

BENZOTHAZOLE IT'S CURRENT PHARMACOLOGICAL PROFILE AND METHODS OF SYNTHESIS

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Summary

Benzothiazole, a heterocyclic ring consisting of N and S at symmetrical position have been studied extensively owing to their interesting pharmacological activities. This review article covers the most active Benzothiazoles derivatives that have shown considerable biological actions such as antimicrobial, anti-inflammatory, anticancer, antilipidemic, antiviral, antihypertensive, and Antitubercular. This review also discusses the structure-activity relationship of the most potent compounds. It can act as an important tool for medicinal chemists to develop newer compounds possessing Benzothiazoles moiety that could be better agents in terms of efficacy and safety.

Keywords: Benzothiazoles, SAR, Biological activity, Total synthesis.

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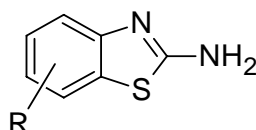
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Introduction

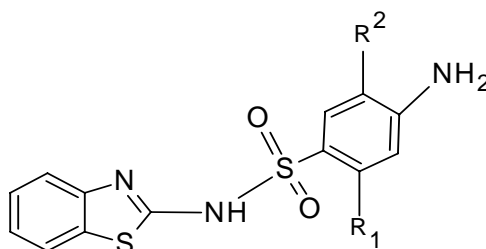
Being a heterocyclic compound, benzothiazoles finds use in research as a starting material for the synthesis of larger, usually bioactive structures. Its aromaticity makes it relatively stable, although as a heterocycle, it has reactive sites which allow for functionalization. Many dyes, such as thioflavin, and pharmaceutical drugs, such as riluzole, have benzothiazoles as a structural motif.

Antimicrobial activity

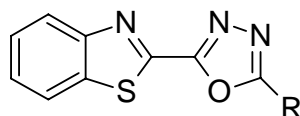
1. A series of potent and selective antitumor agents, mostly from substituted 2-(4-aminophenyl) benzothiazoles, were developed and comprised a novel class of antitumor active compounds, especially against sensitive breast tumor cell lines, *e.g.*, MCF-7 and MDA 468 and extended to certain colon, lung, melanoma, renal, and ovarian tumor cell lines. Some new 2-Amino substituted- benzothiazole were synthesized. The antimicrobial activity of the synthesized compounds was evaluated by disc diffusion method.¹



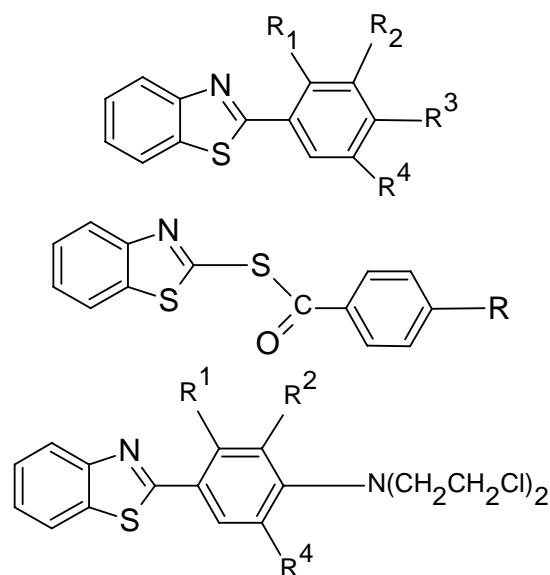
2. A series of sulphonamide derivatives having benzothiazole nucleus have been synthesized by condensation of 2-aminobenzothiazole with 4-acetamidobenzenesulphonyl chloride derivatives in pyridine-acetic anhydride mixture. The identity of the compounds 4-acetamido-*N*-(1,3-benzothiazol-2-yl) benzene sulphonamide and 4-amino-*N*-(1,3-benzothiazol-2-yl)benzene-sulphonamide has been characterized by elemental analysis and spectral data. All the test compounds have been assayed *in vitro* for antibacterial activity against *B. subtilis* and *E. coli*, antifungal activity against *C. albicans* and the antimycobacterial activity against H37Rv strain of *Mycobacterium tuberculosis*.²



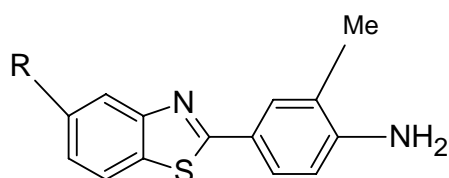
3. Some new 2-(5-substituted-1,3,4-oxadiazole-2-yl)-1,3-benzothiazole (3a-j) were synthesized by refluxing benzothiazolyl carboxyhydrazide with different aryl acids in phosphoryl chloride. Structures of the synthesized compounds were established on the basis of ¹H NMR and Mass spectral data. The antimicrobial activity of the synthesized compounds was evaluated by disc diffusion method.³

**Anticancer activity**

1. Substituted 2-phenyl-benzothiazole were synthesised by condensing substituted benzoic acid with 2-amino thiophenol in the presence of phosphoric acid and 3-benzothiazole-2-yl-4-substituted carbothiaote derivatives were prepared by condensing 2-mercaptobenzothiazole with substituted acidchloride. Structures of all the compounds were characterized by spectral and elemental analysis. All the synthesized novel compounds were screened for anticancer activity.⁴

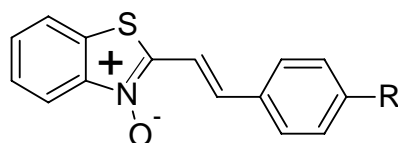


- The 2-arylsubstituted benzothiazole derivatives were synthesized by refluxing o-aminothiophenol with substituted benzoic acids in the presence of polyphosphoric acid at 220°. 2-Mercaptobenzothiazole was used along with thionyl chloride to get the carbothioates. The physical and spectral data such as mp, Rf, IR, NMR was obtained for the synthesized compounds and the structures were confirmed. Compounds were found to be significantly cytotoxic as compared to [2-(3-bromo-4-aminophenyl) benzothiazole] against the human cervical cancer cell lines.⁵
- New fluorinated 2-aryl-benzothiazoles, -benzoxazoles, and -chromen-4-ones have been synthesized and their activity against MCF-7 and MDA 468 breast cancer cell lines compared with the potent antitumor benzothiazole.⁶



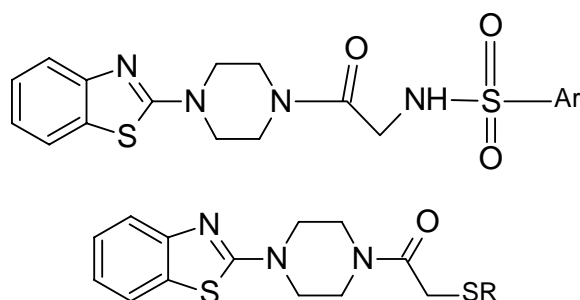
Antibacterial activity

Eleven new 2-styrylbenzothiazole-*N*-oxides have been prepared by aldol – type condensation reactions between 2-methylbenzothiazole-*N*-oxide and *para*-substituted benzaldehydes. Compounds with cyclic amino substituents showed typical push-pull molecule properties. Four compounds were tested against various bacterial strains as well as the protozoan *Euglena gracilis* as model microorganisms.⁷

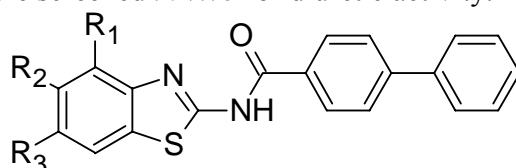


Antiproliferative activity

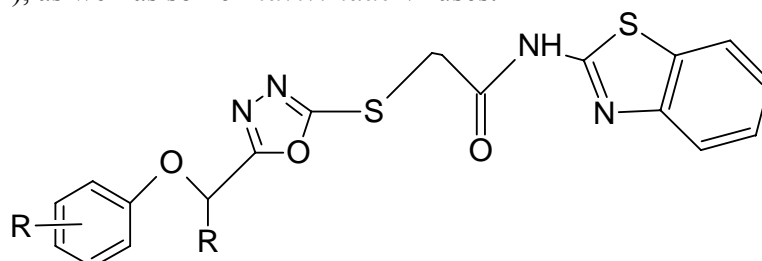
A series of benzothiazole bearing piperazino-arylsulfonamides (5a-k), and arylthiol analogues (6a-j) as well as substituted benzothiazoles having sulfonamides (9b, 9l-n and 10) have been synthesized. All compounds were evaluated, *in vitro*, for their antiproliferative activity against a large panel of human tumor-derived cell lines.⁸

**Diuretic Activity**

A series of N-{(substituted)1,3-benzothiazol-2-yl}-1,1i-biphenyl-4-carboxamides was synthesized by reaction between biphenyl acid chloride and 2-aminobenzothiazole. The synthesized compounds were screened *in vivo* for diuretic activity.⁹

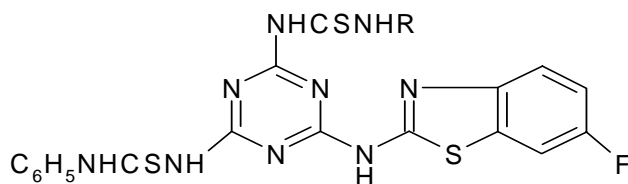
**Antiviral activity**

A series of new benzothiazole derivatives have been synthesized, in five steps, from substituted phenols *via* the 1,3,4-oxadiazole-2-thiones. The *in vitro* antitumor activity of the compounds obtained was investigated and the benzothiazole derivatives showed strong effects on leukaemia cell lines CCRF-CEM ($CC50 = 12 \pm 2 \text{ mmol L}^{-1}$, $8 \pm 1 \text{ mmol L}^{-1}$, respectively). These compounds are leading candidates for further development. The title compounds were tested against representatives of several virus families containing single stranded RNA genomes, either positive-sense (ssRNA+), or negative--sense (RNA-), and against double-stranded RNA genomes (dsRNA), as well as some *Flaviviridae* viruses.¹⁰

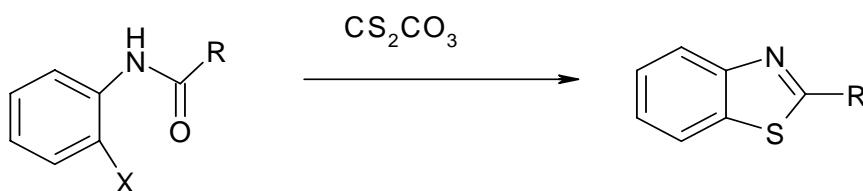


Antifungal activity

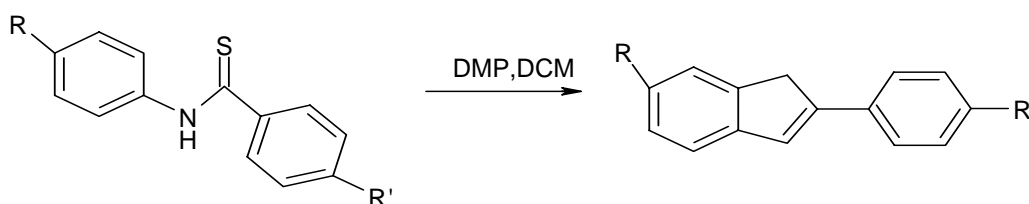
2,4,6-Trichloro-1,3,5-triazine has been reacted selectively with nucleophilic reagents, 6-Fluoro-2-aminobenzothiazole phenyl thioureas and different substituted thioureas to give 2-(6-fluorobenzothiazole-2'-ylamino)-4-(phenylthioureido)-6-(substituted thioureido)-1,3,5-triazine. These compounds are evaluated for their antimicrobial activity. The structure of all these compounds have been confirmed by IR, H NMR, mass spectra data and elemental analysis. Benzothiazoles,-triazenes and thioureas exhibit various biological activities.¹¹

**Method of Synthesis**

1. The one-pot synthesis of benzothiazoles starting from o-haloanilide with a tandem thionation with the Lawesson's reagent and an intramolecular cyclization, the authors propose as mechanism an intramolecular nucleophilic substitution, for me that sounds weird because the best results are obtained with both fluoro and iodo thioanilide, I would propose the formation of radical anion on sulfur or something like this which could be consistent with the results, nonetheless, this is a very interesting transformation.¹²

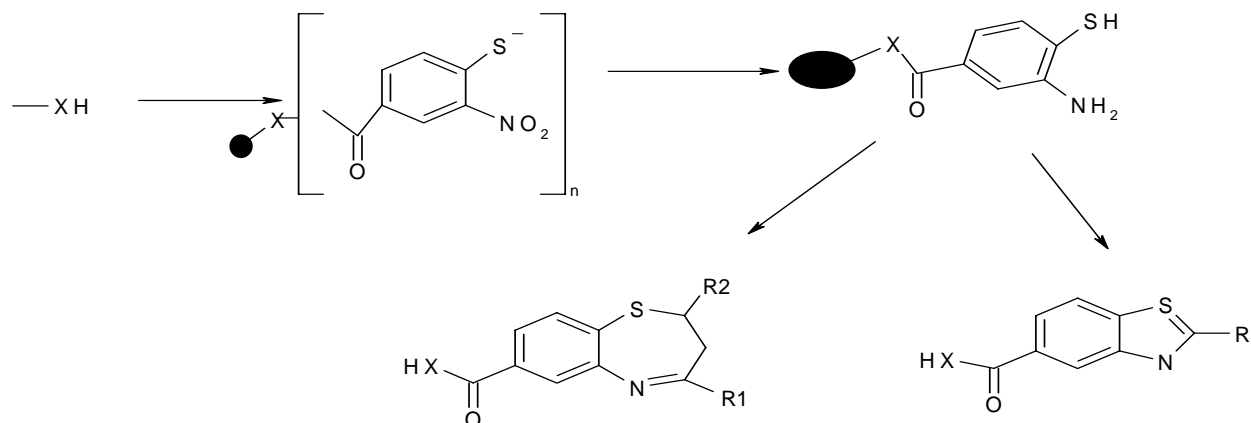


2. That reaction reminds me a 2006 JOC have read some months ago, talking about, of course, the synthesis of benzothiazoles starting from simple thioanilides and using Dess-Martin periodinane to promote the cyclization in only 15minutes in DCM. And in their case they propose a radical intramolecular cyclization.¹³

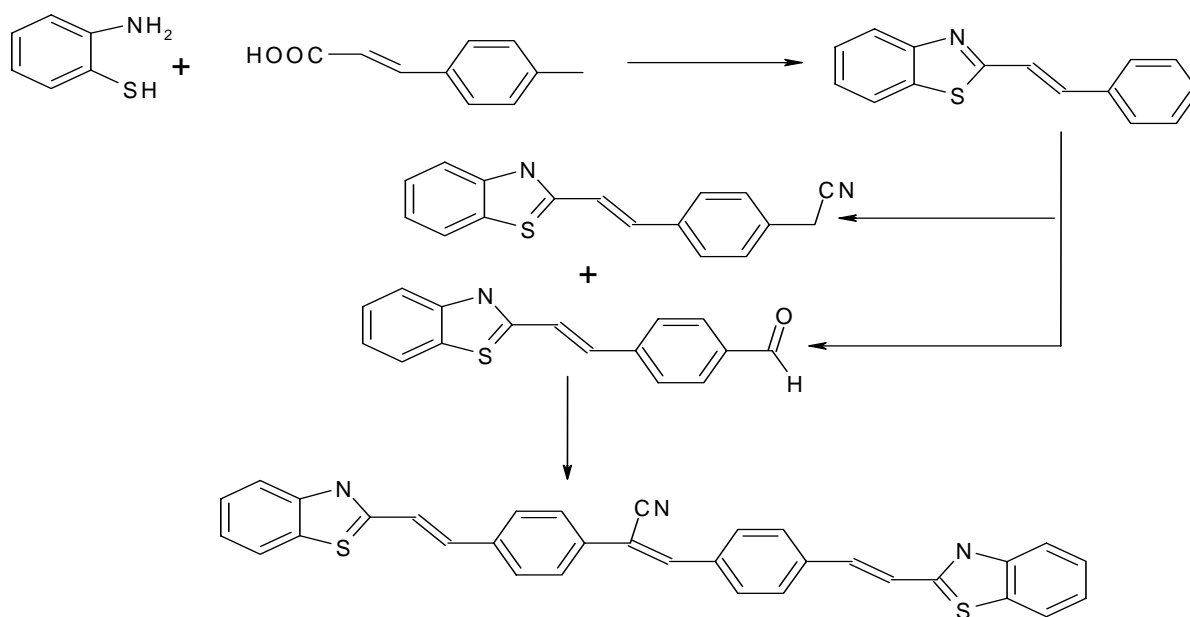


3. Bis-(2-nitro-4-carboxyphenyl) disulfide was loaded on Wang resin and Rink amide resin. The nitro group was reduced to its amine with concomitant cleavage of the disulfide bond using $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ to afford **2**. Condensation of an aldehyde and nucleophilic attack on an α,β -unsaturated ketone, followed by TFA cleavage from the resin, gave benzothiazole **3** and 2,3-dihydro-[1,5]-benzothiazepine **4**, respectively. Reaction of bis-(2-nitro-4-carboxyphenyl) disulfide with the Wang and Rink amide resin followed by reduction, condensation of

aldehyde and nucleophilic attack on an electrophile gave benzothiazole and 2,3-dihydro-[1,5]-benzothiazepine, respectively.¹⁴



4. Novel cyano-substituted benzothiazoles were synthesized, which possess an extended conjugated system. Compound consists of two benzothiazole units with bis(4-vinylphenyl)acrylonitrile as a bridging group and compound two benzothiazole units and twododecyloxy bis(4-vinylphenyl)-acrylonitrile.



Conclusion

Benzothiazole has been studied extensively for its various biological activities along with its route of synthesis. It may be proved as a lead in treatment of various fatal diseases like Cancer, Dementia, Hypertension etc. Thus it can be used as a powerful tool for medicinal chemist to develop and optimize the lead for preferred bioactivity.

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