansal et al. (2000).
Srivastava et al. (2000) synthesized some new (XIX) 2-chlorophenothiazinothiadiazol-2-oxo-azetidines as patent anti microbial and anti inflammatory agents.

Synthesis of β-lactam compounds as inflammation inhibitor have been reported (XX) by Bisacchi et al. (2002).

Some newer 1,2,4 triazolo-thiadiazoles and its 2-oxoazetidine derivatives (XXI) have been synthesized and evaluated for their antibacterial, antifungal, anticonvulsant and anti-inflammatory activities by Srivastava et al. (2002).
Ar = 2-ClC₆H₄, 3-ClC₆H₄, 4-ClC₆H₄, 2-BrC₆H₄,
3-BrC₆H₄, 2-ΟCH₃C₆H₄ etc.

(XXI)

Synthesis and anti-inflammatory activity of alkyl / arylidene-2-amino benzothiazoles
and 1-benzothiazole-2-yl-3-chloro-4-substituted-azetidin-2-ones have been reported
(XXII) by Khedeker et al (2003). The compound 1-benzothiazol-2-yl-3-chloro-4-(2'-methoxy phenyl)-azetidin-2-one was found to be the most potent anti-inflammatory
agent.

(XXII)
Research in the field of phytochemistry has led to discovery of efficacy of a number of plant products for the treatment of inflammatory disorders. The studies have resulted in the discovery of following products:

A. Curcumin: The rhizome of plant Curcuma Longa has used for the treatment of inflammatory disorders since ancient time. Its active principle curcumin (diferulcyemethane) (I) was isolated from Curcuma Longa. The detailed pharmacological evaluation of its activity and mode of action has been done by Ghatak and Basu (1972). It has been reported that it inhibits prostaglandin synthesis as well as platelet prostaglandin production (Thattle and Dahanukar, 1986).

![Chemical structure of Curcumin](image1)

B. Tomatine: The alkoloid tomatine (Lycopersicin) (II), Present in wild tomato plant, has been extracted, which inhibits oedema induced by carrageen an impregnated cotton pallets in rats Filderman and Kovacs, (1986).

![Chemical structure of Tomatine](image2)

C. Griseofulvin: Griseofulvin (III) was isolated from *Pencillium Griseofulvin*. It possessed moderate anti-inflammatory activity with low toxicity.
D. 18 β Glycyrrhetic acid: 18-β-Glycyrrhetic acid (IV) was isolated from the roots of Liquorice. It has anti-inflammatory property. Its methyl as well as diacetate derivatives were also synthesized and were found to possess anti-inflammatory activity Krans, (1960).

E. Cryogenini: Nucifora and Malone (1971) reported anti-inflammatory properties in cryogenine (V), which was isolated from plant *Heimia Salicifolia*.

Gold

Gold in elemental form, has been employed for centuries as an antipruritic to relieve the itching palm. In more modern times, the observation by Robert Koch in 1890 that gold inhibited Mycobacterium tuberculosis in vitro led to trials in arthritis and lupus erythematosus, thought by some to be tuberculosis manifestations. At present, gold derivatives are used in the treatment of rheumatoid arthritis. These derivatives such as Aurothioglucose (I), Gold sodium thiomalate (II) and auranofin (III) are used for the treatment of inflammatory disorders or rheumatoid arthritis (William and Kenneth; 1996) when NSAIDs do not show a satisfactory response.
In all the gold derivatives, possessing potent anti-inflammatory activity, it is important to notice that gold is attached to sulfur.