CHAPTER 1
INTRODUCTION
In general, three approaches are followed in the search for new drug

(1) The general screening approaches in which chemical substances from any source are tested for their effect against predetermined disease or disease state, (2) The chemical modification of existing drug substance whose biological effects are known and (3) mimicking the nature by biochemical design, where a compound is made to exert an action in a manner similar to a known biochemical substance. Any lead compound obtained from these three approaches is usually further modified chemically to gain the biologically most potent representative of the series.

Non-steroidal anti-inflammatory drugs are the most commonly prescribed medications in the world.\(^1\) The many acidic NSAIDs constitute the principal class of agents for controlling the pain, fever and inflammation. Traditional NSAIDs are used in treatment of mild to moderate pain and as an adjunct to opioids in the management of moderate to severe pain.\(^2\) The clinical effects of NSAIDs are based on the inhibition of the enzyme cyclo-oxygenase (COX), which catalyses the rate limiting step in the formation of prostanoids, thromboxane A\(_2\) and prostaglandins (PGs).\(^3,4\)

There are mainly two types of COX enzyme namely COX-1 and COX-2, COX-1 is a constitutive enzyme expressed in most tissues including blood platelets and involved in tissue homeostasis. COX-2 is induced in inflammatory cells when they are activated and the primary inflammatory cytokines, Interleukin-1 and Tumor Necrosis Factor-alpha \(\alpha\) are important in this regard. Thus COX-2 is responsible for the production of the prostanoid mediators of inflammation. Most traditional NSAIDs in current use are inhibitors of both isozymes.\(^5\)

A wide variety of heterocyclic can serve as a template for COX-2 inhibitors i.e., benzthiazole, benzthiazine, isoquinolone, quinazolines seem to be the most appropriate tools for COX-2 specificity.\(^6,7\)

In recent years, microbial infections are associated with rates of attributable morbidity and mortality.\(^8\) The resistance of common pathogens to standard antibiotic therapies is rapidly becoming a major public health concern throughout the world. The incidence of multidrug-resistant Gram-negative and Gram-positive bacteria is increasing and infections caused by them are becoming complex in recent years.\(^9\)
There is a real perceived need for the discovery of new compounds endowed with antimicrobial activity, possibly acting through mechanisms of action, which are distinct from those of well known classes of antimicrobial agents to which many clinically relevant pathogens are now resistant.\textsuperscript{10}

Microbial infections often produce pain and inflammation. In normal practice, the chemotherapeutic, analgesic and anti-inflammatory agents are prescribed concomitantly. There are effective antimicrobial agents in the market, but each drug carries several drawbacks. The presently marketed antimicrobial drugs are either toxic or becoming ineffective due to the appearance of resistant strains, which requires prolonged administration of the available antimicrobial agents.\textsuperscript{11, 12}

This concept of multi drug therapy has dual advantage in the sense that it will not only reduce the number of drugs to be taken at a time but also that the side effect due to multi drug therapy shall be lessened.

The azole antimicrobial may be regarded as a new class of truly effective drugs that inhibit microbes by blocking the biosynthesis of ergosterol, a major component of the microbial plasma membrane, by inhibiting the cytochrome P-450 dependent enzyme lanosterol demethylase.\textsuperscript{13, 14}

Systemic fungal infections are life threatening and have become increasing common in the immune compromised hosts.\textsuperscript{15} The azole antifungal agents have dominated antifungal drug development and clinical use because of their broad spectrum, oral bioavailability and low toxicity.\textsuperscript{16}

Quantitative structure activity relationship (QSAR) as one of the most important areas in chemistry gives information that is useful for drug design and medicinal chemistry. These are mathematical equations relating chemical structure to a wide variety of physical, chemical, biological and technological properties. The derived relationship between molecular descriptors and biological activity are used to estimate the property of other molecules and to find the parameters affecting the biological activity.\textsuperscript{17, 18}
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The literature survey revealed only limited (SAR) information on isoquinolone and benzothiazine nucleus and also no QSAR reports correlating to the structure of isoquinolone or benzothiazine with their biological activities.

Further literature reports revealed that the biological potential of the isoquinolone and benzothiazine are less explored in comparison to other heterocycles, which indicated the availability of wide scope in exploring the biological potential of these heterocycles. On the basis of above information the following investigations were planned. ¹⁹-²⁴


2. Structural elucidation of the synthesized compounds by means of spectral analysis.

3. Evaluation of anti-inflammatory and analgesic activity of the compounds.


5. Correlation of the biological activity with the physicochemical parameters employing QSAR technique and statistical evaluation by standard technique.