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Synthesis, Characterization and Biological Activities of Some New Acid Hydrazones Derived from Ethyl-2-[(N-acetyl)-2,5-dichloroanilido] Acetohydrazide

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A series of new acid hydrazones have been synthesized by the reaction of ethyl-2-[(N-acetyl)-2,5-dichloroanilido] acetohydrazide with various carbonyl compounds in 30-92 % yield. Hydrazones are white, brown and yellow colour solids, having high melting points. Newly synthesized compounds (**1-9, 12-17**) 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 *Candida albicans*, *Aspergillus niger* and *Alternaria alternata* at concentration of 30 mg/mL using savored dextrose agar media. The compounds **2, 5, 12, 13, 14** and **15** shown significant activities and compounds **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. 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 ºC and observed, ethyl-2-[(N-acetyl)-2,5-dichloroanilido] acetohydrazide, ethyl-2-[(N-acetyl)-2,5-dichloroanilido] acetohydrazone of 4-N,N-*bis*-2'-cyanoethylamino benzaldehyde, ethyl-2-[(N-acetyl)-2,5-dichloroanilido]-acetohydrazone of 2- methyl-4-N,N-*bis*-2'-cyanoethylaminobenzaldehyde and ethyl-2-[(N-acetyl)-2,5-dichloroanilido] acetohydrazone of 5-chloro salicylaldehyde inhibited the growth of *Mycobacterium tuberculosis* at 100 mg/mL concentration other compounds were found to be inactive.

Key Words: Malonicester, Acid hydrazide, Acid hydrazones, Synthesis, Characterization, 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

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activities. Acid hydrazides 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], antifungal[11], anticonvulsant[12-15], antihelmintic[16], antitumor[17-20], antileprotic[21], antimalerial[22,23], anticancer[24-31], antidepressant[32], anti HIV[33], analgesic antiinflammatory[34], leishmanicidal[35], vasodilator activities[36].

EXPERIMENTAL

All chemicals used were of AR 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 TLC using silica gel-G. Elemental analysis is performed on Carlo-Erba 1108 analyzer.

Synthesis of ethyl-2-[2, 5-dichloroanilido]ethanoate [1]: A mixture of 2,5-dichloro aniline (10 mL) and diethyl malonate (20 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 diethyl malonate flowed back into the flask. Contents were cooled, 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. 86 ºC, m.w. 276. Analytical calculation for $C_{11}H_{11}NO_3Cl_2$: found. (%): C 39.24, H: 3.22, N: 4.13, Cl: 21.12, calcd. (%) C: 39.21, H: 3.26, N: 4.15, Cl: 21.16. IR [KBr, ν_{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-acetyl)-2,5-dichloroanilido]ethanoate [2]: Acetyl chloride (4.74 g; 0.06 mol), dioxane (6 mL), ethyl-2-(2, 5-dichloroanilido)ethanoate (16.56 g; 0.06 mol) and triethylamine (5.7 g; 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 2 h and kept over night when triethylamine hydrochloride was separated. It was filtered under suction and the filtrate was poured on to crushed ice (*ca.* 180 g) and stirred when ethyl-2-[(N-acetyl)-2,5-dichloroanilido] ethanoate separated and solidified. It was filtered under suction, dried and purified by recrystallization from aqueous methanol (1:1) in white crystals. Yield 76.4 %, m.p. 88 °C. Analytical calculation for $C_{13}H_{13}O_4NCl_2$:

[m.w. 318], calcd. (%): N 2.95, C 45.64, H 3.38, Cl 15.00, found. (%): N 02.94, C 45.62, H 3.37, Cl 15.02. IR [KBr, ν_{max}, cm^{-1}]: 1720 [C=O diketone], 1300 [-C-O-ester], 762 [2,5-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)-2,5-dichloroanilido]acetohydrazide [3]: Ethyl-2-[(N-acetyl)-2,5-dichloroanilido]ethanoate (9.54 g; 0.03 mol), ethanol (10 mL) and hydrazine hydrate (15 mL; 80 %) were mixed together and stirred for 35 min. Ethyl-2-[(N-acetyl)-2,5-dichloroanilido] acetohydrazide was filtered under suction and recrystallized from ethanol in white crystals. Yield 74 %, m.p. 172 °C, m.w. 304. Analytical calculation for $C_{11}H_{11}N_3O_3Cl_2$: Calcd. 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}]: 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).

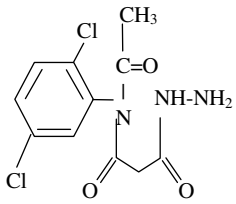
Synthesis of ethyl-2-[(N-acetyl)-2,5-dichloroanilido]acetohydrazone [4]: Ethyl-2-[(N-acetyl)-2,5-dichloroanilido]acetohydrazide (0.001 mol) and (0.001 mol) of aromatic aldehyde or ketone[such as benzaldehyde] dissolved in absolute alcohol and added 2-drops of conc. H_2SO_4 and stirred for 25 min. It was filtered under suction and recrystallized from hot ethanol. m.f. $C_{18}H_{15}O_3N_3Cl_2$, colour: silver white, yield 91 %, m.p. 214 ºC, f.w. 392, analytical calculation for $C_{18}H_{15}O_3N_3Cl_2$, calcd. (%): N 12.04, C 54.85, H 3.71, Cl 20.28, found. (%): N 11.98, C 54.82, H 3.70, Cl 20.26. IR absorption band (cm^{-1}): 3150 (N-H stretching), 2970-2960 (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 (1H, s, NH), 6.96-7.1 (10H, m, ArH. Synthetic strategy has been out lined in **Scheme-I**. Mechanism for the formation of acid hydrazones is given in Fig. 1.

Biological evaluation

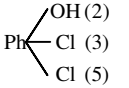
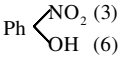
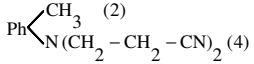
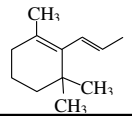
Antibacterial activity: Newly synthesized compounds (**1-9 and 12-17**) have been tested for their antibacterial activity against gram positive bacteria *S. albus*, *S. aureus* and gram negative bacteria *E. coli* and *Pseudomonas piosineus* by agar plate disc diffusion method at 30 μg/mL concentration. Ampicillin and tetracycline were used as a reference compounds. The compounds **2, 3, 5, 12, 13, 14** and **15** show significant activities and compounds **1, 4, 6, 7, 8, 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 compounds **2, 5, 12, 13, 14** and **15** show significant activity and compounds **1, 4, 8, 9, 16** and **17**

TABLE-1
PHYSICAL AND ANALYTICAL DATA OF ACID HYDRAZONES DERIVED
FROM ETHYL-2-[(N-ACETYL)-2,5-DICHLOROANILIDO]ACETOHYDRAZIDE



S. No.	Aldehyde/ketone	R_1	R_2	m.p. (ºC)	Yield (%)	m.w.	m.f.	Colour	Elemental analysis (%): Calcd. (found)			
									C	H	N	Cl
1.	Benzaldehyde	H	Ph	212	91	392	$C_{18}H_{15}N_3O_3Cl_2$	White	54.85 (54. 83)	3.71 (3.70)	12.00 (11.99)	20.28 (20.25)
2.	Vanilline	H	Ph(OMe (3), OH (4))	222	84	438	$C_{19}H_{17}N_3O_5Cl_2$	White	51.51 (51.50)	3.78 (3.75)	10.60 (10.56)	17.92 (17.90)
3.	5-Chloro salicyladehyde	H	Ph(OH (2), Cl (5))	228	88	441.5	$C_{18}H_{13}N_3O_4Cl_3$	White	48.06 (48.03)	2.75 (2.72)	10.51 (10.50)	26.65 (26.61)
4.	5-Bromo salicylaldehyde	H	Ph(OH (2), Br (5))	217	92	534	$C_{18}H_{14}N_3O_4BrCl_2$	Silver White	39.02 (39.01)	2.43 (2.42)	8.53 (8.51)	14.43 (14.42)
5.	2-Nitro vanilline	H	Ph(NO_2 (2), OCH_3 (3), OH (4))	226	75	483	$C_{19}H_{16}N_4O_7Cl_2$	Cream	46.25 (46.25)	3.17 (3.15)	12.69 (12.67)	16.09 (16.06)
6.	*o*-Nitro benzaldehyde	H	Ph – NO_2 (2)	233	91	437	$C_{18}H_{14}N_4O_5Cl_2$	White	48.60 (48.58)	3.03 (3.01)	14.17 (14.15)	17.97 (17.96)
7.	2-Nitro 5-Bromo vanilline	H	Ph(NO_2 (2), OMe (3), OH (4), Br (5))	236	58	609	$C_{19}H_{15}N_4O_7BrCl_2$	Cream	35.97 (35.96)	2.29 (2.29)	9.87 (9.86)	12.52 (12.51)

8.	3, 5- di chloro-2-hydroxy benzal-dehyde	H		232	68	477	$C_{18}H_{13}N_3O_4Cl_4$	White	44.13 (44.11)	2.52 (2.51)	9.65 (9.64)	32.64 (32.64)
9.	3-Nitro-6-hydroxy acetophenone	Me		238	49	467	$C_{19}H_{16}N_4O_6Cl_2$	Cream	48.00 (48.00)	3.29 (3.28)	13.17 (13.16)	16.70 (16.69)
10.	Acetone	Me	Me	217	44	344	$C_{14}H_{15}N_3O_3Cl_2$	Cream	47.68 (47.66)	4.30 (4.28)	13.90 (13.89)	23.50 (23.49)
11.	2-Chloro benzaldehyde	H	Ph – Cl (2)	240	81	426.5	$C_{18}H_{14}N_3O_3Cl_3$	White	49.93 (49.92)	3.12 (3.11)	10.92 (10.90)	27.69 (27.66)
12.	4-N-N-Bis-2' cyano ethyl amino benzaldehyde	H	Ph – N – $(CH_2 - CH_2 - CN)_2$	231	64	513	$C_{24}H_{22}N_6O_3Cl_2$	Light brown	56.05 (56.03)	4.24 (4.23)	17.83 (17.82)	15.07 (15.06)
13.	2-Methyl-4-N-N-bis 2' cyano ethyl amino benzaldehyde	H		241	86	527	$C_{25}H_{24}N_6O_3Cl_2$	Brown	56.90 (56.89)	4.53 (4.53)	17.31 (17.30)	14.63 (14.60)
14.	2-Methoxy-4-N-N-bis 2' cyano ethyl amino benzaldehyde	H		230	64	543	$C_{25}H_{24}N_6O_4Cl_2$	Brown	55.08 (55.07)	4.39 (4.38)	16.76 (16.74)	14.17 (14.16)
15.	Acetophenone	Me	Ph	224	91	406	$C_{19}H_{17}N_3O_3Cl_2$	White	56.04 (56.02)	4.12 (4.11)	11.53 (11.50)	19.50 (19.48)
16.	Salicylaldehyde	H	Ph – OH (2)	236	57	408	$C_{18}H_{15}N_3O_4Cl_2$	White	52.45 (52.44)	3.55 (3.54)	11.47 (11.45)	19.39 (19.38)
17.	Anisaldehyde	H	Ph – OCH_3 (2)	225	71	422	$C_{19}H_{17}N_3O_3Cl_2$	Yellow	53.68 (53.67)	3.94 (3.92)	11.05 (11.04)	18.68 (18.67)
18.	β-Ionone	Me		217	30	488	$C_{25}H_{27}N_3O_3Cl_2$	Buff	61.88 (61.85)	5.60 (5.59)	9.41 (9.39)	15.91 (15.87)

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.

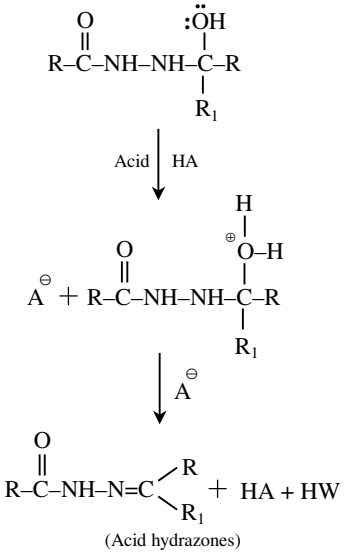
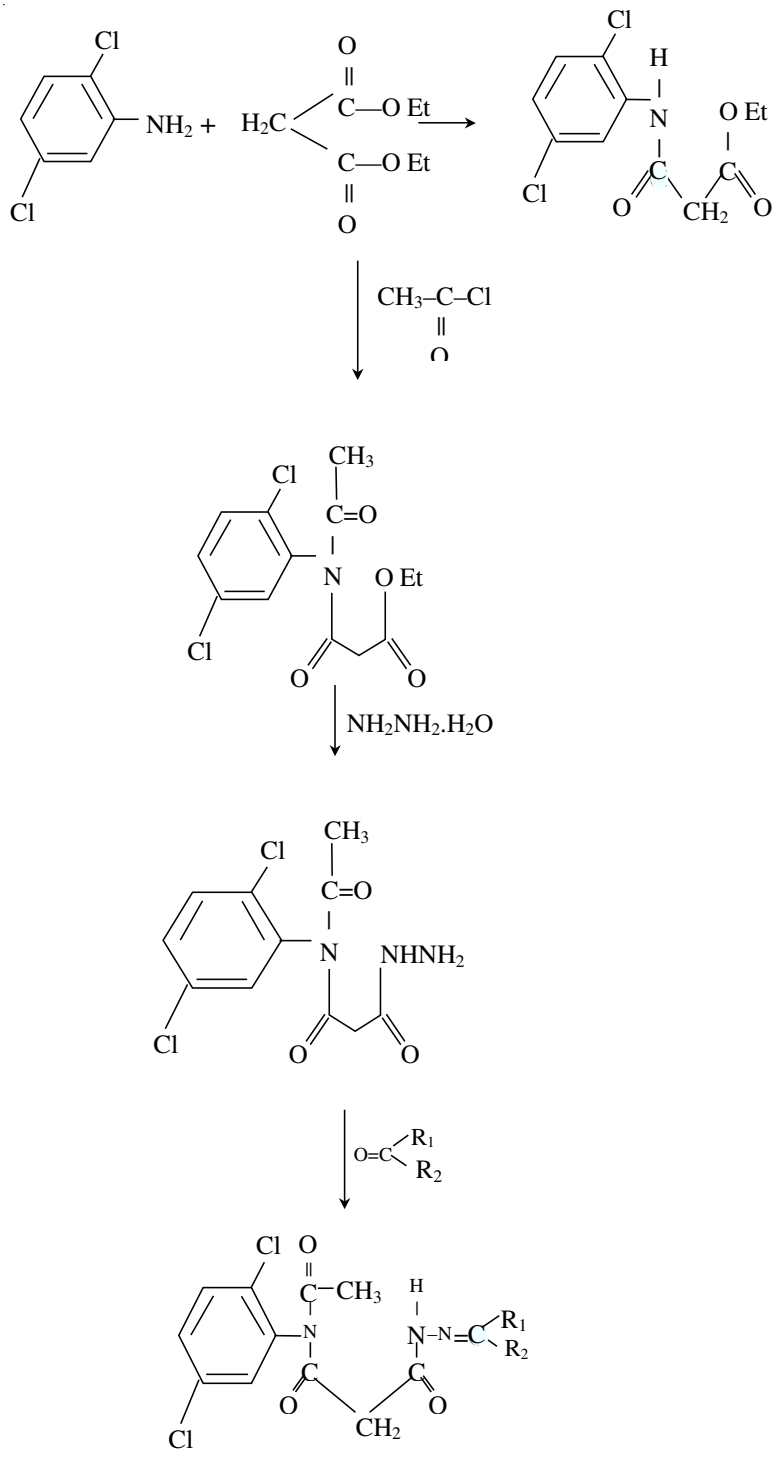


Fig. 1. Mechanism of formation of new acid hydrazones

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 ºC and observed weekly for the growth of organism for 8 weeks. The compound ethyl-2-[(N-acetyl)2, 5-dichloroanilido] acetohydrazide, ethyl-2-[(N-acetyl)-2,5-dichloroanilido] acetohydrazone of 4-N,N-*bis*-2'-cyanoethylaminobenzaldehyde, ethyl-2-[(N-acetyl)-2,5-dichloroanilido]acetohydrazone of 2-methyl-4-N,N-*bis*-2'-cyanoethylaminobenzaldehyde and ethyl-2-[(N-acetyl)-2,5-dichloroanilido]acetohydrazone of 5-chloro salicylaldehyde inhibited the growth of *Mycobacterium tuberculosis* at 100 mg/mL concentration other compounds were found to be inactive.

RESULTS AND DISCUSSION

New acid hydrazones have been synthesized by the reaction of ethyl-2-[(N-acetyl)-2,5-dichloroanilido]acetohydrazide with various carbonyl compounds in 30-92 % yield. Hydrazones are white, brown and yellow colour solids, having high melting points. The structure of all the compounds were confirmed by elemental analysis, IR, PMR and mass spectral data. Newly synthesized compounds (**1-9, 12-17**) have been tested for their antibacterial activity against gram positive bacteria



Scheme-I

TABLE-2
TUBERCULOSTATIC ACTIVITY OF ACID HYDRAZONES

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

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

S. albus, *S. aureus* and gram negative bacteria *E. coli* and *Pseudomonas piosineus*. The compounds **2, 3, 5, 12, 13, 14** and **15** show 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 compounds **2, 5, 12, 13, 14** and **15** show significant activity and compounds **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)-2,5-dichloroanilido]acetohydrazide, ethyl-2-[(N-acetyl)2, 5-dichloroanilido]acetohydrazone of 4-N,N-*bis*-2'-cyanoethylaminobenzaldehyde, ethyl-2-[(N-acetyl)-2,5-dichloroanilido]acetohydrazone of 2-methyl-4-N,N-*bis*-2'-cyanoethylaminobenzaldehyde and ethyl-2-[(N-acetyl)-2,5-dichloroanilido]acetohydrazone of 5-chloro salicylaldehyde inhibited the growth of *Mycobacterium tuberculosis* at 100 mg/mL concentration other compounds were found to be inactive.

Conclusion

Newly synthesized compounds (**1-9, 12-17**) have been tested for their antibacterial activity against gram positive bacteria *i.e.*, *S. albus*, *S. aureus* and gram negative bacteria *e.g.*, *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 compounds **2, 3, 5, 12, 13, 14** and **15** show significant activities and compounds **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 compounds **2, 5, 12, 13, 14** and **15** show significant activities and compounds **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 compounds ethyl-2-[(N-acetyl)-2,5-dichloroanilido]acetohydrazide, ethyl-2-[(N-acetyl)-2,5-dichloroanilido] acetohydrazone of 4-N,N-*bis*-2'-cyanoethylamino benzaldehyde, ethyl-2-[(N-acetyl)-2,5-dichloroanilido]acetohydrazone of 2-methyl-4-N,N-*bis*-2'-cyanoethylaminobenzaldehyde and ethyl-2-[(N-acetyl)-2,5-dichloroanilido]acetohydrazone of 5-chloro salicylaldehyde inhibited the growth of *Mycobacterium tuberculosis* at 100 mg/mL concentration other compounds were found to be inactive.

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