RECENT ADVANCE IN ANTI INFLAMMATORY ACTIVITY OF BENZOTHIAZOLE DERIVATIVES

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ABSTRACT

Different heterocyclic compounds are made to synthesize by large number of efforts and their derivatives were found to possess antitumor, antidiabetic, antimicrobial, anticonvulsant and anthelmintic activities. The small and simple benzothiazole nucleus and its derivatives possess various diverse biological properties. These activities are also possessed by its substituted derivatives as well. Literature revealed that benzothiazole derivatives may serve as an important model on as potent anti-inflammatory agent. When one biological active molecule is linked to another, resultant molecule generally has increased potency. Most of the derivatives showed enhanced anti-inflammatory activity as compared to the standard drug. So, benzothiazole derivatives can serve as future therapeutic leads for the discovery of anti-inflammatory drugs.

Keywords: Heterocyclic compounds, Benzothiazole, Biological properties, Anti-inflammatory agents, Anti-inflammatory drugs.

INTRODUCTION

Nonsteroidal anti-inflammatory drugs (NSAIDs) have been available to small animal practitioners for many years, but their use has remained relatively uncommon. Recently, new discoveries about inflammatory mediators and their interactions in the inflammatory cascade, as well as new data on the biochemical mediators associated with osteoarthritis, have led to increased use of NSAIDs. The arrival of NSAIDs with better defined safety and efficacy profiles for dogs has also dramatically increased their use. NSAIDs are known to provide analgesia, anti-inflammatory and antipyretic capabilities, yet the exact mechanisms of action for this group of drugs is still being elucidated. The classic explanation of their anti-inflammatory mode of action is inhibition of the cyclooxygenase (COX) enzymes. These enzymes are active in the metabolism of arachidonic acid. Furthermore, certain NSAIDs may have selectivity in their actions against these isoenzymes of cyclooxygenase. Likewise, conventional thinking states that NSAIDs act peripherally to provide analgesia. However, recent data also support a central mechanism of action for pain modulation, which may account for a significant portion of the therapeutic benefits they provide when treating osteoarthritis (OA). With these new insights, this article focuses on products used in the management of osteoarthritis.¹

The chemistry and biological study of heterocyclic compounds has been an interesting field for a long time in medicinal chemistry. A number of heterocyclic derivatives containing nitrogen and sulphur atom serve as a unique and versatile scaffolds for experimental drug design.¹ Benzothiazole is a heterocyclic
compound, weak base, having varied biological activities and still of great scientific interest now a days. They are widely found in bioorganic and medicinal chemistry with application in drug discovery. Benzothiazole is one of the most important heterocyclic that has received overwhelming response owing to its diversified molecular design and remarkable optical and electronic properties. Benzothiazole consists of thiazole ring fused with benzene ring and possess multiple applications. The survey of literature related to benzothiazoles reveals the presence of this bicyclic ring system in various amine or terrestrial natural compounds, which have useful biological properties. In recent years heterocyclic compounds analogues and derivatives have attracted strong interest due to their biological and pharmacological properties. Benzothiazole derivatives possess a wide spectrum of biological applications such as antitumor, antimicrobial, schictosomicidal, anti-inflammatory, anticonvulsants, Antidiabetic, antipsychotic and diuretic etc.\(^3\)

**IN THE RECENT YEARS A NUMBER OF BENZOTHIAZOLE DERIVATIVES HAVE BEEN SYNTHESIZED AND FOUND TO DISPLAY ANTI-INFLAMMATORY ACTIVITY**

Singh et al., prepared some new 2-(4'-butyl-3', 5'-dimethylpyrazol-1'-yl)-6-substituted benzothiazoles and 4-butyl-1-(6'-substituted-2'-benzothiazolyl)-3-methylpyrazol-5-ones and were found to display significant anti-inflammatory activity.\(^4\)

![Figure 1: 4-butyl-1-(6'-substituted-2'-benzothiazolyl)-3-methylpyrazol-5-ones](image)

Sawhney et al., have prepared some novel 2-(2-benzothiazolyl)-6-aryl-4, 5-dihydro-3(2 \(H\))-pyridazinone and found that they possessed low to moderate anti-inflammatory activity.\(^5\)

![Figure 2: 2-(2-benzothiazolyl)-6-aryl-4, 5-dihydro-3(2 \(H\))-pyridazinone](image)

Hibi S. et al., reported series of 3-pyridylimethyl-substituted-2-amino-6- hydroxy benzothiazole was synthesized and tested for anti-inflammatory activity. Test compound imparted a dual inhibitory action against leukotriene B\(_4\) and thromboxane A\(_2\), which was a result of direct action on 5-lipoxygenase and TXA\(_2\) synthetase.\(^6\)

Dogruer et al., synthesized sixteen (2-benzothiazolone-3-yl and 2-benzoaxazolone-3yl) acetic acid derivatives and tested them for antinociceptive and anti-inflammatory activity. 4-[2-(6-Benzoyl-2-benzoaxazolone-3-yl) acetyl] morpholino, 4-[2-(6-(2-chloro-benzoyl)-2-benzoaxazolone-3-yl] acetyl] morpholino, 4-[2-(6-(2-chloro-benzoyl)-2-benzoaxazolone-3yl] acetyl] morpholine, 1-[2-(5-chloro-2-benzoaxazolone-3-yl) acetyl] pyrrolidine, methyl ((6-methyl-2-benzoaxazolone-3-yl) acetate and N, \(N\)-diethyl-2- (2-benzothiazolone-3-yl) acetamide have shown more potent antinociceptive activity than others.\(^7\)

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Heitsch H. et al., reported Anti-inflammatory activity of O-substituted-4-benzothiazoles were determined and most of the derivatives were found potent inhibitors of Bradykinin B\textsubscript{2} receptor.\textsuperscript{8}

**Figure 3**: (2-benzothiazolone-3-yl and 2-benzoazole-3yl) acetic acid derivatives

<table>
<thead>
<tr>
<th>Compound</th>
<th>R Group</th>
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<tbody>
<tr>
<td>a</td>
<td>-CH=CH-C\textsubscript{6}H\textsubscript{5}(p-CH\textsubscript{3})</td>
</tr>
<tr>
<td>b</td>
<td>-CH=CH-C\textsubscript{6}H\textsubscript{5}(p-CF\textsubscript{3})</td>
</tr>
<tr>
<td>c</td>
<td>-CH=CH-C\textsubscript{6}H\textsubscript{5}(m-OCH\textsubscript{3})</td>
</tr>
<tr>
<td>d</td>
<td>-CH=CH-(2-furyl)</td>
</tr>
<tr>
<td>e</td>
<td>-CH=CH-CH=CH\textsubscript{2}</td>
</tr>
<tr>
<td>f</td>
<td>-O-CH\textsubscript{2}-C\textsubscript{6}H\textsubscript{5}</td>
</tr>
</tbody>
</table>

**Table 1**

Oketani K. et al., reported In vitro effects of E3040, 6-hydroxy-5, 7-dimethyl-2-(methyl amino)-4-(3-pyridylmethyl) benzothiazole a dual inhibitor of 5-lipoxygenase and Thromboxane A\textsubscript{2} synthetase on eicosanoid production.\textsuperscript{9}

Paramashivappa R. et al., Design, synthesis and biological evaluation of a series of 2-[[2-alkoxy-6-pentadecylphenyl) methyl] thio]-1H-benzimidazoles/benzothiazoles and benzoxazoles from anacardic acid and investigated their ability to inhibit human cyclooxygenase-2 enzyme (COX-2). The active compounds were screened for cyclooxygenase-1 (COX-1) inhibition. Thus, this class of compounds may serve as excellent candidates for selective COX-2 inhibition.\textsuperscript{10}

**Figure 4**: O-substituted-4-benzothiazoles

Das J. et al., reported 2-Amino-heteroaryl-benzothiazole-6-anilides were discovered and evaluated for the anti-inflammatory activity.\textsuperscript{11}

**Figure 5**: 2-[[2-alkoxy-6-pentadecylphenyl) methyl] thio]-1H-benzothiazoles
Khedekar P. et al., reported Synthesis and anti-inflammatory activity of alkyl/arylidene-2-aminobenzothiazoles and 1-benzothiazol-2-yl-3-chloro-4-substituted-azetidin-2-ones.\textsuperscript{12} Geronikaki A. et al., reported Novel thiazolyl, thiazolinyl and benzothiazolyl Schiff bases as possible lipoxygenase inhibitors and anti-inflammatory agents. The referred compounds are reported to act as lipoxygenase inhibitors affecting inflammation and/or psoriasis.\textsuperscript{13} Papadopoulou C. et al., reported Synthesis and biological evaluation of new thiazolyl/benzothiazolyl-amides, derivatives of 4-phenyl-piperazine. In general, the studied compounds were found to be potent anti-inflammatory agents (44–74.1\%). An attempt was made to correlate their biological activity with some physicochemical parameters using a quantitative structure–activity relationship approach.\textsuperscript{14}

Figure 6: 2-Amino-heteroaryl-benzothiazole-6-anilides

Kumar V. et al., reported Synthesis and characterization of novel (N-Substituted-3-chloro-2-azetidinones) anti-inflammatory agents.\textsuperscript{15}

Table 2

<table>
<thead>
<tr>
<th>Compound</th>
<th>R\textsubscript{1}</th>
<th>R\textsubscript{2}</th>
<th>R\textsubscript{y}</th>
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</thead>
<tbody>
<tr>
<td>a</td>
<td>NO\textsubscript{2}</td>
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<td>H</td>
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<td>Cl</td>
<td>H</td>
</tr>
</tbody>
</table>

Figure 8: N-Substituted-3-chloro-2-azetidinones
Venkatesh P. et al., reported synthesis, characterization and anti-inflammatory activity of some novel 2-amino benzothiazole derivatives. Among the compounds tested three compounds 5-chloro-1, 3-benzothiazole-2-amine, 6-methoxy-1, 3-benzothiazole-2-amine and 6-methoxy-1, 3-benzothiazole-2-amine were the most active compounds in these series when compared with diclofenac sodium. In the SAR study, the phenyl ring substituted with chloro at 5 position, methoxy substitution at 4 and 6-position in benzothiazole ring system showed better anti-inflammatory activity.¹⁶

Figure 9: Novel 2-amino benzothiazole derivative

Srivastav M. et al., reported Synthesis and Anti-inflammatory Activity of Some Novel 3-(6-Substituted-1, 3-benzothiazole-2-yl) - 2-[(4-substituted phenyl) amino] methyl] quinazolines-4 (3H)-ones. Synthesized quinazolines-4-one derivative were investigated for their anti-inflammatory and antibacterial activity.¹⁷

Figure 10: 3-(6-Substituted-1, 3-benzothiazole-2-yl) - 2-[(4-substituted phenyl) amino] methyl] quinazolines-4 (3H)-ones

Chaudhary P. et al., reported recent advances in pharmacological activity of benzothiazole derivatives. In the recent years a number of Benzothiazole derivatives have been synthesized and found to posses anti-inflammatory activity. Some new 2-(4'-butyl-3', 5'-dimethylpyrazol-1'-yl)-6-substituted benzothiazole were prepared and 4-butyl-1-(6'-sustituted-2'-benzothiazolyl)-3- methylpyrazol-5-ones were prepared and were found to posses significant anti-inflammatory activity.¹⁸ Gupta A. et al., reported Synthesis of N-{6-fluoro-7-(substituted)-amino]-1, 3-benzothiazole-2-yl}-2 or 3 or 4-nitrobenzamides derivatives was carried out and screened for anti-inflammatory activity.¹⁹

Yadav S. et al., reported synthesis and biological evaluations of benzothiazole derivatives abundantly distributed in nature and have been shown to have very interesting pharmacological activities like antibacterial, anti-inflammatory, antifungal, antitumor, anticancer and anthelmintic. In the present study the two pharmacophore, 2-mercaptop benzothiazole and hydrazine benzothiazole are fused by molecular conjugation to obtain highly potent, more specific and less toxic compounds. All the compounds have been screened for antibacterial, anti-inflammatory activities.²⁰

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Niranjane K. et al., synthesized and reported anti-inflammatory activity of some novel derivatives of 2-amino-3-cyano-14-imino-10-methoxy-4-methylthio pyrimido [2,1-b] pyrazolo [4,5-d] pyrimido [2,1-b] benzothiazole. It was concluded that some of the compounds showed excellent anti-inflammatory activity as compared with others.\textsuperscript{21} Gaochao T. et al., reported mechanism of inhibition of fatty acid amide hydrolase by sulfonamide-containing benzothiazole which is potential target for developing analgesic, anxiolytic, antidepressant, sleep-enhancing and anti-inflammatory drugs.\textsuperscript{22}

\textbf{CONCLUSION}

From review of literature Compounds with bulky geometry and better topology increases biological activity. Most of the derivatives showed enhanced anti-inflammatory activity as compared to the standard drug. So, these type of derivatives of Benzothiazole can serve as future therapeutic leads for the discovery of anti-inflammatory drugs. It can be concluded that this class of compounds certainly holds great promise towards good active leads in medicinal chemistry. A further study to acquire more information concerning pharmacological activity is in progress. The biological profiles of these new generations of benzothiazoles represent much progress with regard to the older compounds.

\textbf{REFERENCES}


