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Research Article

SYNTHESIS AND CHARACTERIZATION OF 2,6-DICHLORO-1-(N-SUBSTITUTED PHENYL)-1,4-DIHYDROPYRIDINE-3,5-DICARBALDEHYDES AND THEIR TRANSFORMATION INTO EFFECTIVE ANTIFUNGAL 4-THIAZOLIDINONE DERIVATIVES

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ABSTRACT

A series of new 4-thiazolidinones **5a-f** were prepared by condensation of thiolactic 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

The therapeutic problem has achieved increasing importance in hospitalized patients, in immuno suppressed patients with AIDS or undergoing anticancer therapy and organ transplants. In spite of a large number of antibiotics and chemotherapeutics available for medicinal use, at the same time the emergence of old and new antibiotic resistance created in the last decades a substantial medical need for new classes of antibacterial agents. A potential approach to overcome the resistance problem is to design innovative agents with a different mode of action so that no cross-resistance with the present therapeuticals can occur[1].

Various substituted 4-thiazolidinone derivatives are associated with diverse pharmacological activities such as antifungal[2], antithyroid[3], local anaesthetic[4], monoamine oxidase inhibition[5] antihyperglycemic[6], anticancer[7], diuretic[8], nematocidal[9], anticonvulsant[10] and antitubercular activity against M. tuberculosis $H_{37}Rv$[11]. More recently, an improved protocol has been reported wherein zinc chloride is used as a dehydrating agent to accelerate the intramolecular cyclization resulting in faster reaction and improved yield[12,13]. The zinc chloride mediated protocol has the advantage of mild reaction conditions, a very short reaction time, and product formation in almost quantitative yields.

In view of the above and in continuation of our work in the synthesis of fused heterocyclic compounds[14-19], we herein report a new series of Schiff bases **4a-f** and substituted 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.**

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

2,6-dichloro-1-(*N*-substituted phenyl)-1,4-dihydropyridine-3,5-dicarbaldehyde (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**.(**Scheme-II**). Physical data of 4a-f(i),(ii) are given **Table-1**. Characterisation data of these compounds are given in **Table-2**.

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

The Schiff bases **4a-f** (1mmole) were refluxed with thiolactic acid (2mmole) in the presence of catalytic amount of anhydrous $ZnCl_2$ in dry 1,4-dioxane (30 ml) for 6 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**.(**Scheme-II**). Physical and elemental analysis data of **5a-f (i),(ii)** are listed in **Table-3.**

4-thiazolidinone 5a (i)

IR(KBr): 2921 (CH str.), 1700 (C=O str.), 827 (C-Cl), 750 (C-S-C str.) cm^{-1}.

^{1}HNMR(DMSO-d_6): δ 1.48 (d, 6H, J=9.0 Hz, $2CH_3$), 2.45 (s, 6H, $2CH_3$), 3.14 (s, 2H, CH_2), 4.1 (q, 2H, J=9.0 Hz, 2CH), 5.39 (s, 2H, 2N-CH), 7.01-6.44 (m, 5H, ArH), 7.16-7.03 (m, 8H, ArH).

4-thiazolidinone 5b (i)

IR(KBr): 2918 (CH str.), 1655 (C=O str.), 816 (C-Cl), 714 (C-S-C str.).cm^{-1}.

^{1}HNMR(DMSO-d_6): δ 1.52 (d, 6H, J=9.0 Hz, $2CH_3$), 2.40 (s, 9H, $3CH_3$), 3.00 (s, 2H, CH_2), 4.0 (q, 2H, J=9.0 Hz, 2CH), 5.40 (s, 2H, 2N-CH), 6.89-6.43 (m, 4H, ArH), 7.15-6.99 (m, 8H, ArH).

4-thiazolidinone 5c (i)

IR(KBr): 2920 (CH str.), 1680 (C=O str.), 795 (C-Cl), 753 (C-S-C str.).cm^{-1}.

^{1}HNMR(DMSO-d_6): δ 1.57 (d, 6H, J=9.0 Hz, $2CH_3$), 2.42 (s, 6H, $2CH_3$), 2.98 (s, 2H, CH_2), 3.97 (q, 2H, J=9.0 Hz, 2CH), 5.31 (s, 2H, 2N-CH), 7.02-6.50 (m, 4H, ArH), 7.17-7.04 (m, 8H, ArH).

4-thiazolidinone 5d (i)

IR(KBr): 2924 (CH str.), 1675 (C=O str.), 800 (C-Cl), 750 (C-S-C str.).cm^{-1}.

^{1}HNMR(DMSO-d_6): δ 1.49 (d, 6H, J=9.0 Hz, $2CH_3$), 2.40 (s, 6H, $2CH_3$), 3.09(s,2H,CH_2), 4.0 (q, 2H, J=9.0 Hz, 2CH), 5.21 (s, 2H, 2N-CH), 7.02-6.42 (m, 4H, ArH),7.18-7.03 (m, 8H, ArH).

4-thiazolidinone 5e (i)

IR(KBr): 2919 (CH str.), 1660 (C=O str.), 777 (C-Cl), 684 (C-S-C str.).cm^{-1}.

^{1}HNMR(DMSO-d_6): δ 1.50 (d, 6H, J=9.0 Hz, $2CH_3$), 2.38 (s, 6H, $2CH_3$), 3.01(s, 2H, CH_2), 4.3 (q, 2H, J=9.0 Hz, 2CH), 5.27 (s, 2H, 2N-CH), 6.97-6.38 (m, 4H, ArH), 7.14-6.98 (m, 8H, ArH).

4-thiazolidinone 5f (i)

IR(KBr):2921 (CH str.), 1695 (C=O str.),1294 (OCH_3), 829 (C-Cl), 690 (C-S-C str.)cm^{-1}.

^{1}HNMR(DMSO-d_6): δ 1.54 (d, 6H, J=9.0 Hz, $2CH_3$), 2.36 (s, 6H, $2CH_3$), 2.96 (s, 2H, CH_2), 3.78 (s, 3H, OCH_3), 3.99 (q, 2H, J=9.0 Hz, 2CH), 5.32 (s, 2H, 2N-CH), 6.92-6.49 (m, 4H, ArH), 7.17-7.10 (m, 8H, ArH).

4-thiazolidinone 5a (ii)

IR(KBr): 2923 (CH str.), 1680 (C=O str.), 759 (C-Cl), 694 (C-S-C str.) cm^{-1}.

^{1}HNMR(DMSO-d_6): δ 1.46 (d, 6H, J=9.0 Hz, $2CH_3$), 3.11 (s, 2H, CH_2), 4.2 (q, 2H, J=9.0 Hz, 2CH), 5.0 (s, 2H, 2N-CH), 7.03-6.56 (m, 5H, ArH), 7.37-7.04 (m, 8H, ArH).

LC-MS [ESI] m/z (%) : 677 (48), 393 (100), 357(31).

4-thiazolidinone 5b (ii)

IR(KBr): 2922 (CH str.), 1690 (C=O str.), 814 (C-Cl), 690 (C-S-C str.) cm^{-1}.

^{1}HNMR(DMSO-d_6): δ 1.49 (d, 6H, J=9.0 Hz, $2CH_3$), 2.35 (s, 3H, CH_3), 3.07 (s, 2H, CH_2), 3.97 (q, 2H, J=9.0 Hz, 2CH), 5.34 (s, 2H, 2N-CH), 7.00-6.49 (m, 4H, ArH), 7.39-7.06 (m, 8H, ArH).

4-thiazolidinone 5c (ii)

IR(KBr): 2924 (CH str.), 1660 (C=O str.), 780 (C-Cl), 696 (C-S-C str.).cm^{-1}.

^{1}HNMR(DMSO-d_6): δ 1.46 (d, 6H, J=9.0 Hz, $2CH_3$), 3.0 (s, 2H, CH_2), 4.2 (q, 2H, J=9.0 Hz, 2CH), 5.10 (s, 2H, 2N-CH), 7.03-6.54 (m, 4H, ArH), 7.40-7.09 (m, 8H, ArH).

4-thiazolidinone 5d (ii)

IR(KBr): 2926 (CH str.), 1668 (C=O str.), 826 (C-Cl), 690 (C-S-C str.) cm^{-1}.

^{1}HNMR($CDCl_3$): δ 1.50 (d, 6H, J=9.0 Hz, $2CH_3$), 2.55(s, 2H, CH_2), 4.0 (q, 2H, J=9.0 Hz, 2CH), 5.35 (s, 2H, 2N-CH), 7.28-7.01 (m, 4H, ArH), 7.87-7.30 (m, 8H, ArH).

4-thiazolidinone 5e (ii)

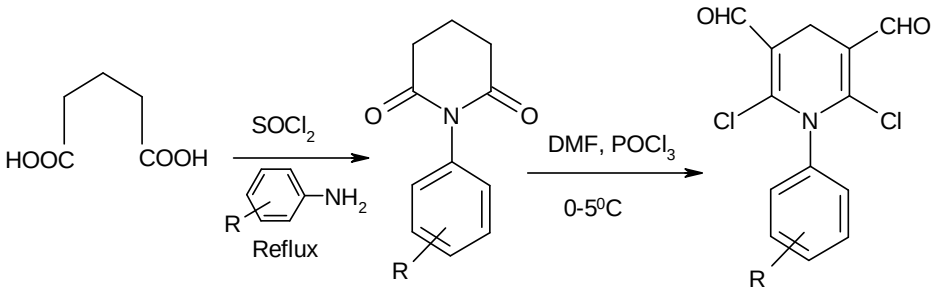
IR(KBr): 2922 (CH str.), 1700 (C=O str.), 780 (C-Cl), 683 (C-S-C str.).cm^{-1}.

^{1}HNMR(DMSO-d_6): δ 1.47 (d, 6H, J=9.0 Hz, $2CH_3$), 2.88 (s, 2H, CH_2), 4.3 (q, 2H, J=9.0 Hz, 2CH), 5.32 (s, 2H, 2N-CH), 7.01-6.50 (m, 4H, ArH), 7.32-7.04 (m, 8H, ArH).

4-thiazolidinone 5f (ii)

IR(KBr): 2922 (CH str.), 1695 (C=O str.), 1299(OCH_3), 828 (C-Cl), 690 (C-S-Cstr.).cm^1.

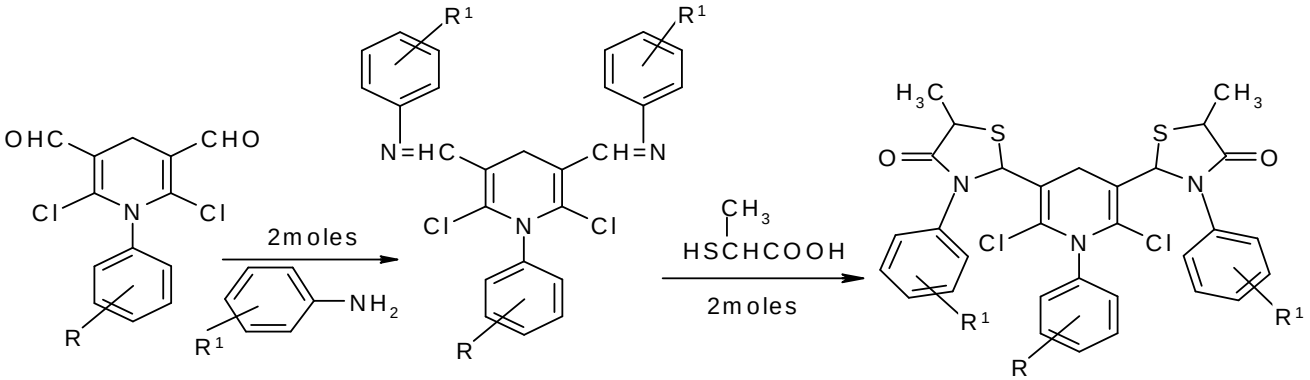
^{1}HNMR(DMSO-d_6): δ 1.48 (d, 6H, J=9.0 Hz, $2CH_3$), 3.13 (s, 2H, CH_2), 3.79 (s, 3H, OCH_3), 3.97 (q, 2H, J=9.0 Hz, 2CH), 5.38 (s, 2H, 2N-CH), 7.05-6.67 (m, 4H, ArH), 7.41-7.12 (m, 8H, ArH).



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

R^1, (i) = - 4Me
(ii) = - 4Cl

Scheme-II

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 microbial screening results of 4-thiazolidinone derivatives 5a-f(i) and 5a-f(ii) revealed that the compound 5b(ii) showed good antibacterial activity against B.subtilis and S.aureus. The compounds 5a(i), 5b(i) and 5d(ii) showed better activity against E. coli and P.aeroginosa.

On the other hand, all the compounds 5a-f(i) and 5a-f (ii) demonstrated an excellent activity against A. niger. The compounds 5a(i), 5a(ii), 5b(i), 5b(ii), 5d(ii), 5e(ii) and 5f(ii) are found more potent than standard against A. niger.(**Table-4**)

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 thiolactic acid afforded corresponding 4-thiazolidinone derivatives 5a-f(i) and 5 a-f(ii) (Scheme-II).

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

Compound No.	R	R^1	M.F.	M.P. (°C)	Yield (%)
4 a(i)	-H	-4Me	$C_{27}H_{23}N_3Cl_2$	143-145	65
4 b(i)	-4Me	-4Me	$C_{28}H_{25}N_3Cl_2$	149-151	72
4 c(i)	-2Cl	-4Me	$C_{27}H_{22}N_3Cl_3$	109-111	62
4 d(i)	-4Cl	-4Me	$C_{27}H_{22}N_3Cl_3$	101-103	78
4 e(i)	-3Cl	-4Me	$C_{27}H_{22}N_3Cl_3$	125-127	85
4 f(i)	-4OMe	-4Me	$C_{28}H_{25}ON_3Cl_2$	119-121	72
4 a(ii)	-H	-4Cl	$C_{25}H_{17}N_3Cl_4$	139-141	62
4 b(ii)	-4Me	-4Cl	$C_{26}H_{19}N_3Cl_4$	128-130	54
4 c(ii)	-2Cl	-4Cl	$C_{25}H_{16}N_3Cl_5$	115-117	52
4 d(ii)	-4Cl	-4Cl	$C_{25}H_{16}N_3Cl_5$	89-91	76
4 e(ii)	-3Cl	-4Cl	$C_{25}H_{16}N_3Cl_5$	122-124	59
4 f(ii)	-4OMe	-4Cl	$C_{26}H_{19}ON_3Cl_4$	144-146	61

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

Compd. No.	IR (KBr) cm^{-1}
4a(i)	2922 (CH_3), 1600 (C=N), 1514 (ArC=C), 1253 (C-N), 756 (C-Cl),
4b(i)	2924 (CH_3), 1598 (C=N), 1512 (ArC=C), 1250 (C-N), 816 (C-Cl).
4c(i)	2925 (CH_3), 1600 (C=N), 1450 (ArC=C), 1248 (C-N), 827 (C-Cl).
4d(i)	2920 (CH_3), 1606 (C=N), 1489 (ArC=C), 1249 (C-N), 815 (C-Cl).
4e(i)	2924 (CH_3), 1593 (C=N), 1470 (ArC=C), 1250 (C-N), 780 (C-Cl).
4f(i)	2924 (CH_3), 1606 (C=N), 1510 (ArC=C),1300 (-OCH_3), 1247 (C-N), 829 (C-Cl).
4a(ii)	1612 (C=N), 1491 (ArC=C), 1249 (C-N), 826 (C-Cl)
4b(ii)	2923 (CH_3), 1598 (C=N), 1407 (ArC=C), 816 (C-Cl), 250 (C-N).
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)

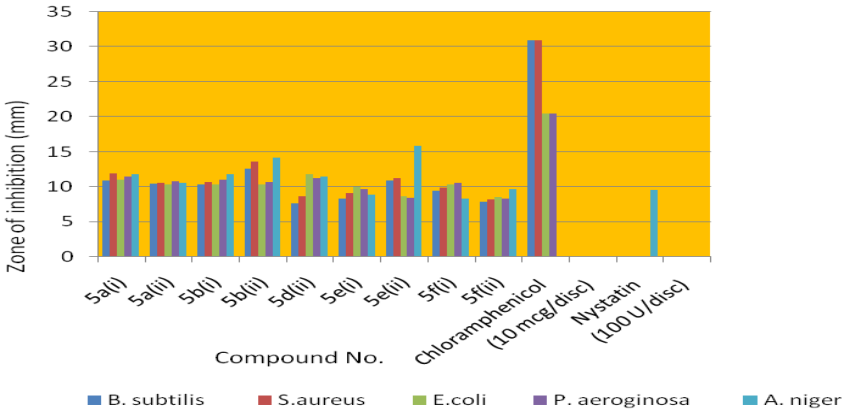
Table 3: Physical Data of Compounds 5a-f(i),(ii)

Compd. No.	R	R^1	M.F.	M..P. (°C)	Yield (%)	% Found (Calcd.)		
						C	H	N
5a(i)	-H	-4Me	$C_{33}H_{31}O_2N_3S_2Cl_2$	169-171	59	62.18 (62.25)	4.81 (4.90)	6.50 (6.60)
5b(i)	-4Me	-4Me	$C_{34}H_{33}O_2N_3S_2Cl_2$	185-187	60	62.68 (62.76)	5.01 (5.11)	6.40 (6.45)
5c(i)	-2Cl	-4Me	$C_{33}H_{30}O_2N_3S_2Cl_3$	121-123	53	58.98 (59.06)	4.42 (4.50)	6.20 (6.26)
5d(i)	-4Cl	-4Me	$C_{33}H_{30}O_2N_3S_2Cl_3$	127-129	53	59.01 (59.06)	4.41 (4.50)	6.18 (6.26)
5e(i)	-3Cl	-4Me	$C_{33}H_{30}O_2N_3S_2Cl_3$	137-139	59	59.03 (59.06)	4.39 (4.50)	6.21 (6.26)
5f(i)	-4OMe	-4Me	$C_{34}H_{33}O_3N_3S_2Cl_2$	114-116	63	61.19 (61.25)	4.89 (4.98)	6.22 (6.30)
5a(ii)	-H	-4Cl	$C_{31}H_{25}O_2N_3S_2Cl_4$	159-161	62	54.87 (54.95)	3.66 (3.71)	6.11 (6.20)
5b(ii)	-4Me	-4Cl	$C_{32}H_{27}O_2N_3S_2Cl_4$	139-141	66	55.51 (55.58)	3.87 (3.93)	5.99 (6.07)
5c(ii)	-2Cl	-4Cl	$C_{31}H_{24}O_2N_3S_2Cl_5$	148-150	58	52.23 (52.30)	3.33 (3.39)	5.82 (5.90)
5d(ii)	-4Cl	-4Cl	$C_{31}H_{24}O_2N_3S_2Cl_5$	134-136	67	52.25 (52.30)	3.32 (3.39)	5.85 (5.90)
5e(ii)	-3Cl	-4Cl	$C_{31}H_{24}O_2N_3S_2Cl_5$	104-106	80	52.21 (52.30)	3.34 (3.39)	5.82 (5.90)
5f(ii)	-4OMe	-4Cl	$C_{32}H_{27}O_3N_3S_2Cl_4$	156-158	77	54.27 (54.32)	3.78 (3.84)	5.86 (5.93)

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)	10.94	11.89	11.01	11.45	11.85
5a(ii)	10.41	10.56	10.39	10.85	10.58
5b(i)	10.32	10.65	10.36	11.02	11.83
5b(ii)	12.63	13.65	10.40	10.69	14.17
5d(ii)	7.66	8.64	11.84	11.26	11.52
5e(i)	8.31	9.12	9.98	9.65	8.92
5e(ii)	10.91	11.27	8.66	8.42	15.87
5f(i)	9.45	9.86	10.30	10.59	8.37
5f(ii)	7.91	8.21	8.57	8.35	9.68
Chloramphenicol (10 mcg/disc)	30.94	30.94	20.52	20.52	NA
Nystatin (100 U/disc)	NA	NA	NA	NA	9.53

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



Biological activities of compounds **5a-f (i), (ii)**

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