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Synthesis, Characterization and Evaluation of Some Novel 5-(2-aryl-4-oxo-1, 3-thiazolidine)-2-(phenoxazinyl methyl)-1,3,4-thiadiazole Derivatives as Antimicrobial and Antitubercular Agents

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ABSTRACT

*In our present study N-(ethyl ethanoate)-phenoxazine compound **1** was prepared from phenoxazine and ethyl chloroacetate. Condensation of compound **1** with equimolar quantity of thiosemicarbazide in methanol afforded N-(acetyl thiosemicarbazido)-phenoxazine compound **2**. Compound **2** on reaction with conc. sulfuric acid yielded 5-amino-2-(phenoxazinyl methyl)-1,3,4-thiadiazoles compound **3**. Compound **3** which on condensation with different aromatic aldehydes yielded respective Schiff bases **4a-h**. The Schiff bases are then cyclised with thioglycolic acid to yield the corresponding phenoxazine bearing 4-thiazolidinone derivatives **5a-h**. The structures of the synthesized compounds have been established based on their analytical and spectral data. The synthesized compounds were evaluated for their antimicrobial and antitubercular activities. Some of compounds exhibited considerable activity but among these one 4-thiazolidinone derivatives having nitro phenyl group at 3rd position **5g** exhibited maximum antimicrobial and antitubercular activities.*

Keywords: Synthesis**,** phenoxazine derivative, Biological active agents.

INTRODUCTION

Heterocyclic compounds continue to attract considerable intrest due to their diverse biological activities. The chemistry of nitrogen-sulfur heteroatom containing aromatic compounds is becoming more popular as an area of research. Phenoxazines are a group of *N*-heterocycles having three six ring structures with nitrogen and oxygen atoms [1]. Phenoxazines showed antitumor [2], antimicrobial [3], antiviral [4], anti-inflammatory [5] and multidrug resistance reversal activity [6]. They have been found to prevent human amyloid disorders [7] and to protect neuronal cells from death by oxidative stress [8]. Thiadiazoles possess antituberculosis[9,10],anticancer[11],antimicrobial[12,13],anti-inflammatory[14,15], antihypertensive[16], anticonvulsant[17], andantitrypanosomal[18] activities. Furthermore, thiazolidines have been shown to possess various remarkable biological activities such as analgesic [19], amoebicidal [20], anti-HIV[21], antibacterial[22], antifungal[23], antiinflammatory[24,25] , antitubercular[26,27] *etc*. Hence in the present study we have synthesized some new phenoxazine derivatives containing 1,3,4-thiadaizole and thiazolidine nuclei with good activity and less toxic effects.

MATERIALS AND METHODS

Melting points were taken in open capillary tubes. Progress of the reaction was monitored by silica gel-G coated TLC plates using $CHCl_3$: MeOH (9:1) system. The spots were exposed to iodine vapours for visualization. IR spectra were recorded on Shimadzu 8201 PC FTIR spectrophotometer (νmax in cm^{-1}); ^{1}HNMR and ^{13}CNMR spectra were measured on Bruker DRX-300 spectrometer in $CDCl_3$ at 300 and 100 MHz, respectively using TMS as an internal standard. All chemical shifts were reported on δ scale. The FAB mass spectra were recorded on a Jeol SX 102 mass spectrometer. Elemental analysis was performed on a Carlo Erba 1108 analyzer providing satisfactory results. For column chromatographic purification of the products Merck Silica Gel 60 (230-400 Mesh) was used. The reagent grade chemicals were purchased from the commercial sources and further purified before use.

Synthesis of N-(ethyl ethanoate)-phenoxazine (1): Equimolar solution of phenoxazine (30 g, 0.16 mol) and ethyl chloroacetate (20.08 g, 0.16 mol) in acetone was refluxed for about 3 h. The solvent was removed in vacuo and the residue thus obtained was purified over the column of silica gel and recrystallized from acetone to furnish compound **1.** Yield 72%; m.p. 180-181ºC; IR [ν, cm^{-1}, KBr]: 3050 (C-H, Ar-H), 1731 (>C=O, ester), 1328 (N-CH_2), 650 (C-O-C); ^{1}HNMR [300 MHz, $CDCl_3$] : δ 7.10-7.61 (m, 8H, Ar-H), 2.60 (s, 2H, N-CH_2), 1.21 (t, 3H, J=7.0 Hz, CH_3), 4.20 (q, 2H, J=7.0 Hz, CH_2) ; ^{13}CNMR [100 MHz, $CDCl_3$]: δ 112.1-125.2 (C of aromatic ring), 168.8 (>C=O, ester), 34.1 (N-CH_2), 61.5 (CH_2), 14.4 (CH_3); Mass (m/z) : 269 $[M]^+$, 196, 182, 166, 87; Anal. (%) for $C_{16}H_{15}O_3N$, Calcd. C, 71.38; H, 5.58; N, 5.20. Found: C, 71.35; H, 5.56; N, 5.18.

Synthesis of N-(acetyl thiosemicarbazido)-phenoxazine (2): Equimolar solution of compound **1** (27 g, 0.10 mol) and thiosemicarbazide (9.13 g, 0.10 mol) in dioxane was refluxed for about 4 h. The solvent was removed in vacuo and the residue thus obtained was purified over the column of silica gel and recrystallized from acetone to furnish compound **2.** Yield 75%; m.p. 170-172ºC; IR (ν, cm^{-1}, KBr] : 3052 (C-H, Ar-H), 1331 (N-CH_2), 1220 (>C=S), 1665 (>C=O, amide), 3315 and 3178 (N-H str.), 652 (C-O-C); ^{1}HNMR [300 MHz, $CDCl_3$] : δ 7.12-7.58 (m, 8H, Ar-H), 8.11 (s, 1H, CONH), 2.62 (s, 2H, N-CH_2), 5.72 (s, 2H, NH_2), 7.94 (s, 1H, NNHCS) ; ^{13}CNMR [100 MHz, $CDCl_3$]: δ 112.8-124.3 (C of aromatic ring), 34.2 (N-CH_2), 169.2 (>C=O, amide), 180.91 (>C=S); Mass (m/z) : 314 $[M]^+$, 224, 182, 166, 132; Anal. (%) for $C_{15}H_{14}O_2N_4S$, Calcd. C, 57.32; H, 4.46; N, 17.83. Found: C, 57.30; H, 4.43; N, 17.81.

Synthesis of 5-amino-2-(phenoxazinyl methyl)-1,3,4-thiadiazoles (3): Equimolar solution of compound **2** (25 g, 0.08 mol) and conc. sulfuric acid (7.80 g, 0.08 mol) in acetone was refluxed for about 6 h. After cooling the solution was neutralized with conc. liquor ammonia and filtered. The solvent was removed in vacuo and the residue thus obtained was purified over the column of silica gel and recrystallized from acetone to furnish compound **3.** Yield 73%; m.p. 176-177ºC; IR (ν, cm^{-1}, KBr] : 3051 (C-H, Ar-H), 1330 (N-CH_2), 1610 (>C=N), 3340 (N-H str.), 653 (C-O-C), 630 (C-S-C); ^{1}HNMR [300 MHz, $CDCl_3$] : δ 7.15-7.65 (m, 8H, Ar-H), 2.65 (s, 2H, N-CH_2), 6.51 (s, 2H, NH_2); ^{13}CNMR [100 MHz, $CDCl_3$]: δ 112.4-125.5 (C of aromatic ring), 34.5 (N-CH_2), 162.27 (1,3,4-thiadiazole, C-5), 155.80 (1,3,4-thiadiazole, C-2); Mass (m/z) : 296 $[M]^+$, 196, 182, 166, 100, 84; Anal. (%) for $C_{15}H_{12}ON_4S$, Calcd. C, 60.81; H, 4.05; N, 18.92. Found: C, 60.79; H, 4.03; N, 18.90.

Synthesis of 5-benzylideneamino-2-(phenoxazinyl methyl)-1,3,4-thiadiazoles (4a): Equimolar solution of compound **3** (2 g, 0.007 mol) and benzaldehyde (0.72 g, 0.007 mol) in dioxane was refluxed for about 5 h. The solvent was removed in vacuo and the residue thus obtained was purified over the column of silica gel and recrystallized from chloroform to furnish compound **4a.** Yield 69%; m.p. 180-181ºC; IR [ν, cm^{-1}, KBr] : 3060 (C-H, Ar-H), 1332 (N-CH_2), 1612 (>C=N), 654 (C-O-C), 632 (C-S-C), 1627 (N=CH); ^{1}HNMR [300 MHz, $CDCl_3$] : δ 7.12-7.69 (m, 13H, Ar-H), 2.63 (s, 2H, N-CH_2), 8.01 (s, 1H, N=CH);

^{13}CNMR [100 MHz, $CDCl_3$]: δ 112.1-124.3 (C of aromatic ring), 34.4 (N-CH_2), 163.11 (1,3,4-thiadiazole, C-5), 156.10 (1,3,4-thiadiazole, C-2), 143.1 (N=CH); Mass (m/z) : 384 $[M]^+$, 270, 242, 196, 188, 166, 160, 114; Anal. (%) for $C_{22}H_{15}ON_4SCl$, Calcd. C, 68.75; H, 4.17; N, 14.58. Found: C, 68.72; H, 4.15; N, 14.56. Other compounds **4b-j** was synthesized similarly by treating compound **3** with various aromatic aldehydes.

Spectral data of 5-(2-chlorobenzylideneamino)-2-(phenoxazinyl methyl)-1,3,4-thiadiazoles (4b): Yield 72%; m.p. 183-184ºC; IR [ν, cm^{-1}, KBr] : 3062 (C-H, Ar-H), 1334 (N-CH_2), 1615 (>C=N), 658 (C-O-C), 634 (C-S-C), 1630 (N=CH), 754 (Ar-Cl); ^{1}HNMR [300 MHz, $CDCl_3$] : δ 7.22-7.79 (m, 12H, Ar-H), 2.63 (s, 2H, N-CH_2), 8.01 (s, 1H, N=CH); ^{13}CNMR [100 MHz, $CDCl_3$]: δ 112.5-124.1 (C of aromatic ring), 34.8 (N-CH_2), 163.20 (1,3,4-thiadiazole, C-5), 156.30 (1,3,4-thiadiazole, C-2), 143.4 (N=CH), 134.5 (C-Cl, aromatic); Mass (m/z) : 418.5 $[M]^+$, 270, 242, 223, 196, 195, 182, 166, 149; Anal. (%) for $C_{22}H_{15}ON_4SCl$, Calcd. C, 63.08; H, 3.58; N, 13.38. Found: C, 63.06; H, 3.55; N, 13.36.

Spectral data of 5-(4-chlorobenzylideneamino)-2-(phenoxazinyl methyl)-1,3,4-thiadiazoles (4c): Yield 72%; m.p. 188-189ºC; IR [ν, cm^{-1}, KBr] : 3064 (C-H, Ar-H), 1336 (N-CH_2), 1618 (>C=N), 662 (C-O-C), 636 (C-S-C), 1633 (N=CH), 755 (Ar-Cl); ^{1}HNMR [300 MHz, $CDCl_3$] : δ 7.23-7.78 (m, 12H, Ar-H), 2.65 (s, 2H, N-CH_2), 8.04 (s, 1H, N=CH); ^{13}CNMR [100 MHz, $CDCl_3$]: δ 111.1-123.5 (C of aromatic ring), 34.7 (N-CH_2), 163.75 (1,3,4-thiadiazole, C-5), 157.10 (1,3,4-thiadiazole, C-2), 143.4 (N=CH), 134.8 (C-Cl, aromatic); Mass (m/z) : 418.5 $[M]^+$, 270, 242, 223, 196, 195, 182, 166, 149; Anal. (%) for $C_{22}H_{15}ON_4SCl$, Calcd. C, 63.08; H, 3.58; N, 13.38. Found: C, 63.07; H, 3.56; N, 13.35.

Spectral data of 5-(2-bromobenzylideneamino)-2-(phenoxazinyl methyl)-1,3,4-thiadiazoles (4d): Yield 70%; m.p. 190-191ºC; IR [ν, cm^{-1}, KBr] : 3061 (C-H, Ar-H), 1338 (N-CH_2), 1613 (>C=N), 655 (C-O-C), 635 (C-S-C), 1629 (N=CH), 615 (Ar-Br); ^{1}HNMR [300 MHz, $CDCl_3$] : δ 7.18-7.68 (m, 12H, Ar-H), 2.66 (s, 2H, N-CH_2), 8.06 (s, 1H, N=CH); ^{13}CNMR [100 MHz, $CDCl_3$]: δ 111.6-123.8 (C of aromatic ring), 34.9 (N-CH_2), 163.55 (1,3,4-thiadiazole, C-5), 157.50 (1,3,4-thiadiazole, C-2), 143.6 (N=CH), 118.5 (C-Br, aromatic); Mass (m/z) : 463 $[M]^+$, 270, 267, 242, 239, 196, 193, 182, 166; Anal. (%) for $C_{22}H_{15}ON_4SBr$, Calcd. C, 57.02; H, 3.24; N, 12.09. Found: C, 57.01; H, 3.21; N, 12.06.

Spectral data of 5-(3-bromobenzylideneamino)-2-(phenoxazinyl methyl)-1,3,4-thiadiazoles (4e): Yield 70%; m.p. 200-201ºC; IR [ν, cm^{-1}, KBr] : 3066 (C-H, Ar-H), 1333 (N-CH_2), 1614 (>C=N), 658 (C-O-C), 637 (C-S-C), 1630 (N=CH), 617 (Ar-Br); ^{1}HNMR [300 MHz, $CDCl_3$] : δ 7.10-7.65 (m, 12H, Ar-H), 2.64 (s, 2H, N-CH_2), 8.04 (s, 1H, N=CH); ^{13}CNMR [100 MHz, $CDCl_3$]: δ 112.6-122.8 (C of aromatic ring), 34.6 (N-CH_2), 163.15 (1,3,4-thiadiazole, C-5), 157.25 (1,3,4-thiadiazole, C-2), 143.3 (N=CH), 118.6 (C-Br, aromatic); Mass (m/z) : 463 $[M]^+$, 270, 267, 242, 239, 196, 193, 182, 166; Anal. (%) for $C_{22}H_{15}ON_4SBr$, Calcd. C, 57.02; H, 3.24; N, 12.09. Found: C, 57.00; H, 3.22; N, 12.07.

Spectral data of 5-(2-nitrobenzylideneamino)-2-(phenoxazinyl methyl)-1,3,4-thiadiazoles (4f): Yield 73%; m.p. 205-206ºC; IR [ν, cm^{-1}, KBr] : 3065 (C-H, Ar-H), 1337 (N-CH_2), 1615 (>C=N), 656 (C-O-C), 639 (C-S-C), 1633 (N=CH), 1524, 1325 (Ar-NO_2); ^{1}HNMR [300 MHz, $CDCl_3$] : δ 7.15-7.69 (m, 12H, Ar-H), 2.68 (s, 2H, N-CH_2), 8.09 (s, 1H, N=CH); ^{13}CNMR [100 MHz, $CDCl_3$]: δ 112.3-122.5 (C of aromatic ring), 34.9 (N-CH_2), 163.85 (1,3,4-thiadiazole, C-5), 157.20 (1,3,4-thiadiazole, C-2), 143.2 (N=CH), 142.6 (C-NO_2, aromatic); Mass (m/z) : 429 $[M]^+$, 270, 242, 233, 205, 196, 182, 166, 159; Anal. (%) for $C_{22}H_{15}O_3N_5S$, Calcd. C, 57.26; H, 3.38; N, 13.92. Found: C, 57.23; H, 3.35; N, 13.90.

Spectral data of 5-(3-nitrobenzylideneamino)-2-(phenoxazinyl methyl)-1,3,4-thiadiazoles (4g): Yield 74%; m.p. 194-195ºC; IR [ν, cm^{-1}, KBr] : 3063 (C-H, Ar-H), 1338 (N-CH_2), 1616 (>C=N), 659 (C-O-C), 640 (C-S-C), 1629 (N=CH), 1522, 1323 (Ar-NO_2); ^{1}HNMR [300 MHz, $CDCl_3$] : δ 7.25-7.70 (m, 12H, Ar-H), 2.70 (s, 2H, N-CH_2), 8.10 (s, 1H, N=CH); ^{13}CNMR [100 MHz, $CDCl_3$]: δ 111.3-121.9 (C of aromatic

ring), 35.1 (N-CH_2), 163.65 (1,3,4-thiadiazole, C-5), 157.60 (1,3,4-thiadiazole, C-2), 143.5 (N=CH), 142.7 (C-NO_2, aromatic); Mass (m/z) : 429 $[M]^+$, 270, 242, 233, 205, 196, 182, 166, 159; Anal. (%) for $C_{22}H_{15}O_3N_5S$, Calcd. C, 57.26; H, 3.38; N, 13.92. Found: C, 57.24; H, 3.36; N, 13.89.

Spectral data of 5-(2-methoxybenzylideneamino)-2-(phenoxazinyl methyl)-1,3,4-thiadiazoles (4h): Yield 68%; m.p. 196-197ºC; IR [ν, cm^{-1}, KBr] : 3069 (C-H, Ar-H), 1333 (N-CH_2), 1613 (>C=N), 662 (C-O-C), 635 (C-S-C), 1630 (N=CH), 2826 (Ar-OCH_3) ; ^{1}HNMR [300 MHz, $CDCl_3$] : δ 7.18-7.60 (m, 12H, Ar-H), 2.68 (s, 2H, N-CH_2), 8.09 (s, 1H, N=CH), 3.91 (s, 3H, OCH_3); ^{13}CNMR [100 MHz, $CDCl_3$]: δ 111.7-122.6 (C of aromatic ring), 35.3 (N-CH_2), 163.48 (1,3,4-thiadiazole, C-5), 157.52 (1,3,4-thiadiazole, C-2), 143.6 (N=CH), 55.3 (OCH_3); Mass (m/z) : 414 $[M]^+$, 270, 242, 218, 196, 190, 182, 166, 144; Anal. (%) for $C_{23}H_{18}O_2N_4S$, Calcd. C, 66.67; H, 4.35; N, 7.73. Found: C, 66.65; H, 4.33; N, 7.70.

Spectral data of 5-(4-methoxybenzylideneamino)-2-(phenoxazinyl methyl)-1,3,4-thiadiazoles (4i): Yield 68%; m.p. 199-200ºC; IR [ν, cm^{-1}, KBr] : 3067 (C-H, Ar-H), 1338 (N-CH_2), 1616 (>C=N), 660 (C-O-C), 638 (C-S-C), 1636 (N=CH), 2825 (Ar-OCH_3) ; ^{1}HNMR [300 MHz, $CDCl_3$] : δ 7.13-7.62 (m, 12H, Ar-H), 2.71 (s, 2H, N-CH_2), 8.10 (s, 1H, N=CH), 3.94 (s, 3H, OCH_3); ^{13}CNMR [100 MHz, $CDCl_3$]: δ 111.9-122.8 (C of aromatic ring), 35.2 (N-CH_2), 163.90 (1,3,4-thiadiazole, C-5), 157.96 (1,3,4-thiadiazole, C-2), 143.8 (N=CH), 55.5 (OCH_3); Mass (m/z) : 414 $[M]^+$, 270, 242, 218, 196, 190, 182, 166, 144; Anal. (%) for $C_{23}H_{18}O_2N_4S$, Calcd. C, 66.67; H, 4.35; N, 7.73. Found: C, 66.64; H, 4.34; N, 7.71.

Spectral data of 5-(4-methylbenzylideneamino)-2-(phenoxazinyl methyl)-1,3,4-thiadiazoles (4j): Yield 67%; m.p. 202-203ºC; IR [ν, cm^{-1}, KBr] : 3070 (C-H, Ar-H), 1340 (N-CH_2), 1618 (>C=N), 663 (C-O-C), 640 (C-S-C), 1637 (N=CH), 2922 (Ar-CH_3); ^{1}HNMR [300 MHz, $CDCl_3$] : δ 7.23-7.69 (m, 12H, Ar-H), 2.73 (s, 2H, N-CH_2), 8.11 (s, 1H, N=CH), 2.36 (s, 3H, CH_3); ^{13}CNMR [100 MHz, $CDCl_3$]: δ 112.9-123.8 (C of aromatic ring), 35.4 (N-CH_2), 164.20 (1,3,4-thiadiazole, C-5), 157.75 (1,3,4-thiadiazole, C-2), 143.9 (N=CH), 22.3 (CH_3); Mass (m/z) : 398 $[M]^+$, 270, 242, 202, 196, 182, 174, 166, 128; Anal. (%) for $C_{23}H_{18}ON_4S$, Calcd. C, 69.35; H, 4.52; N, 14.07. Found: C, 69.33; H, 4.50; N, 14.04.

Synthesis of 5-(2-phenyl-4-oxo-1,3-thiazolidine)-2-(phenoxazinyl methyl)-1,3,4-thiadiazoles (5a): Equimolar solution of compound **4a** (1.5 g, 0.004 mol) and thioglycolic acid (0.36 g, 0.004 mol) with a pinch of anhydrous $ZnCl_2$ in acetone was refluxed for about 5 h. The solvent was removed in vacuo and the residue thus obtained was purified over the column of silica gel and recrystallized from chloroform to furnish compound **5a.** Yield 72%; m.p. 195-196ºC; IR [ν, cm^{-1}, KBr]: 3055 (C-H, Ar-H), 1335 (N-CH_2), 655 (C-O-C), 635 (C-S-C), *-1615 (>C=N), 1720 (>C=O, cyclic), 2980 (N-CH-S); ^{1}HNMR [300 MHz, $CDCl_3$] : δ 7.10-7.80 (m, 13H, Ar-H), 2.65 (s, 2H, N-CH_2), 4.15 (s, 1H, -N-CH), 3.30 (s, 2H, CH_2, cyclic); ^{13}CNMR [100 MHz, $CDCl_3$]: δ 111.8-125.4 (C of aromatic ring), 34.6 (N-CH_2), 163.30 (1,3,4-thiadiazole, C-5), 156.70 (1,3,4-thiadiazole, C-2), 171.5 (>C=O, cyclic), 43.9 (CH_2 of thiazolidine ring), 40.5 (N-CH-S) ; Mass (m/z): 458 $[M]^+$, 280, 262, 252, 234, 196, 182, 178, 166, 150, 136; Anal. (%) for $C_{24}H_{18}N_4S_2O_2$, Calcd. C, 62.88; H, 3.93; N, 12.23. Found: C, 62.86; H, 3.91; N, 12.21. Other compounds **5b-j** was synthesized similarly by using compounds **4b-j** respectively.

Spectral data of 5-[2-(2-chlorophenyl)-4-oxo-1,3-thiazolidine]-2-(phenoxazinyl methyl)-1,3,4-thiadiazoles (5b): Yield 75%; m.p. 192-193ºC; IR [ν, cm^{-1}, KBr]: 3057 (C-H, Ar-H), 1336 (N-CH_2), 658 (C-O-C), 637 (C-S-C), 1616 (>C=N), 1722 (>C=O, cyclic), 2983 (N-CH-S), 751 (Ar-Cl); ^{1}HNMR [300 MHz, $CDCl_3$] : δ 7.12-7.75 (m, 12H, Ar-H), 2.67 (s, 2H, N-CH_2), 4.16 (s, 1H, -N-CH), 3.31 (s, 2H, CH_2, cyclic); ^{13}CNMR [100 MHz, $CDCl_3$]: δ 111.6-125.1 (C of aromatic ring), 34.8 (N-CH_2), 163.39 (1,3,4-thiadiazole, C-5), 156.80 (1,3,4-thiadiazole, C-2), 171.8 (>C=O, cyclic), 44.1 (CH_2 of thiazolidine ring), 40.7 (N-CH-S), 134.3 (C-Cl, aromatic); Mass (m/z): 493 $[M]^+$, 297, 280, 269, 252, 213, 196, 185, 182, 171, 166; Anal. (%) for $C_{24}H_{17}N_4S_2O_2Cl$, Calcd. C, 58.48; H, 3.45; N, 11.37. Found: C, 58.45; H, 3.43; N, 11.35.

Spectral data of 5-[2-(4-chlorophenyl)-4-oxo-1,3-thiazolidine]-2-(phenoxazinyl methyl)-1,3,4-thiadiazoles (5c):
Yield 76%; m.p. 194-195ºC; IR [ν, cm^{-1}, KBr]: 3058 (C-H, Ar-H), 1338 (N-CH_2), 656 (C-O-C), 638 (C-S-C), 1618 (>C=N), 1725 (>C=O, cyclic), 2981 (N-CH-S), 753 (Ar-Cl); ^{1}HNMR [300 MHz, $CDCl_3$] : δ 7.22-7.73 (m, 12H, Ar-H), 2.66 (s, 2H, N-CH_2), 4.19 (s, 1H, -N-CH), 3.33 (s, 2H, CH_2, cyclic); ^{13}CNMR [100 MHz, $CDCl_3$]: δ 111.3-125.4 (C of aromatic ring), 34.9 (N-CH_2), 163.45 (1,3,4-thiadiazole, C-5), 156.25 (1,3,4-thiadiazole, C-2), 171.7 (>C=O, cyclic), 44.3 (CH_2 of thiazolidine ring), 40.8 (N-CH-S), 134.5 (C-Cl, aromatic); Mass (m/z) : 493 $[M]^+$, 297, 280, 269, 252, 213, 196, 185, 182, 171, 166; Anal. (%) for $C_{24}H_{17}N_4S_2O_2Cl$, Calcd. C, 58.48; H, 3.45; N, 11.37. Found: C, 58.46; H, 3.44; N, 11.34.

Spectral data of 5-[2-(2-bromophenyl)-4-oxo-1,3-thiazolidine]-2-(phenoxazinyl methyl)-1,3,4-thiadiazoles (5d):
Yield 75%; m.p. 187-188ºC; IR [ν, cm^{-1}, KBr]: 3060 (C-H, Ar-H), 1340 (N-CH_2), 659 (C-O-C), 640 (C-S-C), 1621 (>C=N), 1726 (>C=O, cyclic), 2983 (N-CH-S), 619 (Ar-Br); ^{1}HNMR [300 MHz, $CDCl_3$] : δ 7.32-7.79 (m, 12H, Ar-H), 2.69 (s, 2H, N-CH_2), 4.20 (s, 1H, -N-CH), 3.35 (s, 2H, CH_2, cyclic); ^{13}CNMR [100 MHz, $CDCl_3$]: δ 111.6-125.1 (C of aromatic ring), 35.2 (N-CH_2), 163.66 (1,3,4-thiadiazole, C-5), 156.29 (1,3,4-thiadiazole, C-2), 171.9 (>C=O, cyclic), 44.5 (CH_2 of thiazolidine ring), 40.9 (N-CH-S), 118.2 (C-Br, aromatic); Mass (m/z) : 537 $[M]^+$, 341, 313, 280, 257, 252, 229, 215, 196, 182, 166; Anal. (%) for $C_{24}H_{17}N_4O_2S_2Br$, Calcd. C, 53.63; H, 3.17; N, 10.43. Found: C, 53.61; H, 3.15; N, 10.41.

Spectral data of 5-[2-(3-bromophenyl)-4-oxo-1,3-thiazolidine]-2-(phenoxazinyl methyl)-1,3,4-thiadiazoles (5e):
Yield 75%; m.p. 182-183ºC; IR [ν, cm^{-1}, KBr]: 3061 (C-H, Ar-H), 1343 (N-CH_2), 661 (C-O-C), 642 (C-S-C), 1623 (>C=N), 1727 (>C=O, cyclic), 2985 (N-CH-S), 617 (Ar-Br); ^{1}HNMR [300 MHz, $CDCl_3$] : δ 7.29-7.75 (m, 12H, Ar-H), 2.71 (s, 2H, N-CH_2), 4.22 (s, 1H, -N-CH), 3.36 (s, 2H, CH_2, cyclic); ^{13}CNMR [100 MHz, $CDCl_3$]: δ 110.9-124.8 (C of aromatic ring), 35.4 (N-CH_2), 163.86 (1,3,4-thiadiazole, C-5), 156.45 (1,3,4-thiadiazole, C-2), 172.2 (>C=O, cyclic), 44.6 (CH_2 of thiazolidine ring), 41.2 (N-CH-S), 118.6 (C-Br, aromatic); Mass (m/z) : 537 $[M]^+$, 341, 313, 280, 257, 252, 229, 215, 196, 182, 166; Anal. (%) for $C_{24}H_{17}N_4O_2S_2Br$, Calcd. C, 53.63; H, 3.17; N, 10.43. Found: C, 53.62; H, 3.14; N, 10.42.

Spectral data of 5-[2-(2-nitrophenyl)-4-oxo-1,3-thiazolidine]-2-(phenoxazinyl methyl)-1,3,4-thiadiazoles (5f): Yield 78%; m.p. 185-186ºC; IR [ν, cm^{-1}, KBr]: 3063 (C-H, Ar-H), 1344 (N-CH_2), 663 (C-O-C), 644 (C-S-C), 1622 (>C=N), 1729 (>C=O, cyclic), 2987 (N-CH-S), 1524, 1324 (Ar-NO_2); ^{1}HNMR [300 MHz, $CDCl_3$] : δ 7.39-7.79 (m, 12H, Ar-H), 2.73 (s, 2H, N-CH_2), 4.20 (s, 1H, -N-CH), 3.33 (s, 2H, CH_2, cyclic); ^{13}CNMR [100 MHz, $CDCl_3$]: δ 111.9-125.8 (C of aromatic ring), 35.2 (N-CH_2), 163.76 (1,3,4-thiadiazole, C-5), 156.33 (1,3,4-thiadiazole, C-2), 172.4 (>C=O, cyclic), 44.4 (CH_2 of thiazolidine ring), 41.3 (N-CH-S), 142.7 (C-NO_2, aromatic); Mass (m/z) : 503 $[M]^+$, 307, 280, 279, 252, 223, 196, 195, 182, 181, 166; Anal. (%) for $C_{24}H_{17}N_5O_4S_2$, Calcd. C, 57.26; H, 3.38; N, 13.92. Found: C, 57.23; H, 3.36; N, 13.90.

Spectral data of 5-[2-(3-nitrophenyl)-4-oxo-1,3-thiazolidine]-2-(phenoxazinyl methyl)-1,3,4-thiadiazoles (5g): Yield 80%; m.p. 190-191ºC; IR [ν, cm^{-1}, KBr]: 3062 (C-H, Ar-H), 1341 (N-CH_2), 662 (C-O-C), 642 (C-S-C), 1624 (>C=N), 1727 (>C=O, cyclic), 2987 (N-CH-S), 1526, 1325 (Ar-NO_2); ^{1}HNMR [300 MHz, $CDCl_3$] : δ 7.33-7.76 (m, 12H, Ar-H), 2.70 (s, 2H, N-CH_2), 4.22 (s, 1H, -N-CH), 3.36 (s, 2H, CH_2, cyclic); ^{13}CNMR [100 MHz, $CDCl_3$]: δ 110.6-124.8 (C of aromatic ring), 35.4 (N-CH_2), 163.45 (1,3,4-thiadiazole, C-5), 156.69 (1,3,4-thiadiazole, C-2), 171.8 (>C=O, cyclic), 44.6 (CH_2 of thiazolidine ring), 41.1 (N-CH-S), 142.5 (C-NO_2, aromatic); Mass (m/z) : 503 $[M]^+$, 307, 280, 279, 252, 223, 196, 195, 182, 181, 166; Anal. (%) for $C_{24}H_{17}N_5O_4S_2$, Calcd. C, 57.26; H, 3.38; N, 13.92. Found: C, 57.24; H, 3.35; N, 13.91.

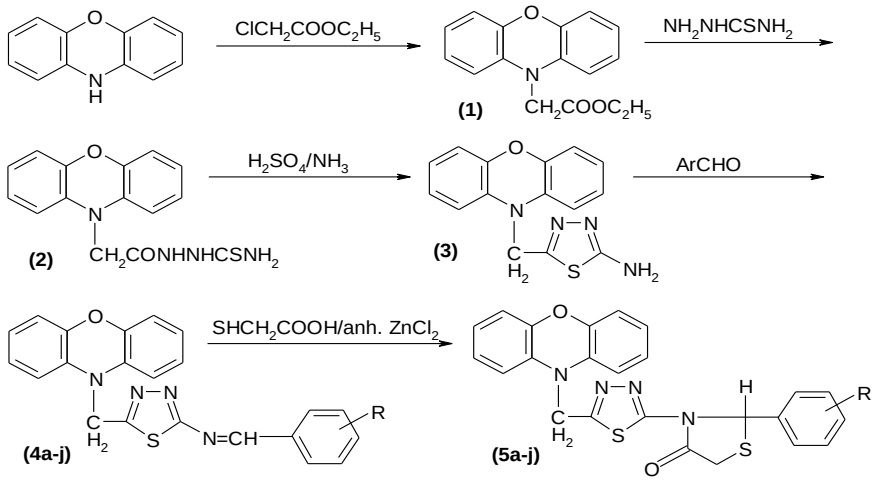
Spectral data of 5-[2-(2-methoxyphenyl)-4-oxo-1,3-thiazolidine]-2-(phenoxazinyl methyl)-1,3,4-thiadiazoles (5h): Yield 72%; m.p. 192-193ºC; IR [ν, cm^{-1}, KBr]: 3064 (C-H, Ar-H), 1343 (N-CH_2), 658 (C-O-C), 644 (C-S-C), 1620 (>C=N), 1729 (>C=O, cyclic), 2988 (N-CH-S), 2827 (Ar-OCH_3); ^{1}HNMR [300 MHz, $CDCl_3$] : δ 7.38-7.74 (m, 12H, Ar-H), 2.72 (s, 2H, N-CH_2), 4.20 (s, 1H, -N-CH), 3.35 (s, 2H, CH_2, cyclic), 3.92 (s, 3H, OCH_3); ^{13}CNMR [100 MHz, $CDCl_3$]: δ 110.9 -124.5 (C of aromatic ring), 35.1 (N-CH_2), 163.56 (1,3,4-thiadiazole, C-5), 156.58 (1,3,4-thiadiazole, C-2), 172.2 (>C=O, cyclic), 44.5 (CH_2 of thiazolidine ring), 41.3 (N-CH-S), 55.4 (OCH_3); Mass (m/z) : 488 $[M]^+$, 292, 280, 264, 252, 208, 196, 182, 180, 166; Anal. (%) for $C_{25}H_{20}N_4O_3S_2$, Calcd. C, 61.48; H, 4.10; N, 11.48. Found: C, 61.46; H, 4.08; N, 11.46.

Spectral data of 5-[2-(4-methoxyphenyl)-4-oxo-1,3-thiazolidine]-2-(phenoxazinyl methyl)-1,3,4-thiadiazoles (5i): Yield 72%; m.p. 195-196ºC; IR [ν, cm^{-1}, KBr]: 3062 (C-H, Ar-H), 1344 (N-CH_2), 663 (C-O-C), 643 (C-S-C), 1623 (>C=N), 1727 (>C=O, cyclic), 2987 (N-CH-S), 2829 (Ar-OCH_3); ^{1}HNMR [300 MHz, $CDCl_3$] : δ 7.39-7.71 (m, 12H, Ar-H), 2.74 (s, 2H, N-CH_2), 4.22 (s, 1H, -N-CH), 3.36 (s, 2H, CH_2, cyclic), 3.94 (s, 3H, OCH_3); ^{13}CNMR [100 MHz, $CDCl_3$]: δ 111.4 -125.2 (C of aromatic ring), 35.3 (N-CH_2), 163.49 (1,3,4-thiadiazole, C-5), 156.48 (1,3,4-thiadiazole, C-2), 172.4 (>C=O, cyclic), 44.6 (CH_2 of thiazolidine ring), 41.1 (N-CH-S), 55.1 (OCH_3); Mass (m/z) : 488 $[M]^+$, 292, 280, 264, 252, 208, 196, 182, 180, 166; Anal. (%) for $C_{25}H_{20}N_4O_3S_2$, Calcd. C, 61.48; H, 4.10; N, 11.48. Found: C, 61.45; H, 4.09; N, 11.45.

Spectral data of 5-[2-(4-methylphenyl)-4-oxo-1,3-thiazolidine]-2-(phenoxazinyl methyl)-1,3,4-thiadiazoles (5j): Yield 72%; m.p. 197-198ºC; IR [ν, cm^{-1}, KBr]: 3065 (C-H, Ar-H), 1345 (N-CH_2), 665 (C-O-C), 645 (C-S-C), 1624 (>C=N), 1730 (>C=O, cyclic), 2990 (N-CH-S), 2921 (Ar-CH_3); ^{1}HNMR [300 MHz, $CDCl_3$] : δ 7.10-7.80 (m, 12H, Ar-H), 2.75 (s, 2H, N-CH_2), 4.23 (s, 1H, -N-CH), 3.37 (s, 2H, CH_2, cyclic), 2.31 (s, 3H, CH_3); ^{13}CNMR [100 MHz, $CDCl_3$]: δ 111.8 -125.4 (C of aromatic ring), 35.5 (N-CH_2), 163.55 (1,3,4-thiadiazole, C-5), 156.56 (1,3,4-thiadiazole, C-2), 172.5 (>C=O, cyclic), 44.7 (CH_2 of thiazolidine ring), 41.4 (N-CH-S), 22.2 (CH_3); Mass (m/z) : 472 $[M]^+$, 280, 276, 252, 248, 196, 192, 182, 166, 164, 150; Anal. (%) for $C_{25}H_{20}N_4O_2S_2$, Calcd. C, 63.56; H, 4.24; N, 11.86. Found: C, 63.53; H, 4.22; N, 11.84.

Biological Activities: The synthesized 4-thiazolidinones were screened for their antibacterial activity against two different strains of Gram negative (*Escherichia coli* and *Salmonella typhi)* and Gram positive (*Streptococcus aureus* and *Bacillus subtilis*) bacteria. The antifungal activity was performed against *Aspergillus flavus, Aspergillus fumigatus, Candida albicans and Fusarium oxysporum* fungi. The antitubercular activity was screened against *Mycobacterium tuberculosis* H37Rv strain. Minimum inhibitory concentration (MIC) values of synthesized compounds **5a-j** were determined by using tube dilution technique for antibacterial and antifungal screening and L.J. medium method for antimycobacterial activity. Standard antibacterial Streptomycin and antifungal Griseofulvin were also tested under the similar conditions for comparison. For the antitubercular activity Isoniazid and Rifampicin were used as standard and also screened under the similar conditions for comparison. Results of all given activities of compounds were given in **tables 1** and **2.**

Compd. 3, 4	R	Compd. 3, 4	R
a	H	F	2-NO_2
b	2-Cl	G	3-NO_2
c	4-Cl	H	2-OCH_3
d	2-Br	I	4-OCH_3
e	3-Br	J	4-CH_3



Scheme-1

Table 1: Antibacterial activity of the synthesized compounds **5a-j** (MIC µg mL^{-1})

Compound	R	*E. coli*	*S. typhi*	*B. subtilis*	*S. aureus*
5a	H	16	19	21	17
5b	2-Cl	12	15	17	14
5c	4-Cl	11	14	16	12
5d	2-Br	15	18	20	15
5e	3-Br	14	16	18	14
5f	2-NO_2	10	13	15	11
5g	3-NO_2	9	11	13	10
5h	2-OCH_3	17	22	24	20
5i	4-OCH_3	17	20	23	18
5j	4-CH_3	18	22	26	21
Streptomycin	-	8	10	12	9

Table 2 Antifungal and antitubercular activity of the synthesized compounds **5a-j** (MIC µg mL^{-1})

Compound	R	*A. flavus*	*F. Oxysporum*	*A. Fumigatus*	*C. albicans*	H37Rv
5a	H	19	14	18	12	5.20
5b	2-Cl	15	12	14	8	3.70
5c	4-Cl	13	11	12	8	3.50
5d	2-Br	17	13	16	11	4.50
5e	3-Br	15	13	15	9	4.00
5f	2-NO_2	12	9	10	7	3.10
5g	3-NO_2	11	8	9	6	2.90
5h	2-OCH_3	21	17	21	15	6.70
5i	4-OCH_3	20	16	20	13	5.90
5j	4-CH_3	24	19	23	16	7.50
Griseofulvin	-	9	6	6	5	-
Rifampicin	-	-	-	-	-	2.50
Isoniazid	-	-	-	-	-	1.25

RESULTS AND DISCUSSION

Phenoxazine on reaction with ethyl chloroacetate yielded N-(ethyl ethanoate)-phenoxazine **1**. In IR spectrum of compound **1** the absorption band characteristic for >C=O, ester group was identified at 1731 cm^{-1} and in ^{1}HNMR spectrum peaks at δ 1.21 and δ 4.20 ppm due to CH_3 and CH_2 respectively in $–COOCH_2CH_3$ (J=7 Hz). Furthermore in the ^{13}CNMR spectrum a peak at δ 168.8 ppm was appeared due to >C=O of ester and peak at δ 61.5 ($COOCH_2CH_3$) and δ 14.4 ppm ($COOCH_2CH_3$) confirmed the formation of compound **1**. The compound **1** on reaction with thiosemicarbazide yielded N-(acetyl thiosemicarbazido) phenoxazine **2**. In IR spectrum of compound **2** the bands at 1665 cm^{-1} (>C=O of amide), 1220 cm^{-1} (>C=S), 3315 and 3178 cm^{-1} (NH-str.) were observed. In the ^{1}HNMR spectra of compound **2** the peak at δ 8.11 ppm was observed due to CONH- and peak at 7.94 was observed due to NNHCS and their peak at δ 5.72 ppm was due to $–NH_2$. Furthermore, in ^{13}CNMR spectrum a peak at δ 169.2 ppm was due to (-CONH) and 180.91 due to (>C=S) confirmed the formation of compound **2**. The compound **2** which on reacted with conc. sulfuric acid yielded 5-amino-2-(phenoxazinyl methyl)-1,3,4-thiadiazoles **3**. In IR spectrum of the compound **3**, the band at 3340 for NH_2 and 1610 cm^{-1} for >C=N were observed. In the ^{1}HNMR spectrum, the peak at 6.51 ppm was due to NH_2. Furthermore in the ^{13}CNMR spectrum a peak at δ162.27 ppm was due to (1,3,4-thiadiazole, C-5) and δ155.80 ppm was due to (1,3,4-thiadiazole, C-2) confirmed the formation of compound **3**. The compound **3** on condensation with various aromatic aldehydes yielded 5-arylideneamino-2-(phenoxazinyl methyl)-1,3,4-thiadiazoles **4a-j**. Formation of compounds **4a-j** was confirmed by the appearance of peaks at δ 8.01-8.11 ppm due to N=CH and IR bands at 1627-1637 cm^{-1} were due to –N=CH of arylidenes. Furthermore in the ^{13}C NMR spectra the peaks in the range of δ 143.1-143.9 ppm were due to –N = CH group, which confirmed the formation of compounds **4a-j**. The compounds **4a-j** on reaction with thioglycolic acid underwent dehydrative annulation to afford 5-(2-aryl-4-oxo-1,3-thiazolidine)-2-(phenoxazinyl methyl)-1,3,4-thiadiazoles **5a-j,** Scheme-1**.** Formation of the compounds **5a-j** was confirmed by the appearance of peaks at δ 3.30-3.38 ppm appeared due to CH_2 in the thiazolidine ring. In IR spectra the bands at 1720-1730 cm^{-1} for >C=O, cyclic were also observed. Furthermore in the ^{13}CNMR spectra, peaks at δ 43.9-44.7 ppm were appeared due to $S-CH_2$ and peaks at δ 171.5-172.5 ppm were observed due to >C=O, cyclic which confirmed the formation of compounds **5a-j**. FAB-Mass spectra of all the synthesized compounds were showed appropriate parent ion peaks corresponding to their molecular weight respectively.

APPLICATIONS

The synthesized compounds generally possess very good antimycobacterial activity with MIC values in the range of 2.90-7.50 µg mL^{-1}. Best activity against *M.tuberculosis* H37Rv was observed for 3-nitro substituted thiazolidine derivative, **(5g)** which is slightly less potent than the standard drug Rifampicin.

CONCLUSIONS

The results of antimicrobial screening data revealed that all the compounds **5a-j** showed considerable and varied activity against the selected microorganisms. Structure activity relationship (SAR) study of the substitution pattern of the aryl group towards antibacterial and antifungal activity have shown that electron withdrawing and donating groups causes, respectively more and less activity. The compounds **5f** and **5g** showed the maximum antibacterial activity (MIC 10 and 9 µg mL^{-1}) against *E.coli* and antifungal activity (MIC 7 and 6 µg mL^{-1}) against *Candida albicans*. The compounds **5f** and **5g** in which a nitro group is present at ortho and meta positions of the aryl ring respectively possess stronger antibacterial and antifungal activity than others. The compounds **5b, 5c, 5d** and **5e** (halo substituents) having a less electron withdrawing groups show less antibacterial and antifungal activity as compared to **5f** and **5g.** The unsubstituted benzene has shown less antibacterial and antifungal activity as compared to nitro and halo substituents. The compounds **5h, 5i** and **5j** show very less antibacterial and antifungal activity as compared

to others because of the presence of the electron donating groups such as methoxy and methyl. The sequence of the activity is in the following:

$$NO_2 > Cl > Br > OCH_3 > CH_3$$

As seen from data of **table-2,** most of the synthesized compounds generally possess very good antimycobacterial activity with MIC values in the range of 2.90-7.50 µg mL^{-1}. Best activity against M.tuberculosis H37Rv was observed for 3-nitro substituted thiazolidine derivative, **(5g)** which is slightly less potent than the standard drug Rifampicin. The 2-nitro, 2,4-chloro and 2,3-bromo substituted thiazolidine derivatives **5f, 5b, 5c, 5d** and **5e** show less activity as compared to 3-nitro substituent derivative. Rest of the compounds showed less activity.

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