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Synthesis and Evaluation of Biological activities of Thiosemicarbazones derivatives

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Abstract: A series of thiosemicarbazones(A_1,A_2,A_3,A_4,A_5,A_6,A_7) have been synthesized by treating thio - semicarbazide with different substituted aromatic aldehydes and then these compounds were further treated with acetic anhydrides to obtain acylated compounds (B_1,B_2,B_3,B_4,B_5,B_6 and D_1,D_2) respectively. The structures of the compounds were characterized on the basis of their IR and ^{1}H-NMR data. All the synthesized compounds were evaluated for antibacterial, antifungal and locomotor activity.

Key words: Thiosemicarbazones, antibacterial, antifungal and locomotor.

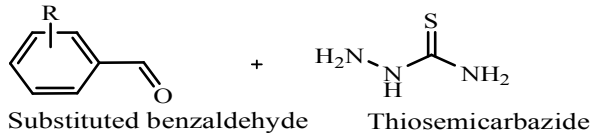
Introduction

Semi carbazones was initially used in the synthesis of antibacterial sulfathiazole[1]. Subsequent testing of isonicotinic acid hydrazide, destined for the synthesis of a particular thiosemicarbazone, revealed the powerful tuberculostatic activity of the precursor which has since become a major antitubercular drug [2].The small synthetic program reported here depends on the similarities of the synthesized compounds with a known reference structure. The reference selected in this case is the thiosemicarbazone structure.A thiosemicarbazone is a very useful intermediate for the development of molecules of pharmaceutical or biological interest[3].

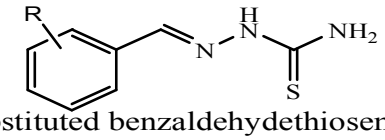
Experimental

All protocols of animal experiments have been approved by the Institutional Animal Ethics Committee (IAEC). Most of the solvents used were of L.R grade and purified before use in different reactions. Chemicals used were obtained from Central Drug House Pvt. Ltd. (CDH). The melting points of synthesized compounds were determined by melting point apparatus and were uncorrected. All the reactions were monitored on thin layer chromatography (TLC) prepared by using silica gel G.

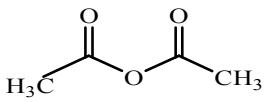
Scheme



Substituted benzaldehyde Thiosemicarbazide

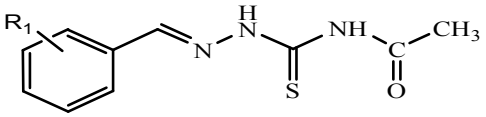


Substituted benzaldehydethiosemicarbazone $(A_1\text{-}A_7)$



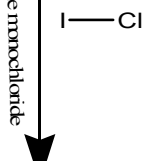
Acetic anhydride

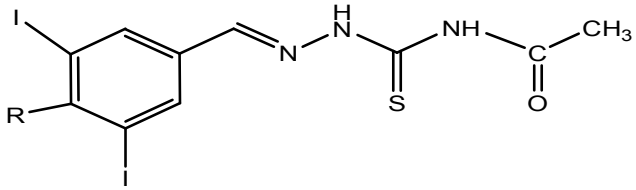
heat



substituted (*E*)-4-acetyl-1-benzylidenethiosemicarbazide $(B_1\text{-}B_6)$

iodine monochloride





substituted(*E*)-1-(3,5-diiodobenzylidene)-4-acetylthiosemicarbazide $(D_1\text{-}D_2)$

Table1-Physical properties of synthesised compounds (A_1-A_7)

S.NO	CODE	R	MELTING POINT °C	%YIELD
1	A_1	H	161-162	81
2	A_2	4-CH_3	120-121	96
3	A_3	3-NO_2	227-228	78
4	A_4	4-OH	225-226	50
5	A_5	4-$N(CH_3)_2$	189-190	78
6	A_6	3-OCH_3-4-OH	218-219	80
7	A_7	2-furyl	181-182	70

Table2-Physical properties of synthesised compounds (B_1-B_6)

S.NO	CODE	R	MELTING POINT °C	%YIELD
1	B_1	H	169-170	30.20
2	B_2	CH_3	168-169	62.15
3	B_3	NO_2	234-235	43.75
4	B_4	4-OH	209-210	46.91
5	B_5	4-N(CH_3)	201-202	37
6	B_6	2-furyl	195-196	48.22

Table3- Physical properties of synthesised compounds (D_1-D_2)

S.NO	CODE	R	MELTING POINT °C	%YIELD
1	D_1	4-OH	229-230	48.2
2	D_2	4-N(CH_3)$_2$	264-265	35.6

Synthesis of benzaldehyde thio semicarbazone compounds (A_1-A_7)

A solution of 0.05 mol. Substituted benzaldehyde in warm alcohol (300 ml) and a solution of 0.05 mol thiosemicarbazide in 300 ml water were mixed slowly .The product, which separated, was filtered off after cooling and recrystallised from ethanol. The purity of compound was checked by the TLC. Other thiosemicarbazones were prepared in the same way.

Synthesis of substituted 4 acetyl 1 benzylidinethiosemicarbazide (B_1-B_6)

In a 100 ml round bottom flask 4 g of an aromatic aldehydethiosemicarbazone and 30 ml acetic anhydride were heated for 2 hr on a water bath at temperature of 80- 90 °C. At the end of the reaction, the solution was poured on crushed ice and the separated solid was filtered, washed with water, dried and recrystallised from ethanol. The purity of compound was checked by the TLC.

Synthesis of substituted (E)-1-(3, 5-iodobenzyl -idene)-4-acetylthiosemicarbazide (D_1-D_2)

In warm glacial acetic acid (3 ml), 0.5 g of acylated product was added slowly with continous stirring and 1.2 g of iodine monochloride was dissolved in dilute HCl (4 ml). After this it was diluted with 25 ml water and warmed up to 90ºC for 15 min., cooled to room temperature and filtered. Di-iodo product was purified by dissolving in dil. NaOH and ppted by dil. HCl and recrystallised by ethanol.

Spectral data

A_1

IR(KBr) Vmax cm-1 :3422(N-H Streching),1591(C=C Streching),1227(C=S Streching).1543(C=N Streching);1H NMR(DMSO):7.5(5H),1.6(2H),7.4(1H)

A_2

IR(KBr) Vmax cm-1 :3424(N-H Streching),1593(C=C Streching),1229 (C=S Streching).1540(C=N Streching);1H NMR(DMSO):7.8(5H),1.4(2H),7.7(1H)

A_3

IR(KBr) Vmax cm-1 :3420 (N-H Streching), 1597 (C=C Streching),1220(C=S Streching). 1546(C=N Streching); 1H NMR (DMSO):7.5 (5H), 1.7(2H), 7.3 (1H)

A_7

IR(KBr) Vmax cm-1: 3406(N-H Streching),1582(C=C Streching),1227(C=S Streching).1687(C=N Streching); 1H NMR DMSO):6.3(3H),1.6(2H),7.5(1H)

B_3

IR(KBr) Vmax cm-1: 3216(N-H Streching),1699(C=O Streching),1235(C=S Streching).1636(C=N Streching) 1527(N=O); 1H NMR (DMSO):7.6(4H), 2.2(2H), 8.1(1H),2.2(3H)

B_4

IR(KBr) Vmax cm-1: 3219(N-H Streching),1777(C=O Streching),1264(C=S Streching).1705(C=N Streching)3219(O-H Streching); 1H NMR (DMSO):6.8(4H),2.1(1H),8.9(1H),2.2(3H),5.0(1H)

B_5

IR(KBr) Vmax cm-1: 3209(N-H Streching),1698(C=O Streching),1290(C=S Streching).1520(C=N Streching); 1H NMR (DMSO):6.6(4H),2.1(1H),8.1(1H),2.1(3H),2.2(6H).

Biological activity

Antimicrobial activity

The synthesized compounds were screened *in vitro* for their antibacterial activity against pathogenic organisms *bacillus subtilis* and *E. coli* using ofloacin as standard at a concentration of 50 and 100µg/ml with DMF as the solvent. The activity data is given in table4 and table 5.

Locomotor activity

The synthesized compounds were tested for locomotor activity by actophotometer apparatus. Healthy male albino mice of approximately same age, weighing about 25-30 gm were used and were divided in to 3 groups. They were maintained under standard conditions (12 hr light/ 12 hr dark cycle, 25 ± 30C, 36-60 % humidity). One group served as positive control[5] (received chlorpromazine 3mg/kg; i.p), one group as negative control (received 5% gum acacia 5 ml/kg) and rest of the groups received test compounds (80 mg/kg orally. The sedative hypnotic activity of mice was observed by recording actophotometer readings after every 30 mins for 120 mins and is shown in Table6.

Table 4: Antibacterial activity data of synthesized compounds

COMPOUND CODE	Zone of inhibition in mm			
	B. subtilis (MTCC-441)		*E. coli (ATCC-11775)*	
	50 µg	**100 µg**	**50 µg**	**100µg**
A_1	20	16	21	17
A_4	14	12	13	12
B_2	19	17	22	18
B_3	21	18	22	20
B_5	22	18	16	14
B_6	20	13	20	17
Control	-	-	-	-
Ofloxacin	**26**	**21**	**25**	**24**

Table 5 Antifungal activity data of synthesized compounds

COMPOUND CODE	Zone of inhibition in mm			
	A. niger		*C.albicans*	
	50 µg	**100 µg**	**50 µg**	**100µg**
A_1	7	6	8	7
A_4	12	9	10	11
B_2	11	17	12	18
B_3	9	8	8	6
B_5	13	11	15	14
B_6	9	12	13	11
D_1	14	10	10	9
D_2	13	9	11	7
Control	-	-	-	-
Fluconazole	**22**	**21**	**25**	**23**

Table 6: Locomoter activity data of synthesized compounds

TREATMENT	DOSE	30 MINS	60 MINS	90 MINS	120 MINS
CONTROL	5 ml/kg	98 ± 4.5	59 ± 2.9	55.54 ± 2.3	56.58 ± 2.6
CHLORPROMAZINE	3 mg/kg	92.81± 3.31	93.83± 3.31	92.79±1.74 .23	156.6± 2.92
A_1	80 mg/kg	62.3± 2.24**	60.5± 0.76*	94.3± 1.92*	168± 2.61**
A_2	80 mg/kg	71± 3.48**	52.3± 1.71*	87.67± 1.6*	177.5± 1.84**
B_1	80 mg/kg	66.3± 2.67*	93.67± 4.145*	133± 3.9**	78.83± 2.62**
B_2	80 mg/kg	65.83± 2.07**	39.3± 1.41*	88.6± 2.33*	137.3± 1.81**
B_3	80 mg/kg	53.5± 2.29**	56.67± 1.43*	77.67± 2.27**	126± 2.25**
B_4	80 mg/kg	83.16± 6.44**	41.16± 2.96*	124± 5.56**	156.67± 1.94*

$P < 0.001$, considered extremely significant.* - $P > 0.05$,**- $P < 0.01$

Result and Conclusion

In actphotometer method amongst the entire tested compounds acylated compound showed better activity than thiosemicarbazones, a few showed activities even better than standard.From the antifungal activity data, it was found that the synthesized compounds exhibited mild to moderate antifungal activity against A. Niger and C. albicans at a concentration of 50µg/ml and 100µg/ml

It has been found that compounds A_1, A_4, B_2, B_3, B_5, and B_6 showed significant activity against both of strain as compared to Ofloxacin. B_6 compound was found more potent as compared to other synthesized compounds against gram positive *Bacillus subtilis* in non dose-dependent manner. The solvent control i.e DMF did not show any activity.

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