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SYNTHESIS, CHARACTERISATION AND BIOLOGICAL ACTIVITY OF N^1 -4-METHYL. SALICYLOLYL -3- METHYL -4 (SULPHA/SUBSTITUTEDAZO) -1,2 PYRAZOLIN-5 ONES

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ABSTRACT
A novel series of N^1-4Methyl salicylolyl -3Methyl -4-(sulpha/substituted azo) - 1,2 Pyrazolin - 5 one derivatives were synthesised by the condensation of N^1 - 4 (sulpha/subsitituted aryl azo) ethyl acetate with 4- methyl salicylic acid hydrazide in presence of glacial acetic acid. The newly synthesised compounds were characterised by IR, ^{1}H NMR spectroscopy and also screened for their promising biological activity.

KEYWORDS: 1, 2 Pyrazolin -5 one, sulpha/substitute azo ethyl acetate, salicylic acid hydrazide, biological activity, antibacterial activity.

INTRODUCTION

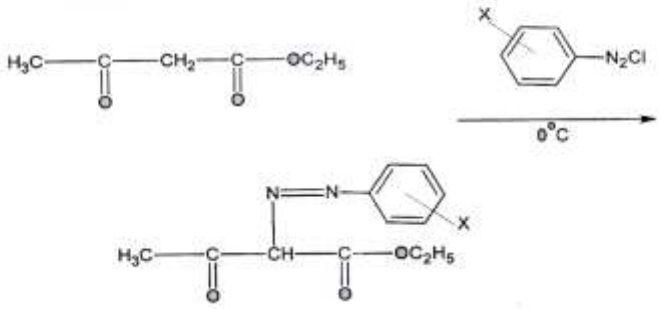
Simple Nitrogen containing heterocyclic compounds attached to suphonamido moieties have received a large amount of attention in literature as consequence to their exciting biological properties and their role as pharmacophores of considerable historical importance. Heterocyclic sulphonamides are used as carbonic anhydrase inhibitors[1-3], anti bacterial agents[4], anticancer, anti – inflammatory and analgestic agents.[5] In this context, The compounds having a pyrazole ring as a part of the condensed ring system showed considerable biological activities, thus steroids condensed with a pyrazole ring have been found to possess psychopharmacological properties and reported to produce changes in the endocrinological activity.[6] Certain 4 - substituted alkyl and cycloalkyl pyrazoles were found to be strong inhibitors of liver alcohol dehydrogenase.[7] Their activity seemed to be correlated with the lopophilicity of substituted. H.Willitzer et.al.[8] have found that lopophilicity of the substitutent can be increased by adding each methylene group to an unbranched chains and also proved that branching or cyclisation of chain lowers the activity. Pyrazoles represent one of the most active classes of compound possessing wide spectrum of biological activities.[9-11] Many of the therapeutically useful[12] oxyphen butazone, celecoxib[13] belonging to pyrazoles exhibited anti – inflammatory, antipyretic and analgesic properties. Moreover, Pyrazoline derivatives also constitute an intresting class of organic compounds with diverse chemical and pharmacological applications.[14-16] Mohammad Emad Azab et. al synthesised a novel series of heterocyclic compounds containing sulfonamido moeity and evaluated the antibacterial activity of these compounds.[17] Clen. et.al.[18] studied the antiviral activity of newly synthesised -1,3,4 thiodiazole derivatives. H.A. Saad et.al.[19] gave the microwave assisted synthesis of some new fused 1,2,4 triazine bearing thiophene moiety of expected pharmacological activity. Literature surgery revels that no work has been done on substituted 1,2 pyrazolin -5-ones of Sulpha/substituted Salicylic acid hydrazide. This paper deals with the synthesis of N^1-(4-methyl Salicylolyl)- 3 methyl- 4 (sulpha/substitutedazo) -1,2-pyrazolin- 5-ones.

Experimental Section

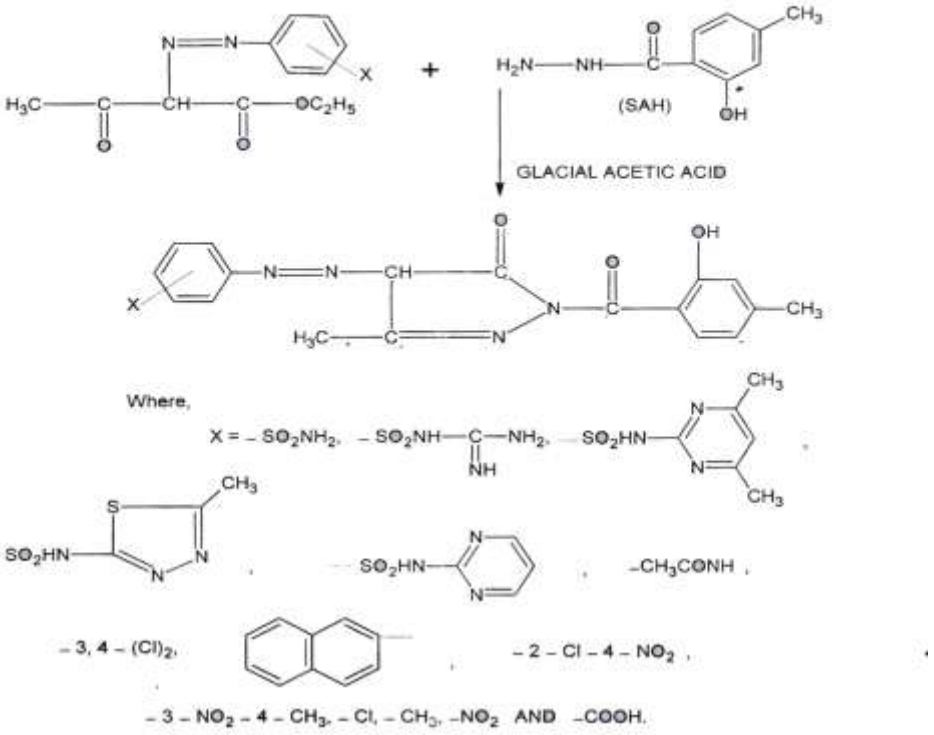
MATERIAL: Solvents and chemicals were carried of S.D. Fine Chem. and E.Merck grade; were purified and dried by convential method.[20] Sulpha drugs were obtained from Indian Drugs and Pharmaceuticals Limited, Hyderabad. All other chemicals of S.D. Fine chem. and E. Merck grade have checked for their purity before use. The homogeneity and purity of the compounds were checked over thin layer chromatography coated with silical gel-G (thickness 0.5mm) developing solvent acetone / DMF (3:1) non-saturated chamber at room temp. (20±1^o C).

General: The melting points of newly synthesised compounds were determined by capillary method and were uncorrected. The IR spectra were recorded on a Perkin Elmer Model 621 and 177 using Kbr Pellets while `HNMR-Spectra were recorded at 300MHz on Bruker Ft. NMR spectrophotometer using TMS as internal standard.

(A) SYNTHESIS OF SUBSTITUTED SULPHONAMIDO/ARYLAZO–β–KETO ESTER



(B) SYNTHESIS OF 1,2–PYRAZOLIN–5–ONES BY THE CONDENSATION OF SUBSTITUTED SULPHONAMIDO/ ARYLAZO–β–KETOESTER (i.e. ETHYL ACETO ACETATE) WITH 4–METHYL SALICYLIC ACID HYDRAZIDE (SAH)



Procedure

A. Synthesis of Sulpha/substituted aryl azo β- Keto ester

This reaction[21,22] were carried out by adding the solution of Sulpha/substituted aryl diazonium salts gradually to a well cooled stirred mixture of β-Keto ester (i.e. ethyl acetoacete) and sodium acetate in alcohol. By stirring the sulpha/substituted phenyl azo derivatives separated out as coloured compounds in varing colour from yellow to orange and red. The synthesised azo compounds were recrystallised from ethanol and DMF mixture.

B. Synthesis of different 1,2- Pyrazolin – 5 Ones by the condensation of sulpha/substituted aryl azo-β-Keto ester (i.e.Ethyl acetoacetate) with 4-methyl salicylic acid hydrazide(SAH)

1. Synthesis of N^1 –(4 methyl salicyloyl)-3 methyl - 4[N^1 - 2 (4,6 dimethyl) pyrimidyl sulphonoamide benzene azo] – 1,2 pyrazolin – 5 ones

A solution of N^1-2-(4, 6 dimethyl) pyrimidyl sulphonoamido benzene azo ethylacetate (1.40gm) and 4-methyl salicylic acid hydrazide (0.5gm) in glacial acetic acid was condensed on a water bath for about 3 hours. It was kept overnight to give a dark yellow solid mass, which was filtered, washed well with water; dried

and recrystallised from ethanol and DMF mixture to give shining dark yellow powder.

RESULT

Yield = 76% Colour = Shining dark yellow powder
M.P. = 231°C, Mol. For. = $C_{24}H_{23}N_7O_5S$ (Found N= 18.70%, Cal. N = 18.80%)
R_f value = 0.890
IR (KBr) (v_{max} in cm^{-1}) : 1590 (N=N), 1635 (C=O, cyclic)
1320 (C=N), 3250 C-C-OH), 1160 (-SO2NH), 1715 (C= O benzolyic) ,1585 – 1580 (C = N, C = C)
^{1}HNMR (CDCl3 + DMSO d_6) (δ in ppm):
1.95 (s, 6H, CH3 – Ar); 2.5 (s, 3H, CH_3 – C) ; 6.5(s, 1H, H –C)
6.8 (m, 1H, H – O – C), 6.9 (s, 1H, N – H) 7.4 – 8.2(m,9H,H-Ar)

2. Synthesis of N^1–4-methyl Salicyloyl – 3-methyl-4 (N^1–2 sulphonoamidobezeneazo) – 1,2 pyrazolin – 5 ones

some produce were adopted.

Result

Yield = 82% Colour = light yellow colour M.P = 216^0 Mol.For. = C_{18} H_{17} N_5O_5S (Found = 13.38%, Cal N = 13.43%)
R_f value = 0.809
IR (v_{max} in cm^{-1}) = 760 (C - C), 1245 (C - N),
1560 (C = C or aromatic ring)
3040 (aromatic C - H)
3345 (N - H), 1445 (N = N)
1153 (- SO_2 -), 3280 (NH_2)
1635 (C = O, cyclic)
1710 (C = O, benzoylic).
NMR (CdCl3+DMSO d_6) (δ in ppm): 5.9(b, H, NH),
7.75 – 6.40 (m, 16H, Ar-H)
6.5 (s, 1H, H-C),
6.9 (s, 1H, H-N)
11.5 (b, 2H,SO_2NH_2)

3. Synthesis of N^1 –4-methyl Salicyloyl – 3-methyl – 4-(3-methyl phenyl azo) – 1,2 pyrazolin – 5 ones:

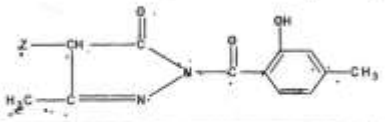
Same procedure were adopted

RESULT

Yield = 72% Colour = SGYN (slight green yellow needle)
M.P. = 155°C Mol. For. = $C_{19}H_{18}N_4O_3$(Found N= 15.91, Cal. N =16.0%)
R_f value = 0.764
IR (V_{max} in cm^{-1}) = 1590 (N=N), 1635 (C=O, cyclic)
1320(C=N), 3215 (C-C-OH)
1585 – 1580 (C = N, C = C)
760 (C-C),
3042 (aromatic, C-H)
^{1}H NMR ($CDCl_3$ + DmSO d_6) (δ in ppm) : 1.95(s, 6H, CH_3 - Ar)
2.5 (s, 3H, CH_3 - C)
6.9 (s, 1H, H - N)
6.5 (s, H, H - C)
7.4-8.2 (m, 9H, H-Ar)

By adopting above procedure N^1 – (4 methyl Salicyloyl) – 3- methyl -5- (4 (sulpha/substitutedazo) 1,2 pyrazolin -5- ones were synthesised their characteristic are recorded in Table 1.

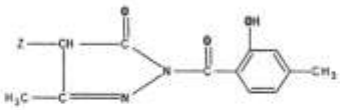
TABLE 1
CHARACTERISTICS OF N^1–SALICYLOYL–3–METHYL–4–(Z)–1,2–PYRAZOLIN–5–ONES



S.No.	Z	M.P. (°C)	Colour*	Molecular Formula	% Chemical analysis Found (Calc.)			R_f values
					C	H	N	
1	2	3	4	5	6	7	8	9
1.	N^1–2–sulphanilamidobenzeneazo	216	GYPr	$C_{18}H_{17}N_5O_5S$	51.95 (52.04)	4.0 (4.09)	13.38 (13.43)	0.809
2.	N^1–2–guanyl sulphanilamidobenzeneazo	239	DyYPr	$C_{19}H_{19}N_7O_5S$	50.93 (51.0)	4.18 (4.25)	21.80 (21.92)	0.825
3.	N^1–2–(4,6–dimethyl)pyrimidyl sulphanilamidobenzeneazo	231	SDyPr	$C_{24}H_{23}N_7O_5S$	55.15 (55.27)	4.31 (4.41)	18.70 (18.80)	0.890
4.	N^1–2–(5–methyl)–1,3,4–thiadiazolyl sulphanilamidobenzeneazo	225	DyPr	$C_{21}H_{19}N_7O_5S_2$	49.0 (49.12)	3.61 (3.70)	19.02 (19.10)	0.792
5.	N^1–2–pyrimidyl sulphanilamido–benzeneazo	194	LYPr	$C_{22}H_{19}N_7O_5S$	53.45 (53.54)	3.80 (3.85)	19.78 (19.87)	0.821
6.	4–Acetamidophenylazo	188	SLBPr	$C_{28}H_{19}N_7O_4$	56.91 (57.0)	4.43 (4.51)	23.20 (23.27)	0.713
7.	3,4–Dichlorophenylazo	152	SLYPr	$C_{18}H_{14}N_4O_3Cl_2$	53.25 (53.33)	3.38 (3.45)	13.75 (13.82)	0.708

TABLE 1 Contd...

CHARACTERISTICS OF N¹–SALICYLOYL–3–METHYL–4–(Z)–1,2–PYRAZOLIN–5–ONES



S.No.	Z	M.P. (°C)	Colour*	Molecular Formula	% Chemical analysis Found (Calc.)			R_f values
					C	H	N	
1	2	3	4	5	6	7	8	9
8.	2–Naphthylazo	143	YPr	$C_{22}H_{18}N_4O_3$	68.31 (68.39)	4.55 (4.66)	14.40 (14.50)	0.781
9.	2–Chloro–4–nitrophenylazo	178	LOPy	$C_{18}H_{14}N_5O_5Cl$	51.91 (51.98)	3.30 (3.36)	16.74 (16.84)	0.748
10.	3–Nitro–4–methylphenylazo	158	DYPr	$C_{19}H_{17}N_5O_5$	57.60 (57.72)	4.20 (4.30)	17.60 (17.72)	0.727
11.	Phenylazo	148	SLYF	$C_{18}H_{16}N_4O_3$	64.15 (64.28)	4.65 (4.76)	16.53 (16.66)	0.770
12.	3–Chlorophenylazo	120	SPYPr	$C_{18}H_{15}N_4O_3Cl$	58.15 (58.29)	3.91 (4.04)	15.0 (15.11)	0.918
13.	4–Chlorophenylazo	162	OF	$C_{18}H_{15}N_4O_3Cl$	58.15 (58.29)	3.92 (4.04)	15.0 (15.11)	0.655
14.	3–Methylphenylazo	136	SBYF	$C_{19}H_{18}N_4O_3$	65.02 (65.14)	5.02 (5.14)	15.90 (16.0)	0.774

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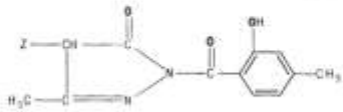
CHARACTERISTICS OF N¹–SALICYLOYL–3–METHYL–4–(Z)–1,2–PYRAZOLIN–5–ONES



S.No.	Z	M.P. (°C)	Colour*	Molecular Formula	% Chemical analysis Found (Calc.)			R_f values
					C	H	N	
1	2	3	4	5	6	7	8	9
15.	4–Methylphenylazo	155	SGYN	$C_{19}H_{18}N_4O_3$	65.02 (65.14)	5.02 (5.14)	15.91 (16.0)	0.764
16.	3–Nitrophenylazo	167	SYPr	$C_{18}H_{15}N_5O_5$	56.60 (56.69)	3.82 (3.93)	18.26 (18.37)	0.821
17.	4–Nitrophenylazo	191	SDON	$C_{18}H_{15}N_5O_5$	56.60 (56.69)	3.82 (3.93)	18.27 (18.37)	0.776
18.	4–Carboxyphenylazo	234	PYPr	$C_{19}H_{16}N_4O_5$	59.92 (60.0)	4.15 (4.21)	14.60 (14.73)	0.720

Yield range between 50–80%

* D = dark, Dy = dirty, P = pale, Y = Yellow, L = Light, B = Brown, Pr = Powder, O = Orange, G = Golden, F = Flakes, N = Needles, S = Shining.

The Rf values for all the compounds were determined on silica gel–G plates (thickness 0.5–0.6 mm) with developer acetone/dimethylformamide (2:2) in saturated chamber at room temperature.

RESULT AND DISCUSSION

Antibacterial Activity Evalution.

The newly synthesised compound were screened in vitro for their antibacterial activities against Gram positive bacteria [C Staphylococcus aureus (ATCC 25923) and Bacillus cereus (ATCCC 10987)], Gram negative bacteria [Serratia marcesens (ATCC274) and proteus mirabilis (SM 514) using agar diffusion technique. The results of antibacterial activity test are shown in table 2.

Table 2 Antibacterial activity data of the newly synthesised compound : Agar Diffiusion method.

S.No.	Compound No.	Gram positive		Gram negative	
		Stabhylococcus aureus	Bacillus cereas	Serratia maresens	Ptroteus mirabilies
1	1	++	++	++	++
2	2	-	-	+	+
3	5	++	++	+	+
4	9	+	+	+	+
5	11	+	-	+	+
6	12	+++	+++	+++	+++
7	15	++	+++	++	++

The width of the zone of inhibition indicates the potency of antibacterial activity; (-) no antibacterial activity.
(+) mild activity with diameter of zones equal to 0.5 – 0.8cm., (++) moderate activity with diameter of the zones equal to 1.1 – 1.2 cm., (+++) maked high activity with the diameter of the zones equal to 1.8 – 2.0 cm., Most of synthesised compounds were found to possess some antibacterial activity founds all the microganism. compound 1,2, 15 and 17 possess the highest antibacterial activites.

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