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Research Article

Synthesis and biological evaluation of benzothiazole derivatives

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Abstract

Benzothiazole derivatives are abundantly distributed in nature and have been shown to have very interesting pharmacological activities like antibacterial, anti-inflammatory, antifungal, antitumor, anticancer and anthelmintic. When one biological active molecule is linked to another, te resultant molecule generally has increased potency. Hence in the present study the two pharmacophore, 2-mercapto benzothiazole and hydrazine benzothiazole are fused by molecular conjugation to obtain highly potent, more specific and less toxic compounds. We have now chosen 2-hydrazino benzothiazole for the present investigation. This was successfully prepared from 2-mercapto benzothiazole by refluxed with hydrazine hydrate; yielded product i.e. 2-hydrazino benzothiazino benzothiazole was obtained.4-substituted aniline obtained was used as a starting material for the synthesis of some 2-amino-6-substituted benzothiazole derivatives by condensation by bromine and glacial acetic acid using potassium thiocynate. It also react with chloroacetyl chloride to form 2-chloroacetyl amino-6-substituted benzothiazole derivatives were also subjected to reaction with 2-mecapto benzothiazole to form 2-(1,3-benzothiazol2-yl-thio)-N-(6-substituted-1,3-benzothiazol-2-yl)acetamide and also reaction with 2-hydrazino benzothiazole to form 2-[2-(1,3-benzothiazol-2yl)hydrazine]N-(6-substituted-1,3-benzoyjiazol)acetamide.

The structures of all these compounds have been established on the basis of IR, MASS, NMR spectra. All the compounds have been screened for antibacterial, anti-inflammatory activities. Among the compound tested for their antibacterial activity, the entire compounds are their moderately active against Gram –ve bacteria. Out of the compound tested in all the series for their antibacterial activity against A. Niger, most of the compounds i.e. $5a_2$, $5a_2$, $5a_3$, $5a_4$, $6a_1$, $6a_2$, $6a_3$, and $6a_5$ showed moderate activity except $5a_1$, $5a_5$ and 6a4 that are found to be highly active as an antibacterial activity. While all ten compounds 5a1, $5a_2$, $5a_3$, $5a_4$, $5a_5$, $6a_1$, $6a_2$, $6a_3$, and $6a_5$ at dose 200mg/kg significant anti-inflammatory activity in acute inflammatory models in rat. Compounds i.e. $5a_1$, $5a_2$, $5a_3$, $5a_4$, $5a_5$, $6a_1$, $6a_2$, $6a_3$, $6a_4$, and $6a_5$ exhibited maximum inhibition of 84.18%, 70.54%, 81.81%, 86.36%, 54.54%, 69.09%, 56.36%, 84.00%, 83.27%, 70.54% respectively where as standard Diclofenac sodium showed reduction in edema by 90.90% in induced rat hind paw edema model.

Keywords: Cyclooxygenase, Dimethyl Formamide, Electron Impact Mass Spectroscopy, Lethal Dose, Retardation Factor, Tetra Methyl Silane, antibacterial ant anti-inflammatory activity.

Introduction

Benzothiazole derivatives are widely distributed in nature and have been shown to have very interesting pharmacological activities like antibacterial, anti-inflammatory, antifungal, antitumor, anticancer and anthelmintic. Benzothiazole derivatives play a vital role in the field of medicinal chemistry. Some of the thiazolotriazolesl-4 are reported to posses the biological activities like anti microbial5 and antitubercular.
Various derivatives of Benzothiazole derivatives have been synthesized by several investigators and have been reported to exhibit wide range of biological activities like antibacterial, anti-inflammatory, antitubercular, anthelmintic, antiulcer etc. Benzothiazoles may be prepared by the action of acid anhydrides or acid chlorides on 0-amino thiophenols and formic acid in the presence of acetic anhydride. This nitrogen ring system is known to posses' wide range of therapeutic properties. Benzorthiazoles are also formed by the action of phosphorous penta sulphide on o-acylaminophenols. Mannich bases are acquiring greater importance because of their useful biological activity6-9 and synthetic utility. Mannich bases of Isatins have been reported to posses a variety of biological activities like anthelmintic antimicrobial and CNS depressant[1-5].

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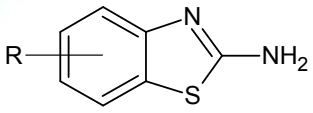
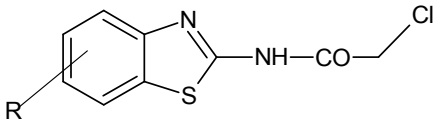
Material and methods[5-9]

The material used in the synthesizing benzothiazole derivatives are
Aniline, Glacial acetic acid, ammonia solution, benzene, chloroacetyl chloride, sodium bicarbonate solution, 2-mercapto benzothiazole, hydrazine hydrate and pyridine.
We have now chosen 2-hydrazino benzothiazole for the present investigation. This was successfully prepared from 2-mercapto benzothiazole by refluxed with hydrazine hydrate; yielded product i.e. 2-hydrazino benzothiazole was obtained.
4-substituted aniline obtained was as a starting material for the synthesis of some 2-amino-6-substituted benzothiazole derivatives ($1a_1$-a_5) by condensation with bromine and glacial acetic acid using potassium thiocynate. The 2-amino-6-substituted benzothiazole derivatives were reacted with chloroacetyl chloride to form 2-chloroacetylamino-6-substituted benzothiazole derivatives ($2a_1$-a_5) were also subjected to reaction with 2-mercapto benzothiazole to form 2-(1,3-benzothiazole-2ylthio)-N-(6-substituted-1,3-benzothiazole-2-yl)acetamide (5a1-$5a_5$) and also reaction with 2-hydrazino benzothiazole to form 2-[2-(1,3-benzothiazol-2yl)hydrazine]-N-(6-substituted-1,3-benzothiazole)acetamide ($6a_1$-a_5).
The 4-substuted aromatic amine fused with potassium thiocynate and bromine in glacial acetic acid and refluxed, yielded product i.e. 2-amino-6-substituted benzothiazole ($1a_1$-a_5).



($1a_1$-a_5)
R= H, CH_3, OCH_3, F, Cl

The compound ($1a_1$-a_5) again fused with chloroacetyl chloride, yielded product i.e. 2-chloro acetyl amino 6-substituted benzothiazole ($2a_1$-a_5).



($2a_1$-a_5)

The compound ($2a_1$-a_5) ($5a_1$-a_5) and ($6a_1$-a_5) again fused with 2-mercapto benzothiazole, yielded compound i.e. ($5a_1$-a_5) and also fused with 2-hydrazino benzothiazole, yielded compound i.e. ($6a_1$-a_5).
The structures of all these compounds have been established on the basis of IR, MASS, NMR spectra. All the compounds have been screened for antibacterial, antifungal and anti-inflammatory activities.

Result and discussion

Antibacterial activity:

The compound tested for their antibacterial activity is moderately active against Gram -ve bacteria. Particularly compounds
$5a_2$, $5a_3$, $5a_4$, $6a_1$, $6a_2$, $6a_3$ and $6a_5$ are moderately active against E. coli and compounds $5a_1$, $5a_5$ and $6a_4$ are moderately active against P.vulgaris.

Anti-inflammatory activity:

All compounds $5a_1$, $5a_2$, $5a_3$, $5a_4$, $5a_5$, $6a_1$, $6a_2$, $a6a_3$, $6a_4$ and $6a_5$ exhibited significant anti-inflammatory activity. Out of the five compounds tested for anti-inflammatory activity, compounds $4b_3$ was found to be moderately active, compounds $4c_3$, $4e_5$, $4f_2$ found to be significantly active as anti-inflammatory agents. However compound $4a_1$ were found to be mild active.
From the antibacterial and anti-inflammatory screening, it was found that the compounds showed significant activity and were to be good with respect to the standard at the given concentration levels.

Conclusion

The two moieties i.e. 2-substituted benzothiazole and 2 chloroacetamido-6-substituted independently are showing anti bacterial activity. Here when the two moieties are fused and screened for anti bacterial studies they showed a broad spectrum of antibacterial activity. They showed good activity against Gram +ve and Gram –ve bacteria.

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