

Synthesis, characterization and biological activities of some new 1-[(N-cinnamoyl) 2, 5-dichloroanilinomalonyl] 3, 5-dimethyl-4-(unsubstituted/substituted phenylazo) pyrazole derivatives

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ABSTRACT

1-[(N-cinnamoyl) 2, 5-dichloroanilinomalonyl] 3, 5-dimethyl-4-(Unsubstituted/substituted phenylazo) pyrazoles have been synthesized in 38 to 66% yield, by the reaction of 2, 4-diketo-3-(Unsubstituted/substituted phenylazo) pentanes with Ethyl-2-[(N-cinnamoyl) 2, 5-dichloroanilido] acetohydrazide. Pyrazoles are brown and yellow color solids, having high melting points. Identity of products has been established by elemental analysis and spectral data. Newly synthesized compounds [5a-f] have been tested for their antibacterial activity against gram positive bacteria *S.albus*, *S.aureus* and gram negative bacteria *E.Coli* and *Pseudomonas piosineus*. The compound 5a, 5c, 5d, 5e, 5g and 5h shown significant activity and compound 5b, 5f, 5i, 5j, 5k, 5n and 5p have shown moderate activity. The same compounds were tested for their antifungal activity against *Candida albicans*, *Aspergillus Niger* and *Alternaria alternata* at concentration of 30 mg/ml using sabouraud dextrose agar media. Compounds 5a, 5c, 5d, 5g, 5j, 5m, and 5p were found to be moderately active against *Candida albicans* and *Aspergillus Niger*. All the other compounds did not show significant activity against the fungi at the concentration used.

Key words: Arylazopyrazoles, Synthesis, Characterization & Biological activities.

INTRODUCTION

Pyrazoles and their derivatives are important on account of use in therapy in different diseases¹⁻¹² Antibacterial¹³⁻²⁰, fungicidal²¹⁻²⁷, antidiuretic²⁸⁻³⁰, anticancer³¹⁻³⁷ and anti-HIV³⁸⁻⁴² -antitumour⁴³, antianalgesic-inflammatory⁴⁴⁻⁴⁸, anticonvulsant^{49,50} properties of pyrazoles have been reported in the literature. Synthesis and interesting aspect of biological activity of arylazopyrazoles have been reported⁵¹⁻⁵². In view of potential biological activities of pyrazoles and arylazopyrazoles we report here in the synthesis of new 1-[(N-cinnamoyl) 2, 5-dichloro anilinomalonyl] 3, 5-dimethyl- 4 - (Unsubstituted/substituted phenylazo) pyrazoles. The present communication deals with the reaction of acetyl acetone with diazotized aromatic primary amine in presence of sodium acetate which furnished 2,4-diketo-3- (Unsubstituted/substituted

phenylazo) pentane (I) which on treatment with ethyl-2-[(N-cinnamoyl)2, 5-dichloroanilido] acetohydrazide (II) in acetic acid medium resulted in the formation of 1-[(N-cinnamoyl) 2, 5-dichloroanilinomalonyl] 3, 5-dimethyl-4-(Unsubstituted/substituted phenylazo) pyrazoles (5a-f) in varying yield 38-66% (Table-1). Antibacterial and antifungal activities of new arylazopyrazoles were determined.

EXPERIMENTAL

All the chemicals were used for synthesis are of analytical reagent grade. Melting points are taken in open capillaries and are uncorrected. Purity of the compounds was checked by TLC. All the compounds gave satisfactory elemental analysis. IR Spectra were recorded on a Perkin-Elmer Spectrum RX1 FT IR Spectrophotometer using KBr

pallatisation technique and NMR Spectra were recorded on Broker DRX-300 NMR Spectrophotometer. The NMR peaks were recorded on δ scale (ppm) against TMS. The solvent employed was DMSO (3.33-3.35 δ). The elemental analysis of all the compounds done on elemental Vireo EL-III Carlo Erba 1108. 2, 4-Diketo-3- (Unsubstituted/ substituted phenylazo) pentane were synthesized by reported method⁵³. Ethyl-2-[(N-cinnamoyl) 2, 5-dichloroanilido] acetohydrazide was prepared by an adaptation of the procedure given by Rathore and Ittyerah⁵⁴.

Synthesis of Ethyl-2-[2, 5-dichloroanilido] Ethanoate [1]

A mixture of 2, 5-dichloroaniline (10ml) and diethylmalonate (20ml) was refluxed for forty five minutes in a round bottomed flask fitted with an air condenser of such a length (14") that ethanol formed escaped and diethylmalonate flowed back into the flask. Contents were cooled, ethanol (30 ml) was added, when malon-2,5dichlorodianilide separated out. It was filtered under suction. The filtrate was poured on to crushed ice (Ca160g) and stirred when ethyl-2-(2, 5-dichloroanilido) ethanoate precipitated as green mass. On recrystallization from aqueous ethanol (50%), ester was obtained as white crystals. Yield; 81%, M.P.88°C, M.W.276. Anal. Calculation for $C_{11}H_{11}N_1O_3Cl_2$: Found; C 39.20, N 4.14, Cl 21.5, Calcd. C 39.21, Cl 21.6, N 04.15 IR [KBr] V_{max} cm^{-1} : 1665-1660 [C=O diketone], 1290 [-C-O- Ester], 760-755 [2, 5- disubstituted benzene], 1250 [C-Cl Stretching], 1590, 1520, 1440 [C=C Ring stretching], 3150 [N-H Stretching], 3040 [C-H aromatic], 1330-1322 [C-H Stretching]. PMR (DMSO): δ 4.42 (2H, s, CO-CH₂-CO), 4.0 (2H, s, NH₂), 7.4-8.6 (3H, m, Ar-H), 9.2 (1H, s, CO-NH D₂O exchangeable), 10.6 [1 H, s, Ar-NH D₂O exchangeable].

Synthesis of Ethyl-2-[(N- cinnamoyl) 2, 5-dichloroanilido] ethanoate [2]

Cinnamoyl chloride (10gm; 0.06mol), dioxane (6ml), Ethyl-2-(2,5-dichloroanilido) ethanoate (16.5 gm; 0.06 mol) and Triethylamine (6.06 gm; 0.06 mol) were placed in a round bottomed flask carrying reflux condenser having calcium chloride guard tube. The contents were heated on a boiling water bath for three hours and kept over night when triethylamine hydrochloride

separated. It was filtered under suction and the filtrate was poured on to crushed ice (Ca180g) and stirred when Ethyl-2-[(N-cinnamoyl) 2, 5-dichloroanilido] ethanoate separated or solid. It was filtered under suction, dried and purified by recrystallisation from aqueous methanol (1:1) in white crystals. Yield = 74 %, MP = 97°C Anal. calculation for $C_{20}H_{17}N_1O_4Cl_2$: [FW = 406], Calculated: N 02.60, C 43.7, H 03.10, O 11.7, Cl 12.9, Found: N 02.64, C 43.6, H 03.3, O 11.5, Cl 12.8. IR [KBr] V_{max} cm^{-1} : 1740 [C=O diketone], 1310 [-C-O- Ester], 765 [2, 5- disubstituted benzene], 1095 [C-Cl Stretching], 1590, 1520, 1440 [C=C Ring stretching], 3170 [N-H Stretching], 3040 [C-H aromatic], 1330-1320 [C-H Stretching]. PMR (DMSO): δ 4.5 [2H, s, CO-CH₂-CO], 4.2 [2H, s, NH₂], 7.2-8.5 [3H, m, Ar-H], 9.5 [1H, s, CO-NH D₂O exchangeable], 10.7 [1H, s, Ar-NH D₂O exchangeable].

Synthesis of Ethyl-2-[(N- cinnamoyl) 2, 5-dichloroanilido] acetohydrazide [3]

Ethyl-2-[(N- cinnamoyl) 2, 5-dichloroanilido] ethanoate (12.2 gm; 0.03 mol), ethanol (8 ml) and hydrazine hydrate (15 ml; 80%) were mixed together and stirred for forty five minutes. Ethyl-2-[(N-cinnamoyl) 2, 5-dichloroanilido] acetohydrazide was filtered under suction and recrystallised from ethanol in white crystals. Yield; 71%, MP = 184°C, MW 392 Anal. calculation for $C_{18}H_{15}N_3O_3Cl_2$: Calculated; N 7.6, C 39.1, Cl 12.9, Found; N 7.4, C 38.9, Cl 12.7. IR [KBr] V_{max} cm^{-1} : 3170 [N-H Stretching], 3055 [C-H aromatic], 1665 [C=O diketone], 1440 [C-Cl aromatic], 1590, 1530, 1440 [C=C ring stretching]. PMR (DMSO): δ 4.4 (2H, s, CO-CH₂-CO), 4.1 (2H, s, NH₂), 7.3-8.6 (3H, m, Ar-H), 9.5 (1H, s, CO-NH D₂O exchangeable), 10.8 (1H, s, Ar-NH D₂O exchangeable).

Synthesis of 2, 4- diketo-3-(phenylazo) pentane (R = H) [4]

Aniline (9.3 ml, 0.1mol) was dissolved in aqueous hydrochloric acid (80 ml, 1:1). The contents were stirred, cooled (0-2°C) and cold solution of sodium nitrite (12.0 g in 30 ml water) was slowly added maintaining the temperature between 0-2°C. The cold diazotized solution was added drop wise with stirring to a well cooled mixture of acetyl acetone (0.1 mol, 10 ml) and sodium acetate (12 g

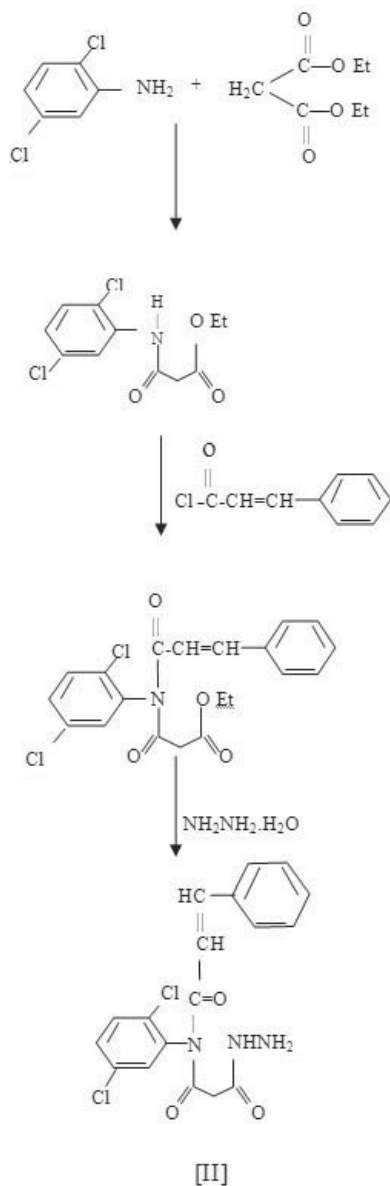
dissolved in 10 ml of 50% aqueous ethanol). Stirring was further continued for forty five minutes, when yellow crystals separated. The product was filtered under suction, washed with water and recrystallised from aqueous ethanol.

Analytical [%] for $C_{11}H_{12}N_2O_2$: Found; C 38.17, H 03.47, O 9.25, N 08.09, Calcd.; C 38.16, H 03.46, O 9.23, N 8.00, Yield; 59 %,

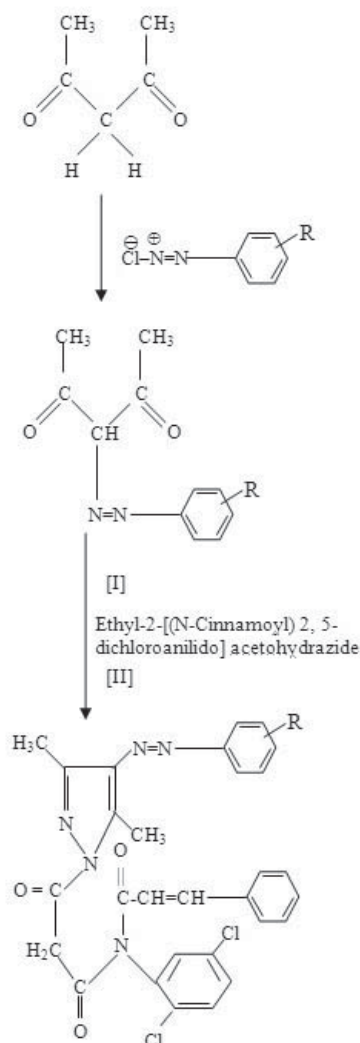
M.P.; 96°C, [MW 204], Other 2, 4-diketo-3-(Unsubstituted/substituted phenylazo) pentane were prepared by above mentioned procedure.

Synthesis of 1-[(N-cinnamoyl) 2, 5-dichloroanilinomalonyl] 3, 5-dimethyl-4-phenylazo pyrazoles [5]

2, 4-diketo-3-(phenylazo) pentane (0.204g, 0.001 mol) and ethyl-2-[(N-cinnamoyl) 2, 5-



Scheme 1.



Scheme 2.

dichloroanilido] acetohydrazide (0.392g, 0.001mol) were dissolved in glacial acetic acid (10ml) and the solution was refluxed for 14 hrs. The resulting solid was purified by repeated washing with acetic acid and recrystallized from acetic acid as yellow crystals. Yield; 57%, M.P.; 262°C Analysis (%) : Found; N 7.1, Cl 7.2 $C_{29}H_{23}N_5O_3Cl_2$ [FW 559], Calculated; N 7.0, Cl 7.1 IR (KBr) ν_{max} cm^{-1} : 3270-3060 (N—H Sec. amide hydrogen bond), 2980 (C—H Stretching Aromatic), 1665 (C=N Pyrazole), 1560 (C=C Aromatic), 1060 (C—Cl Aromatic). PMR (DMSO): δ 2.4 (2H, s, CH_2), 4.2 (1H, s, NH), 6.90-7.10 S (7H, s, Ar-H). Other 1-[(N-cinnamoyl) 2, 5-dichloroanilinomalonyl] 3, 5-dimethyl-4-((Unsubstituted/substituted phenylazo) pyrazoles were prepared by above mentioned procedure.

Biological activities

Anti-bacterial activity

Newly synthesized compounds (5a-t) have been tested for their anti-bacterial activity against gram-positive bacteria *S.albus*, *S.aureus* and gram negative bacteria *E.coli* and *P. piosineus* by agar

plate disc diffusion method at 30 μ g/mL concentrations. Ampicillin and tetracycline were used as a reference compounds. The compound 5a, 5c, 5d, 5e, 5g and 5h shown significant activity and compound 5b, 5f, 5i, 5j, 5k, 5n, and 5p have shown moderate activity.

Anti-fungal activity

The same compounds were tested for their anti-fungal activity against *Candida albicans*, *Aspergillus Niger* and *Alternaria alternata* at concentration of 30 mg/ml using sabouraud dextrose agar media. Compounds 5a, 5c, 5d, 5g, 5j, 5m and 5p were found to be moderately active against *Candida albicans* and *Aspergillus Niger*. All the other compounds did not show significant activity against the fungi at the concentration used.

RESULTS AND DISCUSSION

1-[(N-cinnamoyl) 2, 5-dichloroanilinomalonyl] 3, 5-dimethyl-4-((Unsubstituted/substituted phenylazo) pyrazoles

Table 1.

CS. No.	R	Color	M.P. (°C)	Yield (%)	Molecular Formula
5a.	H	Yellow	262	57	$C_{29}H_{23}N_5O_3Cl_2$
5b.	$CH_3(o)$	Light Yellow	245	62	$C_{30}H_{25}N_5O_3Cl_2$
5c.	$CH_3(m)$	Yellow	239	57	$C_{30}H_{25}N_5O_3Cl_2$
5d.	$CH_3(p)$	Light Yellow	237	49	$C_{30}H_{25}N_5O_3Cl_2$
5e.	Cl(o)	Yellow	268	47	$C_{29}H_{23}N_5O_3Cl_3$
5f.	Cl(m)	Yellow	264	51	$C_{29}H_{23}N_5O_3Cl_3$
5g.	Cl(p)	Light Yellow	270	53	$C_{29}H_{23}N_5O_3Cl_3$
5h.	O- $CH_3(o)$	Light Yellow	265	58	$C_{30}H_{25}N_5O_4Cl_2$
5i.	O- $CH_3(m)$	Yellow	259	52	$C_{30}H_{25}N_5O_4Cl_2$
5j.	O- $CH_3(p)$	Light Yellow	267	54	$C_{30}H_{25}N_5O_4Cl_2$
5k.	F(p)	Yellow	254	42	$C_{29}H_{23}N_5O_3Cl_2F_1$
5l.	Br(o)	Dark brown	251	56	$C_{29}H_{23}N_5O_3Cl_2Br$
5m.	O- $C_2H_5(o)$	Brown	268	48	$C_{31}H_{27}N_5O_4Cl_2$
5n.	O- $C_2H_5(m)$	Brown	259	44	$C_{31}H_{27}N_5O_4Cl_2$
5o.	O- $C_2H_5(p)$	Brown	256	38	$C_{31}H_{27}N_5O_4Cl_2$
5p.	$CO_2H(o)$	Brown	254	41	$C_{30}H_{23}N_5O_5Cl_2$
5q.	$CO_2H(m)$	Brown	259	45	$C_{30}H_{23}N_5O_5Cl_2$
5r.	$CO_2H(p)$	L. brown	261	42	$C_{30}H_{23}N_5O_5Cl_2$
5s.	Br(m)	Brown	249	51	$C_{29}H_{23}N_5O_3Cl_2Br$
5t.	Br(p)	Brown	245	53	$C_{29}H_{23}N_5O_3Cl_2Br$

% All compounds gave satisfactory elemental analysis.

have been synthesized by the reaction of 2, 4-diketo-3- (Unsubstituted/substituted phenylazo) pentane with Ethyl-2-[(N-cinnamoyl) 2, 5-dichloroanilido] acetohydrazide in 38 to 66% yield, Pyrazoles are brown and yellow color solids, having high melting points. The structure of all the compounds are confirmed by IR, PMR, and Mass spectral data and are further supported by correct elemental analysis (Experimental part). All the newly synthesized compounds (5a-t) have been screened for their antibacterial activity against gram positive bacteria *S.albus*, *S.aureus* and gram negative bacteria *E.Coli* and *Pseudomonas piosineus* The compound 5a, 5c, 5d, 5e, 5g and 5h shown significant activity and compound 5b, 5f, 5i, 5j, 5k, 5n, and 5p have shown moderate activity. The same compounds were screened for their antifungal activity against *Candida albicans*, *Aspergillus Niger* and *Alternaria alternata* at concentration of 30 mg/ml using sabouraud dextrose agar media. Compounds 5a, 5c, 5d and 5g were found to be moderately active against *Candida albicans* and *Aspergillus Niger*. All the other compounds did not show significant activity against the fungi at the concentration used.

CONCLUSION

Newly synthesized compounds (5a-t) have

been tested for their anti-bacterial activity against gram positive bacteria *S.albus*, *S.aureus* and gram negative bacteria *E.Coli* and *Pseudomonas piosineus* by agar plate disc diffusion method at 30 µg/mL concentrations. Ampicillin and tetracycline were used as a reference compounds. The compound 5a, 5c, 5d, 5e, 5g and 5h shown significant activity and compound 5b, 5f, 5i, 5j, 5k, 5n and 5p have shown moderate activity. The same compounds were tested for their anti-fungal activity against *Candida albicans*, *Aspergillus Niger* and *Alternaria alternata* at concentration of 30 mg/ml using sabouraud dextrose agar media. Compounds 5a, 5c, 5d and 5g were found to be moderately active against *Candida albicans* and *Aspergillus Niger*. All the other compounds did not show significant activity against the fungi at the concentration used.

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