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Microwave Assisted Synthesis and Antimicrobial Screening of Pyrazoline-5-ones

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4-Amino-2,3-dimethyl-1-phenyl-3-pyrazoline-5-one **(1)** was condensed with different aromatic aldehydes to yield Schiff bases **(2a–i)**. The Schiff bases on cyclization with chloroacetyl chloride in presence of triethyl amine as catalyst furnished azetidine-2-ones **(3a–i)**. The Schiff bases **(2a–i)** on cyclization with mercaptoacetic acid in the presence of anhydrous aluminium chloride as catalyst offered thiazolidine-4-ones **(4a–i)**. The compounds were synthesized in good yield and characterized by their TLC, chemical analysis and spectral data and were subjected to antimicrobial activity.

Key Words: Synthesis, Antimicrobial, Pyrazoline-5-ones.

INTRODUCTION

In the past few years, many azetidin-2-one derivatives have been found to possess significant antimicrobial[1–3] activity. Thiazolidin-4-ones are also known to have antimicrobial[4–6] activity. Pyrazoles exhibit a wide range of biological activities[7] like anti-invasive, antiviral, etc. Schiff bases of triazoles possess various pharmacological activities such as antimicrobial activity[8].

In recent years, environmentally benign synthetic methods have received considerable attention and solvent free protocols are reported[9–11]. A fast, highly efficient and eco-friendly solvent-free chemical transformation, for the synthesis of title compounds, under microwave irradiation, using basic alumina is designed. The main advantages of the synthetic approach presented here are considerable rate enhancement in comparison with a thermal reaction, improved isolated yields of products and cleaner and environmentally safer reactions. Thus, in continuation to our earlier communications[12–14], we herein report the synthesis of the title compounds using dry media synthesis and study of their antimicrobial activity.

EXPERIMENTAL

The melting points were recorded on electrothermal apparatus and are uncorrected. IR Spectra were recorded in KBr on a Perkin-Elmer-983. PMR

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spectrum on Bruker-Avance 300 MHz instrument using $CDCl_3$ as solvent (chemical shifts in δ ppm), using TMS as internal standard. Mass spectra were charted on Finning LCQ mass spectrometer. Microwave irradiations were carried out in Samsung 28L, model C-103-Fl at 2450 MHz. Elemental analyses were performed on a Heracus CHN Rapid Analyzer.

4-Aminoantipyrine **(1)** was prepared as per literature method[15].

4-(Substituted phenyleneamino)-2,3-dimethyl-1-phenylpyrazole-5-ones (2a–i)

A mixture of equimolar quantities of 4-amino-2,3-dimethyl-1-phenyl-3-pyrazoline-5-one **(1)** (0.1 mol), the appropriate aldehyde (0.1 mol) was dissolved in dichloromethane (30 mL). Basic alumina (aluminium oxide, basic, Brockmann I, *ca.* 150 mesh, 58 Å CAMAG 506-C-I, surface area 155 m^2/g, pH = 8.0) was added to it (20 g). It was stirred for 5 min to assure complete homogeneous mixing. Then dichloromethane was evaporated *in vacuo*. The resultant solid mixture was kept on borosil glass plate (alumina bath) and irradiated for 50–60 s. Completion of reaction was checked by TLC (ethanol : ethyl acetate, 4 : 1). After completion of the reaction, it was poured into ice-cold water. The product was extracted with ether and recrystallized from hot ethanol.

In all cases the products obtained showed single spot on TLC plate.

3-Chloro-4-(substituted phenyl)-1-(2,3-dimethyl-1-phenyl-5-oxo pyrazolyl) azetidin-2-ones (3a–i)

Schiff base (0.1 M), triethylamine (0.1 M), chloroacetyl chloride (0.1 M) were mixed in 30 mL dichloromethane. It was stirred for 5 min, to assure complete homogeneous mixing. Then dichloromethane was evaporated *in vacuo*. The resultant solid mixture was kept on borosil glass plate (alumina bath) and irradiated for 5–6 min. Completion of reaction was checked by TLC (methanol : water, 95 : 5). After completion of the reaction, it was poured in ice-cold water. The product was extracted with ether andrecrystallized from DMSO-water. In all cases the products obtained showed single spot on TLC plate.

2–(Substituted phenyl)-3-(2,3-dimethyl-1-phenyl-5-oxo pyrazolyl)-5H-thiazolidin-4-ones (4a–i).

Schiff base **(2)** (0.1 mol), mercaptoacetic acid (0.02 mol) and anhydrous aluminium chloride (0.05 g) were mixed in 30 mL dichloromethane. It was stirred for 5 min and the dichloromethane was evaporated *in vacuo*. The resultant solid mixture was kept on borosil glass plate (alumina bath) and irradiated for 10–12 min. Completion of reaction was checked by TLC (methanol : acetone, 95 : 5). After completion of the reaction, it was poured in ice-cold 10% sodium bicarbonate solution. The product was extracted with ether and recrystallised. In all cases the products obtained showed single spot on TLC plate.

Antmicrobial and antioxidant activity

The title compounds **(2a–i)**, **(3a–i)** and **(4a–i)** were screened *in vitro* for their antibacterial activity against *Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa* and *Salmonella typhosa* and antifungal activity against *Aspergillus niger, Candida albicans* and *Cryptococcus neoformans* by cup-plate

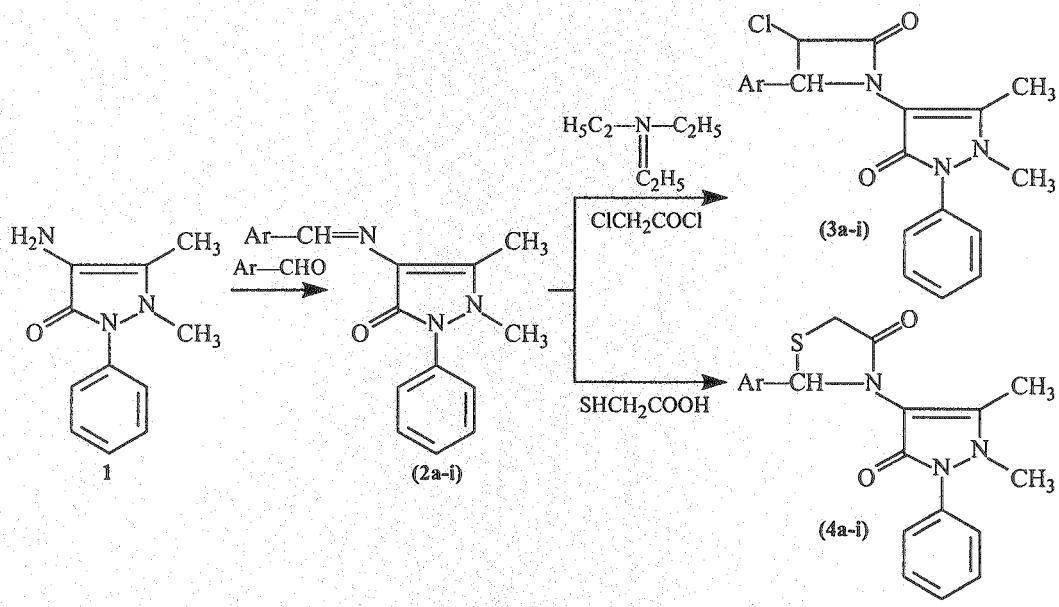
method[16] at concentration 50 mcg/mL. The zone of inhibition was measured in mm and reported in Table-1 for antibacterial and antifungal activities. Nutrient agar was employed as culture medium and DMF was used as solvent control for antimicrobial activity.

Gentamycin and griseofulvin were used as standard for antibacterial and antifungal activities respectively.

TABLE-1
PHYSICAL AND ANTIMICROBIAL DATA

Compd.	Ar	m.p. (°C)	Antibacterial[a]				Antifungal[a]		
			S.a.	P.a.	E.c.	S.t.	A.n.	C.a.	C.n.
2a	C_6H_5-	238	18	17	14	12	06	06	NA
2b	2-ClC_6H_4-	266	18	16	15	24	20	10	13
2c	4-OH-3$OCH_3C_6H_3$-	252	22	20	18	14	05	05	NA
2d	2-OHC_6H_4-	220	25	22	20	16	08	06	NA
2e	4-$OCH_3C_6H_4$-	212	20	20	18	14	20	11	14
2f	4-$(CH_3)_2N$-C_6H_4-	230	32	31	31	29	14	10	08
2g	3,4,5-$(OCH_3)_3C_6H_2$-	222	20	29	30	26	14	10	08
2h	3-$NO_2C_6H_4$-	218	11	17	15	22	19	11	12
2i	4-OHC_6H_4-	288	22	22	20	16	12	08	08
3a	C_6H_5-	254	16	16	12	12	08	06	NA
3b	2-ClC_6H_4-	204	32	30	30	27	05	04	NA
3c	4-OH-3$OCH_3C_6H_3$-	228	18	16	10	12	08	06	NA
3d	2-OHC_6H_4-	215	20	16	10	10	08	05	NA
3e	4-$OCH_3C_6H_4$-	222	22	22	20	16	10	08	08
3f	4-$(CH_3)_2N$-C_6H_4-	220	26	24	22	18	12	10	08
3g	3,4,5-$(OCH_3)_3C_6H_2$-	242	26	24	20	20	11	08	09
3h	3-$NO_2C_6H_4$-	246	24	22	20	18	14	09	10
3i	4-OHC_6H_4-	266	22	11	24	24	13	10	10
4a	C_6H_5-	226	22	22	20	20	12	08	08
4b	2-ClC_6H_4-	268	16	18	12	12	04	03	NA
4c	4-OH-3$OCH_3C_6H_3$-	204	16	16	12	14	06	04	NA
4d	2-OHC_6H_4-	212	32	32	26	24	06	05	NA
4e	4-$OCH_3C_6H_4$-	212	33	34	30	29	06	04	NA
4f	4-$(CH_3)_2N$-C_6H_4-	222	20	18	14	12	06	04	NA
4g	3,4,5-$(OCH_3)_3C_6H_2$-	222	24	10	14	14	08	04	06
4h	3-$NO_2C_6H_4$-	274	21	18	10	18	08	05	05
4i	4-OHC_6H_4-	256	22	12	16	14	10	08	08
Gentamycin		–	34	35	31	30	–	–	–
Griseofulvin		–	–	–	–	–	21	12	15

[a]Zone of inhibition is measured in mm, NA = No activity



Scheme-1

RESULTS AND DISCUSSION

The title compounds were confirmed by the following H^1 NMR spectra.

1 δ 1.2 (s, 3H, CH_3), δ 2.1 (s, 2H, NH_2), δ 2.2 (s, 3H, CH_3), δ 6.8 (s, 2H, ArH), δ 7.2 (s, 1H, ArH), δ 7.7 (s, 2H, ArH).

2b δ 1.2 (s, 3H, CH_3), δ 2.2 (s, 3H, CH_3), δ 6.6 (s, 2H, ArH), δ 6.8 (s, 1H, ArH), δ 7.1 (s, 2H, ArH), δ 7.2 (s, 2H, ArH), δ 7.5 (s, 1H, ArH), δ 8.2 (s, 1H, N=CH).

2d δ 1.2 (s, 3H, CH_3), δ 2.1 (s, 3H, CH_3), δ 4.9 (s, 1H, OH), δ 6.6 (s, 2H, ArH), δ 6.7 (s, 1H, ArH), δ 6.8 (s, 2H, ArH), δ 7.2 (s, 2H, ArH), δ 7.5 (s, 1H, ArH), δ 8.2 (s, 1H, N=CH).

3e δ 1.4 (s, 3H, CH_3), δ 2.6 (s, 3H, CH_3), δ 3.7 (s, 3H, CH_3), δ 4.9 (s, 1H, CH-lactam), δ 5.5 (s, 1H, CH-lactam), δ 6.8 (s, 2H, ArH), δ 7.0 (s, 2H, ArH), δ 7.4 (s, 2H, ArH), δ 7.7 (s, 1H, ArH).

3g δ 1.4 (s, 3H, CH_3), δ 2.6 (s, 3H, CH_3), δ 3.73- δ 3.78 (m, 9H, OCH_3), δ 4.9 (s, 1H, CH-lactam), δ 5.5 (s, 1H, CH-lactam), δ 6.4 (s, 2H, ArH), δ 6.8 (s, 2H, ArH), δ 7.0 (s, 1H, ArH), δ 7.4 (s, 2H, ArH).

4c δ 1.7 (s, 3H, CH_3), δ 2.4 (s, 3H, CH_3), δ 3.3 (s, 2H, CH_2-thiazolidine), δ 3.7 (s, 3H, OCH_3), δ 5.0 (s, 1H, OH), δ 5.9 (s, 1H, CH-thiazolidine), δ 6.1 (s, 1H, ArH), δ 6.2 (s, 1H, ArH), δ 6.7 (s, 2H, ArH), δ 6.8 (s, 1H, ArH), δ 7.0 (s, 1H, ArH), δ 7.2 (s, 2H, ArH).

4d δ 1.7 (s, 3H, CH_3), δ 2.4 (s, 3H, CH_3), δ 3.3 (s, 2H, CH_2-thiazolidine), δ 5.0 (s, 1H, OH), δ 5.9 (s, 1H, CH-thiazolidine), δ 6.6 (s, 1H, ArH), δ 6.7 (s, 2H, ArH), δ 6.8 (s, 2H, ArH), δ 7.0 (s, 2H, ArH), δ 7.2 (s, 2H, ArH).

From the antimicrobial screening it was observed that all the compounds exhibited activity against all the organisms employed. Looking at the structure activity relationship, marked inhibition in bacteria was observed in the com-

pounds bearing Ar = 4-$(CH_3)_2NC_6H_4$ **(2f)**, 3,4,5-$(OCH_3)_3C_6H_2$ **(2g)**, 2-ClC_6H_4 **(3b)**, 2-OHC_6H_4 **(4d)**, 4–$OCH_3C_6H_4$ **(4e)** substituent whereas others showed moderate to least activity.

Fungicidal screening data also revealed that compounds bearing Ar = 2-ClC_6H_4 **(2b)**, 4-$OCH_3C_6H_4$ **(2e)**, 3-$NO_2C_6H_4$ **(2h)** imparted maximum activity to the compounds.

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