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

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ABSTRACT

A series of new acid hydrazones have been synthesized by the reaction of Ethyl-2-[(N-cinnamoyl) 2, 3-dichloroanilido] acetohydrazide with various Carbonyl Compounds in 34 to 83 % 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 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. Some new compounds have been tested for* ***antitubercular*** *activity in-vitro using M. tuberculosis****.*** *The compounds were incorporated into Lowenstein Jensen egg medium having concentrations of 10 and 100 mg/mL and were inoculated with M. tuberculosis,* H_{27}, *Rv strains, incubated at* 37^0*C and observed, the compound* ***03, 12, 13*** *(table-I)* ***& 01*** *(table-II) inhibited the growth of M. 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 bactericidal [9-10], anti-fungal [11], anti-convulsant [12-15], anti-helmintic [16], anti-tumor [17-20], anti-leprotic [21], anti-malarial [22-23], anti-cancer [24-31], anti-depressant [32], anti-HIV [33], analgesic-anti-inflammatory [34], leishmanicidal [35], vasodilator activities [36].

MATERIALS AND METHODS

Experimental

All chemicals used were of A.R. grade (either of B.D.H. or Excel-R or Extra pure E. Merck 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 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, 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: 82%, M. P.: 86^0C, M. W.: 276. Analytical calculation for $C_{11}H_{11}N_1O_3Cl_2$: Found: C 47.8, H: 4.0, O: 17.4, N: 5.1, Cl: 25.7, Calcd. C: 47.5, H: 04.1, O: 17.2, N: 5.1, Cl: 25.4. *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-cinnamoyl) 2, 3- dichloroanilido] ethanoate [2]:

Cinnamoyl chloride (10.02 gm; 0.06 mol), dioxane (6 ml), Ethyl-2-(2, 3-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-cinnamoyl) 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 = 82 %, MP = 99°C

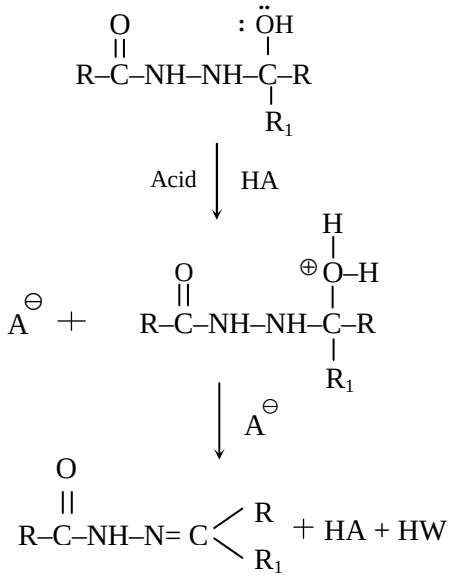
Analytical calculation for $C_{20}H_{17}N_1O_4Cl_2$: [FW = 406] , Calculated: N 3.4 , C 59.1, H 04.2 , O 15.8 , Cl 17.5 , Found : N 3.3, C 59.0 , H 04.1 , O 15.6 , Cl 17. 5. *IR [KBr]* V_{max} cm^{-1}*:* 1730 [C=O diketone], 1320 [-C-O- Ester], 773 [2, 3- disubstituted benzene], 1100 [C-Cl Stretching], 1580, 1530, 1470 [C=C Ring stretching], 3150 [N-H Stretching], 3030[C-H aromatic], 1340-1328 [C-H Stretching].

PMR (DMSO): δ 4.59 [2H, s, CO-CH_2-CO], 4.30 [2H, s, NH_2], 7.4-8.2 [3H, m, Ar-H], 9.8 [1H, s, CO-NH D_2O exchangeable], 10.3 [1H, s, Ar-NH D_2O exchangeable].

Synthesis of Ethyl-2-[(N- cinnamoyl) 2, 3-dichloroanilido] acetohydrazide [3]:
Ethyl-2-[(N-cinnamoyl) 2, 3-dichloroanilido] ethanoate (12.2 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-cinnamoyl) 2, 3-dichloroanilido] acetohydrazide was filtered under suction and recrystallised from ethanol in white crystals. Yield; 78%, MP = 183°C, MW 392 Analytical calculation for $C_{18}H_{15}N_3O_3Cl_2$: Calculated: N 10.7, C 55.1, H 03.8, O 12.2, Cl 18.1, Found: N 10.6, C 55.0, H 03.7, O 12.1, Cl 18.0 *IR [KBr]* V_{max} cm^{-1}*:* 3150 [N-H Stretching], 3060 [C-H aromatic], 1670 [C=O diketone], 1440 [C-Cl aromatic], 1590, 1540, 1455 [C=C ring stretching]. *PMR (DMSO):* δ 4.53 (2H, s, CO-CH_2-CO), 4.4 (2H, s, NH_2), 7.2-8.4 (3H, m, Ar-H), 9.7 (1H, s, CO-NH D_2O exchangeable), 10.3 (1H, s, Ar-NH D_2O exchangeable).

Synthesis of Ethyl-2-[(N-cinnamoyl) 2, 3-dichloroanilido] acetohydrazone [4]:
Ethyl-2-[(N-cinnamoyl) 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 20 minutes. It was filtered under suction and recrystallised from hot ethanol. *M.F.* $C_{25}H_{19}O_3N_3Cl_2$**,** Color: Silver white, Yield: 88%, M.P= 222 ^{0}C, F.W: 480**,** Analytical calculation for $C_{25}H_{19}O_3N_3Cl_2$ Calculated: N 8.8, C 62.5, H 4.0, O 10.0, Cl 14.8, Found: N 8.6, C 62.3, H 4.2, O 10.0, Cl 14.7 *IR Absorption band* (cm^{-1}*):* 3160 (N–H stretching), 2970–2995 (C–H aliphatic), 1655–1660 (C=O Ketone), 780–770 (C–Cl Stretching), 755 (2, 3-disubstituted benzene). *NMR Spectra: (*δ *DMSO*), 2.16(2 H, s, CH_2), 4.20(1 H, s, NH), 6.90–7.3 (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



(Acid hydrazones)

[Mechanism of formation of acid hydrazones]

SCHEME – I

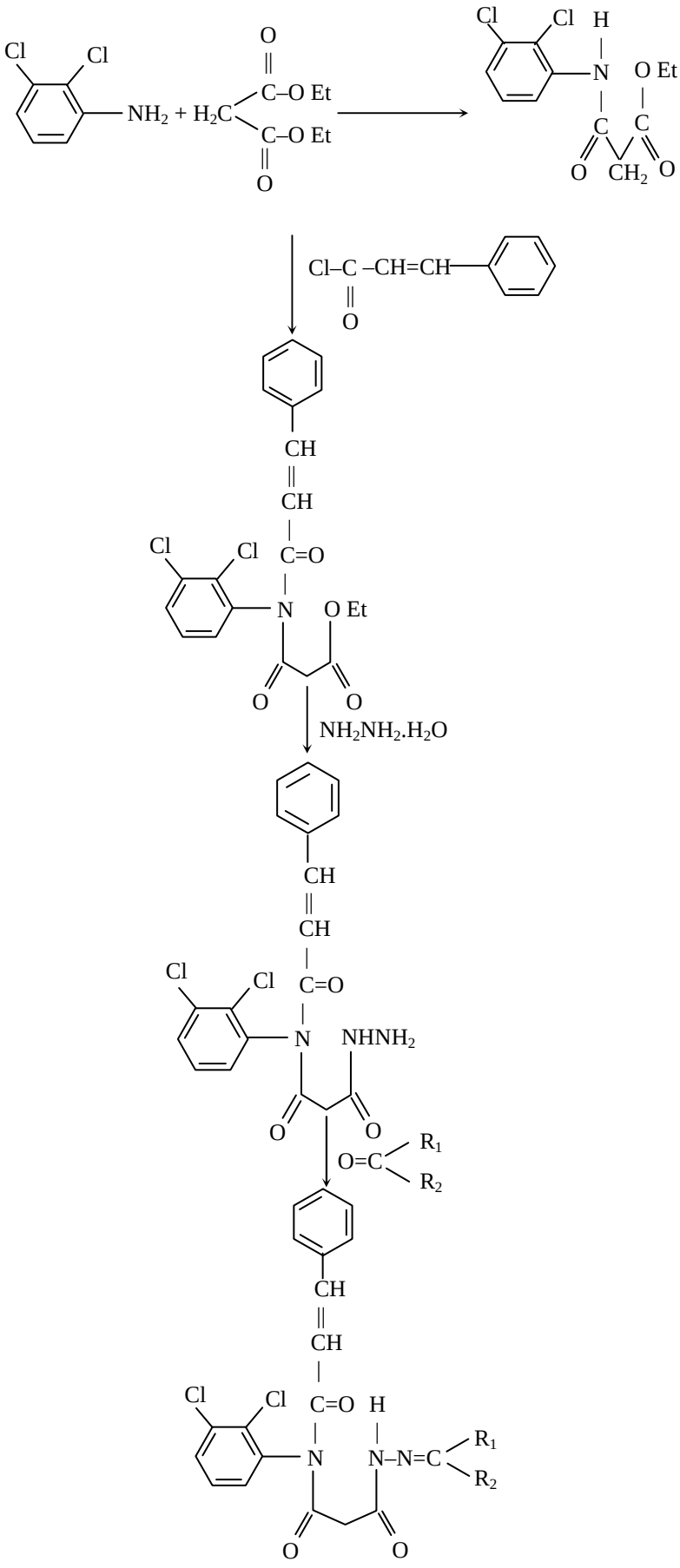
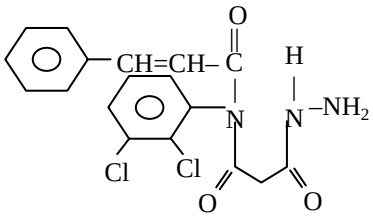
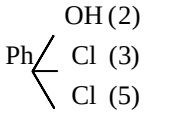
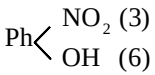
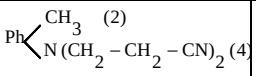
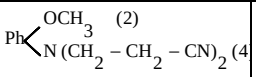
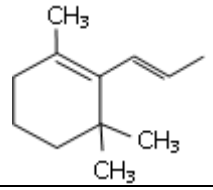

Cl
Cl
NH2 + H2C
O
C–O Et
C–O Et
O
Cl
Cl
H
N
O Et
C
C
O
CH2
O
Cl–C –CH=CH
O
CH
CH
C=O
Cl
Cl
N
O Et
O
O
NH2NH2.H2O
CH
CH
C=O
Cl
Cl
N
NHNH2
O
O
O=C
R1
R2
CH
CH
C=O
H
Cl
Cl
N
N–N=C
R1
R2
O
O

Table – I: Physical and analytical data of acid hydrazones derived from ethyl-2-[(N-cinnamoyl) 2, 3- dichloroanilido] acetohydrazide



S. No.	Aldehyde / Ketone	R_1	R_2	MP (°C)	Yield (%)	Formula Weight	Molecular formula	Color	Elemental analysis Calcd. and Found				
									C	H	O	N	Cl
1.	Benzaldehyde	H	Ph	222	88	480	$C_{25}H_{19}O_3N_3Cl_2$	White	62.5 (62.3)	4.0 (4.1)	10.0 (10.0)	8.8 (8.6)	14.8 (14.7)
2.	Vanillin	H	Ph: OMe (3), OH (4)	209	82	526	$C_{26}H_{21}O_5N_3Cl_2$	White	59.3 (59.2)	4.0 (4.0)	15.2 (15.1)	8.0 (8.2)	13.5 (13.4)
3.	5-Chloro salicyladehyde	H	Ph: OH (2), Cl (5)	217	86	530.5	$C_{25}H_{18}O_4N_3Cl_3$	White	56.6 (56.5)	3.4 (3.2)	12.1 (12.0)	7.9 (7.5)	20.1 (20.0)
4.	5-Bromo salicyladehyde	H	Ph: OH (2), Br (5)	214	83	575	$C_{25}H_{18}O_4N_3Cl_2Br$	Silver White	52.2 (52.0)	3.1 (3.0)	11.1 (11.0)	7.3 (7.1)	12.3 (12.2)
5.	2-Nitro vanillin	H	Ph: NO_2 (2), OCH_3 (3), OH (4)	210	77	571	$C_{26}H_{20}O_7N_4Cl_2$	Cream	54.6 (54.2)	3.5 (3.1)	19.6 (19.5)	9.8 (9.7)	12.4 (12.3)
6.	O-Nitro Benzaldehyde	H	Ph – NO_2 (2)	228	86	524	$C_{25}H_{17}O_5N_4Cl_2$	White	57.3 (57.2)	3.2 (3.0)	15.3 (15.1)	10.7 (10.3)	13.5 (13.4)
7.	2-Nitro 5-Bromo vanillin	H	Ph: NO_2 (2), OMe (3), OH (4), Br (5)	220	57	697	$C_{26}H_{19}O_7N_4Cl_2Br$	Cream	44.8 (44.7)	2.7 (2.4)	16.1 (16.0)	8.0 (8.0)	10.2 (10.1)

8.	3, 5-dichloro-2-hydroxy benzal dehyde	H		217	70	565	$C_{25}H_{17}O_4N_3Cl_4$	White	53.1 (53.0)	3.0 (3.1)	11.3 (11.2)	7.4 (7.2)	25.1 (25.0)
9.	3-Nitro-6-hydroxy acetophenone	Me		231	52	556	$C_{26}H_{21}O_6N_4Cl_2$	Cream	56.1 (56.0)	3.8 (3.5)	10.1 (10.2)	17.3 (17.2)	12.8 (12.5)
10.	Acetone	Me	Me	208	47	432	$C_{21}H_{19}O_3N_3Cl_2$	Cream	58.3 (58.2)	4.4 (4.2)	11.1 (11.0)	9.7 (9.4)	16.4 (16.3)
11.	2-Chloro Benzaldehyde	H	Ph – Cl (2)	232	79	514.5	$C_{25}H_{18}O_3N_3Cl_3$	White	58.3 (58.3)	3.5 (3.2)	9.3 (9.0)	8.2 (8.0)	25.7 (25.6)
12.	4-N-N-Bis-2' cyano ethyl amino Benzaldehyde	H	Ph – N – $(CH_2 - CH_2 - CN)_2$	241	66	601	$C_{31}H_{26}O_3N_6Cl_2$	Light brown	61.9 (61.7)	4.3 (4.2)	8.0 (8.1)	14.1 (14.0)	11.8 (11.4)
13.	2-Methyl-4-N-N-bis 2' cyano ethyl amino Benzaldehyde	H		226	82	615	$C_{32}H_{28}O_3N_6Cl_2$	Brown	62.4 (62.3)	4.6 (4.2)	7.8 (7.5)	13.7 (13.3)	11.5 (11.4)
14.	2-Methoxy-4-N-N-bis 2' cyano ethyl amino Benzaldehyde	H		235	60	631	$C_{32}H_{28}O_4N_6Cl_2$	Brown	60.9 (60.6)	4.4 (4.3)	10.1 (9.9)	13.3 (13.1)	11.3 (11.2)
15.	Acetophenone	Me	Ph	220	87	494	$C_{26}H_{21}O_3N_3Cl_2$	White	63.2 (63.0)	4.3 (4.1)	9.7 (9.8)	8.5 (8.3)	14.4 (14.1)
16.	Salicyladehyde	H	Ph – OH (2)	229	59	496	$C_{25}H_{19}O_4N_3Cl_2$	White	60.5 (60.1)	3.8 (3.6)	12.9 (12.7)	8.5 (8.4)	14.3 (14.1)
17.	Anisicaldehyde	H	Ph – OCH_3 (2)	211	73	510	$C_{26}H_{21}O_4N_3Cl_2$	Yellow	61.2 (61.0)	4.1 (4.1)	12.5 (12.6)	8.2 (8.1)	13.9 (13.6)
18.	β-Ionone	Me		219	42	581	$C_{32}H_{36}O_3N_3Cl_2$	Buff	66.1 (66.0)	6.2 (6.1)	8.3 (8.2)	7.2 (7.2)	12.2 (12.0)

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.

Table-II: Tuberculostatic Activity of new acidhydrazide & hydrazones

S.No.	Compounds	Growth at conc. [mg/mL] 10	100
1.	Ethyl-2-[(N-cinnamoyl)2,3-dichloroanilido] acetohydrazide	+	**0**
2.	Ethyl-2-[(N-cinnamoyl)2,3-dichloroanilido] acetohydrazone of 3-Nitro 6-hydroxy acetophenone	+	+
3.	Ethyl-2-[(N-cinnamoyl)2,3-dichloroanilido] acetohydrazone of 4-N,N-Bis 2'- cyanoethylamino Benzaldehyde	+	**0**
4.	Ethyl-2-[(N-cinnamoyl)2,3-dichloroanilido] acetohydrazone of 2- methyl-4-N,N-Bis 2' cyanoethylamino Benzaldehyde	+	**0**
5.	Ethyl-2-[(N-cinnamoyl)2,3-dichloroanilido] acetohydrazone of 2-methoxy 4-N,N-Bis 2'- cyanoethylamino Benzaldehyde	+	+
6.	Ethyl-2-[(N-cinnamoyl)2,3-dichloroanilido] acetohydrazone of acetophenone	+	+
7.	Ethyl-2-[(N-cinnamoyl)2,3-dichloroanilido] acetohydrazone of salicyladehyde	+	+
8.	Ethyl-2-[(N-cinnamoyl)2,3-dichloroanilido] acetohydrazone of Anisicaldehyde	+	+
9.	Ethyl-2-[(N-cinnamoyl)2,3-dichloroanilido] acetohydrazone of 2-Nitro vanillin	+	+
10.	Ethyl-2-[(N-cinnamoyl)2,3-dichloroanilido] acetohydrazone of 2-chloro Benzaldehyde	+	+
11.	Ethyl-2-[(N-cinnamoyl)2,3-dichloroanilido] acetohydrazone of Benzaldehyde	+	+
12.	Ethyl-2-[(N-cinnamoyl)2,3-dichloroanilido] acetohydrazone of β-Ionone	+	+
13.	Ethyl-2-[(N-cinnamoyl)2,3-dichloroanilido] acetohydrazone of Vanillin	+	+
14.	Ethyl-2-[(N-cinnamoyl)2,3-dichloroanilido] acetohydrazone of 5-Chloro Salicyladehyde	+	**0**
15.	Ethyl-2-[(N-cinnamoyl)2,3-dichloroanilido] acetohydrazone of 5-bromo Salicyladehyde	+	+
16.	Ethyl-2-[(N-cinnamoyl)2,3-dichloroanilido] acetohydrazone of o-Nitro benzalaldehyde	+	+
17.	Ethyl-2-[(N-cinnamoyl)2,3-dichloroanilido] acetohydrazone of 2-Nitro 5-bromo vanillin	+	+
18.	Ethyl-2-[(N-cinnamoyl)2,3-dichloroanilido] acetohydrazone of 3,5-dichloro-2-hydroxy Benzaldehyde	+	+

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

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 *M. 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 ***03, 12, 13*** (table-I) ***& 01*** (table-II) inhibited the growth of *M. tuberculosis* at 100mg/mL concentration other compounds were found to be inactive. Results are assembled in table-II.

RESULTS AND DISCUSSION

New acid hydrazones have been synthesized by the reaction of Ethyl-2-[(N- cinnamoyl) 2, 3-dichloroanilido] acetohydrazide with various Carbonyl Compounds in 34 to 83% yield. Hydrazones are white, brown and yellow color 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 *(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 *M. tuberculosis.* The compound ***03, 12, 13*** (table-I) ***& 01 (***table-II) inhibited the growth of *M. 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 ***03, 12, 13*** (table-I) ***& 01*** (table-II) *inhibited* the growth of *M. tuberculosis* at 100mg/mL concentration other compounds were found to be inactive.

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