# CHAPTER I

## INTRODUCTION

Inflammation is a local tissue response to injury caused by chemical or physical agents. Its cardinal symptoms are redness, heat at the site of inflammation, swelling, pain, and loss of motion. These symptoms can be explanined as follow; capillary dilation occur at the site of injury, resulting in the increased flow of fluid into tissue spaces. This fluid transfer caused edema (swelling) and produces pressure on nerve endings; pain ensues. The increased blood supply underlines the heat at the site of inflammation. For many years, scientists have sought to determine whether injuries of all types caused the local release of a "mediator" substance that may be responsible for the increased capillary permeability. Among the many candidates nominated for this mediator role in inflammation are histamine, serotonin, bradykinin, and the prostaglandins.

Prostaglandins of the E series are believed to be the most important chemical mediators of the inflammatory response, and it is thought that aspirin-like compounds may produce their antiinflammatory effects by inhibiting prostaglandin synthesis in the body (1).

However, the exact mechanism of action of these agents is not known. Although, it has been proposed that their primary clinical effect are related to inhibition of the prostaglandin synthesis, since the action of the prostaglandin have been reported to include hyperalgesia (pain), fever, edema, and erythrema. But there is a paucity of data in man on the effect of prostaglandin, on various organs and tissues, so the precise mechanism of the various inhibitors cannot be stated definitely (2,3).

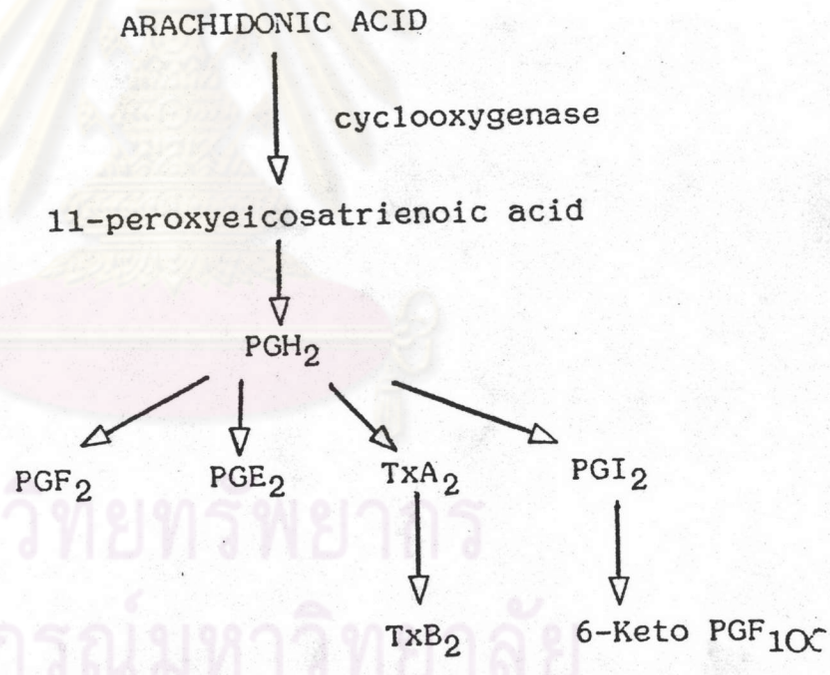


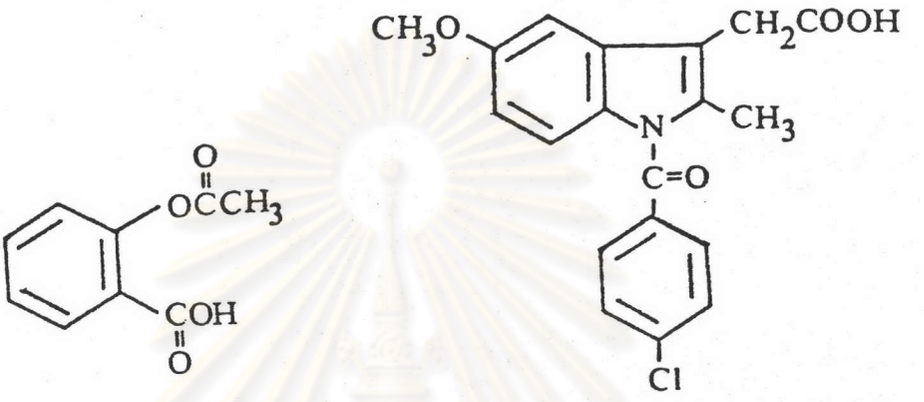

Figure 1 : Proposed mechanism of action of aspirin-like compound in inhibiting the prostaglandin synthesis ( PG=prostaglandin; Tx=thromboxane)

Nowadays, a large number of aspirin-like compounds were developed and catagorized as Nonsteroidal Antiinflammatory Drugs (NSAIDs). NSAIDs, a class of chemical possess antiinflammatory,analgesic and antipyretic action, are mostly developed in the past decade.

In early practice of the several antipyretics, it was noted that some were excellent analgesics for the relief of minor aches and pains. These drugs have survived to the present time on the basis of the analgesic rather than the antipyretic effect. Although these drugs are still widely utilized for the alleviation of minor aches and pains, they are also employed extensively in the symptomatic treatment of rheumatic fever, rheumatoid arthritis and osteoarthritis. The dramatic effect of salicylates in reducing the inflammatory effects of rheumatic fever is time-honored and even with the development of the corticosteroids, these drugs are still of great value in this respect. It has been reported that the steroids are no more effective than the salicylates in preventing the cardiac complications of rheumatic fever (4).

Considerable research has continued in an effort to find new nonsteroidal antiinflammatory agents. Newly characterized pharmacological models greatly facilitated the discovery of indomethacin, fenamates and ibuprofen in the early sixties. Intensive efforts to improve their

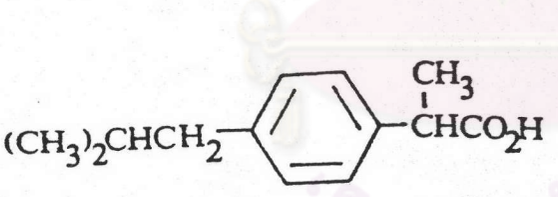
potency, duration of action and patient tolerance resulted in the developmemt of more than 60 NSAIDs worldwide (5).



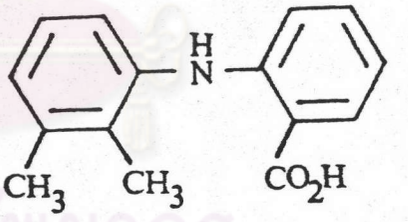
Aspirin



Indomethacin



Ibuprofen



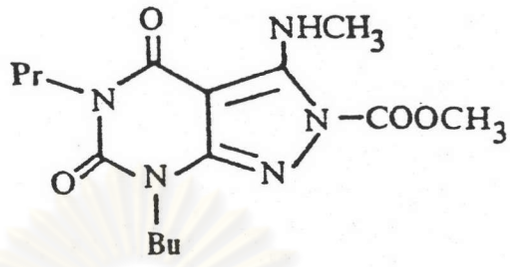
Mefenamic acid

Figure 2 : Some commonly used antiinflammatory agents

Although numerous products have been introduced over the years, almost all contain a carboxylic acid function or equivalent. These products are subjected to the serious, limiting side effects of gastrointestinal irritation and ulceration, probably due to their commonly shared ability to inhibit the cyclooxygenase enzyme in the gastrointestinal tract. In addition, they do not affect the long-term prognosis of the disease state (6).

In an attempts to discover new and useful drugs for the treatment of inflammatory diseases, a series of isothiazolopyrimidine derivatives which have been reported to possess an interesting profile of biological activity such as antiviral activity (7), sedative (8,9,10), diuretic (11), cyclic nucleotide phosphodiesterase inhibitor (10), oncostatic activity (13) and antiinflammatory activity (8,10,11), were examined in this research.

Recently, Naka *et al* (12) found that some 3-aminopyrazolo [3,4-d] pyrimidine derivatives especially 7-butyl-2-methoxycarbonyl-3-methylamino-5-propylpyrazolo [3,4-d] pyrimidine-4,6-dione (I), which is non-acidic agent, has potent antiinflammatory, analgesic and antipyretic actions.



(I)

From the structural point of view, both I and the reported isothiazolopyrimidine derivatives share similarity of functional groups at 3, 3a, 4, and 5 which may essential for activity. Here, 5-substituted-3-(substituted) amino-6-hydroxy[or (substituted) amino] isothiazolo [3,4-d] pyrimidine-4-one derivatives, which have never been synthesized before would be of interest and may possess the antiinflammatory activity. The target compounds can be synthesized by the following scheme (Figure 3) :

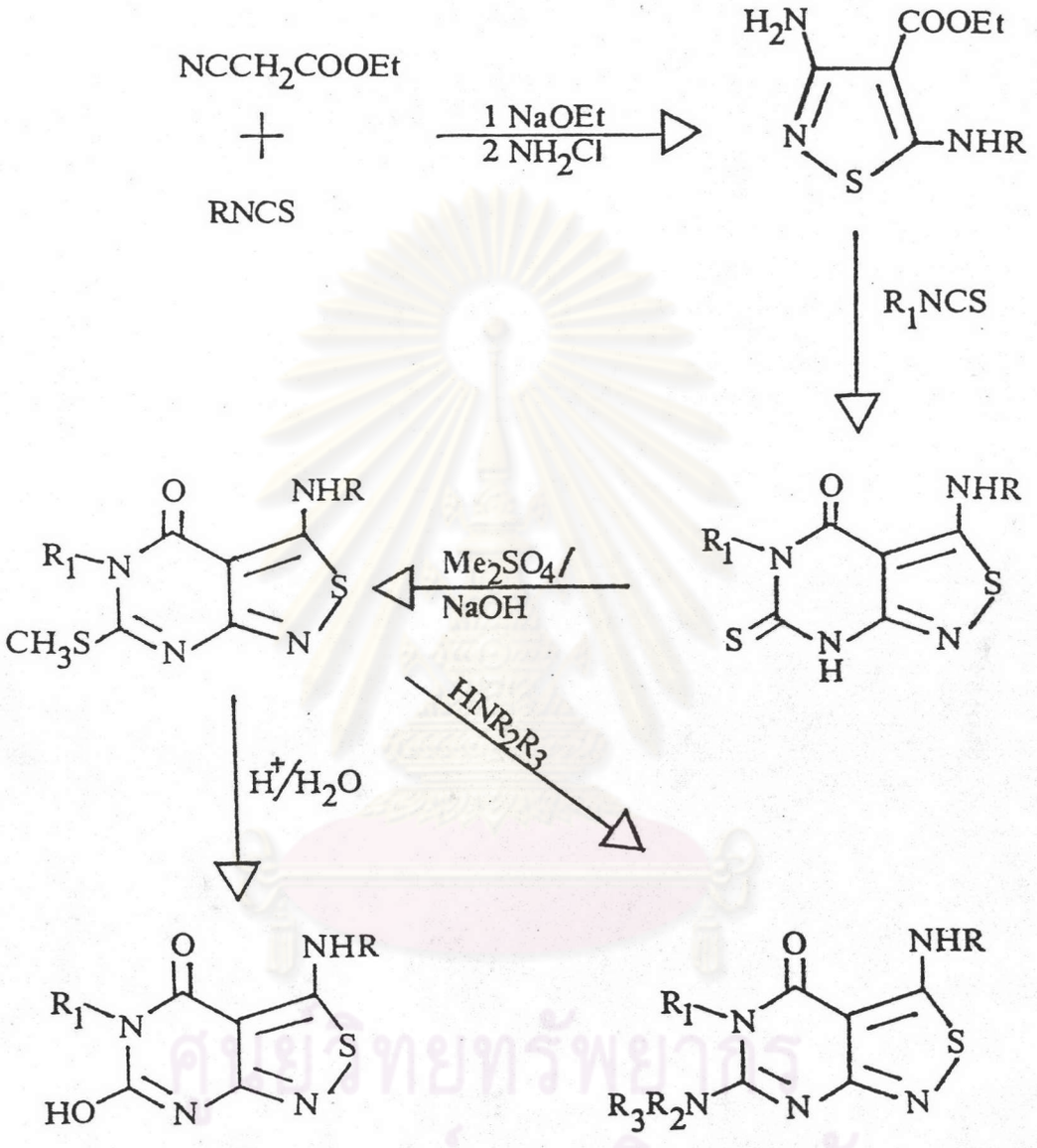



Figure 3 : Scheme for the synthesis of isothiazolo [3,4-d] pyrimidine derivatives