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Synthesis, characterization and biological activities of some new acid hydrazones derived from ethyl-2-(2, 5-dichloroanilido) acetohydrazide

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ABSTRACT

A series of new acid hydrazones have been synthesized by the reaction of ethyl-2-(2, 5-dichloroanilido) acetohydrazide with various carbonyl compounds in 27 to 92 % 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 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 37^0C and observed, the compound *Ethyl-2-(2,5-dichloroanilido) acetohydrazide, Ethyl-2-(2, 5-dichloroanilido) acetohydrazone of 4-N,N-Bis -2'- cyanoethylamino benzaldehyde, Ethyl-2-(2,5-dichloroanilido) acetohydrazone of 2-methyl-4-N,N-Bis-2'-cyanoethylaminobenzaldehyde and Ethyl-2-(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.

Key words: 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 analyzer.

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: 72%, M. P.: 87^{0}C, M. W.: 276. Analytical calculation for $C_{11}H_{11}N_1O_3Cl_2$: Found: C 39.22, H: 03.20, O: 14.23, N: 4.13, Cl: 21.12, Calculated. C: 39.21, H: 03.26, O: 14.26, N: 04.15, Cl: 21.16. *IR [KBr]* V_{max} Cm^{-1} : 1670-1665 [C=O diketone], 1290 [-C-O- Ester], 780-775 [2,5- disubstituted benzene], 1590, 1520 , 1440 [C=C Ring stretching], 3155 [N-H Stretching], 3040[C-H aromatic], 1330-1322 [C-H Stretching].

NMR Spectra (δ Me_2CO), 1.2-1.3 (3H, t, CH_3), 2.23 (2H, s, CH_2), 4.1-4.24 (2H, q, CH_2), 7.1-7.26 (4H, m, ArH).

Synthesis of Ethyl-2-(2, 5- dichloroanilido) acetohydrazide [2]

Ethyl-2-(2, 5-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-(2, 5-dichloroanilido) acetohydrazide was filtered under suction and recrystallised from ethanol in white crystals. Yield; 80%, MP = 168°C, MW 262:

Analytical calculation for $C_9H_9N_3O_2Cl_2$

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], 1670 [C=O diketone], 1432 [C-Cl aromatic], 1595, 1520, 1445 [C=C ring stretching]. NMR Spectra (δ DMSO): 2.44 (2H, s, CH_2), 3.2 (3H, s, CH_3), 4.22-4.32 (1H, t, N-H), 7.2-7.6 (3H, m, ArH).

Synthesis of Ethyl-2-(2, 5-dichloroanilido) acetohydrazone [3]

Ethyl-2-(2, 5-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. *M.F.* $C_{16}H_{13}O_2N_3Cl_2$**,** Colour: Silver white, Yield: 91%, M.P= 214 ^{0}C, F.W: 350**,**

Analytical calculation for $C_{16}H_{13}O_2N_3Cl_2$, 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), 760-765 (2, 5-disubstituted benzene).

NMR Spectra

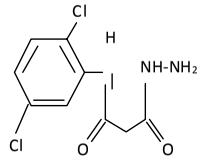
(δ *DMSO*), 2.20(2H, s, CH_2), 4.22(1H, s, NH), 6.96–7.1 (10 H, m, ArH. Synthetic strategy has been out lined in scheme-I. Mechanism for the formation of acid hydrazones is given in chart-I.

Biological evaluation

Anti-bacterial activity

Newly 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 *P. piosineus* by agar

Table 1: Physical and analytical data of new compounds: Acid hydrazones derived from 2-(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	90	350	$C_{16}H_{13}O_2N_3Cl_2$	White	54.84 (54.82)	3.70 (3.68)	9.15 (9.12)	12.04 (11.97)	20.26 (20.23)
2.	Vanilline	H	Ph < OMe (3), OH (4)	208	83	396	$C_{17}H_{15}O_4N_3Cl_2$	White	51.51 (51.50)	3.77 (3.74)	16.16 (16.16)	10.62 (10.55)	17.91 (17.90)
3.	5-Chloro salicyladehyde	H	Ph < OH (2), Cl (5)	225	87	399.5	$C_{16}H_{11}O_3N_3Cl_3$	White	48.05 (48.02)	2.72 (2.70)	12.03 (12.01)	10.56 (10.52)	26.67 (26.63)
4.	5-Bromo salicylaldehyde	H	Ph < OH (2), Br (5)	217	92	492	$C_{16}H_{12}O_3N_3Cl_2Br$	Silver White	39.04 (39.03)	2.48 (2.45)	9.74 (9.71)	8.55 (8.53)	15.41 (15.40)
5.	2-Nitro vanilline	H	Ph < NO_2 (2), OCH_3 (3), OH (4)	226	74	441	$C_{17}H_{14}O_6N_4Cl_2$	Cream	45.24 (45.22)	3.18 (3.15)	21.77 (21.75)	12.71 (12.69)	16.12 (16.09)
6.	O-Nitro benzaldehyde	H	Ph – NO_2 (2)	228	89	395	$C_{16}H_{12}O_4N_4Cl_2$	White	48.64 (48.59)	3.03 (3.01)	16.24 (16.21)	14.16 (14.15)	17.99 (17.95)
7.	2-Nitro	H	Ph < NO_2 (2), OMe (3), OH (4), Br (5)	219	58	567	$C_{17}H_{13}O_6N_4Cl_2Br$	Cream	35.97	2.29	16.93	9.87	12.52

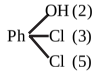
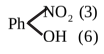
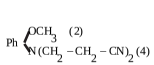
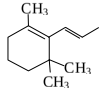
	5-Bromo vanillilne								(35.96)	(2.29)	(16.92)	(9.86)	(12.51)
8.	3, 5 di chloro-2-	H		238	67	435	$C_{16}H_{11}O_3N_3Cl_4$	White	44.13	2.52	11.03	9.65	32.64
	hydroxy benzal dehyde								(44.11)	(2.51)	(11.01)	(9.64)	(32.64)
9.	3-Nitro-6-hydroxy	CH_3		230	48	425	$C_{17}H_{14}O_5N_4Cl_2$	Cream	48.00	3.29	18.82	13.17	16.70
	acetophenone	/ Me							(48.00)	(3.28)	(18.81)	(13.16)	(16.69)
10.	Acetone	Me	Me	212	43	302	$C_{12}H_{13}O_2N_3Cl_2$	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)	236	80	384.5	$C_{16}H_{12}O_2N_3Cl_3$	White	49.93	3.12	8.32	10.92	27.69
									(49.92)	(3.11)	(8.31)	(10.91)	(27.68)
12.	4-N-N-Bis-2' cyano	H		229	63	471	$C_{22}H_{20}O_2N_6Cl_2$	Light	56.05	4.24	6.79	17.83	15.07
	ethyl amino benzaldehyde							brown	(56.04)	(4.23)	(6.78)	(17.82)	(15.06)
13.	2-Methyl-4-N-N-	H		207	87	485	$C_{23}H_{22}O_2N_6Cl_2$	Brown	56.90	4.53	6.59	17.31	14.63
	bis 2' cyano ethyl amino benzaldehyde								(56.89)	(4.53)	(6.58)	(17.30)	(14.61)
14.	2-Methoxy-4-N-N-	H		199	63	501	$C_{23}H_{22}O_3N_6Cl_2$	Brown	55.08	4.39	9.58	16.76	14.17
	bis 2' cyano ethyl amino benzaldehyde								(55.07)	(4.38)	(9.57)	(16.75)	(14.16)
15.	Acetophenone	Me /	Ph	216	90	364	$C_{17}H_{15}O_2N_3Cl_2$	White	56.04	4.12	8.79	11.53	19.50
		CH_3							(56.03)	(4.11)	(8.78)	(11.52)	(19.48)
16.	Salicylaldehyde	H	Ph – OH (2)	226	58	366	$C_{16}H_{13}O_3N_3Cl_2$	White	52.45	3.55	13.11	11.47	19.39
									(52.44)	(3.54)	(13.10)	(11.46)	(19.38)
17.	Anisic aldehyde	H		228	72	380	$C_{17}H_{15}O_3N_3Cl_2$	Yellow	53.66	3.95	12.64	11.06	18.69
									(53.65)	(3.93)	(12.62)	(11.03)	(18.68)
18.	β-Ionone	Me /		190	27	446	$C_{23}H_{25}O_2N_3Cl_2$	Buff	61.87	5.62	7.18	9.42	15.93
		CH_3							(61.84)	(5.59)	(7.16)	(9.39)	(15.90)

Table 2: Tuberculostatic Activity of new acid hydrazones

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

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

Chart 1: Mechanism of formation of new acid hydrazones]

plate disc diffusion method at 30 ìg/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

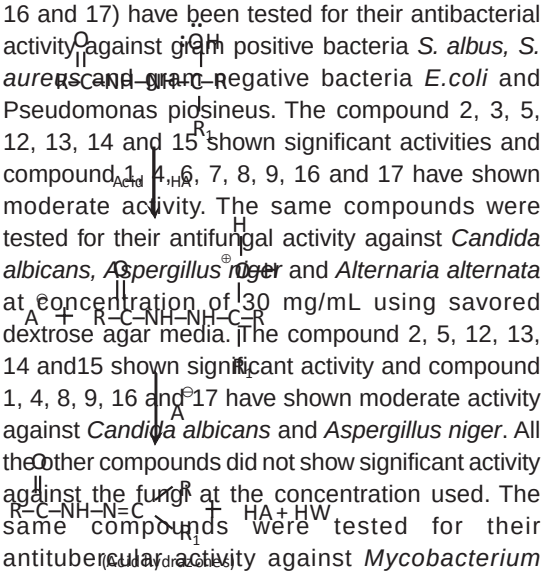
The same compounds were tested for their antifungal activity against *Candida albicans, Aspergillus niger and Alternaria alternata* at concentration of 30 mg/mL using Savored dextrose agar media. The compound *2, 5, 12, 13, 14 and15* shown significant activity and compound 1, 4*, 8, 9, 16 and 17* have 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 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^{0}C and observed weekly for the growth of organism for eight weeks. The compound Ethyl-2-(2,5-dichloroanilido) acetohydrazide, Ethyl-2-(2, 5-dichloroanilido) acetohydrazone of 4-N,N-Bis -2'- cyanoethylamino benzaldehyde, Ethyl-2-(2,5-dichloroanilido) acetohydrazone of 2-methyl-4-N,N-Bis-2'-cyanoethylaminobenzaldehyde and Ethyl-2-(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 2.

RESULTS AND DISCUSSION

New acid hydrazones have been synthesized by the reaction of Ethyl-2-(2, 5-dichloroanilido) acetohydrazide with various Carbonyl Compounds in 27 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 pidsineus. 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 and15 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-(2,5-dichloroanilido) acetohydrazide, Ethyl-2-(2, 5-dichloroanilido) acetohydrazone of 4-N,N-Bis -2'- cyanoethylamino benzaldehyde, Ethyl-2-(2,5-dichloroanilido) acetohydrazone of 2-methyl-4-N,N-Bis-2'- cyanoethylaminobenzaldehyde and Ethyl-2-(2, 5-dichloroanilido) acetohydrazone of 5-Chloro Salicylaldehyde inhibited the growth of



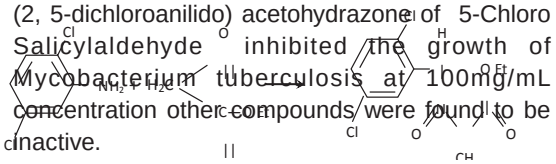


Fig. 1.

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-(2,5-dichloroanilido) acetohydrazide, Ethyl-2-(2, 5-dichloroanilido) acetohydrazone of 4-N,N-Bis -2'-cyanoethylamino benzaldehyde, Ethyl-2-(2,5-dichloroanilido) acetohydrazone of 2-methyl-4-N,N-Bis-2'- cyanoethylaminobenzaldehyde and Ethyl-2-(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.

ACKNOWLEDGEMENTS

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