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Synthesis, Characterization and Biological Activities of some New Acid Hydrazones Derived from 2-[(N-Benzoyl) 2, 5-Dichloroanilido] Acetohydrazide

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ABSTRACT: A series of new acidhydrazones have been synthesized by the reaction of 2-[(N-benzoyl) 2, 5-dichloroanilido]acetohydrazide with various Carbonyl Compounds in 37 to 91 % yield. Hydrazones are white, brown and yellow colour solids, having high melting points. Newly synthesized compounds (**1, 2, 3, 4, 5, 6, 7, 8, 9, 12, 13, 14, 15, 16 and 17)** 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 **2, 3, 5, 12, 13, 14,** and **15** shown significant activity and compound **1, 4, 6, 7, 8, 9, 16 and 17** have shown moderate activity. The same compounds were tested for their **antifungal activity** against C**andida albicans, Aspergillus niger and Alternaria alternata** at concentration of 30 mg/mL using savored dextrose agar media. The compound **2, 5, 12, 13, 14,** and **15** shown significant activities and compound **1, 4, 8, 9, 16 and 17** have shown moderate activity against C**andida albicans** and A**spergillus niger.** All the other compounds did not show significant activity against the fungi at the concentration used. Some new compounds have been tested for **antitubercular** activity in-vitro using **Mycobacterium tuberculosis.** The compounds were incorporated into Lowenstein Jensen egg medium having concentrations of 10 and 100 mg/mL and were inoculated with Mycobacterium tuberculosis, $H_{27,}$ Rv strains, incubated at 37^0C and observed, **2-[(N-benzoyl)2,5-dichloroanilido] acetohydrazide, 2-[(N-benzoyl)2,5-dichloroanilido] acetohydrazone of 4-N,N-Bis -2'- cyanoethylamino benz aldehyde, 2-[(N-benzoyl)2,5-dichloroanilido] acetohydrazone of 2- methyl-4-N,N-Bis -2' – cyanoethyl amino ben zaldehyde and 2-[(N-benzoyl)2,5-dichloroanilido] acetohydrazone of 5-Chloro Salicylaldehyde** inhibited the growth of Mycobacterium tuberculosis at 100mg/mL concentration other compounds were found to be inactive.
KEYWORDS: Malonicester, Acidhydrazide, Acidhydrazones, 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. Acidhydrazides 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 structures 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 points 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.

Synthesis of Ethyl-2-[2, 5-dichloroanilido] Ethanoate [1]:

A mixture of 2, 5-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, 5dichlorodianilide separated out. It was filtered under suction. The filtrate was poured on to crushed ice (Ca160g) 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.:** 86^0C, **M. W.:** 276. Analytical calculation for $\mathbf{C_{11}\,H_{11}\,N_1\,O_3\,Cl_2}$: Found: C 39.24, H: 03.22, O: 14.23, N: 4.13, Cl: 21.12, Calcd. C: 39.21, H: 03.26, O: 14.26, N: 04.15, Cl: 21.16.

IR [KBr] V_{max} Cm^{-1} : 1665-1660 [C=O diketone], 1290 [-C-O- Ester], 760-755 [2,5 disubstituted benzene], 1255 [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 4.40 (2H, s, CO-CH_2-CO), 4.14 (2H, s, NH_2), 7.3-8.5 (3H, m, Ar-H), 9.5 (1H, s, CO-NH D_2O exchangeable), 10.5 [1H, s, Ar-NH D_2O exchangeable].

Synthesis of Ethyl-2-[(N-benzoyl) 2, 5-dichloroanilido] ethanoate [2]:

Benzoyl chloride (8.46 gm; 0.06 mol), dioxane (6 ml), Ethyl-2-(2, 5-dichloroanilido) ethanoate (16.5 gm; 0.06 mol) and Triethylamine (6.06 gm; 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 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-benzoyl) 2, 5-dichloroanilido]ethanoate separated or solid. It was filtered under suction, dried and purified by recrystallisation from aqueous methanol (1:1) in white crystals.

Yield = 76.8 %, MP = 97°C

Analytical calculation for $\mathbf{C_{18}\,H_{15}\,N_1\,O_4\,Cl_2}$: [FW = 380] , Calculated: N 02.95 , C 45.64, H 03.38 , O 13.50 , Cl 16.00 , Found : N 02.94, C 45.62 , H 03.37 , O 13.52 , Cl 16.05.

IR [KBr] V_{max} cm^{-1}: 1720 [C=O diketone], 1300 [-C-O- Ester], 762[2, 5- disubstituted benzene], 1095 [C-Cl Stretching], 1590, 1520, 1440 [C=C Ring stretching], 3160 [N-H Stretching], 3040[C-H aromatic], 1330-1322 [C-H Stretching].

PMR (DMSO): δ 4.44 [2H, s, CO-CH_2-CO], 4.15 [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].

Synthesis of 2-[(N-benzoyl) 2, 5-dichloroanilido] acetohydrazide [3]:

Ethyl-2-[(N-benzoyl) 2, 5-dichloroanilido]ethanoate (10.98 gm; 0.03 mol), ethanol (8 ml) and hydrazine hydrate (15 ml; 70%) were mixed together and stirred for thirty five minutes. Ethyl-2-[(N-benzoyl) 2, 5-dichloroanilido] acetohydrazide was filtered under suction and recrystallised from ethanol in white crystals.

Yield; 74%, MP = 178°C, MW 366

Analytical calculation for $\mathbf{C_{16}\,H_{13}\,N_3\,O_3\,Cl_2}$: Calculated: N 09.04 ,C 41.32 ,H 03.03 ,O 10.33, Cl 15.29, Found: N 09.02, C 41.30, H 03.01, O 10.31, Cl 15.26.

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 4.42 (2H, s, CO-CH_2-CO), 4.2 (2H, s, NH_2), 7.1-8.6 (3H, m, Ar-H), 9.3 (1H, s, CO-NH D_2O exchangeable), 10.7 (1H, s, Ar-NH D_2O exchangeable)

Synthesis of 2-[(N-benzoyl) 2, 5-dichloroanilido]acetohydrazone [4]:

Ethyl-2-[(N-benzoyl) 2, 5-dichloroanilido] acetohydra -zide (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 15 minutes. It was filtered under suction and recrystallised from hot ethanol.

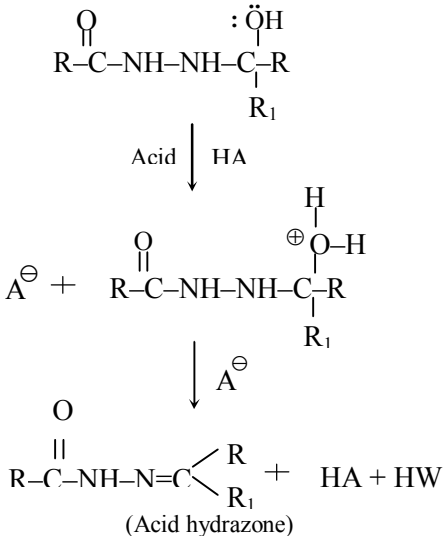
M.F. $C_{23}H_{18}O_3N_3Cl_2$**,** Colour: Silver white, Yield: 91%, M.P= 216 ^{0}C, F.W: 455**,**

Analytical calculation for **$C_{23}H_{18}O_3N_3Cl_2$** 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), 760 (2, 5-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.

CHART – I



[Mechanism of formation of acid hydrazones]

BIOLOGICAL EVALUATION

Anti-bacterial activity:

Newly synthesized compounds (**1, 2, 3, 4, 5, 6, 7, 8, 9, 12, 13, 14, 15, 16 and 17)** 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 **2, 3, 5, 12, 13, 14** and **15** shown significant activities and compound **1, 4, 6, 7, 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 **2, 5, 12, 13, 14** and**15** shown significant activity and compound **1, 4, 8, 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.

Tuberculostatic Activity:

Some new compounds have been tested for ant tubercular activity in-vitro using **Mycobacterium tuberculosis.** The compounds were incorporated into Lowenstein Jensen egg medium having concentrations of 10 and 100 mg/mL and were inoculated with Mycobacterium tuberculosis, $H_{27,}$ Rv strains, incubated at 37^{0}C and observed weekly for the growth of organism for eight weeks. **2-[(N-benzoyl)2,5-dichloroanilido] acetohydrazide, 2-[(N-benzoyl)2,5-dichloroanilido] acetohydrazone of 4-N,N-Bis 2'-cyanoethylamino benzaldehyde, 2-[(N-benzoyl)2,5-dichloroanilido] acetohydrazone of 2- methyl-4-N,N-Bis 2'-cyanoethylaminobenzaldehyde and 2-[(N-benzoyl)2,5-dichloroanilido] acetohydrazone of 5-Chloro Salicylaldehyde** inhibited the growth of Mycobacterium tuberculosis at 100mg/mL concentration other compounds were found to be inactive . Results are assembled in table-II.

SCHEME – I

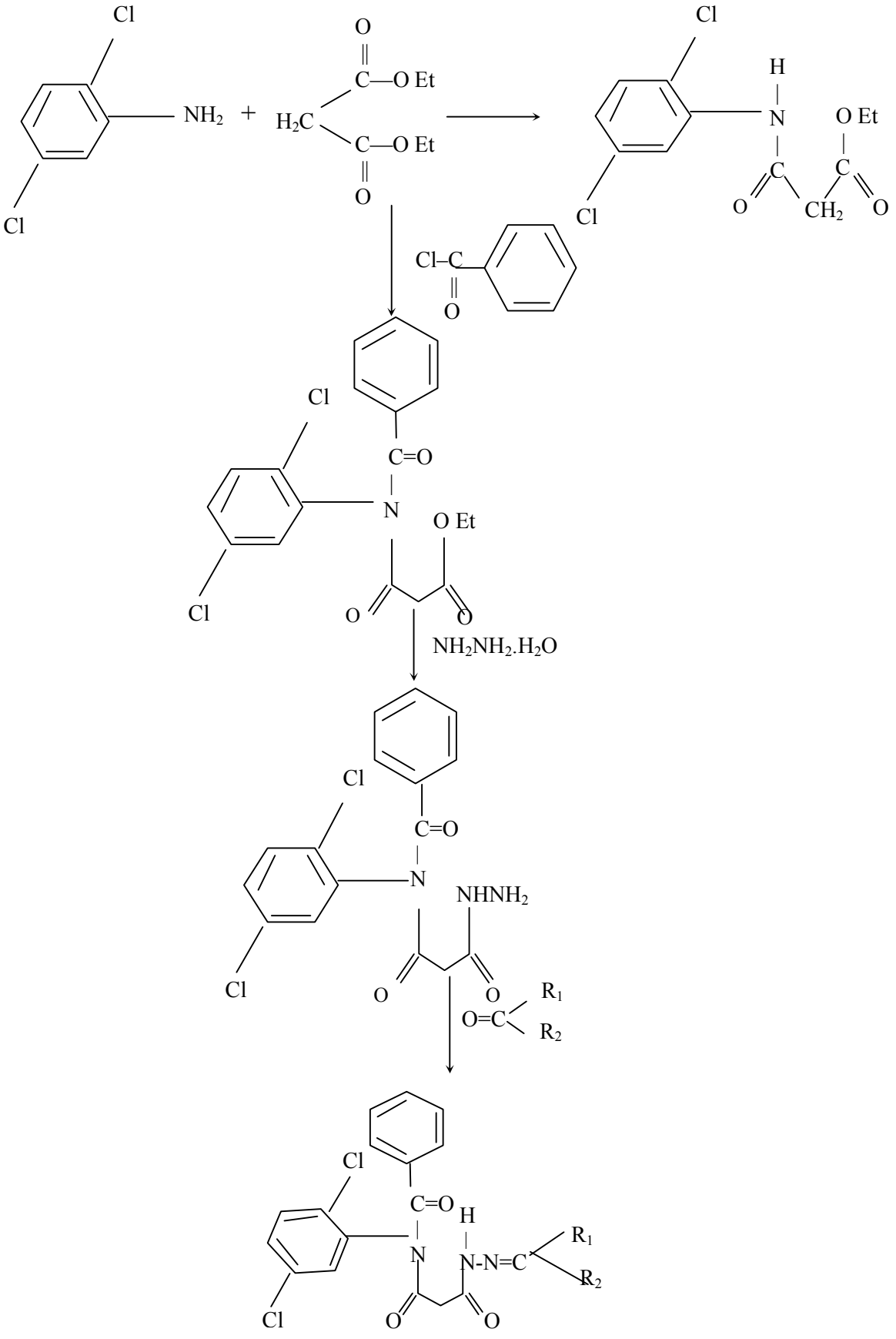
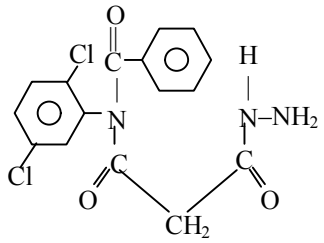

Cl
NH2
+
H2C
O
C—O Et
C—O Et
O
Cl
H
N
O Et
C
C
O
CH2
O
Cl–C
C=O
N
O Et
NH2NH2.H2O
NHNH2
R1
O=C
R2

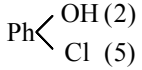
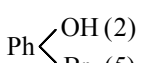
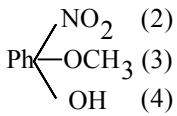
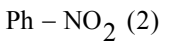
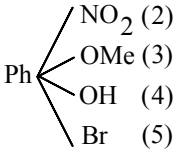
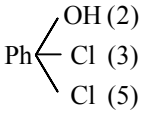
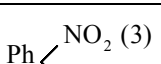
Table – I

Physical and analytical data of new compounds:

.Acid hydrazones derived from 2-[(N-benzoyl) 2, 5- dichloroanilido] acetohydrazide.



S. No.	Aldehyde / Ketone	R_1	R_2	MP (°C)	Yield (%)	Formula Weight	Molecular formula	Colour	Elemental analysis Calcd. and Found				
									C	H	O	N	Cl
1.	Benzaldehyde	H	Ph	218	91	455	$C_{23}H_{18}O_3N_3Cl_2$	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)	204	84	501	$C_{24}H_{20}O_5N_3Cl_2$	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		219	88	504.5	$C_{23}H_{16}O_4N_3Cl_3$	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		216	92	597	$C_{23}H_{17}O_4N_3Cl_2Br$	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		212	75	546	$C_{24}H_{19}O_7N_4Cl_2$	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		224	90	500	$C_{23}H_{17}O_5N_4Cl_2$	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		228	58	672	$C_{24}H_{18}O_7N_4Cl_2Br$	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		223	68	540	$C_{23}H_{16}O_4N_3Cl_4$	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	Me		227	49	530	$C_{24}H_{19}O_6N_4Cl_2$	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	204	44	407	$C_{19}H_{18}O_3N_3Cl_2$	Cream	47.68 (47.66)	4.30 (4.28)	10.59 (10.58)	13.90 (13.89)	23.50 (23.49)

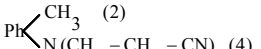
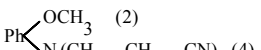
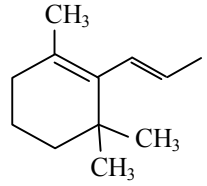
11.	2-Chloro benzaldehyde	H	Ph – Cl (2)	230	81	489.5	$C_{23}H_{17}O_3N_3Cl_3$	White	49.93 (49.92)	3.12 (3.11)	8.32 (8.31)	10.92 (10.91)	27.69 (27.68)
12.	4-N-N-Bis-2' cyano ethyl amino benzaldehyde	H	Ph – N – $(CH_2 - CH_2 - CN)_2$	235	64	576	$C_{29}H_{25}O_3N_6Cl_2$	Light brown	56.05 (56.04)	4.24 (4.23)	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		224	86	590	$C_{30}H_{27}O_3N_6Cl_2$	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		229	64	606	$C_{30}H_{27}O_4N_6Cl_2$	Brown	55.08 (55.07)	4.39 (4.38)	9.58 (9.57)	16.76 (16.75)	14.17 (14.16)
15.	Acetophenone	Me	Ph	218	91	469	$C_{24}H_{20}O_3N_3Cl_2$	White	56.04 (56.03)	4.12 (4.11)	8.79 (8.78)	11.53 (11.52)	19.50 (19.48)
16.	Salicylaldehyde	H	Ph – OH (2)	232	57	471	$C_{23}H_{18}O_4N_3Cl_2$	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	Ph – OCH_3 (2)	2229	71	485	$C_{24}H_{20}O_4N_3Cl_2$	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		216	38	551	$C_{30}H_{30}O_3N_3Cl_2$	Buff	61.88 (61.87)	5.60 (5.59)	7.17 (7.14)	9.41 (9.39)	15.91 (15.89)

Table-II
Tuberculostatic Activity of new acidhydrazones:

S.No.	Compounds	Growth at conc. [mg/mL]	
		10	**100**
1.	2-[(N-benzoyl)2,5-dichloroanilido] acetohydrazide	+	**0**
2.	2-[(N-benzoyl)2,5-dichloroanilido] acetohydrazone of 3-Nitro 6-hydroxy acetophenone	+	+
3.	2-[(N-benzoyl)2,5-dichloroanilido] acetohydrazone of 4-N,N-Bis 2'- cyanoethylamino benzaldehyde	+	**0**
4.	2-[(N-benzoyl)2,5-dichloroanilido] acetohydrazone of 2- methyl-4-N,N-Bis 2' cyanoethylamino benzaldehyde	+	**0**
5.	2-[(N-benzoyl)2,5-dichloroanilido] acetohydrazone of 2-methoxy 4-N,N-Bis 2'- cyanoethylamino benzaldehyde	+	+
6.	2-[(N-benzoyl)2,5-dichloroanilido] acetohydrazone of acetophenone	+	+
7.	2-[(N-benzoyl)2,5-dichloroanilido] acetohydrazone of salicylaldehyde	+	+
8.	2-[(N-benzoyl)2,5-dichloroanilido] acetohydrazone of anisicaldehyde	+	+
9.	2-[(N-benzoyl)2,5-dichloroanilido] acetohydrazone of 2-Nitro vanilline	+	+
10.	2-[(N-benzoyl)2,5-dichloroanilido] acetohydrazone of 2-chloro benzaldehyde	+	+
11.	2-[(N-benzoyl)2,5-dichloroanilido] acetohydrazone of benzaldehyde	+	+
12.	2-[(N-benzoyl)2,5-dichloroanilido] acetohydrazone of β-Ionone	+	+
13.	2-[(N-benzoyl)2,5-dichloroanilido] acetohydrazone of Vanilline	+	+
14.	2-[(N-benzoyl)2,5-dichloroanilido] acetohydrazone of 5-Chloro Salicylaldehyde	+	**0**
15.	2-[(N-benzoyl)2,5-dichloroanilido] acetohydrazone of 5-bromo Salicylaldehyde	+	+
16.	2-[(N-benzoyl)2,5-dichloroanilido] acetohydrazone of o-Nitro benzalaldehyde	+	+
17.	2-[(N-benzoyl)2,5-dichloroanilido] acetohydrazone of 2-Nitro 5-bromo vanilline	+	+
18.	2-[(N-benzoyl)2,5-dichloroanilido] acetohydrazone of 3,5-dichloro-2-hydroxy benzaldehyde	+	+

'+' and ' **0'** indicate presence and inhibition of growth respectively.

RESULTS AND DISCUSSION

New acidhydrazones have been synthesised by the reaction of 2-[(N-benzoyl) 2, 5-dichloroanilido] acetohydrazide with various Carbonyl Compounds in 37 to 91% yield. Hydrazones 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 **(1, 2, 3, 4, 5, 6, 7, 8, 9, 12, 13, 14, 15, 16 and 17)** 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 **2, 3, 5, 12, 13, 14** and **15** shown significant activities and

compound **1, 4, 6, 7, 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 sabouraud dextrose agar media. The compound **2, 5, 12, 13, 14** and**15** shown significant activity and compound **1, 4, 8, 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. The same compounds were tested for their **antitubercular activity** against **Mycobacterium tuberculosis. 2-[(N-benzoyl)2,5-dichloroanilido] acetohydrazide, 2-[(N-benzoyl)2,5-dichloroanilido] acetohydrazone of 4-N,N-Bis 2'- cyanoethylamino benzaldehyde, 2-[(N-benzoyl)2,5-dichloroanilido] acetohydrazone of 2-methyl-4-N,N-Bis 2' –cyanoethylaminobenz - aldehyde and 2-[(N-benzoyl)2,5-dichloroanilido] acetohydrazone of 5-Chloro Salicylaldehyde** inhibited the growth of Mycobacterium tuberculosis at 100mg/mL concentration other compounds were found to be inactive .

CONCLUSION

Newly synthesized compounds **(1, 2, 3, 4, 5, 6, 7, 8, 9, 12, 13, 14, 15, 16 and 17)** 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 **2, 3, 5, 12, 13, 14** and **15** shown significant activities and compound **1, 4, 6, 7, 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 **2, 5, 12, 13, 14** and **15** shown significant activities and compound **1, 4, 8, 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. The same compounds were tested for their **antitubercular activity** against Mycobacterium tuberculosis**. 2-[(N-benzoyl)2,5-dichloroanilido] acetohydrazide, 2-[(N-benzoyl)2,5-dichloroanilido] acetohydrazone of 4-N,N-Bis 2'-cyanoethylamino benzaldehyde, 2-[(N-benzoyl)2,5-dichloroanilido] acetohydrazone of 2- methyl-4-N,N-Bis 2'- cyanoethylaminobenzaldehyde and 2-[(N-benzoyl)2,5-dichloroanilido] acetohydrazone of 5-Chloro Salicylaldehyde** inhibited the growth of **Mycobacterium tuberculosis** at 100mg/mL concentration other compounds were found to be inactive .

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