Material Science: An Indian Journal

Materials Science
ISSN: 0974-7486

Research | Vol 15 Iss 2

# Synthesis of Some New Substituted Triazole Fused with Benzothiazoles and their Antibacterial Activity

**Bhagat TM**

P. G. Department of Chemistry, G. S. Gawande College, Umarkhed, Yavatmal, Maharashtra, India

***Corresponding author:** Bhagat TM, P. G. Department of Chemistry, G. S. Gawande College, Umarkhed, Yavatmal, Maharashtra, India, Tel: +919890013219; E-mail: bhagat.tm@gmail.com

**Received:** July 16, 2017; **Accepted:** August 14, 2017; **Published:** August 19, 2017

## Abstract

**The compound 4-ethoxy acetanilide (phenatidine) 1 on treatment with bromine in acetic acid followed by hydrolysis with dil. HCl/NaOH solution, yielded 2-bromo-4-ethoxy aniline 2 which on treatment with sodium thiocyanate in acetic acid afforded 2-amino-4-bromo-6-ethoxy benzothiazole 3. Compound 3 in ethylene glycol was heated at 150°C with 80% hydrazine hydrate to get 4-bromo-6-ethoxy-2-hydrazino benzothiazole 4. This hydrazino compound 4 on heating with formic acid for three hours, yielded 4-bromo-6-ethoxy 2-hydrazinoformyl benzothiazole 5. Same compound 4 when heated independently with formic acid for six hours/urea for three hours/carbon disulphide in alkali afforded 5-bromo-7-ethoxy 6/5-bromo-3-hydroxy-7-ethoxy 7/5-bromo-3-mercapto-7-ethoxy 8-1, 2, 4-triazolo [3, 4-*b*]-benzothiazoles. Compound 4 on heating with acetic acid/acetic anhydride gave acetyl benzothiazolyl derivative 9 which on cyclization with orthophosporic acid yielded 5-bromo-7-ethoxy-3-methyl-1, 2, 4-triazolo-[3, 4-*b*]-benzothiazole 10. All these newly synthesized compounds were screened for antimicrobial activity against *E. coli* (Gram –ve), *B. subtilis* (Gram +ve), *E. carotovara* and *Xanthomonas citri* using *Ampicillin*, *Streptomycin* and *Penicillin* as a standard for comparison.**

***Keywords:** Benzothiazole; Triazolobenzothiazole; Biological screening*

## Introduction

The compound 1, 2, 4-triazole and their derivatives are important class of organic compounds with diverse agriculture, industrial and biological activities [1-3], including antimicrobial [4,5] anti-convulsant [6,7] and anti-inflammatory [8]. Similarly benzothiazoles are known to possess different activities such as anticancer [9], anthelmintic activity [10], antitubercular activity [11].

A survey of literature reveals such fused substituted tricyclic triazoles are prepared by different methods [12] but little work is carried out on bromo derivative of such fused tricyclic triazoles. Hence it was thought worthwhile to synthesize 5-bromo-

**Citation:** Bhagat TM. Synthesis of Some New Substituted Triazole Fused with Benzothiazoles and their Antibacterial Activity. Mat Sci Ind J. 2017;15(2):118

7-ethoxy as a substituent on benzene moiety in the 1, 2, 4-triazolo-[3, 4-b]-benzothiazole system by following series of reactions and study the chemistry and biological activity of these compounds.

As the first step, 2-bromo 4-methyl aniline (2) was prepared by treating 4-ethoxy acetanilide (1) with bromine in acetic acid, followed by hydrolysis with dil. HCl/NaOH solution.

To the solution of sodium thiocynate in glacial acetic acid, 2-bromo-4-methyl aniline (2) was added. The mixture was stirred well and bromine in glacial acetic acid was added drop by drop maintaining the temperature below 5°C. The residue filtered, dissolved in hot water and neutralized by alkali. The obtained product 2-amino-4-bromo-6-ethoxy benzothiazole (3) was recrystallized by using ethanol.

On the basis of elemental analysis and spectral data the resulting product [3] has assigned the structure 2-amino-4-bromo-6-ethoxy benzothiazole. The I.R. spectrum showed absorption bands at 3440 $cm^{-1}$ and 3340 $cm^{-1}$ due to asymmetric and symmetric stretching of $-NH_2$ group respectively. The PMR spectrum exhibited triplet at δ 1.4 and quatrate at δ 4.2 due to $-OCH_2CH_3$, broad peak of δ 6.0 due to $-NH_2$ protons and two singlet in the region δ 7.0-7.5 due to two Ar-H protons. The mass spectrum reveals molecular ion peaks at 274 (M+2, 98%) and 272 (M+, 100%). It also confirmed the presence of one bromine atom.

The compound 2-Amino-4-bromo-6-ethoxy benzothiazole (3) in ethylene glycol as solvent was heated with 80% hydrazine hydratehydrochloride over an oil bath for three hours keeping temperature at 150°C to get the product, 4-bromo-6-ethoxy-2-hydrazino benzothiazole (4). The I.R. spectrum of (4) showed absorption bands at 3320 $cm^{-1}$ and 3203 $cm^{-1}$ due to $-NH_2$ asymmetric and symmetric stretching respectively. The mass spectrum exhibits molecular ion peaks of equal intensity at 289 (M+2) and 287(M+) which also confirming the formation of compound (4) with one bromine atom.

The Compound (4) was heated with formic acid for three hours to get expected tricyclic triazolo benzothiazole (6), but it resulted in the formation of 4-bromo-6-ethoxy-2-hydrazinoformyl benzothiazole (5). The structure to the resulting product has been assigned on the basis of elemental analysis and spectral data. IR spectrum of the compound (5) in KBr showed absorption bands at 3246 $cm^{-1}$, 3184 $cm^{-1}$ due to N-H stretching and absorption band of medium intensity at 2856 $cm^{-1}$ accompanied by a strong carbonyl (-C=O) stretching absorption band at 1683 $cm^{-1}$ indicating the presence of an aldehyde group. The 1HNMR spectrum in CDCl3 showed peak at triplet at δ 1.4 and quadrate at δ 4.2 due to $-OCH_2CH_3$, δ 2.7 due to –NH proton, δ 7.4-7.7 due to Ar-H and δ 9.5 due to aldehydic proton.

Mass spectrum of the compound exhibits peaks of equal intensity at 317 (M+2, 48%) and 315 (M+, 50%) which corresponds to the molecular weight and also confirms the presence of one bromine atom.

When same reaction mixture was refluxed for six hours, then expected tricyclic triazolo benzothiazole, 5-bromo-7-ethoxy-1, 2, 4-trizolo-[3, 4-b]-benzothiazole (6) was obtained. IR spectrum showed the absence of absorption band at 3246 $cm^{-1}$, 3184 $cm^{-1}$, 2856 $cm^{-1}$ and 1683 $cm^{-1}$ indicating the absence of -NH and -CHO group respectively. It supports the formation of cyclized product. 1HNMR spectrum exhibits triplet at δ 1.4 and quadrate at δ 4.2 due to $-OCH_2CH_3$ peaks at δ 7.4-7.7 due to

Ar-H and singlet at δ 8.3 due to aryl –CH proton. Moreover mass spectrum exhibits molecular ion peak of equal intensity at 299 (M+2, 68%) and 297 (M+, 70%) which corresponds to its molecular weight and confirms the presence of one bromine atom.

Compound (4) on heating with urea at 200°C for three hours, afforded the product to which on the basis of elemental analysis and spectral data was assigned the structure 5-bromo-7-ethoxy-3-hydroxy-1, 2, 4-triazolo-[3, 4-b]-benzothiazole (7). IR spectrum showed characteristics absorption bands at 3470 $cm^{-1}$ and C–O stretching band at 1215 $cm^{-1}$ which indicates the presence of –O–H group. Moreover, it also exhibits strong absorption band at 1725 $cm^{-1}$ due to C=O group. It indicates that compound (7) exists in its tautomeric form.

1HNMR spectrum of (7) compound in DMSO showed two singlet at δ 7.4 and 7.6 due to two Ar-H protons. The singlet at δ 2.6 can be assigned to O-H proton. The mass spectrum shows molecular ion peaks of equal intensity at 315 (M+2) and 313 (M+).

Another 3-substituted tricyclic triazolo benzothiazole, 5-bromo-7-ethoxy-3-mercapto-1, 2, 4-triazolo-[3, 4-b]-benzothiazole (8) was obtained by refluxing 4-bromo-6-ethoxy-2-hydrazino-benzothiazole (4) with carbon disulphide in presence of alkali for three hours, followed by neutralization with hydrochloric acid solution.

The compound dissolves in sodium hydroxide solution and gets re-precipitated with hydrochloric acid solution indicating the presence of mercapto (-SH) group.

IR spectrum shows the absorption band at 2747 $cm^{-1}$ due to mercapto group. 1HNMR spectrum of compound (8) in DMSO showed singlet at δ 3.6, δ 7.6 and δ 7.9 due to -S-H and two Ar-H protons respectively. The mass spectrum exhibits molecular ion peaks of equal intensity at 331(M+2) and 329 (M+) which corresponds to its molecular weight.

The preparation of trisubstituted triazolo benzothiazole was undertaken with 3-methyl substituent on triazolo ring and 5-bromo-7-ethoxy substituent on benzene ring. 4-Bromo-6-ethoxy-2-hydrazino-benzothiazole (4) on heating with acetic acid/acetic anhydride gave acetyl thiazolyl derivative (9). The acetyl derivative shows IR absorption bands at 3274 $cm^{-1}$, 3188 $cm^{-1}$ and 1710 $cm^{-1}$ due to NH and C=O stretching respectively. 1HNMR spectrum exhibits peaks triplet at δ 1.4 and quatrate at δ 4.2 due to -$OCH_2CH_3$, δ 2.6, δ 7.3-7.5, δ 10.1 and δ 10.5 due to, -$COCH_3$, Ar-H, and N-H protons respectively. Mass spectrum exhibits molecular ion peak equal intensity at 331 (M+2, 98%) and 329 (M+, 100%) which corresponds to its molecular weight.

The acetyl thiazolyl derivative (9) on cyclization with ortho phosphoric acid afforded the product to which, on the basis of elemental analysis and spectral data assigned the structure, 5-bromo-7-ethoxy-3-methyl-1, 2, 4 triazolo [3, 4-b ] benzothiazole (10).

The IR spectrum of [10] showed the absence of strong absorption band in the region 1650 $cm^{-1}$-1750 $cm^{-1}$ indicating the absence of –$COCH_3$ group. The 1HNMR spectrum exhibited singlet at δ 2.5 due to –CH3 attached to triazole ring and two singlets at δ 7.4 and δ 7.6 due to Ar-H protons.

## Experimental

Melting points were determined in open capillaries and are uncorrected. Infrared spectra were recorded in Nujol/potassium bromide pellets on Bomen MB 104 FT infrared spectrophotometer. 1HNMR spectra were obtained on a Gemini 200 Mz spectrometer with TMS as an internal standard and mass spectra on FT VG-7070H mass spectrometer using the GI technique at 70 ev. Elemental analysis was carried out on a Heraeus CHN-O Rapid analyzer. Purity of the compound was checked by TLC.

**Synthesis of 2-Amino-4-bromo-6-ethoxy benzothiazole (3)**

2-Bromo-4-methyl aniline (21.6 g, 0.2 M) and sodium thiocynate (16 g, 0.2 M) were dissolved in glacial acetic acid (150 ml). The solution was cooled in freezing mixture. Bromine (32 g, 10 ml, 0.2 M) in glacial acetic acid (25 ml) was added with stirring and maintaining temperature below 25°C. The mixture was allowed to stand for one hour at room temp. The resulting hydro bromide was dissolved in hot water and neutralized with 10% NaOH to obtain base. The amine thus obtained was filtered, washed with water and recrystallized in aq. alcohol to get the product 13 g (60%), M.P 210°C, IR (KBr): 3440 $cm^{-1}$ (Asymmetric stretching of -$NH_2$), 3340 $cm^{-1}$ (N-H Symmetrical stretching of -$NH_2$), 3052$cm^{-1}$ (Ar-H stretching), 1630 $cm^{-1}$ (-C=N stretching), 1325 $cm^{-1}$ (Ar–C–O stretching), 1HNMR (CDCl3): δ 1.4 (triplet, 3H, $CH_3$) and δ 4.2 (quadrate, 2H, $CH_2$) due to -$OCH_2CH_3$, δ 6.0 (broad, 2H, $NH_2$), δ 7.0-7.5 (two singlet, 2H, Ar-H), m/z 244 (M+2, 98%), 242 (M+¸100%), 163, 136.

**4-Bromo-6-ethoxy-2-hydrazino benzothiazole (4)**

Hydrazine hydrate (80%, 9 ml) was taken in a flask, cooled to 5°C and concentrated HCl (6 ml) was added to it with stirring. The flask was kept at room temperature for few minutes and then 2-amino-4-bromo-6-ethoxy benzothiazole (6 g) was added in portions. Ethylene glycol (24 ml) was added into the flask. The contents of the flask were heated at 140°C on an oil bath for three hours and then cooled. The separated product, 4-bromo-6-ethoxy-2-hydrazino benzothiazole was filtered, washed with cold water and crystallized from ethyl alcohol to give 3.8 g (61%), M. P. 280°C, IR (KBr): 3320 $cm^{-1}$ (asymmetric N-H stretching of -$NH_2$), 3203 $cm^{-1}$ (symmetric N-H stretching of -$NH_2$) m/z: 289 (M+2), 287 (M+).

**4-Bromo-6-ethoxy-2-hydrazinoformyl benzothiazole (5)**

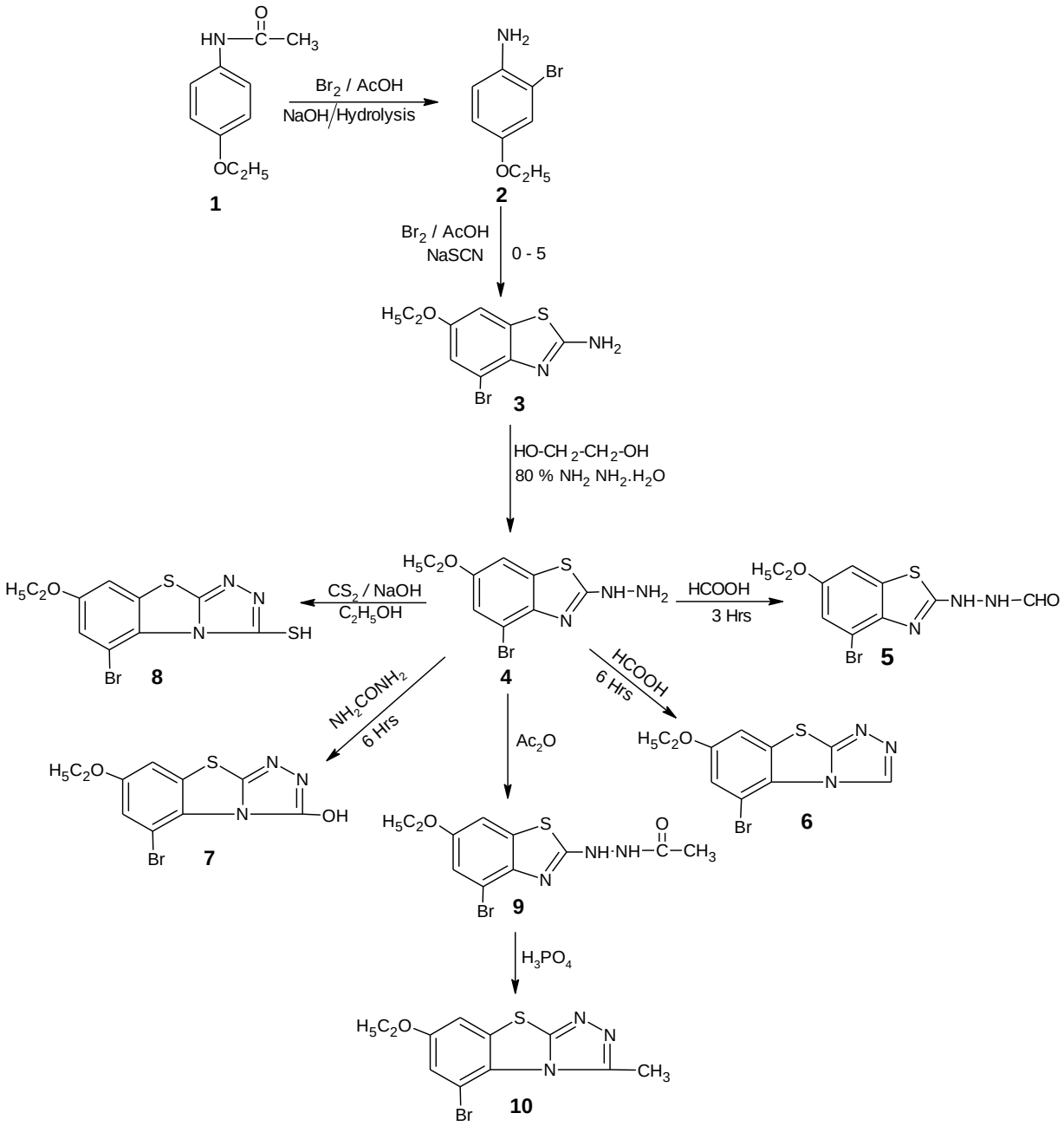
A mixture of 4-bromo-6-ethoxy-2-hydrazino benzothiazole (0.576 g, 0.002 M) and formic acid (5 ml) in 50 ml round bottom flask was refluxed on an oil bath at 150°C for three hours. The contents of the flask were cooled and poured on crushed ice with stirring. The white precipitate obtained was recrystallized from ethanol to give 0.43 g (74.65%), M.P. 268°C, IR (KBr): 3246 $cm^{-1}$-3184 $cm^{-1}$ (N-H stretching), 2856 $cm^{-1}$ (C-H stretching of CHO group ), 1683 $cm^{-1}$ ¬(C=O stretching of CHO), 1HNMR (CDCl3): δ 1.4 (t, 3H, -$CH_3$) and δ 4.2 (q, 2H, -$CH_2$-O), δ 2.7 (s, 2H, -$NH_2$), δ 7.4-7.7 (2s, 2H, Ar-H), δ 9.5 (s, 1H, CHO), m/z: 317 (M+2, 48%), 315 (M+, 50%).

**5-Bromo-7-ethoxy-1, 2, 4-triazolo-[3, 4-b] benzothiazole (6)**

The compound 4-bromo-6-ethoxy-2-hydrazino benzothiazole (2.88, 0.01 M) and formic acid (15 ml) were refluxed on an oil bath at 150°C for three hours. The contents of the flask were cooled and poured with stirring on crushed ice. The separated product was filtered, washed with cold water, recrystallized form 1, 4-dioxane to obtained 1.6 g (53.69%), M. P. 248°C, I. R.

(KBr): shows absence of absorption bands in the region 3100 $cm^{-1}$-3400 $cm^{-1}$ due to $NH_2$ group, M/z: 299 (M+2, 68%), 297 (M+, 70%).

**Scheme-1**




**5-Bromo-7-ethoxy-3-hydroxy-1, 2, 4-triazolo-[3, 4-b] benzothiazole (7)**

The compound 4-Bromo-6-ethoxy-2-hydrazino benzothiazole (1.44 g, 0.005 M) was mixed intimately with urea (3 g, 0.05 M). The powdered form was transferred into 50 ml round bottom flask and heated on oil bath for two hours at 200°C and then cooled. The solid obtained was then dissolved in 10% NaOH solution and filtered. The clear filtrate on acidification with HCl. afforded the product, it was recrystallized form 1, 4-dioxane to give 1.02 g (64.9%), M.P: 267°C, IR (KBr) : 3470 $cm^{-1}$ (O-H stretching), 1725 $cm^{-1}$ (C=O stretching), 1215 $cm^{-1}$ (C-O stretching ), Mass spectrum: 315 (M+2), 313 (M+ ), 1HNMR : δ 1.4 (t, 3H, $-CH_3$), δ 4.2 (q, 2H, $-OCH_2$) δ 2.6 (s, 1H, O-H ), δ 7.8-7.5 (2s, 2H, Ar-H).

**5-Bromo-3-mertcapto-7-methyl-1, 2, 4-triazolo [3, 4-b] benzothiazole (8)**

4-Bromo-6-ethoxy-2-hydrazino benzothiazole (1.44g, 0.005 M) in ethanol (40 ml) was mixed with sodium hydroxide (0.4 g, in 5 ml water) and carbon disulphide (5 ml). The mixture was refluxed on water bath for two hours. The excess of carbon disulphide and ethanol distilled off. The solid left behind was dissolved in 10% NaOH solution was filtered, the filtrate on acidification with conc. HCl afforded product. It was washed with water and re-crystalized from DMF to give 0.98 g (59.3%), M.P: 246°C, IR (KBr): 2747 $cm^{-1}$ (S-H stretching) 1HNMR: δ 1.4 (t, 3H, $-CH_3$), δ 4.2 (q, 2H, $-OCH_2$) δ 3.6 (s, 1H, S-H), δ 7.6 – 7.9 (2s, 2H, Ar-H), Mass (m/e): 331(M+2) and 329 ( M+).

**2-Acetyl-4-bromo-6-ethoxy benzothiazole (9)**

4-Bromo-6-ethoxy-2-hydrazino benzothiazole (1.44 g, 0.005 M) was refluxed with acetic anhydride (2.5 ml) and glacial acetic acid (5 ml) on oil bath at 140°C for one and half hour. On cooling, it was poured over crushed ice. The acetyl derivative thus obtained was filtered, washed with cold water and recrystallized from ethanol to obtained 1.2 g (73%), M.P: 273°C, IR (KBr): 3246 $cm^{-1}$-3184 $cm^{-1}$ (N-H stretching), 1710 $cm^{-1}$ (C-O stretching in C=O), 1HNMR: δ 1.3 (t, 3H, $-CH_3$), δ 4.2 (q, 2H, $-OCH_2$), δ 2.6 (s, 3H, COCH3), δ 7.3-7.5 (s, 2H, Ar-H), δ 10.5 (s, 1H, N-H), m/z: 331 (M+2, 98%), 329 (M+, 100%).

**5-Bromo-3-methyl-7-ethoxy-1, 2, 4-triazolo-[3, 4-b]-benzothiazole (10)**

The acetyl derivative (1g) was refluxed with acetic anhydride (5ml) and syrupy phosphoric acid (3ml) on an oil bath for one hour. Contents were cooled, poured in 100 ml ice cold water with stirring then rendered alkaline with ammonia. The separated solid was filtered, washed with cold water and then recrystallized from hot ethyl alcohol to give 0.62 g (65%), M. P: 240°C, IR (KBr), Absence of absorption band in the region 3100 $cm^{-1}$-3400 $cm^{-1}$ indicates cyclization of acetyl derivative. 1HNMR: δ 1.4 (t, 3H, of $-OCH_2CH_3$), δ 4.2 (q, 2H, of $-OCH_2CH_3$), δ 2.5 (s, 3H, $-CH_3$ attached to triazolo ring), δ 7.8 – 8.0 (s, 2H, Ar-H), Mass: 313 (M+2, 96%), 311 (M+, 98%).

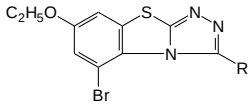



TABLE 1. **Evaluation of antimicrobial activity of 3-substituted 5-bromo 7-ethoxy 1, 2, 4 triazolo [3, 4, -b] benzothiazole.**

| Sr. No. | Compound | R | Antimicrobial activity (zone of inhibition in mm) | | | |
|---|---|---|---|---|---|---|
| | | | ***E. coli*** | ***Erwinia cartovora*** | ***Bacillus subtilis*** | ***Xanthomo-nas citri*** |
| 1 | 6 | -H | 3.5 | 04 | 02 | 01 |
| 2 | 7 | -OH | 00 | 00 | 00 | 00 |
| 3 | 8 | -SH | 00 | 00 | 00 | 00 |
| 4 | 10 | $-CH_3$ | 01 | 03 | 02 | 2.5 |
| 5 | Ampicillin | | 16 | 21 | 17 | 18 |
| 6 | Streptomycin | | 20 | 22 | 22 | 18 |

| | | | | | |
|---|---|---|---|---|---|
| 7 | Penicillin | 15 | 24 | 18 | 20 |
| 8 | Control | 00 | 00 | 00 | 00 |

## Results and Discussion

### Antimicrobial screening

The compound 6, 7, 8, 10 were tested for their antimicrobial activity by cup plate agar diffusion method against *E. coli* (Gram –ve), *B. subtilis* (Gram +ve), *E. carotovara* and *Xanthomonas citri* using ampicillin, streptomycin and penicillin as a standard for comparison. The antibacterial screening data of the compounds is presented in TABLE 1. Dimethyl sulphoxide was used as a control (solvent). Compound 6 is active against *E. coli* and *E. carotovara* species while compound 10 active against *Xanthomonas citri* and *E. carotovara* species. Compound 7 and 8 are inactive against all four species tested.

## Conclusion

This study reported that 5-bromo-7-ethoxy-1, 2, 4-trizolo-[3,4-b]-benzothiazole active against *E. coli* and *E. carotovara* species. However, further study for more properties is recommended.

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