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Synthesis and Biological Properties of New Piperidine Substituted Benzothiazole Derivatives

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ABSTRACT

In present work, ethyl 2-aminobenzo[*d*]thiazole-6-carboxylate was reacted to piperidine using copper(II) bromide to get ethyl 2-(piperidin-1-yl)benzo[*d*]thiazole-6-carboxylate. The reaction of ethyl 2-(piperidin-1-yl)benzo[*d*]thiazole-6-carboxylate with NaOH produces 2-(piperidin-1-yl)benzo[*d*]thiazole-6-carboxylic acid. The inter-mediate 2-(piperidin-1-yl)benzo[*d*]thiazole-6-carboxylic acid have been isolated as stable compounds. The chemical structures of synthesized compounds were established based on the ^{1}H & ^{13}C NMR and IR spectral data. The mass of the novel compounds was established with the help of the LC-MS technique. The photoluminescence spectra explain the optical property of the compound. The biological studies of synthesized compounds show that the compound **5e** possesses good antibacterial activity and compound **5d** has good antifungal activity.

KEYWORDS

Piperidine derivatives, Benzothiazole, Crystallization, Optical activity, Biological property.

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 [1], antimicrobial [2,3], antifungal agents [4,5], as well as imaging agents for β-amyloid [6], anticancer [7], anti-tuberculosis [8], antiviral [9], antioxidant [10]. Several substituted benzothiazoles have been identified as potent anthelmintic drugs [11-14].

Aminobenzothiazoles have manifested a large scale of biological activities such as antiparkinsonian, dopamine antagonist [15,16], schistosomicidal agents [17], anticonvulsant activity [18], antileishmanial activity [14], analgesic agents [19] and antiasthmatic drugs [20]. Moreover, compounds containing condensed pyrimidines have been used as herbicide antidotes [21], antibacterials [22-24] and diuretics [25]. The BTA act as an effective catalyst [26] and the crystal nature shows fluorophore property [27]. Based on earlier studies, an attempt is made to synthesize and characterize benzothiazole derivatives.

EXPERIMENTAL

The chemicals *viz.* ethyl2-aminobenzo[*d*]thiazole-6-carboxylate, copper(II) bromide, *t*-nitrosobutane, piperidine, cesium carbonate, sodium hydroxide, acetonitrile, dimethyl-

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formamide, propane phosphonic 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.

The Perkin-Elmer spectrum 100 series spectrophotometer was used for FTIR studies of the sample. The ^{1}H NMR spectra were recorded on a 400 MHz Varian spectrometer. ^{13}C NMR spectrum of compound was taken at 100 MHz Brucker spectrometer with TMS as an 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 performed with silica gel 60-120 mesh. 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).

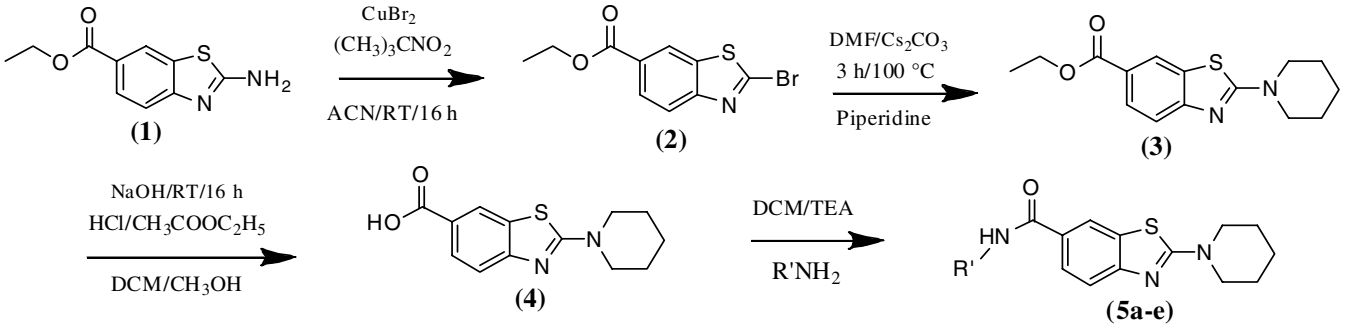
Synthesis of ethyl 2-bromobenzo[*d*]thiazole-6-caroxylate (2): In a round bottom flask, 5 g ethyl-2-aminobenzo[*d*]-thiazole-6-carboxylate dissolved in 1 equiv. of acetonitrile solvent then added 1 equiv. of copper(II) bromide with *t*-nitrosobutane. The reaction mixture was stirred up to 16 h at room temperature. The whole mixture was monitored by TLC complies. After that the reaction mixture was diluted with ethyl acetate, washed with 1.5 N HCl, water and brine solution. Now the mixture was dried over sodium sulphate and concentrated below 50 ºC. The crude has proceeded to the next step without purification and obtained as yellow solid. Yield: 54%. (LC-MS: 95% purity). b.p.: 139-40 ºC, IR (KBr, ν_{max}, cm^{-1}): 1742 (C=O), 1647 (C=N), 1324 (C-N), 684 (C-S), 610 (C-Br). ^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 8.420 (s, 1H, ArH), 7.453-7.482 (d, 2H, *J* = 11.6 Hz ArH), 4.302 (m, 2H, -CH_2), 1.289-1.301 (t, 3H, *J* = 4.8 Hz -CH_3). ^{13}C NMR (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. Anal. calcd. (found) % for $C_{10}H_8NO_2SBr$: C, 41.97 (42.04); H, 2.82 (2.90); N, 4.89 (4.92); O, 11.19 (11.13); S, 11.21 (11.15); Br, 27.92 (27.86). LCMS [M+1]$^+$: *m/z* 287.1.

Synthesis of ethyl 2-(piperidin-1-yl)benzo[*d*]thiazole-6-caroxylate (3): Compound **2** was dissolved in DMF and added to *N*-alkylation base (Cs_2CO_3 1.5 equiv.) followed by the addition of piperidine (1.1 equiv.) and then heated up to 100 ºC for 3 h. The reaction mixture was allowed to cool and purified to get compound **3** as orange solid with 56% yield, (LCMS: 95.7% purity), m.p.: 161-162 ºC, IR (KBr, ν_{max}, cm^{-1}): 1740 (C=O), 1643 (C=N), 1326 (C-N), 681 (C-S). ^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 1.536-1.553 (m, 6H, -CH_2), 3.691-3.724, (t, 4H, *J* = 13.2 Hz -CH_2) 8.414 (s, 1H, ArH), 7.697-7.721 (d, 2H, *J* = 9.2 Hz ArH), 4.292 (m, 2H, -CH_2), 1.292-1.313 (t, 3H, *J* = 8.4 Hz -CH_3). ^{13}C NMR (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. Anal. calcd. (found) % for $C_{15}H_{18}N_2O_2S$: C, 62.04 (61.98); H, 6.25 (6.27); N 9.65 (9.69); O, 11.02 (11.05); S, 11.04 (11.01). LCMS [M+1]$^+$: *m/z* 291.3.

Synthesis of 2-(piperidin-1-yl)benzo[*d*]thiazole-6-carboxylic acid (4): Compound **3** (2 g) dissolved in methanol was added in 2 equiv. NaOH solution and stirred for 1 h 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, eluted with DCM and methanol (2.4%) to get the desired product as yellow solid of 67% yield. LCMS: 95.3% purity, m.p.: 169-70 ºC, IR (KBr, ν_{max}, cm^{-1}): 3242 (O-H), 1761 (C=O), 1645 (C=N), 1321 (C-N), 684 (C-S). ^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 1.546-1.5621 (m, 6H, -CH_2), 3.716-3.734 (t, 4H, *J* = 7.2 Hz, -CH_2) 8.618, (s, 1H, ArH), 7.882-7.894 (d, 2H, *J* = 74.8 Hz, ArH), 11.121 (s, 1H, -OH). ^{13}C NMR (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. Anal. calcd. (found) % for $C_{13}H_{14}N_2O_2S$: C, 59.52 (59.59); H, 5.38 (5.41); N, 10.68 (10.72); O, 12.20 (12.12); S, 12.22 (12.16). LCMS [M+1]$^+$: *m/z* 263.3.

Synthesis of benzothiazole derivatives (5a-e): Compound **4** (1 equiv.) dissolved in dichloromethane (1 mL) was added to a mixture of simple amine (1 equiv.) and triethylamine (2 equiv.) and stirred for 2 h. Then cooled to 0 ºC. Now, propane phosphoric acid anhydride (T3P) (50% in ethyl acetate) (1.5 equiv.) was added and again stirred for 12 h. After completion of the reaction, monitor by TLC, ice water was added and extracted with dichloromethane. The product was washed with water followed by brine solution, dried over sodium sulphate and then finally 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**. (**Scheme-I**).

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.p.: 145-146 ºC, IR (KBr, ν_{max}, cm^{-1}): 2936 (C-H), 1623 (C=O), 1557 (C=N, *str.* benzothiazole), 1525 (C=C), 1289 (C-N) and 610



Scheme-I: The reaction scheme

(C-S). ^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 1.558-580 (m, 12H, -CH_2), 3.740-3.760 (t, 8H, *J* = 8 Hz -CH_2), 7.921-7.939 (d, 1H, *J* = 7.2 Hz ArH), 7.630-7.639 (d, 1H, *J* = 3.6 Hz ArH) and 8.380 (s, 1H, ArH). ^{13}C NMR (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. Elemental analysis calcd. (found) % for $C_{18}H_{23}N_3OS$: C, 65.62 (65.68); H, 7.04 (7.01); N, 12.75 (12.69); O, 4.86 (4.83); S, 9.73 (9.79%). LCMS $[M+1]^+$: *m/z* 329.9.

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.p.: 185-86 °C, IR (KBr, ν_{max}, cm^{-1}): 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}H NMR (400 MHz, DMSO-d_6, ppm): δ 1.548-1.591 (m, 6H, -CH_2), 3.690-3.701 (t, 4H, *J* = 4.4 Hz -CH_2), 4.316-4.333 (d, 2H, *J* = 6.8 Hz -CH_2), 7.291-7.392 (m, 5H, ArH), 7.672-7.685 (d, 1H, *J* = 5.2 Hz ArH), 7.878-7.895 (d, 1H, *J* = 6.8 Hz ArH), 8.392 (s, 1H, ArH) and 8.058 (t, 1H, -NH). ^{13}C NMR (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. Elemental analysis calcd. (found) % for $C_{20}H_{21}N_3OS$: C, 68.35 (68.41); H, 6.02 (6.09), N, 11.96 (11.92); O, 4.55 (4.51); S, 9.12 (9.07). LCMS $[M+1]^+$: *m/z* 351.9.

Synthesis of *N*-cyclobutyl-2-(piperidin-1-yl)benzo[*d*]-thiazole-6-carboxamide (5c): The cyclobutyl 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.p.: 215-216 °C. IR (KBr, ν_{max}, cm^{-1}): 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}H NMR (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* = 6.8 Hz -CH_2), 4.089-4.120 (m, 1H, -CH), 7.626-7.644 (d, 1H, *J* = 7.2 Hz ArH), 7.904-7.914 (d, 1H, *J* = 4 Hz ArH), 8.100-8.107 (d, 1H, *J* = 2.8 Hz -NH) and 8.388 (s, 1H, ArH). ^{13}C NMR (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. Elemental analysis calcd. (found) % for $C_{17}H_{21}N_3OS$: C, 64.73 (64.68); H, 6.71 (6.65); N, 13.32 (13.38); O, 5.07 (5.16); S, 10.17 (10.13). LCMS $[M+1]^+$: *m/z* 317.8.

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.p.: 163-64 ºC, IR (KBr, ν_{max}, cm^{-1}): 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}H NMR (400 MHz, DMSO-d_6, ppm): δ 1.554-1.581 (m, 6H, -CH_2), 3.755-3.784 (t, 6H, *J* = 11.6 Hz -CH_2), 7.923-7.938 (d, 1H, *J* = 6 Hz ArH), 7.632-7.639 (d, 1H, *J* = 2.8 Hz 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}C NMR (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. Elemental analysis calcd. (found) % for $C_{16}H_{21}N_3O_2S$: C, 60.16 (60.09); H, 6.63 (6.67); N, 13.16 (13.21), O, 10.02 (10.06); S, 10.04 (9.97). LCMS $[M+1]^+$: *m/z* 319.7.

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-bromoaniline. It was obtained as a white crystalline solid with a 62% yield. (LCMS: 95.6% purity), m.p.: 217-18 ºC, IR (KBr, ν_{max}, cm^{-1}): 3289 (N-H), 1624 (C=O), 1624 (C=N), 1327 (C-N), 685 (C-S), 603 (C-Br). ^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 1.524-691 (m, 6H, -CH_2), 3.732-3.751 (t, 4H, *J* = 7.6 Hz -CH_2), 7.912-7.932 (d, 1H, *J* = 8 Hz ArH), 7.371-7.393 (d, 5H, *J* = 8.8 Hz ArH), 8.386 (S, 1H, ArH), 9.163 (S, 1H, -NH). ^{13}C NMR (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. Elemental analysis calcd. (found) % for $C_{19}H_{18}N_3OSBr$: C, 54.81 (54.90); H, 4.36 (4.42); Br, 19.19 (19.12); N, 10.09 (10.02), O, 3.84 (3.79), S, 7.70 (7.75). LCMS $[M+1]^+$: *m/z* 416.5.

Biological activity

Antibacterial activity: The antibacterial activity of all the synthesized compounds was tested *in vitro* against pathogenic *Enterococcus feacalis*, *Staphylococcus aureus*, *Escherichia coli* and *Salmonella typhi*. A simple susceptibility screening test using the agar well diffusion method. Each microorganism was suspended in Brain Heart Infusion (BHI) 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) 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 ºC. 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 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. Dilutions of plant extracts from 1.0 to 0.25 mg/mL were used. Test bacteria culture was used at the concentration of 10^5 CFU/mL. MIC values were taken as the lowest plant extracts concentration that prevents visible bacterial growth after 24 h of incubation at 37 ºC and MBC was the lowest concentration that completely inhibited bacterial growth. Ciprofloxacin was used as a reference and each experiment was made three times.

Antifungal activity: The antifungal activity of all the synthesized compounds was tested *in vitro* against pathogenic *Aspergillus niger*, *Aspergillus flavus*, *Candida albicans* and *Penicillium* sp. Antifungal activity was measured using a dilution in agar technique. The compounds (100 mg) were solubilized in 1 mL of DMSO and serially two-fold diluted in yeast nitrogen base phosphate (YNBP) agar (Merck) to obtain a concentration range of 31.25-1000 µL/mL. The 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 1×10^6 CFU/mL). This suspension was used as the inoculum for the test in the agar plates. Fungal suspen-

sions (3 µL) were inoculated using an automatic micropippete 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 each experiment was made three times.

RESULTS AND DISCUSSION

The functional groups present in all the compounds were identified by FTIR spectra of these compounds. Compound **5c** shows an additional peak due to C-F functional group at 1240 cm^{-1}. The result of FTIR confirms the formation of the synthesized compounds. In ^{1}H NMR, all the compounds display the almost same chemical shift values. However, in compound **5d** 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}H NMR spectrum of compounds **5a** and **5c**, it is observed that the doublet at δ 7.635-7.641 ppm is changed as a singlet at δ 7.742 ppm. It is due to the substitution of fluorine that replaces hydrogen at C-3 in aniline. The same result was also obtained in ^{13}C NMR the chemical shift value changes from δ 126.89-121.87 ppm.

It is observed that the melting point of the synthesized compounds is almost the same except for compound **5d**. Compound **5d** shows a lower melting point value. The addition of heterocyclic compound (morpholine) weakens the bond and hence reduces the melting point. The results of LCMS analysis establish the formation of the products. These values agreed with theoretically calculated values. Hence the formation of the products is also confirmed from this analysis.

Photoluminescence: In photoluminescence spectrum, 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. Fig. 1 shows the PL spectra of the synthesized compounds (**5a-e**). These spectra give the absorption wavelength at 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 colour filter.

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 LCMS study indicates the good yield of all the compounds. The synthesized compounds exhibited antibacterial and antifungal activities. From the antibacterial test the compounds **5e, 5a & 5d, 5a** and **5c** show the highest activity of *Enterococcus feacalis, Staphylococcus aureus, Escherichia coli* and *Salmonella typhi*, respectively (Table-1). In the antifungal activity test the compounds **5a, 5d & 5e,**

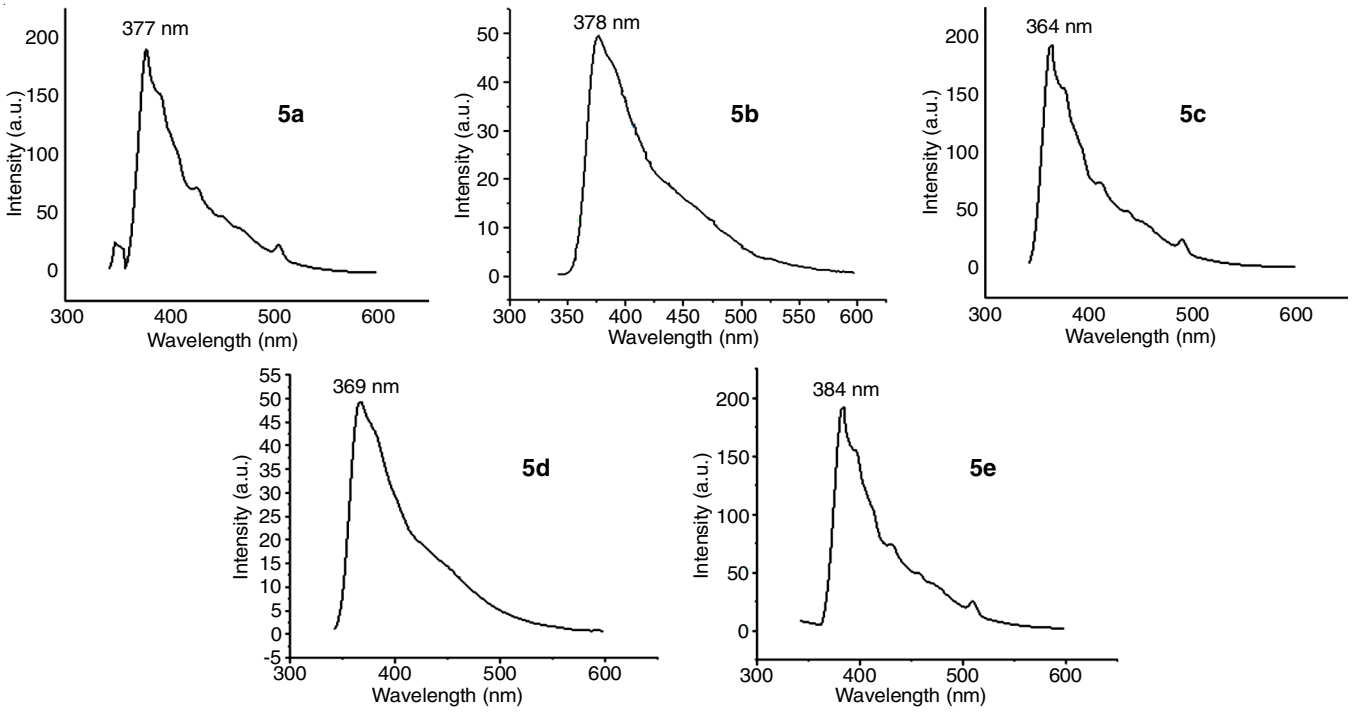


Fig. 1. Photoluminescence spectra of synthesized compounds (**5a-e**)

TABLE-1
ANTIBACTERIAL ACTIVITY DATA OF THE SYNTHESIZED COMPOUNDS (**5a-e**)

Microorganisms	Zone of inhibition (mm)					
	5a	**5b**	**5c**	**5d**	**5e**	Ciprofloxacin
Enterococcus faecalis	10.5 ± 0.55	11.24 ± 0.67	18.45 ± 0.44	07.44 ± 0.56	11.54 ± 0.67	35.56 ± 0.55
Staphylococcus aureus	08.42 ± 0.10	07.12 ± 0.10	10.56 ± 0.66	12.34 ± 0.30	07.55 ± 0.10	40.54 ± 0.48
Escherichia coli	07.55 ± 0.00	08.15 ± 0.00	11.87 ± 0.54	13.44 ± 0.45	08.45 ± 0.00	38.54 ± 0.60
Salmonella typhi	06.67 ± 0.22	09.21 ± 0.00	08.22 ± 0.00	08.57 ± 0.00	09.45 ± 0.00	35.76 ± 0.10

TABLE-2
ANTIFUNGAL ACTIVITY DATA OF THE SYNTHESIZED COMPOUNDS (**5a-e**)

Microorganisms	Zone of inhibition (mm)					
	5a	**5b**	**5c**	**5d**	**5e**	Ketoconazole
Aspergillus niger	07.32 ± 0.10	08.13 ± 0.00	10.55 ± 0.20	10.67 ± 0.10	08.34 ± 0.00	12.54 ± 0.50
Aspergillus flavus	06.35 ± 0.00	06.64 ± 0.10	08.22 ± 0.01	09.56 ± 0.30	07.10 ± 0.10	09.30 ± 0.30
Candida albicans	08.34 ± 0.10	11.24 ± 0.20	07.35 ± 0.00	10.45 ± 0.00	12.15 ± 0.20	12.44 ± 0.40
Penicillium sp.	07.10 ± 0.00	07.15 ± 0.10	07.50 ± 0.00	08.25 ± 0.02	07.40 ± 0.10	15.34 ± 0.10

5d, 5c and **5a & 5d** show the higher activity of *Aspergillus niger*, *Aspergillus flavus*, *Candida albicans and Penicillium* sp., respectively (Table-2). The synthesized compounds also show good optical nature as studied from PL spectra. Hence, the synthesized compounds can be used as colour filter and in pharmaceutical applications.

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