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

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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

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spectrophotometer (vmax). ¹H NMR spectra (CDCl₃) 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 (1) and the corresponding 4-thiazolidinones (2) were prepared according to literature method⁵.

2-Phenyl (substituted)-3-aryl-5-benzilidene (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.

3a₁: IR(KBr, cm⁻¹): 3285(Ar-OH), 3052 (Ar-CH),1739 (C=O),1542 (Ar-NO₂). b₁: IR (KBr, cm⁻¹): 3294 (Ar-

OH), 3045 (Ar-CH), 1736(C=O), 1538 (Ar-NO₂), d₁: IR (KBr, cm⁻¹): 3292 (Ar-OH), 3038 (Ar-CH), 1733 (C=O), 747 (C-Cl). a₂: IR (KBr, cm⁻¹): 3289 (Ar-OH), 3026 (Ar-CH), 1722 (C=O), 754 (C-Cl). d₂: IR (KBr, cm⁻¹): 3049 (Ar-CH), 1746 (C=O),751 (C-Cl). a₃: IR (KBr, cm⁻¹): 3295 (Ar-OH), 3031 (Ar-CH), 1742 (C=O), 742 (C-Cl). C₃: IR (KBr, cm⁻¹): 3064 (Ar-CH),1752 (C=O), 1546 (Ar-NO₂), 759 (C-Cl). b₄: IR (KBr, cm⁻¹): 3068 (Ar-CH), 1756 (C=O), 746 (C-Cl). c₄: IR (KBr, cm⁻¹): 3059 (Ar-CH), 1731 (C=O), 1560 (Ar-NO₂), 745 (C-Cl). d₄: 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.

4a₁: IR (KBr, cm⁻¹): 3289 (Ar-OH), 3064(Ar-CH), 1539 (Ar-NO₂), 1671 (C=N), 1266 (C-N); ¹HNMR δ: 3.15 (s,1H,CH), 5.84 (s,1H,CH), 6.58-8.74 (m,17H,Ar-H), 11.14(s,1H,OH). b₁: IR (KBr, cm⁻¹): 3290(Ar-OH), 3031(Ar-CH), 1663(C=N), 1539 (Ar-NO₂), 1260(C-N); ¹HNMR δ: 1.13 (s,6H,2xCH₃), 2.95(s,1H,CH),5.64(s,1H,CH), 6.5-9.24(m,17H,Ar-H). d₁: IR (KBr, cm⁻¹): 3284(Ar-OH), 3045 (Ar-CH), 1548 (ArNO₂), 1656 (C=N), 1264 (C-N), 748 (C-Cl); ¹HNMR 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'		
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 ₂ O ₅ S	62.84	62.80	3.83	3.80	6.66	6.64
b ₁	C ₂₄ H ₂₁ N ₃ O ₄ S	64.41	64.37	4.73	4.69	9.39	9.37
c ₁	C ₂₂ H ₁₅ N ₃ O ₆ S	58.79	58.74	3.36	3.32	9.34	9.32
d ₁	C ₂₂ H ₁₅ ClN ₂ O ₄ S	60.20	59.80	3.44	3.40	6.38	6.37
e ₁	C ₂₃ H ₁₈ N ₂ O ₅ S	63.58	63.55	4.17	4.14	6.44	6.42
a ₂	C ₂₄ H ₂₁ ClN ₂ O ₂ S	65.96	65.92	4.84	4.81	6.41	6.30
d ₂	C ₂₄ H ₂₀ Cl ₂ N ₂ O ₅ S	63.28	36.24	4.42	4.38	6.14	6.12
a ₃	C ₂₂ H ₁₄ BrClNO ₂ S	57.84	57.80	3.30	2.9	3.06	3.03
c ₃	C ₂₂ H ₁₄ BrClNO ₃ S	55.88	55.84	3.19	3.16	2.96	2.95
d ₃	C ₂₂ H ₁₄ BrCl ₂ NOS	53.71	53.68	2.87	2.84	2.85	2.83
b ₄	C ₂₈ H ₂₃ ClN ₂ O ₅ S	71.39	71.35	4.92	4.88	5.94	5.93
c ₄	C ₂₆ H ₁₇ Cl ₂ O ₅ S	66.02	65.09	3.62	6.58	5.92	5.90
d ₄	C ₂₆ H ₁₇ Cl ₂ NOS	67.52	67.48	3.70	3.30	3.02	3.00
e ₄	C ₂₇ H ₂₀ ClNO ₂ S	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.

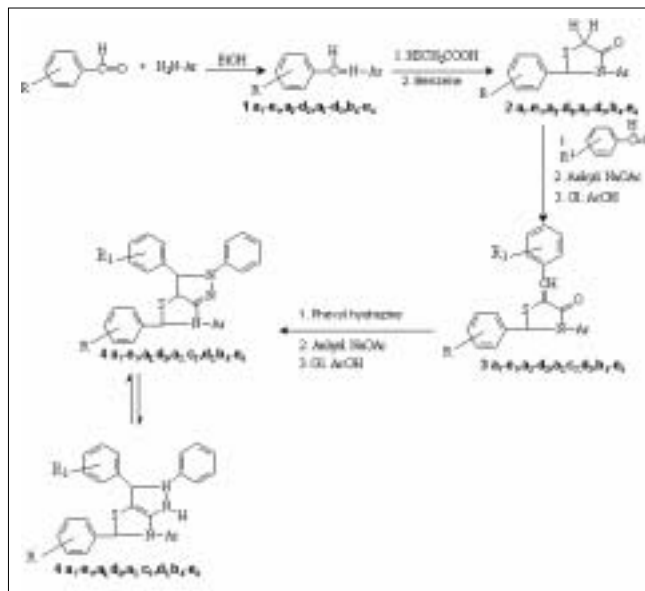
Compound	Substituents			mp(°)	Yield (%)
	Ar	R	R'		
4a ₁	4-NO ₂ Phenyl	2-OH	2-OH	98	99.9
b ₁	4-NO ₂ Phenyl	4-N (CH ₃) ₂	2-OH	138	94.96
c ₁	4-NO ₂ Phenyl	4-NO ₂	2-OH	108	95
d ₁	4-NO ₂ Phenyl	4-Cl	2-OH	140	97.1
e ₁	4-NO ₂ Phenyl	4-OCH ₃	2-OH	150	99
a ₂	4-Cl Phenyl	2-OH	4-N (CH ₃) ₂	242	99.75
d ₂	4-Cl Phenyl	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). a₂: IR(KBr, cm⁻¹): 3286 (Ar-OH), 3063 (Ar-CH), 1683 (C=N), 1276 (C-N), 751 (C-Cl); ¹HNMR δ: 1.40 (s,1H, 2×CH₃), 3.22 (s,1H, CH), 5.75 (s,1H, CH), 5.90-7.97 (m,17H, Ar-CH), 10.99 (s,1H, OH). d₂: IR (KBr, cm⁻¹): 3062 (Ar-CH), 1674 (C=N), 1272 (C-N), 756 (C-Cl); ¹HNMR δ: 2.02 (s, 6H, 2×CH₃), 3.19 (s,1H,CH), 5.79 (s,1H,CH), 6.52-8.68 (m,17H,Ar-H). a₃: IR (KBr, cm⁻¹): 3294 (Ar-OH), 3030 (Ar-CH), 1668 (C=N), 1279 (C-N), 755 (C-Cl); ¹HNMR δ: 2.17 (s,1H,CH), 5.85 (s,1H,CH), 7.02-9.18 (m,17H,Ar-H), 11.20 (s,1H,OH). c₃: IR (KBr, cm⁻¹): 3076 (Ar-CH), 1672 (C=N), 1552 (Ar-NO₂), 1274 (C-N); ¹HNMR δ: 3.06 (s,1H,CH), 5.72 (s,1H,CH), 5.90-7.97 (m,17H,Ar-H). b₄: IR (KBr, cm⁻¹): 3049 (Ar-CH), 1677 (C=N), 1267 (C-N), 744 (C-Cl); ¹HNMR δ: 1.98 (s,6H, 2×CH₃), 3.22 (s,1H,CH), 5.85 (s,1H,CH), 6.39-8.88 (m,20H,Ar-H). c₄: IR (KBr, cm⁻¹): 3078 (Ar-OH), 1661 (C=N), 1564 (Ar-NO₂), 1270 (C-N), 743 (C-Cl); ¹H NMR δ: 2.22 (s,1H,CH), 5.08 (s,1H,CH), 5.83-8.88 (m,20H,ArH). d₄: IR (KBr, cm⁻¹):

3067 (Ar-CH), 1673 (C=N), 1273 (C-N), 753 (C-Cl); ¹HNMR 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 (1a₁-e₁, a₂-d₂, a₃-d₃, b₄-e₄), 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 a₁-e₁; Ar = 4-NO₂-C₆H₄, a₂-d₂; Ar = 4-Cl-C₆H₄, a₃-d₃; Ar = 4-Br-C₆H₄, b₄-e₄; Ar = Naphthyl. 1,2,3,4 a₁₋₃; R = 2-OH, b₁₋₄; R = 4-N (CH₃)₂, c₁₋₄; R = 4-NO₂, d₁₋₄; R = 4-Cl, e₁₋₄; R = 4-OCH₃, 3,4 a_{1-e1}; R₁ = 2-OH, a₂-d₂; R₁ = 4-N (CH₃)₂, a₃-d₃, b₄-e₄; R₁ = 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 ₄ O ₄ S	65.86	65.82	4.34	4.30	10.97	10.95
b ₁	C ₃₀ H ₂₇ N ₅ O ₃ S	67.02	66.98	5.06	4.96	13.02	13.01
c ₁	C ₂₈ H ₂₁ N ₅ O ₂ S	62.32	62.28	3.92	3.89	12.97	12.96
d ₁	C ₂₈ H ₂₂ ClN ₄ O ₃ S	68.13	68.10	4.28	4.25	11.35	11.33
e ₁	C ₂₉ H ₂₄ N ₄ O ₄ S	66.39	66.35	4.61	4.57	10.67	10.66
a ₂	C ₃₀ H ₂₇ ClN ₅ S	68.35	68.33	5.16	5.14	10.62	10.60
d ₂	C ₃₀ H ₂₆ Cl ₂ N ₄ S	66.03	65.99	4.80	4.50	10.27	10.26
a ₃	C ₂₈ H ₂₁ BrClN ₃ OS	59.73	59.70	3.76	3.74	7.46	7.44
c ₃	C ₂₈ H ₂₀ BrClN ₄ O ₂ S	65.75	65.71	3.01	2.93	3.06	3.05
d ₃	C ₂₈ H ₂₀ BrCl ₂ N ₃ S	57.83	57.80	3.46	3.44	7.22	7.20
b ₄	C ₃₄ H ₂₉ ClN ₄ S	72.76	72.72	5.02	4.17	9.98	9.96
c ₄	C ₃₂ H ₂₃ ClN ₄ O ₂ S	68.25	68.21	4.11	4.08	9.94	9.93
d ₄	C ₃₂ H ₂₃ Cl ₂ N ₃ S	69.55	69.51	4.19	4.15	7.60	7.59
e ₄	C ₃₃ H ₂₆ ClN ₄ OS	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*

(2a₁-e₁, a₂-d₂, a₃-d₃, b₄-c₄). The latter on reacting with substituted benzaldehydes in anhydrous sodium acetate afforded 2-phenyl(substituted)-3-aryl-5-benzilidene(substituted)thiazolidine-4-ones (3a₁-e₁, a₂, d₂, a₃, c₃, d₃, b₄-e₄), 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 (4a₁-e₁, a₂, d₂, a₃, c₃, d₃, b₄-e₄).

All compounds were screened for their *in vitro* antibacterial activity by agar cup plate method⁷ 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 4d₁, d₂, d₃, c₄, and d₄ were found to be the most active against all the microbes. However, all the compounds were comparatively less active than the standard drug.

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