

# Synthesis and Antimicrobial Profile of Newer Schiff Bases and Thiazolidinone Derivatives

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## II. MATERIAL AND METHODS

**Abstract**—Esterification of *p*-bromo-*m*-cresol led to formation of 2-(4-bromo-3-methylphenoxy)acetate (1). 2-(4-Bromo-3-methylphenoxy)acetohydrazide (2) is derived from Compound (1) by hydrazination. Compound (2) was reacted with different aromatic aldehydes to yield *N*-(substituted benzylidene)-2-(4-bromo-3-methylphenoxy)acetamide (3a-c). Cyclization of compound (3a-c) with thioglycolic acid yielded 2-(4-bromo-3-methylphenoxy)-*N*-(4-oxo-2-arylthiazolidin-3-yl) acetamide (4a-c). The newly synthesized compounds were characterized on the basis of spectral studies and evaluated for antibacterial and antifungal activities.

**Keywords**—Imines, Thiazolidinone, Schiff base, Antimicrobial.

## I. INTRODUCTION

THIAZOLIDINONES, imines and phenolic moieties are very well known to potentiate the antiviral [1], anticancer [2], [3], anti-tubercular [4], and antimicrobial [5]-[17] activities of organic molecules. As per the literary investigations, it was known that phenolic moieties can be converted into imines [17], [18]; which are precursors for thiazolidinones [19]-[23]. As per the literary reports azoles are particularly desirable structures for screening and are prevalent in drugs that have reached market place. Development of simple and general synthetic routes for widely used organic compounds from readily available reagents is one of major challenges to the organic chemists. To meet facile results of these tough challenges thiazolidinone nucleus was being considered. Among wide variety of heterocycles explored for developing pharmaceutical molecules, thiazolidinone derivatives played a vital role in medicinal chemistry. Hence, as per various reports, literature, prospects of antibiotics in global pharmaceutical market, also the activities associated with phenols, imines and thiazolidinones; an attempt was made to generate novel potent antimicrobials by converting phenolic ester moiety (1) into some novel 2-(4-bromo-3-methylphenoxy)-*N*-(4-oxo-2-arylthiazolidin-3-yl) acetamide (4a-e) via synthesis of hydrazide (2) and imines (3a-e) as key intermediates [23]. The novel compounds were further characterized and evaluated for their antimicrobial activities.

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## A. Material

Melting points of newly synthesized compounds were determined in open capillary tubes. IR spectra were recorded (in KBr) on Bruker PCIR, <sup>1</sup>HNMR spectra on Bruker, DPX 300 and mass spectra on MASPEC (MSW/9629) apparatuses. Purity of synthesized compounds was checked by TLC on aluminium sheets with silica gel 60 F<sub>254</sub> (0.2 mm).

## B. Methods

### 1. Synthesis of 2-(4-Bromo-3-MethylPhenoxy)Acetate (1)

A mixture of *p*-bromo-*m*-cresol (0.1mol), ethylchloroacetate (0.1mol) and anhydrous potassium carbonate (0.15mol) was refluxed for 16 hours. The resultant mixture was filtered and filtrate after distillation, was poured onto ice-cold water and stirred well. The obtained mixture was extracted with ether. The organic extract layer was dried and kept overnight with anhydrous sodium sulphate. Finally the dried organic mixture was purified under reduced pressure to yield pure compound (1). IR (KBr, cm<sup>-1</sup>): 2994, 2928 (C-H), 1715 (C=O of ester), 1238 (C-O of ester). <sup>1</sup>HNMR (CDCl<sub>3</sub>, δ ppm): 2.01 (3H, t, CH<sub>3</sub>), 2.34 (3H, s, Ar-CH<sub>3</sub>), 4.15 (2H, q, CH<sub>2</sub>), 4.86 (2H, s, OCH<sub>2</sub>), 6.50-7.04 (3H, m, Ar-H). MS (m/z): 272 (M<sup>+</sup>), 274 (M<sup>+</sup>+2), 199 (base Peak), 185, 95. Anal.(Calcd.) Found: C (48.37) 48.35, H (4.80) 4.78.

### 2. Synthesis of 2-(4-Bromo-3-MethylPhenoxy)Aceto Hydrazide(2)

A mixture of ethyl aryloxyacetate (1) (0.05 mol) and hydrazine hydrate (0.075 mol) in ethanol was refluxed for 6 h. The reaction mixture was distilled to remove solvent and the crystals formed were recrystallized from methanol to yield pure compound (2). IR (KBr, cm<sup>-1</sup>): 3275, 3284 (NH and NH<sub>2</sub>), 1742 (CO of ester), 1587, 1472, 1285, 1198, 1174, 1126, 1090, 864, 773 (C=C and C-H of aromatic ring). <sup>1</sup>HNMR (CDCl<sub>3</sub>, δ ppm): 2.32 (3H, s, CH<sub>3</sub>), 4.82 (2H, s, OCH<sub>2</sub>), 5.62 (2H, br, NH<sub>2</sub>), 6.52 (1H, d, *J* = 2.74 Hz, Ar-H<sub>2</sub>), 6.53 (1H, dd, *J* = 2.77, 6.31, 2.70 Hz, Ar-H<sub>6</sub>), 7.05 (1H, d, *J* = 6.68 Hz, Ar-H<sub>5</sub>), 9.52 (1H, s, NH). MS (m/z): 258 (M<sup>+</sup>), 260 (M<sup>+</sup>+2), 185 (base Peak), 243, 242, 197, 95. Anal.(Calcd.) Found: C(41.72)41.69, H(4.28)4.24, N(10.81)10.78.

### 3. General Procedure for Synthesis of 2-[(4-Bromo-3-Methyl)Phenoxy]-*N*-[SubstitutedBenzylidene]Aceto Hydrazides (3a-c):

A mixture of compound (2) (0.01 mol) and aromatic aldehyde (0.01 mol) in the presence of few drops of sulfuric

acid was refluxed for 6 h. The product formed was isolated and recrystallized from methanol to yield compounds (3a-c).

*a. N-(4-(dimethylamino)benzylidene)-2-(4-bromo-3-methylphenoxy)acetohydrazide (3a)*

IR (KBr,  $\text{cm}^{-1}$ ): 1645 (CO of CONH), 3214, 1632 (NH of CONH), 1594, 1471, 1296, 1190, 1166, 1121, 1081, 867, 836, 770 (C=C & C-H of aromatic ring).  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ,  $\delta$  ppm): 2.39 (3H, s,  $\text{CH}_3$ ), 2.87 (6H, s,  $\text{N}(\text{CH}_3)_2$ ), 4.83 (2H, s,  $\text{OCH}_2$ ), 6.51 (1H, d,  $J = 2.71$  Hz, Ar-H2), 6.53 (1H, dd,  $J = 2.74, 6.32, 2.71$  Hz, Ar-H6), 6.62 (2H, d,  $J = 6.32$  Hz, Ar-H3 & 5), 6.95 (2H, d,  $J = 6.96$  Hz, Ar-H2 & 6), 7.04 (1H, d,  $J = 6.32$  Hz, Ar-H5), 8.00 (1H, s,  $\text{N}=\text{CH}$ ), 9.50 (1H, s, NH). MS (m/z) 390 ( $\text{M}^+$ ), 392 ( $\text{M}^+ + 2$ ), 190 (base Peak), 243, 200, 186, 147, 120. Anal.(Calcd.) Found: C(55.39)55.36, H(5.16)5.14, N(10.77)10.73.

*b. N-(4-chlorobenzylidene)-2-(4-bromo-3-methylphenoxy)acetohydrazide (3b)*

IR (KBr,  $\text{cm}^{-1}$ ): 1647 (CO of CONH), 3258, 1627 (NH of CONH), 1591, 1465, 1292, 1160, 1130, 1082, 861, 836, 774 (C=C & C-H of aromatic ring).  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ,  $\delta$  ppm): 2.35 (3H, s,  $\text{CH}_3$ ), 4.90 (2H, s,  $\text{OCH}_2$ ), 6.51 (1H, d,  $J = 2.81$ , Ar-H2), 6.54 (1H, dd,  $J = 2.76, 6.32, 2.74$  Hz, Ar-H6), 7.04 (1H, d,  $J = 6.28$  Hz, Ar-H5), 7.10 (2H, d,  $J = 6.32$  Hz, Ar-H2 & 6), 7.21 (2H, d,  $J = 6.85$  Hz, Ar-H3 & 5), 8.04 (1H, s,  $\text{N}=\text{CH}$ ), 9.26 (1H, s, NH). MS (m/z): 381 ( $\text{M}^+$ ), 383 ( $\text{M}^+ + 2$ ), 181 (base Peak), 366, 243, 200, 186, 138, 111. Anal.(Calcd.) Found: C (50.35) 50.31, H (3.70) 3.67, N (7.34) 7.30.

*c. N-(2,4-dihydroxybenzylidene)-2-(4-bromo-3-methylphenoxy)acetohydrazide (3c)*

IR (KBr,  $\text{cm}^{-1}$ ): 1655 (CO of CONH), 3316, 1626 (NH of CONH), 3513, 3520 (OH on phenyl ring), 1594, 1448, 1288, 1197, 1178, 1158, 904, 798 (C=C & C-H of aromatic ring).  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ,  $\delta$  ppm): 2.35 (3H, s,  $\text{CH}_3$ ), 4.82 (2H, s,  $\text{OCH}_2$ ), 5.18 (1H, s, OH), 5.28 (1H, s, OH), 6.21 (1H, d,  $J = 2.82$  Hz, Ar-H3), 6.32 (1H, dd,  $J = 2.74, 6.73, 2.72$  Hz, Ar-H5), 6.54 (1H, d,  $J = 2.73$  Hz, Ar-H2), 6.55 (1H, dd,  $J = 2.68, 6.34, 2.68$  Hz, Ar-H6), 7.07 (1H, d,  $J = 6.67$  Hz, Ar-H5), 7.31 (1H, d,  $J = 6.67$  Hz, Ar-H6), 8.11 (1H, s,  $\text{N}=\text{CH}$ ), 9.18 (1H, s, NH). MS (m/z): 379 ( $\text{M}^+$ ), 381 ( $\text{M}^+ + 2$ ), 179 (base Peak), 364, 243, 200, 186, 136, 109. Anal.(Calcd.) Found: C (50.68) 50.65, H (3.99) 3.95, N (7.39) 7.38.

**4. General Procedure for Synthesis of 2-(4-Chloro-3-Methylphenoxy)-N-(4-Oxo-2-Substituted ArylThiazolidin-3-yl)Acet Amides (4a-c)**

A mixture of compound (3a-c) (0.01 mol) and thioglycolic acid (0.02 mol) in the presence of zinc chloride was refluxed for 12 h. The product formed was isolated and recrystallized from methanol to yield compounds (4a-c).

*a. 2-(4-bromo-3-methylphenoxy)-N-(2-(4-(dimethylamino)phenyl)-4-oxothiazolidin-3-yl)acetamide (4a)*

IR (KBr,  $\text{cm}^{-1}$ ): 3255 (NH of CONH), 1760 (CO of Thiazolidinone ring), 1655 (CO of CONH), 1580, 1468, 1270, 1170, 1076, 878 (C=C & C-H of aromatic ring), 1148 and 697 (C-S of Thiazolidinone ring).  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ,  $\delta$  ppm): 2.41

(3H, s, Ar- $\text{CH}_3$ ), 2.84 (6H, s,  $\text{-N}(\text{CH}_3)_2$ ), 3.35 (2H, s,  $\text{CH}_2\text{-S}$ ), 4.84 (2H, s,  $\text{OCH}_2$ ), 5.85 (1H, s,  $\text{-N-CH-S-}$ ), 6.44 (1H, d,  $J = 7.9$  Hz, Ar-H3 & 5), 6.35 (1H, d,  $J = 2.8$  Hz, Ar-H2), 6.48 (1H, dd,  $J = 2.9, 8.1$  Hz, Ar-H6), 6.77 (1H, d,  $J = 8.3$  Hz, Ar-H2 & 6), 7.06 (1H, d,  $J = 8.3$  Hz, Ar-H5), 8.76 (1H, s, for NH). MS (m/z): 464 ( $\text{M}^+$ ), 466 ( $\text{M}^+ + 2$ ), 243 (base peak), 449, 264, 221, 200, 186, 120. Anal.(Calcd.) Found: C(51.73)51.70, H(4.77)4.76, N(9.05)9.03.

*b. 2-(4-bromo-3-methylphenoxy)-N-(2-(4-chlorophenyl)-4-oxothiazolidin-3-yl)acetamide (4b)*

IR (KBr,  $\text{cm}^{-1}$ ): 3260 (NH of CONH), 1750 (CO of Thiazolidinone ring), 1658 (CO of CONH), 1586, 1477, 1276, 1180, 1099, 870 (C=C & C-H of aromatic ring), 1140 and 680 (C-S of Thiazolidinone ring).  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ,  $\delta$  ppm): 2.43 (3H, s, Ar- $\text{CH}_3$ ), 3.39 (2H, s,  $\text{CH}_2\text{-S}$ ), 4.90 (2H, s,  $\text{OCH}_2$ ), 5.93 (1H, s,  $\text{-N-CH-S-}$ ), 6.39 (1H, d,  $J = 2.8$  Hz, Ar-H2), 6.48 (1H, dd,  $J = 2.7, 8.1$  Hz, Ar-H6), 7.04 (1H, d,  $J = 8.0$  Hz, Ar-H2 & 6), 7.08 (1H, d,  $J = 8.2$  Hz, Ar-H5), 7.20 (1H, d,  $J = 8.4$  Hz, Ar-H3 & 5), 8.82 (1H, s, NH). MS (m/z): 455 ( $\text{M}^+$ ), 457 ( $\text{M}^+ + 2$ ), 186 (base peak), 440, 255, 243, 212, 200, 111. Anal.(Calcd.) Found: C(47.44)47.42, H(3.54)3.52, N(6.15)6.12.

*c. 2-(4-bromo-3-methylphenoxy)-N-(2-(2,4-dihydroxyphenyl)-4-oxothiazolidin-3-yl)acetamide (4c)*

IR (KBr,  $\text{cm}^{-1}$ ): 3525 (OH), 3248 (NH of CONH), 1770 (CO of Thiazolidinone ring), 1664 (CO of CONH), 1595, 1465, 1285, 1190, 1072, 894 (C=C & C-H of aromatic ring), 1138 and 691 (C-S of Thiazolidinone ring).  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ,  $\delta$  ppm): 2.43 (3H, s, Ar- $\text{CH}_3$ ), 3.34 (2H, s,  $\text{CH}_2\text{-S}$ ), 4.85 (2H, s,  $\text{O-CH}_2$ ), 5.34 (1H, s, 4-OH), 5.38 (1H, s, 2-OH), 5.87 (1H, s,  $\text{-N-CH-S-}$ ), 6.15 (1H, d,  $J = 2.7$  Hz, Ar-H2), 6.33 (1H, dd,  $J = 2.7, 8.1$  Hz, Ar-H6), 6.46 (1H, d,  $J = 8.0$  Hz, Ar-H2 & 6), 7.12 (1H, d,  $J = 8.5$  Hz, Ar-H5), 7.34 (1H, d,  $J = 8.5$  Hz, Ar-H3 & 5), 8.64 (1H, s, NH). MS (m/z): 453 ( $\text{M}^+$ ), 455 ( $\text{M}^+ + 2$ ), 438 (base peak), 253, 243, 210, 200, 186, 109. Anal.(Calcd.) Found: C(47.69)47.66, H(3.78)3.77, N(6.18)6.16.

**C. Antimicrobial Activity**

The synthesized compounds (3a-3c & 4a-4c) were screened for antibacterial (*S. aureus*, *E. coli*, *P. aeruginosa*) and antifungal (*C. albicans*, *A. flavus*, *A. fumigatus*) activities by disk diffusion method at a concentration of 2 mg/mL using DMF as a solvent. The results were recorded in duplicate using Ciprofloxacin and Fluconazole as standards.

**III. RESULTS AND DISCUSSION**

2-(4-bromo-3-methylphenoxy)acetate(1) was synthesized by the esterification of p-Bromo-m-cresol which is a phenol. The 2-(4-Bromo-3-methylphenoxy)acetohydrazide (2) was derived from Compound (1) by hydrazination reaction. The N-(substituted benzylidene)-2-(4-bromo-3-methylphenoxy)acetamides (3a-c), which prepared from 2-(4-Bromo-3-methylphenoxy)acetohydrazide (2) via schiffs reaction, when cyclized with thioglycolic acid yielded potent antibacterial and antifungal 2-(4-bromo-3-methylphenoxy)-N-(4-oxo-2-arylthiazolidin-3-yl)acetamides(4a-c). The physical data of

newly synthesized compounds 3a-c and 4a-c are presented in the Table I.

TABLE I  
PHYSICAL DATA OF COMPOUNDS (3A-3C & 4A-4C)

Compd.	Molecular formula	Molecular weight	Yield (%)	m.p. (°C)
3a	C <sub>18</sub> H <sub>20</sub> N <sub>3</sub> O <sub>2</sub> Br	390.27	72.03	195-196
3b	C <sub>16</sub> H <sub>14</sub> N <sub>2</sub> O <sub>2</sub> BrCl	381.65	65.55	215-216
3c	C <sub>16</sub> H <sub>15</sub> N <sub>2</sub> O <sub>4</sub> Br	379.20	60.38	222-223
4a	C <sub>20</sub> H <sub>22</sub> N <sub>3</sub> O <sub>3</sub> BrS	464.38	71.53	128-129
4b	C <sub>18</sub> H <sub>16</sub> N <sub>2</sub> O <sub>3</sub> ClBrS	455.76	65.32	126-127
4c	C <sub>18</sub> H <sub>17</sub> N <sub>3</sub> O <sub>3</sub> BrS	453.31	62.45	168-169

The synthetic procedure for conversion of compound 1, 2, 3a-c and 4a-c is suggested in Fig. 1.

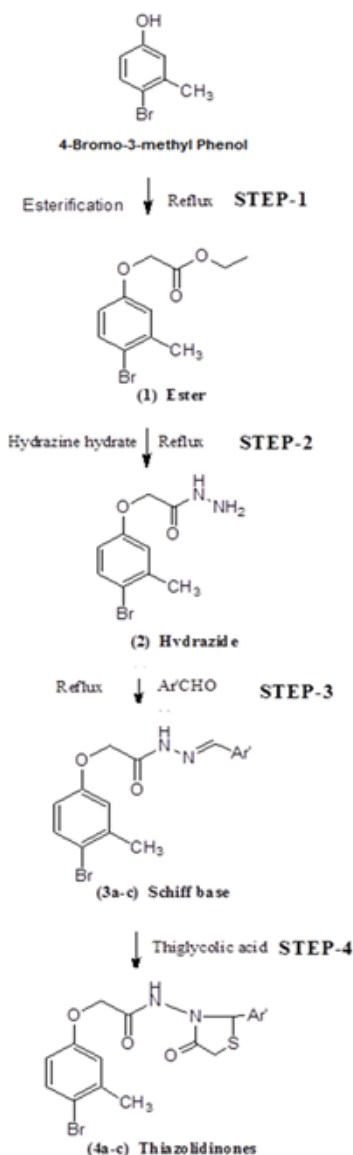


Fig. 1 Conversion of 4-bromo-3methyl phenol

The assigned structure, molecular formulae and the anomeric configuration of the newly synthesized compounds 3a-c and thiazolidinones 4a-c were further confirmed by and supported by mass, <sup>1</sup>H-NMR, elemental analysis and IR spectral data, based on occurrence of molecular ion peak of the assigned structures, downfield shifting of protons and different stretching bands of the compounds. The newly synthesized compounds were further evaluated for their antimicrobial potential (Data given in Tables II & III)

TABLE II  
ANTIBACTERIAL ACTIVITY OF COMPOUNDS (3A-3C & 4A-4C)

Compd.	Zone of Inhibition (mm)		
	<i>S. aureus</i>	<i>E. coli</i>	<i>P. aeruginosa</i>
3a	18.3 ± 0.33	19.3 ± 0.00	20 ± 0.00
3b	21.3 ± 0.33	22.3 ± 0.00	21.2 ± 0.00
3c	21 ± 0.00	22.2 ± 0.00	21.3 ± 0.33
4a	19.3 ± 0.00	19.3 ± 0.00	21.3 ± 0.33
4b	21.3 ± 0.67	23.3 ± 0.00	23.2 ± 0.00
4c	22.3 ± 0.00	21.5 ± 0.67	23.3 ± 0.33
Ciprofloxacin	27 ± 0.00	28 ± 0.00	27 ± 0.00
DMF	-	-	-

\* All the values are expressed as mean ± SEM of triplicates

TABLE III  
ANTIFUNGAL ACTIVITY OF COMPOUNDS (3A-3C & 4A-4C)

Compd.	Zone of Inhibition (mm)		
	<i>C. albicans</i>	<i>A. fumigatus</i>	<i>A. flavus</i>
3a	10.3 ± 0.00	13 ± 0.00	12.2 ± 0.00
3b	12.3 ± 0.33	10.3 ± 0.00	8.3 ± 0.00
3c	13.2 ± 0.00	12.3 ± 0.00	10.2 ± 0.00
4a	12.3 ± 0.00	10.2 ± 0.00	14 ± 0.00
4b	12.3 ± 0.33	14.3 ± 0.00	14.2 ± 0.00
4c	13.3 ± 0.00	12.3 ± 0.00	10 ± 0.00
Fluconazole	17 ± 0.00	23 ± 0.00	22 ± 0.00
DMF	-	-	-

\* All the values are expressed as mean ± SEM of triplicates

#### IV. CONCLUSION

After carrying out the antimicrobial studies of newly synthesized compounds, it was found that each compound 3a-c and 4a-c possesses antibacterial and antifungal activities to certain extent. Among the newly synthesized derivatives, compound 4c was found to be most effective against *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Candida albicans* while compound 4b was found to be most effective against *Escherichia coli*, *Asperigillus flavus* and *Asperigillus fumigatus*. Some of the tested compounds: 3b, 3c, and 4a, have shown good antibacterial and antifungal activity whereas, the remaining compounds have shown moderate activity on the tested organisms. After comparing the antimicrobial results of newly synthesized compounds 3a-c and 4a-c, it was concluded that incorporation of thiazolidinone moiety in the aryloxy derivatives potentiates their antimicrobial activity.

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