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# PREPARATION AND ANTIMICROBIAL ACTIVITIES OF NEW PIPERIDINE SUBSTITUTED BENZOTHIAZOLE DERIVATIVES

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**Abstract:**
In recent years heterocyclic compounds analogs and derivatives have attracted wide attention due to their useful biological and pharmacological properties. Benzothiazoles have played an important role in the field of biochemistry and medicinal chemistry due to their highly pharmaceutical and biological activity. The development of synthetic processes is undoubtedly one of the most significant problems facing researchers. In this paper, we reported the synthesis of piperidine substituted benzothiazole derivatives. The synthesis was done by the reaction of ethyl2-aminobenzo[d]thiazole-6-carboxylate with copper (II) bromide followed by the addition of piperidine and get Ethyl 2-(piperidin-1-yl)benzo[d]thiazole-6-caroxylate. The reaction of Ethyl 2-(piperidin-1-yl)benzo[d]thiazole-6-caroxylate with NaOH produces 2-(piperidin-1-yl)benzo[d]thiazole-6-caroxylic acid. The intermediate 2-(piperidin-1-yl)benzo[d]thiazole-6-caroxylic acid have been isolated as stable compounds.
The chemical structures of synthesized compounds were established based on spectral data of 1HNMR, 13CNMR, and IR. The mass of the novel compounds was established with the help of the LCMS test. The biological studies of synthesized compounds show that the piperidine, amine, and bromine substituted aniline substituted compounds have good antibacterial activity. The compound amine substituted compound exhibits good antifungal activity. The formation of the crystal was confirmed by powder XRD and the average crystalline size was 54 nm. The photoluminescence data explain the optical property of the compound. The biological studies of synthesized compounds show that compound 5e possesses good antibacterial activity and compound 5d has good antifungal activity.
**Keywords**: Piperidine derivatives; benzothiazole; biological property; crystallization; optical activity.

## 1. Introduction

The study of benzothiazole derivatives is of considerable current interest as a result of their important biological and bio-physical properties such as antitumor and metabolic activities[I], antimicrobial[II], antifungal agents[III-IV], as well as imaging agents for β- amyloid[V] anti-cancer[VI], anti-tuberculosis[VII], anti-viral[VIII], anti-oxidant[IX]. Several substituted benzothiazoles have been identified as potent anthelmintic drugs[X-XIII]. Aminobenzothiazoles have manifested a large

scale of biological activities such as antiparkinsonian, dopa-mine antagonist[XIV-XV], schistosomicidal agents[XVI], anticonvulsant activity[XVII], antileishmanial activity[XVIII], analgesic agents[XIX], and antiasthmatic drugs[XX]. Moreover, compounds containing condensed pyrimidines have been used as herbicide antidotes[XXI], antibacterials[XXII-XXIV], and diuretics[XXV]. The BTA act as an effective catalyst[XXVI] and the crystal nature shows fluorophore property[XXVII]. Based on earlier studies, an attempt is made to prepare benzothiazole derivatives. The prepared samples were characterized for their potential applications.

## 2. Experimental

### 2.1 Materials

The chemicals ethyl2-aminobenzo[d]thiazole-6-carboxylate, copper (II) bromide, t-nitrosobutane, piperidine, cesium carbonate, sodium hydroxide, acetonitrile, dimethylformamide, methanol, hydrochloric acid, ethyl acetate, dichloromethane, triethyl amines, sodium sulphate, propanephosphonic acid anhydride, substituted amines were purchased from Sigma-Aldrich and used without purification. The dry ethyl acetate, hexane, and ethanol were obtained from Spectrochem for the crystallization process.

### 2.2 Instruments and methods

The Perkin-Elmer spectrum 100 series spectrophotometer was used for FTIR studies of the sample. The information about the nature and number of protons was studied from the 1HNMR spectrum. The $^{1}$HNMR spectra were recorded on a 400MHz Varian spectrometer. The information about carbon was obtained from the $^{13}$CNMR spectrum of compound which was taken for the samples by subjected to 100MHz Brucker spectrometer with TMS as internal standard.

The mass spectra are recorded on Shimadzu mass spectrometer. All the reactions were monitored by TLC plates and their spots were visualized by exposing them to a UV lamp, iodine chamber, or $KMnO_4$, and it was performed with silica gel 60-120mesh. The crystal formation and optical properties were ensured by powder XRD and photoluminescence studies respectively. The data were taken by XPERT-PRO- Gonio scan- 2 m diffractometer and Cary Eclipse- EL08083851 photo spectrometer. The elemental analysis was done by the Varian instrument (VARIO EL-3 series analyzer).

### Synthesis and characterization

### 3.1 Synthesis of Ethyl 2-bromobenzo[d]thiazole-6-caroxylate (2):

In a round bottom flask, 5 g of ethyl2-aminobenzo[d]thiazole-6-carboxylate dissolved in 1eq of acetonitrile solvent then added 1eq of copper (II) bromide with t-nitrosobutane. The reaction mixture was stirred up to 16 h at room temperature. The whole mixture was monitored by TLC complies. After that, the reaction mixture was diluted with ethyl acetate, washed with 1.5N HCl, water, and brine solution. Now the mixture was dried over sodium sulphate, and concentrated below 50 °C. The crude has proceeded to the next step without purification.

It was obtained as yellow solid. The yield was 54%. (LCMS: 95% purity). B.pt.139-40 °C, IR (KBr, $cm^{-1}$): $\nu_{max}$ 1742(C=O), 1647(C=N), 1324(C-N), 684(C-S), 610(C-Br). $^{1}$HNMR (400 MHz, DMSO-$d_6$, ppm): δ 8.420 (s, 1H, ArH), 7.453-7.482 (d, 2H, *J*=11.6Hz ArH), 4.302 (m, 2H, -$CH_2$), 1.289-1.301 (t, 3H, *J*=4.8Hz -$CH_3$). $^{13}$CNMR (100 MHz, DMSO-$d_6$, ppm): δ 14.32, 60.50, 121.34, 123.52, 126.40, 128.63, 141.36, 155.77, 165.62. For $C_{10}H_8BrNO_2S$, Calculated: C-41.97%, H-2.82%, Br-27.92%, N-4.89%, 0-11.19%, S-11.21%. Found: C-42.04%, H-2.90%, Br-27.86%, N-4.92%, 0-11.13%, S-11.15%. LCMS [M+1] $^{+}$: m/z 287.1.

### 3.2 Synthesis of Ethyl 2-(piperidin-1-yl)benzo[d]thiazole-6-caroxylate (3):

The obtained compound 2 was dissolved in DMF and added to the N-alkylation base ($CS_2CO_3$ 1.5 eq). Now piperidine (1.1 eq) was added and then heated up to 100 °C for 3 h. After complies the reaction mixture was cooled and purified to get compound 3.

It was obtained as orange solid with 56% yield, (LCMS: 95.7% purity), m.pt.161-162 °C, IR (KBr, $cm^{-1}$): $v_{max}$ 1740(C=O), 1643(C=N), 1326(C-N), 681(C-S). $^{1}$HNMR (400 MHz, DMSO-$d_6$, ppm): δ 1.536-1.553 (m, 6H, -$CH_2$), 3.691-3.724, (t, 4H, *J*=13.2Hz -$CH_2$) 8.414 (s, 1H, ArH), 7.697-7.721 (d, 2H, *J*=9.2Hz ArH), 4.292 (m, 2H, -$CH_2$), 1.292-1.313 (t, 3H, *J*=8.4Hz -$CH_3$). $^{13}$CNMR (100 MHz, DMSO-$d_6$, ppm): δ 14.44, 24.21, 25.45, 54.2, 61.02 116.55, 123.26, 126.57, 130.61, 157.62, 165.87, 168.13. For $C_{15}H_{18}N_2O_2S$, Calculated: C-62.04%, H-6.25%, N-9.65%, 0-11.02%, S-11.04%. Found: C-61.98%, H-6.27%, N-9.69%, 0-11.05%, S-11.01%. LCMS $[M+1]^+$: m/z 291.3.

**3.3 Synthesis of 2-(piperidin-1-yl)benzo[d]thiazole-6-caroxylic acid (4):**

The 2 g measured compound 3 was dissolved in methanol. Now, 2 eq sodium hydroxide solution (NaOH dissolved in water) was added and stirred for 1h at room temperature. After TLC complies, acidified with 1.5 N HCl and extracted with ethyl acetate. The organic layer was washed with water, dried, and concentrated. The crude was purified by column chromatography and compound eluted with DCM and methanol (2.4%) to get the desired product.

It was obtained as yellow solid of 67% of yield, (LCMS: 95.3% purity), m.pt.169-70 °C, IR (KBr, $cm^{-1}$): $v_{max}$ 3242(O-H), 1761(C=O), 1645(C=N), 1321(C-N), 684(C-S). $^{1}$HNMR (400 MHz, DMSO-$d_6$, ppm): δ 1.546-1.5621 (m, 6H, -$CH_2$), 3.716-3.734 (t, 4H, *J*=7.2Hz -$CH_2$) 8.618, (s, 1H, ArH), 7.882-7.894 (d, 2H, *J*=74.8Hz ArH), 11.121 (s, 1H, -OH). $^{13}$CNMR (100 MHz, DMSO-$d_6$, ppm): δ 24.14, 25.52, 54.36, 116.74, 123.62, 126.88, 130.73, 158.55, 166.72, 168.15. For $C_{13}H_{14}N_2O_2S$, Calculated: C-59.52%, H-5.38%, N-10.68%, 0-12.20%, S-12.22%. Found: C-59.59%, H-5.41%, N-10.72%, 0-12.12%, S-12.16%. LCMS $[M+1]^+$: m/z.263.3.

**3.4 Preparation of benzothiazole derivatives (5a-e)**

The one equivalent (100 mg) weighed compound 4 was dissolved in dichloromethane (1 mL), and added to simple amine (1 eq), triethylamine (2 eq). The mixture was stirred for 2h. Then cooled to zero degrees Celsius. Now, propane phosphoric acid anhydride (T3P) (50% in ethyl acetate) (1.5 eq) was added and again stirred for 12h. After completion of the reaction, monitor by TLC, ice water was added and extracted with dichloromethane. Then it was washed with water and brine solution. And now dried over sodium sulphate, then concentrated. The crude was purified by column chromatography (using silica gel) eluent (50 – 70% of ethyl acetate and petroleum ether) to get desired product (5a-e). All the reaction schemes were shown in Fig.1. The yield and melting point of these samples are presented in Table.1.

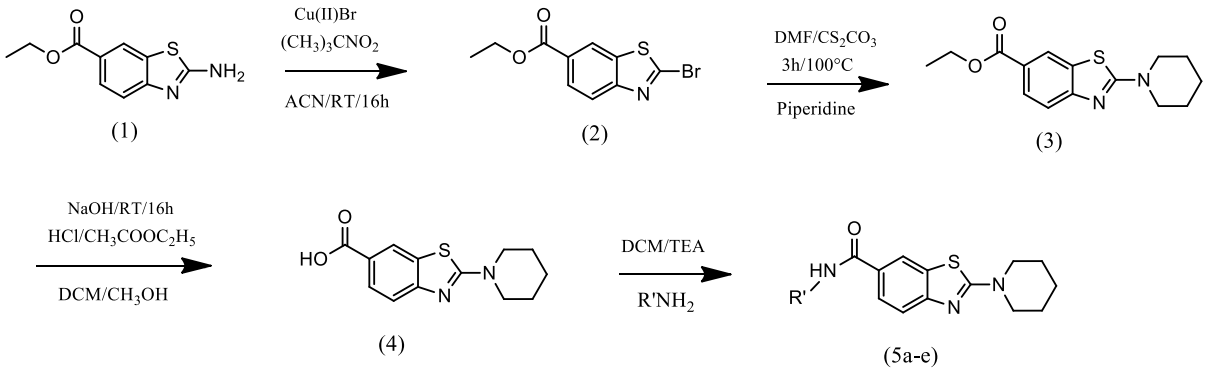



**Fig. 1. The reaction scheme**

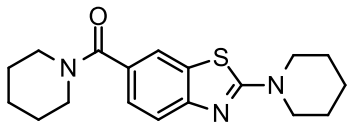
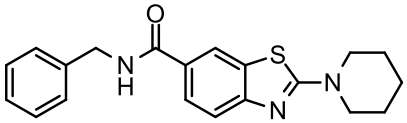
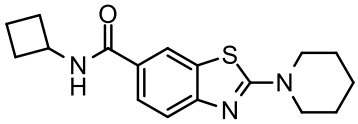
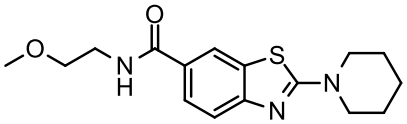
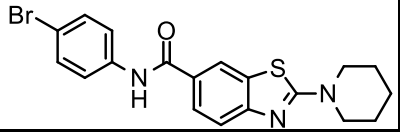
| Compound | Simple amine | Product | Yield % | m.pt °C |
|---|---|---|---|---|
| 5a | Piperidine |  | 70 | 145 - 46 |
| 5b | Benzyl amine |  | 66 | 185 - 86 |
| 5c | Cyclo butyl amine |  | 73 | 215 - 16 |
| 5d | 2-methoxy ethyl amine |  | 72 | 163 - 64 |
| 5e | 4 - bromo aniline |  | 62 | 217 - 18 |

**Table .1. Results of reaction**

### 3.5 Synthesis of piperidin-1-yl(2-(piperidin-1-yl)benzo[d]thiazol-6-yl)-methanone (5a)

The piperidine was added in this reaction. It gives the compound 5a which was also a pale white solid with a 70% yield. (LCMS: 95% purity), m.pt.145-46°C, IR (KBr, $cm^{-1}$): $v_{max}$ 2936 (C-H), 1623 (C=O), 1557 (C=N, str benzothiazole), 1525 (C=C), 1289 (C-N), and 610 (C-S). $^{1}$HNMR (400 MHz, DMSO-$d_6$, ppm): δ 1.558-580 (m, 12H, -$CH_2$), 3.740-3.760 (t, 8H, *J*=8Hz -$CH_2$), 7.921-7.939 (d, 1H, *J*=7.2Hz ArH), 7.630-7.639 (d, 1H, *J*=3.6Hz ArH), and 8.380 (s, 1H, ArH). $^{13}$CNMR (100 MHz, DMSO-$d_6$, ppm): δ 24.46, 25.38, 47.75, 54.54, 121.08, 121.67, 123.88, 130.83, 156.65, 168.09, and 172.45. For $C_{18}H_{23}N_3OS$, Calculated: C-65.62%, H-

7.04%, N-12.75%, 0-4.86%, S-9.73%. Found: C-65.68%, H-7.01%, N-12.69%, 0-4.83%, S-9.79%. LCMS $[M+1]^+$: m/z.329.9.

**3.6 Synthesis of N-benzyl-2-(piperidin-1-yl)benzo[d]thiazole-6-carboxamide (5b)**

To get the compound 5b, benzyl amine was added to the compound 4 and results pale white solid with a 66% yield. (LCMS: 95.3% purity), m.pt.185-86°C, IR (KBr, $cm^{-1}$): $v_{max}$ 3288 (N-H), 2933 (C-H), 1624 (C=O), 1523 (C=N, str benzothiazole), 1451 (C=C), 1287 (C-N), and 687 (C-S). $^1$HNMR (400 MHz, DMSO-$d_6$, ppm): δ 1.548-1.591 (m, 6H, -$CH_2$), 3.690-3.701 (t, 4H, *J*=4.4Hz -$CH_2$), 4.316-4.333 (d, 2H, *J*=6.8Hz -$CH_2$), 7.291-7.392 (m, 5H, ArH), 7.672-7.685 (d, 1H, *J*=5.2Hz ArH), 7.878-7.895 (d, 1H, *J*=6.8Hz ArH), 8.392 (s, 1H, ArH), and 8.058 (t, 1H, -NH). $^{13}$CNMR (100 MHz, DMSO-$d_6$, ppm): δ 24.52, 25.45, 44.16, 54.42, 121.11, 121.65, 123.92, 126.89, 128.54, 131.08, 137.79, 156.65, 167.78, and 168.11. For $C_{20}H_{21}N_3OS$, Calculated: C-68.35%, H-6.02%, N-11.96%, 0-4.55%, S-9.12%. Found: C-68.41%, H-6.09%, N-11.92%, 0-4.51%, S-9.07%. LCMS $[M+1]^+$: m/z.351.9.

**3.7 Synthesis of N-cyclobutyl-2-(piperidin-1-yl)benzo[d]thiazole-6-carboxamide (5c)**

The cyclo butyl amine was added to compound 4 and reacted to produce the compound 5c . It was obtained as white crystalline solid with 73 % yield. (LCMS: 95.6 % purity), m.pt.215-216 °C. IR (KBr, $cm^{-1}$): $v_{max}$ 3265 (N-H), 2937 (C-H), 1614 (C=O), 1524 (C=N, str benzothiazole), 1454 (C=C), 1288 (C-N), and 688 (C-S). $^1$HNMR (400 MHz, DMSO-$d_6$, ppm): δ 1.536-1.569 (m, 6H, -$CH_2$), 2.018-2.389 (m, 6H, -$CH_2$), 3.701-3.718 (t, 4H, *J*=6.8Hz -$CH_2$), 4.089-4.120 (m, 1H, -CH), 7.626-7.644 (d, 1H, *J*=7.2Hz ArH), 7.904-7.914 (d, 1H, *J*=4Hz ArH), 8.100-8.107 (d, 1H, *J*=2.8Hz -NH), and 8.388 (s, 1H, ArH). $^{13}$CNMR (100 MHz, DMSO-$d_6$, ppm): δ 3.21, 15.22, 24.54, 25.43, 48.55, 54.48, 121.05, 121.74, 123.96, 130.76, 131.07, 156.56, 167.25, and 168.10. For $C_{17}H_{21}N_3OS$, Calculated: C-64.73%, H-6.71%, N-13.32%, 0-5.07%, S-10.17%. Found: C-64.68%, H-6.65%, N-13.38%, 0-5.16%, S-10.13%. LCMS $[M+1]^+$: m/z.317.8.

**3.8 Synthesis of N-(2-methoxyethyl)-2-(piperidin-1-yl)benzo[d]thiazole-6-carboxamide (5d)**

The addition of 2-methoxy ethyl amine yields compound 5d. It was obtained as a white crystalline solid with a 72% yield. (LCMS: 96.2% purity), m.pt.163-64°C, IR (KBr, $cm^{-1}$): $v_{max}$ 3277 (N-H), 2928 (C-H str alkane), 1617 (C=O), 1520 (C=N, str benzothiazole), 1446 (C=C), 1321 (C-N), 1244 (C-O) and 682(C-S). $^1$HNMR (400 MHz, DMSO-$d_6$, ppm): δ 1.554-1.581 (M, 6H, -$CH_2$), 3.755-3.784 (T, 6H, *J*=11.6Hz -$CH_2$), 7.923-7.938 (D, 1H, *J*=6Hz ArH), 7.632-7.639 (D, 1H, *J*=2.8Hz ArH), 8.402 (S, 1H, ArH), 8.100-8.121 (T, 1H, -NH), 3.401-432 (M, 2H, -$CH_2$), 3.401 (S, 3H, -$CH_3$). $^{13}$CNMR (100 MHz, DMSO-$d_6$, ppm): δ 24.49, 25.42, 39.46, 54.53, 59.10, 70.12, 121.05, 121.67, 123.93, 130.81, 156.63, 167.45, and 168.06. For $C_{16}H_{21}N_3O_2S$, Calculated: C-60.16%, H-6.63%, N-13.16%, 0-10.02%, S-10.04%. Found: C-60.09%, H-6.67%, N-13.21%, 0-10.06%, S-9.97%. LCMS $[M+1]^+$: m/z.319.7.

**3.9 Synthesis of N-(4-bromophenyl)-2-(piperidin-1-yl)benzo[d]thiazole-6-carboxamide (5e**)

The compound 5e was obtained by the addition of 4-bromo aniline. It was obtained as a white crystalline solid with a 62% yield. (LCMS: 95.6% purity), m.pt.217-18°C, IR (KBr, $cm^{-1}$): $v_{max}$ 3289(N-H), 1624(C=O), 1624(C=N), 1327(C-N), 685(C-S), 603(C-Br). $^1$HNMR (400 MHz, DMSO-$d_6$, ppm): δ 1.524-691 (M, 6H, -$CH_2$), 3.732-3.751 (T, 4H, *J*=7.6Hz -$CH_2$), 7.912-7.932 (D, 1H, *J*=8Hz ArH), 7.371-7.393 (D, 5H, *J*=8.8Hz ArH), 8.386 (S, 1H, ArH), 9.163 (S, 1H, -NH). $^{13}$CNMR (100 MHz, DMSO-$d_6$, ppm): δ 14.67, 24.51, 25.56, 54.47, 121.12, 121.67, 121.87, 122.34, 123.91, 130.82, 131.07, 131.68, 136.92, 156.63, 168.11. For $C_{19}H_{18}BrN_3OS$, Calculated: C-54.81%, H-4.36%, Br-19.19%, N-10.09%, 0-3.84%, S-7.70%. Found: C-54.90%, H-4.42%, Br-19.12%, N-10.02%, 0-3.79%, S-7.75%. LCMS $[M+1]^+$: m/z.416.5.

## 3. Result and discussion

The functional groups present in all the compounds were identified by FTIR spectra of these compounds. The compound 5e shows an additional peak due to the C-Br functional group at 603 $cm^{-1}$. The result of FTIR confirms the formation of the synthesized compounds. In $^{1}$HNMR, all the compounds display the almost same chemical shift values. However, in compound 5b singlet due to N-H is disappeared. It is because of the presence of two R-groups instead of one R-group and one H-atom which were present in all other groups. Similarly, when comparing the $^{1}$HNMR spectrum of the compounds 5b and 5e, it is observed that the multiplet at δ (77.291-7.392 ppm) is changed as a doublet at δ (7.371-7.393 ppm). It is due to the substitution of bromine that replaces hydrogen at $C_4$ in aniline. The same result was also obtained in $^{13}$CNMR the chemical shift value changes from 126.89 to 121.87 ppm. The structure of these compounds was confirmed from the $^{1}$HNMR and $^{13}$CNMR. From the table.1, it is observed that the melting point of the synthesized compounds is almost the same except for compounds 5a and 5d. These compounds have a lower melting point due to the presence of the heterocyclic compound. The results of LCMS analysis establish the formation of the products. The percentage of the elements present in the products was obtained from elemental analysis. These values agree with theoretically calculated values. Hence the formation of the products is also confirmed from this analysis.

### 4.1 Antibacterial and antifungal activity

#### 4.1.1 Antibacterial activity

A simple susceptibility screening test using the agar well diffusion method as adapted earlier was used (Perez et al., 1999; Bagamboula et al., 2004; Erdemoglu et al., 2003; Perez et al., 1990) to examine the antibacterial activity of the compounds. Each microorganism was suspended in Brain Heart Infusion (BHI) (Difco, Detroit, MI) broth and diluted to approximately $10^6$ colony-forming units (cfu) per mL. They were "flood-inoculated" onto the surface of BHI agar and Sabouraud Dextrose Agar (SDA) (Difco, Detriot, MI) and then dried. For *C. albicans* and *C. tropicalis*, SDA was used. Five-millimeter diameter wells were cut from the agar using a sterile cork-borer and 25 µL of the sample solutions were delivered into the wells. The plates were incubated for 18 h at 35 °C. Antimicrobial activity was evaluated by measuring the zone of inhibition against the test microorganisms. Ciprofloxacin (10 µg/mL) was the standard drug for antibacterial activities. The tests were carried out in duplicates. The results were interpreted in terms of the diameter of the inhibition zone.

The estimation of the Minimal Inhibitory Concentration (MIC) and Minimal Bactericidal Concentration (MBC) was carried out by the broth dilution method (Van der Berghe and Vlietinck, 1991). Dilutions of plant extracts from 1.0 to 0.25 mg/mL were used. Test bacteria culture was used at the concentration of 105 CFU/mL. MIC values were taken as the lowest plant extracts concentration that prevents visible bacterial growth after 24 h of incubation at 37 °C, and MBC was the lowest concentration that completely inhibited bacterial growth. Ciprofloxacin was used as a reference and appropriate controls with no plant extracts were used. Each experiment was made three times.

The antibacterial activity of all the synthesized compounds was tested in-vitro against pathogenic *Enterococcus feacalis, Staphylococcus aureus, Escherichia coli,* and *Salmonella typhi*. The results are presented in Table.2.

**Table .2 Antibacterial activity of the compounds**

| **Microorganisms** | **Control** | **5a** | **5b** | **5c** | **5d** | **5e** | **Ciprofloxacin** |
|---|---|---|---|---|---|---|---|
| | | **Zone of inhibition in mm** | | | | | |
| *Enterococcus faecalis* | - | 08.24±0.56 | 11.2±0.55 | 12.32±0.67 | 07.12±0.56 | 17.40±0.44 | 35.56±0.55 |
| *Staphylococcus aureus* | - | 11.41±0.30 | 08.12±0.10 | 08.00±0.10 | 11.86±0.30 | 10.32±0.66 | 40.54±0.48 |
| *Escherichia coli* | - | 14.21±0.45 | 08.13±0.00 | 08.95±0.00 | 13.14±0.45 | 11.64±0.54 | 38.54±0.60 |
| *Salmonella typhi* | - | 08.72±0.00 | 07.26±0.22 | 09.92±0.00 | 08.27±0.00 | 08.62±0.00 | 35.76±0.10 |


**Fig. 2. Antibacterial activity**

**4.1.2 Antifungal activity**

Antifungal activity was measured using a dilution in agar technique (Alves and Cury, 1992). The plant extracts (100 mg) were solubilized in 1 mL of dimethyl sulfoxide (DMSO) and serially two-fold diluted in Yeast Nitrogen Base Phosphate (YNBP) agar (Merck, Germany) to obtain a concentration range of 31.25-1000 µL/mL. YNBP agar plates containing only DMSO diluted in the same way, which did not influence fungal growth, were included as controls. All fungal strains were suspended in sterile physiological Tris buffer (pH 7.4, 0.05 M), homogenized, and adjusted to an OD (530 nm) of 0.05 (equivalent to $10^6$ CFU/mL). This suspension was used as the inoculum for the test in the agar plates. Fungal suspensions (3µL) were inoculated using an automatic micropippete (Brand), and plates (diameter: 25 cm) were incubated at 37 $^oC$ for 48 h. The minimal inhibitory concentration (MIC) was defined as the minimal concentration of the plant extracts which completely inhibited the visible growth of

the fungus. Ketoconazole was used as a reference and appropriate controls with no plant extracts were used. Each experiment was made three times.

The antifungal activity of all the synthesized compounds was tested in-vitro against pathogenic *Aspergillus niger*, *Aspergillus flavus, Candida albicans,* and *Penicillium sps*. The results are given in Table.3.

| **Microorganisms** | **Control** | **5a** | **5b** | **5c** | **5d** | **5e** | **Ketoconazole** |
|---|---|---|---|---|---|---|---|
| | | **Zone of inhibition in mm** | | | | | |
| *Aspergillus niger* | - | 10.21±0.10 | 07.43±0.10 | 07.89±0.00 | 10.36±0.10 | 10.12±0.20 | 12.54±0.50 |
| *Aspergillus flavus* | - | 08.86±0.30 | 06.45±0.00 | 07.21±0.10 | 09.25±0.30 | 08.32±0.01 | 09.30±0.30 |
| *Candida albicans* | - | 10.65±0.00 | 08.62±0.10 | 17.85±0.20 | 10.24±0.00 | 07.42±0.00 | 12.44±0.40 |
| *Penicillium sps* | - | 08.51±0.02 | 07.18±0.00 | 07.23±0.10 | 08.12±0.02 | 07.45±0.00 | 15.34±0.10 |

**Table .3. Antifungal activity of the compounds**


**Fig. 3. Antifungal activity**

### 4.2 Powder XRD studies

The powder XRD pattern is shown in fig.4. From the graph, it is observed that the peaks are sharp and intense. This shows that the sample is pure and crystalline in nature.

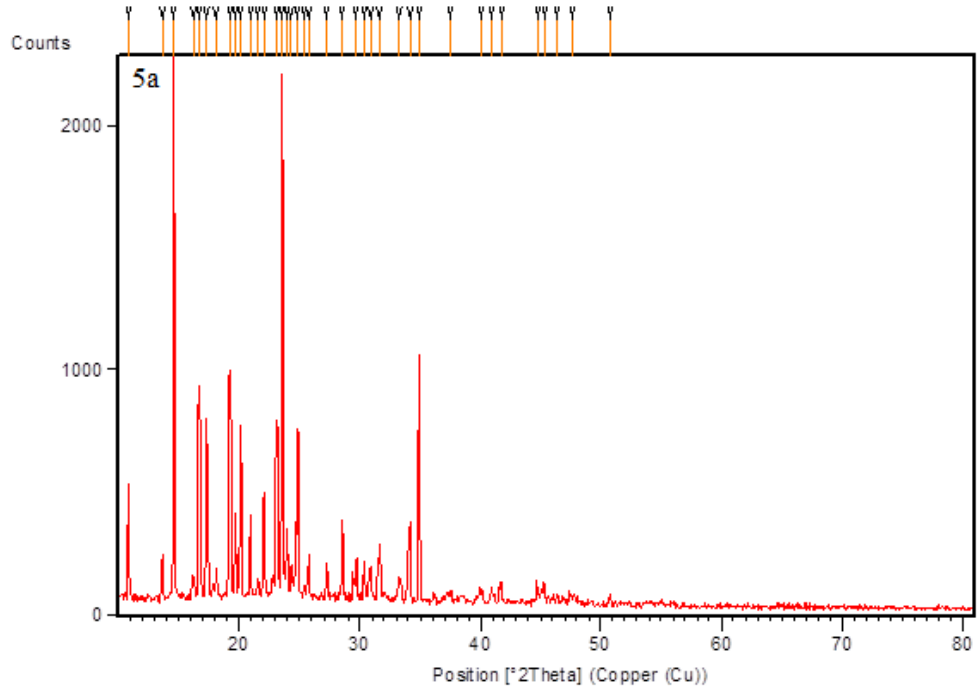



**Fig.4 piperidin-1-yl(2-(piperidin-1-yl)benzo[d]thiazol-6-yl)-methanone (5a)**

The crystalline size is calculated from the Debye-scherrer formula

$$D = \frac{K\lambda}{\beta \text{Cose}\theta} \quad \text{where } k = 0.9$$

$$D = \frac{0.9\lambda}{\beta \text{Cose}\theta}$$

$\lambda \rightarrow$ wavelength 1.546 A°
$\beta \rightarrow$ Full width half (0.1476 deg = 0.002576 rad)
$\theta \rightarrow$ Angle of diffraction (15.7262/2 = 7.8631deg = 0.13724 rad)
D = 0.9 X 0.154/0.002576 X Cos (0.13724)
D = 54.3340 nm.
The powder XRD pattern is shown in fig.5. From the graph, it is observed that the peaks are sharp and intense. This shows that the sample is pure and crystalline in nature.

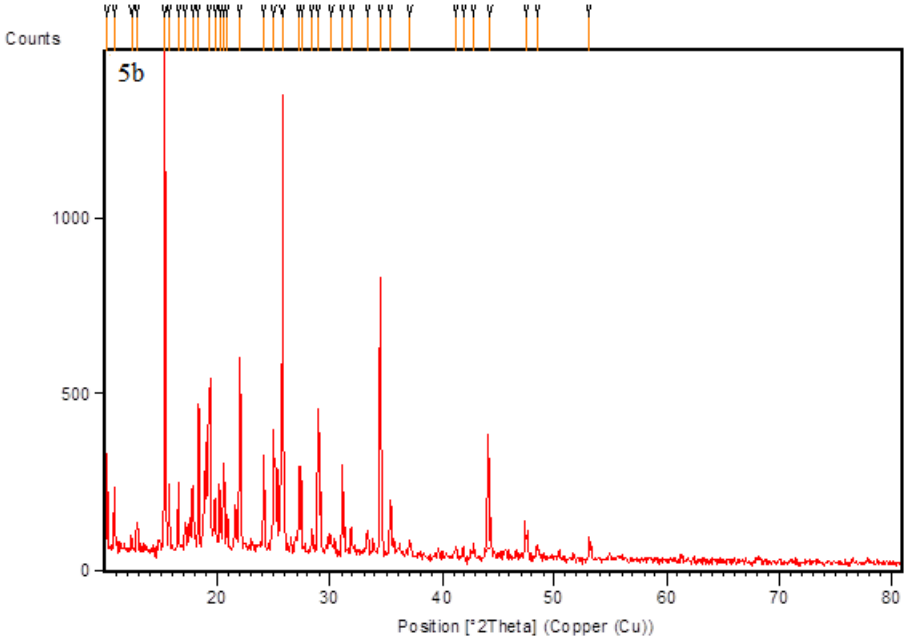



**Fig.5 N-benzyl-2-(piperidin-1-yl)benzo[d]thiazole-6-carboxamide (5b)**

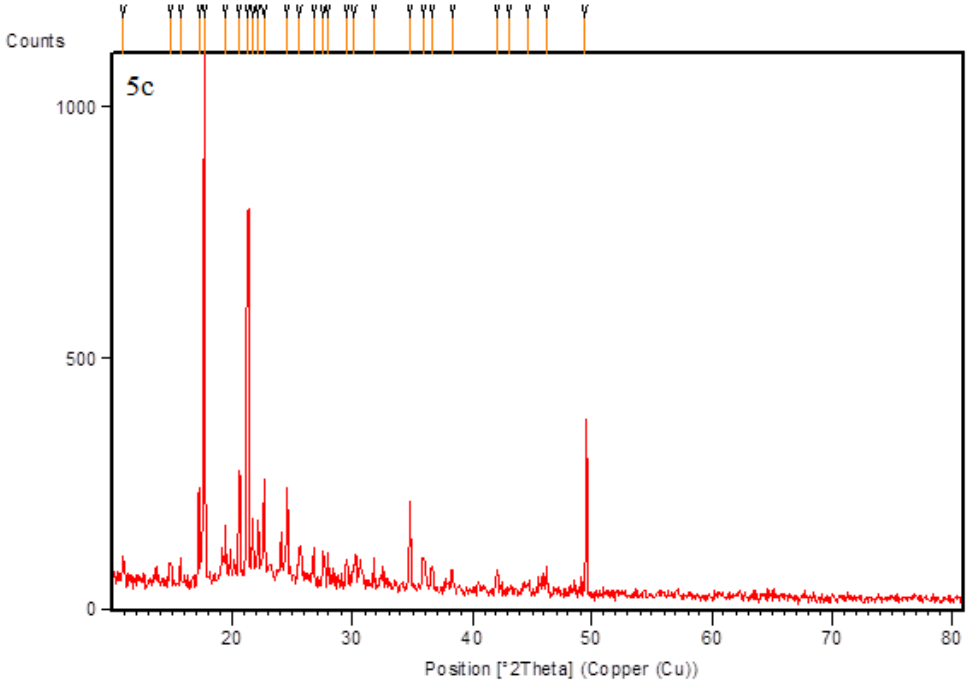



**Fig.6 N-cyclobutyl-2-(piperidin-1-yl)benzo[d]thiazole-6-carboxamide (5c)**

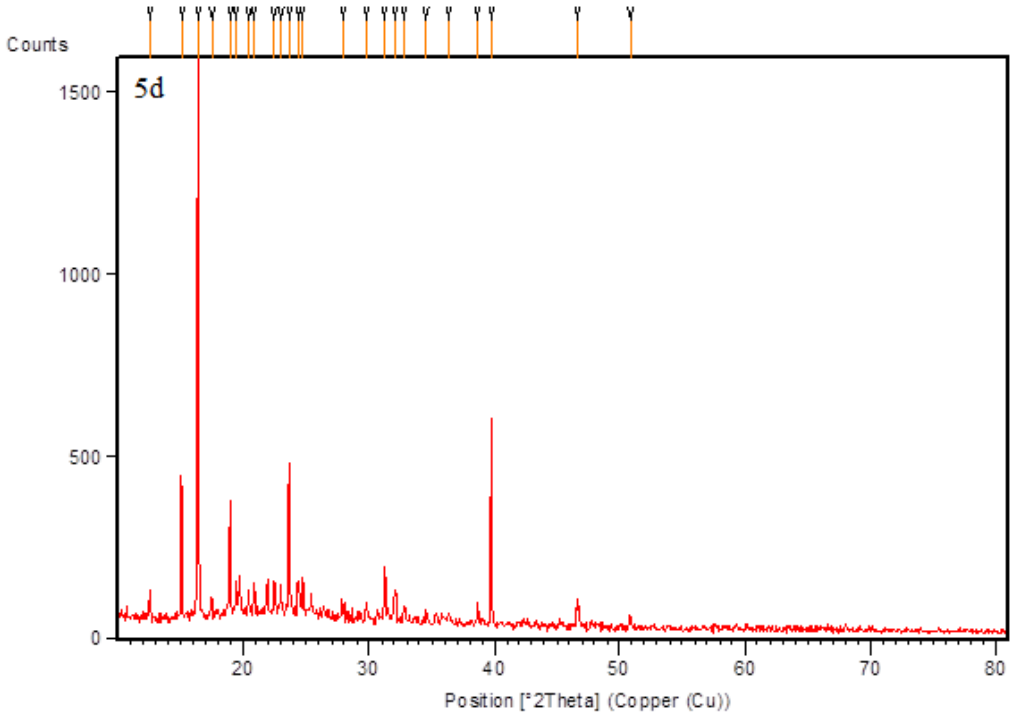



**Fig.7 N-(2-methoxyethyl)-2-(piperidin-1-yl)benzo[d]thiazole-6-carboxamide (5d)**

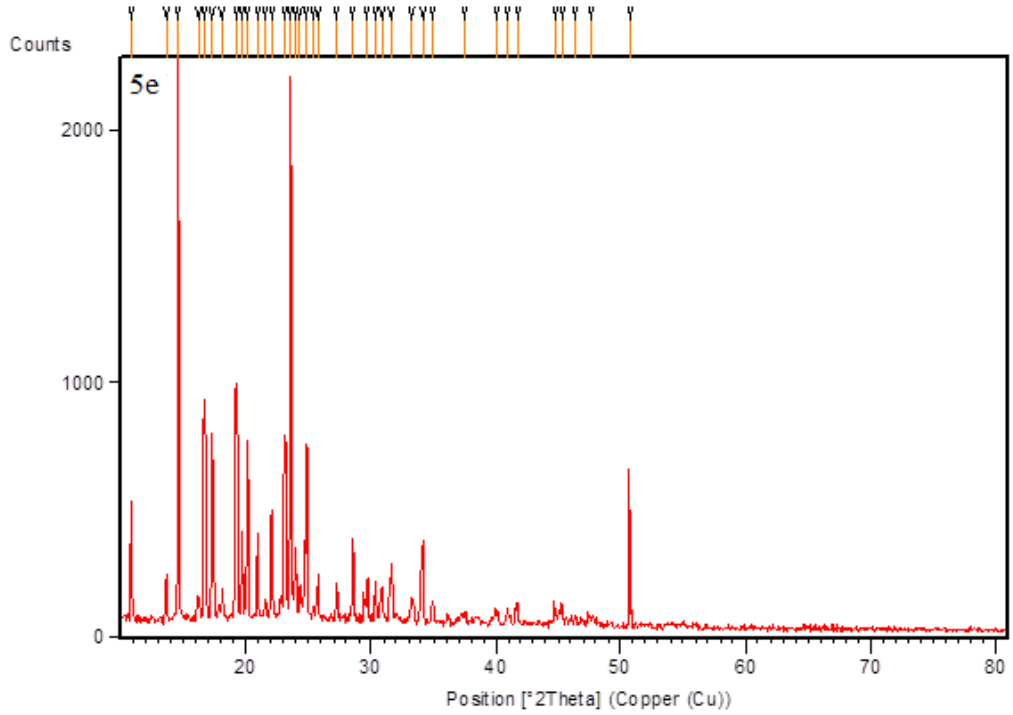



**Fig.8 N-(4-bromophenyl)-2-(piperidin-1-yl)benzo[d]thiazole-6-carboxamide (5e)**

The crystalline size of the samples are calculated and presented in Table.4

**Table.4 Crystalline size of the compounds**

| S.No | Compound name | Size (nm) |
|---|---|---|
| 1 | 5a | 54.4273 |
| 2 | 5b | 54.334 |
| 3 | 5c | 54.4562 |
| 4 | 5d | 54.4369 |
| 5 | 5e | 54.2678 |

Generally, the crystalline size value will increase or decrease depending on the ordering inside the material. So when materials are added it will disturb the order of the parent compound also the additional compound produces strain inside the crystal. For example, the crystalline size of compounds 5b and 5c are compared and presented in table.4. It is observed that the crystalline size of compound 5b is less than that of compound 5c. It is because in compound 5b more carbon atoms are present when compared with compound 5c. The more carbon atoms produce more amount of strain that restricts the growth and size of the crystal.

### 3.2 Photoluminescence

The photoluminescence (PL) spectrum examines material for its wide applications in the field of medical, biochemical, and chemical research. In PL spectroscopy, generally, a beam of light excites the electrons in the molecule of given materials and causes them to emit light in a longer wavelength than the observed radiation. The figures Fig.9 and Fig.13 show the PL spectra of the samples. These spectra give the absorption wavelength range from 364 to 384 nm which means the emission of blue radiation. The absorption peak is due to the band-to-band electronic transition in a material. The result predicts the use of the materials as a color filter.

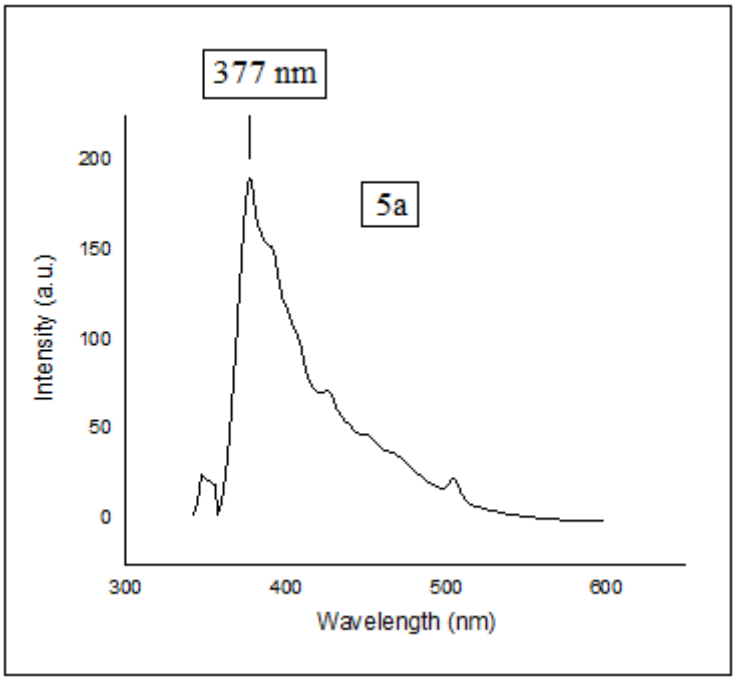



**Fig.9 piperidin-1-yl(2-(piperidin-1-yl)benzo[d]thiazol-6-yl)-methanone (5a)**

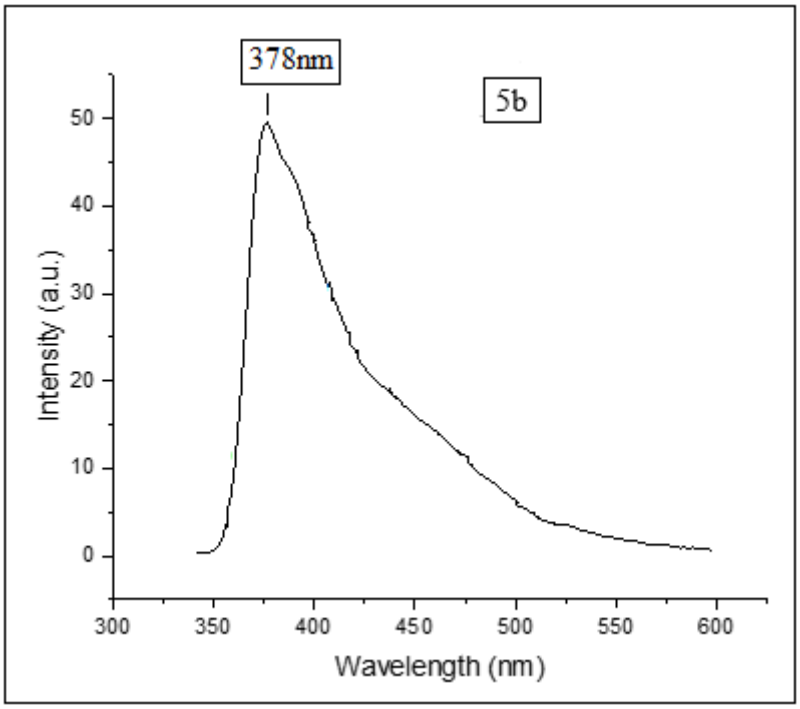



**Fig.10 N-benzyl-2-(piperidin-1-yl)benzo[d]thiazole-6-carboxamide (5b)**

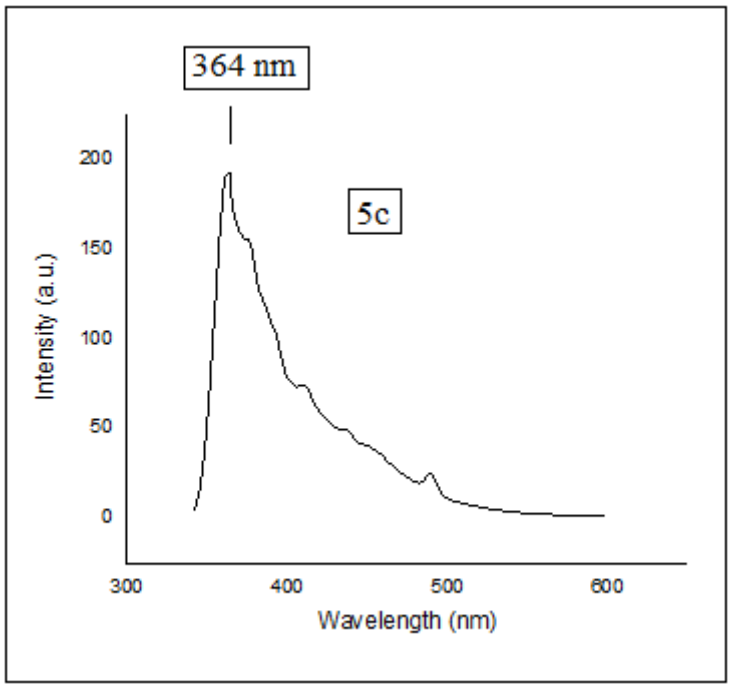



**Fig.11 N-cyclobutyl-2-(piperidin-1-yl)benzo[d]thiazole-6-carboxamide (5c)**

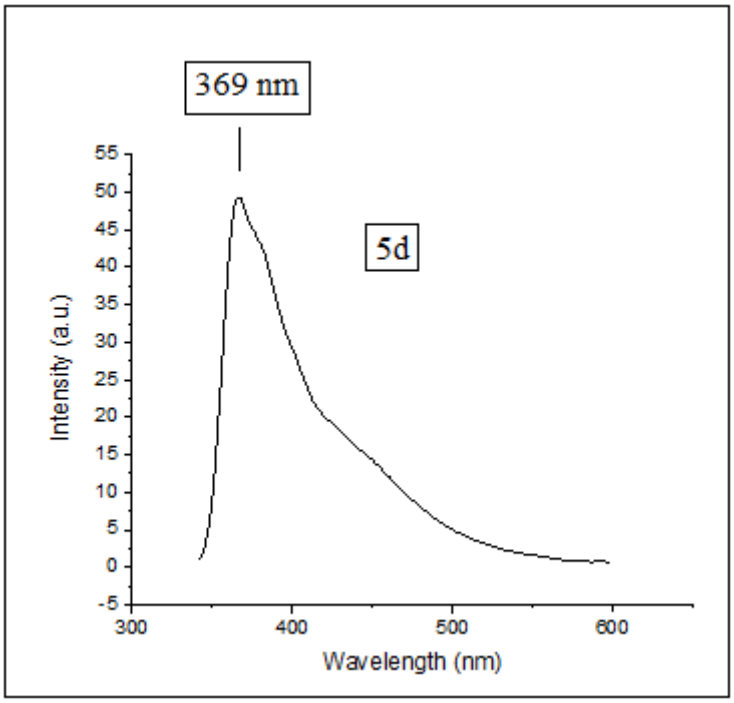



**Fig.12 N-(2-methoxyethyl)-2-(piperidin-1-yl)benzo[d]thiazole-6-carboxamide (5d)**

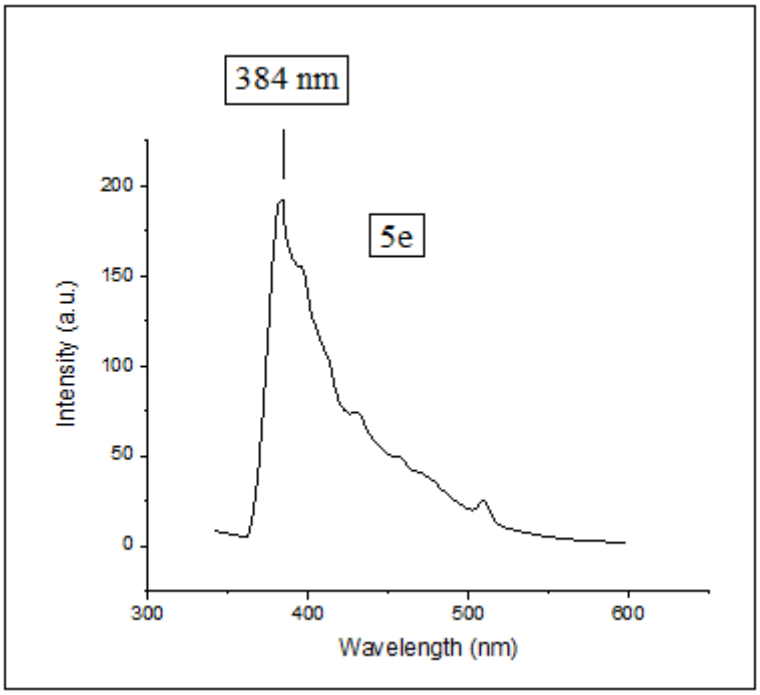



**Fig.13 N-(4-bromophenyl)-2-(piperidin-1-yl)benzo[d]thiazole-6-carboxamide (5e)**

## 4. Conclusion

The synthesis of derivatives of benzothiazole (5a-e) was carried out. The functional groups present in the samples were studied from the FTIR spectra and thus it confirms the synthesis of the compounds. The proton and carbon positions of these were obtained through 1HNMR and 13CNMR spectra respectively. The LCMS study indicates the good yield of all the compounds. The synthesized compounds were tested for antibacterial and antifungal activities. From the antibacterial test the compounds 5e, 5a &5d, 5a, and 5c are show the highest activity of *Enterococcus feacalis*, *Staphylococcus aureus*, *Escherichia coli*, and *Salmonella typhi*, respectively. In the antifungal activity test the compounds 5a, 5d & 5e, 5d, 5c, and 5a & 5d are show the higher activity of *Aspergillus niger*, *Aspergillus flavus*, *candida albicans*, and *Penicillium sps*, respectively. The crystalline nature of the samples was confirmed by the powder X-ray diffraction studies. These samples show good optical nature as studied from PL study. Hence the synthesized compounds can be used as color filters and in pharmaceutical applications.

## Reference

I. Akhtar J, Khan AA, Ali Z. Structure-activity relationship (SAR) study and design strategies of nitrogen-containing heterocyclic moieties for their anticancer activities. Eur J Med Chem 2017;5:143-89.

II. Keri SR, Patil RM, Patil AS, Budagumpi S. A comprehensive review in current developments of benzothiazole-based molecules in medicinal chemistry. Eur J Med Chem 2015; 89:207-51.

III. Venkatesh P, Pandeya NS. Synthesis, characterisation and anti-inflammatory activity of some 2-amino benzothiazole derivatives. Int J ChemTech Res 2009;1:1354-58.

IV. Dogruer DS, Ünlü S, Sahin MF, Yqilada E. Anti-nociceptive and anti-inflammatory activity of some (2-benzoxazolone-3-yl and 2-benzothiazolone-3-yl) acetic acid derivatives. Il Farmaco. 1998;53:80-84.

V. Liu Y, Wang Y, Dong G. Novel benzothiazole derivatives with a broad antifungal

spectrum: design, synthesis and structure–activity relationships. Med Chem Commun 2013;4:1551-61.

VI. Mats ME, Shani BG, Pasternak L. Synthesis and mechanism of hypoglycemic activity of benzothiazole derivatives. J Med Chem 2013;56:5335-50.

VII. Bele DS, Singhvi I. Synthesis and analgesic activity of some Mannich bases of 6-substituted-2-aminobenzothiazole. Res J Pharm and Tech 2008;1:22-24.

VIII. Padalkar SV, Gupta DV, Phatangare RK. Synthesis of novel dipodal-benzimidazole, benzoxazole and benzothiazole from cyanuric chloride: structural, photophysical and antimicrobial studies. J Saudi Chem Soc 2014;18:262-68.

IX. Cai J, Sun M, Wu X. Design and synthesis of novel 4- benzothiazole amino quinazolines Dasatinib derivatives as potential anti-tumor agents. Eur J Med Chem 2013;63:702-12.

X. Hutchinson I, Jennings SA, Vishnuvajjala BR, Westwell A.D, Stevens MFG. Antitumor benzothiazoles. 16. Synthesis and pharmaceutical properties of antitumor 2-(4-aminophenyl) benzothiazole amino acid prodrugs. J. Med. Chem. 2002;45:744-47.

XI. Delmas F, Avellaneda A, Giorgio DC. Synthesis and antileishmanial activity of (1,3-benzothiazol-2-yl) amino-9- (10H)-acridinone derivatives. Eur J Med Chem 2004;39: 685-90.

XII. Munirajasekhar D, Himaja M, Sunil VM. Synthesis and anthelmintic activity of 2-amino-6-substituted benzothiazoles. Int Res J Pharm 2011;2:1-7.

XIII. Yadav SP, Devprakash D, Senthilkumar GP. Benzothiazole: different methods of synthesis and diverse biological activities. Int J Pharm Sci Drug Res 2011;3:1-7.

XIV. Alaimo RJ, Pelosi SS, Freedman R. Synthesis and Antibacterial Evaluation of 2-(Substituted Phenylureido)-4-thiocyanatobenzothiazoles. J. Pharm. Sci. 1978;67:281-82.

XV. Caleta I, Grdiša M, Mrvoš-Sermek D, Cetina M, Trali´c-Kulenovi V, Paveli K, Karminski-Zamola K. Synthesis, crystal structure and antiproliferative evaluation of some new substituted benzothiazoles and styrylbenzothiazoles. Il Farmaco. 2004;59:297-05.

XVI. Vicini P, Geronikaki A, Incerti M, Busonera B, Poni G, Cabras CA, Colla PL. Synthesis and biological evaluation of benzo [d] isothiazole, benzothiazole and thiazole Schiff bases. Bioorg. Med. Chem, 2003;11:4785-89.

XVII. Cressier D, Prouillac C, Hernandez P, Amourette C, Diserbo M, Lion C, Rima G. Synthesis, antioxidant properties and radioprotective effects of new benzothiazoles and thiadiazoles. Bioorg. Med. Chem. 2009;17:5275-84.

XVIII. Siddiqui N, Rana A, Khan AS. Synthesis of benzothiazole semicarbazones as novel anticonvulsants—the role of hydrophobic domain. Bioorg Med Chem Lett 2007;17: 4178-82.

XIX. Jimonet P, Audiau F, Barreau M, Blanchard JC, Boireau A, Bour Y, Coleno MA, Doble A, Doerflinger G, Huu CD. Riluzole series. Synthesis and in vivo "antiglutamate" activity of 6-substituted-2-benzothiazolamines and 3-substituted-2-imino-benzothiazolines. J. Med. Chem. 1999;42:2828-43.

XX. Siddiqui N, Rana A, Khan SA, Haque SE, Alam MS, Ahsan W, Ahmed S. Anticonvulsant and Toxicity Evaluation of Newly Synthesized 1-[2-(3, 4-disubstituted phenyl)-3-chloro4-oxoazetidin-1-yl]-3-(6-substituted-1, 3-benzothiazol-2-yl) ureas. Acta Chim. Slov. 2009; 56:462-69.

XXI. Rajeeva B, Srinivasulu N, Shantakumar SM. Synthesis and Antimicrobial Activity Of Some New 2-Substituted Benzothiazole Derivatives. J. Chem. 2009;6:775-79.

XXII. Danzeisen R, Schwalenstoecker B, Gillardon F, Buerger E, Krzykalla V, Klinder K,

Schild L, Hengerer B, Ludolph AC, Dorner-Ciossek C. Targeted antioxidative and neuroprotective properties of the dopamine agonist pramipexole and its nondopaminergic enantiomer SND919CL2x [(+) 2-amino-4, 5, 6, 7-tetrahydro-6-Lpropylamino-benzathiazole dihydrochloride]. J. Pharmacol. Exp. Ther. 2006;316: 189-99.

XXIII. Mylari BL, Larson ER, Beyer TA, Zembrowski WJ, Aldinger CE, Dee MF, Siegel TW. Singleton DH. Novel, potent aldose reductase inhibitors: 3,4-dihydro-4-oxo-3-[[5-(trifluoromethyl)-2-benzothiazolyl] methyl]-1-phthalazineacetic acid (zopolrestat) and congeners. J. Med. Chem. 1991;22:108-22.

XXIV. Gunawardana GP, Koehn FE, Lee AY. Pyridoacridine alkaloids from deep water marine sponges of the family Pachastrellidae: structure revision of dercitin and related compounds and correlation with the Kuanoniamines. J Org Chem 1992;57:1523-26.

XXV. Bryson M, Fulton B, Benfield P. Riluzole a review of its pharmacodynamic and pharmacokinetic properties and therapeutic potential in amyotrophic lateral sclerosis. Drugs 1996;52:549-63.

XXVI. Vladimir B. Birman, Ximin Li. Org. Lett., 2008;10(6):1115-18.

XXVII. Fan Fang-Lua, Jing Jin-Qiua, Chen Xue-Meib. Journal of Chemical Research. 2015;36:661-64.

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