

**ANTI-INFLAMMATORY SUBSTITUTED
2-BENZYL-MERCAPTO-IMIDAZOLE AND
PYRIMIDINE DERIVATIVES COMPOSITIONS
AND METHOD OF USE THEREFOR**

BACKGROUND OF THE INVENTION

The present invention relates to novel 2-benzyl-mercapto-imidazoles and analogs useful as anti-inflammatory agents. 2-(p-nitrobenzylthio)-imidazolines (U.S. Pat. No. 3,772,440 and U.S. Pat. No. 4,146,649) have been known to have anti-parkinsonism and hypotensive activities. However, these patents did not disclose the novel compounds of the present invention, nor did they disclose the anti-inflammatory activity of these compounds.

Recent studies demonstrated that macrophages participate in the development and progression of chronic inflammatory diseases such as rheumatoid arthritis. During the progression of inflammatory conditions, there is generally an appearance and/or presence of macrophages and lymphocytes, especially macrophages and polymorphonuclear leukocytes. Macrophages are known to secrete various products in response to inflammatory stimuli. For example:

- (1) Neutral proteinases—the destructive peptide bond cleaving enzyme which has been shown to be directly involved in rheumatoid cartilage destruction; and
- (2) Prostaglandins (PG) (e.g., E₂ and I₂ by mouse peritoneal macrophages) and other arachidonic acid derivatives derived from both the cyclooxygenase and the lipoxigenase pathways.

These arachidonic acid oxygenation products have been identified as the critical mediators of various inflammatory conditions.

Interruption of these pathways by enzyme inhibition has been explored for effective therapy. For example, non-steroidal anti-inflammatory drugs (NSAID) such as aspirin, indomethacin and diflunisal are known cyclooxygenase inhibitors which inhibit the process wherein arachidonic acid is oxygenated via cyclooxygenase to prostaglandins and thromboxanes.

Recently, it has been observed that certain leukotrienes are responsible for diseases related to immediate hypersensitivity reactions such as human asthma, allergic disorders, and skin diseases. In addition, certain leukotrienes and derivatives thereof are believed to play an important role in causing inflammation (B. Samuelsson, *Science*, 220, 568 (1983); D. Bailey et al. *Ann. Rpts. Med. Chem.*, 17, 203 (1982)).

Conditions involving elevated intraocular pressures which are too high for normal function may result in irreversible loss of visual function. For example, glaucoma, if untreated, may lead to ocular hypertension, inflammation, and eventually blindness.

To be an effective and acceptable topical agent, for treating inflammation in the eye, such as that caused by glaucoma or other eye diseases, the drug must not only penetrate the ophthalmic tissues to reach the active sites within the eye, but it must also be devoid of those side effects including irritation, allergic reaction and the like which would interfere with long term administration.

Pharmacological agents which are capable of inhibiting the formation of, the release of a mediator from, or the function of macrophages or polymorphonuclear leukocytes may also be effective agents in the treatment of various inflammatory conditions, e.g., pain, fever, rheumatoid arthritis, osteoarthritis, bronchial inflamma-

tion, inflammatory bowel disease, asthma, allergic disorders, skin diseases, cardiovascular disorders, glaucoma, emphysema, acute respiratory distress syndrome, spondylitis, lupus, gout, psoriasis, and other prostaglandin and/or leukotriene mediated diseases.

Accordingly, an object of this invention is to provide novel compounds as inhibitors of cyclooxygenase and lipoxigenase useful as anti-inflammatory agents.

Another object of this invention is to provide appropriate processes for the preparation of the novel compounds.

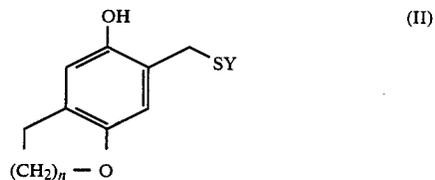
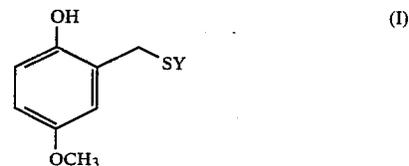
Still a further object of the present invention is to provide a pharmaceutically acceptable composition containing an effective amount of the active compound for the treatment of various inflammatory conditions.

Finally, it is the object of this invention to develop a method of treating inflammation via the administration of a therapeutically effective amount of the novel compounds a pharmaceutically acceptable composition containing one or more of these active compounds.

**DETAILED DESCRIPTION OF THE
INVENTION**

A. Scope of the Invention

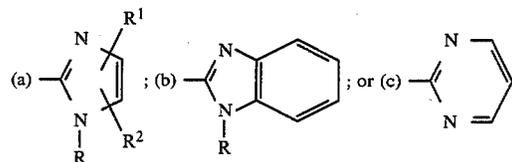
This invention relates to novel compounds of formula (I) or formula (II)



or a pharmaceutically acceptable salt thereof.

wherein

Y is



R is

- (a) loweralkyl especially C₁₋₆ alkyl, e.g. CH₃, C₂H₅, (CH₃)₂CH and butyl;
- (b) lower alkanoyl especially C₁₋₆ alkanoyl;
- (c) lowerhaloalkyl;
- (d) haloloweralkanoyl especially halo C₁₋₆ alkanoyl such as trifluoroacetyl;
- (e) H;
- (f) aryl especially phenyl or phenyl substituted with one or more R¹ which is as defined below;

R¹ and R² independently are

- (1) hydrogen;