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Synthesis, characterization and biological activities of some new hypophosphorousadducts of acidhydrazones derived from 2-[(N-acetyl) 2, 3-dichloroanilido] acetohydrazide

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ABSTRACT

*A new series of hypophosphorousadducts of acidhydrazones have been synthesized by the reaction of 2-[N- (acetyl) 2, 3-dichloroanilido acetohydrazide with various Carbonyl Compounds in 39 to 67% 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, 2, 3, 5, 7, 10, 12, 15**) shown significant activities and compound (4, 6, 9, 13, 14, 17) 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 (**3, 5, 7, 9, 11**, **14**) shown significant activities and compound (2, 4, 6, 12, 13, 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.*

Keywords: Malonicester, dianilide, acidhydrazides, hydrazones, hypophosphorousadducts.

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 acid hydrazones with anticipated biological activities.

EXPERIMENTAL SECTION

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 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 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 (-O*H* and -N*H*) 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 ±0.6% of the theoretical values.

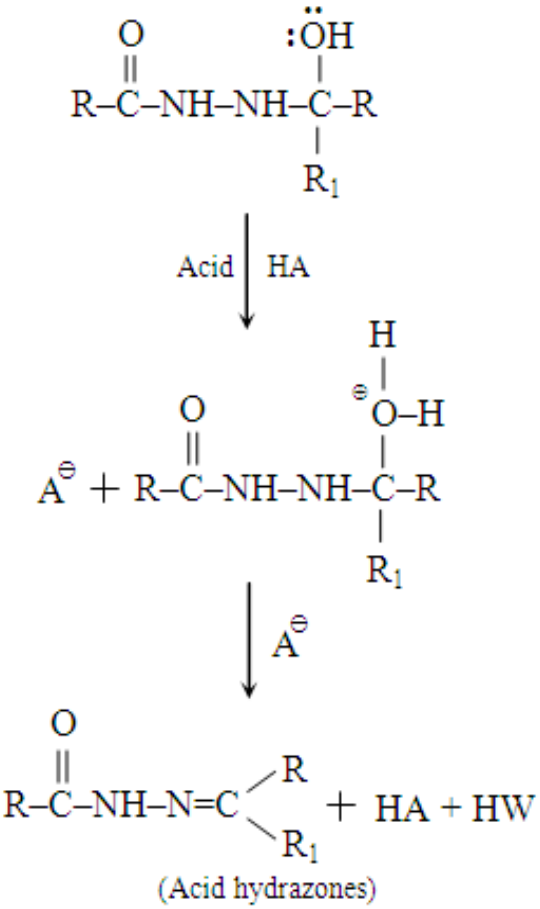
Synthesis of Ethyl-2-(2, 3-dichloroanilido) ethanoate [1]:

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^{0}C, 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].

Synthesis of Ethyl-2-[(N-acetyl) 2, 3- dichloroanilido] ethanoate [2]:

Acetyl chloride (4.74 gm; 0.06 mol), dioxane (6 ml), Ethyl-2-(2, 3-dichloroanilido) ethanoate (16.56 gm; 0.06 mol) and triethylamine (5.7 gm; 0.06 mol) were placed in a round bottomed flask carrying reflux condenser 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-acetyl) 2, 3-dichloroanilido] ethanoate separated or solid. It was filtered under suction, dried and purified by recrystallisation from aqueous methanol (1:1) in white crystals. Yield = 76.4 %, MP = 88°C Analytical calculation for $C_{13}H_{13}O_4N_1Cl_2$: [FW = 318] , 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], 765 [2,3- disubstituted benzene], 1090 [C-Cl Stretching], 1590, 1520 , 1440 [C=C Ring stretching], 3160 [N-H Stretching], 3040[C-H aromatic], 1330-1325 [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].

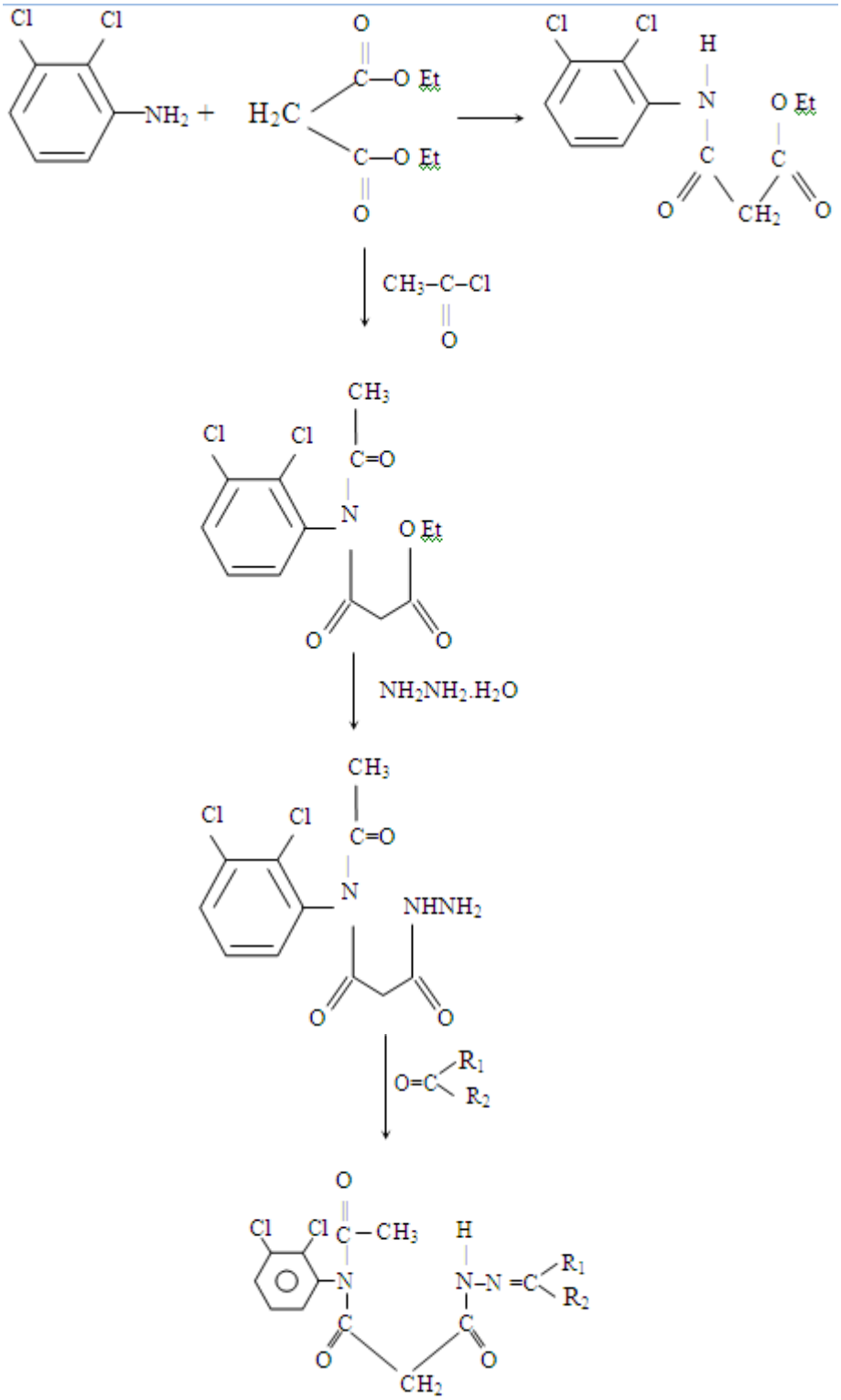
CHART – I



(Acid hydrazones)

[Mechanism of formation of new acidhydrazones]

Scheme –I



Synthesis of 2-[(N-acetyl) 2, 3- dichloroanilido] acetohydrazide [3]:

Ethyl-2-[(N-acetyl) 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. 2-[(N-acetyl) 2, 3-dichloroanilido] acetohydrazide was filtered under suction and recrystallised from ethanol in white crystals. Yield; 74%, MP = 172°C, MW 304: Analytical calculation for C_{11} H_{11} N_3 O_3 Cl_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), 10.7 (1H, s, Ar-NH D_2O exchangeable).

Synthesis of 2-[(N-acetyl) 2, 3-dichloroanilido] acetohydrazones [4]:

2-[(N-acetyl) 2, 3-dichloroanilido] acetohydrazide (0.001 mol) and (0.001 mol) of aromatic aldehyde or ketone [such as benzaldehyde] dissolve in absolute alcohol and added 2-drops of conc. H_2SO_4 and stirred for 25 minutes. It was filtered under suction and recrystallised from hot ethanol. Color: Silver white, Yield: 91%, M.P= 214 ^{0}C, F.W: 392, Analytical calculation for $C_{18}H_{15}O_3N_3Cl_2$, Calculated: N 12.04, C 54.85, H 03.71, O 09.14, Cl 20.28, Found: N 11.98, C 54.82, H 03.70, O 10.31, Cl 20.26. *IR Absorption band (cm^{-1}):* 3150 (N–H stretching), 2960–2970 (C–H aliphatic), 1662–1660 (C=O Ketone), 790–780 (C–Cl Stretching), 765 (2, 3-disubstituted benzene). *NMR Spectra: (δ DMSO*), 2.20(2 H, s, CH_2), 4.22(1 H, s, NH), 6.96–7.1 (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.

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, 2, 3, 5, 7, 10, 12, 15)*** shown significant activities and compound (*4,* 6, *9, 13, 14, 17*) have shown moderate activity.

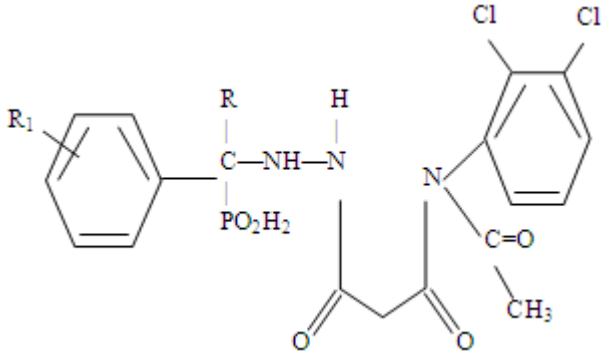
Anti-fungal activity

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 (***3, 5, 7, 9, 11, 14)*** shown significant activity and compound (*2, 4, 6, 12, 13, 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.

RESULTS AND DISCUSSION

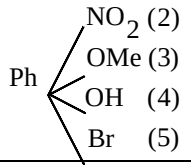
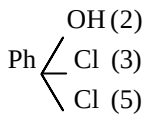
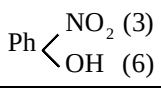
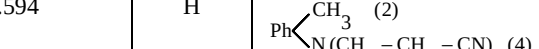
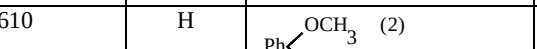
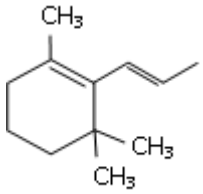
Hypophosphorousadducts of various acidhydrazones have been synthesized by the reaction of 2-[N- (acetyl) 2, 3-dichloroanilido] acetohydrazide with various Carbonyl Compounds in 39 to 67% yield. Hydrazonephosphorousadducts are white, brown and yellow colour solids, having high melting points. The structure of all the compounds are confirmed by IR, NMR, 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, 2, 3, 5, 7, 10, 12, 15)*** shown significant activities and compound (*4,* 6, *9, 13, 14, 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 (***3, 5, 7, 9, 11, 14)*** shown significant activities and compound (*2, 4, 6, 12, 13, 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.

Table–I Reaction conditions for the formation of hypophosphorousadducts of acidhydrazones.



(i)Quantity of acidhydrazone = 0.001 mol.
(ii)Quantity of hypophosphorous acid = 2.0 g
(iii)Quantity of absolute alcohol = 20 ml.
(iv) Hours of heating =3.5 hours.
(v) Solvent for crystallization - ethanol.

S. No.	***Acidhydrazones***	***Quantity of Acidhydrazone (g)***	***Adducts***		***MP (°C)***	***Yield (%)***	***Formula weight***	***Molecular formula***	***Colour***
			R_1	*R_2*					
01.	Benzaldehyde-2-[(N-acetyl) 2, 3-dichloroanilido] acetohydrazone	0.458	H	Ph	263	67	458	$C_{18}H_{19}O_5N_3Cl_2P$	White
02.	Vanilline-2-[(N-acetyl) 2, 3-dichloroanilido] acetohydrazone	0.504	H	Ph, OMe (3), OH (4)	256	62	504	$C_{19}H_{21}O_7N_3Cl_2P$	White
03.	5-chloro Salicylaldehyde-2-[(N- acetyl) 2, 3-dichloro anilido] acetohydrazone	0.509.5	H	Ph, OH (2), Cl (5)	246	54	509.5	$C_{18}H_{19}O_6N_3Cl_3P$	White
04.	5-Bromo Salicylaldehyde-2-[(N- acetyl) 2, 3-dichloroanilido] acetohydrazone	0.554	H	Ph, OH (2), Br (5)	222	58	554	$C_{18}H_{19}O_6N_3Cl_2BrP$	Silver White
05.	2-Nitro Vanilline-2-[(N- acetyl) 2, 3-dichloroanilido]acetohydrazone	0.553	H	Ph, NO_2 (2), OCH_3 (3), OH (4)	235	67	553	$C_{19}H_{21}O_9N_4Cl_2P$	Cream
06.	O-Nitrobenzaldehyde-2- [(N- acetyl) 2, 3-dichloroanilido] acetohydrazone	0.504	H	Ph – NO_2 (2)	247	57	504	$C_{18}H_{13}O_7N_4Cl_2P$	White

07.	2-Nitro-5-Bromo Vanilline-2-[(N- acetyl) 2, 3-dichloroanilido)] acetohydrazone	0.629	H		253	53	629	$C_{19}H_{20}O_9N_4Cl_2BrP$	Cream
08.	3,5-dichloro-2-hydroxy benzaldehyde-2-[(N-acetyl) 2, 3- dichloroanilido] acetohydrazone	0.544	H		240	64	544	$C_{18}H_{18}O_6N_3Cl_4P$	White
09.	3-Nitro- 6-hydroxy acetophenone-2- [(N-acetyl) 2, 3-dichloro anilido] acetohydrazone	0.534	Me		252	53	534	$C_{19}H_{21}O_8N_4Cl_2P$	Cream
10.	Acetone-2-[(N-acetyl) 2, 3-di chloroanilido] acetohydrazone	0.410	Me	Me	258	49	410	$C_{14}H_{19}O_5N_3Cl_2P$	Cream
11.	2-Chlorobenzaldehyde-2-[(N- acetyl) (2, 3-dichloroanilido)] acetohydrazone	0.493.5	H	$Ph-Cl\,(2)$	229	61	493.5	$C_{18}H_{19}O_5N_3Cl_3P$	White
12.	4-NN-Bis-2'-cyanoethylamino benzaldehyde-2-[(N-acetyl) 2, 3- dichloroanilido] acetohydrazone	0.580	H	$Ph-N-(CH_2-CH_2-CN)_2$	244	66	580	$C_{24}H_{27}O_5N_6Cl_2P$	Light brown
13.	2-Methyl-4-N-N-Bis-2'-cyanoethyl aminobenzaldehyde [(N-acetyl) 2, 3-dichloroanilido] aceto hydrazone	0.594	H		259	49	594	$C_{25}H_{29}O_5N_6Cl_2P$	Brown
14.	2-Methoxy-4-N-N-bis-2'-cyanoethylamino benzaldehyde [(N-acetyl) 2, 3- dichloro anilido] acetohydrazone	0.610	H		242	67	610	$C_{27}H_{27}O_6N_6Cl_2$	Brown
15.	Acetophenone-2-[(N-acetyl) 2, 3-dichloroanilido] acetohydrazone	0.472	Me	Ph	243	58	472	$C_{19}H_{21}O_5N_3Cl_2P$	White
16.	Salicylaldehyde-2-[(N-acetyl) 2, 3-dichloroanilido] aceto hydrazone	0.475	H	$Ph-OH\,(2)$	256	52	475	$C_{18}H_{20}O_6N_3Cl_2P$	White
17.	Anisicaldehyde-2-[(N-acetyl) 2, 3-dichloroanilido] acetohydrazone	0.489	H	$Ph-OCH_3\,(2)$	232	61	489	$C_{19}H_{22}O_6N_3Cl_2P$	Yellow
18.	β-Ionone-2-[(N-acetyl) (2, 3-di chloroanilido] acetohydrazone	0.546	Me		226	39	546	$C_{24}H_{35}O_5N_3Cl_2P$	Buff

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, 2, 3, 5, 7, 10, 12, 15)*** shown significant activities and compound (*4*, 6, *9, 13, 14, 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 (***3, 5, 7, 9, 11***, ***14)*** *shown* significant activities and compound (*2, 4, 6, 12, 13, 16)* have shown moderate activity against *Candida* against the fungi at the concentration used.

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