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SYNTHESIS, CHARACTERIZATION AND MICROBIAL STUDIES OF BENZOXAZOLE CLUBBED THIOL DERIVATIVES

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ABSTRACT:
The lead compounds 2-(5-nitrobenzo[d]oxazol-2-yl-thio)-N-arylacetamide Derivatives $4_{a\text{-}n}$ and 2-(5-methylbenzo[d]oxazol-2-yl-thio)-N-arylacetamide $4_{aa\text{-}an}$ were synthesised by three steps. The target molecules were confirmed by means of various spectral analytical techniques like IR, ^{1}H NMR, ^{13}C NMR, Elemental analysis and mass spectrum.The antimicrobial properties of the synthesized derivatives measured. Their ZOI values were evaluated by using the diffusion method against Gram-positive bacteria (*Bacillus subtilis)*, Gram-negative bacteria (*Escherichia coli)* and fungi (*Aspergillus niger).*

KEYWORDS: 2-(5-nitrobenzo[d]oxazol-2-yl-thiol)-N-arylacetamide, 2-(5 methylbenzo[d]oxazol-2-yl-thiol)-N-arylacetamide, ZOI, antimicrobial activity

INTRODUCTION:

Heterocyclic nucleuses are carbon-based cyclic compositions that include at least one heteroatom, such as oxygen, nitrogen, or sulphur[i]. They are potent therapeutic building blocks and have a big character in the cellular metabolism[ii]. Many researchers throughout the world have been drawn to these therapeutically useful oxazole conjugates in order to scout and synthesise this appealing skeleton for clinically unique latent beneficial intermediates.Oxazole compounds as the bioisostere of thiazoles[iii-iv],imidazoles and benzimidazoles[v],triazoles[vi-viii]and tetrazoles[ix]have attracted increasingly attentions. Recently, numerous researchers have been devoting to oxazole compounds as medicinal agents and hopefully discover novel chemical scaffold compounds with broad spectrum, high bioactivity, low toxicity and excellent pharmacokinetic property[x-xii]. The utilization of the oxazole moiety by naturally occurring composites revealed energising results like anticancer, antimicrobial, anti-hyperglycemic, anti-inflammatory, anticancer, antimicrobial,antiviral, antifungal, and antibacterial

properties.Because of their shape and compositional diversity, oxazole-based molecules, as a central scaffold, not only enable various types of interactions with various receptors and enzymes, exhibiting broad biological activities, but also occupy a core position in medicinal chemistry, demonstrating enormous development value and facilitating the discovery of newer potential therapeutic agents[xiii-xvii]. Because of the wide range of therapeutic response profiles, chemical synthesis of oxazole and its derivatives has become a major goal, attracting the attention of pharmacologists and chemists across the world to be investigated properly for the benefit of humanity.The oxazole is being considered as a major molecular framework for the discovery of new therapies also.

EXPERIMENTAL:

Merck Itd., sdfine chemicals and LOBA chemie provided the necessary reagents and solvents for the synthesis. The open-end capillary method was used to estimate the melting points of the final derivatives, which were reported uncorrected. TLC plates(TLC silica gel 60 F_{254}) were acquired from Merck and the mobile phase was a 6:4 mixture of ethyl acetate and n-hexane. Bruker FT-IR alpha-t was used to obtain the IR spectra for each derivative (ATR). Bruker spectrometers(400 MHz and 100 MHz, respectively) were used to obtain ^{1}H and ^{13}C NMR data (DMSO-d_6 was used as solvent and TMS as reference).A Schmindzu mass spectrophotometer was used to determine the mass spectra data for each derivative. The elemental data was collected using a perkin-Elmer 2400 CHN analyzer.

GENERAL PROCEDURE:

Step-1: Synthesis of 5-aryl-benzo[d]oxazole-2-thiol

In ethanol, 2-amino-4-aryl phenol (0.01mol) was refluxed with potassium hydroxide (0.01mol) and CS_2(0.02mol) for 16-18 hours. The reaction mixture was allowed to cool and then poured into crushed ice and the solution was neutralised with diluted HCl. The precipitate was filtered and recrystallized in ethanol.

Step-2: Synthesis of 2-chloro-N-(aryl) acetamide derivatives

Various substituted amines (0.01 mol) were added to a solution of DMF (35 ml) containing TEA (3–4 drops). The mixture was stirred for 10 min at room temperature. Chloroacetylchloride (0.015 mol, 113 g/mol, 1.19 ml) was added to the above mixture, maintaining the temperature between 0 and 5 °C. The obtained solution was then stirred at room temperature for 4–6 h. The completion of reaction was monitored with TLC using toluene: acetone (8:2) as mobile phase. The solution was then added onto crushed ice and the separated precipitates were filtered and dried. The product was crystallized from ethanol

Step-3: Synthesis of final compounds $4_{a\text{-}n}$

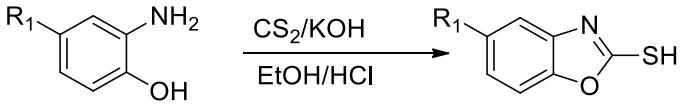
5-nitro-1, 3-benzoxazol-2-thiol (0.01 mol) was made soluble in acetone. To this well stirred solution of different derivatives of 2-chloro-N-phenyl acetamide (0.01 mol) were added. K_2CO_3 (0.02 mol) was added to the above mixture and was allowed to stir for 4 h at room temperature. The completion of reaction was monitored using TLC plate with mobile phase ethyl acetate: n-hexane (6:4). The final products thus obtained were poured into ice cold water. The precipitates were filtered and washed with water. The final products were crystallized from alcohol.

Step-3: Synthesis of final compounds $4_{aa\text{-}an}$

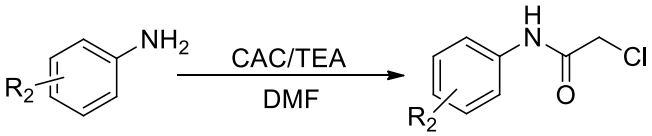
In a round bottom flask containing 5-methyl-1, 3-benzoxazol-2-thiol (0.01 mol) in acetone, various derivatives of 2-chloro-N-phenyl acetamide (0.01 mol) were added. K_2CO_3 (0.02 mol) was added to the above mixture and was allowed to stir for 4 h at room temperature. The completion of reaction was monitored using TLC plate with mobile phase ethyl acetate: n-

hexane (6:4). The final products were poured into ice cold water. The precipitates were filtered and washed with water. The final products were crystallized from alcohol.

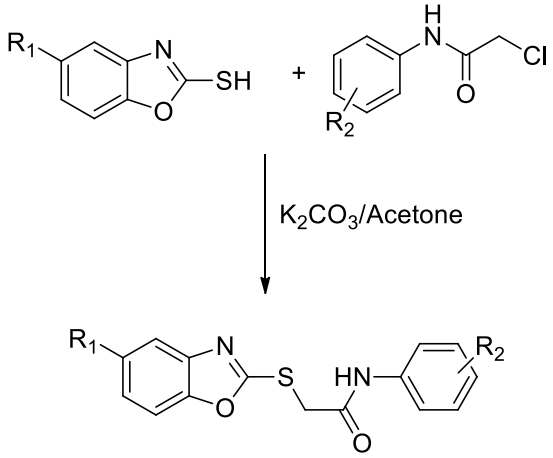
Synthesis of 5-aryl-benzo[d]oxazole-2-thiol (Step-I)



Synthesis of 2-chloro-N-(aryl) acetamide derivatives (Step-II)



Synthesis of 2-(5-aryl-benzo[d]oxazol-2-ylthio)-N-arylacetamide (Step-III)



4_{a-n}and4_{aa-an}

Scheme-1

ANALYTICAL DISCUSSION:

Synthesis of2-((5-nitrobenzo[d]oxazol-2-yl)thio)-N-phenyl acetamide(4_a)

IR(ATR): 3352,2965,2922,1682,1456,1342,1136,1112 cm^{-1}. ^1H NMR(400 MHz,DMSO-d6,δ,ppm): δ=4.42 (s,2H,C$\underline{H}_2$), 7.04-8.42 (m, 8H, Ar-$\underline{H}$), 10.43(s,1H,N$\underline{H}$). ^{13}C NMR(100 MHz,DMSOd_6,δ,ppm):δ=37.0,110.5,113.7,119.1,120.1,123.5,128.2,128.7,138.4,141.7,154.9, 164.3,168.1. MS (m/z): 330 M^+. Anal. cald. for $C_{15}H_{11}N_3O_4S$(329):C,54.71; H,3.37; N,12.76;O,19.43;S, 9.73 %. Found C,54.69; H,3.30; N,12.75; S, 9.70 %.

Synthesis of 2-((5-nitrobenzo[d]oxazol-2-yl)thio)-N-(2-nitrophenyl) acetamide(4_b)

IR(ATR): 3345, 2957, 2923, 1673, 1544, 1434, 1323, 1132, 1118 cm^{-1}. ^1H NMR(400 MHz,DMSO-d_6,δ,ppm): δ=4.40 (s,2$\underline{H}$,CH_2), 7.00-8.41 (m,7H, Ar-$\underline{H}$), 10.42(s,1H,N$\underline{H}$). ^{13}C NMR(100MHz,DMSOd_6,δ,ppm):δ=37.0,110.5,113.7,119.1,120.1,123.5,128.2,128.7,138.4,14 1.7,154.9,164.3,168.1. MS (m/z): 375 M^+. Anal. cald. for $C_{15}H_{10}N_4O_6S$(374):C,48.13; H,2.69; N,14.97;O, 25.94;S, 8.56 %. Found C,48.10; H,2.56; N,14.75;O, 25.92 S, 8.60%.

Synthesis of 2-((5-nitrobenzo[d]oxazol-2-yl)thio)-N-(3-nitrophenyl) acetamide(4_c)

IR(ATR): 3348,2970,2928,1676,1541,1439,1344,1139,1116 cm^{-1}. ^1H NMR(400 MHz,DMSO-d_6, δ, ppm): δ=4.32 (s,2H,C$\underline{H}_2$), 7.06-8.45 (m, 7H, Ar-$\underline{H}$), 10.49(s,1H,N$\underline{H}$). ^{13}C NMR(100MHz,DMSOd_6,δ,ppm):δ=38.4,110.7,114.6,119.5,120.3,124.2,128.7,129.3,138.7,14 2.0,155.3,165.1,168.7. MS (m/z): 375 M^+. Anal. cald. for $C_{15}H_{10}N_4O_6S$ (374):C,48.34; H,2.67; N,14.95;O, 25.85 ; S, 8.49 %. Found C,48.28; H,2.58; N,14.94;O, 25.79 S, 8.47%.

Synthesis of 2-((5-nitrobenzo[d]oxazol-2-yl)thio)-N-(4-nitrophenyl) acetamide(4_d)

IR(ATR): 3349,2983,2934,1680,1564,1444,1346,1142,1121 cm^{-1}. ^1H NMR(400 MHz,DMSO-d_6,δ,ppm): δ=4.40 (s,2H,C$\underline{H}_2$), 7.00-8.41 (m, 7H, Ar-$\underline{H}$), 10.42(s,1H,N$\underline{H}$). ^{13}C NMR(100MHz,DMSOd_6,δ,ppm):δ=38.5,110.8,115.0,119.8,121.1,124.3,128.8,129.7,138.9,142.3,155.9,165.1,169.3. MS (m/z): 375 M^+. Anal. cald. for $C_{15}H_{10}N_4O_6S$ (374):C,48.24; H,2.72; N,15.34;O, 26.10; S, 8.61 %. Found C,48.18; H,2.68; N,15.40;O, 26.08 S, 8.64%.

Synthesis of 2-((5-nitrobenzo[d]oxazol-2-yl)thio)-N-(o-tolyl)acetamide(4_e)

IR(ATR): 3410,3070,2957,1710,1467,1354,1153,1126 cm^{-1}. ^1H NMR(400 MHz,DMSO-d_6,δ,ppm): δ=2.19 (s,3H,C$\underline{H}_3$)4.43 (s,2H,C$\underline{H}_2$), 7.00-8.41 (m, 7H, Ar-$\underline{H}$), 10.42 (s,1H,N$\underline{H}$).^{13}CNMR(100MHz,DMSOd_6,δ,ppm):δ=17.3,37.0,110.5,113.7,119.1,120.1,123.5,128.2,128.7,138.4,141.7,154.9,164.3,168.1. MS (m/z): 344 M^+. Anal. cald. for $C_{16}H_{13}N_3O_4S$(343):C,55.97; H,3.82; N,12.24;O,18.64;S,9.34 %. Found C,55.90; H,3.80; N,12.25;O, 18.62 S, 9.30%.

Synthesis of 2-((5-nitrobenzo[d]oxazol-2-yl)thio)-N-(m-tolyl)acetamide(4_f)

IR(ATR): 3416,3067,2965,1712, 1468,1359,1151,1132 cm^{-1}. ^1H NMR(400 MHz,DMSO-d6,δ,ppm): δ=2.26 (s,3H,C$\underline{H}_3$), 4.53 (s,2H,C$\underline{H}_2$), 7.12-8.55 (m,7H, Ar-$\underline{H}$), 10.57 (s,1H,N$\underline{H}$).^{13}CNMR(100MHz,DMSOd_6,δ,ppm):δ=18.4,37.2,110.7,115.7,119.5,120.6,123.9,128.9,130.8,138.3,142.2,156.1,164.6,169.2. MS (m/z): 344M^+. Anal. cald. for $C_{16}H_{13}N_3O_4S$ (343):C,56.12; H,3.88; N,12.21;O,18.72;S,9.41 %. Found C, 56.02; H, 3.79; N, 12.22; O, 18.69 S, 9.36%.

Synthesis of 2-((5-nitrobenzo[d]oxazol-2-yl)thio)-N-(p-tolyl)acetamide(4_g)

IR (ATR): 3428, 3082, 2978, 1721, 1476, 1367, 1154, 1138 cm^{-1}. ^1H NMR(400 MHz, DMSOd_6,δ,ppm):δ=2.31 (s,3H,C$\underline{H}_3$), 4.67 (s,2H,C$\underline{H}_2$), 7.15-8.63 (m,7H, Ar-$\underline{H}$), 10.62 (s,1H,N$\underline{H}$).^{13}CNMR(100MHz,DMSOd_6,δ,ppm):δ=19.7,38.0,111.2,115.9,119.7,121.1,124.4,129.8,131.8,138.9,143.9,156.9,165.0,170.1. MS (m/z): 344 M^+. Anal. cald. for $C_{16}H_{13}N_3O_4S$ (343): C,56.22; H,3.87; N,12.22;O,18.74;S,9.52 %. Found C, 56.19; H,3.92; N,12.19; O,18.65 S, 9.40%.

Synthesis of N-(2-methoxyphenyl-2-((5-nitrobenzo[d]oxazol-2-yl)thio)acetamide(4_h)

IR(ATR): 3420, 3010, 2982, 1712, 1467, 1356, 1145, 1122 cm^{-1}. ^1H NMR(400 MHz,DMSO-d_6,δ,ppm):δ=3.85(s,3H,OC$\underline{H}_3$), 4.40 (s,2H,C$\underline{H}_2$), 7.12-8.57 (m,7H, Ar-$\underline{H}$), 10.48 (s,1H,N$\underline{H}$).^{13}CNMR(100MHz,DMSOd_6,δ,ppm):δ=37.0,55.8,111.5,114.9,121.5,124.8,129.2,131.9,139.1,143.2,157.1,166.3,170.3. MS (m/z): 360M^+. Anal. cald. for $C_{16}H_{13}N_3O_5S$(359):C,53.48; H,3.65; N,11.69;O,22.26;S,8.92 %. Found C,53.45; H,3.60; N,12.25;O, 21.62 S, 8.30%.

Synthesis of N-(3-methoxyphenyl-2-((5-nitrobenzo[d]oxazol-2-yl)thio)acetamide(4_i)

IR(ATR): 3422, 3008, 2985, 1715, 1471, 1353, 1151, 1127 cm^{-1}. ^1H NMR(400 MHz,DMSO-d_6,δ,ppm): δ=3.93 (s,3H,OC$\underline{H}_3$),4.43 (s,2H,C$\underline{H}_2$), 7.17-8.52 (m,7H, Ar-$\underline{H}$), 10.50(s,1H,N$\underline{H}$).^{13}CNMR(100MHz,DMSOd_6,δ,ppm):δ=38.2,56.6,110.8,114.0,119.8,120.4,124.8,129.5,130.7,142.9,155.4,164.9,168.8. MS (m/z): 360 M^+. Anal. cald. for $C_{16}H_{13}N_3O_5S$ (359):C,53.83; H,3.76; N,12.03;O,22.43;S,8.95 %. Found C,53.78; H,3.64; N,12.07;O, 22.34 S, 8.87%.

Synthesis of N-(4-methoxyphenyl-2-((5-nitrobenzo[d]oxazol-2-yl)thio)acetamide(4_j)

IR(ATR): 3427, 3011, 2988,1726, 1476, 1362, 1156, 1130 cm^{-1}. ^1H NMR(400 MHz,DMSO-d_6,δ,ppm): δ=3.87 (s,3H,OC$\underline{H}_3$), 4.51 (s,2H,C$\underline{H}_2$), 7.19-8.59 (m, 7H, Ar-$\underline{H}$), 10.65 (s,1H,N$\underline{H}$).^{13}CNMR(100MHz,DMSOd6,δ,ppm):δ=38.5,56.9,110.8,114.4,119.5,120.4,125.1,129.8,131.1,143.2,155.7,164.8,169.7. MS (m/z): 360 M^+. Anal. cald. for $C_{16}H_{13}N_3O_5S$ (359):C,53.87; H,3.81; N,12.11;O,22.47;S,8.97 %. Found C,53.75; H,3.67; N,12.09;O, 22.62 S, 8.90%.

Synthesis of N-(4-chlorophenyl-2-((5-nitrobenzo[d]oxazol-2-yl)thio)acetamide(4_k)
IR (ATR): 3389, 2987, 2895, 1710, 1465, 1367, 1154, 1127, 773 cm^{-1}. ^1H NMR(400 MHz,DMSO-d_6,δ,ppm): δ=4.23 (s,2H,C<u>H</u>$_2$), 7.23-8.10 (m,7H,Ar-<u>H</u>), 10.76 (s,1H,N<u>H</u>).^{13}CNMR(100MHz,DMSOd_6,δ,ppm):δ=38.9,112.5,120.8,125.5,128.6,130.7,138.6, 142.6,154.4,163.9,167.8. MS (m/z): 364.8M^+. Anal. cald. for $C_{15}H_{10}ClN_3O_4S$(363.5):C,49.83; H,2.92;Cl, 9.75; N,11.55;O,17.59;S,8.81 %. Found C,49.50; H,2.60;Cl,9.70 N,11.25;O, 17.62 S, 8.35%.
Synthesis of N-(4-fluorophenyl-2-((5-nitrobenzo[d]oxazol-2-yl)thio)acetamide(4_l)
IR (ATR): 3374, 3023, 2943, 1695, 1354, 1157, 1128, 1067 cm^{-1}. ^1H NMR(400 MHz,DMSO-d_6,δ,ppm):δ=4.43 (s,2H,C<u>H</u>$_2$), 7.27-8.13 (m,7H, Ar-<u>H</u>), 10.80 (s,1H,N<u>H</u>).^{13}CNMR(100MHz,DMSOd_6,δ,ppm):δ=39.7,112.8,115.1,119.9,121.5,125.5,129.9, 132.1,139.8,143.2,156.4,164.8,168.7. MS (m/z): 348 M^+. Anal. cald. for $C_{15}H_{10}FN_3O_4S$(347):C,51.87; H,2.90;F, 5.47; N,12.10;O,18.43;S,9.23 %. Found C,49.50; H,2.63;F, 5.45 N, 12.23; O, 18.37 S, 9.19 %.
Synthesis of 2-((5-nitrobenzo[d]oxazol-2-yl)thio)N-(3-trifluoromethyl)phenyl)acetamide(4_m)
IR(ATR): 3402, 3065, 2989, 1701, 1367, 1165, 1131, 1092 cm^{-1}. ^1H NMR(400 MHz,DMSO-d_6,δ,ppm): δ=4.57 (s,2H,C<u>H</u>$_2$), 7.31-8.33 (m,7H, Ar-<u>H</u>), 10.92 (s,1H,N<u>H</u>).^{13}C NMR(100MHz,DMSOd_6,δ,ppm):δ=39.9,113.3,115.6,120.2,122.1,127.5,131.3,133.7,140.8,14 5.5,159.2,165.6,169.8. MS (m/z): 398 M^+. Anal. cald. for $C_{16}H_{10}F_3N_3O_4S$(397):C,48.37; H,2.54;F, 14.34; N,2.54;O,18.43;S,9.23 %. Found C,49.50; H,2.60;F, 13.45 N,12.25;O, 18.40 S, 9.20%.
Synthesis of N-(3-chloro-4-fluorophenyl-2-((5-nitrobenzo[d]oxazol-2-yl)thio)acetamide(4_n)
IR(ATR): 3410, 3054, 2991, 1712, 1376, 1213, 1154, 1100, 793 cm^{-1}. ^1H NMR(400 MHz,DMSO-d_6,δ,ppm): δ=4.54 (s, 2H, C<u>H</u>$_2$), 7.18-8.25 (m, 6H, Ar-<u>H</u>), 10.82 (s,1H,N<u>H</u>).^{13}CNMR(100MHz,DMSOd_6,δ,ppm):δ=38.7,112.1,114.9,119.8,122.3,126.9,131.1, 133.4,139.8,142.1,158.8,164.7,169.1. MS (m/z): 382.5 M^+. Anal. cald. for C15H9ClFN3O4S(381.5):C,51.87; H,2.90;F, 5.47; N,12.10;O,18.43;S,9.23 %. Found C,49.50; H,2.60;F,5.45 N,12.25;O, 18.40 S, 9.20%.
Synthesis of 2-((5-methylbenzo[d]oxazol-2-yl)thio)-N-phenylacetamide (4_{aa})
IR (ATR): 3300, 3030, 2915, 2851, 1650, 1499, 1230, 1145, 1100 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6, δ, ppm): δ=2.45 (s, 3H, C<u>H</u>$_3$), 4.05 (s, 2H, C<u>H</u>$_2$), 7.16-7.64 (m, 8H, Ar-<u>H</u>), 10.27 (s,1H,N<u>H</u>).^{13}CNMR(100MHz,DMSOd_6,δ,ppm):δ=21.3,38.5,109.3,119.1,121.6,125.7,128.0,1 28.9,133.2,138.5,141.4,148.9,165.0,168.2.MS(m/z): 299 M^+. Anal cald for $C_{16}H_{14}N_2O_2S$ (298): C, 64.41; H, 4.73; N, 9.39; O, 10.72; S, 10.75%. Found C, 64.40; H, 4.70; N, 9.35; O, 10.70; S, 10.70%.
Synthesis of 2-((5-methylbenzo[d]oxazol-2-yl)thio)-N-(2-nitrophenyl)acetamide (4_{ab})
IR (ATR): 3315, 3025, 2921, 2850, 1652, 1490, 1235, 1140, 1106 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6, δ, ppm**):**δ=2.45 (s, 3H, C<u>H</u>$_3$), 4.05 (s, 2H, C<u>H</u>$_2$), 7.21-8.08 (m, 7H, Ar-<u>H</u>), 10.41 (s,1H,N<u>H</u>).^{13}CNMR(100MHz,DMSOd_6,δ,ppm):δ=21.8,38.8,110.1,119.3,124.8,127.2,131.3,1 33.2,141.4,148.9,164.8. MS (m/z): 344 M^+. Anal cald for $C_{16}H_{13}N_3O_4S$ (343): C, 55.97; H, 3.82; N, 12.24; O, 18.64; S, 9.34%. Found C, 64.40; H, 4.70; N, 9.35;O, 10.70; S,9.30%.
Synthesis of 2-((5-methylbenzo[d]oxazol-2-yl)thio)-N-(3-nitrophenyl)acetamide (4_{ac})
IR (ATR): 3350, 3032, 2915, 2856, 1650, 1499, 1238, 1145, 1116 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6, δ, ppm**):**δ=2.45 (s, 3H, C<u>H</u>$_3$), 4.05 (s, 2H, C<u>H</u>$_2$), 7.27-8.59 (m, 7H, Ar-<u>H</u>), 10.71 (s,1H,N<u>H</u>).^{13}CNMR(100MHz,DMSOd_6,δ,ppm):δ=21.3,38.5,109.3,114.5,119.1,125.7,127.7,1 29.8,133.2,139.4,141.4,148.9,165.0,168.2. MS (m/z): 344 M^+. Anal cald for $C_{16}H_{13}N_3O_4S$ (343) C, 56.06; H, 3.87; N, 12.32; O, 18.57; S, 9.30 %. Found C, 64.43; H, 4.76; N, 9.47; O, 10.78; S, 9.27%.

Synthesis of 2-((5-methylbenzo[d]oxazol-2-yl)thio)-N-(4-nitrophenyl)acetamide (4_{ad})
IR (ATR): 3320, 3020, 2921, 2845, 1650, 1499, 1230, 1157, 1121 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6, δ, ppm**):**δ=2.45 (s, 3H, C<u>H</u>$_3$), 4.05 (s, 2H, C<u>H</u>$_2$), 7.19-8.17 (m, 7H, Ar-<u>H</u>), 10.27 (s,1H,N<u>H</u>).^{13}CNMR(100MHz,DMSOd_6,δ,ppm):δ=21.5,38.7,109.8,119.9,126.5,135.2,141.5,143.7,148.9,168.2. MS (m/z): 344 M^+. Anal cald for $C_{16}H_{13}N_3O_4S$ (343) C, 55.97; H, 3.82; N, 12.24; O, 18.64; S, 9.34%. Found C, 64.5; H, 4.78; N, 9.45; O, 10.87; S, 9.29%.
Synthesis of 2-((5-methylbenzo[d]oxazol-2-yl)thio)-N-(o-tolyl)acetamide (4_{ae})
IR (ATR): 3354, 3015, 2915, 2825, 1650, 1490, 1430, 1238, 1153, 1117 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6, δ, ppm**):** δ= 2.19 (s, 3H, C<u>H</u>$_3$), 2.51 (s, 3H, C<u>H</u>$_3$), 4.23 (s, 2H, C<u>H</u>$_2$), 7.18-7.97 (m, 7H, Ar-<u>H</u>), 9.67 (s, 1H, N<u>H</u>). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): δ=17.3,22.4,38.8,109.3,120.4,126.7,129.9,131.6,136.6,142.4,149.1,168.5.MS(m/z):313M^+.
Analcaldfor $C_{17}H_{16}N_2O_2S$ (312) C,65.36;H,5.16;N,8.97;O,10.24;S,10.26%. Found C, 64.40; H, 5.10;N, 8.39;O,10.70;S,10.30%.
Synthesis of 2-((5-methylbenzo[d]oxazol-2-yl)thio)-N-(m-tolyl)acetamide (4_{af})
IR (ATR): 3345, 3030, 2920, 2825, 1652, 1499, 1431, 1245, 1157, 1123 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6, δ, ppm**):** δ=2.29 (s, 3H, C<u>H</u>$_3$), 2.65 (s, 3H, C<u>H</u>$_3$), 4.41 (s, 2H, C<u>H</u>$_2$), 7.21-8.05 (m, 7H, Ar-<u>H</u>), 10.60 (s, 1H, N<u>H</u>).^{13}CNMR(100MHz,DMSO-d_6,δ,ppm): δ=17.7,22.7,38.9,109.9,120.5,128.8,133.2,138.6,141.4,148.9,166.1,169.2.MS(m/z):313M^+.Analcaldfor $C_{17}H_{16}N_2O_2S$ (312) C,65.43;H,5.23;N,8.97;O,10.32;S,10.29%. Found C, 64.51; H, 5.14; N, 8.37; O, 10.70; S, 10.28%.
Synthesis of 2-((5-methylbenzo[d]oxazol-2-yl)thio)-N-(p-tolyl)acetamide (4_{ag})
IR (ATR): 3350, 3020, 2921, 2851, 1652, 1499, 1430, 1238, 1164, 1127 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6, δ, ppm**):** δ=2.32 (s, 3H, C<u>H</u>$_3$), 2.78 (s, 3H, C<u>H</u>$_3$), 4.67 (s, 2H, C<u>H</u>$_2$), 7.23-8.10 (m, 7H, Ar-<u>H</u>), 10.27 (s, 1H, N<u>H</u>). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): δ= 18.2, 22.9,39.2,110.1,121.5,129.2,135.5,138.8,142.4,149.8,166.7,169.8.MS(m/z): 313 M^+. Anal cald for $C_{17}H_{16}N_2O_2S$ (312) C,65.42;H,5.26;N,8.98;O,10.43;S,10.30%. Found C, 64.67; H, 5.14; N, 8.45; O, 10.74; S, 10.38%.
Synthesis of N-(2-methoxyphenyl)-2-((5-methylbenzo[d]oxazol-2-yl)thio)acetamide (4_{ah})
IR (ATR): 3410, 3030, 2990, 2925, 2850, 1690, 1520, 1240, 1167, 1131 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6, δ, ppm**):** δ= 2.45 (s, 3H, C<u>H</u>$_3$), 3.85 (s, 3H, OC<u>H</u>$_3$), 4.11 (s, 2H, C<u>H</u>$_2$), 7.13-7.95 (m, 7H, Ar-<u>H</u>), 10.02 (s, 1H, N<u>H</u>). ^{13}CNMR(100MHz,DMSO-d_6,δ,ppm): δ=18.4, 21.3,38.5,55.8,109.3,112.8,120.3,125.7,128.2,133.2,141.7,149.3,169.1. MS (m/z): 329M^+. Anal cald for $C_{17}H_{16}N_2O_3S$ (328) C,62.18;H,4.91;N,8.53;O,14.62;S,9.76%. Found C, 62.10; H, 5.10; N, 8.39; O, 14.60; S, 9.60%.
Synthesis of N-(3-methoxyphenyl)-2-((5-methylbenzo[d]oxazol-2-yl)thio)acetamide (4_{ai})
IR (ATR): 3435, 3053, 2997, 2943, 2878, 1702, 1518, 1256, 1169, 1138 cm^{-1}. ^1H NMR (400 MHz, DMSO-d6, δ, ppm**):** δ= 2.53 (s, 3H, C<u>H</u>$_3$), 3.89 (s, 3H, OC<u>H</u>$_3$), 4.14 (s, 2H, C<u>H</u>$_2$), 7.17-7.97 (m, 7H, Ar-<u>H</u>), 10.13 (s, 1H, N<u>H</u>). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): δ=18.7, 21.7,38.8,56.5,109.6,116.4,121.1,126.1,129.9,133.8,142.1,149.9,169.9.MS(m/z):329M+.Anal cald for $C_{17}H_{16}N_2O_3S$ (328) C,62.21;H,4.94;N,8.67;O,14.78;S,9.83%. Found C, 62.13; H, 5.15; N, 8.48; O, 14.78; S, 9.78%.
Synthesis of N-(4-methoxyphenyl)-2-((5-methylbenzo[d]oxazol-2-yl)thio)acetamide (4_{aj})
IR (ATR): 3467, 3061, 2998, 2957, 2882, 1715, 1523, 1265, 1172, 1145 cm^{-1}. ^1H NMR (400 MHz,DMSO-d_6, δ, ppm**):** δ= 2.67 (s, 3H, C<u>H</u>$_3$), 3.98 (s, 3H, OC<u>H</u>$_3$), 4.31 (s, 2H, C<u>H</u>$_2$), 7.18-8.02 (m, 7H, Ar-<u>H</u>), 10.21 (s, 1H, N<u>H</u>). ^{13}C NMR (100 MHz,DMSO-d_6, δ, ppm): δ=19.1, 21.9,39.6,57.1,110.4,118.1,124.9,131.7,136.8,143.4,152.4,170.3. MS (m/z):329 M^+. Anal cald for $C_{17}H_{16}N_2O_3S$ (328) C,62.19;H,4.95;N,8.64;O,14.67;S,9.87%. Found C, 62.11; H, 5.15; N, 8.45; O, 14.57; S,9.64%.

Synthesis of N-(4-chlorophenyl)-2-((5-methylbenzo[d]oxazol-2-yl)thio)acetamide (4_{ak})
IR (ATR): 3390, 3047, 2920, 2851, 1652, 1490, 1230, 1151, 1109, 850 cm^{-1}. ^1H NMR (400 MHz,DMSO-d_6, δ, ppm**):** δ= 2.61 (s, 3H, C<u>H</u>$_3$), 4.27 (s, 2H, C<u>H</u>$_2$), 7.21-7.88 (m, 7H, Ar-<u>H</u>), 10.23 (s, 1H, N<u>H</u>). ^{13}C NMR (100 MHz,DMSO-d_6, δ, ppm): δ= 21.1,38.5,109.3,120.1,129.0,136.6,141.4,148.9,168.1. MS (m/z): 333.5M^+. Anal cald for $C_{16}H_{13}ClN_2O_2S$(332.5)C,57.74;H,3.94;Cl,10.65,N,8.42;O,9.61;S,9.63%.FoundC,57.70;H,3.60;Cl,10.60,N,8.39;O,9.56;S,9.60%.
Synthesis of N-(4-fluorophenyl)-2-((5-methylbenzo[d]oxazol-2-yl)thio)acetamide (4_{al})
IR (ATR): 3401, 3056, 2943, 2864, 1694, 1495, 1235, 1167, 1121, 970 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6, δ, ppm**):** δ= 2.67 (s, 3H, C<u>H</u>$_3$), 4.35 (s, 2H, C<u>H</u>$_2$), 7.27-8.12 (m, 7H, Ar-<u>H</u>), 10.27(s,1H,N<u>H</u>).^{13}CNMR(100MHz,DMSOd_6,δ,ppm):δ=22.3,39.6,110.1,121.6,130.7,137.1,141.9,149.8,169.4. MS(m/z):317M^+. Anal cald for $C_{16}H_{13}FN_2O_2S$ (316)C,60.75;H,4.14;F,6.01;N,8.86;O,10.11;S,10.13%.FoundC,60.70;H,4.10;F,6.00,N,8.39; O,10.10;S,10.12%.
Synthesis of 2-((5-methylbenzo[d]oxazol-2-yl)thio)-N-(3-trifluoromethyl)phenyl)acetamide (4_{am})
IR (ATR): 3352, 3035, 2922, 2851, 1650, 1491, 1238, 1165, 1123 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6, δ, ppm): δ= 2.57 (s, 3H, C<u>H</u>$_3$), 4.21 (s, 2H, C<u>H</u>$_2$), 7.19-8.02 (m, 7H, Ar-<u>H</u>), 10.13(s,1H,N<u>H</u>).^{13}CNMR(100MHz,DMSOd_6,δ,ppm):δ=21.7,38.4,55.8,109.9,120.4,138.1,141.0,148.9,166.9.MS(m/z):367 M^+. Anal cald for $C_{17}H_{13}F_3N_2O_2S$ (366) C,55.73;H,3.58;F,15.56;N,7.65;O,8.73;S,8.75%. Found C,55.70; H,3.50;F,15.50,N,7.55;O,8.70;S,8.70%.
Synthesis of N-(3-chloro-4-fluorophenyl)-2-((5-methylbenzo[d]oxazol-2-yl)thio)acetamide (4_{an})
IR (ATR): 3370, 3053, 3001, 2863, 1667, 1499, 1264, 1178, 1135, 967, 842 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6, δ, ppm): δ= 2.59 (s, 3H, C<u>H</u>$_3$), 4.23 (s, 2H, C<u>H</u>$_2$), 7.17-8.04 (m, 6H, Ar<u>H</u>),10.17(s,1H,N<u>H</u>).^{13}CNMR(100MHz,DMSOd_6,δ,ppm):δ=21.9,39.1,56.5,110.6,122.3,129.8,138.5,142.3,149.9,169.1.MS(m/z):351.5 M^+. Anal cald for $C_{16}H_{12}ClFN_2O_2S$ (350.5) C,54.78;H,3.45;F,5.42;N,7.99;O,9.12;S,9.14%.FoundC,54.70;H,3.40;F,5.40,N,7.90;O,9.10;S, 9.12%.

RESULT AND DISCUSSION:

3.1. Chemistry

The formation of titled derivatives and intermediate was achieved by multi step in scheme-1. Substituted 2-amino phenols were used as a starting material for the synthesis of the title targeted compounds. The substituted aniline were treatedwith Chloro acetyl chloride (CAC), triethylamine (TEA) and dimethylformamide (DMF) resulting in the formation of useful intermediates. The title derivatives were synthesized under mild reaction condition using K_2CO_3 and acetone as a solvent. The % yield of title derivatives were reported in Table 1.

3.2 Pharmacology

Antibacterial activity

Gram-positive bacteria *Bacillus subtilis*and gram-negative bacteria *Escherichia coli*were screened for antimicrobial activity testing of the newly synthesized compounds $4_{a\text{-}n}$and $4_{aa\text{-}an}$ at different concentrations, where ciprofloxacin was used as a standard drug for comparison of antibacterial activity of the synthesized novel compounds. Only three derivatives 4_c (3-NO_2), 4_d (4-NO_2) and 4_{ak} (4-Cl) showed good activity against gram-positive bacteria *Bacillus subtilis* at concentrations of 1000, 500, 250 μg/ml compared to the standard drug ciprofloxacin. The compound 4_l (4-F), 4_{aa} (H) and 4_{ag} (4-CH_3) observed zero activity against gram-positive bacteria

Bacillus subtilis as compared to the standard drugs. Other derivatives showed poor activity against gram-positive bacteria as compared to the standard reported in Table 2 and Table 3.
The novel synthesized compounds were tested against gram-negative bacteria *Escherichia coli*at concentrations of 1000, 500, 250 µg/ml, it was clearly observed only three compound 4_c (3-NO_2), 4_d (4-NO_2) and 4_k (4-Cl) were observed good activity against gram-negative bacteria *Escherichia coli* compared to standard drug. The compound 4_g (4-CH_3), 4_{af}(3-CH_3)and 4_{al}(4-F) showed zero activity against gram-negative bacteria *Escherichia coli* compared to standard drug ciprofloxacin. Other newly synthesized derivatives observed poor activity against gram-negative bacteria compared to standard.

Antifungal activity

The newly synthesized compounds were tested against *Aspergillus niger*for their antifungal activity at different concentrations of 1000, 500, 250 µg/ml. Fluconazole was used as a standard drug for comparison and evaluation of antifungal activity of the synthesized compounds. Compound 4_c (3-NO_2), 4_d (4-NO_2) and 4_{ak} (4-Cl) observed excellent activity compared to standard drug at different concentration. Only four derivatives 4_a (H), 4_b (2-NO_2), 4_k (4-Cl) and 4_{al} (4-F) showed good activity against the standard. Compounds 4_{ae} (2-CH_3)and 4_{af} (3-CH_3)observed zero antifungal activity as compared to the standard drug fluconazole. Other compounds were observed poor activity against the standard drug fluconazole reported in Table 2 and Table 3.

SAR study- Structure Activity Relationship

The use of SAR study helped to the effect of substitutions on the aromatic ring exerted various microbial strains. Both electron-withdrawing and electron-donating functional groups were chosen as substitutions on the target molecules. Compound with electron-donating groups such as methyl and methoxy exhibited lower ZOI value against antibacterial activity compared to the standard drug. On other hand the derivatives with electron-withdrawing groups like –NO_2, -Cl and –F also showed good antibacterial and antifungal activity against standard drug.

Table 1: Physical constant data for the final derivatives 4_{a-n} and 4_{aa-an}

Compound	R_1	R_2	Melting point °C	% Yield
4_a	-NO_2	-H	217 °C	71%
4_b	-NO_2	2-NO_2	229 °C	62%
4_c	-NO_2	3-NO_2	221 °C	53%
4_d	-NO_2	4-NO_2	232 °C	55%
4_e	-NO_2	2-CH_3	207 °C	61%
4_f	-NO_2	3-CH_3	243 °C	64%
4_g	-NO_2	4-CH_3	219 °C	60%
4_h	-NO_2	2-OCH_3	223 °C	68%
4_i	-NO_2	3-OCH_3	197 °C	66%
4_j	-NO_2	4-OCH_3	210 °C	76%
4_k	-NO_2	4-Cl	231 °C	60%
4_l	-NO_2	4-F	203 °C	64%
4_m	-NO_2	3-CF_3	199 °C	68%

4_n	-NO_2	3-Cl-4-F	213 °C	59%
4_{aa}	-CH_3	H	197 °C	78%
4_{ab}	-CH_3	2-NO_2	235 °C	88%
4_{ac}	-CH_3	3-NO_2	218 °C	87%
4_{ad}	-CH_3	4-NO_2	223 °C	84%
4_{ae}	-CH_3	2-CH_3	214 °C	80%
4_{af}	-CH_3	3-CH_3	205 °C	82%
4_{ag}	-CH_3	4-CH_3	189 °C	75%
4_{ah}	-CH_3	2-OCH_3	243 °C	90%
4_{ai}	-CH_3	3-OCH_3	229 °C	88%
4_{aj}	-CH_3	4-OCH_3	215 °C	84%
4_{ak}	-CH_3	4-Cl	212 °C	82%
4_{al}	-CH_3	4-F	217 °C	81%
4_{am}	-CH_3	3-CF_3	189 °C	88%
4_{an}	-CH_3	3-Cl-4-F	227 °C	90%

Table: 2 Zone of Inhibition (ZOI) Values of Newly Synthesized Compounds 4_{a-n}

-R (Derivatives)	**Zone of Inhibition (mm)**								
	***B. subtilis* (Gram-positive bacteria)**			***E. coli* (Gram-negative bacteria)**			***A.niger* (Fungi)**		
	1000 *µg/ml*	**500 *µg/ml***	**250 *µg/ml***	**1000 *µg/ml***	**500 *µg/ml***	**250 *µg/ml***	**1000 *µg/ml***	**500 *µg/ml***	**250 *µg/ml***
(H) 4_a	-	7	-	7	8	7	18	14	13
(2-NO_2) 4_b	10	11	10	8	9	9	17	16	16
(3-NO_2) 4_c	16	14	17	10	12	12	20	17	15
(4-NO_2) 4_d	20	19	21	12	13	11	20	18	17
(2-CH_3) 4_e	-	7	6	7	6	-	12	10	-
(3-CH_3) 4_f	8	8	7	6	-	-	-	-	10
(4-CH_3) 4_g	9	9	9	-	-	-	13	11	9
(2-OCH_3) 4_h	9	8	8	10	9	6	12	10	-
(3-OCH_3) 4_i	10	9	9	8	8	7	12	-	11
(4-OCH_3) 4_j	9	10	12	-	8	10	10	8	-
(4-Cl) 4_k	11	12	10	11	12	8	17	15	15
(4-F) 4_l	-	-	-	8	8	7	12	9	8
(3-CF_3) 4_m	11	11	10	-	9	8	12	11	-
(3-Cl-4-F) 4_n	12	12	11	10	9	9	14	14	11
Fluconazole							**22**	**21**	**19**
Ciprofloxacin	**24**	**24**	**23**	**23**	**22**	**22**			

Table: 3 Zone of Inhibition (ZOI) Values of Newly Synthesized Compounds 4_{aa-an}

-R (Derivatives)	Zone of Inhibition (mm)								
	B. subtilis **(Gram-positive bacteria)**			***E. coli*** **(Gram-negative bacteria)**			***A.niger*** **(Fungi)**		
	1000 ***µg/ml***	**500** ***µg/ml***	**250** ***µg/ml***	**1000** ***µg/ml***	**500** ***µg/ml***	**250** ***µg/ml***	**1000** ***µg/ml***	**500** ***µg/ml***	**250** ***µg/ml***
(H) 4_{aa}	-	-	-	7	8	7	10	10	-
(2-NO_2) 4_{ab}	7	7	6	-	8	8	11	9	8
(3-NO_2) 4_{ac}	-	7	6	8	8	-	12	11	10
(4-NO_2) 4_{ad}	-	9	-	8	7	9	11	-	-
(2-CH_3) 4_{ae}	-	7	7	-	8	-	-	-	-
(3-CH_3) 4_{af}	-	8	-	-	-	-	-	-	-
(4-CH_3) 4_{ag}	-	-	-	-	9	-	10	9	-
(2-OCH_3) 4_{ah}	-	6	-	-	9	7	11	11	10
(3-OCH_3) 4_{ai}	-	7	7	-	9	-	-	-	9
(4-OCH_3) 4_{aj}	8	-	-	-	10	8	9	8	6
(4-Cl) 4_{ak}	11	14	11	-	10	-	18	16	16
(4-F) 4_{al}	8	10	8	-	-	-	13	12	11
(3-CF_3) 4_{am}	9	11	9	9	8	8	11	8	-
(3-Cl-4-F) 4_{an}	8	9	8	-	11	-	8	-	-
Fluconazole							**22**	**21**	**19**
Ciprofloxacin	**24**	**24**	**23**	**23**	**22**	**22**			

CONCLUSION:

In the present research work synthesis of 5-Nitro-1,3-benzoxazole derivative as microorganism growth inhibitors has been studied. The antifungal and antibacterial data displayed significant activity of the synthesized compounds. Nitro (-NO_2) derivative showed better bacterial and fungal growth ZOI inhibition than the standard drugs. It can be concluded that there is a wide scope in developing these compounds as potent lead molecules.

The synthesized 5-Methyl-1,3-benzoxazole derivatives(4_{aa-an}) have executed significant antifungal and antibacterial property. The derivatives bearing Chloro (-Cl) substituted having the better heterocyclic scaffolds possessing potent antibacterial and antifungal properties. Furthermore, there is an ample scope in developing these derivatives as potent lead molecules, which can be used as antimicrobial therapeutics.

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