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Synthesis, characterization and microbial screening of 4-thiazolidinone derivatives of 2,6-dichloro-1-(*N*-substituted phenyl)-1,4-dihydropyridine-3,5-dicarbaldehyde.

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Abstract: A series of new 4-thiazolidinones **5a-f** were prepared by condensation of thioglycolic acid with Schiff bases **4a-f** which in turns have been prepared by the action of amines on 2,6-dichloro-1-(*N*-substituted phenyl)-1,4-dihydropyridine-3,5-dicarbaldehydes **3.** The structures of the newly synthesized compounds have been confirmed on the basis of elemental analysis and spectral studies. The newly synthesized title compounds have been screened for their in *vitro* antimicrobial activities. Some of the compounds exhibited encouraging results.
Keywords:- Dihdropyridines, Schiff bases, 4-thiazolidinones, antimicrobial activity.

Introduction:

Heterocyclic chemistry is of great importance to the medicinal chemists because of their drug utility. Large number of heterocyclic compounds being used as therapeutic agents and these compounds are also essential for the human life. Thiazolidinones and their derivatives are an important group of heterocyclic compounds, having valuable biological activities in the areas of medicine and agriculture[1].

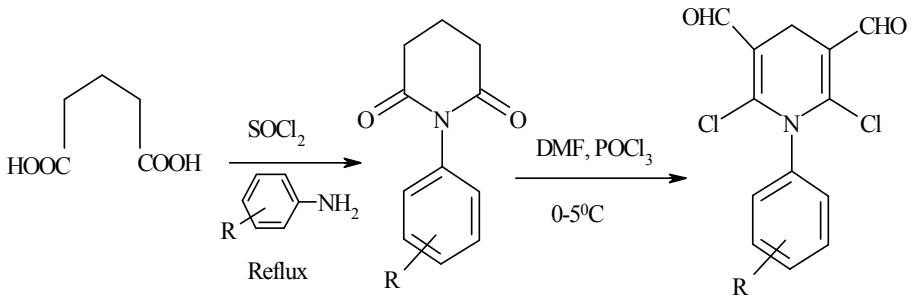
Various substituted 4-thiazolidinone derivatives are associated with diverse pharmacological activities such as antitumor[2,3] antidiabetic[4]. antiparkinsons[5], antiviral[6], anthelminitic[7], anti-inflammatory, anti-proliferative, antihistaminic, anti-HIV[8-10] and antibacterial[11] activities.

Thiazolidinone contain β-lactum ring with sulphar atom and derivatives inhibit the biosynthesis of the peptidoglycan polymer essential for cell wall of bacteria on inactivation of MurB enzyme. MurB enzyme is a unique target for antibacterial activity of thiazolidinone[12]. Various synthetic approaches of 4-thiazolidinones were reported[13,14].

In view of the above and in continuation of our work in the synthesis of fused heterocyclic compounds[15-20], we herein report a new series of Schiff bases **4a-f** and 4-thiazolidinone derivatives **5a-f (Scheme-II).**

Experimental:

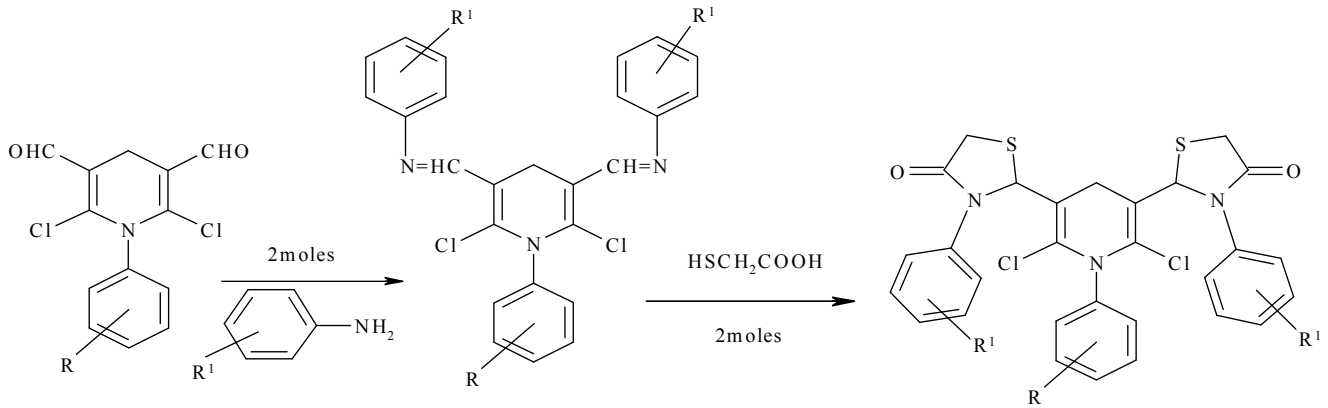
All melting points were determined in open capillary and are uncorrected. The IR spectra were recorded on FT-IR spectrophotometer. ^{1}HNMR spectra were recorded on varian USA Mercury plus 300 MHz NMR spectrometer with DMSO-d_6 as a solvent using TMS as internal reference (chemical shift in δ ppm). The starting compounds were synthesized according to **scheme-I**. Glutaric acid **1** was converted into N-substituted phenyl glutarimides **2a-f** which were then diformylated using Vilsmeier-Haack reaction to form **3a-f.**



1 **2 a-f** **3 a-f**

R, a = -H, b = -4Me, c = -2Cl, d = -4Cl, e = -3Cl, f = -4OMe

Scheme- I.



3 a-f **4 a-f (i), (ii)** **5 a-f (i), (ii)**

R, a = -H, b = - 4Me, c = - 2Cl, d = - 4Cl, e = - 3Cl, f = - 4OMe

R1, (i) = - 4Me
(ii) = - 4Cl

Scheme-II

General procedure for preparation of Schiff bases 4a-f(i),(ii):-

2,6-dichloro-1-(*N*-substituted phenyl)-1,4-dihydropyridine-3,5-dicarbaldehyde **3a-f** (1mmole) was refluxed with two different aromatic primary amines (2mmole) in water bath for 4-5 hours using ethanol as solvent and few drops of glacial acetic acid. The reaction mixture was poured into crushed ice. The product was isolated and recrystalized from ethanol to give **4a-f(i),(ii)** (**Scheme-II**). Physical data of **4a-f(i),(ii)** are given **Table-1**. Characterisation data of these compounds are given in **Table-2**.

Table-1: Physical Data of Compounds 4a-f(i),(ii)

Compound No.	R	R^1	M.F.	M.P. (^{0}C)	Yield (%)
4 a(i)	-H	-4Me	$C_{27}H_{23}N_3Cl_2$	144	50.43
4 b(i)	-4Me	-4Me	$C_{28}H_{25}N_3Cl_2$	152	53.37
4 c(i)	-2Cl	-4Me	$C_{27}H_{22}N_3Cl_3$	110	52.73
4 d(i)	-4Cl	-4Me	$C_{27}H_{22}N_3Cl_3$	102	50.50
4 e(i)	-3Cl	-4Me	$C_{27}H_{22}N_3Cl_3$	126	63.89
4 f(i)	-4OMe	-4Me	$C_{28}H_{25}ON_3Cl_2$	120	71.83
4 a(ii)	-H	-4Cl	$C_{25}H_{17}N_3Cl_4$	140	62.27
4 b(ii)	-4Me	-4Cl	$C_{26}H_{19}N_3Cl_4$	129	53.59
4 c(ii)	-2Cl	-4Cl	$C_{25}H_{16}N_3Cl_5$	116	52.43
4 d(ii)	-4Cl	-4Cl	$C_{25}H_{16}N_3Cl_5$	90	75.84
4 e(ii)	-3Cl	-4Cl	$C_{25}H_{16}N_3Cl_5$	123	58.61
4 f(ii)	-4OMe	-4Cl	$C_{26}H_{19}ON_3Cl_4$	145	60.82

Table-2: Spectral Data of Compounds 4 a-f(i),(ii)

Compd. No.	IR (KBr) cm^{-1}
4a(i)	1596 (C=N), 1491 (ArC=C), 1249 (C-N), 756 (C-Cl), 2922 (CH_3)
4b(i)	1598 (C=N), 1407 (ArC=C), 1512 (ArC=C), 1250 (C-N), 816 (C-Cl), 2924 (CH_3)
4c(i)	1600 (C=N), 1450 (ArC=C), 1248 (C-N), 827 (C-Cl), 2925 (CH_3)
4d(i)	1597 (C=N), 1450 (ArC=C), 1303 (C-N), 827 (C-Cl), 2923 (CH_3)
4e(i)	1593 (C=N), 1470 (ArC=C), 1250 (C-N), 780 (C-Cl), 2924 (CH_3)
4f(i)	1600 (C=N), 1470 (ArC=C), 1247 (C-N), 828 (C-Cl), 1297 (-OCH_3), 2925 (CH_3)
4a(ii)	1612 (C=N), 1491 (ArC=C), 1249 (C-N), 826 (C-Cl)
4b(ii)	1598 (C=N), 1407 (ArC=C), 1250 (C-N), 816 (C-Cl), 2923 (CH_3)
4c(ii)	1595 (C=N), 1442 (ArC=C), 1247 (C-N), 790 (C-N), 827 (C-Cl)
4d(ii)	1597 (C=N), 1450 (ArC=C), 1249 (C-N), 827 (C-Cl)
4e(ii)	1595 (C=N), 1423 (ArC=C), 1248 (C-N), 780 (C-Cl)
4f(ii)	1599 (C=N), 1491 (ArC=C), 1247 (C-N), 1300 (OCH_3), 828 (C-Cl)

General procedure for preparation of 4-thiazolidinones 5a-f(i),(ii):-

The Schiff bases **4a-f(i),(ii)** (1mmole) were refluxed with thioglycolic acid (2mmole) in the presence of catalytic amount of anhydrous $ZnCl_2$ in dry 1,4-dioxane (30 ml) for 7 hours. The mixture was then cooled and poured in to crushed ice and water. The product separated was filtered, dried and recrystallised from ethanol to give **5a-f(i),(ii)** (**Scheme-II**). Physical and elemental analysis data of **5a-f (i),(ii)** are listed in **Table-3.**

Table-3: Physical Data of Compounds 5a-f(i),(ii)

Compound No.	R	R^1	M.F.	M..P. (^{0}C)	Yield (%)	% Found (Calcd.)		
						C	H	N
5a(i)	-H	-4Me	$C_{31}H_{27}O_2N_3S_2Cl_2$	169	83.00	61.10 (61.17)	4.42 (4.47)	6.81 (6.90)
5b(i)	-4Me	-4Me	$C_{32}H_{29}O_2N_3S_2Cl_2$	160	67.96	61.65 (61.73)	4.60 (4.69)	6.68 (6.74)
5c(i)	-2Cl	-4Me	$C_{31}H_{26}O_2N_3S_2Cl_3$	145	43.10	57.85 (57.90)	4.01 (4.07)	6.48 (6.53)
5d(i)	-4Cl	-4Me	$C_{31}H_{26}O_2N_3S_2Cl_3$	135	90.56	57.81 (57.90)	3.97 (4.07)	6.45 (6.53)
5e(i)	-3Cl	-4Me	$C_{31}H_{26}O_2N_3S_2Cl_3$	127	70.75	57.80 (57.90)	4.00 (4.07)	6.49 (6.53)
5f(i)	-4OMe	-4Me	$C_{32}H_{29}O_3N_3S_2Cl_2$	165	78.74	60.02 (60.18)	4.48 (4.57)	6.51 (6.57)
5a(ii)	-H	-4Cl	$C_{29}H_{21}O_2N_3S_2Cl_4$	180	87.59	53.58 (53.63)	3.18 (3.25)	6.40 (6.47)
5b(ii)	-4Me	-4Cl	$C_{30}H_{23}O_2N_3S_2Cl_4$	130	93.04	54.28 (54.31)	3.41 (3.49)	6.27 (6.33)
5c(ii)	-2Cl	-4Cl	$C_{29}H_{20}O_2N_3S_2Cl_5$	138	51.23	50.88 (50.93)	2.89 (2.94)	6.09 (6.14)
5d(ii)	-4Cl	-4Cl	$C_{29}H_{20}O_2N_3S_2Cl_5$	125	75.73	50.90 (50.93)	2.87 (2.94)	6.01 (6.14)
5e(ii)	-3Cl	-4Cl	$C_{29}H_{20}O_2N_3S_2Cl_5$	120	96.32	50.87 (50.93)	2.89 (2.94)	6.08 (6.14)
5f(ii)	-4OMe	-4Cl	$C_{30}H_{23}O_3N_3S_2Cl_4$	135	69.62	49.91 (50.03)	3.36 (3.41)	6.09 (6.18)

2,6-dichloro-3,5-bis(3-P-tolyl-thiazolidin-4-one)-1-(phenyl)-1,4-dihydropyridine 5a(i):-

IR(KBr): 2919 (CH str.), 1684(C=O str.), 755(C-Cl), 697(C-S-C str.), cm^{-1}., ^{1}HNMR(DMSO-d_6): δ 2.32 (s, 6H, 2CH_3), 3.60 (s, 4H, 2CH_2-S), 3.68 (s, 2H, 2N-CH), 7.02-7.62 (m, ArH).

2,6-dichloro-3,5-bis(3-P-tolyl-thiazolidin-4-one)-1-(4-methylphenyl)-1,4-dihydropyridine 5b(i):-

IR(KBr): 2922 (CH str.), 1700 (C=O str.), 817 (C-Cl), 650 (C-S-C str.) cm^{-1}.

2,6-dichloro-3,5-bis(3-P-tolyl-thiazolidin-4-one)-1-(2-chlorophenyl)-1,4-dihydropyridine 5c(i):-

IR(KBr): 2920 (CH str.), 1690 (C=O str.), 780 (C-Cl), 700 (C-S-C str.) cm^{-1}.

2,6-dichloro-3,5-bis(3-P-tolyl-thiazolidin-4-one)-1-(4-chlorophenyl)-1,4-dihydropyridine 5d(i):-

IR(KBr): 2921 (CH str.), 1700 (C=O str.), 818 (C-Cl), 670 (C-S-C str.) cm^{-1}.

2,6-dichloro-3,5-bis(3-P-tolyl-thiazolidin-4-one)-1-(3-chlorophenyl)-1,4-dihydropyridine 5e(i):-

IR(KBr): 2923 (CH str.), 1680 (C=O str.), 779 (C-Cl), 688 (C-S-C str.) cm^{-1}.

2,6-dichloro-3,5-bis(3-P-tolyl-thiazolidin-4-one)-1-(4-methoxyphenyl)-1,4-dihydropyridine 5f(i):-

IR(KBr): 2921 (CH str.),1660 (C=O str.),1297 (OCH_3), 826 (C-Cl), 650(C-S-C str.) cm^{-1}.

^{1}HNMR(DMSO-d_6): δ 2.34(s, 6H, 2CH3), 3.67 (s, 4H, 2CH_2-S), 3.77 (s, 2H, 2N-CH), 3.92(s, 3H, OCH_3), 7.02-8.00 (m, ArH).

2,6-dichloro-3,5-bis[3-(4-chloro-phenyl)-thiazolidin-4-one]-1-(phenyl)-1,4-dihydropyridine 5a(ii):-

IR(KBr): 2921 (CH str.), 1690 (C=O str.), 755 (C-Cl), 694 (C-S-C str.) cm^{-1}.

^{1}HNMR(DMSO-d_6): δ 3.50 (s,4H, 2CH_2-S), 3.64 (s, 2H, 2N-CH), 7.01-7.54 (m, Ar-H).

2,6-dichloro-3,5-bis[3-(4-chloro-phenyl)-thiazolidin-4-one]-1-(4-methylphenyl)-1,4-dihydropyridine 5b(ii):-

IR(KBr): 2922 (CH str.), 1690 (C=O str.), 817 (C-Cl), 650 (C-S-C str.) cm^{-1}.

^{1}HNMR(DMSO-d_6): δ 2.40 (s, 3H, CH_3), 3.57 (s, 4H, $2CH_2$-S), 3.65 (s, 2H, 2N-CH), 6.91-7.60 (m, ArH).

2,6-dichloro-3,5-bis[3-(4-chloro-phenyl)-thiazolidin-4-one]-1-(2-chlorophenyl)-1,4-dihydropyridine 5c(ii):-

IR(KBr): 2920 (CH str.), 1672 (C=O str.), 755 (C-Cl), 696 (C-S-C str.) cm^{-1}.

2,6-dichloro-3,5-bis[3-(4-chloro-phenyl)-thiazolidin-4-one]-1-(4-chlorophenyl)-1,4-dihydropyridine 5d(ii):-

IR(KBr): 2923 (CH str.), 1689 (C=O str.), 827 (C-Cl), 765 (C-S-C str.) cm^{-1}.

^{1}HNMR(DMSO-d_6): δ 3.66(s, 4H, $2CH_2$-S), 3.69(s, 2H, 2N-CH), 7.26-7.76(m, ArH).

2,6-dichloro-3,5-bis[3-(4-chloro-phenyl)-thiazolidin-4-one]-1-(3-chlorophenyl)-1,4-dihydropyridine 5e(ii):-

IR(KBr): 2922 (CH str.), 1690 (C=O str.), 780 (C-Cl), 690 (C-S-C str.) cm^{-1}.

2,6-dichloro-3,5-bis[3-(4-chloro-phenyl)-thiazolidin-4-one]-1-(4-methoxyphenyl)-1,4-dihydropyridine 5f(ii):-

IR(KBr): 2921 (CH str.),1680 (C=O str.),1299(OCH_3), 828 (C-Cl), 680 (C-S-C str.) cm^{-1}.

Antimicrobial activity:-

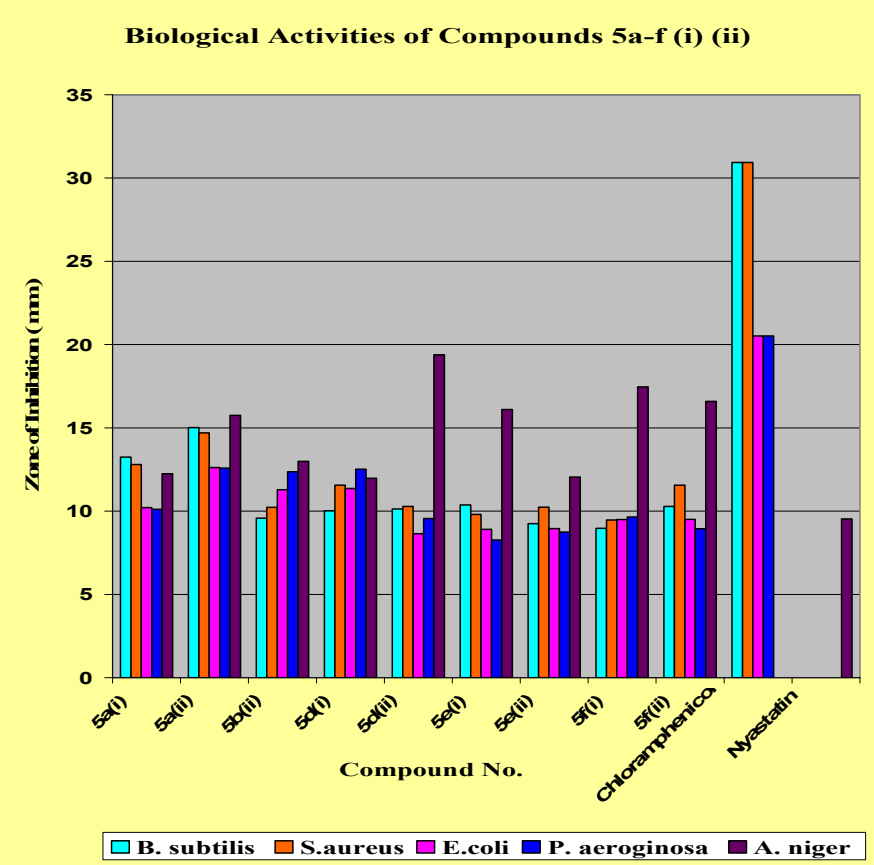
The compounds **5a-f (i),(ii)** were screened for their in vitro antimicrobial activities against *B. subtilis, E. coli, S. aureus, P.aeroginosa* and *A. niger*. The agar diffusion assay (Well method, Disc size 6mm, Hi media) was used. The compounds were tested at the concentration of 100µg/ml in DMF. The results were compared with respective standards Chloramphenicol and Nystatin.

The antimicrobial study revealed that the compound **5f(i)** found to be less active against *B. subtilis*. The compounds **5d (ii), 5e (i)** and **5e (ii)** showed poor activity against *E. coli*. The compounds **5e(i), 5e(ii)** and **5f(ii)** showed poor inhibition against *P.aeroginosa*. On the other hand the compound **5a(ii)** showed good antibacterial activity against *B. Subtilis, S. aureus, E. coli* and *P.aeroginosa*. It is interesting to note that, all the compounds **5a-f (i)** and **5a-f(ii)** are found more potent than standard against *A. niger* **(Table-4).**

Table-4:Results of antimicrobial activity of the compounds 5a-f(i),(ii)

Compound	*B. subtilis*	*S.aureus*	*E.coli*	*P. aeroginosa*	*A. niger*
5a(i)	13.24	12.80	10.21	10.11	12.25
5a(ii)	15.02	14.70	12.62	12.58	15.75
5b(ii)	9.58	10.23	11.29	12.36	12.99
5d(i)	10.02	11.56	11.36	12.52	11.97
5d(ii)	10.13	10.28	8.64	09.56	19.39
5e(i)	10.37	9.80	8.91	8.26	16.10
5e(ii)	9.25	10.24	8.95	8.74	12.05
5f(i)	8.97	9.47	9.49	9.65	17.46
5f(ii)	10.28	11.56	9.50	8.94	16.59
Chloramphenicol (10 mcg/disc)	30.94	30.94	20.52	20.52	NA
Nyastatin (100 U/ml)	NA	NA	NA	NA	9.53

Diameter in mm calculated by digital Vernier Caliper.
"-" means no zone of inhibition, NA "Not Applicable"



Results and Discussion:

From the reports, by realizing the importance of 4-thiazolidinone derivatives, we wanted to develop an innovative synthesis of 4-thiazolidinone derivatives from 2,6-dichloro-1-(*N*-substituted phenyl)-1,4-dihydropyridine-3,5-dicarbaldehyde.

As a results of our studies related to the development of synthetic protocols, we report here a novel and easy access to 4-thiazolidinone derivatives. In this work initially Schiff bases **4a-f(i)** and **4a-f(ii)** were synthesized by treating 2-moles of substituted aromatic primary amines with 1 mole of Vilsmeier-Haack product **3a-f** which on cyclocondensation with 2-moles of thioglycolic acid afforded corresponding 4-thiazolidinone derivatives **5a-f(i)** and **5 a-f(ii) (Scheme-II).**

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