SYNOPSIS

Synopsis entitled: ” A Study on: Synthesis of Newer Heterocyclics and their anti-inflammatory activities.”

Introduction:

Statistical studies show that 800 million people around the world are suffering from inflammatory disorders like arthritis, rheumatic fever, osteo-arthritis, rheumatoid arthritis, etc. Although many specific drugs for the treatment of inflammation/acute pain are non-steroidal anti-inflammatory drugs (NSAIDs/narcotic analgesics) are available. The use of narcotic analgesic is limited in case of inflammatory disorders due to undesirable side effects. The other groups of inflammation inhibitors comprise of non-steroidal anti-inflammatory drugs which are heterogenous groups of compounds and are given below :-

1. **Salicylic acid derivatives** : aspirin, sodium salicylate, cholins magnesium trisalicylate, salsalate, diflunisal, sulfasalazine, olsalazine.
   - **Para-aminophenol derivatives** : acetaminophenol.
   - **Indole and Indene acetic acids**: indomethacin, sulindac.
   - **Heteroaryl acetic acids**: tolmethin, diclofenac, ketorolac.
   - **Arylpropionic acids**: ibuprofen, flurbiprofen, ketoprofen, fenoprofen, oxaprozin.
   - **Naphthalene derivatives**: naproxen, nabumetone.
   - **Anthranilic acids (fenamates)**: meclofenamic acid, mafenamic acid.
   - **Enolic acids**: oxicams (piroxicam, meloxicam).

2. **Selective COX-2 inhibitors**
   - **Diaryl-substituted furanones**: rofecoxib.
   - **Diaryl-substituted pyrazoles**: celecoxib.
   - **Indole acetic acids**: etodolac.
     - **Sulfonanilides**: nimesulide.
Aspirin (acetyl salicylic acid); Indomethacin [1-(p-chlorobenzoyl)-5-methoxy-2-methylindole-3-acetic acid] sulindac [5-fluoro-2-methyl-1-[4-(methyl sulfinyl) phenyl methylene]-1H-indene-3-acetic acid] ; Naproxen (6-methoxy-α-methyl-2-naphthalene-acetic acid) ; Nabumetone [5-methoxy-2-(2-oxabutyl)naphthalene] ; phenylbutazone (4-butyl-1,2-diphenyl-3, 5 pyrazolidine dione) ; Mefenamic acid (2-[(2,3-dimethylphenyl)amino]-benzoic acid) ; ibuprofen (α-methyl-4-(2-methyl propyl) benzene acetic acid, are successfully utilized by clinician for the treatment of inflammatory disorders. These posses serious inherent side effects like gastric haemorrhage, gastric ulcer, gastric perforation and bone marrow depression. In addition to these chemical literature (1-24) which exhibited remarkable anti-inflammatory activity in the congeners of Indole (1-6) Naphthalene (7-10) Thiadiazole (11-14) Thiazolidinones (15-18) Azetidinones (19-21).
Naphthalene Derivatives:

- Nabumetone: ![Nabumetone](image)
- Naproxen: ![Naproxen](image)

Propionic Acid Derivatives:

- Ibuprofen: ![Ibuprofen](image)
- Fenoprofen: ![Fenoprofen](image)

Diaryl Substituted Derivatives:

- Rofecoxib: ![Rofecoxib](image)

Salicylic Acid Derivatives:

- Methyl Salicylate: ![Methyl Salicylate](image)
- Aspirin: ![Aspirin](image)
Pyrazolone and Pyrazole Derivatives

Phenylbutazone  Oxyphenbutazone  Celecoxib

Anthranilic Acid Derivatives:

Mefenamic acid  Meclomenamate Sodium

Indole Derivatives:

Indomethacin  Etodolac
The various derivatives of these following nuclei will be synthesized and screened for their anti-inflammatory, ulcerogenic and acute toxicity studies:

**Thiadiazine**

**Indole**

**β-naphthalene**

**Thiazolidinone**

**Thiadiazole**

**Azetidinone**

**Synthesis:**

The structure of all the newly synthesized compounds will be delineated by melting point, TLC, elemental analysis, IR, $^1$H-NMR and mass spectrometry.

**Indole derivatives (Scheme I):**

Indoles as well as indolinones have been found to be medicinally important versatile compounds, which possess antihypertensive, anti-inflammatory, hypnotic, antipsychotic, antifungal and antibacterial activities. Further, indomethacin and sulindac (Goodman and Gilman, 1996) are derivatives of indoles, which have been successfully utilized for the treatment of inflammation. Several scientists have also reported that modification (at 2/3 position) in indole nucleus by different heterocyclic moieties like thiadiazine, thiadiazole and azetidinone. It is therefore, proposed to synthesize the derivatives of indole by incorporating thiadiazine, thiadiazole and azetidinone moieties at 2/3-position of indole nucleus. Further, these compounds will be evaluated for their anti-inflammatory, ulcerogenic and acute toxicity studies.

**Naphthalene derivatives: (Scheme II)**

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

**Thiadiazoles (Scheme III)**

Several heterocyclic compounds have gained the medicinal importance in the recent years. Among these, thiadiazoles have been the most potent ones. Furthermore, substitution pattern in thiazole nucleus plays a pivotal role in delineating the biological activities like antiinflammatory, anticonvulsant and cardiovascular. However, substitution by different heterocyclic moieties at position 2 and 4 having azetidinone and thiazolidine ring were found to possess potent anti-inflammatory activity. It is therefore, our contention to synthesize some thiadiazolyl-azetidinyl-thiadiazolinylatedidinones with the hope to possess better activity than the standard drugs.

**Animal Studies :**

The newly synthesized compounds will be screened for their anti-inflammatory activity in albino rats. The compounds which exhibits promising activity will be screened for their ulcerogenic activity and acute toxicity also.

**(a) Anti-inflammatory activity :**

The synthesized compounds will be tested for their anti-inflammatory activity against carrageenan induced oedema in albino rats following the method of Winter et al., (22). The percentage of anti-inflammatory activity will be calculated, according to the formula given below

\[
\text{% anti-inflammatory effect} = \frac{V_t}{V_c} \times 100
\]

Where, \(V_t\) and \(V_c\) are the volume of oedema in drug treated and control groups.

**(b) Ulcerogenic activity :**

Ulcerogenic activity of the compounds will be done according to the method of Verma et al. (23).
(c) **Acute toxicity study:**

The compounds which will show significant anti-inflammatory activity will also be tested for their acute toxicity (approximate LD$_{50}$) in the mice according to the method of Smith Q.E., (24).

**Utility:**

To develop newer nonsteroidal anti-inflammatory agents which might be useful in different inflammatory disorders.
REFERENCES


SCHEME-II
SCHEME -III
SCHEME-V
SCHEME VI