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A REVIEW ON BIOLOGICAL ACTIVITY OF BENZOTHIAZOLE DERIVATIVES

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ABSTRACT

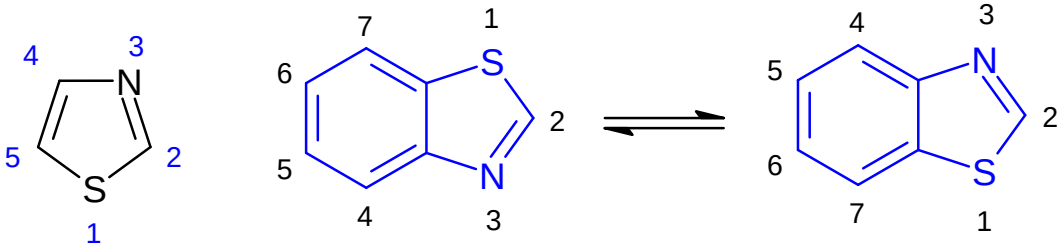
Benzothiazole is a bicyclic heterocycle having thiazole ring and are used worldwide for a variety of therapeutic applications. The core structure of thiazole consists of a five-membered ring containing sulfur and nitrogen atom at 1st and 3rd positions. Benzothiazole and their derivatives represent an important class of compounds possessing a wide spectrum of biological activities. The several analogues containing benzothiazole ring system exhibit significant antitumor, anthelmintic, antitubercular, antimicrobial, antidiabetic, antibacterial, antifungal, antioxidant, anti-inflammatory and other activities. This article is an attempt to present recent scientific literature on different biological activities of benzothiazole compounds.

KEYWORDS: Benzothiazole, Antitumor, Anthelmintic, Antimicrobial, Antioxidant, Antifungal.

INTRODUCTION

Medicinal chemistry works at the boundary of synthetic organic chemistry and biology with principal focus on drug development. In particular, the study of heterocycles are important pharmacophores and have significance to create privileged chemical structures possessing pharmacological activities. In recent years, there has been a growing interest pertaining to the synthesis and biological progression of bioactive compounds in the field of organic chemistry.

Benzothiazole is a bicyclic heterocycle having a thiazole ring. The core structure of thiazole consists of a five-membered ring containing sulfur and nitrogen atoms at 1st and 3rd positions. The numbering in thiazole starts from the sulfur atom. Hantzsch and Waber in 1887 first described thiazole and its structure was further confirmed by Popp in 1889. The basic structure of benzothiazole consists of benzene ring fused with 4th and 5th positions of thiazole ring. These two rings together constitute the basic nucleus 1,3-benzothiazole.



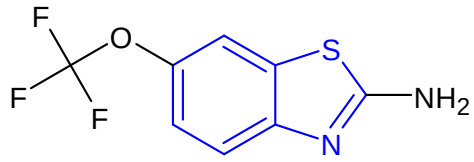
Benzothiazole is a colorless, slightly viscous liquid with a molecular formula C_7H_5NS. It is weakly basic in nature with a melting point of 2°C and a boiling point of 227-228°C. The density of benzothiazole is 1.24 g/mol, and its molecular mass is 135.19 g/mol.

The analogues of benzothiazole and its derivatives were found to be possessing and exhibiting a wide range of astounding medicinal properties some of them being antitumor, anthelminthic, antimicrobial, antibacterial, antioxidant, antidiabetic, antifungal, antitubercular and anti-inflammatory. In addition, benzothiazole act as core nucleus in various drugs due to their diverse biological activities, e.g., riluzole (a neuroprotective agent with anticonvulsant properties), dimazole (antifungal), halethazole (antiseptic and antifungal), zopolrestat (antidiabetic), phortress (anticancer), frentizole (antiviral) and ethoxazolamide (carbonic anhydrase inhibitor), etc.

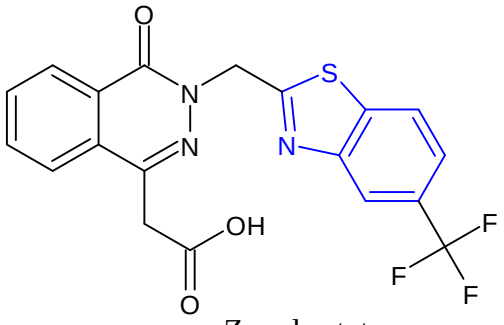
Various other methods have been reported for the synthesis of benzothiazole viz. condensation of 2-aminophenol with carboxylic acid derivatives, respectively, in strong acid at high temperature, oxidative cyclization using barium manganate, intramolecular

cyclization of thioformanilides, one-pot tandem reaction of benzyl halides and o-aminobenzenethiola, Bronsted acid catalyzed cyclization reactions of 2-amino thiophenols and anilines, simple solvent free and catalyst-free synthesis using elemental sulfur as traceless oxidizing agent, green synthesis with samarium triflate as a reusable acid catalyst, and copper-catalyzed condensation.

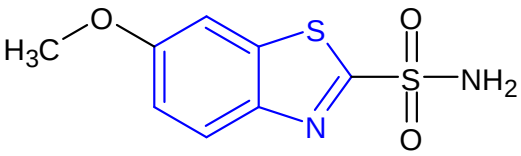
The benzothiazole possesses a wide spectrum of biological activities such as antitumor, antimicrobial, antitubercular, antibacterial, antifungal, anthelmintic, anti-inflammatory, antidiabetic and antioxidant activity.



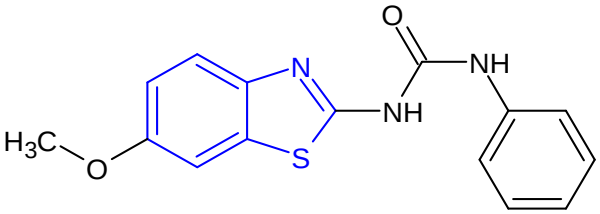
Riluzole



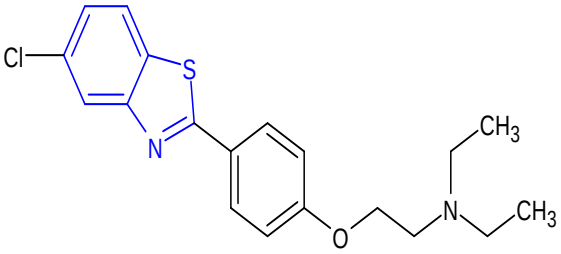
Zopolrestat



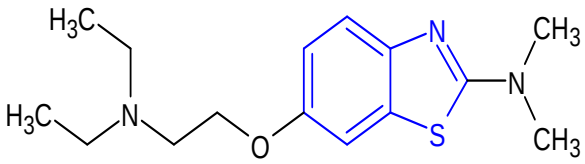
Ethoxazolamide



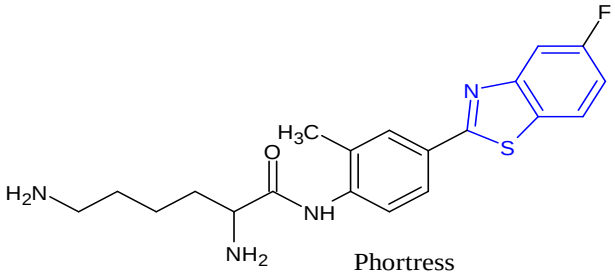
Frentizole



Halethazole



Dimazole

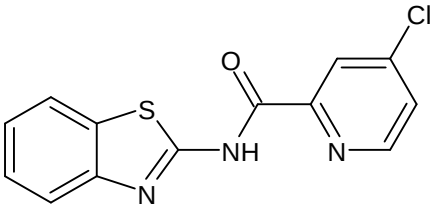


Phortress

BIOLOGICAL IMPORTANCE OF BENZOTHIAZOLE DERIVATIVES

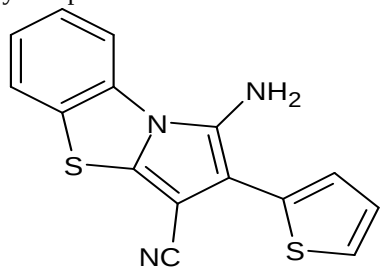
1. Antitumor activity

a. Jing Zhou *et al.*, 2023, synthesized a new series of benzothiazole derivatives which were evaluated for their ability to inhibit the growth of human tumor cells. This may serve as a potentially effective agent against colorectal cancer. For *in-vitro* assay the benzothiazole derivatives was prepared as a 20mM stock solution in 0.1% dimethyl sulfoxide (DMSO) used as a vehicle control and stored in -80C. By the MTT (3-[4,5-dimethylthiazol-2-yl]2,5 diphenyl tetrazolium bromide) assay, cell colony formation assay, western blotting, migration and invasion assay were used to examine the effects of BTD on cell proliferation, apoptosis, metastasis and the cell cycle. From the synthesized derivatives, **compound 1a** suppressed the cell proliferation of HCT116, HT29 and CT26 cells was evaluated by MTT assay where cells were treated with BTD (2.5, 5, or, 10M) or vehicle for 24-72hr.[1]



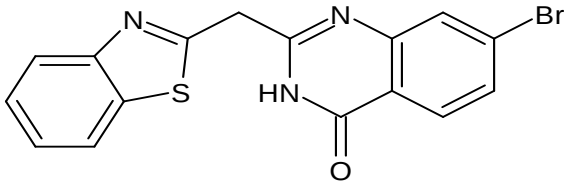
Compound 1a

b. Aamal A. Al-Mutairi *et al.*, 2022, synthesized a new series of benzothiazole derivatives which were evaluated for their ability to inhibit the growth of human tumor cells. The synthesized compounds were tested *in-vitro* for anticancer activity against three tumor cell lines (lung cell NCI-H460, liver cancer HepG2 and colon cancer HCT-116). These compounds were dissolved in DMSO as a stock solution (0.1 mol L^{-1}), after 48 h of incubation, cells were treated with different concentrations of the tested compounds (5,12,25 and 50µmol L^{-1}). For each individual dose triplicate wells were performed. To each well, MTT in phosphate buffered saline (PBS, 5 mg/mL) was added and incubated for 4 h at 37 ˚C. After that, MTT reagent was removed and added DMSO (100 µL) to each well to dissolve formazan crystals. A measure of 100µM of Doxorubicin was used as a standard drug. From the synthesized derivatives, **compound 1b** exhibit higher cytotoxicity compared to doxorubicin.[2]



Compound 1b

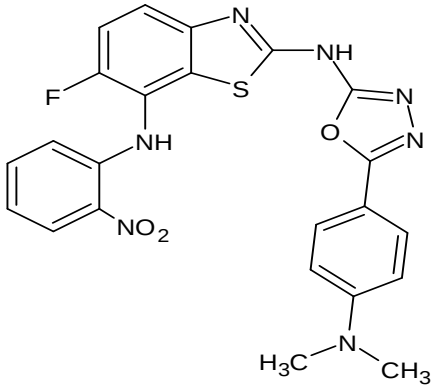
c. Aisha. Y. Hassan *et al.*, 2022, synthesized a new series of benzothiazole derivatives which were evaluated for their *in-vitro* antitumor activity. Twelve of the newly synthesized compounds were selected by the NCI for screening and evaluation of all compounds against 60 human tumor cell lines in a one dose (10µmol) screening. The output from the single 60 cell panel screen is reported as a mean graph and is available for analysis by the COMPARE program. From the synthesized derivatives, **compound 1c** exerted powerful growth inhibition activity against most of the cell lines including Leukemia K-562 (76.81%) and also, it exerted potent anticancer activity against Non-Small Cell Lung Cancer A549/ATCC (39.03%), HOP-62 (62.41%) and showed remarkable activity against Colon Cancer KM12 cell line by 58.56%; respectively.[3]



Compound 1c

2. Anthelmintic activity

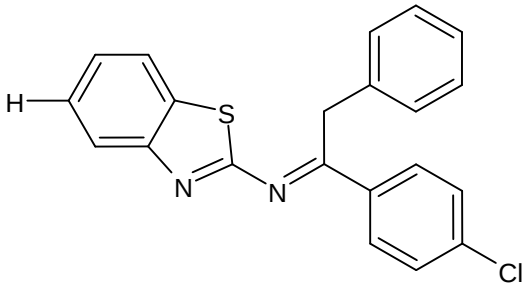
a. Raja Reddy Aleti *et al.*, 2023, synthesized a new series of benzothiazole derivatives which were evaluated for their anthelmintic activity by using earthworms. Six earthworms of nearly equal size were placed in standard drug solution and test compound solutions at room temperature. Normal saline used as control. The standard drug and test compounds were dissolved in minimum quantity of dimethyl formamide (DMF) and adjusted the volume up to 10 ml with normal saline solution to get the concentration of 0.1 % w/v, 0.2 % w/v and 0.5% w/v. Albendazole was used as a standard drug. The compounds were evaluated by the time taken for complete paralysis and death of earthworms. The mean lethal time for each test compound was recorded and compared with standard drug. The time taken by worms to become motionless was noted as paralysis time. To ascertain the death of the motionless worms were frequently applied with external stimuli, which stimulates and induces movement in the worms, if alive. From the synthesized derivatives, **compound 2a** shows significant paralysis and death time in minutes when compared to the standard Albendazole in all three-different concentration.[4]



Compound 2a

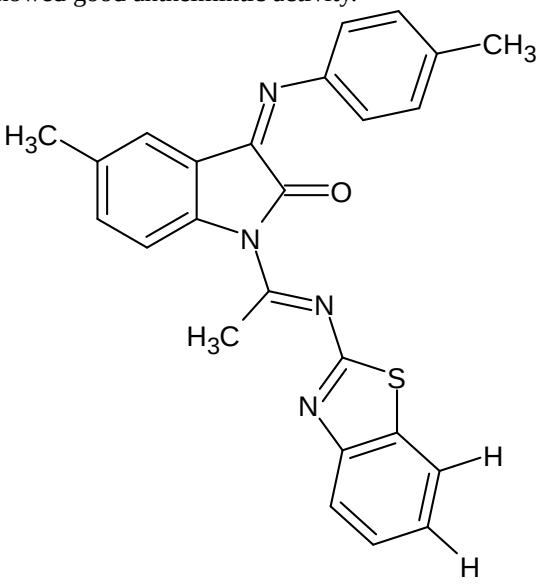
b. Ranjitha N. D. *et al.*, 2022, synthesized a new series of novel Benzothiazole derivatives which were screened for anthelmintic activity by using earth worms. One Earthworm is placed in standard drug solution and test compound's solutions at room temperature. Normal saline used as control. The standard drug and test compounds were dissolved in minimum quantity of dimethyl sulfoxide (DMSO) and adjusted the volume up to 10 ml with normal saline solution to get the concentration of 0.1% w/v, 0.2 % w/v and 0.5% w/v. Albendazole was used as a standard drug. The compounds were evaluated by the time taken for

complete paralysis and death of earthworms. The mean lethal time for each test compound was recorded and compared with standard drug. The time taken by worms to become motionless was noted as paralysis time. To certain the death of the motionless worms was frequently applied with external stimuli, which stimulate and induce movement in the worms, if alive. The mean lethal time and paralysis time of the earthworms for different test compounds and standard drug are Albendazole. From the synthesized derivatives, **compound 2b** shows good anthelmintic activities.[5]



Compound 2b

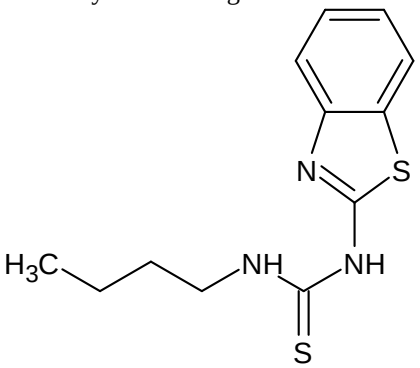
c. Aleti Rajareddy *et al.*, 2019, synthesized a new series of benzothiazole derivatives which were screened for anthelminthic activity using earthworms. Six earthworms of nearly equal size were placed in standard drug solution and test compound's solutions at room temperature. Normal saline was used as a control. The standard drug and test compounds were dissolved in minimum quantity of DMSO and adjusted the volume up to 10 ml with normal saline solution to get the concentration of 0.1% w/v, 0.2 % w/v, and 0.5% w/v. Albendazole was used as a standard drug. The compounds were evaluated by the time taken for complete paralysis and death of earthworms. The mean lethal time for each test compound was recorded and compared with standard drug. From the synthesized derivatives, **compound 2c** is evaluated for anthelmintic activity on Indian earthworms (*Pheretima posthuma*) and it showed good anthelmintic activity.[6]



Compound 2c

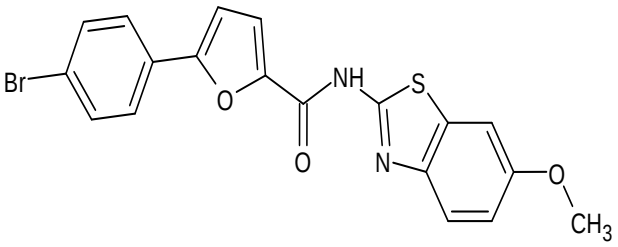
3. Antitubercular activity

a. Shilah Bonnett *et al.*, 2023, synthesized a series of benzothiazole derivatives which were evaluated for their *in-vitro* anti-tubercular activity. We tested a small subset of molecules for activity against *Mycobacterium tuberculosis* cultured in murine macrophage using a high-content microscopy method. This enabled us to test cytotoxicity against infected macrophages simultaneously to reduce artifacts, since toxicity to the macrophages would also prevent mycobacterial growth. From the synthesized derivatives, **compound 3a** had activity against intracellular *M. tuberculosis* and it had excellent potency of <10 mM. Interestingly, the activity against intracellular bacteria was far greater than that against aerobically cultured organisms.[7]



Compound 3a

b. Sudhakar Podha *et al.*, 2022, synthesized a new series of benzothiazole derivatives which were evaluated for their *in-vitro* antitubercular activity. The anti-tubercular activity on *Mycobacterium tuberculosis* H37Rv strain (ATCC27294) by Micro plate alamar blue assay method. Total six compounds were screened for antitubercular activity, out of which three compounds found to have IC_{90} at 5.3, 3.386 and 1.724 µg/mL respectively. From the synthesized derivatives, **compound 3b** shows good activity against tuberculosis.[8]

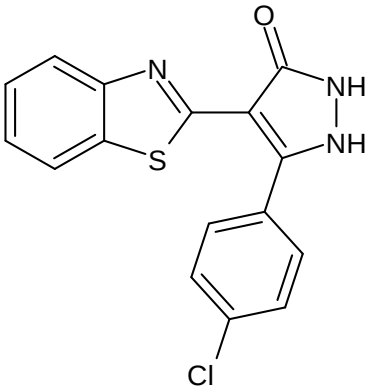


Compound 3b

4. Antimicrobial activity

a. Galal H. Elgemeie *et al.*, 2022, synthesized a new series of benzothiazole derivatives which were evaluated for their *in-vitro* antimicrobial activity. The new synthesized derivatives were tested *in-vitro* to evaluate antibacterial activities against Gram-negative and Gram-positive bacteria, *K. pneumonia* and *P. aeruginosa*, as an example for Gram-negative bacteria, as well as *S. aureus*

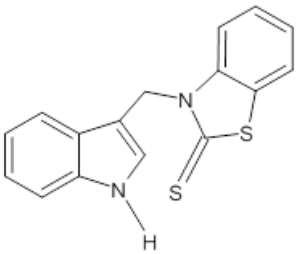
and *S. mutans* for Gram-positive bacteria. The antimicrobial activity of synthesized derivatives was determined using agar well diffusion method by targeting dihydropteroate synthase (DHPS). Eighteen new benzothiazole derivatives were synthesized and tested for their antimicrobial activity against six microbial strains. From the synthesized derivatives, **compound 4a** exhibited superior activity against the *S. aureus* strain with an MIC value of 0.025 mM among all tested derivatives, outperforming both standard drugs, ampicillin and sulfadiazine, as well as having very good activity against *S. mutans* and *K. pneumonia* with MIC values of 0.203 and 0.813 mM, respectively.[9]



Compound 4a

5. Antioxidant activity

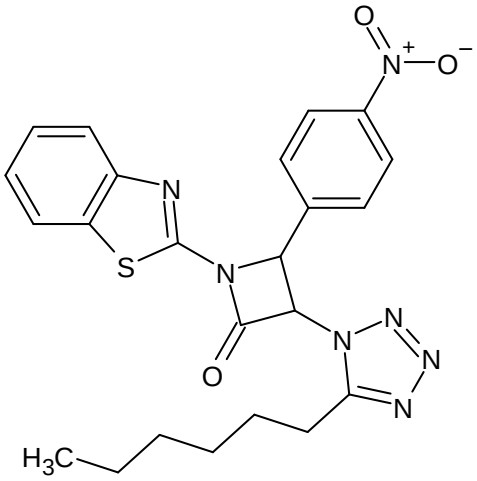
a. Beata Jasiewicz *et al.*, 2023, synthesized a new series of benzothiazole derivatives which were evaluated for their antioxidant activity. The synthesized derivatives were assayed *in-vitro* to assess their antioxidant profiles by means of the 2,2-diphenylpicrylhydrazyl (DPPH), Ferric Reducing Antioxidant Power Assay (FRAP) assays and also by Ferrous Ions (Fe^{2+}) chelating activity. In general, it can be stated that the substitution of the benzimidazole nucleus with benzothiazole has led to a reduction in antioxidant profile, with the exception of compound i.e, indole-benzothiazole-2thione. For antioxidant and cytoprotective properties, data were plotted as the mean value ± standard deviation (SD) of the results of three independent experiments and the statistical significance was defined as $p < 0.05$ss. From the synthesized derivatives, **compound 5a** shows effective antioxidant activity.[10]



Compound 5a

6. Antibacterial activity

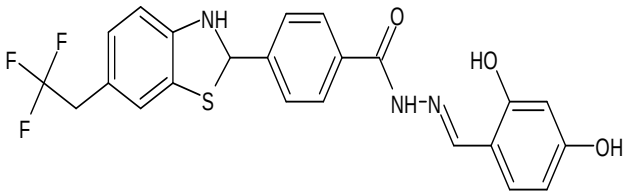
a. Dhurgham Qasim Shaheed *et al.*, 2022, synthesized a new series of benzothiazole derivatives which were evaluated for their antibacterial activity. The synthesize new tetrazole-β-lactams have potential application in antibacterial, antifungal activity etc. Mueller Hinton Agar (MHA) was used to measure antibacterial activity. Each sample was diluted by being dissolved in 1.0mL of dimethyl sulfoxide (DMSO), which was used as the bioassay's negative control, at a concentration of 100g/mL. From the synthesized derivatives, **compound 6a** had good action (MIC values 85-80 g/mL) against the tested bacteria *S. aureus* and *E. coli* when compared to the control drug ampicillin.[11]



Compound 6a

7. Anti-diabetic Activity

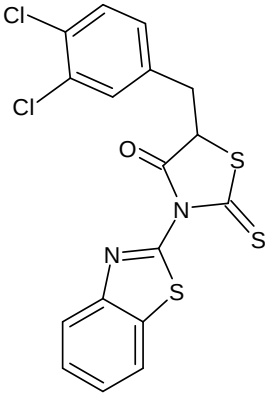
a. Pankaj S. Patil *et al.*, 2023, synthesized a new series of benzothiazole derivatives which were evaluated for their *in-vitro* antidiabetic activity. The synthesized derivatives were evaluated for *in-vitro* antidiabetic potential by employing *in-vitro* α-glucosidase inhibitory assay. First dissolve 0.5 mg of protein in 10 ml of ethanol therefore; a 0.1 M phosphate service was prepared in some other vessel and 15 mg of the substrate added to a 100 ml of ethanol to prepare 5mm of the substrate shape (p-nitrophenyl-α-D-glucopyranoside). Then upload 5 ml of ethanol to the tube, incubated for 30mins and measure absorbance at 400 nm and acarbose turned into used as the standard. From the synthesized derivatives, **compound 7a** shows significant anti-diabetic activity.[12]



Compound 7a

b. Mahendra Gowdru Srinivasa *et al.*, 2021, synthesized a new series of benzothiazole derivatives which were evaluated for their *in-vitro* antidiabetic

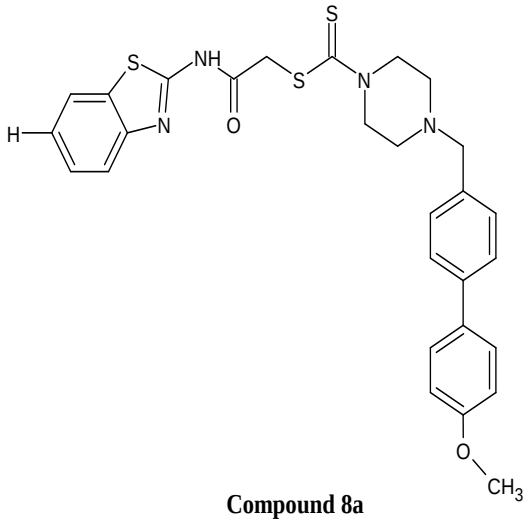
activity. The title compounds benzothiazole-rhodanine derivatives, were prepared by Knoevenagel condensation. All the newly synthesized derivatives were evaluated for *in-vitro* antidiabetic potential by employing α-amylase and α-glucosidase inhibitory assay methods. Acarbose was used as standard. All the compounds were tested at a concentration range of 10-50µg/ml. From the synthesized derivatives, **compound 7b** showed very good inhibitory efficacy in comparison to the standard acarbose in the α-amylase assay.[13]



Compound 7b

8. Antifungal activity

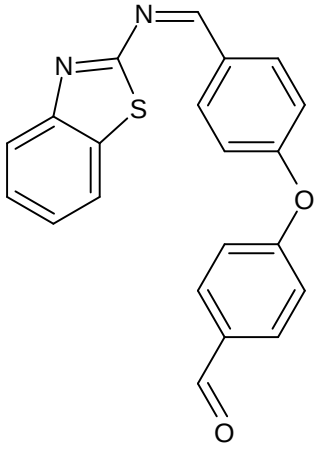
a. Derya Osmaniye *et al.*, 2022, synthesized a new series of benzothiazole derivatives which were evaluated for *in-vitro* antifungal activity. The synthesized derivatives were screened at between 1µg/mL–1.95µg/mL concentrations using various *Candida* strains including *C. albicans* (ATCC 90030), *C. glabrata* (ATCC 90030) *C. krusei* (ATCC 6258) and *C. parapsilopsis* (ATCC 22019). Ketoconazole and fluconazole were used as reference drugs. The minimal inhibitory concentration (MIC) values of the compounds range between 100-800 µg/ml. The antifungal activity potential of the synthesized compound against four fungus strains at various concentrations (800, 400, 200, 100, 50, 25, 12.5, 6.25, 3.75, 1.875 µg/ml) was evaluated. From the synthesized derivatives, **compound 8a** showed antifungal activity against *C. albicans* (800µg/ml*) and C. krusei* with a MIC of 100µg/ml.[14]



Compound 8a

9. Anti-inflammatory activity

a. Arun K Mishra *et al.*, 2023, synthesized a new series of benzothiazole derivatives which were evaluated by using the carrageenan-induced rat paw edema method, the newly synthesized benzo[d]thiazol-2-amine derivatives were assessed for their ability to reduce inflammation in experimental rats. There were fifteen groups of six animals each (n=6). For comparison, Indomethacin (10 mg/kg b.w) was used as the reference drug especially. Acute inflammation was induced by injecting the aqueous suspension of carrageenan (1%, w/v, 0.1 ml) in the right hind paw in the sub plantar region of each rat, after 1h of oral administration of the benzothiazole derivatives and Indomethacin to the test groups and standard drug treatment group, respectively. The paw volume was calculated plethysmometrically at 0, 60, 120, 180 and 240m after the injection of carrageenan. From the synthesized derivatives, compound 9a showed promising anti-inflammatory effect.[15]



Compound 9a

CONCLUSION

Benzothiazoles highlights their synthetic methods and diverse biological functions in the medicinal field. Benzothiazole and its derivatives exhibits a wide range of biological activities, including antitumor, anthelmintic, antitubercular, antimicrobial, antibacterial, antidiabetic, antioxidant, anti-inflammatory, antifungal, etc. Benzothiazole derivatives have become an attractive area of research for identifying novel lead compound due to their intrinsic variety of activities. There is an immense scope of this propitious scaffold because of its different molecular targets. The information provided in this review can be useful to further explore this moiety in order to investigate its biological potential and for further development of pharmacologically useful therapeutic agents.

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