Synthesis, characterization and antimicrobial activities of 2-(5-substituted-3-phenyl-1H-indol-2-yl)-5-substituted-7H-[1,3,4]oxadiazolo / thiadiazolo[3,2-a][1,3,5]triazine-7-thiones

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ABSTRACT

Some novel 2-(5-substituted-3-phenyl-1H-indol-2-yl)-5-methyl / phenyl-7H-[1,3,4]oxadiazolo / thiadiazolo [3,2-a][1,3,5]triazine-7-thiones (6a-f & 7a-f) were prepared from the intramolecular cyclocondensation of N-(5-(5-substituted-3-phenyl-1H-indol-2-yl)-1,3,4-oxadiazol / thiadiazol-2-yl)carbamothioylacetamides / benzamides (4a-f & 5a-f). Which were occurred from the condensation of 5-(5-substituted-3-phenyl-1H-indol-2-yl)-1,3,4-oxadiazol / thiadiazol-2-amine (2a-c & 3a-c) with acetyl and benzoyl chlorides in the presence of ammonium thiocyanate. The compounds 2a-c & 3a-c were obtained from base and acid catalyzed cyclisation reactions of 2-(5-substituted-3-phenyl-1H-indole-2-carbonyl) hydrazine carbothioamides (1a-c) in ethanol. The compounds synthesized were characterized by using their spectral (IR, NMR and Mass) and analytical studies. All synthesized molecules are evaluated to in-vitro antimicrobial activities against various microbial strains. Most of the new molecules are displayed moderate to significant activities toward antibacterial and antifungal strains.

Keywords: 3,5-disubstituted Indoles, fisher indole synthesis, Fused heterocycles, s-triazines, antimicrobial.

INTRODUCTION

Indole and its derivatives occupied a unique place in the chemistry of nitrogen heterocyclic compounds because of their varied biodynamic properties [1-3]. Most of the Indole derivatives are biologically active chemicals present in microorganisms, plants and animals representing an important class of therapeutic agent in medicinal chemistry [4-6]. Some indole derivatives are found to exhibit antibacterial [7-9], antifungal [10-11], antiviral [12-14], antimalarial [15-16] and anti-HIV [17] activities. Furthermore, 1,3,5-triazines are amongst the oldest known organic molecules; originally they were called the symmetric triazines usually abbreviated as S- or Syn-triazines. Some of the substituted 1,3,5-s-triazine have reported to possess diverse biological activities. A wide range of 1,3,5-triazines exhibit selective herbicidal properties, Simazine and atrazines are the organic compounds containing s-triazine skeleton are most important herbicides. Baker triazines are inhibitors of dihydrofolate reductase and some have shown activity against leukemia. Currently Baker antifol (BAF) triazine is undergoing clinical trials as a drug in cancer chemotherapy [18-20]. In addition, the interest in 1,3,4-oxadiazole / thiadiazoles are increased due to the high bioavailability of their derivatives[21-24]. Literature survey evidenced that some substituted bridged substituted 1,3,4-oxadiazolo / thiadiazolo [3,2-a][1,3,5] triazine-7-thione [(6a-f) & (7a-f)] by bridging all bioactive heterocyclic rings as fused...
heterocycles with expectation of enhanced biological activity of the molecule. Hence we have carried out synthesis, characterization and antimicrobial activities of title compounds which are new and are not reported so far elsewhere.

**EXPERIMENTAL SECTION**

All the chemicals used were that of laboratory grade. Melting points were taken in an open capillary tube and are uncorrected. Progress of the reactions was checked by TLC on silica gel and compounds were purified by crystallization with suitable organic commercial solvents. $^1$H NMR spectra was recorded on a Bruker supercon FT NMR (400 MHz) spectrometer in CDCl$_3$, DMSO-$d_6$ and TMS used as an internal standard. The chemical shifts are expressed in $\delta$ units. IR spectra were recorded by using JASCO FT/IR-300 E spectrometer from a KBr pelleted sample. Mass spectra were recorded on a JEOL SX 102/DA-6000 (10 kV) FAB mass spectrometer.

Requisite 3,5-disubstituted indole-2-carboxyhydrazides were prepared by fischer indole synthesis and 2-(3-phenyl-1H-indole-2-carbonyl) hydrazinecarbothioamides were synthesized as per literature method [30,31].

**General procedure for the synthesis of 5-(5-substituted-3-phenyl-1H-indol-2-yl)-1,3,4-oxadiazol-2-amines (2a-c)**

To 5-Substituted-3-Phenyl-1H-indol-2-yl) carbamido-thiosemicarbazide (1a-c) (0.001 mol) suspended in ethanol (95%, 300 ml) was added sodium hydroxide (4 N; 5ml) with cooling and stirring constantly. To the resulting clear solution, iodine in potassium iodide solution (5%) was added gradually with stirring till the color of iodine persisted at room temperature. The contents were then refluxed on a water bath and more iodine solution added carefully till a permanent tinge of excess iodine remained. The reaction mixture was then poured into ice cold water (500ml) and the resulting solid was washed with water and warm carbon disulfide and crystallized from suitable solvent.

![Chemical structure diagram](image-url)

**Scheme I:** General synthetic pathway to 5- Alkyl / aryl-2-(5-substituted 3-phenyl indole)-1,3,4-oxadiazolo / thiodiazolo-[3,2-a]-s-triazine-7-thiones (6a-f, 7a-f)
5-(5-chloro-3-phenyl-1H-indol-2-yl)-1,3,4-oxadiazol-2-amine (2a)
Pale yellow crystals (dil. alcohol), Yield 80%, mp 240-241 °C; IR (KBr) ν cm⁻¹: 3312 (NH₂), 2989(NH), 1533/1541(C=N/C=N), 1260 (-O-); ¹H NMR (400 MHz, CDCl₃) δ ppm: 4.2 (2H, -NH₂), 7.2-7.6 (m, 8H, ArH), 9.2 (s, 1H, Indole-NH); Anal. Calcd for: C₁₅H₁₃ClN₃O₂: C 61.84; H, 3.57; N, 18.03%. Found: C, 61.82; H, 3.54; N, 18.01%.

5-(5-bromo-3-phenyl-1H-indol-2-yl)-1,3,4-oxadiazol-2-amine (2b)
Yellow crystals (ethanol), Yield 72%, mp 159-160 °C; IR (KBr) ν cm⁻¹: 3319 (NH₂), 2985(NH), 1559/1538(C=N/C=N), 1260(-O-); ¹H NMR (400 MHz, CDCl₃) δ ppm: 4.2 (2H, -NH₂), 7.0-7.6 (m, 8H, ArH), 8.2 (s, 1H, Indole-NH); Anal. Calcd for: C₁₅H₁₃BrN₃O₂: C 54.10; H, 3.39; N, 17.14%. Found: C, 54.08; H, 3.30; N, 17.13%.

5-(5-chloro-3-phenyl-1H-indol-2-yl)-1,3,4-thiadiazolo-2-amine (3a)
Pale yellow crystals (ethanol), Yield 68%, mp 209-210 °C; IR (KBr) ν cm⁻¹: 3327(NH₂), 3299(-NH), 1559/1538(C=N/C=N), 1260(-O-); ¹H NMR (400 MHz, CDCl₃) δ ppm: 4.2 (2H, -NH₂), 7.2-7.6 (m, 8H, ArH), 9.1 (s, 1H, indole NH); Anal. Calcd for: C₁₅H₁₃ClN₃S: C 66.64; H, 4.61; N, 18.28%. Found: C, 66.62; H, 4.60; N, 18.28%.

General procedure for the synthesis of 5-(5-substituted-3-phenyl-1H-indol-2-yl)-1,3,4-thiadiazolo-2-amines (3a-c)
The 5-Substituted-3-Phenyl-1H-indol-2-yl) carbamido-thiosemicarbazide (1a-c: 0.02 mol) was added gradually with stirring during 21 min to syrupy phosphoric acid (85%; 20ml) at 120 °C. Thy mixture was heated under stirring at this temperature for further 30 minutes, cooled and then poured into ice-water (400 ml) and left overnight. The resulting solid was washed with water and crystallized from suitable solvent to afford 3a-c. The acidic filtrate on basification with ammonia gave a small amount of solid which was found to be identical with 3a-c.

5-(5-chloro-3-phenyl-1H-indol-2-yl)-1,3,4-thiadiazolo-2-amine (3a)
Pale yellow crystals (ethanol), Yield 68%, mp 209-210 °C; IR (KBr) ν cm⁻¹: 3316 (NH₂), 2988 (NH), 1602/1532 (C=N/C=N), 765 (-S-); ¹H NMR (400 MHz, CDCl₃) δ ppm: 4.3 (2H, -NH₂), 7.2-7.7 (8H, ArH), 9.1 (s, 1H, indole NH); Anal. Calcd for: C₁₅H₁₃ClN₃S: C 64.86; H, 3.39; N, 17.14%. Found: C, 64.80; H, 3.37; N, 17.13%.

5-(5-methyl-3-phenyl-1H-indol-2-yl)-1,3,4-thiadiazolo-2-amine (3c)
Yellow amorphous (ethanol), Yield 55%, mp 184-185 °C; IR (KBr) ν cm⁻¹: 3427(NH₂), 3299(-NH), 1606/1538(C=N/C=N), 796(-S-); ¹H NMR (400 MHz, CDCl₃) δ ppm: 4.2 (2H, -NH₂), 7.1-7.8 (8H, ArH), 9.0 (s, 1H, indole NH); Anal. Calcd for: C₁₅H₁₃N₃S: C 51.76; H, 2.99; N, 15.09%. Found: C, 51.74; H, 2.98; N, 15.07%.

General procedure for the synthesis of N-((5-(5-substituted-3-phenyl-1H-indol-2-yl)-1,3,4-oxadiazol-2-yl)carbamothioyl)acetamides / benzamides (4a-f)
A mixture of ammonium thiocyanate (0.01 mol) and acetyl / benzoyl chloride (0.01 mol) in acetone (25 ml) was refluxed for 30 min. Compound 2- amino -5-(5- substituted 3- Phenyl indole)- 1,3,4-oxadiazole (2a-c) (0.01 mol) was then added to it and the reaction mixture was refluxed further for 2-3 h. It was then poured in to water. The resulting solid (4a-f) was filtered, dried and recrystallized from suitable solvent.

N-((5-chloro-3-phenyl-1H-indol-2-yl)-1,3,4-oxadiazol-2-yl)carbamothioyl)acetamide (4a)
Yellow crystals (1,4-dioxane), Yield 70%, mp 159-161 °C; IR (KBr) ν cm⁻¹: 3312 (NH₂), 2988 / 2989 (NH/NH), 1683 (C=O), 1260 (-O-), 1169 (C=S); ¹H NMR (400 MHz, CDCl₃) δ ppm: 2.1 (s, 3H, CH₃), 7.2-7.6 (m, 8H, ArH), 8.2 (s, 1H, NH), 9.1 (s, 1H, indole-NH), 9.9 (s, 1H, NH); Anal. Calcd for C₁₅H₁₃N₃O₂S: C 55.41; H, 3.43; N, 17.00%. Found: C, 55.39; H, 3.40; N, 17.00%.

N-((5-bromo-3-phenyl-1H-indol-2-yl)-1,3,4-oxadiazol-2-yl)carbamothioyl)acetamide (4b)
Yellow crystals (ethanol), Yield 72%, mp 159-160°C; IR (KBr) ν cm⁻¹: 3304(NH), 3000/2971(NH/NH), 1667(C=O), 1541/1497(C=N/C=N), 1241(-O-), 1161(C=S); ¹H NMR (400 MHz, CDCl₃) δ ppm: 1.9(s, 3H, CH₃), 7.2-7.8 (m, 8H, ArH), 8.1 (s, 1H, NH), 9.2 (s, 1H, indole-NH), 9.9 (s, 1H, NH); Anal. Calcd for C₁₅H₁₃BrN₃O₂S: C 50.01; H, 3.09; N, 15.35%. Found: C, 50.02; H, 3.07; N, 15.32%.
N-((5-(5-methyl-3-phenyl-1H-indol-2-yl)-1,3,4-oxadiazol-2-yl)carbamothioyl)acetamide (5c). Ash green amorphous (dil. Ethanol), Yield 65%, mp 114-116°C; IR (KBr) ν: 3297(NH), 3000/2857(NH/NH), 1646(C=O), 1533/1443 (C=N/C=N), 1143(C=S); 1H NMR (400 MHz, DMSO-d6) δ ppm: 2.4 (s, 3H, CH₃), 7.2-7.6 (m, 8H, ArH), 7.3-7.6 (m, 8H, ArH), 8.4 (s, 1H, NH), 9.1 (s,1H,indole-NH), 9.6 (s, 1H, NH); Anal. Calcd for C₁₀H₁₀N₂S₂: C, 53.33; H, 3.30; N, 16.36%. Found: C, 53.30; H, 3.28; N, 16.36%.

N-((5-chloro-3-phenyl-1H-indol-2-yl)-1,3,4-thiadiazol-2-yl)carbamothioylacetamide (5d) Yellow crystals (acetone + ethanol), Yield 82%; mp 184-186°C; IR (KBr) ν: 3283 / 3152 / 2965 (NH / NH / NH), 3435 / 3298 / 3152 (NH / NH / NH), 1774 (C=O), 1297 / 1206 / 1147 (C=O/C=O). 1H NMR (400 MHz, CDCl₃) δ ppm: 2.4(s, 3H, CH₃), 7.2-7.5 (m, 8H, ArH), 8.4 (s, 1H, NH), 9.1 (s,1H,indole-NH), 9.6 (s, 1H, NH); Anal. Calcd for C₁₀H₁₀N₂O₂S₂Cl: C, 58.83; H, 3.29; N, 14.29%. Found: C, 58.80; H, 3.29; N, 14.28%.

N-((5-bromo-3-phenyl-1H-indol-2-yl)-1,3,4-thiadiazol-2-yl)carbamothioyl)benzamide (5e) Light yellow crystals (ethanol), Yield 65%, mp.178-180 °C, IR (KBr) ν: 3290 / 3144 / 2955 (NH / NH / NH), 1587 / 1507 (C=N/C=N), 1105 (C=S); 1H NMR (400 MHz, CDCl₃) δ ppm: 7.1-7.8 (m, 13H, ArH), 8.2 (s, 1H, NH), 9.1 (s, 1H, indole-NH), 9.9 (s, 1H, NH); Anal. Calcd for C₁₂H₁₄N₂O₂S₂Br: C, 53.94; H, 3.02; N, 13.10%. Found: C, 53.91; H, 3.0; N, 13.08%.
N-((5-(5-methyl-1H-indol-2-yl)-1,3,4-thiadiazol-2-yl)carbamothioyl)benzamide (5f)
Yellow plates (acetone + ethanol), Yield 68%, mp 184-186 °C, IR (KBr) ν: 3425 / 3282 / 3050 (NH / NH), 1662 (C=O), 1602/1542 (C=S/C=N), 1106 (C=S); 1H NMR (400 MHz, DMSO-d6) δ ppm: 2.3, (s, 3H, -CH3), 7.0-8.0 (m, 13H, ArH), 8.1 (s, 1H, NH), 9.1 (s, 1H, indole-NH), 9.9 (s, 1H, NH); Anal. Calcd for: C29H19N3O2S: C, 63.94; H, 4.08; N, 14.91%. Found: C, 63.92; H, 4.06; N, 14.90%.

General procedure for the synthesis of 2-(5-substituted-3-phenyl-1H-indol-2-yl)-5-methyl / phenyl-7H-[1,3,4]oxadiazolo[3,2-a][1,3,5]triazine-7-thione (6a-f)
A mixture of N-((5-(5-substituted-3-phenyl-1H-indol-2-yl)-1,3,4-oxadiazol-2-yl)carbamothioyl)acetamides / benzamides (4a-f) (0.015mol), phosphorous oxychloride (15 ml) and phosphorus pentachloride (0.015 mol) was added to it. The resulting solid (6a-f) was extracted with ethyl acetate / dichloromethane and recrystallized from suitable solvent.

2-(5-chloro-3-phenyl-1H-indol-2-yl)-5-methyl-7H-[1,3,4]oxadiazolo[3,2-a][1,3,5]triazine-7-thione (6a)
Lemon yellow crystals (ethanol), Yield 71%, mp 183-185 °C, IR (KBr) ν: 3134 (NH), 1682 / 1602/1533 (C=N / C=N / C=N), 1169 (C=S); 1H NMR (400 MHz, CDCl3) δ ppm: 1.3 (s, 3H, CH3), 7.3-7.7 (m, 8H, ArH), 9.3 (s, 1H, Indole NH); Anal. Calcd for: C29H18N3O2S: C, 63.94; H, 4.07; N, 14.91%. Found: C, 63.92; H, 4.06; N, 14.90%.

2-(5-bromo-3-phenyl-1H-indol-2-yl)-5-phenyl-7H-[1,3,4]oxadiazolo[3,2-a][1,3,5]triazine-7-thione (6e)
Brown crystals (acetone + ethanol), Yield 73%, mp 148-150 °C, IR (KBr) ν: 3239(NH), 1621 /1495 /1445 (C=N/C=N/C=N), 1138 (C=S); 1H NMR (400 MHz, CDCl3) δ ppm: 2.4 (s, 3H, CH3), 1.3 (s, 3H, CH3), 7.1-7.7 (m, 8H, ArH), 9.8 (s, 1H, Indole NH); Anal. Calcd for: C29H19N3O2SBr: C, 64.33; H, 4.05; N, 18.75%. Found: C, 64.30; H, 4.02; N, 18.73%.

2-(5-chloro-3-phenyl-1H-indol-2-yl)-5-phenyl-7H-[1,3,4]oxadiazolo[3,2-a][1,3,5]triazine-7-thione (6h)
Brown crystals (acetone + ethanol), Yield 73%, mp 223-225 °C, IR (KBr) ν: 3218(NH), 1492/1447 (C=N/C=N/C=N), 1105(C=S), 1260 (C-O); 1H NMR (400 MHz, CDCl3) δ ppm: 6.8-7.9 (m, 13H, ArH), 9.8 (s, 1H, Indole NH); Anal. Calcd for: C24H14N3O2S: C, 67.61; H, 2.82; N, 14.00%. Found: C, 67.60; H, 2.81; N, 14.01%.

General procedure for the synthesis of 2-(5-substituted-3-phenyl-1H-indol-2-yl)-5-methyl / phenyl-7H-[1,3,4]thiadiazolo[3,2-a][1,3,5]triazine-7-thione (7a-f)
A mixture of N-((5-(5-substituted-3-phenyl-1H-indol-2-yl)-1,3,4-thiadiazol-2-yl)carbamothioyl)acetamides / benzamides (5a-f) (0.015mol), phosphorous oxychloride (15 ml) and phosphorus pentachloride (0.015 mol) was refluxed for 3-4 hrs. The excess phosphorous oxychloride was then removed under reduced pressure and crushed ice added to it. The resulting solid (7a-f) was extracted with ethyl acetate / dichloromethane and recrystallized from suitable solvent.
2.94; N, 17.06%. MS: M⁺ at m/e 409.9(12%) and m/e 411(3%) the isotope peak: A₁ at 276(16%); A₂ at 192(100%); A₃ at 231(60%); A₄ at 201(2%) and A₅ at 159(17%).

2-(5-bromo-3-phenyl-1H-indol-2-yl)-5-methyl-7H-[1,3,4]thiadiazolo[3,2-a][1,3,5] triazine-7-thione (7b)

Light brown crystals (dil. alcohol), Yield 66%, mp 159-161 °C, IR (KBr) ν: 3195(NH), 1563/1493/1446 (C=N/C=N/C=N), 1075(C=S), 803(-S-); 1H NMR (400 MHz, CDCl₃) δ ppm: 1.2 (s, 3H, CH₃), 1.3 (s, 3H, CH₃), 7.1-7.9 (m, 8H, ArH), 9.1(s, 1H, Indole NH); Anal. Calcd for: C₂₅H₂₅N₅S₂Br: C, 55.82; H, 2.73; N, 13.56%. Found: C, 55.80; H, 2.72; N, 13.54%.

5-methyl-2-(5-methyl-3-phenyl-1H-indol-2-yl)-7H-[1,3,4]thiadiazolo[3,2-a][1,3,5] triazine-7-thione (7c)

Brown crystals (ethanol), Yield 72%, mp 142-144 °C, IR (KBr) ν: 3218(NH), 1554/1495(C=N/C=N), 1074 (C=S), 803(-S-); 1H NMR (400 MHz, CDCl₃) δ ppm: 2.4 (s, 3H, CH₃), 1.2 (s, 3H, CH₃), 7.0-7.7 (m, 8H, ArH), 9.1(s, 1H, Indole NH); Anal. Calcd for: C₂₅H₂₅N₅S₂: C, 61.67; H, 3.88; N, 17.98%. Found: C, 60.64; H, 3.86; N, 17.96%.

2-(5-chloro-3-phenyl-1H-indol-2-yl)-5-phenyl-7H-[1,3,4]thiadiazolo[3,2-a][1,3,5]triazine-7-thione (7d)

Brown crystals (dil. alcohol), Yield 69%, mp 158-160 °C, IR (KBr) ν: 3210(NH), 1566/1954(C=N/C=N), 1102(C=S), 721(-S-); 1H NMR (400 MHz, CDCl₃) δ ppm: 6.9-7.7 (m, 13H, ArH), 9.9(s, 1H, Indole NH); Anal. Calcd for: C₂₅H₂₅N₅S₂Cl: C, 61.07; H, 2.99; N, 14.84%. Found: C, 61.06; H, 2.97; N, 14.83%.

2-(5-bromo-3-phenyl-1H-indol-2-yl)-5-phenyl-7H-[1,3,4]thiadiazolo[3,2-a][1,3,5] triazine-7-thione (7e)

Brown needle (ethanol), Yield 72%, mp 178-180 °C, IR (KBr) ν: 3281(NH), 1463/1483 /1446 (C=N/C=N/C=N), 1075(C=S), 803(-S-); 1H NMR (400 MHz, CDCl₃) δ ppm: 6.8-7.8 (m, 13H, ArH), 9.4 (s, 1H, Indole NH); Anal. Calcd for: C₂₅H₂₅N₅S₂Br: C, 55.82; H, 2.73; N, 13.56%. Found: C, 55.80; H, 2.72; N, 13.53%.

2-(5-methyl-3-phenyl-1H-indol-2-yl)-5-phenyl-7H-[1,3,4]thiadiazolo[3,2-a][1,3,5] triazine-7-thione (7f)

Brown crystals (ethanol), Yield 73%, mp 193-195 °C, IR (KBr) ν: 3395(NH), 1564/1493 /1446 (C=N/C=N/C=N), 1055(C=S); 1H NMR (400 MHz, CDCl₃) δ ppm: 2.4 (s, 3H, CH₃), 7.0-7.9 (m, 13H, ArH), 9.3 (s, 1H, Indole NH); Anal. Calcd for: C₂₅H₂₅N₅S₂: C, 66.49; H, 3.79; N, 15.51%. Found: C, 66.47; H3.78; N, 15.49%.

Antimicrobial Activities:
The antibacterial activities of compounds 4a-f, 5a-f, 6a-f and 7a-f were carried out using Cup-plate diffusion method [32] and antibacterial species used are two Gram negative species Escherichia coli, Pseudomonas aeruginosa and two Gram positive species Bacillus subtilis, Staphylococcus aureus. Four fungal strains Aspergillus niger, Penicillium chrysogenum, Aspergillus flavus, Aspergillus fumigatus were used for antifungal activity. Solution of each compound at a concentration of 100µg/0.1 mL in DMF was prepared and the inhibition zone diameter in centimeter (IZD) was used as the criterion for measure the microbial activity. Gentamycin, Ciprofloxacin were used as bacterial standards and Fluconazole, Greseofulvin were used as fungal standards for references to evaluate the efficacy of the tested compounds under the same conditions. Dimethyl formamide used as control and solvent to prepare compound solutions as 10 mg per 10 mL.

RESULTS AND DISCUSSION

Chemistry
In the present investigation requisite 3,5-disubstituted indole-2-carboxyhydrazides were prepared by fischer indole synthesis [30] and 2-(3-phenyl-1H-indole-2-carbonyl) hydrazinecarbothioamides were synthesized as per reported method [31]. The compound indole-2-carboxyhydrazides were reacted with potassium thiocyanate in the presence of concentrated hydrochloric acid to get 3,5-disubstituted indole-3-thiosemicarbazide (1a-c). The oxidative cyclisation of 3,5-disubstituted indole-3-thiosemicarbazide (1a-c) using iodine in potassium iodide solution as oxidant gave the corresponding substituted 1,3,4-oxadiazoles containing indole nucleus (2a-c). The compound 1a-c on cyclohydration with phosphoric acid gave the corresponding substituted 1,3,4-thiadiazole containing indole nucleus (3a-c). Compounds 2a-c and 3a-c on treatment with acyl chlorides and ammonium thiocyanate in acetone yields the compounds 4a-f and 5a-f, followed by cyclisation of the resulting compounds 4a-f and 5a-f with phosphorus pentachloride and phosphorus oxychloride yield the corresponding 2-(5-substituted-3-phenyl-1H-indol-2-yl)-5-methyl / phenyl-7H-[1,3,4]oxadiazolo / thiadiazolo[3,2-a][1,3,5]triazine-7-thione (6a-c) & (7a-c) (Scheme-I).
The IR spectrum of compounds 2a exhibited characteristic absorption peak at 3312 (NH), 2989 (NH), 1532/1530 (C=N/C=N), 1260 cm$^{-1}$ (-O-). The $^1$H NMR spectrum of 2a displayed a singlet at 9.2 $\delta$ due to the deshielded indole NH. The singlet at $\delta$ 4.2 (2H, NH$_2$) accounting for two protons is due to NH$_2$ group attached to the oxadiazole ring. A multiplet in the region $\delta$ 7.2 to 7.6 (m, 8H, ArH) accounting for eight aromatic protons. The IR spectrum of compound 3a exhibited characteristic absorption peaks at 3316 (NH$_2$), 2988 (NH), 1602/1532 cm$^{-1}$ (C=N/C=N) and 765 cm$^{-1}$ (-S-). The $^1$H NMR spectrum of compound 3a displayed a singlet at 9.1 $\delta$ (1H, NH) due to the deshielded indole NH. The singlet at $\delta$ 4.3 (2H, -NH$_2$), accounting for two protons is due to NH$_2$ group attached to the thiadiazole ring. A multiplet in the region $\delta$ 7.2 to 7.7 (8H, ArH), accounting for eight protons assigned to aromatic protons. The IR spectrum of compound 4a has displayed peaks at 3312 cm$^{-1}$ for (NH),
The presence of another NH group showed the peak at $\delta$ 9.9 (s, 1H, -NH). The IR spectrum of compound 5a has displayed a characteristic peaks at 3435 cm\(^{-1}\), 3298 cm\(^{-1}\) and 3152 cm\(^{-1}\) due to NH/NH/NH respectively. The carbonyl peak was observed at 1669 cm\(^{-1}\) (C=O), other peaks appeared at 1609 cm\(^{-1}\) /1539 cm\(^{-1}\) (C=N/C=N) and 1109 cm\(^{-1}\) (C=S). The \(^1\)H NMR spectrum of compound 5a has shown peak at $\delta$ 1.8 (s, 3H, CH\(_3\)) is due to the methyl group, a multiplet in the region $\delta$ 7.3-7.6 (m, 8H, ArH) due to eight aromatic protons. Singlet at $\delta$ 8.4 (s, 1H, NH) is for NH attached to the electronegative sulphur, deshielded peak at $\delta$ 9.1 (s, 1H, NH) is due to indole NH and singlet at $\delta$ 9.6 (s, 1H, NH) is the NH group of the compound.
The IR spectrum of compounds 6a exhibited characteristic absorption peaks at 3314 cm\(^{-1}\) (NH) is due to the indole NH, other absorptions at 1682/1602/1533 cm\(^{-1}\) (C=N / C=N / C=N) of the triazine and diazole rings respectively. Absorption peaks at 1260 cm\(^{-1}\) (-O-) and 1169 cm\(^{-1}\) (C=S) recommends the proposed structure of the compound. The \(^1\)H NMR spectrum of compound 6a showed absorptions at \(\delta 1.3\) (s, 3H, CH\(\_3\)) of three protons of the methyl group, the downfield signal at \(\delta 9.3\) (1H) due to the indole NH, a multiplet in the region \(\delta 7.3\) to 7.7 (m, ArH, 8H) accounting for eight aromatic protons. The structure of compound 6a is further supported by its mass spectrum (Scheme-II).

The mass spectrum of compound 6a has shown the molecular ion peak M\(^+\) at m/z 393(6%) and 395(2%), which is the molecular weight of compound. Molecular ion peak has undergone into further fragmentation by two routes. In one route it loses methyl radical and showed peak A\(_3\) at m/z 380(4%) and 382(1%). In another route it has lost C\(_2\)NS and showed A\(_3\) at m/z 299(100%) and 301(32%), which is the base peak of the compound. A\(_1\) eliminate the CS and N\(_2\) and showed fragment A\(_3\) at 307(14%) and 309(4%). This fragment further loses CN and CO and showed peak A\(_3\) at 254(50%) and 256(16%). Fragment A\(_3\) on losing chlorine radical displayed peak A\(_3\) at 219(6%). Other fragments in the mass spectrum are A\(_3\) at 190(30%), A\(_3\) at 154(78%). This fragmentation supports the structure.

Table 1. \textit{In vitro} antimicrobial assay of newly synthesized 4a-f to 7a-f compounds.

<table>
<thead>
<tr>
<th>Comp’s. (R,R)</th>
<th>Zone of inhibition in mm</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>E. coli</td>
</tr>
<tr>
<td>4a (Cl,CH(_3))</td>
<td>15 18 14 16 15 14 18 15</td>
</tr>
<tr>
<td>4b (Br,CH(_3))</td>
<td>16 16 13 16 16 13 12 10</td>
</tr>
<tr>
<td>4c (CH(_3),CH(_3))</td>
<td>14 17 12 16 20 16 13 13</td>
</tr>
<tr>
<td>4d (Cl,Ph)</td>
<td>16 18 15 19 14 13 12 16</td>
</tr>
<tr>
<td>4e (Br,Ph)</td>
<td>17 21 18 17 14 13 12 16</td>
</tr>
<tr>
<td>4f (CH(_3),Ph)</td>
<td>17 18 14 18 20 13 15 11</td>
</tr>
<tr>
<td>5a (Cl,CH(_3))</td>
<td>20 15 16 15 16 15 14 17</td>
</tr>
<tr>
<td>5b (Br,CH(_3))</td>
<td>17 16 15 19 13 13 12 16</td>
</tr>
<tr>
<td>5c (CH(_3),CH(_3))</td>
<td>14 19 12 20 18 13 23 16</td>
</tr>
<tr>
<td>5d (Cl,Ph)</td>
<td>15 22 17 17 20 16 15 21</td>
</tr>
<tr>
<td>5e (Br,Ph)</td>
<td>15 17 19 16 20 17 14 12</td>
</tr>
<tr>
<td>5f (CH,Ph)</td>
<td>16 16 14 15 20 16 12 12</td>
</tr>
<tr>
<td>6a (Cl,CH(_3))</td>
<td>16 15 18 15 17 15 12 13</td>
</tr>
<tr>
<td>6b (Br,CH(_3))</td>
<td>15 14 16 18 16 14 15 14</td>
</tr>
<tr>
<td>6c (CH(_3),CH(_3))</td>
<td>14 17 14 15 15 10 12 14</td>
</tr>
<tr>
<td>6d (Cl,Ph)</td>
<td>17 14 15 14 20 10 11 10</td>
</tr>
<tr>
<td>6e (Br,Ph)</td>
<td>16 30 12 15 17 16 11 10</td>
</tr>
<tr>
<td>6f (CH,Ph)</td>
<td>16 14 15 15 10 10 12 11</td>
</tr>
<tr>
<td>7a (Cl,CH(_3))</td>
<td>17 18 15 14 19 18 19 19</td>
</tr>
<tr>
<td>7b (Br,CH(_3))</td>
<td>18 19 14 15 15 16 12 14</td>
</tr>
<tr>
<td>7c (CH,CH(_3))</td>
<td>21 21 16 16 22 10 12 10</td>
</tr>
<tr>
<td>7d (Cl,Ph)</td>
<td>18 21 16 14 12 14 12 10</td>
</tr>
<tr>
<td>7e (Br,Ph)</td>
<td>14 16 15 18 12 11 14 13</td>
</tr>
<tr>
<td>7f (CH,Ph)</td>
<td>17 15 14 16 10 10 11 12</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>18 18 21 23 - - - -</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>19 20 19 24 - - - -</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>- - - - 18 15 23 21</td>
</tr>
<tr>
<td>Gresefulvin</td>
<td>- - - - 20 18 18 16</td>
</tr>
<tr>
<td>DMP C(Control)</td>
<td>08 08 08 08 08 08 08</td>
</tr>
</tbody>
</table>

The IR spectrum of compounds 7a exhibited characteristic absorption peaks at 3227 cm\(^{-1}\) (NH) is due to indole NH. Spectrum showed absorptions at 1632 / 1552 cm\(^{-1}\) (C=N / C=N) of the triazine and diazole rings respectively. Peaks at 1237 cm\(^{-1}\) (C=S) and 727 cm\(^{-1}\) (C-N=C) recommends the proposed structure of the compound. The \(^1\)H NMR spectrum of compound 7a showed peak at \(\delta 1.3\) (s, 3H, CH\(_3\)) of three protons in the methyl group. The downfield signal at \(\delta 9.3\) (1H) is due to the indole NH, a multiplet in the region \(\delta 7.2\) to 7.7 (m, ArH, 8H) accounting for eight aromatic protons. The structure of compound 7a is further supported by its mass spectral fragmentation. The mass spectrum of compound 7a (Scheme - III), has shown molecular ion peak at m/z 409.9(12%) and another peak at m/z 411(3%), the isotope peak. This is in agreement with molecular weight of 7a. Molecular ion probably has undergone fragmentation by two routes. In the first route it eliminates \(-\text{CN}_2\text{H}_5\text{S}\) and chlorine radical to show fragment A\(_3\) at 276(16%). Fragment A\(_3\) then loses C\(_2\)H\(_3\)S and displayed peak A\(_3\) at 192(100%), which is base peak in the spectrum. In another route molecular ion eliminates CH\(_3\), C\(_6\)H\(_5\), Cl and showed A\(_3\) at 231(60%). This on further fragmentation displayed peaks A\(_3\) at 201(2%) and A\(_3\) at 159(17%). This fragmentation supports the proposed structure of the compound. Structures of other derivatives (7b-f) were confirmed based on their spectral and analytical data reported.
Antimicrobial Activities

Title compounds are screened for in-vitro antimicrobial activities against four bacterial and four fungal microorganisms. The results are depicted in Table 1.

Compounds 5a, 7b, 7c, 7d and 4a, 4d, 4e, 4f, 5c, 5d, 5e, 6c, 7a, 7b, 7c, 7d exhibited relatively significant activity against *Escherichia coli* and *p.aeruginosa* respectively, 4e and 6a against *Staphylococcus aureus* and 4d, 4f, 5b, 6b, 7e with *Bacillus subtilis*. Other compounds of the series have shown moderately to weakly active.

In antifungal activities compound 4c, 4f, 5c, 5d, 5e, 5f, 6d, 7a and 7c displayed highest activity against *Aspergillus niger*, 7a against *P.chrysogenum*, 4a, 5c and 7a against *Aspergillus flavus*, 5d and 7a against *Aspergillus fumigatus* micro-organisms. Other compounds 4b, 4c, 4d, 4f, 5c, 5d, 5f, 6a and 7b compounds have shown moderately active against various antifungal strains. Remaining compounds in antifungal screening were shown weekly to inactive.

**CONCLUSION**

In conclusion, title compounds 2-(5-substituted-3-phenyl-1H-indol-2-yl)-5-methyl / phenyl-7H-[1,3,4]oxadiazolo [3,2-a][1,3,5]triazine-7-thione (6a-f) and 2-(5-substituted-3-phenyl-1H-indol-2-yl)-5-methyl / phenyl-7H-[1,3,4]thiadiazolo[3,2-a][1,3,5]triazine-7-thione (7a-f) were synthesized and characterized them by using spectral and analytical studies. All the synthesized new compounds are screened for *in-vitro* antimicrobial activities against various microbial strains and observed evidently that some of the compounds bearing substituted thidiazol triazine moiety are displayed significantly active than oxadiazol triazine moiety in comparison with the standards used. Also some of the compounds from 4a-f and 5a-f series have shown significantly active to moderately active in screening.

**Acknowledgement**

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**REFERENCES**