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Synthesis of 2-substituted aryl-4-oxo-1,3-thiazolidine derivatives of indole : a new class of biological active compounds

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ABSTRACT

A simple and efficient method has been developed for the synthesis of various 2-substituted aryl-4-oxo-1,3-thiazolidine derivatives of indole using conventional and microwave irradiation techniques. The series of 2-substituted aryl-4-oxo-1,3-thiazolidine derivatives synthesized, were structurally confirmed by analytical and spectral data and evaluated for their antitubercular and antimicrobial activities. Some compounds showed that promising antitubercular and antimicrobial activities.

Keywords: Antitubercular, Antimicrobial, Conventional and Microwave irradiation, Indole, Thiazolidine.

INTRODUCTION

Nitrogen and sulphur containing heterocycles play an important role not only for life science industries but also in many other industries related to fine chemistry. The indole ring system is probably the most important heterocycle in nature. Indole ring possessing wide spectrum of pharmaceutical activities which include antimicrobial, anticancer, anti-inflammatory, analgesic, antitubercular, adrenolytic, antiamoebic [1-8] etc. The indole ring appears in tryptophan, an essential amino acid, and metabolites of tryptophan, are important in the biological chemistry of both plants and animal [9-10]. The thiazolidinone and its derivatives have also taken a considerable pharmacological importance. 4-Thiazolidinones substituted at the 2-position and their derivatives exhibit high *in vitro* antitubercular activity [11]. Thiazolidine and its derivatives are important compounds due to their broad range of biological activities such as antibacterial [12,13], antifungal [14], anti-inflammatory [15] , anticancer [16] and antitubercular [17]. Microwave assisted organic synthesis became an increasingly popular technique in academic and industrial research laboratory due to certain advantages. Microwave reactions under solvent free conditions are attractive offering reduced pollution, low cost and offer high yields together with simplicity in processing and handling. Based on these facts here we report the synthesis of 2-

substituted aryl-4-oxo-1,3-thiazolidine derivatives of indole as antitubercular and antimicrobial agents.

MATERIALS AND METHODS

All the melting points were determined by open capillary method. TLC was carried out on silica gel G coated glass plates. The purification of the compounds was carried out by column chromatography using 100-200 mesh Silica gel. ^{1}H-NMR spectra were recorded on a Bruker DRX 300 instrument at 300 MHz in $CDCl_3$ on δ scale in ppm using TMS as a reference. ^{13}C-NMR spectra were recorded on a Varian AMX 400 spectrophotometer at 50 MHz using $CDCl_3$. The FTIR spectra were recorded on a Perkin-Elmer IR spectrophotometer using KBr disc of the sample in cm^{-1}. Mass spectra of the synthesized compounds have been recorded on a JEOL SX 102/DA-6000 spectrometer.

General Procedure of the synthesis

Synthetic Protocol for the synthesis of N-(chloro propyl)-indole (1)

Conventional method: Indole (25g, 0.21mol) was dissolved in methanol (50 ml) and 1-bromo-3-chloropropane (33.58g, 0.21mol) was added. The mixture was refluxed for about 6 hrs, filtered and the solvent was evaporated to dryness in vacuum. The crude product was readily purified by passing it through a chromatographic column packed with silica gel using chloroform: methanol (7:3 v/v) as eluant to obtain pure derivative. The resulting purified product was recrystallized by chloroform to give compounds **1**. M.P. 62-64 ºC; IR: 3082 (C-H), 1572, 1490, (indole nu.), 1318 (N-CH_2), 732 (C-Cl). ^{1}H-NMR: 6.82-7.41 (m, 4H, Ar.), 6.52 (d, 1H, H_2 $J_{2,3}$=4.0), 6.26 (d, 1H, H_3 $J_{3,2}$=4.0), 2.98 (t, 2H, J=7.03, $\underline{CH_2}CH_2CH_2$), 2.42 (t_1, 2H, J=7.03, $CH_2CH_2\underline{CH_2}$), 1.58 (p, 2H, J=7.03, $CH_2\underline{CH_2}CH_2$). ^{13}C-NMR: 114.87-148.13 (Ar.), 125.67 (C_2), 110.01 (C_2), 42.46 ($\underline{CH_2}CH_2CH_2$), 36.32 ($CH_2CH_2\underline{CH_2}$), 32.13 ($CH_2\underline{CH_2}CH_2$). MS, m/z: 194 $(M)^+$, 158, 144, 130, 116, 89. Anal. calcd. for $C_{11}H_{12}NCl$:C, 68.21; H, 6.24; N, 7.23. Found: C, 68.17; H, 6.18; N, 7.19.

Microwave irradiation method: An equimolar mixture of indole (25g, 0.21mol) and 1-bromo-3-chloropropane (33.58g, 0.21mol) was subjected to microwave irradiation for 2.5 minutes. The crude product was readily purified by passing it through a chromatographic column packed with silica gel using chloroform: methanol (7:3 v/v) as eluant to obtain pure derivative. The resulting purified product was recrystallized by chloroform to give compounds **1**.

Synthesis of N-(hydrazino propyl)-indole (2)

Conventional method: Compound **1** (14g, 0.072mol) was dissolved in acetone (35 ml) and hydrazine hydrate (3.6g, 0.072mol) was added. The well stirred (2 hrs) mixture was refluxed for 7 hrs. After cooling and filtration the solvent was evaporated under in vacuum to obtain a solid crude product. This resulting crude product was purified by passing it through a chromatographic column packed with silica gel using acetone: methanol (6:4 v/v) as eluant to obtain pure derivative. The resulting purified product was recrystallized by ethanol to give compounds **2**. M.P. 74-76ºC; IR: 3362 (-NH_2), 3318 (-NH), 1316 (N-CH_2). ^{1}H-NMR δ: 8.43 (s, 1H, NH), 4.26 (s, 1H, NH_2), 2.96 (t, 2H, J-7.07, $\underline{CH_2}CH_2CH_2$), 2.46 (t_1, 2H, J= 7.07, CH_2 CH_2 $\underline{CH_2}$), 1.63 (p, 2H, J= 7.07, $CH_2\underline{CH_2}CH_2$). ^{13}C-NMR δ: 42.28 ($\underline{CH_2}CH_2CH_2$), 36.99 ($CH_2CH_2\underline{CH_2}$), 32.32 ($CH_2\underline{CH_2}CH_2$). MS, m/z: 189$(M)^+$, 173, 158, 144, 130, 116, 89. Anal. Calcd. for $C_{11}H_{15}N_3$:C, 69.81; H, 7.98; N, 22.20. Found: C, 69.77; H, 8.94; N, 22.17.

Microwave irradiation method: An equimolar mixture of compound **1** (14g, 0.072mol) and hydrazine hydrate (3.6g, 0.072mol) was placed in a microwave oven for 3 minutes. The crude

product was readily purified by passing it through a chromatographic column packed with silica gel using acetone: methanol (6:4 v/v) as eluant to obtain pure derivative. The resulting purified product was recrystallized by ethanol to give compounds **2**.

Synthesis of N-[(benzylidene hydrazine)-propyl]-indole (3a-f)

Conventional **method:** A mixture of compound **2** (2g, 0.01 mol) and benzaldehyde (1.11g, 0.01 mol) in methanol (20ml) in the presence of a catalytic amount of glacial acetic acid was refluxed for 5 hrs. The solvent was removed under reduced pressure to and the resulting crude product was purified by passing it through a chromatographic column packed with silica gel using chloroform: methanol (8:2 v/v) as eluant. Resulting purified product was recrystallized by chloroform to give compounds, **3a**. M.P. 90-92 ºC: IR: 3356 (N-H), 1588 (CH=N, azomethine), 1314 (N-CH_2). ^{1}H-NMR: 8.74 (s,1H, N=CH, azomethine), 8.14 (s,1H, N-H). ^{13}C-NMR: 133.13 (N=CH, azomethine), 126.82 (C_2), 109.11 (C_3), 42.17 ($\underline{CH_2}CH_2CH_2$), 36.75 ($CH_2CH_2\underline{CH_2}$), 32.20 ($CH_2\underline{CH_2}CH_2$). M/S, m/z: 277(M)$^+$, 173, 104, 158, 144, 130, 116, 89, 77. Anal. Calcd. for $C_{18}H_{19}N_3$:C, 77.94; H, 6.90; N, 15.14. Found : C, 77.99; H, 6.93; N, 15.18. MS, m/z: 278 (M)$^+$.

Microwave irradiation method: An equimolar mixture of compound **2** (2g, 0.01 mol) and benzaldehyde (1.11g, 0.01 mol) in the presence of a catalytic amount of glacial acetic acid was placed in a microwave oven for for 4.0 minutes. The resulting crude product was purified by passing it through a chromatographic column packed with silica gel using chloroform: methanol (8:2 v/v) as eluant. Resulting purified product was recrystallized by chloroform to give compounds, **3a**. Other compounds **3b-h** was synthesized in the similar manner by treating compound **2** with selected aromatic aldehydes (Sch.1).

N-[(2-Chlorobenzylidene hydrazino)-propyl]-indole (3b). M.P. 95-96ºC : IR: 3368 (N-H), 1593 (CH=N, azomethine), 1325 (N-CH_2). 712 (Ar-Cl). ^{1}H-NMR: 8.83 (s, 1H, N=CH, azomethine), 8.02 (s,1H N-H). ^{13}C-NMR: 135.25 (N=CH, azomethine), 43.11 ($\underline{CH_2}CH_2CH_2$), 37.89 ($CH_2CH_2\underline{CH_2}$), 34.33 ($CH_2\underline{CH_2}CH_2$). MS, m/z: 312(M)$^+$, 173, 158, 144, 138, 130, 116, 111, 89. Anal. Calcd. for $C_{18}H_{18}N_3Cl$:C, 69.33; H, 5.81; N, 13.47. Found : C, 69.27; H, 5.78; N, 13.43.

N-[(3-bromobenzylidene hydrazino)-propyl]-indole (3c). M.P. 91-92ºC: IR: 3364 (N-H), 1598 (CH=N, azomethine), 1321 (N-CH_2), 667 (Ar-Br). ^{1}H-NMR: 8.76 (s, 1H, CH=N, azomethine), 8.02 (s, 1H, N-H). ^{13}C-NMR: 134.08 (N=CH, azomethine), 43.01 ($\underline{CH_2}CH_2CH_2$), 37.23 ($CH_2CH_2\underline{CH_2}$), 34.18 ($CH_2\underline{CH_2}CH_2$). MS, m/z: 356(M)$^+$, 182, 173, 158, 155, 144, 130, 116, 89. Anal. Calcd. for $C_{18}H_{18}N_3Br_1$:C, 60.68; H, 5.09; N, 11.79. Found : C, 60.63; H, 5.04; N, 11.74.

N-[(2-nitrobenzylidene hydrazino)-propyl]-indole (3d). M.P. 107-109ºC: IR: 3374 (N-H), 1584 (CH=N, azomethine), 1358 (Ar-NO_2), 1342 (N-CH_2). ^{1}H-NMR: 8.89 (s, 1H, CH=N, azomethine), 8.05 (s, 1H, N-H). ^{13}C-NMR: 135.46 (N=CH, azomethine), 43.86 ($\underline{CH_2}CH_2CH_2$), 38.01 ($CH_2CH_2\underline{CH_2}$), 34.79 ($CH_2\underline{CH_2}CH_2$). MS, m/z: 322(M)$^+$, 173, 158, 149, 144, 130, 122, 116, 89. Anal. Calcd. for $C_{18}H_{18}N_4O_2$: C, 67.06; H, 5.62; N, 17.39. Found: C, 67.00; H, 5.56; N, 17.35.

N-[(3-nitrobenzylidene hydrazino)-propyl]-indole (3e). M.P. 104-105ºC: IR: 3367 (N-H), 1591 (CH=N, azomethine), 1349 (Ar-NO_2), 1338 (N-CH_2). ^{1}H-NMR: 8.90 (s,1H, CH=N, azomethine), 8.11 (s,1H,N-H). ^{13}C-NMR: 136.21 (N=CH, azomethine), 43.99 ($\underline{CH_2}CH_2CH_2$), 38.61 ($CH_2CH_2\underline{CH_2}$), 34.68 ($CH_2\underline{CH_2}CH_2$). MS, m/z: 322(M)$^+$, 173, 158, 149, 144, 130, 122, 116, 89. Anal. Calcd. for $C_{18}H_{18}N_4O_2$: C, 67.06; H, 5.62; N, 17.39. Found : C, 67.01; H, 5.57; N, 17.33.

N-[(2-methoxybenzylidene hydrazino)-propyl]-indole (3f). M.P. 98-99ºC: IR: 3358 (N-H), 1582 (CH=N, azomethine), 1337 (N-CH_2), 1240 (Ar-OCH_3). ^{1}H-NMR: 8.72 (s,1H, CH=N, azomethine), 7.92 (s, 1H, N-H), 3.84 (s,3H,O-CH_3). ^{13}C-NMR: 133.33 (CH=N, azomethine),

56.82 (O-CH_3), 43.62 ($\underline{CH_2}CH_2CH_2$), 37.11 ($CH_2CH_2\underline{CH_2}$), 33.28 ($CH_2\underline{CH_2}CH_2$). MS, m/z: 307$(M)^+$, 173, 158, 144, 134, 130, 116, 107, 89. . Anal. Calcd. for $C_{19}H_{21}N_3O$: C, 74.23; H, 6.88; N, 13.66. Found: C, 74.18; H, 6.82; N, 13.63.

Synthesis of 1-[3-{2-(Substituted aryl)-4-oxo-1,3-thiazolidineimino}propyl]-indole (5a-f).
Conventional Method. A mixture of compound **4a** (1g, 0.003 mol) and $SHCH_2COOH$ (0.331g 0.003 mol) in methanol (20 ml) containing a pinch of anhy. $ZnCl_2$ was first stirred for about 2 hours followed by refluxing on a steam bath for about 6 hrs. The reaction mixture was cooled and excess of solvent was evaporated under reduced pressure. The solid crude product was purified by passing it through a chromatographic column packed with silica gel using chloroform: methonal (6:4 v/v) as eluant and again purified by recrystallisation from ethanol to give compound **5a.** M.P. 83-84ºC: IR: 3358 (N-H), 1729 (C=O), 728 (C-S-C). ^{1}H-NMR: 8.10 (s, 1H, N-H), 5.68 (s,1H, N-CH-S), 3.34 (s, 2H, $CO\underline{CH_2}S$). ^{13}C-NMR: 167.27 (C=O), 63.93 (CH-Cl), 47.61 (N-CH-Ar), 35.21 ($COCH_2S$). MS, m/z: 351$(M)^+$, 178, 173, 158, 150, 144, 136, 130, 116, 89, 77, 59. Anal. Calcd. for $C_{20}H_{21}N_3O_1S_1$: C, 68.34; H, 6.02; N,11.95. Found: C, 68.29; H, 5.98; N, 11.91.

Microwave irradiation method. An equimolar mixture of compound **4a** (1g, 0.003 mol) and $SHCH_2COOH$ (0.331g 0.003 mol) with a pinch of anhy. $ZnCl_2$ was subjected to microwave irradiation for 3 minutes. The solid crude product was purified by passing it through a chromatographic column packed with silica- gel using chloroform; methanol (6:4 v/v) as eluant and again purified by rerystallisation from ethanol to give compounds **5a.**
Other compounds **5b-f** was synthesized in the similar manner using compounds **4b-f**.

1-[3-{2-(2-Chlorophenyl)-4-oxo-1,3-thiazolidineimino}propyl]-indole (5b). M.P. 86-87ºC: IR: 3365 (N-H), 1723 (C=O), 729 (C-S-C), 712 (Ar-Cl). ^{1}H-NMR: 8.25 (s, 1H, N-H), 5.72 (s, 1H, N-CH-S), 3.38 (s, 2H, $COCH_2S$). ^{13}C-NMR: 169.31 (C=O), 47.24 (N-CH-Ar), 34.62 ($COCH_2S$). MS, m/z: 386$(M)^+$, 212, 184, 173, 170, 158, 144, 130, 116, 111, 89, 59. Anal. Calcd. for $C_{20}H_{20}N_3O_1S_1Cl_1$: C, 62.24; H, 5.22; N,10.88. Found : C, 62.19; H, 5.18; N, 10.81.
1-[3-{2-(3-Bromophenyl)-4-oxo-1,3-thiazolidineimino}propyl]-indole (5c). M.P.- 84-85ºC IR: 3371 (N-H), 1738 (C=O), 723 (C-S-C), 625 (Ar-Br). ^{1}H-NMR: 8.18 (s, 1H, N-H), 5.68 (s, 1H, N-CH-S), 3.32 (s, 2H, $COCH_2S$). ^{13}C-NMR: 167.93 (C=O), 47.54 (N-CH-Ar), 34.63 ($COCH_2S$). M/S, mz: 430$(M)^+$, 256, 228, 214, 173, 158, 155, 1544, 130, 116, 89, 59. Anal. Calcd. for $C_{20}H_{20}N_3OSBr$: C, 55.80; H, 4.68; N,9.76. Found : C, 55.75; H, 4.63; N, 9.73.
1-[3-{2-(2-Nitrophenyl)-4-oxo-1,3-thiazolidineimino}propyl]-indole (5d). M.P.- 98-99ºC: IR: 3381 (N-H), 1729 (C=O), 738 (C-S-C), 1358 (Ar-NO_2). ^{1}H-NMR: 8.28 (s, 1H, N-H), 5.75 (s, 1H, N-CH-S), 3.40 (s, 2H, $COCH_2S$). ^{13}C-NMR: 169.53 (C=O), 48.85 (N-CH-Ar), 35.87 ($COCH_2S$). MS, m/z: 396$(M)^+$, 223, 195, 181, 173, 158, 144, 130, 122, 116, 89, 59. Anal. Calcd. for $C_{20}H_{20}N_4O_3S$: C, 60.59; H, 5.08; N, 14.13. Found: C, 60.56; H, 5.04; N, 14.10.
1-[3-{2-(3-Nitrophenyl)-4-oxo-1,3-thiazolidineimino}propyl]-indole (5e). M.P. 93-94ºC: IR : 3369 (N-H), 1733 (C=O), 737 (C-S-C), 1350 (Ar-NO_2). ^{1}H-NMR: 8.26 (s, 1H, N-H), 5.76 (s, 1H, N-CH-S), 3.41 (s, 2H, $COCH_2S$). ^{13}C-NMR δ: 169.54 (C=O), 48.77 (N-CH-Ar), 36.19 ($COCH_2S$). MS, m/z: 396$(M)^+$, 223, 195, 181, 173, 158, 144, 130, 122, 116, 89, 59. Anal. Calcd. for $C_{20}H_{20}N_4O_3S$: C, 60.59; H, 5.08; N, 14.13. Found : C, 60.55; H, 5.03; N, 14.08.
1-[3-{2-(2-Methoxyphenyl)-4-oxo-1,3-thiazolidineimino}propyl]-indole (5f). M.P. 89-90ºC: IR: 3353 (N-H), 1728 (C=O), 729 (C-S-C), 1235 (Ar-OCH_3). ^{1}H-NMR: 8.16 (s, 1H, N-H), 5.71 (s, 1H, N-CH-S), 3.73 (s, 1H, -OCH_3), 3.35 (s, 2H, $COCH_2S$). ^{13}C-NMR: 169.48 (C=O), 55.82 (O-CH_3) 46.83 (N-CH-Ar), 34.83 ($COCH_2S$). MS, m/z: 382$(M)^+$, 209, 181, 173, 167, 158, 144, 130, 116, 108, 89, 59. Anal. Calcd. for $C_{21}H_{23}N_3O_2S$: C, 66.11; H, 6.06, N, 11.00. Found : C, 66.08; H, 6.03; N, 10.96.

Evaluation of antitubercular screening

All the synthesized compounds of series **(5a-f)** were evaluated for their antitubercular activity. Drug susceptibility and determination of MIC of the test compounds against *M. tuberculosis* H37Rv was performed by agar micro dilution (L-J) method. Where twofold dilutions of each test compound were added into 7H10 agars supplemented with OADC and organism. The testing tubes were incubated at 37 °C for 24 h followed by streaking of *M. tuberculosis* H37Rv (5 × 104 bacilli per tube). These tubes were then incubated at 37 °C. Growth of bacilli was seen after 30 days of incubation. Tubes having the compounds were compared with control tubes where medium alone was incubated with H37Rv. The concentration at which complete inhibition of colonies occurred was taken as active concentration of test compound. Streptomycin and ethambutol were used as standard drug. The MIC levels of some active compounds **(5a-f)** against these organisms are given in table I.

Table-I: Antitubercular activity of selected Compounds of series 4a-f (MIC µg/ml)

Compounds	MIC (µg ml-1) H37RV	Compounds	MIC(µgml-1) H37RV
5a	>12.5	5d	>3.125
5b	>3.125	5e	3.125
5c	6.25	5f	12.5
Streptomycin	4.0	Ethambutol	2.0

Evaluation of antimicrobial screening

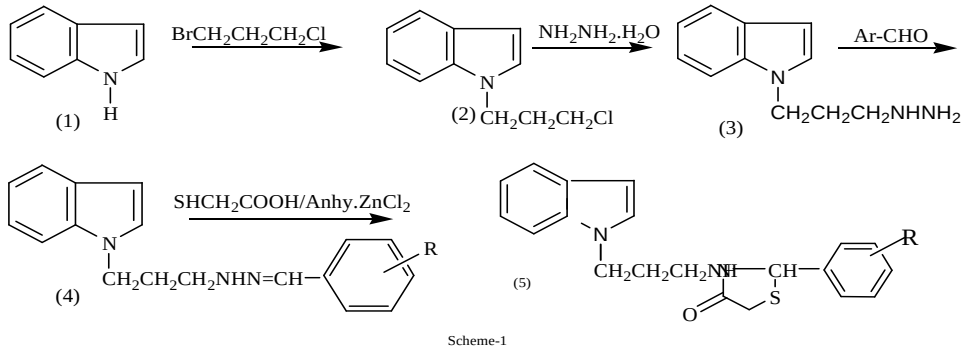
All the synthesized compounds of series **(5a-f)** were tested for their antimicrobial activity. For antibacterial screening a gram-positive bacterium *S. aureus* and two gram-negative bacteria, *E.coli* and *S.pneumoniae* were used. For antifungal activity *C.albicans*, *A. pumigatus* and *A.niger* was taken. Antibacterial and antifungal screenings were performed by dilution method using nutrient agar media. MIC was determined at five concentrations (in µg/ml) ranging from 0.5 µg, 1.0 µg, 5.0 µg, 10.0 µg, 25.0 µg and 50.0 µg of each compounds. The tubes were incubated at 37ºC for 48 hrs. DMSO was used as solvent. The lowest concentration, which showed no visible growth, was taken as an end point for minimum inhibitory concentration (MIC). Oflaxacin was used as standard drug for antibacterial screening in a concentration 0.5 µg/ml/disc and miconazole was used as standard drug for antifungal screening in a concentration 0.5 µg/ml/disc. The MIC levels of some active compounds **(5a-f)** against these organisms are given in table II.

Table-II: Antibacterial and Antifungal activity of Compounds 5a-f (MIC µg/ml)

Comp.	*E.coli.*	*S.pneu.*	*S.aureus*		*C.albicans*	*A.fumi.*	*A.niger*
5a	1.0	1.0	5.0		5.0	1.0	5.0
5b	0.1	0.1	0.5		1.0	1.0	0.5
5c	1.0	0.5	0.5		0.1	0.5	0.1
5d	0.5	0.5	0.1		0.5	0.1	0.5
5e	0.1	0.5	0.1		0.5	0.1	0.1
5f	1.0	1.0	1.0		0.1	0.5	0.5
Oflaxacin	0.1	0.1	0.1		-	-	-
Miconazole	-	-	-		0.1	0.1	0.1

RESULTS AND DISCUSSION

Our synthesis strategy was based on to synthesize a highly biologically active heterocycle containing indole and thiazolidine moieties. As the results, we obtained a series of thiazolidine derivatives of indole by scheme **1**. The analytical and spectral data supported the formation of the products in end step. The microwave assisted synthesis was performed in modified microwave (2450MHz and 800W) using microwave irradiation at 50% power levels. The comparison study data are given in the table III.



Scheme-1

R= H, 2-Cl, 3-Br, 2-NO_2, 3-NO_2, 2-MeO

In general we know that the penicillin and cephalosporins like antibiotics contain thiazolidine ring systems, which are broad spectrum antibiotics. So, all the synthesized compounds of series **(5a-f,** containing thiazolidine ring**)** were screened against *M. tuberculosis* for their antitubercular activity and against some microorganisms for their antimicrobial activities. Generally compounds possessing electron withdrawing groups showed good antibacterial and antitubercular activity. Some derivatives (5b, 5c, 5d, 5e) containing electron withdrawing groups (-Cl, -Br, -NO_2) have shown promising activity against *M. tuberculosis* and some bacteria. Compounds possessing electron donating groups (5f) have shown good antifungal activity. It is thus concluded that new synthesized thiazolidine are good antitubercular and antimicrobial compounds for therapeutic uses.

Table –III: Physical data of the compounds, 1, 2, 3a-f, 4a-f, 5a-f.

Com	Mole.formula	R	Yield(%) Con.	R.T.(hr)Con.	Yield(%) M.W.	R.T.(min.) M.W
2	$C_{11}H_{12}NCl$	-	72	6.0	84	2.5
3	$C_{11}H_{15}N_3$	-	65	7.0	86	3.0
4a	$C_{18}H_{19}N_3$	-H	68	5.0	86	4.0
4b	$C_{18}H_{18}N_3Cl$	2-Cl	62	4.0	89	3.5
4c	$C_{18}H_{18}N_3Br$	3-Br	65	5.0	90	4.0
4d	$C_{18}H_{18}N_4O_2$	2-NO_2	63	3.5	88	3.0
4e	$C_{18}H_{18}N_4O_2$	3-NO_2	61	3.5	91	2.5
4f	$C_{19}H_{21}N_3O$	2-OCH_3	65	5.5	87	5.0
5a	$C_{20}H_{21}N_3OS$	-H	68	6.0	88	3.5
5b	$C_{20}H_{20}N_3OSCl$	2-Cl	63	4.0	89	4.0
5c	$C_{20}H_{20}N_3OSBr$	3-Br	72	5.5	86	4.0
5d	$C_{20}H_{20}N_4O_3S$	2-NO_2	69	4.0	92	2.5
5e	$C_{20}H_{20}N_4O_3S$	3-NO_2	65	4.5	91	3.0
5f	$C_{20}H_{23}N_3O_2S$	2-OCH_3	66	7.0	85	4.0

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