SYNOPSIS

It is estimated that more than 800 million peoples world wide are suffering from one or more type of inflammatory disorders which are treated with different narcotics and nor-narcotics (non-steroidal Anti-inflammatory drugs). These drugs possessed analgesic, antipyretic and analgesics activities. These drugs neither depress CNS nor do not produced any physical dependence. Willow bark (salix alba) had been used far many centuries salicylic acid was obtained by hydrolysis of the bitter glycoside obtained from this plant. Sodium salicylate was used for fever and pain in 1875; its great success led to the introduction of acetyl salicylic acid (aspirin) in 1899. Phenacetian and antipyrine were also synthesized during this period. The next major advance was the development of phenylbutazone in 1949. Indomethacin was introduced in 1963. Other important groups of NSAIDS are propionic acid derivatives (Ibuprofen and Naproxen) etc. Recently some selectively cyclooxygenase-2 (COX-2) inhibitors (Meloxicam, Piroxicam, Nabumetone and Nimesulide) have been introduced. Non-steroidal anti-inflammatory drugs are chemically of diverse nature and most of them are organic acid and these may be classified as follows:

Classification of NSAIDs

A. Analgesic and antiinflammatory

1. Salicylates:  Aspirin Salicylamide, Benorylate diflunisal

2. Pyrazolone derivatives:  Phenylbutazone oxyphenbutazone

3. Indole derivatives:  Indomethacin, Sulindac
4. Propionic acid derivatives: Ibuprofen, Naproxen, Ketoprofen, fenprofen, flurbiprofen

5. Anthranilic acid derivative: Mefenamic acid

6. Aryl-acetic acid derivative: Diclofenac, lolmetin

7. Oxicam derivative: Piroxicam, Temoxicam, meloxicam

8. Pyrrolopyrrole derivative: Ketorolac

9. Sulfonanilide derivative: Nimesulide

10. Alkanones: Nabumetone

B. Analgesic but poor- Antiinflammatory

1. Para aninophenol derivative: Paracetamol (Acetaminphenol)

2. Pyrazolone derivative: Metanizal (Pipyrone, probiphenazone)

3. Benzoxazocine derivative: Nefopam

**Structure of important NSAIDs**

Salicylic acid derivatives:

- Methyl Salicylate
- Aspirin

Pyrazolone Derivative:

- Phenylbutazone
- Oxyphenbutazone
- Celecoxib
Indole Derivative

Intomethacin

Naphthalene Derivative

Nabumetone

Anthranilic Acid Derivatives:

Mefenamic acid

Propionic Acid Derivatives:

Ibuprofen

Diaryl Substituted Derivatives:

Rofecoxib
Most of the non-steroidal and inflammatory drugs (NSAIDs) are highly acidic in nature and are associated with different side effects; the most common drawback of these drugs is gastrointestinal toxicity. Moreover recently developed NSAIDS are either non acidic or weakly acidic drug like Nabumetone, Nemulisiside and meloxicam possessed substantially lower incidence of gastric ulcers, hence it is worth while to explore synthesis of new non-steroidal anti inflammatory inhibitors with an attempt that these newly developed Inflammatory inhibitors will exhibit superiority over the already existing acidic non-steroidal anti-inflammatory and non acidic non-steroidal anti-inflammatory drugs.

In addition to the above mentioned (NSAIDs) a large number of heterocyclic compounds in the chemical literature (1 to 43) exhibited remarkable anti-inflammatory activity in the derivatives of Indole (1-14) Phenothiazine (15-22), Quanazolinone (23-32), Naphthalene (33-37), Azetidinones (38) Thia diazole (39).

In the light of these observation it is our contention that synthesis of new derivative of these heterocyclic nuclei may lead to the development of potent inflammation inhibitors with substantially lower incidences of gastric toxicity i.e. peptic ulcer than the already existing anti-inflammatory agents. The different derivatives of the following nuclei are to be synthesized and screened for their anti inflammatory ulcerogenic and acute toxicity studies.
SYNTHESIS

Structure of all the newly synthesized compound will be elucidated by M.P., TLC, elemental analysis, IR, $^1$HNMR and mass spectrometry.

Indole Derivatives: (Scheme I)

N-(p-chlorobenzoyl)-5-methoxy-2-methyl indole 3-acetic acid (indome-thacin) and 5-chloro-2,3-dihydro-3-(hydroxy-2-thienylmethylene)-2-oxo-1H-indole-1-carboxamide(Tenidap), are the derivatives of indole have been successfully utilized for the treatment of inflammatory disorders. Furthermore, 3-substituted indole derivatives were also found to possess a wide spectrum of biological activities like cardiovascular, CNS-depressant and anti-inflammatory. Moreover, anti-inflammatory activity was also exhibited by several thiazoles/thiazolidinone and formazans.

In the light of these observation, it was thought worthwhile to synthesize a new series of 3-[2-aryl diazenyles-4-(thiazolyl/oxazolyl)] indoles by incorporating the thiazolylthiazolidinone/thiazolylazetidinones/thiazolyl-diazenyles moieties at 3-position of benzopyrrole/substitutedbenzopyrrole nucleus in a single molecular framework. These compound will be tested for anti-inflammatory activity.

Phenothiazine Derivatives: (Scheme II)

Introduction of different heterocyclic moieties like thiazoles, thiazolidinone, azetidinones and formazans at 10-position of phenothiazine/ substituted phenothiazine nucleus markedly affects the biological properties like cardiovascular antipsychotic, CNS and anti-inflammatory. With a view to obtain new molecules with the better anti-inflammatory activity and lesser side effects,
we proposed to synthesize a new series 2-[2-oxo-azetidin-1-yl-4 (thiazolyl/thioxazolyl)]-(1 OH)-phenothiazine/substitutedphenothiazine. All the newly synthesized compounds will be screened for anti-inflammatory activity.

**Naphthalene Derivatives: (Scheme III)**

Nabumetone a non-acidic derivative of naphthalene is currently used for the treatment of different anti-inflammatory disorders, substitution at (3- position of naphthalene nucleus enhance the anti-inflammatory activities. Moreover, thiazole, azetidinone, 4-oxo-thiazolidinone and formazans of different heterocyclic nuclei have also been reported to possess potent anti-inflammatory activity. It was, therefore, thought worth while to synthesize a series 2-amino-[4-aryl formazans-4-thiazolyl)]/[2-azetidin-1-yl]-thiazolyl] naphthalene by incorporating the thiazoly thiazolidinone and thiazolyl formazans moieties at 2-position of naphthalene nucleus. These compounds will be screened for anti-inflammatory activity.

**Quinazolinones: (Scheme IV)**

4 (3H) quinazolinone, a potent pharmacodynamic, heterocyclic nucleus has gained prominence in medicinal chemistry because it possess diverse type of pharmacological properties like antibacterial, cardiovascular, anticonvulsant, hypnotic and sedative and anti-inflammatory activities, substitution at 3 position of quinazolinone enhance the anti-inflammatory activity. There are very few reports in the literature on 1,2,4, triazine containing quinazoline moiety. Thus was through worthwhile to synthesize a new series 2-Ethyl-4-aryl-5 [4′-oxo- 5′-methyl
thiazolidinyl]-10-halosubstituted-[1,2,4]-triazinoquinazoline by incorporating 1,2,4, triazine moiety in quinazolinone nucleus in order to see the effect of these compounds on inflammation. Hence, these compounds will be evaluated for their anti-inflammatory activity.

**Anthranilic Acid Derivatives: (Scheme V)**

The fenomates are a family of non-steroidal anti-inflammatory drugs (NSAIDs), which are derivatives of N-phenylantranilic acid. Furthermore, substitution pattern at N-position of anthranilic acid plays a pivotal role in delineating the anti-inflammatory activity of these agents. It was therefore, thought worth while to synthesize a series of N-2-amino-[acetyl-indolyl-2-pyrazolinyl-thiadiazolyl-methyl]anthranilic acids. These compounds will be screened for anti-inflammatory activity.

**Animal Studies:**

1. **Anti-inflammatory activity:** Newer compounds will be tested for anti-inflammatory activity against carrageenan induced oedema in albino rats following the method of Winter et al. (1992). (Ref: 40). The percentage anti-inflammatory activity will be calculated according to the formula given below:

   \[ DT\% \text{ anti-inflammatory effect} = 1 - \frac{V_c}{V_t} \times 100, \text{ where } V_t \text{ and } V_c \text{ are the volume of oedema in drug treated and the control group.} \]

2. **Ulcerogenic activity:** The compound which will show promising anti-inflammatory activity will be evaluated for their ulcerogenic activity. The
ulcerogenic activity will be done according to the method of Djahanguiri (1969).

(3) **Acute toxicity study:** The compounds which will show significant anti-inflammatory will also be tested for their acute toxicity (approximate LD$_{50}$) in mice according to the method of Smith (1950).
REFERENCES


SCHEME - I
SCHEME - II
SCHEME-IV
SCHEME-V