Indian Journal of Pharmaceutical Sciences

Scientific Publication of the Indian Pharmaceutical Association

Indexed in Ind MED, EMBASE/Excerpta Medica, International Pharmaceutical Abstracts, Chemical Abstracts.

Volume 69 **Number 5** **September-October 2007**

CONTENTS

Synthesis and Antibacterial Activity of 2-phenyl-3,5-diphenyl (substituted) -6-aryl-3,3a,5,6-tetrahydro-2H-pyrazolo[3,4-d]thiazoles

S. K. SAHU*, S. K. MISHRA, R. K. MOHANTA, P. K. PANDA AND MD. AFZAL AZAM[1]
University Department of Pharmaceutical Sciences, Utkal University, Vani Vihar, Bhubaneswar - 751 004, India,
[1]J. S. S. College of Pharmacy, Ootacamund - 643 001, India

A series of Schiff's bases have been prepared by condensation of substituted benzaldehydes with primary arylamines and the corresponding 4-thiazolidinones have been prepared by the reaction of Schiff's bases with thioglycolic acid in benzene. The resulting 4-thiazolidinones on reaction with substituted benzaldehydes in anhydrous sodium acetate by Knoevenagel's condensation have afforded 2-phenyl(substituted)-3-aryl-5-benzilidine(substituted) thiazolidine-4-ones, which on cyclization with phenyl hydrazine in anhydrous sodium acetate have furnished the title compounds. The structures have been established on the basis of spectral data. All the compounds have been screened *in vitro* for their antibacterial activity. The results of antibacterial activity study revealed promising inhibitory activity for 3,3a,5,6-tetrahydro-2H-pyrazolo[3,4-d] thiazole derivatives with 4-chloro and 4-nitro phenyl substitutions at 5-position against all the tested strains.

Selected substituted thiazoles[1,2] as well as different pyrazole ring containing heterocycles[3,4] possess marked antibacterial activity. The present investigation deals with the development of a series of nitrogen heterocyclic system from easily available starting materials. We report herein the synthesis of 2-phenyl (substituted)-3-aryl-5-benzilidine (substituted) thiazolidine-4-ones (3), their conversion to the title compounds (4) and evaluation of latter for their antibacterial activity.

Melting points were determined in open capillaries and were uncorrected. Purity of the compounds was checked by TLC on silica gel G plates. IR spectra (KBr) were recorded on a Jasco FTIR 410

***For correspondence**
E-mail: tutu_kh@yahoo.com

spectrophotometer (vmax). ^{1}H NMR spectra ($CDCl_3$) were taken on a Bruker DRX 300-MHz spectrometer using TMS as an internal standard (chemical shifts in δ ppm). Elemental analysis (C, H, N) was carried out on a Euro EA (Italy) analyser. Schiff's bases (I) and the corresponding 4-thiazolidinones (2) were prepared according to literature method[5].

2-Phenyl (substituted)-3-aryl-5-benzilidine (substituted)-thiazolidine-4-ones (3)[6] were synthesized by refluxing an equimolar mixture (0.001 mol) of compound (2) and substituted benzaldehydes with anhydrous sodium acetate (0.082 g) in glacial acetic acid (20 ml) for 3 h. The reaction mixture was concentrated, cooled and poured into ice cold water. The solid thus separated was filtered, washed with water and crystallized from glacial acetic acid. The physical and elemental analysis data are given in Table 1 and 2, respectively.

$3a_1$: IR(KBr, cm^{-1}): 3285(Ar-OH), 3052 (Ar-CH),1739 (C=O),1542 (Ar-NO_2). b_1: IR (KBr, cm^{-1}): 3294 (Ar-OH), 3045 (Ar-CH), 1736(C=O), 1538 (Ar-NO_2), d_1: IR (KBr, cm^{-1}): 3292 (Ar-OH), 3038 (Ar-CH), 1733 (C=O), 747 (C-Cl). a_2: IR (KBr, cm^{-1}): 3289 (Ar-OH), 3026 (Ar-CH), 1722 (C=O), 754 (C-Cl). d_2: IR (KBr, cm^{-1}): 3049 (Ar-CH), 1746 (C=O),751 (C-Cl). a_3: IR (KBr, cm^{-1}): 3295 (Ar-OH), 3031 (Ar-CH), 1742 (C=O), 742 (C-Cl). C_3: IR (KBr, cm^{-1}): 3064 (Ar-CH),1752 (C=O), 1546 (Ar-NO_2), 759 (C-Cl). b_4: IR (KBr, cm^{-1}): 3068 (Ar-CH), 1756 (C=O), 746 (C-Cl). c_4: IR (KBr, cm^{-1}): 3059 (Ar-CH), 1731 (C=O), 1560 (Ar-NO_2), 745 (C-Cl). d_4: IR (KBr, cm^{-1}): 3071 (Ar-CH),1729 (C=O), 749 (C-Cl). The NMR Spectra of the synthesized compounds (3) of the series revealed peaks around 5.1-5.8 δ (1H, s, C=CH) and 6.5-8.0 δ due to bulk aromatic protons.

2-Phenyl-3,5-diphenyl(substituted)-6-aryl-3,3a,5,6-tetrahydro-2H-pyrazolo-[3,4-d]thiazoles (4)[6] were synthesized by heating under reflux an equimolar (0.001 mol) of compound (3) and phenylhydrazine with anhydrous sodium acetate (0.082 g) in glacial acetic acid (20 ml) for 6 h and cooled to room temperature. The solid thus separated was filtered, washed thoroughly with water and crystallised from glacial acetic acid. The physical and elemental analysis data are given in Tables 3 and 4, respectively.

$4a_1$: IR (KBr, cm^{-1}): 3289 (Ar-OH), 3064(Ar-CH), 1539 (Ar-NO_2), 1671 (C=N), 1266 (C-N); ^{1}HNMR δ: 3.15 (s,1H,CH), 5.84 (s,1H,CH), 6.58-8.74 (m,17H,Ar-H), 11.14(s,1H,OH). b_1: IR (KBr, cm^{-1}): 3290(Ar-OH), 3031(Ar-CH), 1663(C=N), 1539 (Ar-NO_2), 1260(C-N); ^{1}HNMR δ: 1.13 (s.6H,2xCH_3), 2.95(s,1H,CH),5.64(s, 1H,CH), 6.5-9.24(m,17H,Ar-H). d_1: IR (KBr, cm^{-1}): 3284(Ar-OH), 3045 (Ar-CH), 1548 (ArNO_2), 1656 (C=N), 1264 (C-N), 748 (C-Cl); ^{1}HNMR δ: 3.04 (s,1H,CH), 5.78 (s,1H,CH), 6.64-8.78 (m,17H,Ar-H),

TABLE 1: PHYSICAL DATA OF 2-PHENYL-3-ARYL-5-BENZILIDINE (SUBSTITUTED) THIAZOLIDINE-4-ONES

Compound	Substituents			mp(°)	Yield
	Ar	R	R^I		(%)
$3a_1$	4-NO_2 Phenyl	2-OH	2-OH	151	46.34
b_1	4-NO_2 Phenyl	4-$N(CH_3)_2$	2-OH	88	44.05
c_1	4-NO_2 Phenyl	4-NO_2	2-OH	132	25.97
d_1	4-NO_2 Phenyl	4-Cl	2-OH	202	20.06
e_1	4-NO_2-Phenyl	4-OCH_3	2-OH	190	36.74
a_2	4-Cl Phenyl	2-OH	4-$N(CH_3)_2$	108	48
d_2	4-Cl Phenyl	4-Cl	4-$N(CH_3)_2$	118	48
a_3	4-Br Phenyl	2-OH	4-Cl	98	48
c_3	4-Br Phenyl	4-NO_2	4-Cl	88	37
d_3	4-Br Phenyl	4-Cl	4-Cl	130	49
b_4	Naphthyl	4-$N(CH_3)_2$	4-Cl	206	64
c_4	Naphthyl	4-NO_2	4-Cl	99	64
d_4	Naphthyl	4-Cl	4-Cl	83	49
e_4	Naphthyl	4-OCH_3	4-Cl	95	81

TABLE 2: ELEMENTAL ANALYSIS OF 2-PHENYL-3-ARYL-5- BENZILIDINE (SUBSTITUTED) THIAZOLIDINE-4-ONES.

Compound	Molecular formula	C %		H %		N %	
		Calculated	Found	Calculated	Found	Calculated	Found
$3a_1$	$C_{22}H_{16}N_2O_5S$	62.84	62.80	3.83	3.80	6.66	6.64
b_1	$C_{24}H_{21}N_3O_4S$	64.41	64.37	4.73	4.69	9.39	9.37
c_1	$C_{22}H_{15}N_3O_6S$	58.79	58.74	3.36	3.32	9.34	9.32
d_1	$C_{22}H_{15}ClN_2O_4S$	60.20	59.80	3.44	3.40	6.38	6.37
e_1	$C_{23}H_{18}N_2O_5S$	63.58	63.55	4.17	4.14	6.44	6.42
a_2	$C_{24}H_{21}Cl\ N_2O_2S$	65.96	65.92	4.84	4.81	6.41	6.30
d_2	$C_{24}H_{20}Cl_2N_2OS$	63.28	36.24	4.42	4.38	6.14	6.12
a_3	$C_{22}H_{14}BrClNO_2S$	57.84	57.80	3.30	2.9	3.06	3.03
c_3	$C_{22}H_{14}BrClNO_3S$	55.88	55.84	3.19	3.16	2.96	2.95
d_3	$C_{22}H_{14}BrCl_2NOS$	53.71	53.68	2.87	2.84	2.85	2.83
b_4	$C_{28}H_{23}ClN_2OS$	71.39	71.35	4.92	4.88	5.94	5.93
c_4	$C_{26}H_{17}ClN_2O_3S$	66.02	65.09	3.62	6.58	5.92	5.90
d_4	$C_{26}H_{17}Cl_2NOS$	67.52	67.48	3.70	3.30	3.02	3.00
e_4	$C_{27}H_{20}ClNO_2S$	70.01	69.97	4.52	4.48	3.14	3.12

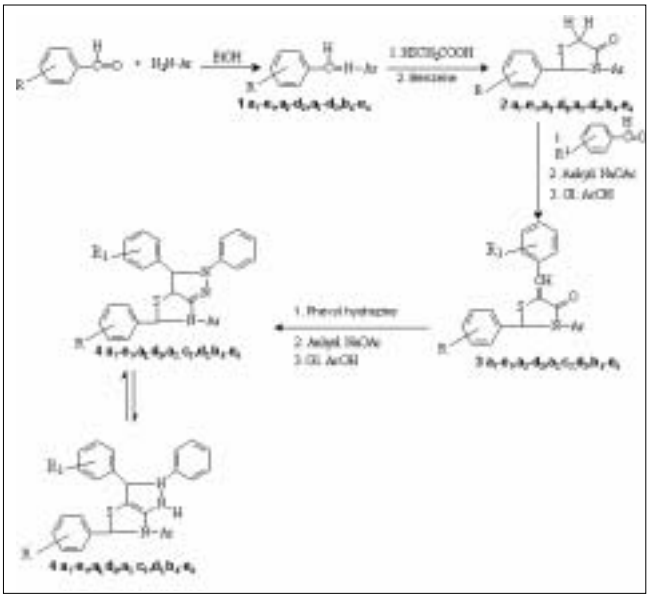
TABLE 3: PHYSICAL DATA OF 2-PHENYL-3,5-DIPHENYL (SUBSTITUTED)-6-ARYL-3,3A, 5,6-TETRAHYDRO-2H-PYRAZOLO [3,4-D] THIAZOLES.

Compound	Substituents			mp(°)	Yield
	Ar	R	R^1		(%)
$4a_1$	4-NO_2Phenyl	2-OH	2-OH	98	99.9
b_1	4-NO_2Phenyl	4-N $(CH_3)_2$	2-OH	138	94.96
c_1	4-NO_2Phenyl	4-NO_2	2-OH	108	95
d_1	4-NO_2Phenyl	4-Cl	2-OH	140	97.1
e_1	4-NO_2Phenyl	4-OCH_3	2-OH	150	99
a_2	4-Cl Phenyl	2-OH	4-N $(CH_3)_2$	242	99.75
d_2	4-Cl Phenyl	4-Cl	4-N $(CH_3)_2$	92	99.7
a_3	4-Br Phenyl	2-OH	4-Cl	121	96.8
c_3	4-Br Phenyl	4-NO_2	4-Cl	105	81.7
d_3	4-Br Phenyl	4-Cl	4-Cl	88	90.74
b_4	Naphthyl	4-N $(CH_3)_2$	4-Cl	87	99.4
c_4	Naphthyl	4-NO_2	4-Cl	160	98.89
d_4	Naphthyl	4-Cl	4-Cl	236	95.5
e_4	Naphthyl	4-OCH_3	4-Cl	120	97.98

10.96 (s,1H,OH). a_2: IR(KBr, cm^{-1}): 3286 (Ar-OH), 3063 (Ar-CH), 1683 (C=N), 1276 (C-N), 751 (C-Cl); ^{1}HNMR δ: 1.40 (s,1H, 2×CH_3), 3.22 (s,1H, CH), 5.75 (s,1H, CH), 5.90-7.97 (m,17H, Ar-CH), 10.99 (s,1H, OH). d_2: IR (KBr, cm^{-1}): 3062 (Ar-CH), 1674 (C=N), 1272 (C-N), 756 (C-Cl); ^{1}HNMR δ: 2.02 (s, 6H, 2×CH_3), 3.19 (s,1H,CH), 5.79 (s,1H,CH), 6.52-8.68 (m,17H,Ar-H). a_3: IR (KBr, cm^{-1}): 3294 (Ar-OH), 3030 (Ar-CH), 1668 (C=N), 1279 (C-N), 755 (C-Cl); ^{1}HNMR δ: 2.17 (s,1H,CH), 5.85 (s,1H,CH), 7.02-9.18 (m,17H,Ar-H), 11.20 (s,1H,OH). c_3: IR (KBr, cm^{-1}): 3076 (Ar-CH), 1672 (C=N), 1552 (Ar-NO_2), 1274 (C-N); ^{1}HNMR δ: 3.06 (s,1H,CH), 5.72 (s,1H,CH), 5.90-7.97 (m,17H,Ar-H). b_4: IR (KBr, cm^{-1}): 3049 (Ar-CH), 1677 (C=N), 1267 (C-N), 744 (C-Cl); ^{1}HNMR δ: 1.98 (s,6H, 2×CH_3), 3.22 (s,1H,CH), 5.85 (s,1H,CH), 6.39-8.88 (m,20H,Ar-H). c_4: IR (KBr, cm^{-1}): 3078 (Ar-OH), 1661 (C=N), 1564 (Ar-NO_2), 1270 (C-N), 743 (C-Cl); ^{1}H NMR δ: 2.22 (s,1H,CH), 5.08 (s,1H,CH), 5.83-8.88 (m,20H,ArH). d_4: IR (KBr, cm^{-1}): 3067 (Ar-CH), 1673 (C=N), 1273 (C-N), 753 (C-Cl); ^{1}HNMR δ: 3.18 (s,1H,CH), 5.82 (s,1H,CH), 6.60-8.81 (m,20H,Ar-H).

No doublet was seen in the NMR spectrum of any of the title compounds, thus indicating that the initial structure got rapid transformation through tautomeric shift of H-atom to the more stable structure as indicated in Scheme 1.

Substituted benzaldehydes on condensation with primary arylamines gave Schiff's bases ($1a_1$-e_1, a_2-d_2, a_3-d_3, b_4-e_4), which on reaction with thioglycolic acid in benzene gave the corresponding 4-thiazolidinone



Scheme 1: Synthetic scheme of title compounds
For 1,2,3,4 a_1-e_1; Ar = 4-NO_2-C_6H_5, a_2-d_2; Ar= 4-Cl-C_6H_5, a_3-d_3; Ar= 4-Br-C_6H_5, b_4-e_4; Ar= Naphthyl. 1,2,3,4 a_{1-3}; R= 2-OH, b_{1-4}; R= 4-N $(CH_3)2$, $_{c1-4}$; R= 4-NO_2, d_{1-4}; R= 4-Cl, e_{1-4}; R= 4-OCH_3. 3,4 a_{1-e1}; R_1= 2-OH, a_2-d_2; R_1= 4-N $(CH_3)2$, a_3-d_3,b4-e_4; R_1= 4-Cl

TABLE 4: ELEMENTAL ANALYSIS OF 2-PHENYL-3,5-DIPHENYL (SUBSTITUTED)-6-ARYL-3,3A,5,6-TETRAHYDRO-2H-PYRAZOLO[3,4-D] THIAZOLES.

Compound	Molecular formula	C %		H %		N %	
		Calculated	Found	Calculated	Found	Calculated	Found
$4a_1$	$C_{28}H_{22}N_4O_4S$	65.86	65.82	4.34	4.30	10.97	10.95
b_1	$C_{30}H_{27}N_5O_3S$	67.02	66.98	5.06	4.96	13.02	13.01
c_1	$C_{28}H_{21}N_5O_5S$	62.32	62.28	3.92	3.89	12.97	12.96
d_1	$C_{28}H_{22}ClN_4O_3S$	68.13	68.10	4.28	4.25	11.35	11.33
e_1	$C_{29}H_{24}N_4O_4S$	66.39	66.35	4.61	4.57	10.67	10.66
a_2	$C_{30}H_{27}ClN_4S$	68.35	68.33	5.16	5.14	10.62	10.60
d_2	$C_{30}H_{26}Cl_2N_4S$	66.03	65.99	4.80	4.50	10.27	10.26
a_3	$C_{28}H_{21}BrClN_3OS$	59.73	59.70	3.76	3.74	7.46	7.44
c_3	$C_{28}H_{20}BrClN_4O_2S$	65.75	65.71	3.01	2.93	3.06	3.05
d_3	$C_{28}H_{20}BrCl_2N_3S$	57.83	57.80	3.46	3.44	7.22	7.20
b_4	$C_{34}H_{29}ClN_4S$	72.76	72.72	5.02	4.17	9.98	9.96
c_4	$C_{32}H_{23}ClN_4O_2S$	68.25	68.21	4.11	4.08	9.94	9.93
d_4	$C_{32}H_{23}Cl_2N_3S$	69.55	69.51	4.19	4.15	7.60	7.59
e_4	$C_{33}H_{26}ClN_3OS$	72.3	72.00	4.78	4.75	7.66	7.64

TABLE 5: ANTIBACTERIAL ACTIVITIES OF 2-PHENYL-3,5-DIPHENYL(SUBSTITUTED)-6-ARYL-3,3A,5,6-TETRAHYDRO-2H-PYRAZOLO [3,4-D] THIAZOLES

Compound	Inhibition zone diameter (mm)*			
	S. a	A. p	E. c	K. a
$4a_1$	18	20	17	19
b_1	19	18	21	20
c_1	17	20	19	18
d_1	19	21	21	22
e_1	17	18	20	19
a_2	19	18	21	20
d_2	21	20	23	22
a_3	19	20	18	21
c_3	20	18	21	19
d_3	21	20	22	24
b_4	17	19	18	20
c_4	19	20	22	21
d_4	20	22	21	23
e_4	18	17	20	21
Ampicillin trihydrate	31	29	30	31

*Average of three readings. S. a is *Staphylococcus aureus*, A. P is *Actinomyces pyogenes*, K. A is *Klebsiella aerogenes* and E. c is *Escherichia coli*

($2a_1$-e_1, a_2-d_2, a_3-d_3, b_4-c_4). The latter on reacting with substituted benzaldehydes in anhydrous sodium acetate afforded 2-phenyl(substituted)-3-aryl-5-benzilidine(substituted)thiazolidine-4-ones ($3a_1$-e_1, a_2 , d_2, a_3 , c_3, d_3, b_4-e_4), which in turn reacted with phenylhydrazine in presence of anhydrous sodium acetate to furnish 2-phenyl-3,5-diphenyl(substituted)-6-aryl-3,3a,5,6-tetrahydro-2H-pyrazolo[3,4-d] thiazoles ($4a_1$-e_1, a_2, d_2, a_3, c_3, d_3, b_4-e_4).

All compounds were screened for their *in vitro* antibacterial activity by agar cup plate method[7] at 100 μg concentration. Solutions of the test compounds were kept in dimethylsulphoxide. Ampicillin trihydrate (100 μg/ml) was used as a standard drug for comparison and solvent control was kept. The antibacterial activity of various compounds against pathogenic strains in nutrient agar is shown in Table 5. Compounds $4d_1$, d_2, d_3, c_4, and d_4 were found to be the most active against all the microbes. However, all the compounds were comparatively less active than the standard drug.

ACKNOWLEDGEMENTS

The authors wish to thank Dr. G. C. Pradhan, Department of Chemistry, Utkal University, Bhubaneswar for facilities and Prof. C. S. Panda, Department of Chemistry, Berhampur University, Berhampur for his valuable suggestions.

REFERENCES

1. Pattan, S.R., Maste, M. and Angadi, J. , **Indian Drugs**, 2002, 39(8), 429.
2. Javed, S.A. and Sidiqui, N., **Indian J. Heterocycl. Chem**., 2004, 13, 287.
3. Solanki, P.R. and Wadodkar K.N., **Indian J. Heterocycl. Chem**., 2003, 13, 135.
4. Havaldar, F.H., Kumar, S. and Mishra, J., **Indian J. Heterocycl. Chem**., 2004, 13, 197.
5. Sharma, R.C. and Kumar, D., **J. Indian Chem**. **Soc**., 2000, 77, 492.
6. Mohan, J. and Khatter, D., **Indian J. Heterocycl. Chem**. 2004, 13, 327.
7. Anonymous, Biritish Pharmacopoeia, Vol II, H.M. S.O. Publication Centre, London, 1998, A205.

Accepted 12 October 2007
Revised 11 April 2007
Received 9 January 2006
Indian J. Pharm. Sci., 2007, 69 (5): 689-692