RESEARCH ARTICLE

Catalytic derivatization of 2-Aminobenzo[*d*]thiazole for observing antibacterial activity and *in silico* analysis

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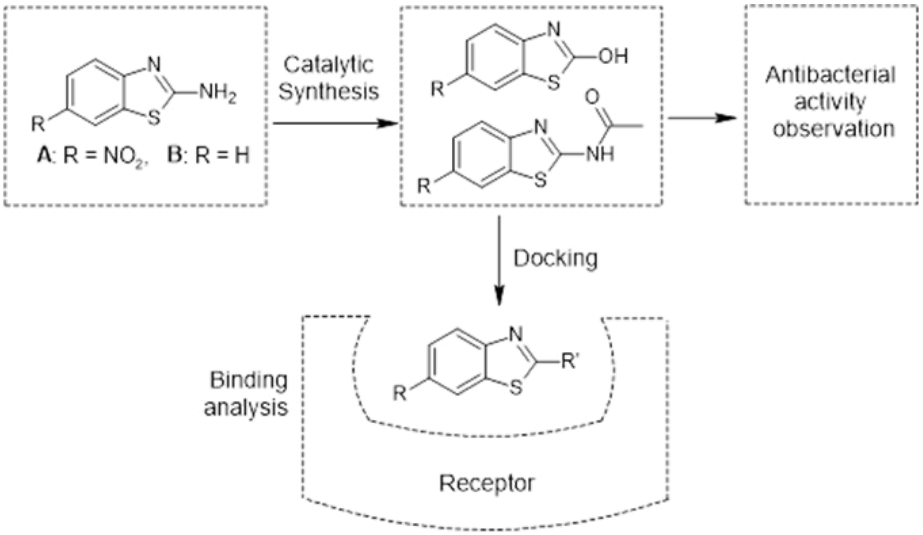

Highlights

- 2-Aminobenzo[*d*]thiazoles have been converted to acetanilides
- 2-hydroxybenzo[*d*]thiazoles have been synthesized from Aminobenzo[*d*]thiazoles by using Bentonite
- Synthesized acetanilides and the 2-hydroxy compounds were tested for antimicrobial potencies against both the gram-positive and gram-negative organisms
- An *in silico* study was done by using the Autodock Vina docking program

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Catalytic derivatization of 2-Aminobenzo[*d*]thiazole for observing antibacterial activity and *in silico* analysis

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Abstract: 2-Aminobenzo[*d*]thiazoles have been converted to corresponding acetanilides and 2-hydroxy compounds for observing antibacterial activities. The acetylation was done by direct use of acetic acid, whereas the corresponding 2-hydroxy derivative was synthesized following various reaction conditions with or without a catalyst for observing the associated yield and ease of the reaction. In this study, the reaction yield was found to be between 20% and 86%. The synthesized acetanilides and the 2-hydroxy compounds were screened for antibacterial activity against various common pathogenic gram-positive and gram-negative organisms. Encouraging antimicrobial potential was noted from these small molecules. Finally, the compounds were taken for *in silico* analysis to observe the possible orientations in the binding site of the alanine racemase enzyme of *Enterococcus faecalis.*

***Keywords*:** Benzothiazole; Acetanilide; Antibacterial; *In silico*; Docking

INTRODUCTION

Multidrug resistance is a global challenge bringing very strong threats to human life in the future. According to a report published by the Antimicrobial Resistance Collaborators, globally there were approximately 1.27 million deaths in 2019 simply due to multidrug-resistant bacterial infections (Collaborators, 2019). There have been predictions that if this current rate of antimicrobial resistance continues and no new effective medicines are introduced, there may result in as high as 10 million deaths worldwide in 2050 from these infections. Moreover, limited access to the required efficient antibacterial agents is keeping many bacterial infections untreated thereby increasing morbidity as well as mortality (de Kraker *et al.*, 2016). Suboptimal dosing is contributing to both the development and propagation of antimicrobial resistance (Ramanan *et al.*, 2016; Annie *et al.*, 2021; Afolami *et al.*, 2018).

Multidrug-resistant variants are rapidly developing in the case of commonly occurring pathogens like *Staphylococcus aureus*, *Escherichia coli, Salmonella*, *Shigella*, etc. (Afolami *et al.*, 2018; Reza *et al.*, 2019; Celso *et al.*, 2014; Doğruer *et al.*, 2012) mainly due to antibiotic abuse worldwide (Ramanan *et al.*, 2016; Annie *et al.*, 2021; Afolami *et al.*, 2018). These multidrug-resistant organisms are resulting in prolonged hospital stays and increased treatment failures, which are leading to increased healthcare costs. Thus worldwide many researchers are providing their utmost efforts for discovering better antimicrobial agents in terms of efficacy and safety (Celso *et al.*, 2014; Ghorab *et al.*, 2017). Even while considering the chemical classes of antibiotics, rapidly increasing antibacterial resistance has been reported against clinically significant antibacterials, like, beta-lactams, quinolones and macrolides (Rangappa *et al.*, 2015; Kruszewska *et al.*, 2004).

Heterocyclic ring containing small molecules play important roles in research in life science, especially medicinal chemistry and drug discovery. Among the various heterocyclic ring systems, the benzothiazole ring has drawn considerable attention from researchers. This ring is very important simply because of its heterocyclic structure, since it may provide derivatives capable of forming hydrogen bonds crucial for drug-receptor interactions in the targeted enzyme pockets. Thus the benzothiazole derivatives comprise a class of therapeutic compounds having diversified biological activities (Rangappa *et al.*, 2015; DeSimone *et al.*, 2004). Even benzothiazole derivatives with diversified biological activities have been found in terrestrial as well as marine compounds (Gunawardana *et al.*, 1992). While searching for better antimicrobials, benzothiazole derivatives appear as one of the most focused antimicrobial scaffolds (Bujdakova *et al.*, 1994). This may be the result of the heterocyclic structure having capacity of forming various bonding interactions as shown in figure 1. Thus the benzothiazole was taken for subsequent molecular exploration.

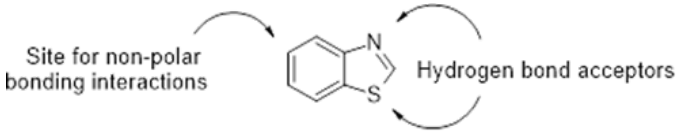

Figure 1: Binding potential of benzo[d]thiazole.

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Though antifungal and antibacterial activities of the benzothiazole derivatives have already been reported by various researchers (Liu *et al.*, 2013; Sukumar *et al.*, 2021; Padalkar *et al.*, 2014), simple 2-acetamido and 2-hydroxy derivatives have not been taken for the antibacterial screening. Thus, these simple scaffolds have been targeted as the starting point of extensive study protocols (Scheme 1).

The compounds, after synthesis in our laboratory and subsequent characterization by ^{1}H NMR and Mass spectroscopy, have been subjected to evaluation for antibacterial activity. Finally, the *in silico* analyses were done for predicting the structural modifications to get new antiinflammatory lead compounds. The synthetic routes for getting the acetamide derivatives have been reported earlier (Sukumar *et al.*, 2021). However, the hydroxy derivative was synthesized by a novel method and the necessary condition optimization was also performed. This report provides these observations including the synthesis and biological evaluation along with the subsequent *in silico* analysis.

MATERIALS AND METHODS

Solvents, chemicals and reagents

For synthesizing the targeted derivatives, the commercially available reagents were collected from Sigma-Aldrich and TCI. The solvents, collected from Daejung Chemicals, were used for regular workups and necessary purification procedures. The reaction progress in every step was checked by analytical thin layer chromatography (TLC) pre-coated silica gel plates (0.25 mm 60 F-254 E. Merck). The synthesized crude compounds were purified by flash column chromatography using silica gel having 200-400 mesh size.

Equipment used

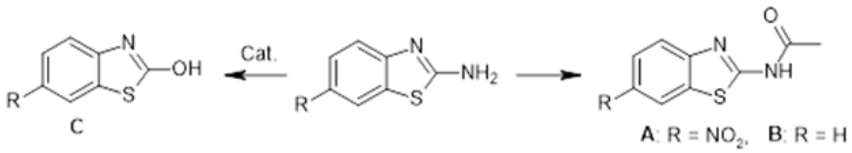
Hot plate with magnetic stirrer was used for running the reaction at various temperatures. Reaction monitoring was done by the TLC check using UV lamp. For usual evaporation, rotary evaporator was used. For characterization of the compounds, the ^{1}H NMR spectra were recorded on a Bruker spectrometer (400 MHz) employing DMSO-*D6* as solvent and TMS as the internal standard. Chemical shifts have been expressed in ppm (δ / ppm) values and coupling constants in Hz (J / Hz). Glass columns and a locally available positive air pump were used for the column chromatography. Ceramic filters or glass filters were used for the filtration works.

General method for the synthesis of acetanilide from 2-aminobenzothiazole

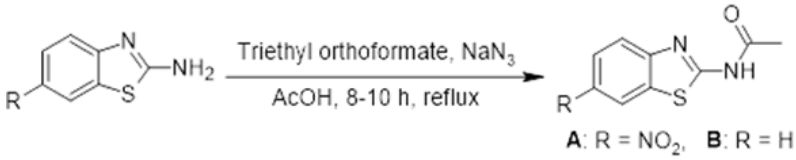
For synthesizing the acetanilides (Sukumar *et al.*, 2021), the 2-aminobenzothiazole, triethyl orthoformate and sodium azide were added to acetic acid under a nitrogen atmosphere (Scheme 2). The mixture was then subjected to heating at the refluxing condition for 8-10 hours followed by evaporation under a vacuum. The residue was suspended in water and the resultant solid was collected by filtration to get the crude acetanilides, which were then purified by flash column chromatography by using an increasing polarity gradient of hexane and ethyl acetate system.

General method for the synthesis of 2-hydroxybenzothiazole from 2-aminobenzothiazole

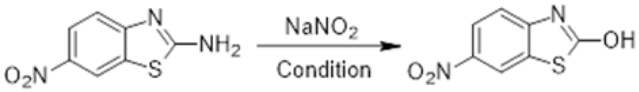
Sodium nitrite was taken in a round-bottomed flask maintained under nitrogen atmosphere and ice-bath system was set (scheme 3). Concentrated sulfuric acid and/or glacial acetic acid were added dropwise to sodium nitrite by slow dropwise addition. After subsequent stirring (with or without bentonite as catalyst) at 0°c for 1 hour, 2-aminobenzothiazole was added and the mixture was allowed to warm to room temperature slowly. The mixture was maintained at various temperatures for observing the reaction progress. At the end of the reaction, water was added by slow dropwise addition using the ice-bath system. After the subsequent addition of ethyl acetate, the organic layer was collected and washed consecutively with brine and water. The organic layer was collected, dried, and evaporated to get the crude 2-hydroxybenzothiazole. The crude product was then purified by flash column chromatography by using increasing polarity gradients of hexane and ethyl acetate system.



Scheme 1: Benzothiazole derivatization for evaluating the antimicrobial activity.



Scheme 2: Synthetic route to *N*-(benzo[*d*]thiazol-2-yl)acetamide.



Scheme 3: Synthetic route to 1,3-benzothiazol-2-ol derivative.

Characterization of the synthesized compounds

The synthesized compounds were characterized by ^{1}H NMR spectroscopy available in the analytical laboratory of Bangladesh Council of Scientific and Industrial Research (BCSIR) located in Dhaka, Bangladesh. The HRMS data was taken from Japan.

Evaluation of the antibacterial activity

The synthesized compounds were tested for the antibacterial activities against various bacterial strains available in the Department of Chemistry of Jagannath University. For evaluating this antimicrobial potential, the disc diffusion method was applied. The antibacterial activities were compared with that of ciprofloxacin, which was taken as the standard drug.

In silico analysis

The synthesized compounds were taken for the *in silico* analysis for predicting the subsequent development options. Since the alanine racemase has been reported (Maria *et al.*, 2014) as the protein target for predicting antimicrobial activities, the available related PBD file (PDB ID: 3E6E) has been collected from RCSB website (Priyadarshi *et al.*, 2009) for this study. After collecting the PDB format, the ligand was removed for subsequent docking activities. The compound structures and the receptor PDB files were then converted to the required PDBQT files by using ChemDraw and Autodock tools. The ligand PDBQT outputs were subsequently docked into the receptor PDBQT by using the reported Autodock Vina software (Trott *et al.*, 2010). The output PDBQT files were visualized by using PyMOL software where only the binding modes with the lowest energy were considered for interaction analysis. The binding interactions were analyzed for predicting the next possible improvements.

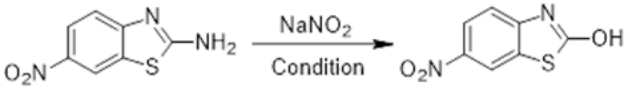
RESULTS AND DISCUSSION

Synthesis of 2-hydroxybenzothiazole

During synthesis of the 2-hydroxybenzothiazole, various reaction conditions were applied for observing the effects of the type of acid, temperature, and time. For observing the effects of acid, sulfuric acid and/or acetic acid were applied. As shown in table 1, the reaction progress was strongly affected by the type of acid. When applied sulfuric acid, the yield was much better as compared to application of acetic acid. As shown in entries 7-9, the yield was drastically reduced due to replacement of sulfuric acid by acetic acid. Even when there was given a mixture of sulfuric acid and acetic acid (1:1), the reaction progress was hampered as shown in entry 6. Again, the reaction was dependent on the temperature. In all of the reaction conditions tried, the higher temperature was giving a better conversion of the 2-aminobenzothiazole to the corresponding 2-hydroxybenzothiazole. Accordingly, the highest yield was at 90°C (entry 5). While considering the reaction time, reaction progress was observed even to 48 hours.

This route of synthesis was further checked for the effect of catalysis by bentonite. As shown in table 2, when 5% bentonite was added, there was significant improvement in the reaction progress (entries 1-3 in table 2 vs entries 1-3 in table 1). Similar observation was found in case of heating at 90°C (entry 3 in table 2), where 43% yield was found within 1 hour of stirring. In the next step, addition of bentonite by 10%, no further significant improvement was observed as shown in entry 4 and 5 in table 2.

Table 1: Condition optimization for the conversion to 6-nitrobenzo[*d*]thiazol-2-ol



Entry	H_2SO_4 used (mL/ mmole)	AcOH used (mL/ mmole)	Temperature (°C)	Time (h)	Yield (%)
1	1	-	25	1	Trace
2	1	-	25	12	23
3	1	-	60	12	43
4	1	-	90	1	12
5	1	-	90	48	93
6	0.5	0.5	25	48	15
7	-	1	25	12	0
8	-	1	90	1	Trace
9	-	1	90	48	20

Table 2: Effect of bentonite catalysis on the conversion to 2-hydroxybenzothiazole.

Entry	Bentonite (%)	Temperature (°C)	Time (h)	Yield (%)
1	5	0	1	Trace
2	5	25	1	18
3	5	90	1	43
4	10	25	1	22
5	10	90	1	49

Characterization data of the synthesized compounds

^{1}H NMR spectra of *N*-(6-nitrobenzo[*d*]thiazol-2-yl) acetamide (**A**): (400 MHz, DMSO-*d6*) δ 12.75 (s, 1H), 9.03 (s, 1H), 8.26 (d, J = 8.8 Hz, 1H), 7.87 (d, J = 8.8 Hz, 1 H), 2.25 (s, 3 H). HRMS: (ESI) m/z 237.9 $[M+H]^+$, (Calculated for $C_9H_7N_3O_3SH^+$ 238.0286).

^{1}H NMR spectra of *N*-(benzo[*d*]thiazol-2-yl) acetamide (**B**): (400 MHz, DMSO-*d6*) δ 12.32 (s, 1H), 7.95 (d, J = 8.0 Hz, 1H), 7.72 (d, J = 8.0 Hz, 1H), 7.42 (t, J = 7.60 Hz, 1 H), 7.29 (t, J = 7.60 Hz, 1H), 2.19 (s, 3 H). HRMS: (ESI) m/z 193.0 $[M+H]^+$ (Calculated for $C_9H_8N_2OSH^+$ 193.0436).

Spectral data of 6-nitrobenzo[*d*]thiazol-2-ol (**C**): ^{1}H NMR (400 MHz, DMSO-*d6*) δ 12.55 (br s, 1H), 8.61 (s, 1H, H-7), 8.16 (d, 1H, H-5), 7.26 (d, 1H, H-4). HRMS: (ESI) m/z 197.0033 $[M+H]^+$ (Calculated for $C_7H_4N_2O_3SH^+$ 197.0021).

Antibacterial activity

The synthesized compounds were tested for *in vitro*

antibacterial activities against some common bacterial strains including both the gram-positive and gram-negative classes by using the disc diffusion methods (Venkateshan *et al.*, 2018) with minor modifications. The antibacterial activities of the synthesized compounds were compared with that of the standard drug, ciprofloxacin (table 3).

While observing the antimicrobial potency against the gram-positive organisms, *Staphylococcus aureus, Bacillus megnaterium* and *Bacillus cereus*, the compounds were found to be very interesting as the antimicrobial scaffold. In the case of *Staphylococcus aureus*, 6-nitrobenzo[*d*] thiazol-2-ol (**C**) was much more potent as compared to the other two compounds as shown in table 3. Even it was significantly closer to the reference compound as indicated by the zone of inhibitions (26 mm vs 40 mm respectively). Though the acetanilides (**A** and **B**) were better in the case of *Bacillus*, the 2-hydroxy derivative was still better (entries 1-3, table 3).

While comparing the antimicrobial activity of the samples against the various forms of *Escherichia coli*, there was more or less similar zone of inhibitions where the *N*-(6-nitrobenzo[*d*]thiazol-2-yl) acetamide (**A**) was relatively more potent (entries 4-6, table 3). The enteropathogenic *Escherichia coli* was also found to be very resistant against the standard ciprofloxacin (entry 4). In the case of *Salmonella*, the 6-nitrobenzo[*d*]thiazol-2-ol (**C**) was relatively more potent (entry 7). The scenario was also similar in cases of various species of *Shigella*, where 6-nitrobenzo[*d*]thiazol-2-ol (**C**) showed 10-25 mm zone of inhibitions, whereas, the other two afforded 8-10 mm zone of inhibitions. Thus, as compared to the 2-acetanilide derivatives (**A** and **B**), the 2-hydroxy derivatives (**C**) were more powerful as the antibacterial agent against both the gram-positive and gram-negative bacteria.

***In silico* analysis with the benzothiazole derivatives as the antimicrobial agents**

The *in silico* analysis was done by docking the synthesized compounds in the reported binding pocket of the alanine racemase enzyme PDB of *Enterococcus faecalis* by using Autodock Vina. The synthesized compounds showed various orientations as observed from the output PDBQT files. The orientations having the lowest energy modes were taken into consideration for subsequent binding potential predictions. Effects of various factors like polarity of the binding pockets, availability of the spaces, hydrogen bonding interaction possibilities, etc. have been considered for making a logical inference.

While comparing the binding potentials of the best possible orientations (figure 2) of *N*-(6-nitrobenzo[*d*]thiazol-2-yl) acetamide (**A**), *N*-(benzo[*d*]thiazol-2-yl)acetamide (**B**) and 6-nitrobenzo[*d*]thiazol-2-ol (**C**) in the binding pocket, there was found a good logical relationship. The compounds, when taken together, as shown in figure 2, compound **A** and **C** were found to take similar orientations. These two compounds were relatively more potent in terms of antibacterial potencies in this study. They have taken the orientations by projecting their polar ends to space **S2** and non-polar ends to space **S1** (figure 2). Compound **C** took a different orientation while considering the lowest energy binding mode. The non-polar benzene rings of compound **A** and **C** appear to get attractions by mainly the LEU-86, whereas, the relatively polar acetamidothiazole or hydroxythiazole moieties, respectively, of these compounds were attracted by the polar interactions of TYR-356, TYR-44, and ASN-206 residues. Thus, the rings seem to be in 'best-fit' in these available spaces of the binding pocket. But compound **B** was not oriented in the same way, rather it was occupying space **S3** (figure 2). This may be due to the absence of the nitro group which could have shown additional interactions in the **S1** site of the receptor.

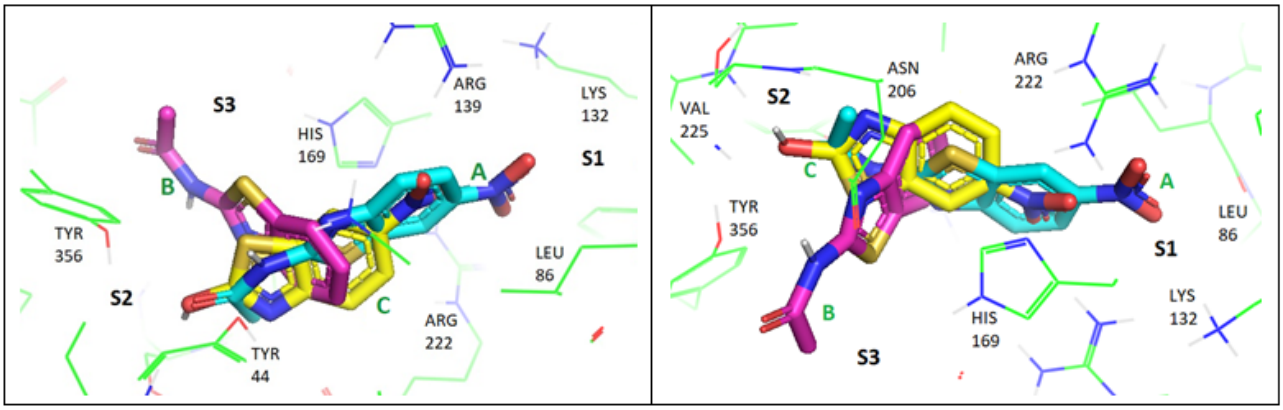
CONCLUSION

The small molecule 6-nitrobenzo[*d*]thiazol-2-ol (**C**) was synthesized by a different method, where the reaction conditions, as well as the bentonite catalysis were tried. Application of heat offered higher yield and shorter reaction times. At the same time, the catalysis by bentonite showed further improvement in the reaction outputs. In

Table 3: Antibacterial activities of the synthesized compounds **A**, **B** and **C.**

Entry	Organism class	Organism	Zone of inhibition (mm)			
			A	**B**	**C**	Reference
1	Gram positive	*Staphylococcus aureus*	8	12	26	40
2		*Bacillus megnaterium*	10	12	15	34
3		*Bacillus cereus*	10	8	17	37
4	Gram negative	Enterotoxigenic *Escherichia coli*	20	10	15	28
5		Enteropathogenic *Escherichia coli*	12	10	16	40
6		*Escherichia coli*	15	15	15	50
7		*Salmonella typhi*	10	16	19	33
8		*Shigella flexneri*	10	8	25	42
9		*Shigella sonnei*	12	10	19	45
10		*Shigella dysentery*	10	10	10	33
11		*Shigella boydii*	-	10	25	32

[a]300 µg per disc was applied; [b]50 µg per disc was used as reference



N.B. Compounds have been marked by A, B and C; Available spaces have been marked as S1, S2 and S3

Figure 2: Orientation of **A**, **B** and **C** in the binding site of alanine racemase enzyme (2 views).

the biological evaluation, 6-nitrobenzo[*d*]thiazol-2-ol (**C**) was the most potent compound as the antibacterial agent against both gram-negative and gram-positive organisms. *N*-(6-nitrobenzo[*d*]thiazol-2-yl)acetamide (**B**) was relatively more potent than *N*-(benzo[*d*]thiazol-2-yl) acetamide (**C**). The subsequent *in silico* study revealed the additional scopes for further derivatizations of the molecules targeting new scaffold with higher efficacy molecules in this therapeutic class.

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DECLARATION OF CONFLICT OF INTEREST

The authors declare no conflict of interest.

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