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Recent Advances of Potential Benzothiazole Derivatives as Bioactive Agents: A Critical Review

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Abstract:

Because of their wide spectrum of pharmacological properties, benzothiazole derivatives have attracted a lot of attention in recent years for study and development. It has been discovered that substances based on benzothiazoles are useful in the treatment of a number of illnesses, such as cancer, microbial infections, and cardiovascular conditions. Research on the synthesis of derivatives of benzothiazole has been ongoing, and more synthetic techniques have been devised to get these molecules. the creation of something new. Improved biological characteristics and specificity of novel scaffolds have been made possible through the use of synthetic methodologies and improvements to existing technologies. Numerous biological actions, such as anticancer, HIV–I protease inhibition, antimicrobial and antiarteriosclerosis properties, have been demonstrated by benzothiazole derivatives. Research on the pharmacological characteristics of benzothiazole derivatives is still an intriguing field with the possibility of finding novel medications and treatments. The current overview of benzothiazole and its derivatives gives a thorough rundown of their biological activity and production. In addition to being a helpful resource for scientists engaged in synthetic chemistry and drug discovery, this review is anticipated to stimulate additional study and creation of benzothiazole-based molecules with improved pharmacological characteristics

1. Introduction:

Because of their many physiological roles, heterocyclic molecules like benzothiazole are particularly important in medicinal chemistry and drug discovery [Ingle, et al., 2012]. The possible biological actions of benzothiazole and its derivatives have been the subject of much research. The Benzothiazole derivatives, especially 2-aminobenzothiazoles, were studied in the 1950s for their potential muscle relaxant effects. Since then, a variety of pharmacological effects, such as those that are analgesic, anticancer, anti-inflammatory, anticonvulsant, antibacterial, anthelmintic, antiviral and antioxidant have been discovered in benzothiazole analogues [Khare, et al., 2019 & Pathak, et al., 2020].

Benzothiazole is a form of heterocycle that has sulfur in it. It is composed of a thiazole ring fused to a benzene ring. Initially found in a range of marine and terrestrial natural substances, the

benzothiazole ring system is known for its potent pharmacological and biological activities. It is now widely used as an imaging reagent, fluorescent material, electroluminescent device, antioxidant, vulcanization accelerator, anti-inflammatory, and plant growth regulator [Carrolla, et al., 2000, Gunawardhan, et al., 1988, Noel, et al., 2013 & Prajapati, et al., 2014]. Particularly, benzothiazole is an important medicinal chemistry compound with a broad range of biological activities [Kok, et al., 2008, Heo, et al., 2006, Alaimo, et al., 1978, Singh, et al., 2014, Aleta, et al., 2004, Das, et al., 2003 & Su, et al., 2006], including anti-tumor [Sreenivasa, et al., 2009, Hutchinson, et al., 2002, Bradshaw, et al., 2004 & Yoshida, et al., 2005], anti-viral [Vicini, et al., 2003, Nagarajan, et al., 2003], anti-oxidant [Cressier, et al., 2009], anti-inflammatory [Dogruer, et al., 1998, EL-Sherbeny, et al., 2000], anti-glutamate and anti-parkinsonism [Jimonet, et al., 1999], anticonvulsant [Siddiqui, et al., 2009], muscle relaxant activities [Rajeeva, et al., 2009], anti-tuberculosis [Aleta, et al., 2004, Das, et al., 2003], anti-diabetic [Su, et al., 2006], and anti-cancer [Kok, et al., 2008, Heo, et al., 2006], among many others. As a result, the synthesis of benzothiazoles is very desirable due to their strong biological activity and high therapeutic potential. Benzothiazole analogues can be synthesized using a variety of techniques. A popular method is the condensation process [Danzeisen, et al., Mylari, et al., 1991], which forms benzothiazole derivatives by reacting esters, nitriles, carboxylic acids, acyl chloride, and o-amino thiophenols with substituted aldehydes. The cyclization of o-halothioformanilide by Pd/Cu/Mn/chloranil is another technique that is frequently used [Asif, et al., 2021, Naresh, et al., 2023].

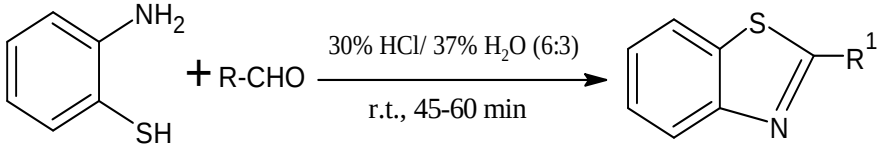
2. Various Methods for Preparation of Benzothiazole and Its Derivatives:

"Figure 1-3" displays various approaches for the synthesis of benzothiazole and its analogs. The condensation of aldehydes with 2-aminothiophenol is a straightforward and effective approach for synthesizing benzothiazole heterocyclic compounds **(Scheme 1)**. H_2O_2/HCl is used to catalyze the process, which lasts for one hour at room temperature. A wide variety of benzothiazole analogs can be synthesized with good yields (85–94%) by using electron-donating substituents and electron-withdrawing aldehydes. One benefit of this approach is its one-pot reaction, which reduces the number of steps required to synthesis benzothiazoles. Additionally, the products separate easily, and the reaction time is not excessively long [Lihumis, et al., 2022] with different substituents at positions 4, 5, and 6, substituted 2-mercaptobenzothiazoles are synthesized in **(Scheme 2)**. One benefit of this procedure is that it doesn't involve using any dangerous reagents [Sharma, et al., 2016]. In ambient settings, 2-mercaptoaniline is treated with an amine molecule in the presence of iodine to initiate the reaction that yields benzothiazole **(Scheme 3)**. Iodine's involvement in the process implies that it functions as a catalyst or oxidizing agent, converting the amine and 2-mercaptoaniline into benzothiazoles [Skok, et al., 2020].

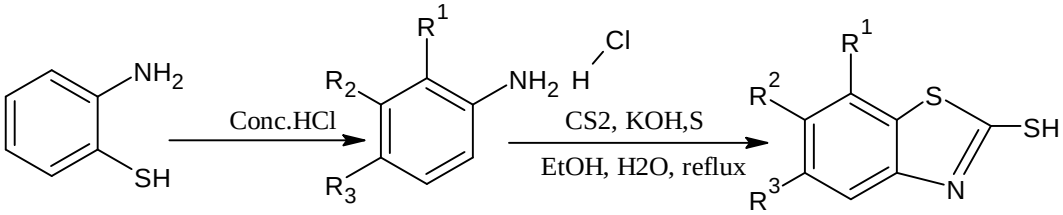
By exposing the reaction mixture to microwave radiation, when a basic, like potassium carbonate (K2CO3), is present, the Suzuki–Miyaura coupling process converts 2-chlorothiazole into the intended product. PhB (OH)2, benzene boronic acid, and Pd (PPh3)4 were the catalytic and reactant species used in the synthesis. **(Scheme 4)**. It demonstrated exceptional regioselectivity.

The reaction's dependability and efficiency are indicated by its excellent regioselectivity [Zhilitskaya, et al., 2021].

Using microwave irradiation and P4S10 as a catalyst, a complete condensation process utilizing 2-aminothiophenol and olefinic chemicals in a solvent-free environment was able to synthesize benzothiazoles with 2-substitution **(Scheme 5)**. This is a very efficient procedure that takes about 3-5 minutes to complete. The quick reaction kinetics were facilitated by the use of solvent-free conditions and microwave irradiation. Its efficacy was further demonstrated by the reaction of the targeted compounds in high yields [Kumar, et al., 2020].

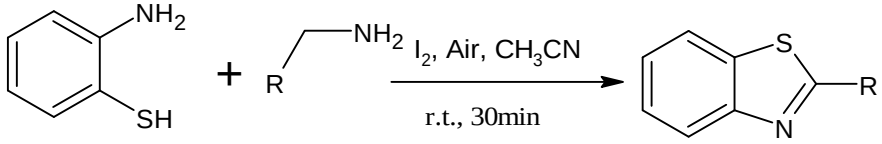


Scheme 1



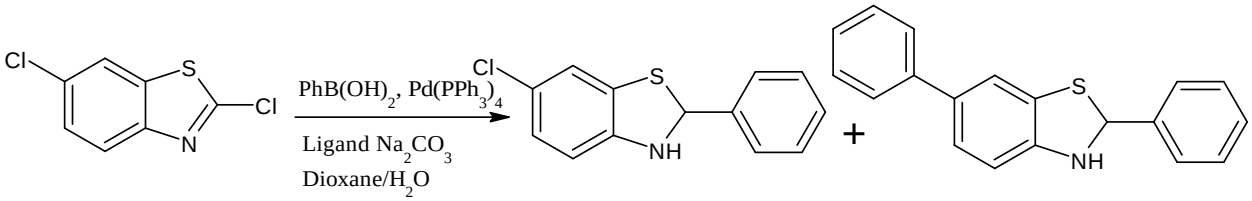
R1-CH3, R2-H, R3-H

Scheme 2

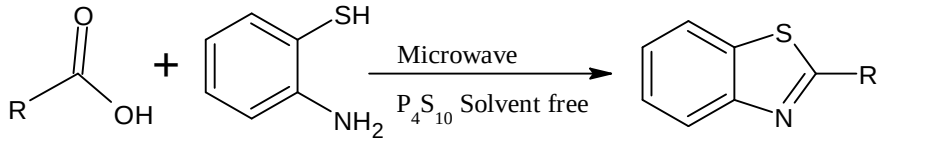


R= Ph, 4-OCH_3-Ph,
3 4-Cl-Ph, 4-Cl-Ph,
4-F-Cl, 4-CH_3-Ph,
4-OCF_3-Ph

Scheme 3



Scheme 4

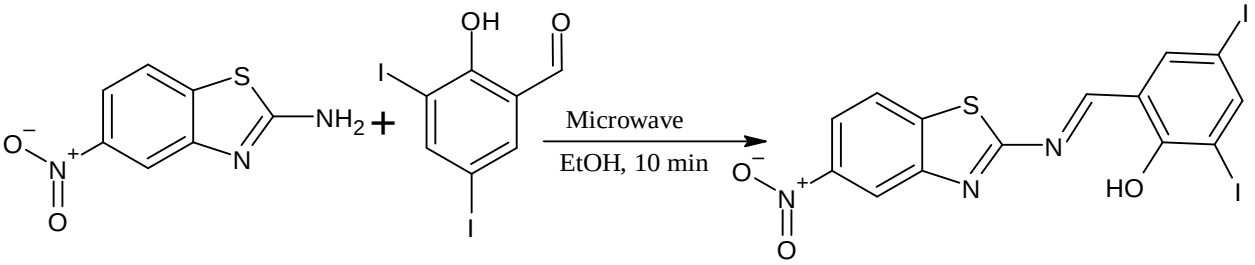


Fatty acid 2-amino thiophenol 2-substituted benzothiazole

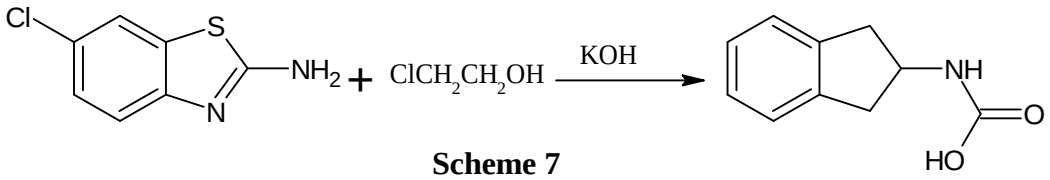
Scheme 5

Figure 1. *Schemes 1, 2, 3, 4, and 5*

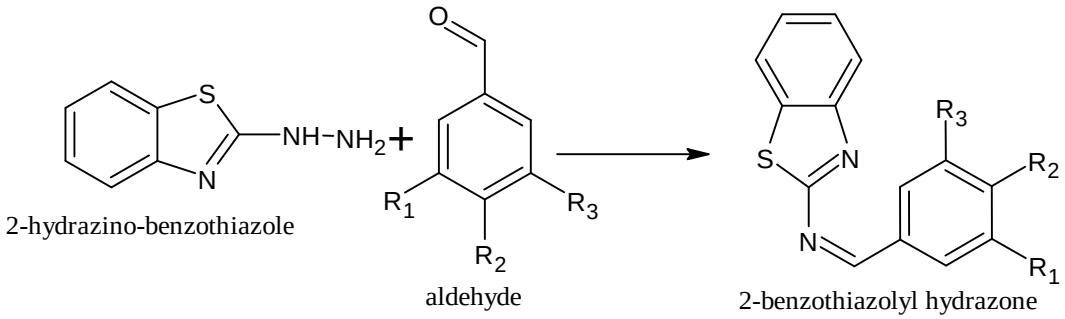
After 8–10 minutes under mild reaction conditions at ambient temperature, the microwave assisted synthesis of Schiff's base derivative from 2- amino-6-nitrobenzothiazole and 3,5-diiodosalicylaldehyde produced a 76–80% yield **(Scheme 6)** [El-Sharief, et al., 2004]. The temperature was maintained between 10 and 100 °C by progressively adding a mixture of bromine in acetic acid while shaking the mixture made up of separate solutions of KSCN and p-chloroaniline in acetic acid that had been chilled and combined [Evindar, et al., 2003]. 6-Chloro-2-aminoacetate benzothiazole was produced by reacting the filtered product with chloroethanol **(Scheme 7)**.



Scheme 6



Scheme 7



2-hydrazino-benzothiazole aldehyde 2-benzothiazolyl hydrazone

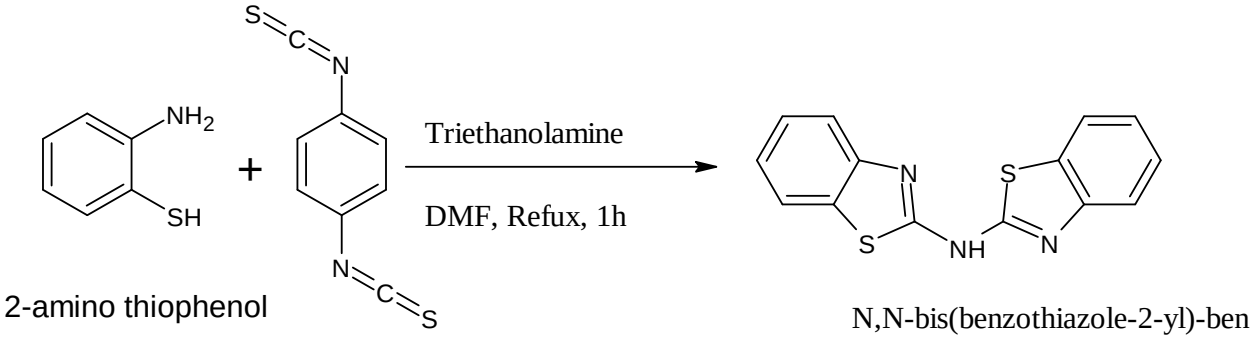
Scheme 8

Figure 2. *Schemes 6, 7 and 8*

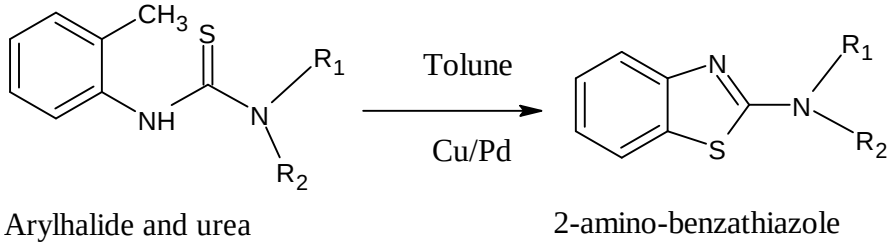
2-hydrazino-benzothiazole reacts with aldehydes to produce antimalarial compounds like benzothiazolyl hydrazones **(Scheme 8)**. It is thought that this particular structural motif interacts with the target molecules involved in the malarial infection process, thereby impairing their functionality and preventing the parasites from growing. N, N-bis (benzothiazole-2-yl) was generated by a condensation reaction between 1,4-phenylene-di-isothiocyanate and 2-aminothiophenol in the presence of triethanolamine and N, N-dimethylformamide as the reaction medium. **Scheme 9**: Benzene-1,4-diamine [Ugwu, et al., 2018].

Using a C–S bond formation strategy with intramolecular bond formation, 2-aminobenzoylhydrazines are synthesized by activating the thiourea moiety within the molecule, resulting in the development of a cyclic intermediate **(Scheme 10)**. Thereafter, an aryl cross-coupling process is catalyzed by palladium. The intended 2-aminobenzoylhydrazine product is generated in this reaction by coupling an aryl halide with the cyclic intermediate created in the preceding step [Osmaniy, et al., 2018].

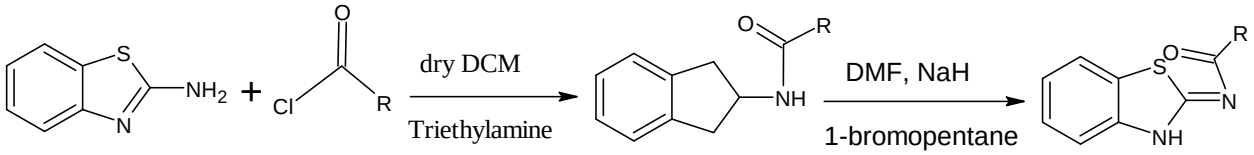
An intermediate is created when different carboxylic acids react with 3-pentylbenzothiazole. Strong anti-inflammatory characteristics are displayed by N-(3-pentyl benzothiazol-2(3H)-ylidene) carboxamides [Gupta, et al., 2022], which are formed when the carboxylic acid interacts with the amino group of 3-pentyl benzothiazole **(Scheme 11)**. During the synthesis, acyl hydrazides made from 2-mercapto benzothiazoles substituted with five distinct groups are combined with p-hetaryl substituted benzaldehydes. Hydrazones of benzothiazolyl acyl compounds are created as a result of the reaction between acyl hydrazides and benzaldehydes (**Scheme 12**) [Morsy, et al., 2020].



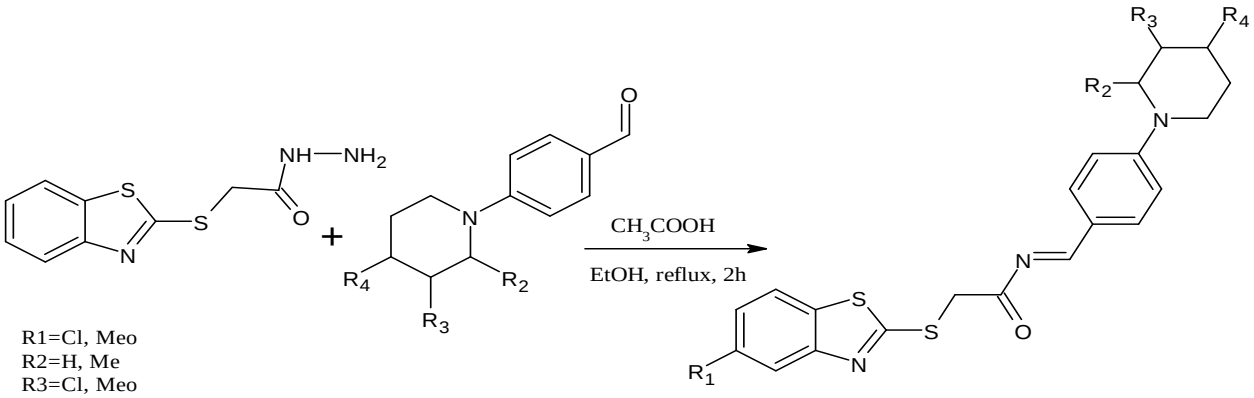
Scheme 9



Scheme 10



Scheme 11



Scheme 12

Figure 3. *Schemes 9, 10, 11 and 12*

3. The following list of benzothiazole compounds and their various pharmacological activities:

Figure 4 lists a few benzothiazole-containing medications that are on the market [Lee, et al., 2007].

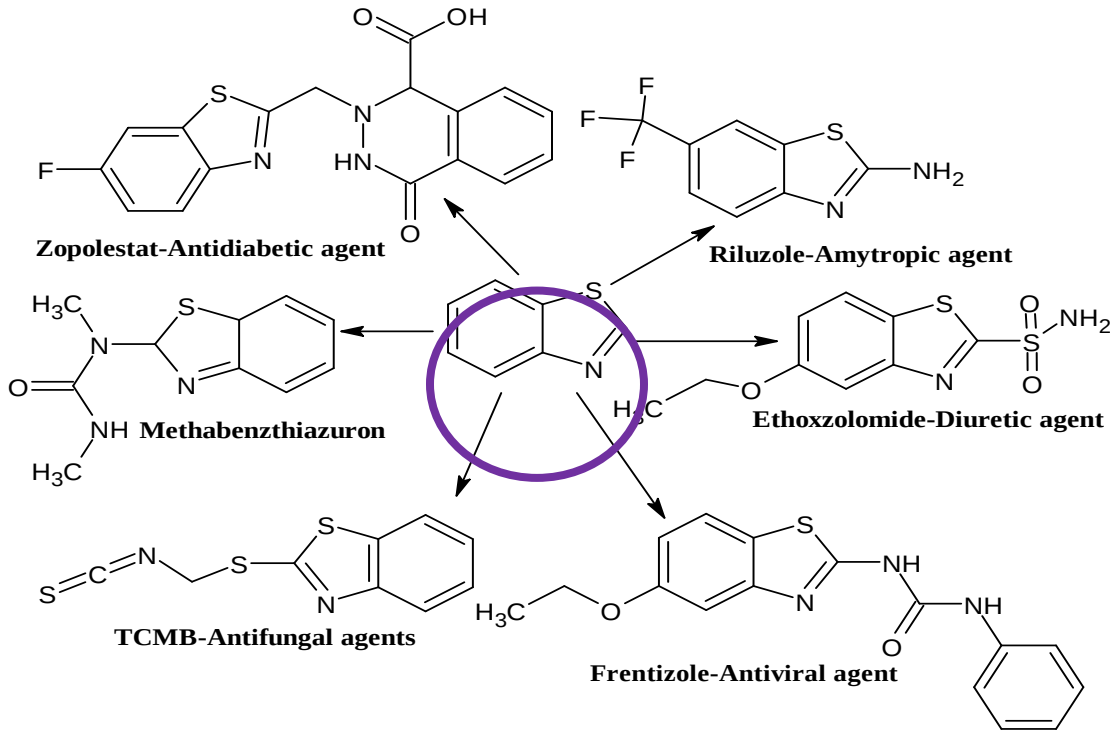
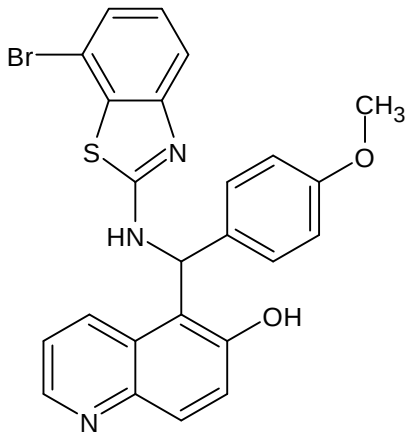


Figure 4. *Benzothiazole ring containing marketed drugs*

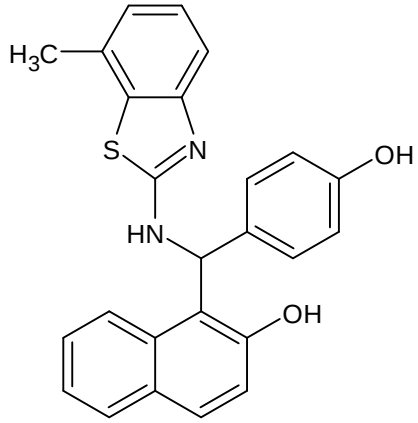
3.1. Antibacterial activity:

Compound 1 was synthesized and tested against S. aureus, B. subtilis and E. coli to determine its antimicrobial activity [Maddili, et al., 2018]. It demonstrated antibacterial properties and mild antifungal properties against Candida albicans and Aspergillus niger. Compound 1 was shown to possess the strongest antibacterial properties, and as a result, it outperformed all other compounds against all tested bacterial species. E. coli dihydro-orotase was investigated and antimicrobial activities were noted in order to better evaluate the docking data obtained for antibiotic characteristics. A vast H-bonding network was generated by the basic ligand HDDP, HIS254, LEU222, ALA266, ARG20, HIS139 and ASN44. When phenol grouping compound 1 **(Figure 5)** enters the cavity containing HDDP, one H-bond forms along with the branch chains of LEU222 [Thakkar, et al., 2017]. Similarly, with Compound 1, an H-bond was created between the oxygen from the methoxy group and the inner chain of ALA266. Furthermore, the naphthalene ring creates hydrophobic interactions with THR143, GLU141, and PRO105 in close proximity to the catalytic E. coli dihydro-orotase cavity. Compound 2 **(Figure 5)**, on the other hand, was only marginally effective against the tested types of bacteria [Rice, et al., 2016].



5-{[(7-bromo-1,3-benzothiazol-2-yl)amino] (4-methoxyphenyl)methyl}quinolin-6-ol

Compound 1



1-{(4-hydroxyphenyl)[(7-methyl-1,3-benzothiazol-2-yl) amino]methyl}naphthalen-2-ol

Compound 2

Figure 5. *Structures of Compound 1 and 2*

3.2. Antifungal activity

Several 4-(20-substituted benzothiazoles) and several 2-substituted benzothiazoles (Compounds 3, 4) 5-mercapto-3 (replaced)Compound 5 (analogues of -1,2,4-triazole) was produced and tested for antibacterial activity against S. aureus and E. coli, as well as antifungal activity against C. albicans and A. niger [Truong, et al., 2013, Khokra, et al., 2011 & Nagaraj, et al., 2011]. Most medications showed positive results for both activities. The following lists compounds with antifungal activity (3, 4) and antibacterial activity (1, 2) **(Figure 6)**.

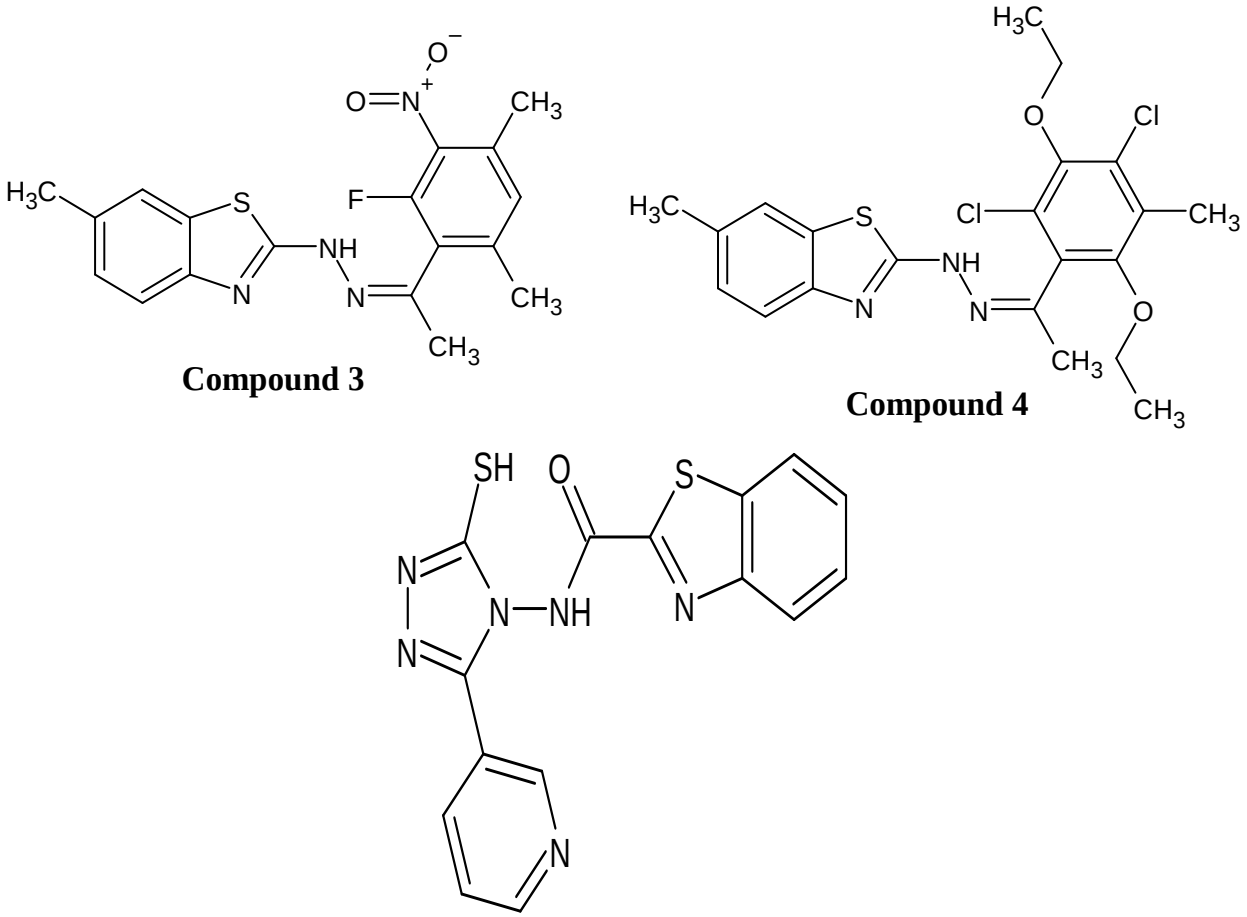
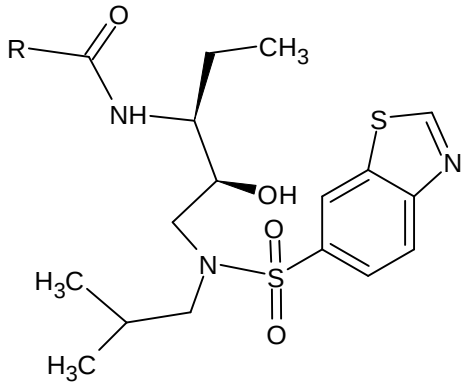


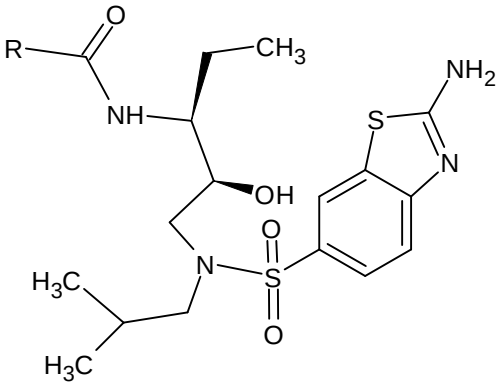
Figure 6. *Structures of compound 3, 4 and 5*

3.3. Antiviral activity

Compounds 6 and 7 **(Figure 7)**, which are novel benzothiazole sulphonamides, were found to inhibit HIV-1 protease with IC50 value of 2-3 nM. It was demonstrated that the carbamate counterparts are stronger HIV-1 protease inhibitors and antiviral medicines. The evaluation focused on the novel substituted 2-pyrimidylbenzothiazoles' antiviral efficacy against either amino molecule, namely its sulphonamide moiety, located at the C_2 of the pyrimidine ring. Several ylidene benzothiazole derivatives were combined with guanidine or N-aryl sulfonated guanidine via the Michael addition technique to create the new ring structure [Geller, et al., 2012].



Compound 6a



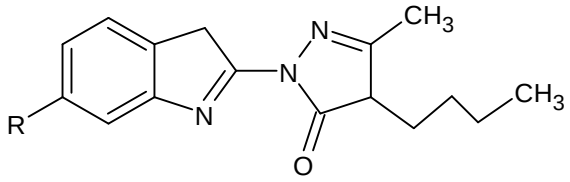
Compound 6b

R=3-pyridylmethoxy
5-thiazolymethoxy
tetrahydrofuranyloxy

Figure 7. *Structures of compounds 6a and 6b*

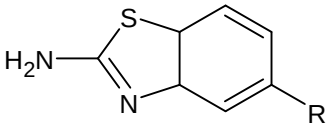
3.4. Anti-inflammatory activity

In order to treat inflammation, a number of novel benzothiazoles were produced, including 2-(40-butyl-30, 50-dimethyl pyrazol-10-yl) with 4-butyl-1-(60-susbtituted-20-benzothiazolyl) benzothiazoles with a 6-substitution. It was discovered that compound 7 **(Figure 8)**, had a strong anti-inflammatory impact [Naresh, et al., 2013, Azzam, et al., 2020, Kumar, et al., 2016 & Kumar, et al., 2014]. Benzothiazole-based anti-inflammatory medications were created, and compound 8 **(Figure 8)**, a novel 2-amino-benzothiazole derivative, was evaluated for its potential to lessen inflammation. When an electron-withdrawing group, such as -OCH_3-NO2, and -Cl_2, was substituted for the 2-amino benzothiazole at positions 4 or 5, it was found that the anti-inflammatory action enhanced dramatically [Venkatesh, et al., 2009].



Compound 7

R=H, F, Cl, CH_3, OCH_3



Compound 8

R-H, Cl

Figure 8. *Structures of compounds 7 and 8*

3.5. Antitubercular activity

Compound 9 showed notable in vitro antitubercular efficacy against Mycobacterium tuberculosis. The antitubercular activity of 6-nitro-2-[4-formyl-3-(phenyl substituted) pyrazolyl] benzothiazoles against the H37RV strain of Mycobacterium TB was produced and examined. Benzothiazoles (compound, 10) showed the most promising activity in antitubercular screening [Sathe, et al., 2010, Wang, et al., 2011]. The antimycobacterial action of adamantanyl benzothiazole derivatives was demonstrated in an amended patent. Among these, compound 11 was shown to be isoniazid-equivalent, with a MIC90 of 0.03 g/ml against H37Rv. With a minimum inhibitory concentration

(MIC) of 224 nM, compound 12 in the series has shown effective growth inhibition of Mycobacterium tuberculosis [Guillemont, et al., 2014]. The MIC of compound 13, nitrofuranyl-benzothiazole hydrazones, as an antitubercular medication, was greater than 16 g/ml [Pellet, et al., 2012] **(Figure 9)**.

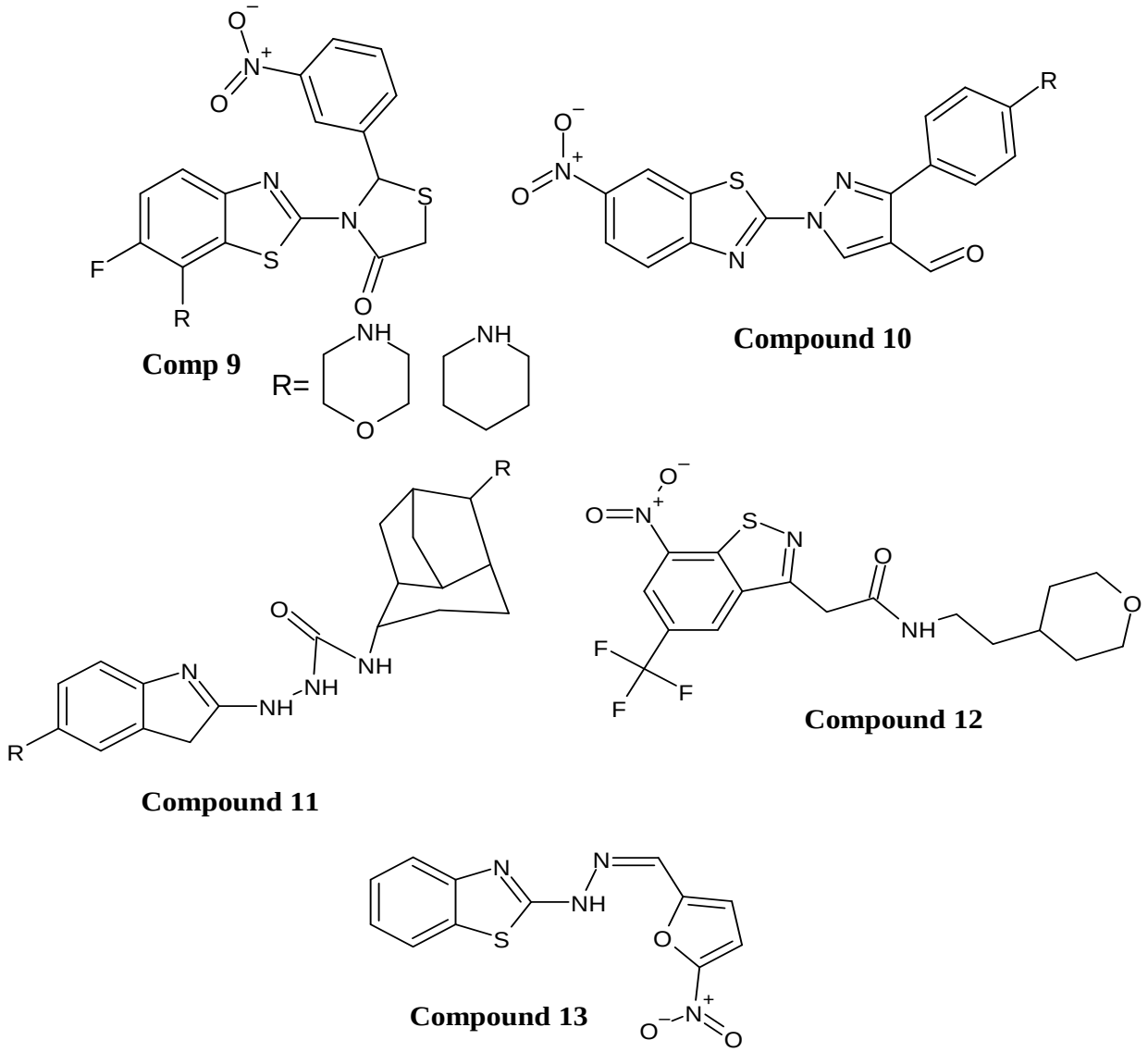
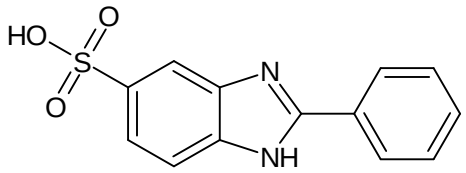


Figure 9. *Structures of compounds 9, 10, 11, 12 and 13*

3.6.Anti-oxidant activity

The anti-oxidant and anticancer properties of indole-hydrazones, benzofuran hydrazones, benzimidalzolidrazones, and aryl benzimidazoles, including benzothiazole analogues, were synthesized and assessed [Djuidje, et al., 2022]. These compounds demonstrated potent antioxidant properties along with advantageous photoprotective or anticancer activity profiles. Compound 14 **(Figure 10)** in particular showed outstanding in vitro antioxidant activity in DPPH and FRAP experiments, finally demonstrating its IC_{50} similar to 9.7 μM against human melanoma cells. It also showed IC50 values of 2 g/ml against the examined dermatophytes.

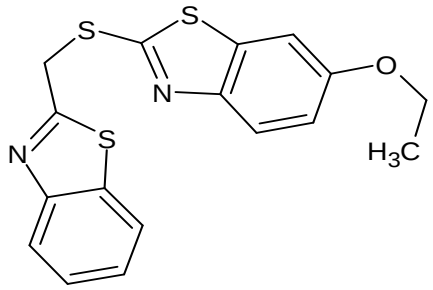


Compound 14

Figure 10. *Structures of compound 14*

3.7.Antidiabetic activity

The utilization of the benzothiazole core in the future may result in the creation of safe antidiabetic medications, as benzothiazole derivatives have antidiabetic properties. Adenosine-50-monophosphate activated protein kinase (AMPK) is one of the initial targets of the newest class of anti-diabetic drugs. Benzoic acid (PT-1) 2-Chloro-5-((Z)-((E)-((4, 5-dimethyl-2-nitrophenyl) furan-2-yl) methylene)-4-oxothiazolidin-2-ylidene) lowers AMPK enzyme auto-inhibition [Meltzer, et al., 2013]. In L6 myocytes, a number of benzothiazoles with comparable structures sped up the absorption of glucose using an AMPK-dependent mechanism. 2-(Benzo[d]thiazol-2-ylmethylthio)-6-ethoxybenzo[d]thiazol, compound 15 had demonstrated a rapid rate of glucose absorption. Benzothiazole is a heterocyclic molecule with a broad range of biological functions [Bhagdev, et al., 2021]. Because of the rapidly increasing scientific interest in creating effective, safe, and medically useful antidiabetic medicines, a significant amount of benzothiazole derivatives have been synthesized [Usman, et al., 2019] **(Figure 11)**.



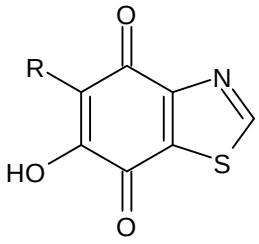
Compound 15

Figure 11. *Structures of compound 15*

3.8.Antimalarial activity

In subtropical and tropical regions of the world, malaria is a major health concern for both travelers and residents of these endemic areas. According to estimates, at least 300 million people worldwide suffer with malaria, and the illness claims the lives of 1-3 million people each year. Of the four kinds of malaria parasites, Plasmodium falciparum is the most virulent and possibly lethal. The most significant problem is that clinically utilized chemotherapeutic medicines like pyrimethamine, mefloquine, and chloroquine cause malaria parasites to become resistant. Consequently, there remains a demand for extremely effective and reasonably cheap antimalarials [Pudhom, et al., 2006]. When Friedman et al. examined 5-n-undecyl and 5-n-pentadecyl-6-hydroxy-4,7-dioxobenzothiazole against Plasmodium gallinaceum in chicks, they discovered that

compound 16 (Figure 12: compound 16) had prophylactic effectiveness at 120 mg/kg in this sporozoite-induced malarial [Seebacher, et al., 2004, Friedman, et al., 1973].



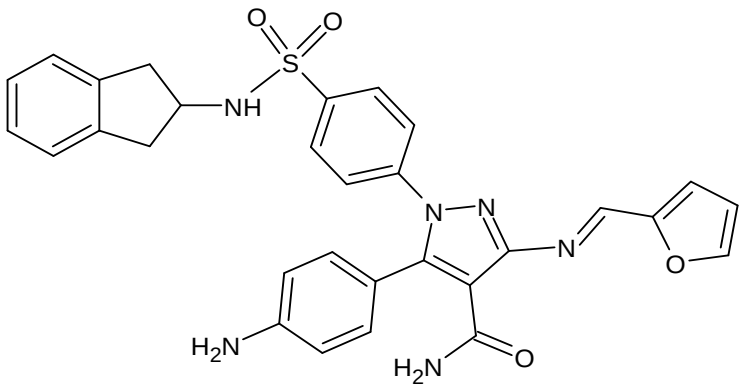
R=n-Undecyl

Compound 16

Figure 12. *Structures of compound 16*

3.9. Anthelmintic activity

In most of the poor world, helminth parasitism is still an unappreciated scourge of humanity. These parasites are present in up to 2 billion people, millions of whom are usually co-infected with hookworms, whipworms, filariae, roundworms, all of which can cause chronic, crippling morbidity [Geary, et al., 2010]. Even now, one of the key issues facing tropical public health is the successful treatment and eventual eradication of filariasis, despite significant advancements in the chemotherapy of parasitic infections. A class of benzothiazoles anthelmintics with strong activity against various helminth parasites have been discovered as a result of efforts to develop novel "structural leads" for helminthiasis chemotherapy [Abuzar, et al., 1986]. Sreenivasa et al. showed the anthelmintic action of fluor benzothiazole, which includes derivatives of sulfonamido pyrazole, against earthworms, Perituma posthuma. Comparing Compounds 17–23 (Figure 13) to the reference medication albendazole1, [Sreenivasa, et al., 2009] considerable action was seen.



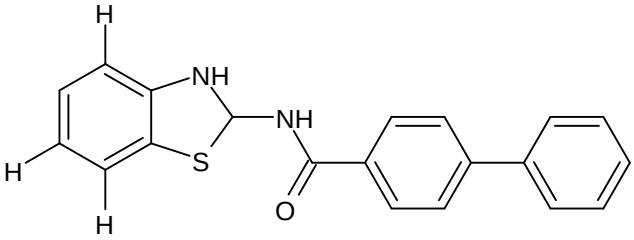
Compounds 17-23

17:R=p-nitro aniline
18:R=aniline
19:R=PABA
20:R=morpholine
21:R=piperazine
22:R=dimethylanine
23:R=diphenylamine

Figure 13. *Structures of compound 17-23*

3.10. Diuretic activity

Shaharyar and Ansari tested N-{(substituted)-1,3-benzothiazol-2-yl}-1,1-biphenyl-4-carboxamide derivatives (Figure 14: compound 24) for their in vivo diuretic efficacy. The synthesized compound's urine production was much higher than the control urine output (>300%), measuring 16.08 ± 0.650 ($p < 0.01$) [Yar, et al., 2009].

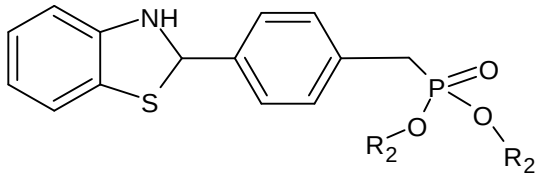


Compound 24

Figure 14. *Structures of compound 24*

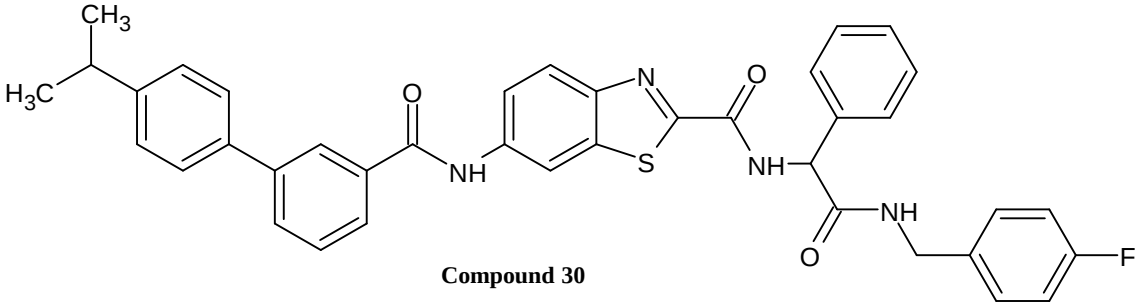
3.11. Developments in cardiovascular activity profile

Yoshino et al. assessed the coronary vasodilatory action of a series of 4-(benzothiazol-2-yl) benzyl phosphonic acid dialkyl ester derivatives in the isolated guinea pig heart using Langendorff's method (Figure 15: compounds 25–29). According to the results, diethyl derivative 25 had more potency than reference substances diltiazem hydrochloride or papaverine hydrochloride [Yoshino, et al., 1986]. A group of triamide derivatives with a BT core were assessed by Vu et al. to be strong inhibitors of microsomal triglyceride transfer protein (Figure 15: compound 30). The findings showed that compound 30 had a low systemic exposure [Vu, et al., 2009] and reduced plasma lipid, insulin and glucose levels at doses as low as 3 mg/kg.



25:R=H, R_2=Et
26:R=H, R_2=n-Pr
27:R=H, R_2=i-Pr
28:R=6-Me; R_2=Et
29:R=6-NHAc; R_2=Et

Compound 25-29



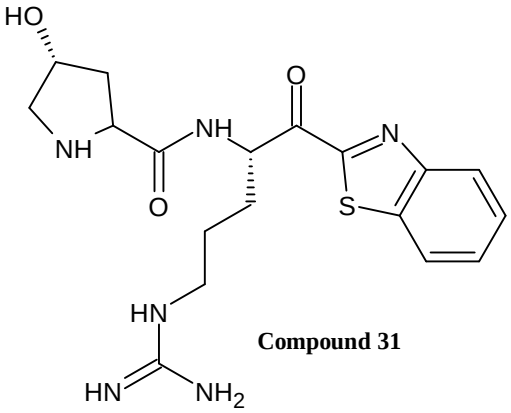
Compound 30

Figure 15: *Chemical composition of benzothiazole derivatives that are active coronary vasodilators (25-30)*

3.12. Antiasthmatic activity

Costanzo et al. investigated benzothiazole ketone as a strong, reversible, low molecular weight tryptase inhibitor. The findings demonstrated the strong tryptase inhibitory activity of transition-

state mimics with a Ki value of 10 nM that have a heterocyclic activated ketone group **(Figure 16: compound 31)** [Costanzo, et al., 2003, Laddha, et al., 2009].

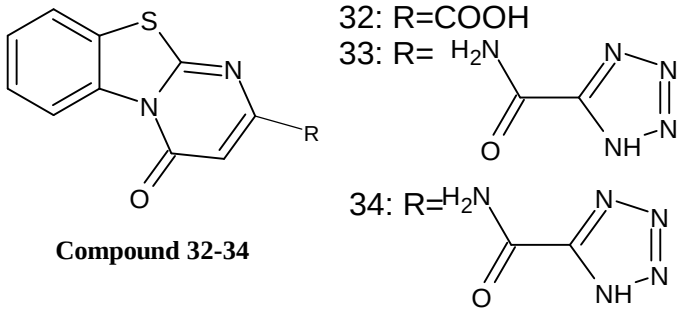


Compound 31

Figure 16. *Chemical structure of substituted benzothiazole ketone*

3.13. Antiallergic activity

2- or 3-carboxy-4H-pyrimido [2,1-b]-benzazol-4-ones were synthesized by Wade et al. (Figure 17: compounds 32–34). The rat passive cutaneous anaphylaxis test was used to evaluate these acidic compounds as possible antiallergic drugs. At the 2- or 3-position of the 4H-pyrimado, an acidic functionality [carboxylic acid, N-(1H-tetrazole-5-yl) carboxamide, or tetrazole] is incorporated [2,1-b]. The 4-one ring structure of benzazole has good antiallergenic properties [Wade, et al., 1983].

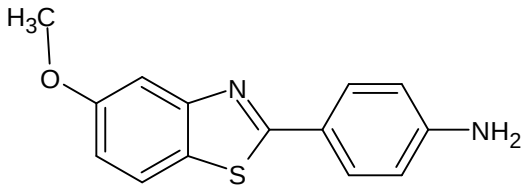


Compound 32-34

Figure 17. *Chemical structure of benzothiazole analogues*

3.14. Role in AD

The pathological characteristics of Alzheimer's disease comprise intraneuronal neurofibrillary tangles and the deposition of β-amyloid (Aβ) peptide into amyloid plaques in the extracellular brain parenchyma. which are brought on by aberrant tau protein phosphorylation151. Emission tomography serves as a forerunner for AD [Sharma, et al., 2009] in vivo imaging. Byeon et al. assessed the specific binding affinities of a few novel BT dimers and ferulic acid to Aβ fibrils. Compound 35 (Figure 18) has superior binding affinity towards Aβ fibrils [Chitra, et al., 2009, Majo, et al., 2003 & Byeon, et al., 2007].



Compound 35

Figure 18. *Chemical structure of benzothiazole analogues*

3.15. Anti-infective activity profile

In the past, anti-infective drug use has been attributed with saving more lives than any other field of medicine that has been found to date [100]. Multidrug resistance and the emergence of infectious diseases together continue to be significant and difficult issues for the treatment of infectious diseases [Sharma, et al., 2010]. Furthermore, immune-compromised patients—such as those with HIV—who are receiving anticancer treatments or organ transplants have more difficult treatment regimens for infectious infections [Chawla, et al., 2010].

4. **Statistical hypothesis of the Example this application:**

Let's consider a hypothetical example where we have a dataset consisting of the chemical structures of benzothiazole derivatives and their corresponding IC50 values (concentration at which 50% inhibition of a biological activity is observed) against a specific target enzyme. We want to develop a QSAR model to predict the IC50 values based on molecular descriptors derived from the chemical structures.

Table 1: Suppose we have a simplified dataset with the following hypothetical data

Comp ID	Mol Weight	LogP value	Hydrogen Bond Donors	Hydrogen Bond Acceptance	IC50(nM)
1	250	3.5	2	5	100
2	280	4.0	3	6	80
3	300	4.2	4	7	60
4	270	3.8	2	4	120

Let's use multiple linear regression (MLR) to build a QSAR model using the molecular descriptors (MW, LogP, Hydrogen Bond Donors, Hydrogen Bond Acceptors) as independent variables and IC50 as the dependent variable.

We'll perform the following steps:

Data Preparation: Split the dataset into independent variables (X) and the dependent variable (Y).

Model Training: Fit a multiple linear regression model to the training data.

Model Evaluation: Assess the performance of the model using appropriate metrics (e.g., R-squared, RMSE).

Prediction: Use the trained model to predict the IC50 values for new benzothiazole derivatives.

Let's perform these steps using Python and the **scikit-learn** library:

```
# Importing necessary libraries
import numpy as np
import pandas as pd
from sklearn.model_selection import train_test_split
from sklearn.linear_model import LinearRegression
from sklearn.metrics import mean_squared_error, r2_score
# Creating a DataFrame with the hypothetical data
data = {
   'MW': [250, 280, 300, 270],
   'LogP': [3.5, 4.0, 4.2, 3.8],
   'Hydrogen Bond Donors': [2, 3, 4, 2],
   'Hydrogen Bond Acceptors': [5, 6, 7, 4],
   'IC50': [100, 80, 60, 120]}
df = pd.DataFrame(data)
# Splitting the data into training and testing sets (80% training, 20% testing)
X = df[['MW', 'LogP', 'Hydrogen Bond Donors', 'Hydrogen Bond Acceptors']]
y = df['IC50']
X_train, X_test, y_train, y_test = train_test_split(X, y, test_size=0.2, random_state=42)
# Training the multiple linear regression model
model = LinearRegression()
model.fit(X_train, y_train)
# Model evaluation on the testing set
y_pred = model.predict (X_test)
rmse = np.sqrt(mean_squared_error (y_test, y_pred))
r2 = r2_score (y_test, y_pred)
print ("Root Mean Squared Error (RMSE):", rmse)
print ("R-squared (R2):", r2)
# Predicting IC50 for a new benzothiazole derivative
new data = np.array([[290, 4.1, 3, 5]])  # Example new molecular descriptors
predicted_ic50 = model. Predict (new data)
print ("Predicted IC50 for the new compound:", predicted_ic50)
```

Output: Root Mean Squared Error (RMSE): 11.389450079413169
R-squared (R2): 0.9056897979331738
Predicted IC50 for the new compound: [77.98166136]

Root Mean Squared Error (RMSE): The RMSE measures the average deviation of the predicted IC50 values from the actual values in the testing set. In this case, the RMSE is approximately 11.39, indicating that, on average, the model's predictions are off by around 11.39 units of IC50 concentration.

R-squared (R2): The R-squared value represents the proportion of variance in the IC50 values explained by the model. An R2 value close to 1 indicates that the model fits the data well. Here,

the R2 value is approximately 0.906, suggesting that the model explains about 90.57% of the variance in the IC50 values.

Predicted IC50 for the new compound: The model predicts an IC50 value of approximately 77.98 for the new benzothiazole derivative with the given molecular descriptors (Molecular Weight: 290, LogP: 4.1, Hydrogen Bond Donors: 3, Hydrogen Bond Acceptors: 5).

These results indicate that the multiple linear regression model performs well in predicting the bioactivity (IC50 values) of benzothiazole derivatives based on their molecular descriptors.

5. Conclusion:

Benzothiazoles have been the subject of contemporary study that emphasizes their various biological activities and synthesis routes. During synthesis, researchers have used a variety of methods, such as the use of biocatalysts to improve yields and reaction conditions. Numerous biological actions, including as antibacterial, anticancer, anti-inflammatory, antidepressant, and antidiabetic effects, are exhibited by the benzothiazole core. Because of the inherent diversity of activities in benzothiazole derivatives, this has made them an appealing research target for the discovery of new lead compounds. The discovery of the aldose reductase inhibitor Zopolrestat has made it possible to investigate the potential medical uses of benzothiazoles. Certain benzothiazole compounds have demonstrated activity that is either on par with or better than current conventional drugs, suggesting that they offer promise as therapeutic agents. This implies that compounds generated from benzothiazoles may be the basis of soon-to-be-marketed medicines.

According to the previously described research, BT is a flexible heterocyclic scaffold with great potential for the synthesis of novel compounds for the treatment of cancer, infectious diseases, and problems affecting the central nervous system and cardiovascular system. A new class of antimicrobials may be developed as a result of the BT compounds' broad spectrum antibacterial and antifungal action. The anti-inflammatory and anticancer properties of BT compounds have shown promise. The potential involvement of 2-(4-aminophenyl) benzothiazole derivatives in these therapies has been underlined by their strong antitumor activity. Therefore, BT scaffold has a wide spectrum of intriguing pharmacological actions in addition to its significance as a synthetic material. These novel BT derivatives' biological characteristics would provide a valuable matrix for the ongoing creation of more effective pharmaceuticals.

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