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Synthesis, characterization and biological activities of some new acid hydrazones

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ABSTRACT

A series of new acidhydrazones have been synthesised by the reaction of 2,3-dichloroanilido acetohydrazide with various carbonyl compounds in 58 to 92% yield. Newly synthesized compounds (1,3,4,7,8,9,12,13,15and16) 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*. The compound 1,3,12,13 and 15 shown significant activity and compound 4,7,8 and 9 have shown moderate activity. The same compounds were tested for their anti-fungal activity against *Candida albicans*, *Aspergillus niger* and *Alternaria alternate* at concentration of 30 mg/ml using sabouraud dextrose agar media. Compounds 12,13 and 15 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: Malonicester, Acidhydrazide, Accidhydrazones, synthesis, Characterization, and Biological Activities.

INTRODUCTION

Hydrazones possessing an azometine -NHN=CH- Proton constitute an important class of compounds for new drug development. Therefore, many researchers have synthesized these compounds as target structures and evaluated their biological activities. Acid hydrazides have frequently been investigated for testing their potentiality as tuberculostats[1-8]. Hydrazides and their condensation products have displayed diverse range of biological properties such as bacteriocidal[9-10], anti-fungal[11], anti-convulsant[12-15], anti-helmintic[16], anti-tumor[17-20], anti-leprotic[21], anti-malerial[22-23], anti-cancer[24-31], anti-depressant[32], anti-HIV[33], analgesic-anti-inflammatory[34], leishmanicidal[35], vasodilator activities[36].

EXPERIMENTAL

All chemicals used were of A.R. grade (either of B.D.H. or Excel-R or extra pure E. Merk quality). The structure of the compounds were determined by elemental analysis, IR and NMR spectral data. IR spectra (KBr) are recorded on a perkin-Elmer 283 spectrophotometer. NMR

spectra ($CDCl_3$) are recorded on varian EM 360 L spectrophotometer. Melting point of the compounds are determined in open capillary tubes and are uncorrected. Purity of the compounds is checked on T.L.C. using silica gel-G. Elemental analysis is performed on Carlo-Erba 1108 analyser.

General procedure

Preparation of Ethyl-2-(2,3-dichloroanilido) ethanoate [1]

A mixture of 2,3-dichloro aniline (5 ml) and diethyl malonate (10ml) was refluxed for 50-55 minutes in a 100 ml r.b. flask fitted with an air condenser of such a length (14²) that ethanol formed escaped and diethyl malonate flowed back in to the flask. Contents were cooled, 30 ml ethanol was added and kept over night, well precipitate found. It was filter under suction and purified by recrystalisation from ethanol.

IR Absorption band (cm^{-1})

3150 (N–H stretching), 1665–1660 (C=O Ketone), 1090 (C–Cl Stretching), 760–755 (Di substituted benzene), NMR spectra (d Me_2CO), 1.1–1.2 (3 H, t, CH_3), 2.21 (2 H, s, CH_2), 4.0–4.22 (2 H, q, CH_2), 7.0–7.21 (4 H, m, ArH).

Preparation of Ethyl-2-(2,3-dichloro anilido) acetohydrazide [2]

Ethyl-2-(2,3-dichloroanilido) ethanoate [.02 mol (5.52 gm)] was dissolved in rectified sprit in a small 3 neck r.b. flask kept on ice bath and set-up mechanical stirrer. Hydrazine hydrate (80%, 13 ml) was added by dropping funnel slowly drop by drop. The contents were stirred for 15-20 minutes. There were evolution of heat and reaction was spontaneous after 20 minutes, solid was filtered under suction and recrystallised from ethanol, then we get silver white crystals in good yield.

IR Absorption band (cm^{-1})

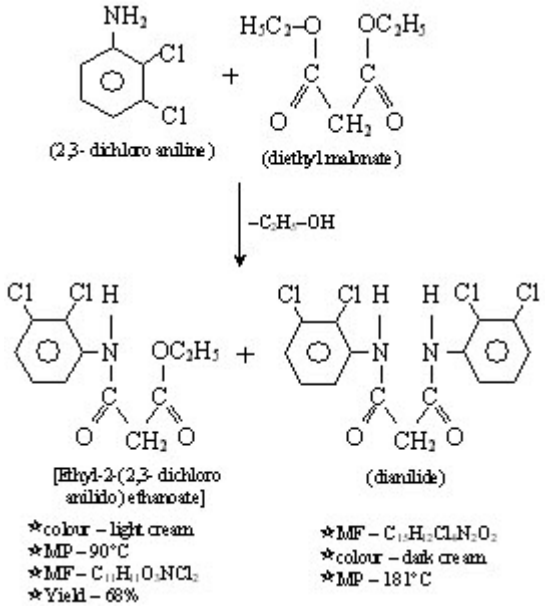
3160 (N–H stretching), 1660 (C=O Ketone), 1595, 1520, 1450 (C=C ring stretching), 760–755 (2, 3 di substituted benzene), NMR spectra (d DMSO), 2.25 (2 H, s, CH_2), 3.15 (3 H, s, CH_3), 4.12–4.31 (1 H, t, NH), 6.95–7.2 (3 H, m, ArH).

Synthesis of new Acidhydrazones [3]

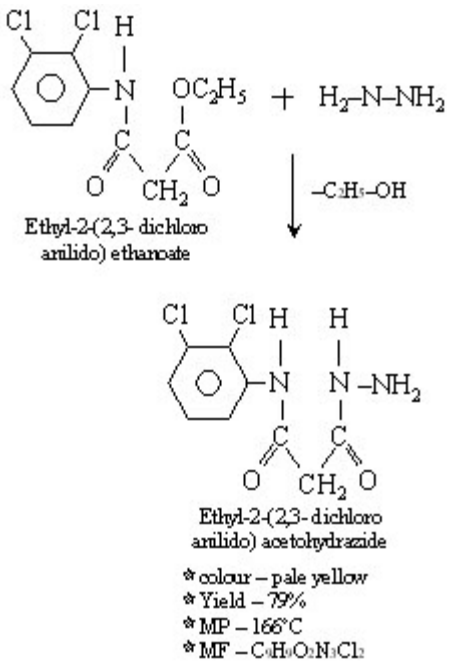
Ethyl-2-(2,3-dichloroanilido)acetohydrazide (.001 mol) and (.001 mol) of aromatic aldehyde or ketone dissolve in absolute alcohol and added 2-drops of conc. H_2SO_4 and stirred for 15 minutes. It was filtered under suction and recrystallised from hot ethanol. Synthetic strategy has been out lined in scheme I,II&III. Mechanism for the formation of acid hydrazones is given in chart-I.

IR Absorption band (cm^{-1})

3150 (N–H stretching), 2960–2970 (C–H aliphatic), 1662–1660 (C=O Ketone), 785–778 (C–Cl Stretching), 760 (2,3-disubstituted benzene),

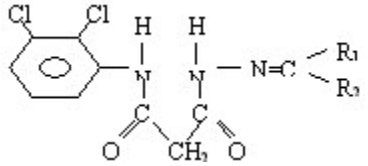


Scheme 1.

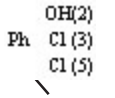
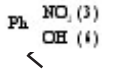
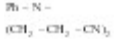
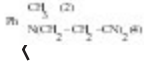
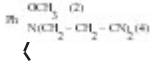
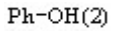
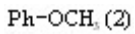


Scheme 2.

Table 1: Physical and analytical data of new compounds: Acid hydrazones derived from 2-(2,3-dichloroanilido) acetohydrazide



S. No.	Aldehyde / Ketone	R_1	R_2	m.p. (°C)	Yield (%)	Formula Weight	Molecular formula	Colour	Elemental analysis Calcd. and (Found)				
									C	H	O	N	Cl
1.	Benzaldehyde	H	Ph	208	91	350	$C_{16}H_{13}O_2N_3Cl_2$	White	54.85 (54.83)	3.71 (3.70)	9.14 (9.10)	12.00 (11.99)	20.28 (20.25)
2.	Vanilline	H	Ph OMe (3) OH (4)	197	84	396	$C_{17}H_{15}O_4N_3Cl_2$	White	51.51 (51.50)	3.78 (3.75)	16.16 (16.16)	10.60 (10.50)	17.92 (17.90)
3.	5-Chloro-salicyladehyde	H	Ph OH(2) Cl (5)	214	88	399.5	$C_{16}H_{11}O_3N_3Cl_3$	White	48.06 (48.00)	2.75 (2.72)	12.01 (12.00)	10.51 (10.50)	26.65 (26.60)
4.	5-Bromo-salicylaldehyde	H	Ph OH(2) Br (5)	210	92	492	$C_{16}H_{12}O_3N_3Cl_2Br$	Silver White	39.02 (39.01)	2.43 (2.42)	9.75 (9.72)	8.53 (8.51)	14.43 (14.42)
5.	2-Nitro vanilline	H	Ph NO_2 (2) OCH_3 (3) OH (4)	195	75	441	$C_{17}H_{14}O_6N_4Cl_2$	Cream	46.25 (46.25)	3.17 (3.15)	21.76 (21.74)	12.69 (12.67)	16.09 (16.00)
6.	O-Nitro benzaldehyde	H	Ph-NO_2 (2)	220	90	395	$C_{16}H_{12}O_4N_4Cl_2$	White	48.60 (48.58)	3.03 (3.01)	16.20 (16.19)	14.17 (14.15)	17.97 (17.96)
7.	2-Nitro 5-Bromo vanillilne	H	Ph NO_2 (2) OMe (3) OH (4) Br (5)	216	58	567	$C_{17}H_{13}O_6N_4Cl_2Br$	Cream	35.97 (35.96)	2.29 (2.29)	16.93 (16.92)	9.87 (9.86)	12.52 (12.51)

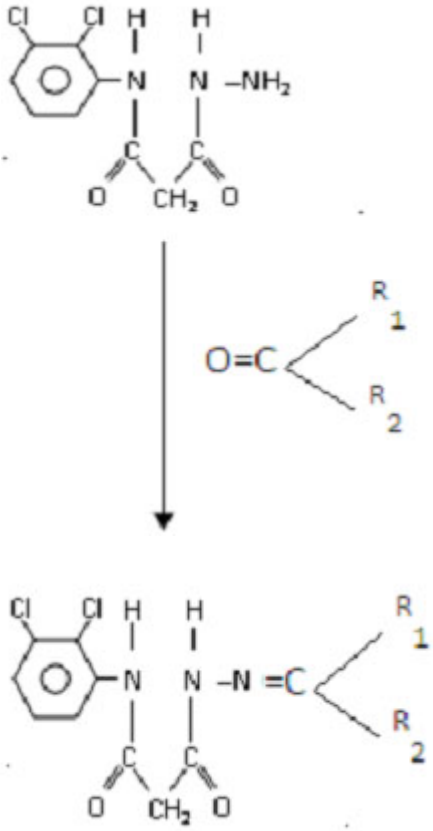
8.	3, 5 di chloro-2-hydroxy benzal dehyde	H		214	68	435	$C_{16}H_{11}O_3N_3Cl_4$	White	44.13 (44.11)	2.52 (2.51)	11.03 (11.01)	9.65 (9.64)	32.64 (32.64)
9.	3-Nitro-6-hydroxy acetophenone	CH_3 / Me		220	49	425	$C_{17}H_{14}O_5N_4Cl_2$	Cream	48.00 (48.00)	3.29 (3.28)	18.82 (18.81)	13.17 (13.16)	16.70 (16.69)
10.	Acetone	Me	Me	194	44	302	$C_{12}H_{13}O_2N_3Cl_2$	Cream	47.68 (47.66)	4.30 (4.28)	10.59 (10.58)	13.90 (13.89)	23.50 (23.49)
11.	2-Chloro benzaldehyde	H		228	81	384.5	$C_{16}H_{12}O_2N_3Cl_3$	White	49.93 (49.92)	3.12 (3.11)	8.32 (8.31)	10.92 (10.91)	27.69 (27.68)
12.	4-N-N-Bis-2' cyano ethyl amino benzaldehyde	H		206	64	471	$C_{22}H_{20}O_2N_6Cl_2$	Light brown	56.05 (56.04)	4.24 (4.23)	6.79 (6.78)	17.83 (17.82)	15.07 (15.06)
13.	2-Methyl-4-N-N-bis 2' cyano ethyl amino benzaldehyde	H		204	86	485	$C_{23}H_{22}O_2N_6Cl_2$	Brown	56.90 (56.89)	4.53 (4.53)	6.59 (6.58)	17.31 (17.30)	14.63 (14.61)
14.	2-Methoxy-4-N-N-bis 2' cyano ethyl amino benzaldehyde	H		195	64	501	$C_{23}H_{22}O_3N_6Cl_2$	Brown	55.08 (55.07)	4.39 (4.38)	9.58 (9.57)	16.76 (16.75)	14.17 (14.16)
15.	Acetophenone	Me / CH_3	Ph	212	91	364	$C_{17}H_{15}O_2N_3Cl_2$	White	56.04 (56.03)	4.12 (4.11)	8.79 (8.78)	11.53 (11.52)	19.50 (19.48)
16.	Salicylaldehyde	H		224	57	366	$C_{16}H_{13}O_3N_3Cl_2$	White	52.45 (52.44)	3.55 (3.54)	13.11 (13.10)	11.47 (11.46)	19.39 (19.38)
17.	Anisic aldehyde	H		222	71	380	$C_{17}H_{15}O_3N_3Cl_2$	Yellow	53.68 (53.67)	3.94 (3.92)	12.63 (12.61)	11.05 (11.03)	18.68 (18.67)
18.	β-Ionone	Me / CH3		180	28	446	$C_{23}H_{25}O_2N_3Cl_2$	Buff	61.88 (61.87)	5.60 (5.59)	7.17 (7.14)	9.41 (9.39)	15.91 (15.89)

NMR spectra (d DMSO), 2.25 (2 H, s, CH_2), 4.21 (1 H, s, NH), 6.95–7.2 (10 H, m, ArH).

Biological evaluation

Anti-bacterial activity

Ten new acid hydrazones (1,3,4,7,8,9,12,13,15 and 16) were screened for their anti-bacterial activity against the gram positive bacteria *S. albus, S. aureus* and gram negative bacteria *E. coli* and *pseudomonas piosineus* using cup-plat agar diffusion technique[13] at 10,15,25 mg/ml concentrations. Maximum inhibition (13-14 mm) was found in 12,13 and 15 against S. albus. Compounds 4,7,8,9 showed moderate activity against S. aureus. No significant activity was displayed by other compounds



Scheme 3.

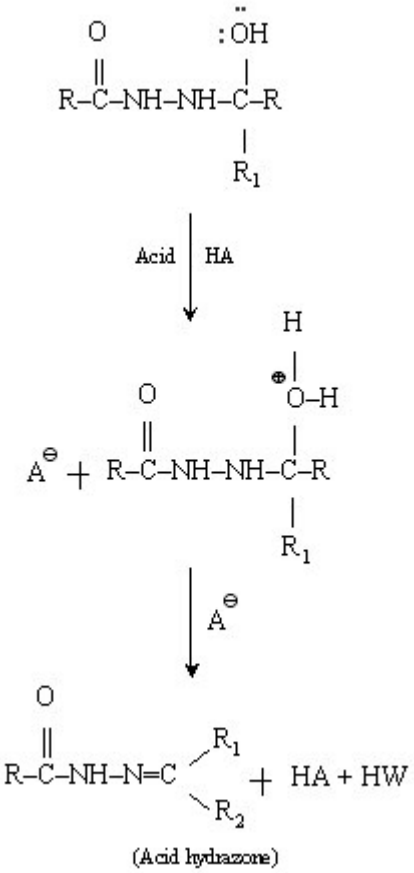


Chart 1: [Mechanism of formation of new acid hydrazones]

Anti-fungal activity

The same compounds were tested for their anti-fungal activity against candida albicans, aspergillus niger and alternaria alternate at concentration of 30 mg/ml using sabouraud dextrose agar media. Compounds 12,13 and 15 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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