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Thienopyridine and Its Derivatives as Potential Anti-Inflammatory Agent: Heterocyclic Chemistry, SAR, COX-2 Inhibition, Molecular Docking and *In Silico* Drug Design

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ABSTRACT

Thienopyridines consist of fused heterocyclic structures that incorporate thiophene and pyridine rings. They are important in medicinal chemistry because different substituents can be introduced into their structure to modify their biological and pharmacological properties. Thienopyridine derivatives have been reported to show several activities, including anti-inflammatory, analgesic, antiplatelet, antimicrobial and anticancer effects. Tinoridine hydrochloride is an important example of a thienopyridine with anti-inflammatory activity and can be used as a reference compound in the development of new derivatives. Some newly studied thienopyridine derivatives have shown anti-inflammatory and antiarthritic activity, with certain compounds showing lower ulcerogenic effects than indomethacin. Cyclooxygenase-2 (COX-2) is an important target for the development of anti-inflammatory drugs. Molecular docking can be used to study the possible binding of thienopyridine derivatives with COX-2, while structure–activity relationship (SAR) studies can help identify structural features related to activity. ADMET prediction can also provide information about the pharmacokinetic and toxicity properties of the compounds. Therefore, combining SAR, molecular docking and ADMET studies may help in the design of new and potentially safer thienopyridine-based anti-inflammatory agents. [1,4,6,11]

Keywords: Thienopyridine; COX-2; Molecular Docking; SAR; NSAIDS; Tinoridine Hydrochloride.

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INTRODUCTION

Inflammation is a biological response involving blood vessels, immune cells and different inflammatory mediators. When inflammation continues for a long period or becomes excessive, it can contribute to diseases such as rheumatoid arthritis and osteoarthritis. Non-steroidal anti-inflammatory drugs (NSAIDs) are commonly used to reduce inflammation because they inhibit cyclooxygenase enzymes and decrease prostaglandin formation. However, conventional NSAIDs may cause gastrointestinal and other adverse effects. Therefore, there is a need to develop anti-inflammatory agents with improved safety and selectivity.

Heterocyclic compounds have a crucial role in medicinal chemistry as the presence of heteroatoms and ring configurations can affect molecular interactions, lipophilicity, polarity, hydrogen bonding, and pharmacokinetic characteristics. Thienopyridines are interesting

heterocyclic systems because they contain fused thiophene and pyridine rings and allow modification at different positions. Tinoridine is an important example of a thienopyridine-related anti-inflammatory drug and can be considered as a reference compound for developing new derivatives. However, tinoridine should not be considered specifically as a highly selective COX-2 inhibitor. Therefore, COX-1/COX-2 studies and molecular docking are required to understand the activity and selectivity of newly developed thienopyridine derivatives. [2,3]

MATERIALS AND METHOD

This review examined published studies on thienopyridine derivatives, with emphasis on the thieno[2,3-b]pyridine scaffold and its reported anti-inflammatory activity against cyclooxygenase-1 (COX-1), cyclooxygenase-2 (COX-2), and 5-lipoxygenase (5-LOX). Tinoridine hydrochloride was considered a reference anti-inflammatory thienopyridine, while indomethacin and celecoxib were considered reference ligands for comparison with conventional and COX-2-selective inhibitors [1, 11, 12].

Thienopyridine as a Heterocyclic Ring System

Thienopyridines are bicyclic heteroaromatic entities created through the amalgamation of a thiophene ring and a pyridine ring. Different fusion patterns give rise to isomers such as thieno[2,3-b] pyridine, thieno[3,2-b]pyridine and thieno[2,3-c]pyridine. The fused ring system provides rigidity to the molecule. The nitrogen atom of the pyridine ring can act as a hydrogen-bond acceptor, while the sulfur-containing thiophene ring contributes to the aromatic and hydrophobic properties of the compound. Substitution at different positions can change the steric, electronic and lipophilic properties of the derivatives. Among these systems, thieno[2,3-b] pyridine

is of interest in anti-inflammatory research because reported derivatives have been studied for their activity against COX-1, COX-2 and/or 5-LOX. [3]

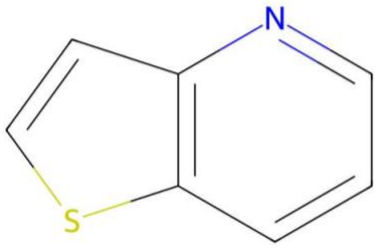


Figure 1: 2D structure of Thienopyridine

Pharmacological Importance of Thienopyridines

The pharmacological properties of thienopyridine derivatives, such as their anti-inflammatory, analgesic, antiplatelet, antibacterial, anticancer, and enzyme-inhibitory properties, have been studied. Although their methods differ from tinoridine's anti-inflammatory activity, clinically used drugs like ticlopidine and clopidogrel also demonstrate the broad pharmacological significance of the thienopyridine scaffold. Therefore, it is incorrect to classify the thienopyridine ring as a COX-2 inhibitor. The kind and location of substituents on the scaffold largely determine the biological activity and target selectivity. [4]

Tinoridine Hydrochloride as a Reference Anti-Inflammatory Thienopyridine

An early example of an anti-inflammatory medication linked to thienopyridines is tinoridine hydrochloride. Its structure includes amino, ester, and benzyl groups in addition to heterocyclic elements that contain nitrogen and sulphur. Tinoridine is a helpful reference molecule for studies on thienopyridine derivatives due to its documented anti-inflammatory properties.

Tinoridine is correlated with effects that stabilise membranes and exhibit antiperoxidative or radical-scavenging functions. Therefore, its activity cannot be explained only by selective COX-2 inhibition. In computational studies, tinoridine can be used as a reference ligand along with known COX inhibitors such as indomethacin and celecoxib. Celecoxib is more suitable as a reference when COX-2 selectivity is being studied, whereas tinoridine is useful as a reference for the thienopyridine anti-inflammatory scaffold. [11,12]

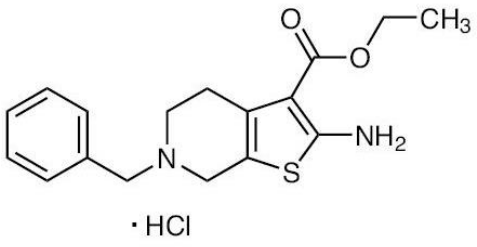


Figure 2:2D structure of Tinoridine Hydrochloride

Cyclooxygenase-2 as a Drug-Design Target

Arachidonic acid is converted into prostaglandins by cyclooxygenase enzymes. While COX-2 is more significantly produced during inflammation, COX-1 is often present under normal physiological settings. COX-2 is therefore a key target in the creation of anti-inflammatory medications.

The COX-2 binding site contains a number of residues, including Arg120, Tyr355, Tyr385, Ser530, Val523, Val434, Leu503, Phe518, Arg513, and His90. Position 523 represents one significant structural distinction between COX-1 and COX-2. Ile523 is present in COX-1, but the smaller Val523 residue is present in COX-2. When designing selective inhibitors, this difference can be taken into account because it adds space to the COX-2 binding area. Thus, the fused thienopyridine ring can occupy the primary hydrophobic channel, and appropriate polar or hydrophobic groups can be provided to interact with this region. [6,7]

Molecular Docking of Thienopyridine Derivatives Against COX-2

When designing selective inhibitors, this difference can be taken into account because it adds space to the COX-2 binding area. Thus, the fused thienopyridine ring can occupy the primary hydrophobic channel, and appropriate polar or hydrophobic groups can be provided to interact with this region. The predicted interactions may include hydrogen bonding, hydrophobic interactions, π–π interactions and electrostatic interactions. However, a good docking score alone cannot confirm biological activity. Therefore, docking results should be considered together with SAR, ADMET and experimental studies. [6]

Structure–Activity Relationship of Thienopyridine COX-2 Inhibitors

The thienopyridine scaffold provides different positions that can be modified to study the relationship between structure and biological activity.

Fused thienopyridine core:

The rigid fused ring system helps maintain the shape and orientation of the molecule and can support hydrophobic and aromatic interactions.

Pyridine nitrogen:

The nitrogen atom can act as a hydrogen-bond acceptor and can influence the electronic properties of the molecule.

Amino group:

An amino group can increase polarity and provide sites for hydrogen bonding. Therefore, 3-amino-thieno[2,3-b] pyridine derivatives are useful for SAR studies.

Aryl group:

The phenyl ring can interact with hydrophobic regions of the COX-2 channel. Changing the substituents on the phenyl ring can affect the electronic and steric properties of the molecule.

Halogen groups:

Fluorine and chlorine substituents can influence lipophilicity and electronic properties. The reported activity of para-chloro-substituted derivatives can provide a basis for studying similar substitutions.

Polar groups:

Groups such as amide, sulfonamide and hydroxyl can participate in hydrogen bonding and may help in positioning the molecule within the COX-2 binding site.

Lipophilicity:

Increasing lipophilicity does not always improve biological activity. Excessive lipophilicity may reduce aqueous solubility and affect pharmacokinetic properties. Therefore, lipophilicity should be balanced with activity and ADMET characteristics. [5,6]

In-Silico Design Strategy

The computational design of new thienopyridine anti-inflammatory agents can begin with a literature study followed by selection of the thieno[2,3-b] pyridine scaffold and tinoridine as a reference compound. Different substituents can then be introduced to obtain a series of new derivatives.

The designed compounds can first be evaluated for their physicochemical and drug-likeness properties using tools such as ChemSketch, Molinspiration or SwissADME. PASS can be used to predict possible biological activities. The COX-2 protein can then be prepared for molecular docking, followed by analysis of the binding poses and ligand–protein interactions. Docking with both COX-1 and COX-2 may provide information about the possible selectivity of the compounds. ADMET and toxicity prediction can further help in selecting compounds for detailed investigation. Selected compounds can later be studied using molecular-dynamics simulations and experimental methods. The proposed derivatives may contain phenyl, fluorophenyl, chlorophenyl, bromophenyl, methylphenyl, methoxyphenyl and trifluoromethylphenyl groups. Heteroaryl groups such as pyridyl, thiazolyl and furyl, as well as polar groups such as sulfonamide, amide and carboxyl groups, can also be explored. [5]

Comparison with Conventional NSAIDs

Conventional NSAIDs such as ibuprofen and indomethacin act mainly through inhibition of cyclooxygenase enzymes, but their use may be associated with gastrointestinal adverse effects.

COX-2-selective inhibitors were developed partly to reduce problems associated with inhibition of COX-1.

Some thienopyridine derivatives have shown anti-inflammatory activity and lower ulcerogenic effects than indomethacin in animal studies. However, these findings cannot be applied to all thienopyridine derivatives. The safety of each individual compound needs to be evaluated experimentally before making conclusions about its safety. [1]

RESULTS AND DISCUSSION

From the above studies, it is clear that the thieno[2,3-b]pyridine scaffold could serve as a valuable starting point for the design of new anti-inflammatory drugs, since some of its derivatives are active against COX-1, COX-2, and 5-LOX; but depending on their structures, their activities and selectivities may vary. Tinoridine hydrochloride could provide useful data for the development of an effective anti-inflammatory agent; however, it is incorrect to conclude that tinoridine acts via selective COX-2 inhibition. Molecular docking and ADMET screening would be beneficial in selecting new derivatives, as well as in assessing their interactions with proteins and drug likeness; comparing COX-1 and COX-2 could serve for studying selectivities. [1-3]

CONCLUSION

Thienopyridines are useful heterocyclic scaffolds in medicinal chemistry because their structures can be modified at different positions. Tinoridine hydrochloride provides an important example of anti-inflammatory activity associated with this class, while thieno[2,3-b] pyridine derivatives provide opportunities for further investigation of COX-1, COX-2 and 5-LOX-related mechanisms.

The structural difference between COX-1 and COX-2, particularly the presence of Val523 in COX-2, provides a useful basis for designing new derivatives with possible COX-2 selectivity. SAR studies can help identify useful structural modifications, while molecular docking can be used to study possible interactions with the target protein. ADMET and toxicity prediction can also help in the early selection of compounds.

However, docking results alone cannot confirm biological activity. Therefore, combining SAR, molecular docking and ADMET studies with synthesis and experimental evaluation of COX-1/COX-2 inhibition and anti-inflammatory activity would provide a more reliable approach for the development of new thienopyridine-based anti-inflammatory agents. [1,5,7]

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