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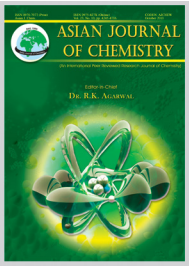

Synthesis, Characterization and Biological Activities of Some New Hypophosphorous Adducts of Acidhydrazones Derived from 2-[(*N*-benzoyl)-2,5-dichloroanilido]acetohydrazide

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A new series of hypophosphorous adducts of acidhydrazones have been synthesized by the reaction of 2-[*N*-(benzoyl)-2,5-dichloroanilido]acetohydrazide with various carbonyl compounds in 43 to 66 % yield. 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, 4, 10, 12, 15**) show significant activities and compound (**2, 6, 9, 16, 17**) show 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, 7, 13, 14, 15**) show significant activities and compound (**2, 5, 8, 16**) 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, Acid hydrazides, Hydrazones, Hypophosphorous adducts.

INTRODUCTION

Acidhydrazones and their condensation products possessing an azomethine -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], antiviral[13-19], antituberculosis[20-22], antitumor[23-28], cardiovascular[29], antifungal[30], anticonvulsant[31-34], antihelmintic[35], antileprotic[36], antimalerial[37,38], antidepressant[39], analgesic[40], leishmanicidal[41], vasodilator activities[42], antiinflammatory[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, anticancer[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 hypophosphorous adducts of acidhydrazones with anticipated biological activities.

EXPERIMENTAL

Anhydrous solvents and all reagents were purchased from, Sigma-Aldrich, B.D.H., Excel-R, Extra pure E. Merck 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 electro thermal melting point or a Köfler apparatus and are uncorrected. Infrared (IR) spectra were recorded as thin films or nujol mulls on KBr plates with a Perkin-Elmer-781 IR or 983-spectrophotometer and are expressed in $\nu(cm^{-1})$. Nuclear magnetic resonance spectra (^1H 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. 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 ± 0.7 % of the theoretical values.

Synthesis of ethyl-2-(2,5-dichloroanilido)ethanoate [1]: A mixture of diethylmalonate (20 mL) and 2,5-dichloroaniline (10 mL) was refluxed for 45 min 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. After cooling the contents, ethanol (30 mL) was added, when malon-2,5-dichlorodianilide separated out. It was filtered under suction. The filtrate was poured on to crushed ice (*ca.* 160 g) 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: 82 %, m.p.: 89 ºC, m.w. 276. Anal. Calculation for $C_{11}H_{11}NO_3Cl_2$: Found: C 47.7, H: 4.0, N: 5.1, Cl: 25.4, calcd. C: 47.8, H: 4.0, N: 5.1, Cl: 25.7. IR [KBr, ν_{max}, cm^{-1}]: 1665-1660 [C=O diketone], 1290 [-O- ester], 760-755 [2,5-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].

Synthesis of ethyl-2-[(*N*-benzoyl)-2,5-dichloroanilido] ethanoate [2]: Benzoyl chloride (8.46 g; 0.06 mol), dioxane (6 mL), ethyl-2-(2,5-dichloroanilido) ethanoate (16.5 g; 0.06 mol) and triethylamine (6.06 g; 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 2 h and kept over night when triethylamine hydrochloride separated. It was filtered under suction and the filtrate was poured on to crushed ice (*ca.* 180 g) and stirred when ethyl-2-[(*N*-benzoyl)-2,5-dichloroanilido] ethanoate separated or solid. It was filtered under suction, dried and purified by recrystallization from aqueous methanol (1:1) in white crystals. Yield = 81 %, m.p. = 96 ºC; analytical calculation for $C_{18}H_{15}NO_4Cl_2$: [FW = 380], calculated: N 2.95, C 45.64, H 3.38, Cl 15.00, found : N 2.94, C 45.62, H 3.37, Cl 15.02.; IR [KBr, ν_{max}, cm^{-1}]: 1725 [C=O diketone], 1310 [-C-O-Ester], 765 [2,5-disubstituted benzene], 1095 [C-Cl stretching], 1580, 1525, 1445 [C=C ring stretching], 3165 [N-H stretching], 3030 [C-H aromatic], 1320-1330 [C-H stretching]; PMR (DMSO): δ 4.45 [2H, s, CO-CH_2-CO], 4.2 [2H, s, NH_2], 7.3-8.5 [3H, m, Ar-H], 9.5 [1H, s, CO-NH D_2O exchangeable], 10.9 [1H, s, Ar-NH D_2O exchangeable].

Synthesis of 2-[(*N*-benzoyl)-2,5-dichloroanilido]acetohydrazide [3]: Ethyl-2-[(*N*-benzoyl)-2,5-dichloroanilido] ethanoate (10.98 g; 0.03 mol), ethanol (8 mL) and hydrazine hydrate (15 mL; 70 %) were mixed together and stirred for thirty 5 min. 2-[(*N*-benzoyl)-2,5-dichloroanilido]acetohydrazide was filtered under suction and recrystallized from ethanol in white crystals; yield; 79 %, m.p. = 176 ºC, m.w. 366; analytical calculation for $C_{16}H_{13}N_3O_3Cl_2$: calculated: N 9.04, C 41.32,H 3.01,Cl 15.28, found: N 9.01, C 41.30, H 3.00, Cl 15.27. IR [KBr, ν_{max}, cm^{-1}] : 3165 [N-H stretching], 3050 [C-H aromatic], 1665 [C=O diketone], 1440 [C-Cl aromatic], 1590, 1525, 1440 [C=C ring stretching]. PMR (DMSO): δ 4.45 (2H, s, CO-CH_2-CO), 4.2 (2H, s, NH_2), 7.2-8.6 (3H, m, Ar-H), 9.5 (1H, s, CO-NH D_2O exchangeable), 10.7 (1H, s, Ar-NH D_2O exchangeable).

Synthesis of 2-[(*N*-benzoyl)-2,5-dichloroanilido]acetohydrazones [4]: 2-[(*N*-benzoyl)-2,5-dichloroanilido] acetohydrazide (0.001 mol) and (0.001 mol) of aromatic aldehyde or ketone (carbonyl compound) dissolve in absolute alcohol and added 2-drops of conc. H_2SO_4 and stirred for 25 min. It was filtered under suction and recrystallized from hot ethanol.; yield: 92 %, m.p. = 223 ºC, F.W: 455, colour: white, analytical calculation for $C_{23}H_{18}O_3N_3Cl_2$ calculated: N 12.04, C 54.85, H 3.71, Cl 20.28, found: N 11.99, C 54.83, H 3.70, Cl 20.25; IR Absorption band (cm^{-1}): 3155 (N-H stretching), 2975-2965 (C-H aliphatic), 1665-1660 (C=O Ketone), 785-770 (C-Cl stretching), 765 (2,5-disubstituted benzene); NMR spectra: (δ DMSO), 2.28(2 H, s, CH_2), 4.22(1 H, s, NH), 6.90-7.5 (10 H, m, ArH. Synthetic strategy has been out lined in **Scheme-I**. Mechanism for the formation of acid hydrazones is given in chart-I.

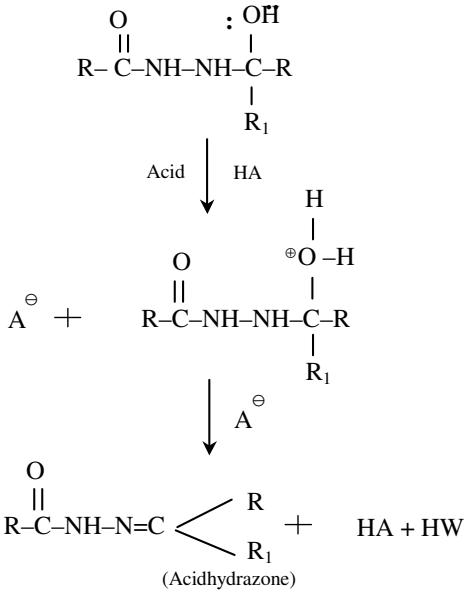
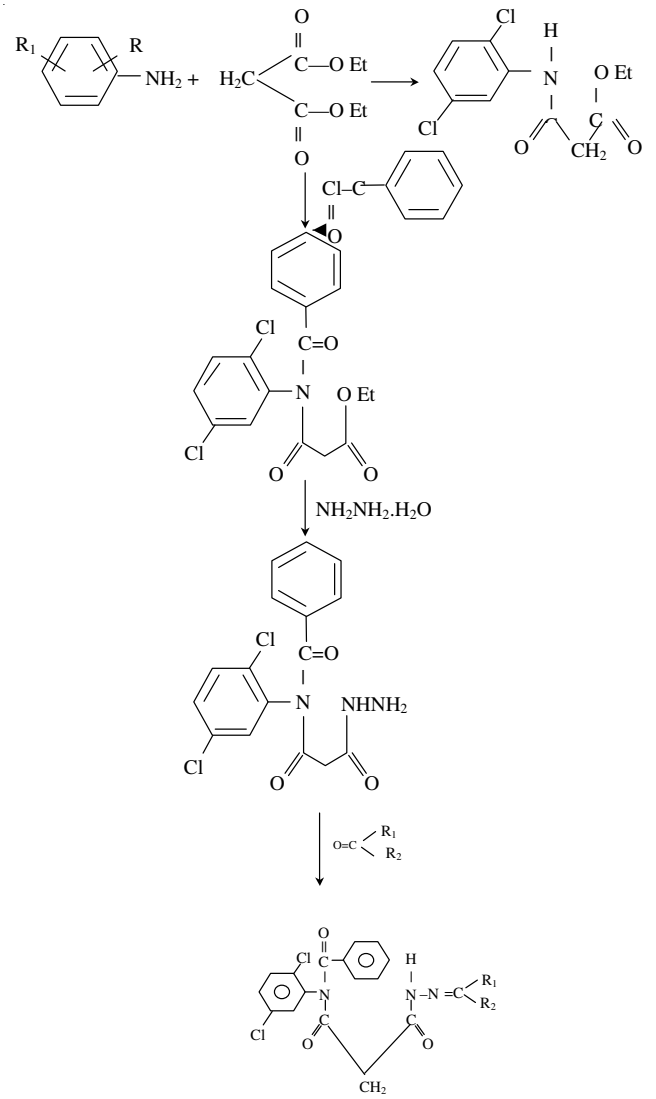


Chart - I [Mechanism: formation of new acidhydrazones]

Biological evaluation

Antibacterial activity: Newly prepared hypophosphorous adducts of acidhydrazones were screened for their antibacterial 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, 4, 10, 12** and **15**) shown significant activities and compound (**2, 6, 9, 16** and **17**) have shown moderate activity.

Antifungal 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, 7, 13, 14, 15**) shown significant activity and compound (**2, 5, 8, 16**) 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.



Scheme-I

RESULTS AND DISCUSSION

Hypophosphorous adducts of various acidhydrazones have been synthesized by the reaction of 2-[*N*-(benzoyl)-2,5-dichloroanilido]acetohydrazide with various carbonyl compounds in 43 to 66 % yield (Table-1). Hydrazone phosphorous adducts 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, 4, 10, 12** and **15**) shown significant activities and compound (**2, 6, 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, 7, 13, 14, 15**) shown significant activities and compound (**2, 5, 8, 16**) 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.

Conclusion

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, 4, 10, 12** and **15**) shown significant activities and compound (**2, 6, 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, 7, 13, 14, 15**) shown significant activities and compound (**2, 5, 8, 16**) have shown moderate activity against *Candida albicans* and *Aspergillus niger* at the concentration used.

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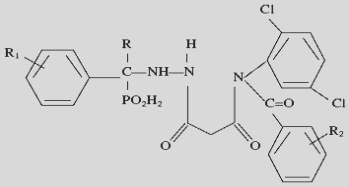
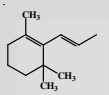
TABLE-1
REACTION CONDITIONS FOR THE FORMATION OF HYPOPHOSPHOROUS ADDUCTS OF ACID HYDRAZONES
(i) Quantity of acid hydrazone = 0.001 mol; (ii) Quantity of hypophosphorous acid = 2 g;
(iii) Quantity of absolute alcohol = 15 mL; (iv) Time of heating = 3 h; (v) Solvent for crystallization=ethanol



S. No.	Acidhydrazones	Acid hydrazone (g)	Adducts		m.p. (°C)	Yield (%)	f.w.	m.f.	Colour
			R_1	R_2					
01	Benzaldehyde-2-[(*N*-benzoyl)-2,5-dichloroanilido]acetohydrazone	0.521	H	Ph	261	54	521	$C_{23}H_{21}O_5N_3PCl_2$	White
02	Vanilline-2-[(*N*-benzoyl)-2,5-dichloroanilido]acetohydrazone	0.566	H	Ph(OMe(3), OH (4))	236	48	566	$C_{24}H_{23}O_7N_3PCl_2$	White
03	5-chloro-salicylaldehyde-2-[(*N*-benzoyl)-2,5-dichloroanilido] acetohydrazone	0.572	H	Ph(OH(2), Cl (5))	247	53	571.5	$C_{23}H_{21}O_6N_3PCl_3$	White
04	5-Bromo-salicylaldehyde-2-[(*N*-benzoyl)-2,5-dichloroanilido] acetohydrazone	0.616	H	Ph(OH(2), Br (5))	231	58	616	$C_{23}H_{21}O_6N_3PBrCl_2$	Silver white
05	2-Nitro vanilline-2-[(*N*-benzoyl)-2,5-dichloroanilido]acetohydrazone	0.612	H	Ph(NO_2 (2), OCH_3 (3), OH (4))	240	60	612	$C_{24}H_{23}O_9N_4PCl_2$	Cream
06	*O*-Nitrobenzaldehyde-2-[(*N*-benzoyl)-2,5-dichloroanilido] acetohydrazone	0.566	H	Ph – NO_2 (2)	244	54	566	$C_{23}H_{21}O_7N_4PCl_2$	White
07	2-Nitro-5-bromo vanilline-2-[(*N*-benzoyl)-2,5-dichloroanilido] acetohydrazone	0.691	H	Ph(NO_2 (2), OMe (3), OH (4), Br (5))	267	65	691	$C_{24}H_{22}O_9N_4PBrCl_2$	Cream
08	3,5-dichloro-2-hydroxy benzaldeh -yde-2-[(*N*-benzoyl)-2,5-dichloroanilido]acetohydrazone	0.606	H	Ph(OH(2), Cl (3), Cl (5))	239	59	606	$C_{23}H_{20}O_6N_3PCl_4$	White
09	3-Nitro-6-hydroxy acetophenone-2- [(*N*-benzoyl)-2,5-dichloro anili -do]acetohydrazone	0.496	Me	Ph(NO_2 (3), OH (6))	247	55	496	$C_{24}H_{23}O_8N_4PCl_2$	Cream
10	Acetone-2-[(*N*-benzoyl)-2,5-di chloroanilido]acetohydrazone	0.472	Me	Me	233	48	472	$C_{19}H_{21}O_5N_3PCl_2$	Cream
11	2-Chlorobenzaldehyde-2-[(*N*-benzoyl)-2,5-dichloroanilido]acetohydrazone	0.456	H	Ph–Cl (2)	228	61	455.5	$C_{23}H_{21}O_5N_3PCl_3$	White
12	4-*NN-bis*-2'-cyanoethylamino benzaldehyde-2-[(*N*-benzoyl)-2,5-dichloroanilido]acetohydrazone	0.642	H	Ph – N – $(CH_2 - CH_2 - CN)_2$	244	66	642	$C_{29}H_{29}O_5N_6PCl_2$	Light brown
13	2-Methyl-4-*N-N-bis*-2'-cyanoethyl aminobenzaldehyde[(*N*-benzoyl)-2,5-dichloroanilido]acetohydrazone	0.656	H	Ph(CH_3 (2), $N(CH_2 - CH_2 - CN)_2$ (4))	252	58	656	$C_{30}H_{31}O_5N_6PCl_2$	Brown
14	2-Methoxy-4-*N-N-bis*-2'-cyanoethylamino benzaldehyde[(*N*-benzoyl)-2,5-dichloroanilido] acetohydrazone	0.672	H	Ph(OCH_3 (2), $N(CH_2 - CH_2 - CN)_2$ (4))	231	54	672	$C_{32}H_{29}O_6N_6PCl_2$	Brown
15	Acetophenone-2-[(*N*-benzoyl)-2,5-dichloroanilido] acetohydrazone	0.534	Me	Ph	238	59	534	$C_{24}H_{23}O_5N_3PCl_2$	White
16	Salicylaldehyde-2-[(*N*-benzoyl)-2,5-dichloroanilido]acetohydrazone	0.537	H	Ph–OH (2)	255	55	537	$C_{23}H_{22}O_6N_3PCl_2$	White
17	Anisicaldehyde-2-[(*N*-benzoyl)-2,5-dichloroanilido]acetohydrazone	0.551	H	Ph–OCH_3 (2)	235	46	551	$C_{24}H_{24}O_6N_3PCl_2$	Yellow
18	β-Ionone-2-[(*N*-benzoyl)-2,5-di chloroanilido]acetohydrazone	0.608	Me		249	43	608	$C_{29}H_{37}O_5N_3PCl_2$	Buff

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