International Journal of ChemTech Research
CODEN(USA): IJCRGG ISSN : 0974-4290
Vol.2, No.2, pp 1070-1079 April-June 2010

Synthesis, Characterization and Biological Activities of some New Acid Hydrazones Derived from Ethyl-2-[(N-Acetyl) 2, 3-Dichloroanilido] Acetohydrazide

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ABSTRACT: A series of new acidhydrazones have been synthesized by the reaction of Ethyl-2-[(N-acetyl) 2, 3-dichloroanilido]acetohydrazide with various Carbonyl Compounds in 28 to 92 % yield. Hydrazones are white, brown and yellow color 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 **anti 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 37^0C and observed, **Ethyl-2-[(N-acetyl)2,3-dichloroanilido] acetohydrazide, Ethyl-2-[(N-acetyl)2, 3-dichloroanilido] acetohydrazone of 4-N,N-Bis -2'- cyanoethylamino benzaldehyde, Ethyl-2-[(N-acetyl)2,3-dichloroanilido] acetohydrazone of 2- methyl-4-N,N-Bis -2' - cyanoethylaminobenzaldehyde and Ethyl-2-[(N-acetyl)2,3-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

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 analyzer.

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, 3dichlorodianilide 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: 82%, **M. P.:** 86^0C, **M. W.:** 276. Analytical calculation for $C_{11}H_{11}N_1O_3Cl_2$: 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 [2,3 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-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], 762[2,3- disubstituted benzene], 1090 [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], 4.1 [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].

Synthesis of Ethyl-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. Ethyl-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 $C_{11}H_{11}N_3O_3Cl_2$: 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 Ethyl-2-[(N-acetyl) 2, 3-dichloroanilido] acetohydrazone [4]:

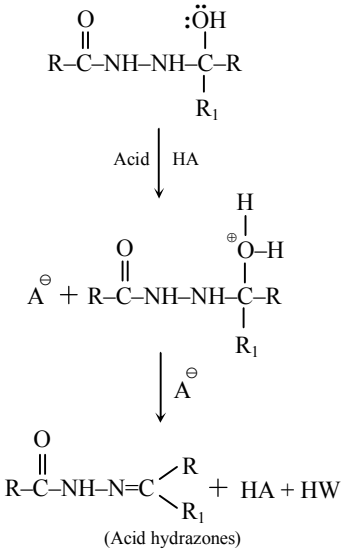
Ethyl-2-[(N-acetyl) 2, 3-dichloroanilido] aceto hydrazide (0.001 mol) and (0.001 mol) of aromatic aldehyde or ketone [such as benzaldehyde] dissolve in absolute alcohol and added 2-drops of conc. H_2SO_4 and stirred for 25 minutes. It was filtered under suction and recrystallised from hot ethanol.

M.F. $C_{18}H_{15}O_3N_3Cl_2$**,** 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), 760 (2, 3-disubstituted benzene).

CHART – I



[Mechanism of formation of new acidhydrazones]

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 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 weekly for the growth of organism for eight weeks. The compound **Ethyl-2-[(N-acetyl)2, 3-dichloroanilido] acetohydrazide, Ethyl-2-[(N-acetyl)2, 3-dichloroanilido] aceto hydrazone of 4-N,N-Bis -2'- cyanoethyl amino benzaldehyde, Ethyl-2-[(N-acetyl)2,3-dichloro anilido] acetohydrazone of 2- methyl-4-N,N-Bis -2' -cyanoethylaminobenzaldehyde and Ethyl-2-[(N-acetyl)2, 3-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

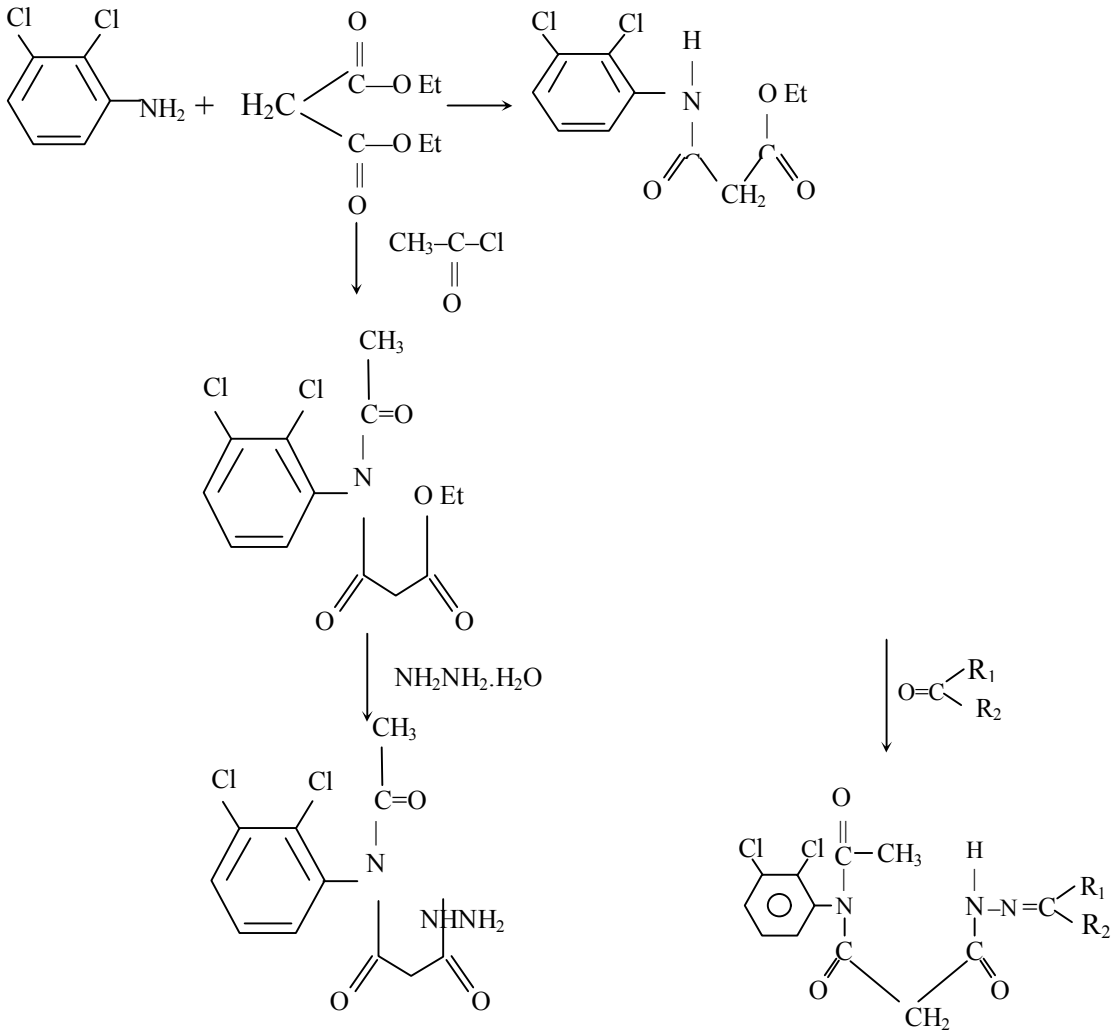
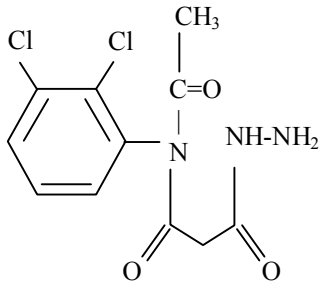


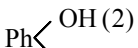
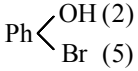
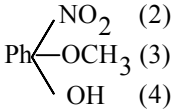
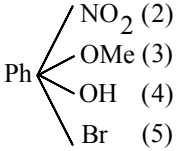
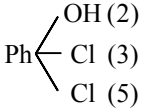
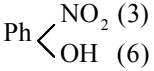
Table – I

Physical and analytical data of new compounds:

.Acid hydrazones derived from ethyl-2-[(N-acetyl) 2, 3- 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	214	91	392	$C_{18}H_{15}O_3N_3Cl_2$	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)	223	84	438	$C_{19}H_{17}O_5N_3Cl_2$	White	51.51 (51.50)	3.78 (3.75)	16.16 (16.16)	10.60 (10.56)	17.92 (17.90)

3.	5-Chloro salicyladehyde	H		229	88	441.5	$C_{18}H_{13}O_4N_3Cl_3$	White	48.06 (48.03)	2.75 (2.72)	12.01 (12.00)	10.51 (10.50)	26.65 (26.61)
4.	5-Bromo salicylaldehyde	H		219	92	534	$C_{18}H_{14}O_4N_3Cl_2Br$	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		227	75	483	$C_{19}H_{16}O_7N_4Cl_2$	Cream	46.25 (46.25)	3.17 (3.15)	21.76 (21.74)	12.69 (12.67)	16.09 (16.06)
6.	O-Nitro benzaldehyde	H		234	91	437	$C_{18}H_{14}O_5N_4Cl_2$	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		234	58	609	$C_{19}H_{15}O_7N_4Cl_2Br$	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		239	68	477	$C_{18}H_{13}O_4N_3Cl_4$	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		232	49	467	$C_{19}H_{16}O_6N_4Cl_2$	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	216	44	344	$C_{14}H_{15}O_3N_3Cl_2$	Cream	47.68	4.30	10.59	13.90	23.50

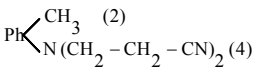
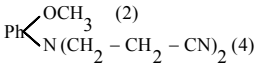
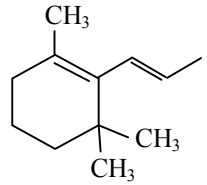
									(47.66)	(4.28)	(10.58)	(13.89)	(23.49)
11.	2-Chloro benzaldehyde	H	Ph – Cl (2)	241	81	426.5	$C_{18}H_{14}O_3N_3Cl_3$	White	49.93 (49.92)	3.12 (3.11)	8.32 (8.31)	10.92 (10.90)	27.69 (27.66)
12.	4-N-N-Bis-2' cyano ethyl amino benzaldehyde	H	Ph – N – $(CH_2 - CH_2 - CN)_2$	234	64	513	$C_{24}H_{22}O_3N_6Cl_2$	Light brown	56.05 (56.03)	4.24 (4.23)	6.79 (6.76)	17.83 (17.82)	15.07 (15.06)
13.	2-Methyl-4-N-N-bis 2' cyano ethyl amino benzaldehyde	H		240	86	527	$C_{25}H_{24}O_3N_6Cl_2$	Brown	56.90 (56.89)	4.53 (4.53)	6.59 (6.58)	17.31 (17.30)	14.63 (14.60)
14.	2-Methoxy-4-N-N-bis 2' cyano ethyl amino benzaldehyde	H		231	64	543	$C_{25}H_{24}O_4N_6Cl_2$	Brown	55.08 (55.07)	4.39 (4.38)	9.58 (9.55)	16.76 (16.74)	14.17 (14.16)
15.	Acetophenone	Me	Ph	223	91	406	$C_{19}H_{17}O_3N_3Cl_2$	White	56.04 (56.02)	4.12 (4.11)	8.79 (8.77)	11.53 (11.50)	19.50 (19.48)
16.	Salicylaldehyde	H	Ph – OH (2)	233	57	408	$C_{18}H_{15}O_4N_3Cl_2$	White	52.45 (52.44)	3.55 (3.54)	13.11 (13.10)	11.47 (11.45)	19.39 (19.38)
17.	Anisic aldehyde	H	Ph – OCH_3 (2)	229	71	422	$C_{19}H_{17}O_3N_3Cl_2$	Yellow	53.68 (53.67)	3.94 (3.92)	12.63 (12.61)	11.05 (11.04)	18.68 (18.67)
18.	β-Ionone	Me		214	28	488	$C_{25}H_{27}O_3N_3Cl_2$	Buff	61.88 (61.85)	5.60 (5.59)	7.17 (7.14)	9.41 (9.39)	15.91 (15.87)

Table-II
Tuberculostatic Activity of new acidhydrazones:

S. No.	Compounds	Growth at conc. [mg/mL] 10	100
1.	Ethyl-2-[(N-acetyl)2,3-dichloroanilido] acetohydrazide	+	**0**
2.	Ethyl-2-[(N-acetyl)2,3-dichloroanilido] acetohydrazone of 3-Nitro 6-hydroxy acetophenone	+	+
3.	Ethyl-2-[(N-acetyl)2,3-dichloroanilido] acetohydrazone of 4-N,N-Bis 2'- cyanoethylamino benzaldehyde	+	**0**
4.	Ethyl-2-[(N-acetyl)2,3-dichloroanilido] acetohydrazone of 2-methyl -4-N,N-Bis 2'- cyanoethylamino benzaldehyde	+	**0**
5.	Ethyl-2-[(N-acetyl)2,3-dichloroanilido] acetohydrazone of 2-methoxy -4-N,N-Bis 2'- cyanoethylamino benzaldehyde	+	+
6.	Ethyl-2-[(N-acetyl)2,3-dichloroanilido] acetohydrazone of acetophenone	+	+
7.	Ethyl-2-[(N-acetyl)2,3-dichloroanilido] acetohydrazone of salicylaldehyde	+	+
8.	Ethyl-2-[(N-acetyl)2,3-dichloroanilido] acetohydrazone of anisicaldehyde	+	+
9.	Ethyl-2-[(N-acetyl)2,3-dichloroanilido] acetohydrazone of 2-Nitro vanilline	+	+
10.	Ethyl-2-[(N-acetyl)2,3-dichloroanilido] acetohydrazone of 2-chloro benzaldehyde	+	+
11.	Ethyl-2-[(N-acetyl)2,3-dichloroanilido] acetohydrazone of benzaldehyde	+	+
12.	Ethyl-2-[(N-acetyl)2,3-dichloroanilido] acetohydrazone of β-Ionone	+	+
13.	Ethyl-2-[(N-acetyl)2,3-dichloroanilido] acetohydrazone of Vanilline	+	+
14.	Ethyl-2-[(N-acetyl)2,3-dichloroanilido] acetohydrazone of 5-Chloro Salicylaldehyde	+	**0**
15.	Ethyl-2-[(N-acetyl)2,3-dichloroanilido] acetohydrazone of 5-bromo Salicylaldehyde	+	+
16.	Ethyl-2-[(N-acetyl)2,3-dichloroanilido] acetohydrazone of o-Nitro benzalaldehyde	+	+
17.	Ethyl-2-[(N-acetyl)2,3-dichloroanilido] acetohydrazone of 2-Nitro 5-bromo vanilline	+	+
18.	Ethyl-2-[(N-acetyl)2,3-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 synthesized by the reaction of Ethyl-2-[(N-acetyl) 2, 3-dichloro anilido]acetohydrazide with various Carbonyl Compounds in 28 to 92% 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 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. The same compounds were tested for their **antitubercular activity** against **Mycobacterium tuberculosis.** The compound **Ethyl-2-[(N-acetyl)2, 3-dichloroanilido] acetohydrazide, Ethyl-2-[(N-acetyl)2, 3-dichloro anilido] acetohydrazone of 4-N,N-Bis -2'-cyanoethylaminobenzaldehyde, Ethyl-2-[(N-acetyl) 2, 3-dichloroanilido] acetohydrazone of 2- methyl-4-N,N-Bis -2' - cyanoethylaminobenzaldehyde and Ethyl-2-[(N-acetyl)2, 3-dichloroanilido] aceto hydrazone 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**.** The compound **Ethyl-2-[(N-acetyl)2, 3-dichloroanilido] acetohydrazide, Ethyl-2-[(N-acetyl)2, 3-dichloroanilido] aceto hydrazone of 4-N,N-Bis -2'- cyanoethylamino benzaldehyde, Ethyl-2-[(N-acetyl)2, 3-dichloro anilido] acetohydrazone of 2- methyl-4-N,N-Bis -2' -cyanoethylaminobenzaldehyde and Ethyl-2-[(N-acetyl)2, 3-dichloroanilido] aceto hydrazone of 5-Chloro Salicylaldehyde** inhibited the growth of **Mycobacterium tuberculosis** at 100mg/mL concentration other compounds were found to be inactive .

ACKNOWLEDGEMENT

The authors are thankful to Director, C. D. R. I. Lucknow (Uttar Pradesh), for elemental analysis, Director, Tuberculosis Research Centre, Amargadh (Gujrat), for testing tuberculostatic activity and Director, D. R. D. E. Gwalior (Madhya Pradesh), for spectral studies, and Director, Cancer Hospital and Research Institute, Gwalior (Madhya Pradesh), for Biological activities. We are also greatful to principal SMS Government Model Science College, Gwalior (Madhya Pradesh), for providing research facilities.

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