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Synthesis of Some New 2-[3-(2-chloro quinolinyl)]-3-aryl-4-thiazolidinones as Potent Antibacterial Agents

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4-thiazolidinone derivatives were prepared by the cyclocondenastion of mercaptoacetic acid with quinoline aldimines which in turn were obtained by reacting 2-chloro-3-formylbenzo(h)quinoline and 2,6-dichloro-3-formyl-4-phenylquinoline with various substituted amines. The compounds have been characterized by spectral data. Selected compounds were screened for their antibacterial activity.

Key Words: Synthesis, 2-[3-(2-chloro quinolinyl)] -3-aryl-4-thiazolidinones Antibacterial activity.

INTRODUCTION

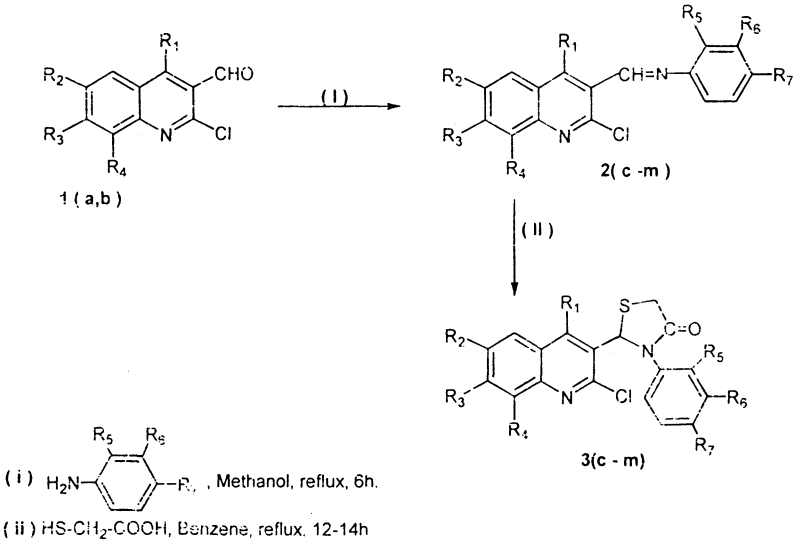
Schiff bases generally have been used as substrates in the formation of industrial compounds[1, 2] as well as in the synthesis of a number of nitrogen containing heterocycles. Furthermore, the various reported pharmaceutical properties such as organoleptic, diuretic, antileukemic, antiparasital[3, 4], anticonvulsant, anaesthetic and sedative properties[5–10] of thiazolidinones prompted us to synthesize the new thiazolidinone derivatives.

As a part of ongoing work, aimed at the synthesis of 4-thiazolidinones, we employed quinoline Schiff bases toward their synthesis **(Scheme-1)** Our objective also involves the comparision of the antibacterial activities of the above synthesized compounds.

EXPERIMENTAL

Melting points were determined on the Mettler FP 51 instrument and are uncorrected. IR spectra were recorded on Shimadzu FT-IRP (S) 8201 spectrophotometer as KBr pellets. ^{1}H NMR spectra were recorded on an AMX 400 spectrophotometer in $CDCl_3$. Elemental analyses were performed by Perkin-Elmer model 240 B CHN analyzer and the values are within the permissible limits (±0.5). Proceedings of the reactions were monitored by using TLC with silica gel-G. Petroleum ether and ethylacetate were used as irrigant and spots were visualized with iodine.

Synthesis of 2-chloro-3-formylbenzo(h)quinoline (1a): 2-Chloro-3-formylbenzo(h)quinoline was synthesized by Vilsmeir-Haack reaction of N-acyl-1-napthylamine with $POCl_3$/DMF[11a, 11b].



Scheme-I

1a. $R_1 = R_2 = H$; $R_3, R_4 = —CH=CH—CH=CH—$

1b. $R_1 = C_6H_5$; $R_2 = Cl$; $R_3 = R_4 = H$

c. $R_1 = R_2 = R_5 = R_6 = —H$; $R_3, R_4 = —CH=CH—CH=CH—$;

d. $R_1 = R_2 = R_5 = R_6 = H$; $R_3, R_4 = —CH=CH—CH=CH—$, $R_7 = —OCH_3$

e. $R_1 = R_2 = R_5 = R_6 = H$; $R_3, R_4 = —CH=CH—CH=CH—$; $R_7 = —CH_3$

f. $R_1 = R_2 = R_5 = R_7 = —H$; $R_3, R_4 = —CH=CH—CH=CH—$, $R_6 = —CH_3$

g. $R_1 = R_2 = R_6 = R_7 = H$; $R_3, R_4 = —CH=CH—CH=CH—$, $R_5 = —CH_3$,

h. $R_1 = R_2 = R_6 = —H$; $R_3, R_4 = —CH=CH—CH=CH—$, $R_5 = —CH_3$, $R_7 = CH_3$

i. $R_1 = R_2 = R_5 = R_6 = —H$; $R_3, R_4 = —CH=CH—CH=CH—$, $R_7 = —Cl$

j. $R_1 = R_2 = R_5 = H$; $R_3, R_4 = —CH=CH—CH=CH— = R_6, R_7$

k. $R_1 = —C_6H_5$; $R_2 = —Cl$; $R_3 = R_4 = R_5 = R_6 = R_7 = —H$

l. $R_1 = C_6H_5$; $R_2 = —Cl$; $R_3 = R_4 = R_5 = R_6 = H$; $R_7 = —OCH_3$

m. $R_1 = C_6H_5$; $R_2 = —Cl$; $R_3 = R_4 = R_5 = R_6 = H$; $R_7 = —CH_3$

Synthesis of 2,6-dichloro-3-formyl-4-phenylquinoline (1b): 2-Chloro-3-vinyl-4-phenyl-2-quinoline[12] was oxidized with alkaline $KMnO_4$ to give *cis*-diol. The *cis*-diol of the vinyl compound was then subjected to $NaIO_4$ oxidation[13] to obtain 2-chloro-3-formyl-4-phenylquinoline.

Synthesis of Schiff bases 12(c–m): Schiff base **2** was synthesized by refluxing equimolar mixture of aldehyde **1** (0.01 lmol) and aniline (0.01 mol) in 20 mL of dry methanol for 6 h. After completion of the reaction, the reaction mixture was washed with petroleum ether. The solid product obtained was column chromatographed over silica gel with petroleum ether : ethyl acetate (98 : 2) as eluant. The product obtained was recrystallized from methanol. (Table-1)

TABLE-1
SPECTRAL AND ANALYTICAL DATA OF COMPOUNDS **2(c–m)**

Compound	m.p. (°C)[a] (Yield %)	Elemental analysis, found (calculated) (%)			IR (cm^{-1})
		Carbon	Hydrogen	Nitrogen	
2c	123 (88)	75.77 (75.83)	4.09 (4.14)	8.84 (8.86)	1620 (C=N) 1026 (C—Cl)
2d*	136 (73)	72.20 (76.60)	4.31 (4.36)	8.00 (8.01)	1618 (C=N) 1056 (C—Cl)
2e	140 (80)	76.19 (76.26)	4.52 (4.57)	8.41 (8.46)	1610 (C=N) 1033 (C—Cl)
2f	144 (80)	76.10 (76.19)	4.52 (4.57)	8.41 (8.46)	1605 (C=N) 1056 (C—Cl)
2g	138 (71)	76.10 (76.19)	4.52 (4.51)	8.41 (8.46)	1618 (C=N) 1056 (C—Cl)
2h	128 (80)	76.57 (76.63)	4.71 (4.91)	8.07 (8.12)	1622 (C=N) 1050 (C—Cl)
2i	114 (65)	72.59 (72.62)	4.31 (4.36)	8.00 (8.08)	1610 (C=N) 1050 (C—Cl)
2j	132 (73)	78.51 (78.15)	4.12 (4.65)	7.58 (7.60)	1618 (C=N) 1050 (C—Cl)
2k	182 (50)	70.40 (70.04)	3.50 (3.74)	7.35 (7.42)	1616 (C=N) 1035 (C—Cl)
2l	162 (50)	67.64 (67.82)	3.54 (3.96)	6.80 (6.88)	1618 (C=N) 1022 (C—Cl)
2m	165 (50)	70.05 (70.59)	4.01 (4.12)	6.98 (7.15)	1618 (C=N) 1022 (C—Cl)

a: Recrystallized from methanol;
*^{1}H NMR ($CDCl_3$), 2d: δ 3.8 (S, 3H, —OCH_3); δ 7.4–9.8 (m, 12H, ArH, CH-methine proton)

Synthesis of 2-[3-(2-chloro-benzo(h)quinolinyl)]-3-(4′-methoxy phenyl)-4-thiazolidinones 3(c–m): A mixture of Schiff base **2** (0.01 mol) and mercaptoacetic acid (0.01 mol) was refluxed in dry benzene for 12–14 h. Then the reaction mixture was washed with 10% $NaHCO_3$ solution. The benzene layer thus separated on evaporation gave a pale brown solid which on column chromatography over silica gel with petroleum ether : ethyl acetate (96 : 4) mixture gave a white compound. The product was recrystallized from petroleum ether (Table-2).

TABLE-2
SPECTRAL AND ANALYTICAL DATA OF COMPOUNDS **3(c–m)**

Compound	m.p. (°C)[a] (Yield %)	Elemental analysis, found (calculated) (%)			IR (cm^{-1})
		Carbon	Hydrogen	Nitrogen	
3c	92 (58)	67.49 (67.60)	3.82 (3.87)	7.12 (7.16)	1614 (C=O) 1056 (C—Cl) 750 (C—S—C)
3d*	89 (70)	68.15 (65.62)	3.60 (4.07)	6.62 (6.66)	1685 (C=O) 750 (C—S—C)
3e	86 (57)	68.80 (68.82)	4.20 (4.23)	6.65 (6.92)	1680 (C=O) 750 (C—S—C)
3f	83 (56)	68.80 (68.82)	4.20 (4.23)	6.87 (6.92)	1685 (C=O) 748 (C—S—C)
3g	83 (56)	68.80 (68.17)	4.20 (4.3)	6.87 (6.92)	1685 (C=O) 748 (C—S—C)
3h	81 (58)	68.70 (68.81)	4.50 (4.57)	6.65 (6.69)	1680 (C=O) 748 (C—S—C)
3i	76 (68)	64.50 (64.90)	3.50 (3.32)	6.54 (6.59)	1685 (C=O) 752 (C—S—C)
3j	106 (58)	70.41 (70.50)	4.21 (4.50)	6.25 (6.32)	1690 (C=O) 754 (C—S—C)
3k	119 (48)	63.35 (63.86)	3.48 (3.57)	7.25 (7.43)	1716 (C=O) 750 (C—S—C)
3l	115 (35)	64.35 (64.37)	3.68 (4.11)	6.95 (7.01)	1690 (C=O) 752 (C—S—C)
2m	123 (50)	62.0 (62.23)	3.68 (4.11)	6.95 (7.01)	1716 (C=O) 750 (C—S—C)

a: Recrystallized from $CHCl_3$ and petroleum ether.
*^{1}H NMR ($CDCl_3$) 3d: δ (6.6–9.6) (m, 12H, C_2-H, Ar—H), δ 4.0 (dd, J = 16.2 Hz, 2H, C_5-H), 3.67 (S, 3H, OCH_3) 3m: δ 2.3 (S, 3H 4′ —CH_3), δ 6–9 (m, 13H, Ar—H, C_2H).

Antibacterial Activity: Antibacterial activity of the compounds was determined by agar diffusion technique[14]. The bacterial cells were swabbed onto a nutrient agar medium. [prepared from NaCl (5.0 g), peptone (5.0 g), beef extract (3.0 g), yeast extract powder (3.0 g), agar (20.0 g) in 100 mL of distilled water, pH = 7.5 ± (0.02)] in petriplates. The compounds to be tested were dissolved in chloroform to a final concentration of 25 μg/mL, 50 μg/mL, 100 μg/mL and soaked in filter paper discs of 5 mm diameter and 1 mm in thickness. These discs were placed on the already seeded plates and incubated at 35 ± 2°C for 24 h. Streptomycin was used as standard. The zone, of inhibition around the disc were measured after 24 h (Table-3)

TABLE-3
ANTIBACTERIAL ACTIVITY

Compound	Diameter inhibition zone in mm											
	Vibrio cholerae (μg/mL)			*Pseudomonas aeruginosa* (μg/mL)			*Salmonella* species (μg/mL)			*Escherichia coli* (μg/mL)		
	25	50	100	25	50	100	25	50	100	25	50	100
1a	7	6	7	6	6	7	6	7	6	7	7	6
3d	8	7	7	8	7	7	7	8	6	8	8	6
3f	8	6	6	8	8	7	—	—	—	7	6	6
3l	7	8	7	8	8	7	6	7	8	6	7	7
Streptomycin (Standard)	12	15	17	10	14	18	14	17	20	9	12	17

RESULTS AND DISCUSSION

The hitherto unknown thiazolidinone derivatives were prepared from the aldehydes **1a** and **1b** *via* Schiff bases. An equimolar mixture of 2-chloro-3-formylbenzo(h)quinoline **(1a)** and *p*-methoxy aniline in dry methanol was refluxed for 6 h, followed by usual work upto give a product of yield 87% with m.p. 127°C. IR spectrum of the compound showed bands at 1618 cm^{-1} (>C=N—) group and 1033 cm^{-1} (C—Cl) group with disappearance of a peak at 1685 cm^{-1} (>C=O—) group. ^1H NMR spectrum showed signals at δ 3.8 (S, 3H, —OCH_3); δ 7.4–9.8 (m, 12H, ArH, CH— methine proton). Thus the compound was identified as N-(4′-methoxy phenyl)-2-chloroquinolin-3-yl azomethine **(2d)**. The above reaction sequence was then extended to synthesize the compounds **2(c–m).**

Cyclocondensation of Schiff base **2d** (0.01 mol) and mercaptoacetic acid (0.01 mol) in dry benzene, after usual work up and on purification, furnished a compound which melts at 89°C. The yield was 70.0%. IR spectrum of compound showed bands at 1685 cm^{-1} ν(>C=O) group, 750 cm^{-1} ν(C—S—C) group and 1052 cm^{-1} ν(C—Cl) group . ^1H NMR spectrum showed signals at δ 6.6–9.6 (m, 12 H, C_2H, ArH), δ 4.0 (dd, J = 16.2 Hz, 2H, C_5-H), δ 3.6 (s, 3H, —OCH_3). Mass spectrum showed peaks at m/z 421(M), 423 (M + 2). The elemental analysis showed the molecular formula to be ($C_{23}H_{15}N_2O_2ClS$) Thus the compound was identified as 2-[3-(2-chlorobenzo(h)qunolinyl)]-3-(4′-methoxy phenyl)-4-thiazolidinone **(3d)**. The above reaction sequence was then extended to synthesize compounds **3(c–m)**.

Antibacterial activity: The compounds **1a, 3d, 3f** and **3l** were tested *in vitro* for their antibacterial activity against *Vibrio cholerae, Pseudomonas aeruginosa, Salmonella* species, *Escherichia coli* at various concentrations such as 25 μg/mL, 50 μg/mL and 100 μg/mL. The activities of the compounds were compared with the standard streptomycin under identical conditions. From Table-3, it was concluded that the compound 2-chloro-3-formyl benzo(h)quinoline **(1a)** showed moderate activity. The compound 2[-3-(2-chlorobenzo[h]quinolinyl)-3-(4′-methyl

phenyl)-4-thiazolidinone (**3f**) was active against *Vibrio cholerae, Pseudomonas aeroginosa, Escherichia coli* but inactive towards *Salomonella* species.

The compound 2-[3-(2-chlorobenzo[h]quinolinyl)]-3-(4′-methoxyphenyl)-4 thiazolidinone (**3d**) was active against all species and the activity is more when compared to the compounds **1a** and **3f.** This might be due to the presence of —OCH_3 group in 4′ position of the compound **3d.**

The activity of the compound 2-[3-(2,6-dichloro-4-phenylquinolinyl)-3-(4′-methoxy phenyl)-4-thiazolidinone **3*l*** was good when compared to the compounds such as **1a, 3f** and **3d**. This might be due to the presence of —OCH_3 group at 4′-position as well as a phenyl group at 4-position of the compound **3l**. Though the compounds possess antibacterial activity against various species, none can reach the activity of the standard streptomycin.

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