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Synthesis, Characterization, and Biological activities of Some New Arylazopyrazoles

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ABSTRACT: 1-[(N-benzoyl)2,5-dichloroanilinomalonyl]3,5-dimethyl-4-(unsubstituted/substituted phenylazo) pyra zoles have been synthesised in 35 to 62% yield, by the reaction of 2,4-diketo-3- (unsubstituted/substituted phenylazo) pentanes with Ethyl-2-[(N-benzoyl)2,5-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,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.
Keywords: Arylazopyrazoles, Synthesis, Characterization & Biological activities.

INTRODUCTION

Pyrazoles and their derivatives are important on account of use in therapy in different diseases[1-12] 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-benzoyl) 2,5-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-benzoyl)2,5-dichloroanilido] acetohydrazide (II) in acetic acid medium resulted in the formation of 1-[(N-benzoyl) 2,5-dichloro anilinomalonyl]3,5-dimethyl-4-(unsubstituted/substituted phenylazo) pyrazoles (5a-t) in varying yield 35-62% (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 Bruker 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 Elementar vario EL III Carlo Erba 1108. 2,4-Diketo-3-(unsubstituted/substituted phenylazo) pentane were synthesise by reported method[53]. Ethyl-2-[(N-benzoyl)2,5-dichloroanilido]acetohydrazide was prepared by an adoptation of the procedure given by Rathore and Ittyerah[54].

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^{0}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
IR [KBr] V_{max} cm^{-1} : 1665-1660 [C=O diketone], 1290 [-C-O- Ester], 760-755 [2,5 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): δ 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-benzoyl) 2,5- dichloro anilido] ethanoate [2]:
Benzoyl chloride (8.46 gm; 0.06 mol), dioxane (6 ml), 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 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-benzoyl) 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 = 78.4 % , MP = 94°C
Anal. calculation for $C_{18}H_{15}N_1O_4Cl_2$: [FW = 380] , 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[2,5- 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): δ 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-benzoyl) 2,5-dichloro anilido]acetohydrazide [3]:
Ethyl-2- [(N-benzoyl)2,5-dichloroanilido] ethanoate (10.98 gm; 0.03 mol), ethanol (8 ml) and hydrazine hydrate (15 ml; 70%) were mixed together and stirred for thirty five minutes. Ethyl-2-[(N-benzoyl)2,5-dichloroanilido]acetohydrazide was filtered under suction and recrystallised from ethanol in white crystals. Yield; 76% , MP = 172°C , MW 366
Anal. calculation for $C_{16}H_{13}N_3O_3Cl_2$: 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): δ 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), 10.9 (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 (0-2˚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 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; 59 %, M.P.; 96˚C , [MW 204],

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

Synthesis of 1-[(N-benzoyl)2,5-dichloro aniline malonyl]3,5-dimethyl-4-phenylazo)pyrazoles [5]:
2,4-diketo-3-(phenylazo)pentane (0.204g, 0.001 mol) and ethyl-2-[(N-benzoyl)2,5-dichloroanilido] aceto hydrazide (0.366g, 0.001mol) were dissolved in glacial acetic acid (10ml) and the solution was refluxed for 12 hrs. The resulting solid was purified by repeated

washing with acetic acid and recrystallized from acetic acid as yellow crystals.

Yield; 56%, M.P.; 258˚C

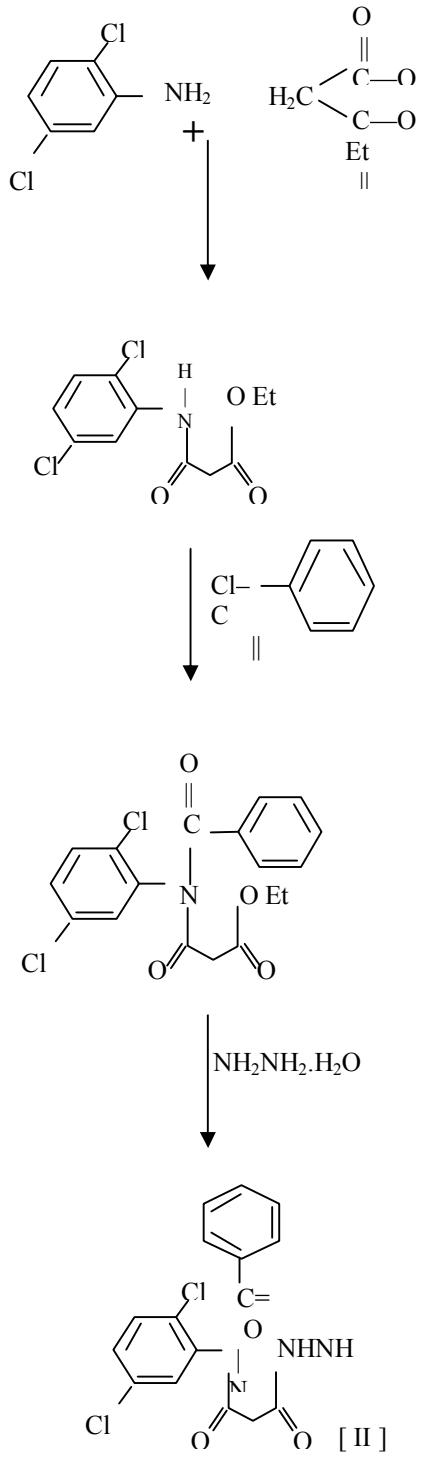
Analysis (%) : Found; N 7.55, Cl 7.14 ***$C_{27}H_{21}N_5O_3Cl_2$*** [FW 534] , Calculated; N 7.56, Cl 7.16

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

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

SCHEME – I



SCHEME-II

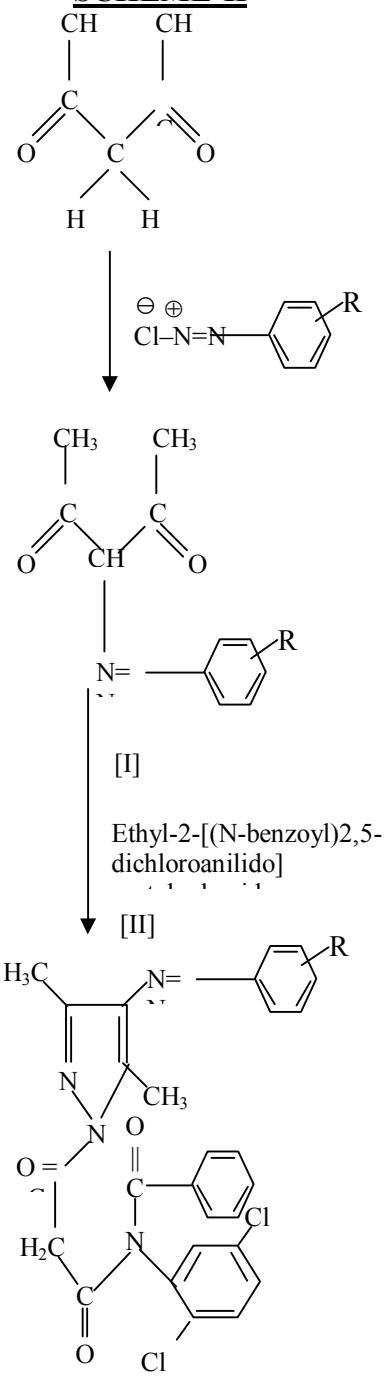


TABLE-I

CS. No.	R	Colour	M.P. (˚C)	Yield (%)	Molecular Formula
5a.	H	Yellow	258	57	$C_{27}H_{21}N_5O_3Cl_2$
5b.	CH_3(o)	Light Yellow	263	62	$C_{28}H_{23}N_5O_3Cl_2$
5c.	CH_3(m)	Yellow	223	51	$C_{28}H_{23}N_5O_3Cl_2$
5d.	CH_3(p)	Light Yellow	239	49	$C_{28}H_{23}N_5O_3Cl_2$
5e.	Cl(o)	Yellow	269	47	$C_{27}H_{20}N_5O_3Cl_3$
5f.	Cl(m)	Yellow	257	41	$C_{27}H_{20}N_5O_3Cl_3$
5g.	Cl(p)	Light Yellow	271	52	$C_{27}H_{20}N_5O_3Cl_3$
5h.	O-CH_3(o)	Light Yellow	266	56	$C_{28}H_{23}N_5O_4Cl_2$
5i.	O-CH_3(m)	Yellow	242	43	$C_{28}H_{23}N_5O_4Cl_2$
5j.	O-CH_3(p)	Light Yellow	268	46	$C_{28}H_{23}N_5O_4Cl_2$
5k.	F(p)	Yellow	233	32	$C_{27}H_{20}N_5O_3Cl_2$
5l.	Br(o)	Dark brown	253	64	$C_{27}H_{20}N_5O_3Cl_2Br$
5m.	O-C_2H_5 (o)	Brown	261	48	$C_{29}H_{25}N_5O_4Cl_2$
5n.	O-C_2H_5 (m)	Brown	244	42	$C_{29}H_{25}N_5O_4Cl_2$
5o.	O-C_2H_5 (p)	Brown	239	38	$C_{29}H_{25}N_5O_4Cl_2$
5p.	CO_2H (o)	Brown	244	34	$C_{28}H_{22}N_5O_5Cl_2$
5q.	CO_2H (m)	Brown	252	39	$C_{28}H_{22}N_5O_5Cl_2$
5r.	CO_2H (p)	L. brown	260	43	$C_{28}H_{22}N_5O_5Cl_2$
5s.	Br(m)	Brown	236	37	$C_{27}H_{20}N_5O_3Cl_2Br$
5t.	Br(p)	Brown	246	41	$C_{27}H_{20}N_5O_3Cl_2Br$

- All compounds gave satisfactory elemental analysis.

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,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-acetyl)2,5-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)2,5-dichloroanilido] acetohydrazide in 35 to 62% 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.

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 5**a,5c,5d,5e,5g** and 5**h** shown significant activity and compound 5**b,5f,5i,5j,**5**k,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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