PART-I

INTRODUCTION AND SCOPE FOR THE WORK
INTRODUCTION

Any human being has inevitably experience certain unpleasant events at certain times in life. Inflammation may be considered to be one such unpleasant, at least at times, an unavoidable phenomenon. Inflammation is the body’s reaction to invasion by an infection, antigen challenge, and even just physical, chemical or traumatic damage. The body's response is initiated by the release of inflammatory mediators, which result in the mobilization of an array of cellular and vascular materials that are meant to get rid of the stimulus.\(^1\) This is a defensive response of the body to help in maintaining homeostasis.

Once the aberrant stimulus are appropriately dealt with, the system returns to normalcy, but inflammatory stimulus persists or if the defenses of the body are inappropriately mobilized, inflammation becomes chronic\(^2\) Chronic inflammatory diseases like rheumatoid arthritis (RA), osteoarthritis (OA), ankylosing spondylitis etc., result in a great deal of morbidity, which affects the quality of life. In 1997, it was estimated that about 5-6% of world population in many regions have RA while OA claimed to affect about 10% of the world's population of which 50 % were the elderly population.

Since the dawn of civilization, mankind endeavors to make life free of pain and for this meritorious objective, he has tried to find remedies. Treatment of pain is multifaceted and therapy is focused among multiple areas, on decreasing the subjective intensity and duration of the pain complaint, and decreasing the potential for conversion of acute pain to chronic pain. A rapid onset of action and fast relief are the key requirements for drugs that are used to manage pain.

Anti-inflammatory refers to the property of a substance or treatment that reduces inflammation. Anti-inflammatory drugs make up about half of analgesics, remedying pain by reducing inflammation as opposed to opioid which affect the central nervous system.

The anti-inflammatory substances or drugs may be divided or classified as anti-inflammatory herbs, steroids and non-steroidal anti-inflammatory drugs (NSAIDS). Following is a brief review covering various classes of anti-inflammatory agents along with their limitations as the drugs.
A) Anti-inflammatory Herbs

In India, herbal drugs are known from centuries. In Ayurveda, several plants are mentioned to possess anti-inflammatory activity. In traditional methods, the indigenous anti-inflammatory medicinal plants have been used in fresh paste, juice or dry powder forms, which contain both the organic and inorganic constituents.

Following are herbs having anti-inflammatory activity.

1) White Willow Bark

White willow bark is a tree native to Europe and Asia. The name "white willow" comes from the color of the leaves, which are covered with fine white hair. The use of white willow bark medicinally goes far back. Ancient Egyptians used white willow for inflammation. The Greek physician Hippocrates wrote about white willow's medicinal uses in 5th century B.C. In 1829, scientists in Europe identified what was believed to be the active ingredient in white willow bark a compound called salicin.

Containing aspirin-like compounds, this herb was found to be as effective as conventional medicine in lessening pain among people with mild to fairly severe knee and hip problems in a 2008 study. White willow barks may also alleviate acute back pain, joint pain, and osteoarthritis.

2) Devil’s Claw

Devil's claw is a plant native to Southern Africa. Its name comes from the small hooks on the plant's fruit. The active ingredients in devil's claw are believed to be iridoid glycosides called harpagosides, which are found in the secondary root.

This plant is traditionally used to treat rheumatoid arthritis. Devil's claw may also soothe pain resulting from osteoarthritis, tendonitis, and back and neck troubles. In a 2007 study of 259 people with rheumatic conditions, researchers found that 60% of study members either reduced or stopped their pain medication after eight weeks of taking devil's claw.

3) Bromelain

Bromelain is a group of enzymes extracted primarily from the stem of a pineapple, a member of the bromeliad (Bromeliaceae) family of plants. While bromelain is also in the delicious flesh of the pineapple, it is only available in low levels. Some enzymes cannot survive in the stomach, however bromelain seems to survive with little problem.
Bromelain reportedly reduces the swelling from sports injuries, post-operational surgery, allergic rhinitis, and traumatic injury. It also reduces knee pain and ulcerative colitis, among its long list of uses. The mechanism by which it works seems to be related to its constituents ability to inhibit platelet aggregation and it may be able to alter leukocyte response and activation. Bromelain is activated by magnesium, two of the other compounds in this formulation, trypsin and rutin; appear to work synergistically to accentuate its effects, specifically in regard to reduced knee and hip pain associated with the normal age-related deterioration of the joints.

4) Curcumin

Curcumin is the active constituent in the spice turmeric that gives the spice, and the many "curry" dishes which it flavors, their distinctive taste and strong yellow color. The use of turmeric in Indian culture has taken on almost mystical properties, perhaps due in part to its many uses in Ayurvedic Medicine. In this tradition, curcumin, by way of turmeric, is used for a wide variety of stomach ailments, headache, liver and gallbladder ailments, respiratory infections, cancer and other inflammations (To be clear, we only mean this as a factual statement, that is, turmeric is presently used for these purposes in Ayurvedic medicine, whether or not such use is justified). Curcumin’s method of action seems to be multi-fold. First it is an antioxidant and as such it helps to protect against the damaging effects of free radicals. Second it stimulates the body to naturally produce more histamine-lowering cortisone. Curcumin also appears to protect the liver from toxic compounds, which in turn, may improve general health. It also seems to inhibit platelet clumping, which may reduce arterial scaring and reduce swelling due to blunt force injuries. The most important aspect of curcumin is its apparent ability to inhibit mediators of inflammation, such as cyclooxygenase-2 (COX-2), lipooxygenase (LOX). The combined effect of these mechanism makes curcumin a very potent anti-inflammatory substance.

5) Ginger

Most people know ginger as a spice used in food, but ginger also has a long history as a medicine in many cultures. In the Ayurvedic and Tibbetian systems of medicine it is commonly used to soothe stomach ailments and to reduce nausea, for inflammation, rheumatism and generalized muscular discomfort. Ginger has been found to stimulate digestion and ease the movement of substances through the digestive tract, lessening
irritation to the intestines. Ginger may also protect the stomach from the damaging effects of NSAIDs and alcohol, and may possibly help protect against the development of ulcers from the use of NSAIDs. More importantly to this formulation, ginger has also been found to have broad anti-inflammatory action that "modulates biochemical pathways activated in chronic inflammation." That is to say, it appears as though ginger also inhibits COX and LOX pathways. Finally, both small-scale animal and human studies have found that ginger root reduces the presence of inflammatory mediators, such as prostaglandin-E2 (PGE$_2$) and thromboxane B2 (TXB$_2$).

6) Boswellia

Boswellia serrata (also known as Indian Frankincense or olibanum) is a relatively small tree that is native to much of the dried regions of India. In traditional use the tree trunk is tapped, releasing a gummy sap or "oleoresin," called a "guggal" in Ayurvedic. Any resin that is collected in this manner is called a guggal. It is from this naming convention from which the traditional name, "salai guggal" comes.

The oleoresin contains essential oils, terpenoids and boswellic acids. It is the boswellic acids that are believed to be the active components. In several studies these boswellic acids have been found to have anti-inflammatory activity similar to that of the non-steroidal anti-inflammatory drugs (NSAIDs) used in conventional medicines. However, unlike NSAIDs, boswellia does not seem to cause stomach irritation or ulceration. In fact, one small study found that boswellia may actually be helpful in the treatment of ulcerative colitis.

Boswellia has been used in Indian Ayurvedic medicine for centuries, perhaps millennia by some accounts. While boswellia has had many benefits attributed to it in that time. It is boswellia's uses as an anti-inflammatory, anti-arthritis, and analgesic that have garnered the most attention in Western medicine. After previous studies had found boswellia more effective than placebo, the Indian government funded research on boswellia in a comparison study against a type of NSAID, Cyclooxygenase-2 (COX-2) inhibitors. Selective COX-2 inhibitors are the latest class of anti-inflammatory drugs that have been found high effective, but which most have more recently been shown to cause serious cardiac risk.
The researchers in this study stated in conclusion that "in terms of safety, efficacy and duration of action, the present study shows that Boswellia serrata extract was superior to valdecoxib, except for the slower onset of action compared to valdecoxib.

7) Neem

Known as the ‘Divine Tree’ in India, Neem oil is used in Ayurvedic medicine to calm inflammatory skin conditions, joint pains and muscle aches. Extracts of neem leaves and seeds have also demonstrated anti-fungal, antibacterial, anti-diabetic and anti-viral properties in various studies.23

8) Holy Basil (Tulsi)

A type of basil native to India, holy basil or tulsi not only plays an important role in Ayurveda, it’s also revered by worshipers as a symbol of a deity. Traditionally, this herb is used in cooking and also as a medicine to treat cold, flu and sore throat. Holy basil oil is found to possess anti-inflammatory, antioxidant and other medicinal properties that are effective against arthritis,24 diabetes, high cholesterol, peptic ulcers as well as chemotherapy and radiation poisoning.

9) Aloe Vera

Aloe Vera is well known for healing wounds and soothing skin burns. It is also found to display well anti-inflammatory property.25 When ingested aloe cools inflammation in the digestive tract such as in the case of peptic ulcers, and it may also be beneficial for other inflammatory conditions. In Traditional Chinese Medicine, aloe vera is prescribed when there’s excessive heat in the liver.

Aloe Vera gel can be consumed internally, or used topically to treat burns and other skin irritations such as acne and psoriasis. The juice obtained from the gel is also a popular detoxification beverage.

10) Licorice

Licorice, the sweet root of this plant is commonly used to make candies. Healing-wise, the strong anti-inflammatory compounds 26 found in licorice root have been found to be effective against coughs, colds, mouth ulcers, peptic ulcers and even chronic hepatitis infection. Licorice is available as chopped roots, which can be brewed as tea, and also in powder and capsule forms.
11) Feverfew

Related to the chrysanthemum, feverfew produces pretty daisy-like flowers with white petals and yellow centers. As its name implies, this anti-inflammatory herb\(^{27}\) can help to lower fever and it’s also effective in reducing the severity and frequency of headaches and migraines. But taking feverfew during a migraine attack is unlikely to help, as it takes time for the herb to display effect. As such, it’s more useful as a preventive measure.

**Drawbacks or Limitation of herbal ant-inflammatory agents**

Severe complications until are not reported with herbal drugs, but nausea, vomiting, gastric problems were the common adverse effects reported with herbal remedies.

**B ) Steroidal anti-inflammatory drugs**

Many steroids, specifically glucocorticoids (GC\(_S\)) (1.1), reduce inflammation or swelling by binding to glucocorticoid receptors, which is present in each vertebrate animal cell. They are often as corticosteroids.

GCs are part of the feedback mechanism in the immune system that turns immune activity (inflammation) down. They are therefore used in medicine to treat diseases that are caused by an overactive immune system, such as allergies, asthma, autoimmune diseases and sepsis. GCs have many diverse (apheliotropic) effects, including potentially harmful side effects, and as a result are rarely used.\(^{28}\) GC\(_S\) also interfere with some of the abnormal mechanisms in cancer cells, so they are used in high doses to treat cancer.

GCs cause their effects by binding to the glucocorticoid receptor (GR). The activated GR complex in turn up-regulates the expression of anti-inflammatory proteins in the nucleus (a process known as Trans activation) and represses the expression of pro-inflammatory proteins in the cytosol by preventing the translocation of other transcription factors from the cytosol into the nucleus (Trans repression).

Glucocorticoids are distinguished from mineral corticoids and sex steroids by their specific receptors, target cells, and effects. In technical terms, corticosteroid refers to both glucocorticoids and mineralocorticoids (as both are mimics of hormones produced by the adrenal), but is often used as a synonym for glucocorticoid.

Cortisol (or hydrocortisone) is the most important human glucocorticoid. It is essential for life and it regulates or supports a variety of important cardiovascular, metabolic, immunologic, and homeostatic functions. Various synthetic glucocorticoids are
available; these are used either as replacement therapy in glucocorticoid deficiency or to suppress the immune system.

\[
\text{(1.1)}
\]

**Cortisol**

A variety of synthetic glucocorticoids, some far more potent than cortisol, have been created for therapeutic use. They differ in the pharmacokinetics (absorption factor, half-life, volume of distribution, clearance) and in pharmacodynamics (for example the capacity of mineralocorticoid activity: retention of sodium (\(\text{Na}^+\)) and water; renal physiology. Because they permeate the intestines easily, they are primarily administered orally (by mouth), and also by other methods, such as topically on skin. More than 90 percent of them bind different plasma proteins, however with a different binding specificity. Endogenous glucocorticoids and some synthetic corticoids have high affinity to the protein transcortin (also called CBG, corticosteroid-binding globulin), whereas all of them bind albumin. In the liver, they quickly metabolise by conjugation with a sulfate or glucuronic acid, and are secreted in the urine.

Glucocorticoid potency, duration of effect, and overlapping mineralocorticoid potency varies. Cortisol (hydrocortisone) is the standard of comparison for glucocorticoid potency. Hydrocortisone is the name used for pharmaceutical preparations of cortisol. Data refer to oral dosing, except when mentioned. Oral potency may be less than parenteral potency because significant amounts (up to 50% in some cases) may not be absorbed from the intestine. Fludrocortisone, DOCA (Deoxycorticosterone acetate), and aldosterone are, by definition, not considered glucocorticoids, although they may have minor glucocorticoid potency, and are included in this table to provide perspective on mineralocorticoid potency.

Glucocorticoids are potent anti-inflammatory agents; Glucocorticoids' primary anti-inflammatory mechanism is lipocortin-1 synthesis. Lipocortin-1 suppresses phospholipase A2, thereby blocking eicosanoid production, and inhibits various leukocyte inflammatory
events (epithelial adhesion, emigration, chemotaxis, phagocytosis, respiratory burst, etc.).
In other words, Glucocorticoids not only suppress immune response, but also inhibit the
two main products of inflammation, prostaglandins and leukotrienes. Glucocorticoids
inhibit prostaglandin synthesis at the level of phospholipase A2 as well as at the level of
cyclooxygenase/PGE isomerase (COX-1 and COX-2), the latter effect being much like
that of NSAIDs, potentiating the anti-inflammatory effect.

In addition, glucocorticoids also suppress cyclooxygenase expression. Glucocorticoids marketed as anti-inflammatories are often topical formulations, such as
nasal sprays for rhinitis or inhalers for asthma. These preparations have the advantage of
only affecting the targeted area, thereby reducing side effects or potential interactions. In
this case, the main compounds used are beclometasone, budesonide, fluticasone,
mometasone and ciclesonide. In rhinitis, sprays are used. For asthma, glucocorticoids are
administered as inhalants with a metered-dose or dry powder inhaler.

**Table 1.1 Comparative steroid potencies**

<table>
<thead>
<tr>
<th>Name</th>
<th>Glucocorticoid potency</th>
<th>Mineralocorticoid potency</th>
<th>Duration of action (1/2 in hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrocortisone (Cortisol)</td>
<td>1</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td>Cortisone acetate</td>
<td>0.8</td>
<td>0.8</td>
<td>oral 8, intramuscular 18+</td>
</tr>
<tr>
<td>Prednisone</td>
<td>3.5-5</td>
<td>0.8</td>
<td>16-36</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>4</td>
<td>0.8</td>
<td>16-36</td>
</tr>
<tr>
<td>Methylprednisolone</td>
<td>5-7.5</td>
<td>0.5</td>
<td>18-40</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>25-80</td>
<td>0</td>
<td>36-54</td>
</tr>
<tr>
<td>Betamethasone</td>
<td>25-30</td>
<td>0</td>
<td>36-54</td>
</tr>
<tr>
<td>Triamcinolone</td>
<td>5</td>
<td>0</td>
<td>12-36</td>
</tr>
<tr>
<td>Beclometasone</td>
<td>8 puffs 4 times a day equals 14 mg oral prednisone once a day</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Fludrocortisone acetate</td>
<td>15</td>
<td>200</td>
<td>24</td>
</tr>
<tr>
<td>Deoxycorticosterone acetate (DOCA)</td>
<td>0</td>
<td>20</td>
<td>-</td>
</tr>
<tr>
<td>Aldosterone</td>
<td>0.3</td>
<td>200-1000</td>
<td>-</td>
</tr>
</tbody>
</table>
Side effect of steroidal anti-inflammatory drugs

- Immunosuppression.
- Hyperglycemia due to increased gluconeogenesis, insulin resistance, and impaired glucose tolerance ("steroid diabetes"); caution in those with diabetes mellitus.
- Increased skin fragility, easy bruising.
- Negative calcium balance due to reduced intestinal calcium absorption.
- Steroid-induced osteoporosis: reduced bone density (osteoporosis, osteonecrosis, higher fracture risk, slower fracture repair).
- Weight gain due to increased visceral and truncal fat deposition (central obesity) and appetite stimulation.
- Adrenal insufficiency (if used for long time and stopped suddenly without a taper).
- Muscle breakdown (proteolysis), weakness; reduced muscle mass and repair.
- Expansion of malar fat pads and dilation of small blood vessels in skin.
- Anovulation, irregularity of menstrual periods.
- Growth failure, pubertal delay.
- Increased plasma amino acids, increased urea formation; negative nitrogen balance.
- Excitatory effect on central nervous system (euphoria, psychosis).
- Glaucoma due to increased cranial pressure and Cataracts.

C ) Non-steroidal anti-inflammatory drugs (NSAIDS )

Nonsteroidal anti-inflammatory drugs, usually abbreviated to NSAIDs or NAIDs, but also referred to as nonsteroidal anti-inflammatory agents/analgesics (NSAIAs) or nonsteroidal anti-inflammatory medicines (NSAIMs), are drugs with analgesic and antipyretic (fever-reducing) effects and which have, in higher doses, inflammatory effects.

The term "nonsteroidal" is used to distinguish these drugs from steroids, which, among a broad range of other effects, have a similar eicosanoid-depressing, anti-inflammatory action. As analgesics, NSAIDs are unusual in that they are non-narcotic.

Non-steroidal anti-inflammatory drugs comprise a heterogenous group of medications, majority of which are organic acids for e.g. aspirin, ibuprofen and naproxen. NSAID₃s alleviate pain by counteracting the cyclooxygenase (COX) enzyme. On its own COX enzyme synthesizes prostaglandins, creating inflammation. In whole the NSAIDS prevent the prostaglandins from ever being synthesized, reducing or eliminating the pain.
Mechanism of action of NSAIDs

Despite the wide use of NSAIDs over the last century, their mechanism of action was not fully appreciated until 1971, when Vane published his seminal observations proposing that the ability of NSAIDs to suppress inflammation rests primarily on their ability to inhibit the cyclooxygenase (COX) or PGH synthase enzyme. This would limit the production of proinflammatory prostaglandins (PGs) at a site of injury. Given this, NSAIDs have been used by scientists for the last 25 years to dissect the critical role that both the COX enzyme and the eicosanoids derived from this pathway have in normal and abnormal physiologic states.

The chemistry of the eicosanoid biosynthetic pathway is well known. Prostaglandins are formed by the oxidative cyclization of the central 5 carbons within 20 carbon polyunsaturated fatty acids. The key regulatory enzyme of this pathway is COX, which catalyzes the conversion of arachidonic acid (or other 20 carbon fatty acids) to PGG\(_2\) and PGH\(_2\). PGH\(_2\) and are subsequently converted to a variety of eicosanoids that include PGE\(_2\), PGD\(_2\), PGF\(_2\), PGI\(_2\), and thromboxane (TX) A\(_2\) (Fig. 1.2 and 1.3).
Introduction and Scope for the Work

Arachidonic acid

\[
\text{Cyclooxygenase activity (COX-1, COX-2)}
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Prostaglandin G2

Peroxydase activity

Prostaglandin H2

Prostaglandin I2

Thromboxane A2

Prostaglandin D2

Prostaglandin E1

Prostaglandin E2

Fig. 1.3. Chemical structure of prostaglandins.

Gs are found in animals as primitive as the coelenterates and are present in a wide variety of human tissues. PGs not only play a central role in inflammation, but also regulate other critical physiological responses. In humans, prostaglandins are involved in diverse functions, including blood clotting, ovulation, initiation of labor, bone metabolism, nerve growth and development, wound healing, kidney function, blood vessel tone, and immune responses.

The systemic suppression of PG synthesis through inhibition of COX can lead to unwanted side effects. In particular, individuals taking NSAIDs for even short periods of time can experience gastrointestinal and renal side effects in addition to effects on other physiological systems. Prostaglandins and other eicosanoids by the cyclooxygenase enzymes.

The different effects of PGs can be explained by considering their varied chemistry, the diversity of PG receptors, and modulation of PG synthesis by local
upstream and downstream effects. Since NSAIDs clearly have proven efficacy in treating human disease, while having well-documented deleterious side effects, an intense amount of research over the last 5–10 years has been devoted in distinguishing the role of each type of COX isoform.

Less than a decade ago, it was demonstrated that the COX enzymes existed in two isoforms: COX-1, which is constitutively expressed in various tissues, and COX-2, an inducible isoenzyme unregulated in response to stress inflammatory stimuli in many tissues. More recently, the presence of a new isoform COX-3 has been speculated upon.\(^\text{35}\)

COX-1 isoform does housekeeping activity in stomach, kidney and blood vessels hence known as ‘Constitutive enzyme’. Housekeeping activities include for example secretion of mucus for protection of gastric mucus against gastric acid, haematosis, maintenance of renal functions, etc.\(^\text{36}\) COX-1 is the only isoform in the normal gastric mucosa and platelets and is responsible primarily for the biosynthesis of eicosanoids involved in gastrointestinal mucosal cytoprotection and the maintenance of platelet function.\(^\text{35}\)

COX-2 was discovered in 1991 and the first lead inhibitors were described in 1992. A mere 10 years later, few selective inhibitors have been introduced in the market, as of now several isoform of COX have been reported\(^\text{37}\) COX-2 isoform is known as "Inducible Cox" because it is normally present in insignificant amounts but levels increase with in leukocytes and inflammatory cells drastically in response to inflammatory and pathological changes. Stimulants include cytokines, growth factors, etc.\(^\text{36}\) COX-2, on the other hand, is involved in many physiologic responses, but mainly in the amplification of inflammation and pain. This new knowledge was the major impetus for the development of compounds that specifically target COX-2 while sparing COX-1 at therapeutic doses. It was hypothesized that COX-2 specific inhibition could alleviate pain and inflammation without disrupting the homeostatic functions mediated by COX-1 derived prostanoids. Thus, many of the deleterious side effects of conventional NSAIDs which cannot distinguish between the COX-1 and COX-2 isoforms could be avoided.\(^\text{35}\) Compounds that selectively inhibit the COX-2 enzyme have been shown to possess anti-inflammatory property and reduced ulcerogenicity in animal models and would have tremendous therapeutic potential if these properties translated in humans.\(^\text{38}\)
Clinically used NSAIDs:

Clinically established NSAIDs can be broadly classified based on their chemical structure as follow.

- Salicylates
- Propionic acid derivatives
- Acetic acid derivatives
- Enolic acid (Oxicam) derivatives
- Fenamic acid derivatives
- Selective COX-2 inhibitors (Coxibs)
- Sulphonanlides
- Others
1) Salicylates

The salicylates are derivatives of 2-hydroxybenzoic acid (salicylic acid). The salicylates were discovered in 1838 following the extraction of salicylic acid from willow bark. \(^3^9\) Salicylic acid was used medicinally as the sodium salt but replaced therapeutically in the late 1800s by the acetylated derivative, acetylsalicylic acid (ASA) or aspirin. Therapeutic utility is enhanced by esterification of the phenolic hydroxyl group as in aspirin \((1.4)\), and by substitution of a hydrophobic/lipophilic group at C-5 as in diflunisal \((1.5)\). The salicylates are strong organic acids and readily form salts with alkaline materials. The carboxyl group is substantially more acidic (and ionizes readily at physiologic pH) than the phenolic hydroxyl. \(^4^0\)

The difluorophenyl analogue of salicylic acid differs from other members of the salicylate class and that it has primarily analgesic and antipyretic activity. It is used to treat the pain associated with RA, OA and muscle pain. It reported that this causes less GI tract ulceration than aspirin and has lower auditory side effects. This drug is cleared primarily by phenol and carboxyl O-glucuronidation similar to the salicylates.

Salsalate \((1.6)\), or salicylsaliclic acid, is a dimmer of salicylic acid. It is insoluble in gastric juices but is soluble in the small intestine where it is hydrolyzed to two molecules of salicylic acid and absorbed. It does not cause GI blood loss and can be given to aspirin sensitive patients.

The salicylates have potent anti-inflammatory activity \(^4^1\) with mild analgesic and antipyretic activities. These compounds are mainly COX-1 selective. They have high affinity to COX-1. Toxicities include GI irritation, hypersensitivity reactions, inhibition of platelet aggregation, and ototoxicity (tinnitus).
2) Propionic acid

This class includes following six clinical agents,

![Chemical structures](image)

(1.7) Ibuprofen  (1.8) Fenoprofen  (1.9) Naproxen

(1.10) Ketoprofen  (1.11) Flurbiprofen  (1.12) Oxaprozin

Some of the most useful NSAIDs are structurally derived from aryl acetic acids. These compounds are often referred to as the “profens” based on the suffix of the prototype member, ibuprofen (1.7). Like the salicylates these agents are all strong organic acids (pKa = 3-5) and thus form water soluble salts with alkaline reagents. The arylpropionic acids are characterized by the general structure Ar-CH(CH₃)-COOH which conforms to the required general structure. All of these compounds are predominantly ionized at physiologic pH and more lipophilic than ASA or salicylic acid.⁴²

The CH₃ substituent present in the profens increases cyclooxygenase inhibitory activity and reduces toxicity of the profens. The carbon in these compounds is chiral and the S-(+) enantiomer of the profens is the more potent cyclooxygenase inhibitor. Most profen products, except naproxen (1.9), are marketed as the racemates. In addition to the metabolism described below, the profens undergo a metabolic inversion at the chiral carbon involving stereospecific transformation of the inactive R-enantiomers to the active S-enantiomers.⁴³ This is believed to proceed through an activated (more acidic -carbon) thioester intermediate. Normally only the S-(+) isomer is present in plasma.

A recent addition (1993) to this class of agents is oxaprozin (DayproTM) another nonselective COX inhibitor.⁴⁸ It differs slightly in that substitution of the propionic moiety is at the 3 position rather that at the 2 position as in other agents of this class. It is metabolized by glucuronidation and uncharacterized oxidation products.
These compounds are anti-inflammatory agents with analgesic and antipyretic activity. Generally the profens are considered being slightly COX-1 selective. Naproxen appears to be more selective for COX-2 than other members of this series. They are used for RA, OA and as analgesics and antipyretics. They produce less GI ulceration than the salicylates, but may cause some thrombocytopenia, headache, dizziness, fluid retention edema.

3) Acetic acid derivatives

This class includes Sulindac, Indomethacin, and Etodolac, Ketorolac, Diclofenac and Nabumetone non-steroidal anti-inflammatory drugs.

These compounds are also derivatives of acetic acid, but in this case the substituent at the 2-position is a heterocycle or related carbon cycle. This does not significantly affect the acidic properties of these compounds. Indomethacin (1.14) contains benzyolated indole nitrogen. The methyl group at the 2 position of the indole ring prevents free rotation about the C-N bond and keeps the two aromatic rings in the correct relationship for COX binding and therapeutic activity. Indomethacin is COX-1 selective and produces primarily anti-inflammatory actions with some analgesic and antipyretic activities. It is used for RA, OA, ankylosing spondylitis, to suppress uterine contraction (preterm labor), and to promote closure of patent ductus artiosus in neonates (premature infants). These are accompanying with GI ulceration and hemorrhage (these limit the use). CNS toxicity ranging from headaches to delusions to psychoses and suicidal tendencies occur along with bone marrow depression: aplastic anemia and thrombocytopenia.
Sulindac Structure: This relationship between aromatic rings observed for indomethacin is preserved by restricted rotation about the carbon-carbon double bond in Sulindac (1.13). In this agent the indole N has been eliminated which reduces the drugs resemblance to 5-HT and therefore fewer CNS side effects are seen. This compound has pharmacologic actions similar to indomethacin (COX-1 selective and anti-inflammatory primarily). However, sulindac is a prodrug function; it is reduced to a sulfide which is 50 X more active. It is used for RA, OA, AS, and acute gout and to inhibit uterine contractions. Overall Sulindac produces less GI ulceration, probably as a result of its prodrug function. Some CNS toxicity, hepatic damage and prolongs clotting time.

Etodolac (Lodine) (1.15): is an analogue of indomethacin with similar profile; anti-inflammatory mainly with analgesic and antipyretic activity and uricosuric action. It is used for RA, OA and as a post-operative analgesic. It may cause GI ulceration and hemorrhage at high doses.

Ketorolac (1.16) which lacks this benzylic methyl group is not susceptible to the type of oxidation observed for tolmetin and as a result its half-life is longer (4-6 hours). This drug is unique in that it is formulate for orally and IM administration. It has good oral activity with primarily analgesic activity, but also has anti-inflammatory activity and antipyretic actions. It is also used in management of post-operative pain.

4) Enolic acid (Oxicam) derivatives

This class includes piroxicam, meloxicam, Droxicam, and Lornoxicam drugs.

Oxicams (Piroxicam (1.19) and Meloxicam (1.20)) are having 4-hydroxybenzothiazine heterocyclic ring system. The acidity of the oxicams is attributed to the 4-OH with the enolate anion being stabilized by intramolecular H-bonding to the amide N-H group. Also, the presence of the carboxamide substituent at the 3-position of the benzothiazine ring contributes toward acidity by stabilizing the negative charge formed during ionization (resonance stabilization). Although these compounds are acidic (pKa = 6.3), they are somewhat less acidic than carboxylic acids class of NSAIDs. Yet
the oxicams are primarily ionized at physiologic pH and acidity is required for COX inhibitory activity. It has higher COX-2 selectivity than many other NSAIDs, particularly meloxicam. These agents have utility in treatment of RA and OA.

5) Fenamic acid derivatives

These agents are considered to be N-aryl substituted derivatives of anthranilic acid which itself is a bioisostere of salicylic acid. These agents retain the acidic properties that are characteristic of this class of agents; however, note that while mefenamic acid (1.23) and meclofenamic acid (1.24) are derivatives of anthranilic acid, diclofenac is derived from 2-arylacetic acid. The most active fenamates have small alkyl or halogen substituents at the 2’, 3’ and/or 6’ position of the N-aryl moiety (meclofenamate is 25 times more potent than mefenamate). Among the disubstituted N-aryl fenamates the 2’, 3’-derivatives are most active, suggesting that the substituents at the 2’, 3’-positions serve to force the N-aryl ring out of coplanarity with the anthranilic acid. Hence this steric effect is proposed to be important in the effective interaction of the fenamates at their inhibitory site on cyclooxygenase.

The anthranilates have primarily anti-inflammatory activity and are non-COX selective. The anthranilates are used as mild analgesics and occasionally to treat inflammatory diseases. Diclofenac is used for RA, OA, AS and post-operational pain, Meclofenanamte for RA (as a secondary agent), and Mefenamic acid have been used as RA and analgesic for dysmenorrhea respectively. The utility of the class of agents is limited by a number of adverse reactions including nausea, vomiting, diarrhea, ulceration, headache, drowsiness and hematopoietic toxicity.

6) Selective COX-2 inhibitors (Coxibs)

All COX-2 inhibitors are diaryl-5-membered heterocycles. Celecoxib (1.27) has a central pyrazole ring and two adjacent phenyl substituents, one containing a methyl group and the other a polar sulfonamide moiety; the sulfonamide binds to a distinct hydrophilic region that is present on COX-2 but not COX-1. Rofecoxib (1.28) has a central furanone
ring and two adjacent phenyl substituents, one containing a methyl sulfone group, unlike celecoxib. Valdecoxib (1.29) has a central oxazole ring and one phenyl ring with a polar sulfonamide like celecoxib.\textsuperscript{5\textdegree} The COX-2 inhibitors have analgesic, antipyretic and inflammatory activities comparable to NSAIDs and are used therapeutically in OA (all), RA (celecoxib and Valdecoxib), acute pain (Celecoxib and Rofecoxib) and primary dysmenorrhea (all). These compounds produce less GI ulceration and hemorrhage than NSAIDs due to their COX-2 selectivity.\textsuperscript{5\textdegree} Also they do not inhibit platelet aggregation and have minimal renal and CV side effects.

![Chemical structures of COX-2 inhibitors](image)

7) Sulphonanilides

This important class of COX-2 inhibitors derives from two chemically close compounds: nimesulide or 4-nitro-2-phenoxyethanesulphonanilide (1.33) and NS-398 (1.34). Since these two agents were found to possess anti-inflammatory activity\textsuperscript{53, 5\textdegree} with an interesting degree of COX-2 selectivity,\textsuperscript{5\textdegree} a renewed interest was focused on this class of anti-inflammatory agents leading to the synthesis of a great number of analogues. Structurally, these COX-2 inhibitors are characterized as alkylsulphonanilides. The alkyl portion (R) (1.35) of the sulfonyl group is typically a methyl substituent, although halogenated substituents, such as trifluoromethyl substituent, have also been reported.\textsuperscript{5\textdegree}
The 2-position is frequently substituted with an arylxy or arylsulfanyl group but cycloalkyloxy or cycloalkylsulfanyl groups are commonly described. The 4-position invariably bears an electron withdrawing group, sometimes incorporated as part of an adjacent ring (1.35). Thus, all the members of the sulfonanilide class of COX-2 inhibitors have three common structural features summarized in Fig. (1.35). Nimesulide is a relatively COX-2 selective, non-steroidal anti-inflammatory drug (NSAID) with analgesic and antipyretic properties. Its approved indications are the treatment of acute pain, the symptomatic treatment of osteoarthritis and primary dysmenorrhoea in adolescents and adults above 12 years old. Due to concerns about the risk of hepatotoxicity, nimesulide has been withdrawn from market in many countries.

8) Others

Licofelone (1.36) is a dual COX/LOX inhibitor\(^\text{57}\) being considered as a treatment for osteoarthritis\(^\text{58}\) and which is under development by Merck GmbH with partners Alfa Wassermann and Lacer.

Licofelone is both an analgesic and an anti-inflammatory agent. Inhibition of 5-LOX may reduce the gastrointestinal toxicity associated with other non-steroidal anti-inflammatory drugs, which only inhibit COX (cyclooxygenase). Licofelone is the first drug to inhibit both. It has passed the phase III trials.\(^\text{59}\)
Heterocyclic NSAIDs

Heterocyclic compounds occur widely in nature and in a variety of non-naturally occurring compounds. A large number of heterocyclic compounds are essential to life. Various compounds such as alkaloids, antibiotics, essential amino acids, the vitamins, hemoglobin, the hormones and a large number of synthetic drugs and dyes contain heterocyclic ring systems.

 Approximately 60 % clinically used NSAIDs are heterocycles. In search of safer ant-inflammatory drugs, various types of heterocyclic compounds have been synthesized and screened for the activity. The heterocycles such as pyrimidines, pyridines, thiazoles, imidazoles, oxazoles, pyrazoles and pyrroles, acridines etc are synthesized and some of them have shown anti-inflammatory activity.

Here in this review focus is on those heterocycles selectively bearing therapeutics which have displayed COX-2 inhibitory activity and established as drugs and some of them are likely to coming forward as new leads to treat inflammation.

A) Diarylheterocycles with a central 5-membered pyrazole ring

The 1, 5-diarylpyrazole classes of compounds proved to be a fertile source for highly potent and selective COX-2 inhibitors. The first compound, (1.37) examined in this series exhibited excellent in vitro COX-2 inhibitory potency and selectivity (COX-2 IC\textsubscript{50} = 0.24 μM, COX-1 IC\textsubscript{50} > 100 μM; SI > 417) with potent anti-inflammatory activity in animal models with no tendency to cause GI damage. During the initial stage of the development of the 1, 5-diarylpyrazole class of selective COX-2 inhibitors, SC-58125 (1.38) was one of the most extensively characterized compounds. Compound (1.38) possessed a very long in vivo half life of > 200 hours in animal models making it unacceptable for clinical use.

Replacement of the \textit{para}-SO\textsubscript{2}Me group by a SO\textsubscript{2}NH\textsubscript{2} substituent provided a significant improvement in the pharmacological profile. Compounds of this type exhibited superior pharmacological and oral bioavailability than their methylsulfone (MeSO\textsubscript{2}) Counterparts. Extensive studies within this class of compounds led to the successful development of the potent and selective COX-2 inhibitors SC-58635 (celecoxib) (in vitro COX-2 IC\textsubscript{50} = 0.04 μM; COX-1 IC\textsubscript{50} = 13 μM; SI = 325) with potent in vivo anti-inflammatory activity. Compound celecoxib was selected for clinical
evaluation and subsequent introduction to the market as celecoxib (Celebrex®), the first diarylheteterocyclic selective COX-2 inhibitor approved for clinical use. In an elegant study, Knaus and coworkers showed that the para-SO$_2$NH$_2$ pharmacophore in celecoxib and the para-SO$_2$Me pharmacophore in rofecoxib can be replaced by a linear azide (N3) or a sulfonyl azido group. This was the first example where a crucial binding site structural difference in COX-1 and COX-2 was exploited. Replacement of His513 in COX-1 by Arg513 in COX-2 has been reported to play a key role in the hydrogen-bond network of the COX active site. Molecular modeling studies indicated that azide and sulfonyl azide groups were undergoing electrostatic interactions with the polar Arg513 residue within the COX-2 active site.

The azido compound (1.39) exhibited good COX-2 inhibitory potency/selectivity (COX-2 IC$_{50}$ = 1.55 μM, COX-1 IC$_{50}$ > 100 μM; SI > 64.5) in conjunction with in vivo activity. In contrast, the sulfonylazido compound (1.40) did not inhibit the COX-2 isoform at 100 μM indicating the subtle requirements needed for COX-2 binding. Celecoxib is a highly lipophilic water insoluble drug that is administered orally. A recent investigation demonstrated that one can develop parenteral (water soluble) formulations of selective COX-2 inhibitors that possess a central pyrazole ring. For example, the water soluble sodium salt of the N-propionylsulfonamide compound (1.41) is a weak
COX-2 inhibitor that is a prodrug which is converted to the respective sulfonamide compound (1.42) in vivo. The sulfonamide compound (1.42) exhibits good COX-2 inhibitory potency and selectivity (COX-2 IC$_{50}$ = 1.7 µM; COX-1 IC$_{50}$ > 100; SI > 59). Selective COX-2 inhibitors belonging to the 1, 5-diarylpyrazole class are still being pursued.$^{67}$

**B) Diaryl heterocycles possessing a central 5-membered isoxazole ring**

A large number of regioisomeric diarylisoxazoles have been evaluated as selective COX-2 inhibitors. Scientists at Searle reported that the isoxazoles (1.43) is a potent and selective COX-2 inhibitor (COX-2 IC$_{50}$ = 0.18 µM, COX-1 IC$_{50}$ > 1000 µM; SI > 5555) that shows an excellent in vivo activity profile.$^{60}$ Lead optimization with the diarylisoxazole class of compounds culminated in the development of a potent and selective COX-2 inhibitor which had a para-SO2NH2 substituent (Valdecoxib, (1.44), COX-2 IC$_{50}$ = 0.005 µM, COX-1 IC$_{50}$ = 140 µM; SI = 28000). The 5-methyl substituent in Valdecoxib (1.44) undergoes bioconversion in an in vivo rodent model to the active 5-hydroxymethyl (CH$_2$OH) metabolite (1.43). Low levels of the hydroxymethyl metabolite (1.43) have also been detected in humans (100). The isoxazole compound (1.44) was marketed as valdecoxib (Bextra®), a second generation selectiveCOX-2 inhibitor with analgesic and anti-inflammatory properties$^{68}$

Valdecoxib, like rofecoxib, was subsequently withdrawn from the clinical market. The water soluble prodrug of valdecoxib (Parecoxib sodium, Dynastat®) was launched as an injectable COX-2 inhibitor possessing anti-inflammatory and analgesic activities.$^{69}$ In addition, Knaus and coworkers showed that regioisomeric 3, 4-diarylisoxazoles with a para-SO2Me substituents exhibit excellent in vitro COX-2 inhibitory activity and in vivo anti-inflammatory activities.$^{70}$ For example, the isoxazole regioisomer (1.45) is a potent and highly selective COX-2 inhibitor (COX-2 IC$_{50}$ < 0.005 µM, COX-1 IC$_{50}$ > 500 µM; SI > 100,000) that is marketed by Cayman Chemicals as a research biochemical. In contrast, the corresponding regioisomer (1.46) was a less potent and selective COX-2 inhibitor (COX-2 IC$_{50}$ = 0.23 µM, COX-1 IC$_{50}$ = 256 µM; SI = 1113).

**C) Diaryl heterocycles possessing a central 5-membered oxazole and isoxazoles ring**

A large number of oxazole based inhibitors have been investigated by different laboratories. It was clearly demonstrated that regioisomeric oxazoles showed very different in vitro activities.$^{71}$ For example, compound (1.47) showed a COX-1 IC$_{50}$ 100
μM and a COX-2 IC$_{50}$ = 10 μM whereas regioisomer (1.48) has a COX-1 IC$_{50}$ 100 μM and a COX-2 IC$_{50}$ = 0.14 μM. In general, sulfonamide analogues showed an enhanced potency against both COX-1 and COX-2. This finding is illustrated by the profile of compound (1.49) which shows a COX-1 IC$_{50}$ = 25 μM and a COX-2 IC$_{50}$ = 0.02 μM and causes 50% inhibition at 0.2 mg/kg per os in the carrageenan induced paw oedema assay in rats. Replacement of the phenyl ring of (1.49) with a cyclohexyl ring and introduction of a fluorine atom adjacent to the Sulfonamide moiety led to JTE 522 (1.50) which was found, in comparison to compound (1.49), to be more selective and more potent against COX-2.

Investigations performed in the isoxazole series also gave interesting results. e.g. hydroxymethylisoxazole (1.51) exhibited a selectivity ratio superior than 5000-fold and caused 50% inhibition at the dose of 1.1 mg/kg per os in the carrageenan-induced foot edema model.

![Chemical structures](image)

D) Diaryl heterocycles with a central 6-membered pyridine ring

Tricycles with either a 2,3-diarylpyridine or 3,4-diarylpyridine ring system have been investigated as selective COX-2 inhibitors where in compounds (1.52) and (1.53) exhibited good in vitro COX-2 selectivity profiles. However, compounds (1.52) and (1.53) exhibited poor in vivo anti-inflammatory activity. From this novel class of compounds, Merck Ltd. successfully developed the orally active potent and selective
COX-2 inhibitor, etoricoxib (1.54), Arcoxia®) which exhibited clinically acceptable anti-inflammatory and analgesic activities with no reports of gastric damage in animal studies and during clinical trials. This second generation selective COX-2 inhibitor showed an in vitro COX-2 IC\textsubscript{50} = 0.08 \mu M and COX-1 IC\textsubscript{50} = 12 \mu M; SI = 150.\textsuperscript{75,76} Although etoricoxib is not an approved drug in the US and Canada due to its cardiovascular toxicity, it has been approved and is marketed in 63 other countries. A recent study assessed the cardiovascular outcomes of etoricoxib in comparison with diclofenac. These studies suggested that both drugs carry similar cardiovascular risks.\textsuperscript{77}

![Chemical structures](image)

E) Diarylheterocycles with a central 5-membered Pyrrole ring

A series of 1, 2-diarylpyrroles have been synthesized and were found to contain potent and selective COX-2 inhibitory property.\textsuperscript{78} For example, compound (1.55) shows a great COX-2 inhibitory potency (COX-1 IC\textsubscript{50} > 100 \mu M; COX-2 IC\textsubscript{50} = 0.06 \mu M) and appears to be potent in the carrageenan-induced oedema in rats (25% inhibition in the paw oedema assay at the dose of 10 mg per kg p.o.). In order to evaluate the importance of the 1, 2-diaryl arrangement in (1.55), the N-aryl ring was replaced with hydrogen atom, benzyl, and alkyl or cycloalkyl substituents. Neither of these new compounds showed inhibition of the COX enzymes up to 100 \mu M. Only the cyclohexyl compound (1.56) gave interesting results (COX-1 IC\textsubscript{50} > 100 \mu M; COX-2 IC\textsubscript{50} = 0.52 \mu M) although it was eight times less potent than (1.55), suggesting that the 1, 2-diaryl arrangement was crucial for the selectivity and potency against COX-2 in this series.

Replacement of the fluoro substituent in (1.55) with hydrogen, a trifluoromethyl or a methyl group gave compounds showing a comparable profile. In contrast, replacement of the fluoro substituent of (1.55) with an acetyl group led to a considerably less active
compound, suggesting that minor modifications of the size and/or the polarity on the N-aromatic ring can seriously alter the activity against COX-2.

Regioisomer of (1.55), represented by compound (1.57), showed a good potency against COX-2 (COX-1 IC$_{50}$ > 100 µM; COX-2 IC$_{50}$ = 0.05 µM) and appeared to be more potent than (1.55) in the carrageenan-induced paw oedema in rats (42% inhibition at the dose of 10 mg/kg). This result suggests that the in vivo potency is enhanced when the 4-fluorophenyl group is in position 2 of the pyrrole ring. The isosteric sulfonamide derivative (1.58) of (1.57) was less selective but more potent than (1.57) against COX-2 (COX-1 IC$_{50}$ = 10.5 µM; COX-2 IC$_{50}$ = 0.014 µM).

Placement of substituents at the 4-position of the pyrrole ring led to interesting tetrasubstituted pyrroles such as compound (1.59), which appeared remarkably selective and potent against COX-2 (COX-1 IC$_{50}$ > 100 µM; COX-2 IC$_{50}$ = 0.03 µM). The 2,3-Diaryl pyrrole series$^{79,80,81}$ was also extensively studied. A series of 2-(4-methylsulphonylphenyl) 3-(4-fluorophenyl) pyrroles bearing different substituents in the 5-position of the pyrrole ring (1.60) has been prepared and evaluated by the DuPont Merck group. In this series, best in vitro results were obtained by placing electron withdrawing groups like chlorine (1.60) or bromine (1.61) in the 5-position. In the adjuvant arthritis assay, (1.60) and (1.61) had ED$_{50}$ of 0.5 and 1.05 mg/kg respectively.
Side effects of clinically used NSAIDs

NSAIDs are associated with several side effects. The frequency of side effects varies among NSAIDs. Followings are some side effects, caused from the practiced NSAIDs.

- The most common side effects are nausea, vomiting, diarrhea, constipation, decreased appetite, rash, dizziness, headache, and drowsiness.
- NSAIDs may also cause fluid retention, leading to edema. The most serious side effects are kidney failure, liver failure, ulcers and prolonged bleeding after an injury or surgery.
- Some individuals are allergic to NSAIDs and may develop shortness of breath when an NSAID is taken. People with asthma are at a higher risk for experiencing serious allergic reaction to NSAIDs.
- Use of aspirin in children and teenagers with chickenpox or influenza has been associated with the development of Reye's syndrome.
- NSAIDs may increase the risk of potentially fatal, stomach and intestinal adverse reactions (for example, bleeding, ulcers, and perforation of the stomach or intestines). These events can occur at any time during treatment and without warning symptoms. Elderly patients are at greater risk for these adverse events.
- NSAIDs (except low dose aspirin) may increase the risk of potentially fatal heart attacks, stroke, and related conditions. This risk may increase with duration of use and in patients who have underlying risk factors for heart and blood vessel disease.
- NSAIDs should not be used for the treatment of pain resulting from coronary artery bypass graft (CABG) surgery.
- NSAIDs reduce blood flow to the kidneys and therefore reduce the action of diuretics and decrease the elimination of lithium (Eskalith) and methotrexate (Rheumatrex).
- NSAIDs also decrease the ability of the blood to clot and therefore increase bleeding. When used with other drugs that also increase bleeding
Nonsteroidal anti-inflammatory drugs also may increase blood pressure in patients with hypertension (high blood pressure) and therefore antagonize the action of drugs that are used to treat hypertension.

Scope for the work:

Literature survey reveals that the herbal anti-inflammatory drugs are having limited applications as being raw ingredients; these lead slow physiological activity and cannot be used in chronic and acute inflammatory conditions. Steroidal anti-inflammatory agents find use in tropical or localized applications due to serious and long term physiological side effects.

In the above mentioned contest established clinically used NSAIDs do not have alternative as they are rapid in action and comparatively with fewer side effects. But still there is scope to improve existing therapeutic agents as they are likely to in time being become outdated due to the observed side effects and clinical overuses. So, continuous hunt for new therapeutic agents is everlasting.

There are many structural classes viz. sulfonated diaryl heterocycles (thiazoles, pyrazoles, oxazoles and pyrazolines etc), heteryl ethers, thioethers, thiohydantoins, thiazolidinones and 2, 4-thiazolidine-diones that have been proved to possess appreciable anti-inflammatory activity.

From the above literature survey it is clear that thiazoles and thiazolidinone diones bearing heterocyclic NSAIDs are yet to be established as clinical agents. That’s why we thought that it would be better to focus on them. With logical and rational approach therefore we have identified and selected thiazoles, pyrazoles and 2, 4-thiazolidine-diones as heterocyclic core and methyl sulphonamido and methyl sulphonyl as pharmacophores to design and synthesize new heterocyclic analogues of Nimesulide and celecoxib with expectation that those COX-2 inhibitors will be with high potency and selectivity and having fewer side effects more bioavailability and thus would be definitely better leads. Keeping this in mind it was thought to work on the theme, “Newer convenient synthetic protocols for non-steroidal anti-inflammatory agents.”

In this retro synthetic and computer aided synthetic era, there would be many synthetic protocols possible and available to synthesize the deired molecules.
them those which are convenient and environmentally benign are important and acceptable in this eco-aware world.

So while synthesizing target molecules, here care has been taken to modify some synthetic protocols and also to develop new synthetic protocols using one pot synthesis, green media (water, PEG, alcohol, methanol), ambient temperature conditions, less hazardous and recyclable catalysts. The synthetic details of newly synthesized compounds and their anti-inflammatory evaluation are incorporated in the forthcoming part-II and part-III.
References:


