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Synthesis, characterization and antimicrobial activities of 2-(5-substituted-3-phenyl-1*H*-indol-2-yl)-5-substituted-7*H*-[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 **(6&7a-f)** were prepared from the intra molecular cyclocondensation of N-((5-(5-substituted-3-phenyl-1H-indol-2-yl)-1,3,4-oxadiazol / thiadiazol-2-yl)carbamothioyl)acetamides / benzamides (**4& 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 (**2&3a-c**) with acetyl and benzoyl chlorides in the presence of ammonium thiocynate. 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 towards 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]-s-triazines are excellent bioavailable compounds with incorporation of various pharmacophores as antibacterial[25], antifungal[26,27] and fungicidal[28].

In view of these observations and in continuation of our work on the search of bioactive indole analogs[29], it was contemplated to synthesis 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-thione **[(6a-f) & (7a-f)]** by bridging all bioactive heterocyclic rings as fused

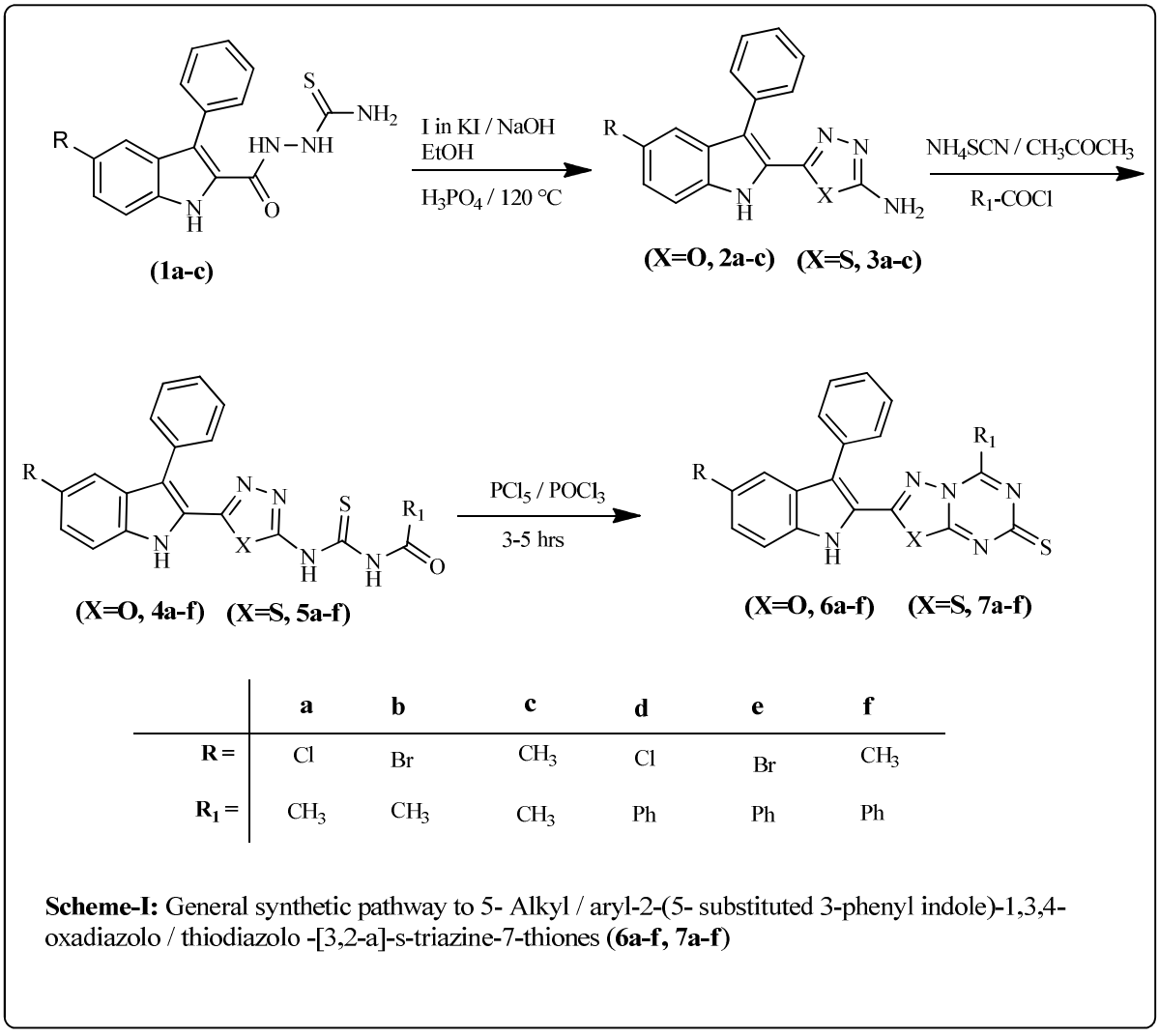
heterocycles with expectation of enhanced biological activity of the molecule. Hence we have carried out synthesis, characterization and antimicrobial activities of title compounds which are new and are not reported so far elsewhere.

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-*d6* and TMS used as an internal standard. The chemical shifts are expressed in δ 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.



	a	b	c	d	e	f
R =	Cl	Br	CH_3	Cl	Br	CH_3
R_1 =	CH_3	CH_3	CH_3	Ph	Ph	Ph

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) *v* in cm^{-1}: 3312 (NH_2), 2989(NH), 1533/1495(C=N/C=N), 1260 (-O-), ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 4.2 (2H, -NH_2), 7.2-7.6 (m, 8H, ArH), 9.2 (s, 1H, Indole-NH); Anal. Calcd for: $C_{16}H_{11}ClN_4O$: C61.84; 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 60%, mp 191-193 °C; IR (KBr) *v*: 3327(NH_2), 3299(-NH-), 1559/1538(C=N/C=N), 1260(-O-); ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 4.4 (2H, -NH_2), 7.0-7.6 (m, 8H, ArH), 8.2 (s, 1H, Indole-NH); Anal. Calcd for: $C_{16}H_{11}BrN_4O$: C 54.10; H, 3.12; N, 15.77%. Found: C, 54.08; H, 3.10; N, 15.75%.

5-(5-methyl-3-phenyl-1H-indol-2-yl)-1,3,4-oxadiazol-2-amine (2c)
Yellow crystals (ethanol), Yield 72 %, mp 178-180 °C; IR (KBr) *v*: 3319 (NH_2), 3252(NH), 1555/1562(C=N/C=N), 1211(-O-); ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 2.5 (3H, -CH_3), 4.0 (2H, -NH_2), 7.0-7.6 (m, 8H, ArH), 8.1 (s, 1H, Indole-NH); Anal. Calcd for: $C_{17}H_{14}N_4O$: C 70.33; H, 4.86; N, 19.30%. Found: C, 70.31; H, 4.84; N, 19.29%.

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) *v*: 3316 (NH_2), 2988 (NH), 1602/1532 (C=N/C=N), 765 (-S-); ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 4.3 (2H, -NH_2), 7.2-7.7 (8H, ArH), 9.1 (s, 1H, indole NH); Anal. Calcd for: $C_{16}H_{11}ClN_4S$: C 58.80; H, 3.39; N, 17.14%. Found: C, 58.79; H, 3.37; N, 17.13%.

5-(5-bromo-3-phenyl-1H-indol-2-yl)-1,3,4-thiadiazol-2-amine (3b)
Light green crystals (ethanol), Yield 55%, mp 184-185 °C; IR (KBr) *v*: 3427(NH_2), 3299(-NH-), 1606/1538(C=N/C=N), 796(-S-); ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 4.2 (2H, -NH_2), 7.1-7.8 (8H, ArH), 9.0 (s, 1H, indole NH); Anal. Calcd for $C_{16}H_{11}BrN_4S$:: C 51.76; H, 2.99; N, 15.09%. Found: C, 51.74; H, 2.98; N, 15.07%.

5-(5-methyl-3-phenyl-1H-indol-2-yl)-1,3,4-thiadiazol-2-amine (3c)
Yellow amorphous (ethanol), Yield 76%, mp. 191-192°C; IR (KBr) *v*: 3307 (NH_2), 3152(NH), 1505/1600(C=N/C=N),796(-S-); ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 2.5 (3H, -CH_3), 4.2 (2H, -NH_2), 7.1-7.6 (8H, ArH), 9.1 (s, 1H, indole NH); Anal. Calcd for: $C_{17}H_{14}N_4S$: C 66.64; H, 4.61; N, 18.29%. Found: C, 66.62; H, 4.60; N, 18.28%.

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 thiocynate (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-oxadiaozole **(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-(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) *v*: 3312 (NH), 2988 / 2898 (NH/NH), 1683 (C=O), 1260 (-O-), 1169 (C=S); ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 2.1(s, 3H, CH_3), 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 $C_{19}H_{14}N_5O_2SCl$: C, 55.41; H, 3.43; N, 17.00%. Found: C, 55.39; H, 3.40; N, 17.00%.

N-((5-(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) *v*: 3304(NH), 3000/2971(NH/NH), 1667(C=O), 1541/1497(C=N/C=N), 1241(-O-), 1161(C=S); ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 1.9(s, 3H, CH_3), 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 $C_{19}H_{14}BrN_5O_2S$: 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 (4c). Pale yellow crystals (1,4-dioxane), Yield 81%, mp 184-186°C; IR (KBr) *v*: 3335(NH), 3000/2800 (NH/NH), 1667(C=O), 1366/1298(C=N/C=N); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 2.4(s, 3H, CH_3), 1.8 (s, 3H, CH_3), 7.2-7.6 (m, 8H, ArH), 8.2 (s, 1H, NH), 9.0 (s, 1H, indole-NH), 9.8 (s, 1H, NH); Anal. Calcd for $C_{20}H_{17}N_5O_2S$: C, 61.37; H, 4.38; N, 17.89%. Found: C, 61.36; H, 4.36; N, 17.88%.

N-((5-(5-chloro-3-phenyl-1H-indol-2-yl)-1,3,4-oxadiazol-2-yl)carbamothioyl)benzamide (4d). Yellow crystals (Ethanol), Yield 70%, mp 109-111°C; IR (KBr) *v*: 3304(NH), 2971/2985(NH/NH), 1667 (C=O), 1541/1494(C=N/C=N), 1049(C=S); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.0-7.8 (m, 13H, ArH), 8.2 (s, 1H, NH), 9.1 (s, 1H, indole-NH), 9.9 (s, 1H, NH); Anal. Calcd for $C_{24}H_{16}ClN_5O_2S$: C, 60.82; H, 3.40; N, 14.78%. Found: C, 60.80; H, 3.38; N, 14.76%.

N-((5-(5-bromo-3-phenyl-1H-indol-2-yl)-1,3,4-oxadiazol-2-yl)carbamothioyl)benzamide (4e). Yellow Plates (ethanol), Yield 65%, mp 114-116°C; IR (KBr) *v*:3297(NH), 3000/2857(NH/NH), 1646(C=O), 1533/1443 (C=N/C=N), 1143(C=S); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.2-7.8 (m, 13H, ArH), 8.3 (s, 1H, NH), 9.3 (s, 1H, indole-NH), 9.8 (s, 1H, NH); Anal. Calcd for $C_{24}H_{16}BrN_5O_2S$: C, 55.61; H, 3.11; N, 13.51%. Found: C, 55.59; H, 3.09; N, 13.50%.

N-((5-(5-methyl-3-phenyl-1H-indol-2-yl)-1,3,4-oxadiazol-2-yl)carbamothioyl)benzamide (4f). Ash green amorphous (dil. Ethanol), Yield 67%, mp 114-116°C; IR (KBr) *v*: 3200(NH), 2847/2391(NH/NH), 1692(C=O), 1510/1500(C=N/C=N), 1002(C=S); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 2.4 (s, 3H, CH_3), 2.4, (s, 3H, -CH_3), 7.2-8.0 (m, 13H, ArH), 8.3 (s, 1H, NH), 9.3 (s, 1H, indole-NH), 9.8 (s, 1H, NH); Anal. Calcd for $C_{25}H_{19}N_5O_2S$: C, 66.21; H, 4.22; N, 15.44%. Found: C, 66.20; H, 4.21; N, 15.42%.

General procedure for the synthesis of N-((5-(5-substituted-3-phenyl-1H-indol-2-yl)-1,3,4-thiadiazol-2-yl)carbamothioyl)acetamides / benzamides (5a-f)

A mixture of ammonium thiocynate (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-Thidiazole **(3a-c)** (0.01 mol) was then added to it and the reaction mixture was refluxed further for 3-4 h. It was then poured in to water. The resulting solid **(5a-f)** was dried and recrystallized from suitable solvent.

N-((5-(5-chloro-3-phenyl-1H-indol-2-yl)-1,3,4-thiadiazol-2-yl)carbamothioyl)acetamide (5a)

Yellow crystals (acetone + Ethanol), Yield; 83%, mp. 202-203 °C; IR (KBr) *v*: 3435 / 3298 / 3152 (NH / NH / NH), 1669 (C=O), 1609 / 1539 (C=N/C=N), 1109 (C=S); ^{1}H NMR (400 MHz, DMSO-d6) δ ppm: 1.8 (s, 3H, CH_3), 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 $C_{19}H_{14}ClN_5OS_2$: C, 53.33; H, 3.30; N, 16.37%. Found: C, 53.30; H, 3.28; N, 16.36%.

N-((5-(5-bromo-3-phenyl-1H-indol-2-yl)-1,3,4-thiadiazol-2-yl)carbamothioyl)acetamide (5b)

Yellow needles (abs. ethanol), Yield 72%; mp 188-190 °C; IR (KBr) *v*: 3298/3152/2965 (NH /NH / NH), 1669(C=O), 539/1497 (C=N/C=N), 1109(C=S); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 2.0 (s, 3H, CH_3), 7.2-7.5 (m, 8H, ArH), 8.4 (s,1H, NH), 9.2 (s,1H,indole NH), 9.6 (s, 1H, NH); Anal. Calcd for: $C_{19}H_{14}N_5OS_2Br$: C, 48.31; H,2.99; N, 14.83%. Found: C, 48.29; H, 2.96; N, 14.81%.

N-((5-(5-methyl-3-phenyl-1H-indol-2-yl)-1,3,4-thiadiazol-2-yl)carbamothioyl)acetamide (5c)

Yellow crystals (Acetone + ethanol), Yield 82%; mp 162-163 °C; IR (KBr) *v*: 3283 / 3024 / 2916 (NH / NH / NH), 1662(C=O), 540/1497 (C=N/C=N), 1156(C=S): ^{1}H NMR (400 MHz, DMSO-d6) δ ppm: 2.4(s, 3H, CH_3), δ 2.0 (s, 3H, CH_3), 7.2-7.5 (m, 8H, ArH), 8.4 (s, 1H, NH), 9.2 (s,1H,indole NH), 9.6 (s, 1H, NH); Anal. Calcd for: $C_{20}H_{17}N_5OS_2$: C, 58.95; H, 4.20; N, 17.19%. Found: C, 58.94; H, 4.21; N, 17.17%.

N-((5-(5-chloro-3-phenyl-1H-indol-2-yl)-1,3,4-thiadiazol-2-yl)carbamothioyl) benzamide (5d)

Yellow crystals (ethanol),Yield 79%, mp 197-195 °C, IR (KBr) *v*: 3296 /3158 /2962 (NH /NH /NH), 1673(C=O), 1538/1495 (C=N/C=N), 1108(C=S); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.0-7.8 (m, 13H, ArH), 8.2 (s, 1H, NH), 9.1 (s, 1H, indole-NH), 9.9 (s, 1H, NH); Anal. Calcd for: $C_{24}H_{16}N_5OS_2Cl$: C, 58.83; H, 3.29; N, 14.29%. Found: C, 58.80; H, 3.29; N, 14.28%.

N-((5-(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) *v*: 3290 / 3144 / 2955 (NH / NH / NH), 1587 / 1507 (C=N/C=N), 1670(C=O), 1105 (C=S): ^{1}H NMR (400 MHz, $CDCl_3$) 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: $C_{24}H_{16}N_5OS_2Br$: C, 53.94; H, 3.02; N, 13.10%. Found: C, 53.91; H, 3.0; N, 13.08%.

N-((5-(5-methyl-3-phenyl-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) *v*: 3425 / 3282 / 3050 (NH /NH / NH), 1662 (C=O), 1602/1542 (C=N/C=N), 1106 (C=S); ^{1}H NMR (400 MHz, DMSO-d6) δ ppm: 2.3, (s, 3H, -CH_3), 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: $C_{25}H_{19}N_5OS_2$: 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) were refluxed for 3-4 hrs. The excess phosphorous oxychloride was then removed under reduced pressure and crushed ice 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) *v*: 3314 (NH), 1682 / 1602/1533 (C=N / C=N / C=N), 1260(-O-), 1169 (C=S); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 1.3 (s, 3H, CH_3), 7.3-7.7 (m, 8H, ArH), 9.3 (s, 1H, Indole NH); Anal. Calcd for: $C_{19}H_{12}N_5OSCl$: C, 57.94; H, 3.07; N, 17.78%. Found: C, 57.91; H, 3.06; N, 17.76%. MS: $M^{+\cdot}$ *m/z* 393(6%) and 395(2%); A_1 at *m/z* 380(4%) and 382(1%); A_2 at *m/z* 299(100%) and 301(32%), A_3 at 307(14%) and 309(4%). A_4 at 254(50%) and 256(16; A_5 at 219(6%). ; A_6 at 190(30%), A_7 at 154(78%).

2-(5-bromo-3-phenyl-1H-indol-2-yl)-5-methyl-7H-[1,3,4]oxadiazolo[3,2-a][1,3,5]triazine-7-thione (6b)
Light brown amorphous (ethanol), Yield 68%, mp 125 °C, IR (KBr) *v*: 3200(NH), 1466 / 1455 (C=N/C=N), 1172(C=S), 1231(-O-); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 1.4 (s, 3H, CH_3), 7.2-7.9 (m, 8H, ArH), 9.4 (s, 1H, Indole NH); Anal. Calcd for: $C_{19}H_{12}N_5OSBr$: C, 52.07; H, 2.76; N, 15.98%. Found: C, 52.06; H, 2.76; N, 15.99%.

5-methyl-2-(5-methyl-3-phenyl-1H-indol-2-yl)-7H-[1,3,4]oxadiazolo[3,2-a][1,3,5] triazine-7-thione (6c)
Deep yellow crystals (ethanol), Yield 72%, mp 180 °C, IR (KBr) *v*: 3239(NH), 1621 /1495 /1445 (C=N/C=N/C=N), 1138(C=S); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 2.4 (s, 3H, CH_3), 1.3 (s, 3H, CH_3), 7.1-7.7 (m, 8H, ArH), 9.8 (s, 1H, Indole NH); Anal. Calcd for: $C_{20}H_{15}N_5OS$: 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 (6d)
Brown crystals (acetone + ethanol), Yield 73%, mp. 223- 225 °C, IR (KBr) *v*: 3271(NH), 1681/1603/1573 (C=N/C=N/C=N), 1259 (-O-), 1154 (C=S); ^{1}H NMR (400 MHz, DMSO-d6) δ ppm: 7.1-7.9 (m, 13H, ArH), 9.9 (s, 1H, Indole NH); Anal. Calcd for: $C_{24}H_{14}N_5OSCl$: C, 63.23; H, 3.10; N, 15.36%. Found: C, 63.21; H, 3.08; N, 15.35%.

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 (1,4-diaxane), Yield 60%, mp 135 °C, IR (KBr) *v*: 3418(NH), 1492/1447 (C=N/C=N), 1105(C=S), 1260(-O-); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 6.8-7.9 (m, 13H, ArH), 9.8m (s, 1H, Indole NH); Anal. Calcd for: $C_{24}H_{14}N_5OSBr$: C, 57.61; H, 2.82; N, 14.00%. Found: C, 57.60; H, 2.81; N, 14.01%.

2-(5-methyl-3-phenyl-1H-indol-2-yl)-5-phenyl-7H-[1,3,4]oxadiazolo[3,2-a][1,3,5] triazine-7-thione (6f)
Brown crystals (1,4-diaxane), Yield 68%, mp. 148-150 °C, IR (KBr) *v*: 3230(NH), 1496/1445 (C=N/C=N), 1172(C=S), 1261(-O-); 1H NMR (400 MHz, $CDCl_3$) δ ppm: 2.3 (s, 3H, CH_3), 7.1-7.9 (m, 13H, ArH), 9.3 (s, 1H, Indole NH); Anal. Calcd for: $C_{25}H_{17}N_5OS$: C, 68.95; H, 3.93; N, 16.08%. Found: C, 68.93; H, 3.92; N, 16.06%.

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-(5-chloro-3-phenyl-1H-indol-2-yl)-5-methyl-7H-[1,3,4]thiadiazolo[3,2-a][1,3,5] triazine-7-thione (7a)
Light brown crystals (ethanol), Yield 75%, mp.158-160 °C, IR (KBr) *v*: 3227(NH), 1632/1552/1448 (C=N/C=N/C=N), 1237(C=S), 703(C-S-C); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 1.2 (s, 3H, CH_3), 7.2-7.7 (m, 8H, ArH), 9.1(s, 1H, Indole NH); Anal. Calcd for: $C_{19}H_{12}N_5S_2Cl$: C, 55.67; H, 2.95; N, 17.08%. Found: C, 55.65; H,

2.94; N, 17.06%. MS: $M^{+\cdot}$ at *m/z* 409.9(12%) and *m/z* 411(3%) the isotope peak: A_1 at 276(16%); A_2 at 192(100%); A_3 at 231(60%); A_4 at 201(2%) and A_5 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) *v*: 3195(NH), 1563/1493/1446 (C=N/C=N/C=N), 1075(C=S); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 1.3 (s, 3H, CH_3), 7.0-7.7 (m, 8H, ArH), 9.8(s, 1H, Indole NH); Anal. Calcd for: $C_{19}H_{12}N_5S_2Br$: C, 50.22; H, 2.66; N, 15.41%. Found: C, 50.20; H, 2.64; N, 15.38%.

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) *v*: 3218(NH), 1554 /1495(C=N/C=N), 1074 (C=S), 803(-S-); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 2.4 (s, 3H, CH_3), 1.2 (s, 3H, CH_3), 7.1-7.9 (m, 8H, ArH), 9.1(s, 1H, Indole NH); Anal. Calcd for: $C_{20}H_{15}N_5S_2$: 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) *v*: 3210(NH), 1566/1954(C=N/C=N), 1102(C=S), 721(-S-); 1H NMR (400 MHz, $CDCl_3$) δ ppm: 6.9-7.7 (m, 13H, ArH), 9.9(s, 1H, Indole NH); Anal. Calcd for: $C_{24}H_{14}N_5S_2Cl$: C, 61.07; H, 2.99; N, 14.84%. Found: C, 61.06; H, 2.97; N, 14.83%.

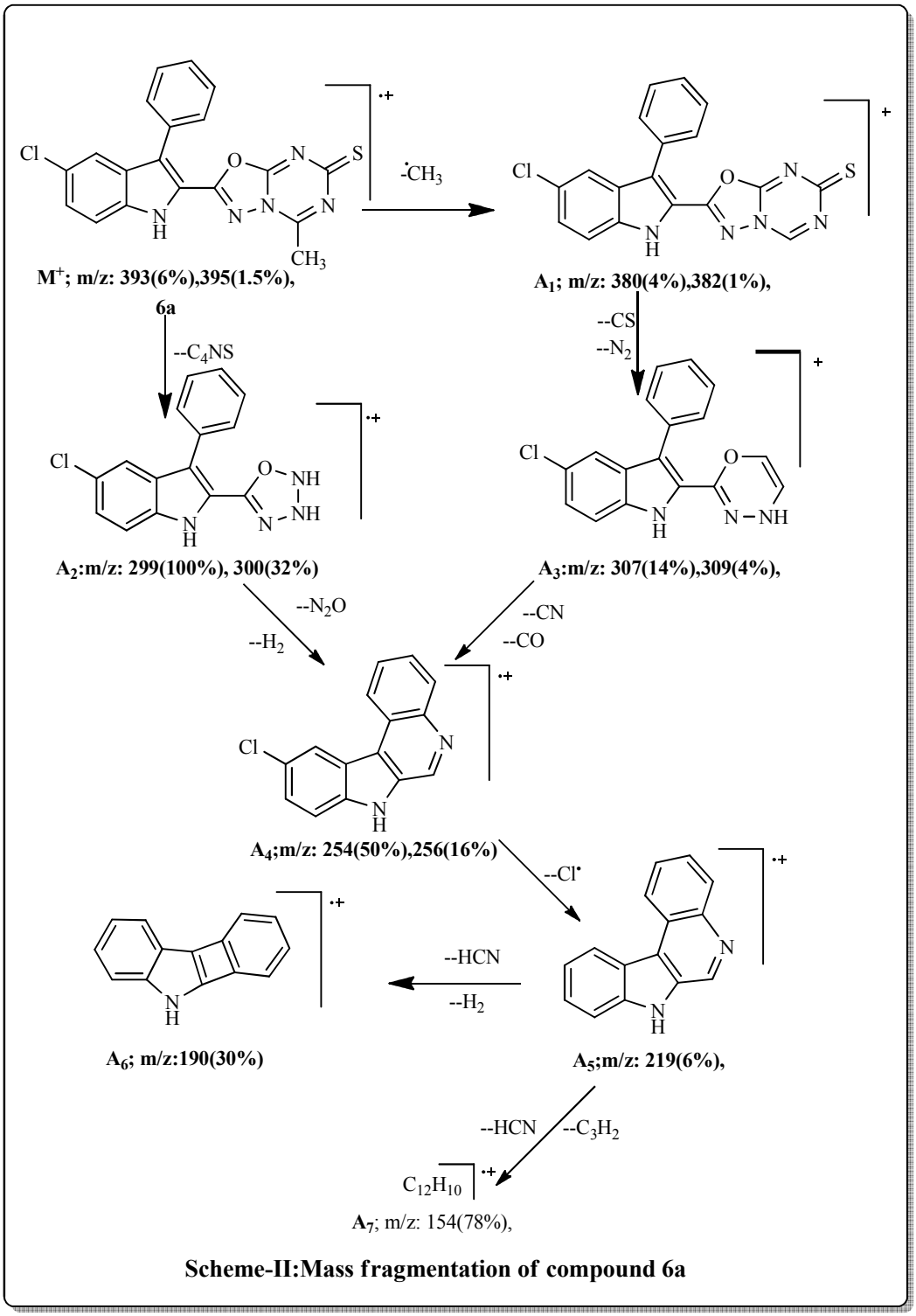
2-(5-bromo-3-phenyl-1H-indol-2-yl)-5-phenyl-7H-[1,3,4]thiadiazolo[3,2-a][1,3,5] triazine-7-thione (7e)
Brown needle (ethanol), Yield 72%, mp. 178-180 °C, IR (KBr) *v*: 3295(NH), 1463/ 1483 /1446 (C=N/C=N/C=N), 1175(C=S); 1H NMR (400 MHz, $CDCl_3$) δ ppm: 6.8-7.8 (m, 13H, ArH), 9.4 (s, 1H, Indole NH); Anal. Calcd for: $C_{24}H_{14}N_5S_2Br$: 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) *v*: 3395(NH), 1564/ 1493 /1446(C=N/C=N/C=N), 1055(C=S); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 2.4 (s, 3H, CH_3), 7.0-7.9 (m, 13H, ArH), 9.3 (s, 1H, Indole NH); Anal. Calcd for: $C_{25}H_{17}N_5S_2$: 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 farmamide used as control and solvent to prepare compound solutions as 10 mg per 10 mL.

RESULTS AND DISCUSSION

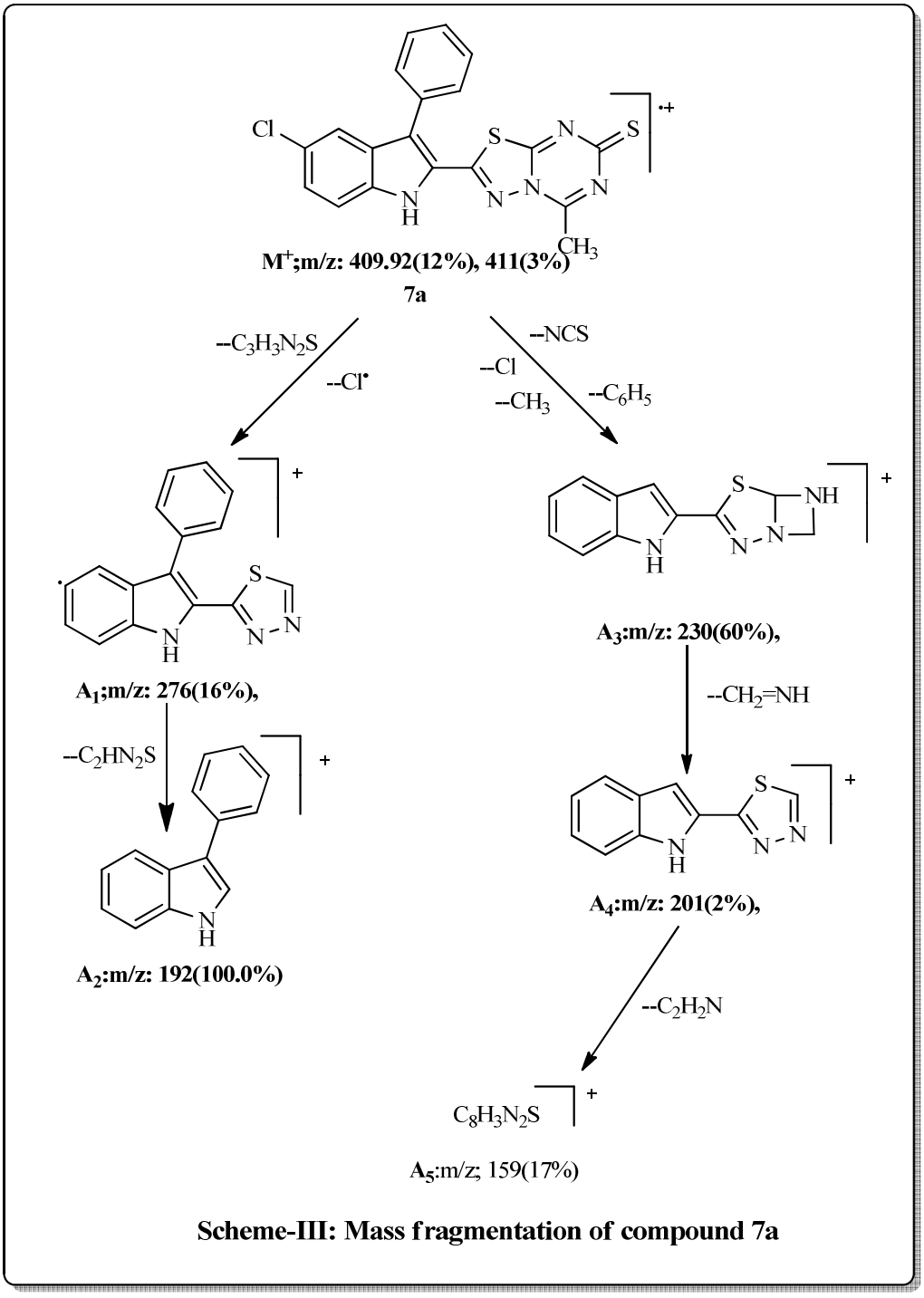
Chemistry
In the present investigation requisite 3,5-disubstituted indole-2-carboxyhydrazides were prepared by fischer indole synthesis [30] and 2-(3-phenyl-1H-indole-2-carbonyl) hydrazinecarbothioamides were synthesized as per reported method [31]. The compound indole-2-carboxyhydrazides were reacted with potassium thiocynate 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 cyclodehydration 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 thiocynate 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).**



Scheme-II:Mass fragmentation of compound 6a

The IR spectrum of compounds **2a** exhibited characteristic absorption peak at 3312(NH_2), 2989(NH), 1533/1495(C=N/C=N), 1260(-O-) cm-1. The ^{1}H NMR spectrum of **2a** displayed a singlet at 9.2 δ due to the deshielded indole NH, The singlet at δ 4.2 (s,2H,NH_2) accounting for two protons is due to NH_2 group attached to the oxadiazole ring. A multiplet in the region δ 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 cm^{-1} (NH_2), 2988 cm^{-1} (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 δ (s, 1H, NH) due to the deshielded indole NH. The singlet at δ 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 δ 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 3312cm^{-1} for (NH),

2988/2898 cm^{-1} (NH/NH), 1683 cm^{-1} (C=O), 1260 cm^{-1} (-O-) and 1169 cm^{-1} (C=S). The ^1H NMR spectrum of compound **4a** has shown peaks between δ 7.2-7.6 (m, 8H, ArH) are due to the eight aromatic protons. Singlet at δ 8.2 (s, 1H, NH) is due to the deshielded proton. The singlet at δ 9.1(s, 1H, NH) is shows the dishielded indole NH.



Scheme-III: Mass fragmentation of compound 7a

The presence of another NH group showed the peak at δ 9. 9 (s, 1H, -NH). The IR spectrum of compound **5a** has displayed a characteristic peaks at 3435cm^{-1}, 3298cm^{-1} and 3152cm^{-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 ^1H NMR spectrum of compound **5a** has shown peak at δ 1.8 (s, 3H, CH_3) is due to the methyl group, a multiplet in the region δ 7.3-7.6 (m, 8H,ArH) due to eight aromatic protons. Singlet at δ 8.4 (s,1H,NH) is for NH attached to the electronegative sulphur, deshielded peak at δ 9.1 (s,1H,NH) is due to indole NH and singlet at δ 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 peaks at δ 1.3 (s, 3H, CH_3) of three protons of the methyl group, the downfield signal at δ 9.3 (1H) is due to the indole NH, a multiplet in the region δ 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 $M^{+\cdot}$ 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_1 at m/z 380(4%) and 382(1%). In another route it has lost C_4NS and showed A_2 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_4 at 254(50%) and 256(16%). Fragment A_5 on losing chlorine radical displayed peak A_5 at 219(6%). Other fragments in the mass spectrum are A_6 at 190(30%), A_7 at 154(78%). This fragmentation supports the structure.

Table 1. *In vitro* antimicrobial assay of newly synthesized 4a-f to 7a-f compounds.

Comp's. (R,R_1)	Zone of inhibition in mm							
	Antibacterial activity				Antifungal activity			
	E. coli	*P. aeruginosa*	*S. aureus*	*B. subtilis*	*A. niger*	*P. chrysogenium*	*A. flavus*	*A. fumigatus*
4a (Cl,CH_3)	15	18	14	16	14	12	18	15
4b (Br,CH_3)	16	16	13	16	16	13	12	10
4c (CH_3,CH_3)	14	17	12	16	20	16	13	13
4d (Cl,Ph)	16	18	15	19	14	13	12	16
4e (Br,Ph)	17	21	18	17	14	13	15	12
4f (CH_3, Ph)	17	18	14	18	20	13	15	11
5a (Cl,CH_3)	20	15	16	15	16	15	14	17
5b (Br,CH_3)	17	16	15	19	13	13	12	16
5c (CH_3,CH_3)	14	19	12	20	18	13	23	16
5d (Cl,Ph)	15	22	17	17	20	16	15	21
5e (Br,Ph)	15	17	19	16	20	17	14	12
5f (CH_3,Ph)	16	16	14	15	20	16	12	12
6a (Cl,CH_3)	16	15	18	15	17	15	12	13
6b (Br,CH_3)	15	14	16	18	16	14	15	14
6c (CH_3,CH_3)	14	17	14	15	15	10	12	14
6d (Cl,Ph)	17	14	15	14	20	10	11	10
6e (Br,Ph)	16	30	12	15	17	16	11	10
6f(CH_3,Ph)	16	14	15	15	10	10	12	11
7a (Cl,CH_3)	17	18	15	14	19	18	19	19
7b (Br,CH_3)	18	19	14	15	15	16	12	14
7c (CH_3,CH_3)	21	18	12	16	22	10	12	10
7d (Cl,Ph)	18	21	16	14	12	14	12	10
7e (Br,Ph)	14	16	15	18	12	11	14	13
7f (CH_3,Ph)	17	15	14	16	10	10	11	12
Gentamicin	18	18	21	23	-	-	-	-
Ciprofloxacin	19	20	19	24	-	-	-	-
Fluconazole	-	-	-	-	18	15	23	21
Greseofulvin	-	-	-	-	20	18	18	16
DMF(Control)	08	08	08	08	08	08	08	08

Inactive : less than 12 mm, Weakly active : 12-14 mm,
Moderately active : 15-17 mm, Highly active : more than 17 mm

The IR spectrum of compounds **7a** exhibited characteristic absorption peaks at 3227cm^{-1} (NH) is due to indole NH. Spectrum showed absorptions at 1632 / 1552 cm^{-1} (C=N / C=N) of the triazine and 1448 cm^{-1} (C=N) diazole rings respectively. Peaks at 1237 cm^{-1} (C=S), 703 cm^{-1}(C-S-C) recommends the proposed structure of the compound. The ^{1}H NMR spectrum of compound **7a** showed peak at δ 1.2 (s, 3H, CH_3) of three protons in the methyl group. The downfield signal at δ 9.1 (s, 1H,NH) is due to the indole NH, a multiplet in the region δ 7.2 to 7.7 (m, ArH, 8H) accounting for eight aromatic protons. The structure of compound **7a** 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 $–C_3H_3N_2S$ and chlorine radical to show fragment A_1 at 276(16%). Fragment A_1 then loses C_2HN_2S and displayed peak A_2 at 192(100%), which is base peak in the spectrum. In another route molecular ion eliminates $^{\cdot}CH_3$, $^{\cdot}C_6H_5$, $^{\cdot}Cl$ and showed A_3 at 231(60%). This on further fragmentation displayed peaks A_4 at 201(2%) and A_5 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, 6e, 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.Chrysogenium*, **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.

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