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Synthesis, Characterization and biological activities of some new hypophosphorousadducts of acidhydrazones derived from 2, 3-dichloroanilidoacetohydrazide

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ABSTRACT

A new series of hypophosphorousadducts of acidhydrazones have been synthesised by the reaction of 2, 3-dichloroanilidoacetohydrazide with various Carbonyl Compounds in 34 to 68% yield. Newly synthesized compounds 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 activities 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 alternata at concentration of 30 mg/ml using Savored dextrose agar media. The compound 1, 3, 12, 13, 14 and 15 shown significant activities and compound 2, 4, 9, 16 and 17 have shown moderate activity 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, dianilide, acidhydrazides, hydrazones, hypophosphorousadducts.

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INTRODUCTION

Acidhydrazones and their condensation products possessing an azometine -NHN=CH-Proton constitute an important class of compounds for new drug development. In the past several years, numerous compounds with diverse structural features have been reported. Therefore, many researchers have synthesized these compounds as target structures and evaluated their biological activities. Hydrazides, hydrazones and their adducts have displayed diverse range of biological properties such as potential biological activities [1-12], anti-viral [13-19], anti-tuberculosis [20-22], anti-tumor [23-28], cardiovascular [29], anti-fungal [30], anti-convulsant [31-34], anti-helmintic [35], anti-leprotic [36], anti-malerial [37-38], anti-depressant [39], analgesic [40], leishmanicidal [41], vasodilator activities [42], anti-Inflammatory [43-47]. Therapeutic protocols for the treatment of HIV infection are mainly based on the combined use of reverse transcriptase, protease, and more recently, of cell fusion and entry inhibitors. Although drugs targeting reverse transcriptase and protease are in wide use and have shown effectiveness, the rapid emergence of resistant variants, often cross-resistant to the members of a given class, limits the efficacy of existing antiretroviral drugs. Therefore, it is critical to develop new agents directed against alternate sites in the viral life cycle, anti-cancer [48-56], anti-HIV [57-64]. Moreover, many selectively chloro-substituted organic compounds show peculiar pharmacological and agrochemical properties. The work reported herein was aimed at the preparation of some new hypophosphorousadducts of acidhydrazones with anticipated biological activities.

EXPERIMENTAL

General

Anhydrous solvents and all reagents were purchased from, Sigma-Aldrich, B.D.H., Excel-R, Extra pure E. Merk quality, Acros or Carlo Erba. Reactions involving air- or moisture-sensitive compounds were performed under a nitrogen atmosphere using oven-dried glassware and syringes to transfer solutions. Melting points (m.p.) were determined using an electrothermal melting point or a Köfler apparatus and are uncorrected. Infrared (IR) spectra were recorded as thin films or nujol mulls on NaCl plates with a Perkin-Elmer-781 IR or 983 -Spectrophotometer and are expressed in ν (cm-^{1}). Nuclear magnetic resonance spectra (^{1}H-NMR and ^{13}C-NMR) were determined in $CDCl_3$/DMSO-d_6 (in 3/1 ratio) or DMSO-d_6 and were recorded on a Varian XL-200 (200 MHz) or a Varian VXR-300 (300 MHz). Chemical shifts (δ scale) are reported in parts per million (ppm) downfield from tetramethylsilane (TMS) used as internal standard. Splitting patterns are designated as follows: s, singlet; d, doublet; t, triplet; q, quadruplet; m, multiplet; brs, broad singlet; dd, double doublet. The assignment of exchangeable protons (-OH and -NH) was confirmed by addition of D_2O. Analytical thin-layer chromatography (TLC) was carried out on Merck silica gel, F-254 plates. For flash chromatography Merck Silica gel-60 was used as stationary phase with a particle size 0.040-0.063 mm (230-400 mesh ASTM). Elemental analyses were performed on a Perkin-Elmer-2400 spectrometer, and were within ±0.5% of the theoretical values.

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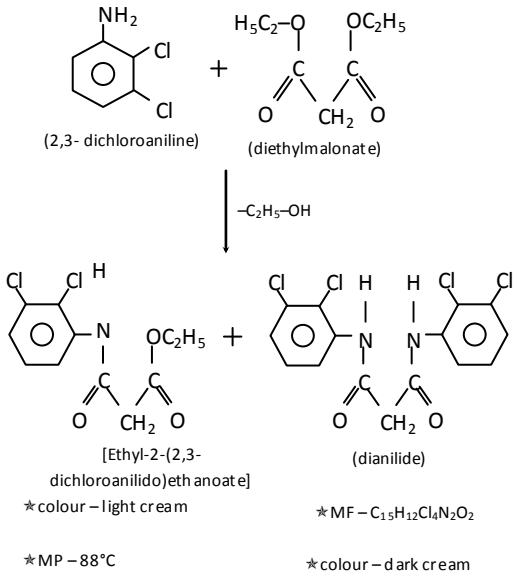
General procedure for the synthesis of Ethyl-2-(2, 3-dichloroanilido) ethanoate [1]:

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, 3-dichlorodianilide 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: 81%, M. P.: 88^0C, M. W.: 276. Anal. Calculation for $C_{11}H_{11}N_1O_3Cl_2$: Found: C 47.7, H: 4.0, O: 17.2, N: 5.1, Cl: 25.4, Calcd. C: 47.8, H: 4.0, O: 17.4, N: 5.1, Cl: 25.7. IR [KBr] V_{max} Cm^{-1} : 1665-1660 [C=O diketone], 1290 [-O- Ester], 760-755 [2,3-disubstituted benzene], 1090 [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 [1H, s, Ar-NH D_2O exchangeable].

Scheme – I



Preparation of 2-(2, 3-dichloroanilido) acetohydrazide [2]:

Ethyl-2-(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. There were evolution of heat and reaction was spontaneous after 30 minutes, 2-(2, 3-dichloroanilido) acetohydrazide was filtered under suction and recrystallised from ethanol in silver white crystals. Yield; 80%, MP = 168°C, MW 262: Analytical calculation for $C_9H_9N_3O_2Cl_2$: Calculated ; N 09.04 ,C 41.32, O 10.33, Cl 15.28, Found; N 09.01, C 41.30, O 10.31, Cl 15.27 IR [KBr] V_{max}

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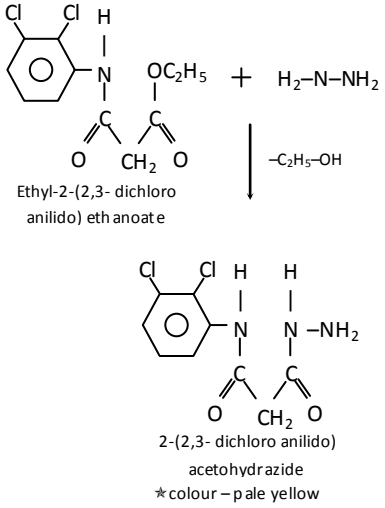
cm^{-1}: 3160 [N-H Stretching], 3048 [C-H aromatic], 1660 [C=O diketone], 1430 [C-Cl aromatic], 1595, 1520, 1445 [C=C ring stretching]. NMR Spectra (δ DMSO): 2.44 (2H, s, CH_2), 3.2 (3H, s, CH_3), 4.22-4.32 (1H, t, N-H), 7.2-7.6 (3H, m, ArH).

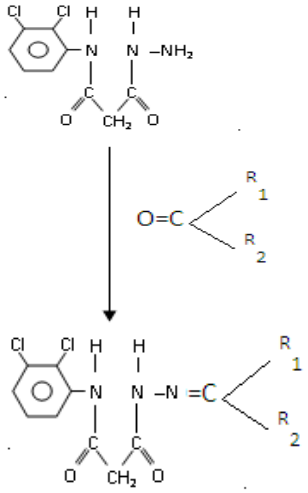
Scheme –II



Synthesis of new acidhydrazones [3]:

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 15-20 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 acidhydrazones is given in chart-I.

Scheme – III



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IR absorption band (cm^{-1}): 3150 (N–H stretching), 2960–2970 (C–H aliphatic), 1665–1660 (C=O Ketone), 785–780 (C–Cl Stretching), 760-755 (2, 3-disubstituted benzene), NMR spectra (δ DMSO), 2.25 (2 H, s, CH_2), 4.21 (1 H, s, NH), 6.95–7.2 (10 H, m, ArH).

Chart – I

[Mechanism of formation of new acidhydrazones]

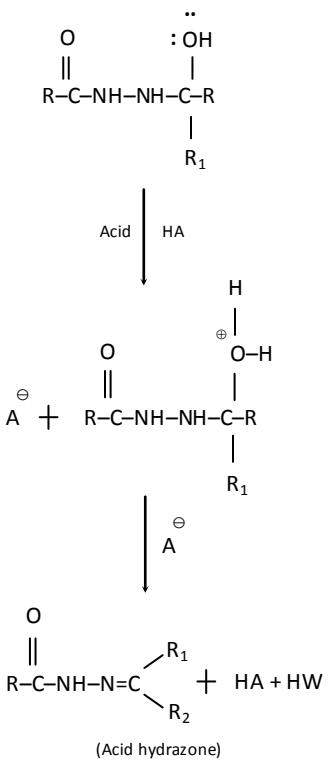

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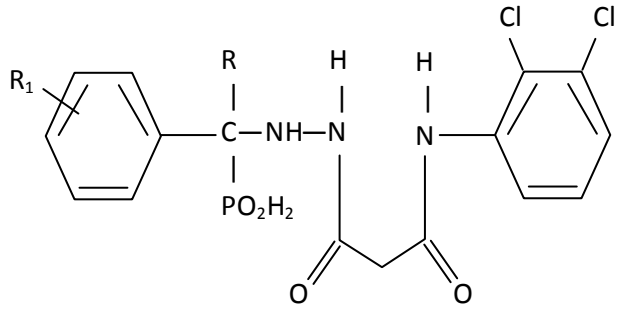
Table – I

Reaction conditions for the formation of new hypophosphorousadducts of acidhydrazones.



(i) Quantity of acidhydrazone = 0.001 mol.

(ii) Quantity of hypophosphorous acid = 2.0 g

(iii) Quantity of absolute alcohol = 15 ml.

(iv) Hours of heating = 3 hours.

(v) Solvent for crystallization – ethanol.

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S. No.	Acidhydrazones	Quantity of acidhydrazones (g)	Adducts		MP (°C)	Yield (%)	Formula weight	Molecular formula	Colour
			R_1	R_2					
01.	Benzaldehyde -2- (2, 3-dichloroanilido) acetohydrazone	0.416	H	Ph	248	61	416	$C_{16}H_{16}O_4N_3Cl_2P$	White
02.	Vanilline -2- (2, 3-dichloroanilido) acetohydrazone	0.462	H	Ph (OMe (3), OH (4))	226	64	462	$C_{17}H_{18}O_6N_3Cl_2P$	White
03.	5-chloro Salicylaldehyde-2-(2, 3-dichloro anilido) acetohydrazone	0.468	H	Ph (OH (2), Cl (5))	235	58	467.5	$C_{16}H_{16}O_5N_3Cl_3P$	White
04.	5-Bromo Salicylaldehyde-2-(2, 3-dichloroanilido) acetohydrazone	0.512	H	Ph (OH (2), Br (5))	224	52	512	$C_{16}H_{16}O_5N_3Cl_2BrP$	Silver White
05.	2-Nitro Vanilline -2- (2, 3- dichloroanilido) acetohydrazone	0.508	H	Ph (NO_2 (2), OCH_3 (3), OH (4))	232	65	508	$C_{17}H_{18}O_8N_4Cl_2P$	Cream
06.	O-Nitrobenzaldehyde-2-(2, 3- dichloroanilido) acetohydrazone	0.462	H	Ph – NO_2 (2)	241	51	462	$C_{16}H_{16}O_6N_4Cl_2P$	White
07.	2-Nitro-5-Bromo Vanilline -2- (2, 3-dichloroanilido) acetohydrazone	0.587	H	Ph (NO_2 (2), OMe (3), OH (4), Br (5))	244	48	587	$C_{17}H_{17}O_8N_4Cl_2BrP$	Cream
08.	3, 5-dichloro-2-hydroxy benzaldehyde-2-(2, 3-dichloroanilido) acetohydrazone	0.502	H	Ph (OH (2), Cl (3), Cl (5))	231	62	502	$C_{16}H_{15}O_5N_3Cl_4P$	White
09.	3-Nitro- 6-hydroxy acetophenone-2- (2, 3-dichloroanilido) acetohydrazone	0.492	Me	Ph (NO_2 (3), OH (6))	230	49	492	$C_{17}H_{18}O_7N_4Cl_2P$	Cream
10.	Acetone -2- (2, 3-dichloroanilido) acetohydrazone	0.368	Me	Me	253	44	368	$C_{12}H_{16}O_4N_3Cl_2P$	Cream
11.	2-Chlorobenzaldehyde -2- (2, 3-dichloroanilido) acetohydrazone	0.452	H	Ph – Cl (2)	236	64	451.5	$C_{16}H_{16}O_4N_3Cl_3P$	White

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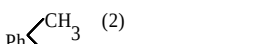
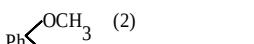
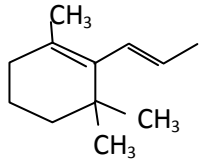
12.	4-NN-bis-2'-cyanoethylamino benzaldehyde-2-(2, 3- dichloroanilido) acetohydrazone	0.538	H	$Ph-N-(CH_2-CH_2-CN)_2$	237	68	538	$C_{22}H_{24}O_4N_6Cl_2P$	Light brown
13.	2-Methyl-4-N-N-bis-2'-cyanoethyl aminobenzaldehyde (2, 3- dichloroanilido) acetohydrazone	0.552	H		243	46	552	$C_{23}H_{26}O_4N_6Cl_2P$	Brown
14.	2-Methoxy-4-N-N-bis-2'-cyanoethylamino benzaldehyde (2, 3- dichloroanilido) acetohydrazone	0.568	H		245	60	568	$C_{25}H_{24}O_5N_6Cl_2P$	Brown
15.	Acetophenone -2-(2, 3- dichloroanilido) acetohydrazone	0.430	Me	Ph	228	55	430	$C_{17}H_{18}O_4N_3Cl_2P$	White
16.	Salicylaldehyde-2-(2, 3- dichloroanilido) aceto hydrazone	0.433	H	$Ph-OH\ (2)$	241	47	433	$C_{16}H_{17}O_5N_3Cl_2P$	White
17.	Anisicaldehyde -2- (2, 3-dichloroanilido) acetohydrazone	0.447	H	$Ph-OCH_3\ (2)$	229	59	447	$C_{17}H_{19}O_5N_3Cl_2P$	Yellow
18.	β-Ionone -2- (2, 3- dichloroanilido) acetohydrazone	0.504	Me		237	34	504	$C_{22}H_{32}O_4N_3Cl_2P$	Buff

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Biological evaluation

Anti-bacterial activity

Newly prepared hypophosphorousadducts of acidhydrazones 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 by agar plate disc diffusion method at 30 µg/mL concentration. Ampicillin and Tetracycline were used as a reference compounds. The compound 1, 3, 7, 12, 13, 14 and 15 shown significant activities and compound 2, 4, 6, , 8, 9, 16 and 17 have shown moderate activity.

Anti-fungal 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 Savored dextrose agar media. The compound 1, 3, 12, 13, 14 and 15 shown significant activity and compound 2, 4, 9, 16 and 17 have shown moderate activity 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

Hypophosphorousadducts of various acidhydrazones have been synthesized by the reaction of 2-(2, 3-dichloroanilido) acetohydrazide with various Carbonyl Compounds in 34 to 68% yield. Hydrazonephosphorousadducts are white, 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. Newly synthesized compounds 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 1, 3, 7, 12, 13, 14 and 15 shown significant activities and compound 2, 4, 6, 8, 9, 16 and 17 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 savored dextrose agar media. The compound 1, 3, 12, 13, 14 and 15 shown significant activities and compound 2, 4, 9, 16 and 17 have shown moderate activity against Candida albicans and Aspergillus Niger. All the other compounds did not show significant activity against the fungi at the concentration used.

CONCLUSIONS

Newly synthesized compounds have been tested for their antibacterial 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 1, 3, 7, 12, 13, 14 and 15 shown significant activities and compound 2, 4, 6, , 8, 9, 16 and 17 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 albicans and Aspergillus niger. All the other compounds did not show significant activity mg/mL using Savored dextrose agar media. The compound 1, 3, 12, 13, 14 and 15 shown significant activities and compound 2, 4, 9, 16 and 17 have shown moderate activity against Candida against the fungi at the concentration used.

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