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Synthesis, characterization and biological evaluation of some new arylazopyrazoles

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ABSTRACT : 1-[(N-acetyl)2,3-dichloroanilinomalonyl]3,5-dimethyl-4-(unsubstituted/substituted phenylazo) pyrazoles have been synthesised in 34 to 65% yield, by the reaction of 2,4-diketo-3- (unsubstituted/substituted phenylazo) pentane with Ethyl-2-[(N-acetyl)2,3-dichloroanilido] acetohydrazide. Pyrazoles are brown and yellow colour solids, having high melting points. Identity of products has been established by elemental analysis and spectral data. Newly synthesized compounds[5a-t] 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 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.

Keywords : Arylazopyrazoles, Synthesis, Characterization & Biological activities.

I. INTRODUCTION

Pyrazoles and their derivatives are important on account of use in therapy in different diseases [1-120 Antibacterial [13-20], fungicidal [21-27], antidiuretic [28-30], anticancer [31-37] and anti-HIV [38-42]-antitumour [43], antianalgesic-inflamatory [44-48], anticonvulsant [49, 50] properties of pyrazoles have been reported in the literature. Synthesis and interesting aspect of biological activity of arylazopyrazoles have been reported [51-52]. In view of potential biological activities of pyrazoles and arylazopyrazoles we report here in the synthesis of new 1-[(N-acetyl) 2, 3-dichloro anilinomalonyl] 3, 5-dimethyl- 4 -(unsubstituted/substituted phenylazo) pyrazoles. The present communication deals with the reaction of acetyl acetone with diazotised aromatic primary amine in presence of sodium acetate which furnished 2, 4-diketo-3-(unsubstituted/ substituted phenylazo) pentanes (I) which on treatment with ethyl-2-[(N-acetyl)2, 3-dichloroanilido] acetohydrazide (II) in acetic acid medium resulted in the formation of 1-[(N-acetyl) 2, 3-dichloro anilinomalonyl]3, 5-dimethyl-4-(unsubstituted/ substituted phenylazo) pyrazoles (5a-t) in varying yield 34-65% (Table-1). Antibacterial and antifungal activities of new arylazopyrazoles were determined.

II. 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 Bruker DRX-300 NMR Spectrophotometer. The NMR peaks were recorded on d scale (ppm) against TMS. The solvent employed was DMSO (3.33-3.35 d). The elemental analysis of all the compounds done on Elementar vario EL III Carlo Erba 1108. 2,4-Diketo-3-(unsubstituted/substituted phenylazo) pentane were synthesise by reported method [53]. Ethyl-2-[(N-acetyl)2, 3-dichloroanilido]acetohydrazide was prepared by an adoptation of the procedure given by Rathore and Ittyerah [54].

Synthesis of Ethyl-2-[2,3-dichloroanilido] Ethanoate [1]:

A mixture of 2, 3-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, 3dichlorodianilide separated out. It was filtered under suction. The filtrate was poured on to crushed ice (Ca160g) and stirred when ethyl-2-(2,3-dichloroanilido) ethanoate precipitated as green mass. On recrystallization from aqueous ethanol (50%), ester was obtained as white crystals.

Yield; 82%, M.P.86°C, M.W.276.

Anal. calculation for $C_{11}H_{11}N_1O_3Cl_2$: Found ; C 39.20, H 03.24, O 14.25, N 4.14, Cl 21.09, Calcd. C 39.21, H 03.26, O 14.26, N 04.15,Cl 21.04

IR [KBr] V_{max} cm^{-1} : 1665-1660 [C=O diketone], 1290 [-C-O- Ester], 760-755 [2,3- di substituted 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): d 4.42 (2H, s, CO-CH_2-CO), 4.0 (2H, s, NH_2), 7.4-8.6 (3H, m, Ar-H), 9.2 (1H, s, CO-NH D_2O exchangeable), 10.6 [1 H, s , Ar-NH D_2O exchangeable].

Synthesis of Ethyl-2-[(N-acetyl) 2,3- dichloroanilido] ethanoate [2]:

Acetyl chloride (4.74 gm; 0.06 mol), dioxane (6 ml), Ethyl-2-(2,3-dichloroanilido) ethanoate (16.56 gm; 0.06 mol) and Triethylamine (5.7 gm; 0.06 mol) were placed in a round bottomed flask carrying reflux condensor having calcium chloride guard tube. The contents were heated on a boiling water bath for two hours and kept over night when triethylamine hydrochloride separated. It was filtered under suction and the filtrate was poured on to crushed ice (Ca180 g) and stirred when ethyl-2-[(N-acetyl) 2,3-dichloroanilido]ethanoate separated or solid. It was filtered under suction, dried and purified by recrystallisation from aqueous methanol (1:1) in white crystals. Yield = 76.4 % , MP = 88°C

Anal. calculation for $C_{13}H_{13}O_4N_1Cl_2$: [FW = 318], Calculated: N 02.95 , C 45.64, H 03.38 , O 13.50 , Cl 15.00 , Found : N 02.94, C 45.62 , H 03.37 , O 13.52 , Cl 15.02.

IR [KBr] V_{max} cm^{-1} **:** 1720 [C=O diketone], 1300 [-C-O-Ester], 762[2,3- disubstituted benzene], 1090 [C-Cl Stretching], 1590, 1520 , 1440 [C=C Ring stretching], 3160 [N-H Stretching], 3040[C-H aromatic], 1330-1322 [C-H Stretching].

PMR (DMSO): d 4.44 [2H, s, CO-CH_2-CO], 4.1 [2H, s, NH_2], 7.2-8.5 [3H, m, Ar-H], 9.4 [1H, s, CO-NH D_2O exchangeable], 10.8 [1H, s, Ar-NH D_2O exchangeable].

Synthesis of Ethyl-2-[(N-acetyl) 2,3-dichloroanilido] acetohydrazide [3]:

Ethyl-2-[(N-acetyl)2,3-dichloroanilido]ethanoate (9.54 gm; 0.03 mol), ethanol (10 ml) and hydrazine hydrate (15 ml; 80%) were mixed together and stirred for thirty five minutes. Ethyl-2-[(N-acetyl)2,3-dichloroanilido]acetohydrazide was filtered under suction and recrystallised from ethanol in white crystals. Yield; 74% , MP = 172°C , MW 304 :

Anal. calculation for $C_{11}H_{11}N_3O_3Cl_2$: Calculated ; N 09.04 ,C 41.32 ,H 03.01 ,O 10.33, Cl 15.28, Found; N 09.01, C 41.30, H 03.00, O 10.31, Cl 15.27 .

IR [KBr] V_{max} cm^{-1} **:** 3160 [N-H Stretching], 3048 [C-H aromatic], 1660 [C=O diketone], 1432 [C-Cl aromatic],1595,1520, 1445 [C=C ring stretching].

PMR (DMSO): d 4.44 (2H, s, CO-CH_2-CO), 4.1 (2H, s, NH_2), 7.2-8.5 (3H, m, Ar-H), 9.4 (1H, s, CO-NH D_2O exchangeable), 10.7 (1H, s, Ar-NH D_2O exchangeable).

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

Aniline (9.3 ml, 0.1 mol) was dissolved in aqueous hydrochloric acid (80 ml, 1:1). The contents were stirred, cooled (0-2ÚC) and cold solution of sodium nitrite (12.0 g in 30 ml water) was slowly added maintaining the temperature between 0-2ÚC. The cold diazotized solution was added dropwise with stirring to a well cooled mixture of acetylacetone (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; 62 %, M.P.; 96ÚC , [MW 204],

Other 2,4-diketo-3- (unsubstituted/substituted phenylazo) pentanes were prepared by above mentioned procedure.

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

2,4-diketo-3-(phenylazo)pentane (0.204g, 0.001 mol) and Ethyl-2-[(N-acetyl)2,3-dichloroanilido] acetohydrazide (0.305g, 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; 56%, M.P.; 248ÚC

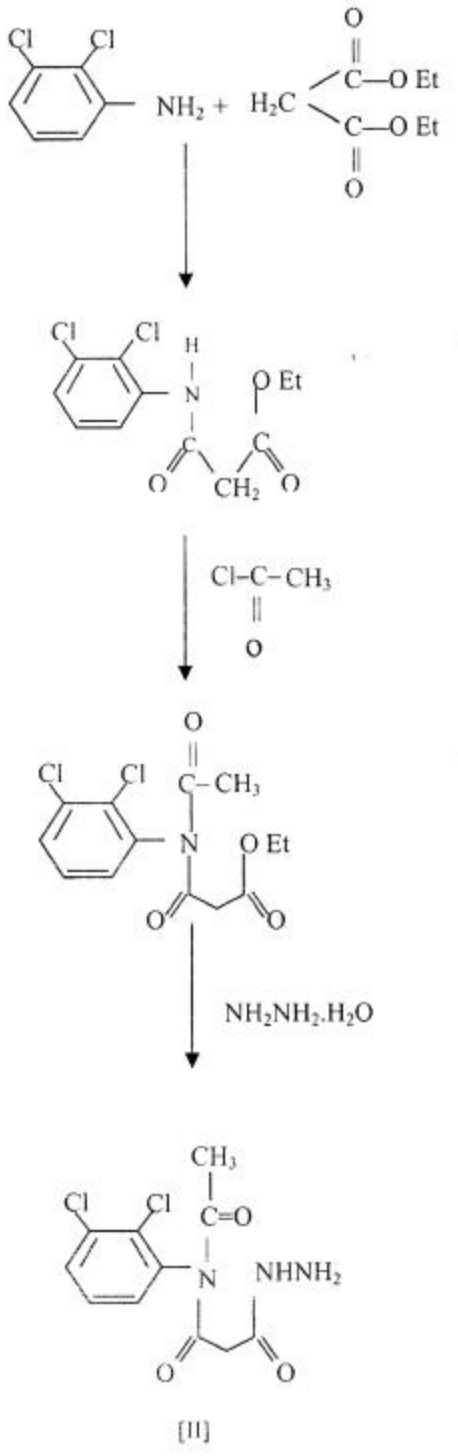
Analysis (%) : Found; N 7.55, Cl 7.14 $C_{22}H_{19}N_5O_3Cl_2$ [FW 472] , Calculated; N 7.56, Cl 7.16

IR (KBr) V_{max} cm^{-1} **:** 3268-3062 (N—H Sec. amide hydrogen bond), 2970 (C—H Stretching Aromatic), 1660 (C=N Pyrazole), 1550 (C=C Aromatic), 1056 (C–Cl Aromatic).

PMR (DMSO**):** d 2.36 (2H, s, CH_2), 4.14 (1H, s, NH), 6.90-7.05 S(7H, s, Ar-H).

Other 1-[(N-acetyl)2,3-dichloroanilinomalonyl]3,5-dimethyl-4-((unsubstituted/substituted phenylazo) pyrazoles were prepared by above mentioned procedure.

SCHEME – I



SCHEME-II

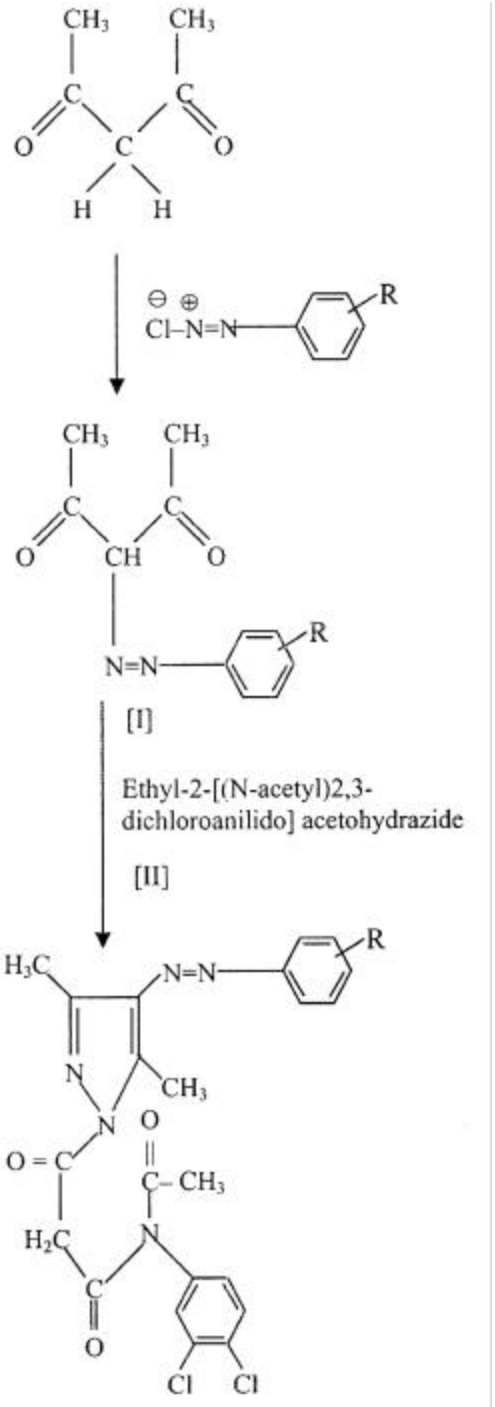


TABLE-I

CS. No.	R	Colour	M.P. (°C)	Yield (%)	Molecular Formula
5a.	H	Yellow	281	58	$C_{27}H_{21}N_5O_3Cl_2$
5b.	CH_3(o)	Light Yellow	264	61	$C_{28}H_{23}N_5O_3Cl_2$
5c.	CH_3(m)	Yellow	219	54	$C_{28}H_{23}N_5O_3Cl_2$
5d.	CH_3(p)	Light Yellow	238	53	$C_{28}H_{23}N_5O_3Cl_2$
5e.	Cl(o)	Yellow	271	57	$C_{27}H_{20}N_5O_3Cl_3$
5f.	Cl(m)	Yellow	246	51	$C_{27}H_{20}N_5O_3Cl_3$
5g.	Cl(p)	Light Yellow	273	50	$C_{27}H_{20}N_5O_3Cl_3$
5h.	O-CH_3(o)	Light Yellow	264	57	$C_{28}H_{23}N_5O_4Cl_2$
5i.	O-CH_3(m)	Yellow	239	44	$C_{28}H_{23}N_5O_4Cl_2$
5j.	O-CH_3(p)	Light Yellow	272	48	$C_{28}H_{23}N_5O_4Cl_2$
5k.	F(p)	Yellow	229	32	$C_{27}H_{20}N_5O_3Cl_2$
5l.	Br(o)	Dark brown	252	64	$C_{27}H_{20}N_5O_3Cl_2Br$
5m.	O-C_2H_5 (o)	Brown	257	49	$C_{29}H_{25}N_5O_4Cl_2$
5n.	O-C_2H_5 (m)	Brown	242	47	$C_{29}H_{25}N_5O_4Cl_2$
5o.	O-C_2H_5 (p)	Brown	238	41	$C_{29}H_{25}N_5O_4Cl_2$
5p.	CO_2H (o)	Brown	243	39	$C_{28}H_{22}N_5O_5Cl_2$
5q.	CO_2H (m)	Brown	243	39	$C_{28}H_{22}N_5O_5Cl_2$
5r.	CO_2H (p)	Light brown	265	43	$C_{28}H_{22}N_5O_5Cl_2$
5s.	Br(m)	Brown	234	36	$C_{27}H_{20}N_5O_3Cl_2Br$
5t.	Br(p)	Brown	246	41	$C_{27}H_{20}N_5O_3Cl_2Br$

• All compounds gave satisfactory elemental analysis.

III. 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 *Pseudomonas piosineus* by agar plate disc diffusion method at 30 µg/mL concentration. 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 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.

IV. RESULTS AND DISCUSSION

1-[(N-acetyl)2,3-dichloroanilinomalonyl]3,5-dimethyl-4-(unsubstituted/substituted phenylazo) pyrazoles have been synthesised by the reaction of 2,4-diketo-3- (unsubstituted/ substituted phenylazo) pentane with Ethyl-2-[(N-acetyl)2,3-dichloroanilido] acetohydrazide in 34 to 65% yield,. Pyrazoles are brown and yellow colour 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.

V. 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 concentration. 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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