SYNTHESIS AND ANTIBACTERIAL ACTIVITY OF 1-(3-HYDROXY-2-NAPHTHOYL)-4-SUBSTITUTED THIOSEMICARBAZIDES

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SUMMARY

1-(3-Hydroxy-2-naphthoyl)-4-substituted thiosemicarbazides were obtained by the addition of 3-hydroxy-2-naphthoic acid hydrazide to various isothiocyanates. The structures of the synthesized compounds were confirmed using UV and ^{1}H-NMR spectral methods together with elemental analysis.

KEY WORDS

1,4-disubstituted thiosemicarbazides, structure elucidation, antibacterial activity

INTRODUCTION

Some aroylthiosemicarbazide derivatives have recently been reviewed. The considerable biological activities of aroylthiosemicarbazides are responsible for this interest. The investigations showed that 1-aroyl-4-substituted thiosemicarbazides have antimicrobial activity /1-6/. The development of resistance to current antibacterial therapy continues to drive the search for more effective agents.

These observations prompted us to synthesize new 1-(3-hydroxy-2-naphthoyl)-4-substituted thiosemicarbazides that may have antibacterial activity. Ten compounds were synthesized and tested for their possible antibacterial activity against *Staphylococcus aureus, Escherichia coli, Pseudomonas*, *Klebsiella* and *Proteus.*

For the synthesis of 1-(3-hydroxy-2-naphthoyl)-4-substituted thiosemicarbazides, 3-hydroxy-2-naphthoic acid hydrazide was added to various isothiocyanates and then heated under reflux for 2 hours. The structures of these compounds were confirmed by UV and ^{1}H-NMR spectral methods together with elemental analysis.

MATERIALS AND METHODS

Chemicals used in the experiments were purchased from Aldrich and Fluka companies. Melting points were determined on a Buchi 530 melting point apparatus and uncorrected. UV spectra were obtained on a Shimadzu UV 2100 S spectrophotometer (1 mg/100 ml in ethanol). Elemental analysis (C,H,N,S) was performed on a Leco CHNS-932 instrument. ^{1}H-NMR spectra were obtained on a Bruker AVANC-DPX 400 spectrometer in DMSO with TMS as internal reference; chemical shifts are expressed in δ (ppm).

Synthesis of 1-(3-hydroxy-2-naphthoyl)-4-substituted thiosemicarbazides (I-XI) (Fig. 1)

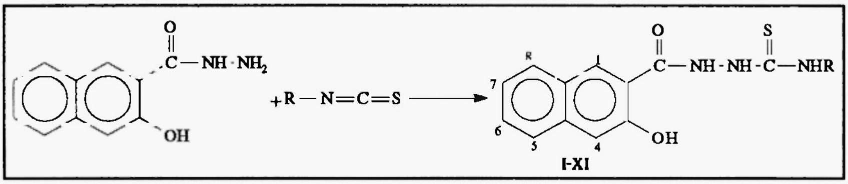


Fig. 1: Synthesis of 1-(3-hydroxy-2-naphthoyl)-4-substituted thiosemicarbazides.

3-Hydroxy-2-naphthoic acid hydrazide (0.0062 mol) in ethanol (50 ml) was heated until dissolved. Equimolar amounts of phenyl, 4-bromophenyl, 4-chlorophenyl, 2-fluorophenyl, 3-fluorophenyl, 3-trifluoromethylphenyl, 4-methoxyphenyl, 4-nitrophenyl, phenethyl, allyl and tollyl isothiocyanates were added and the mixtures refluxed for 3 hours. The crystalline product was recrystallized from ethanol /1,3/.

Microbiology

All microorganisms are deposited at the Microbiology Department Collection of Medicine Faculty of Uludağ University. Ciprofloxazine was used as positive control substance for bacteria.

The compounds were dissolved in DMSO. Two-fold dilution of each compounds was made in nutrient broth (Bisco) (concentration range 0.05-100 µg/ml) /7/. All microorganisms were incubated at 37°C for 18 h. The cultures were diluted to 1/100. These dilutions (100 µl) were inoculated into tubes with compound solutions. For each compound, a control was included. The tests were carried out in triplicate and MIC values were calculated.

RESULTS AND DISCUSSION

Physicochemical properties of the synthesized compounds are listed in Table 1.

According to the UV spectroscopic data (Table 2), π-π^* transitions of thiosemicarbazides (K band) were observed at the range of 235.4-243.4 nm.

The ^{1}H-NMR spectra of the compounds displayed the N_1H, N_2H and N_3H resonances of thiosemicarbazides at 11.40-11.74 ppm, 11.03-11.74 ppm and 9.61-10.37 ppm as a singlet, respectively. The hydroxyl proton attached to the naphthoyl ring was observed at 9.92-10.75 ppm as a singlet. The other protons of the compounds are shown in Table 3.

The *in vitro* evaluation of antimicrobial activity was carried out against some gram-positive and gram-negative bacteria, by means of the tube dilution method. Results were expressed as minimum inhibitory concentrations (MIC) and are reported in Table 4.

The highest activity was exhibited by the 4-nitrophenyl derivative (**XI**). **XI** was found to be active against all tested microorganisms. The 4-methoxyphenyl derivative (**X**) showed antibacterial activity against *S. aureus* greater than **III**, **VI** and **VII**. The non-substituted phenyl derivative (**III**) was active against *S. aureus* and *Klebsiella*. While the 4-bromophenyl and 4-chlorophenyl derivatives (**IV** and **V**) did not show any inhibitory potency, the 2- and 3-fluorophenyl derivatives (**VI** and **VII**) were active against *S. aureus* and *Klebsiella*. Compounds **I**, **II**, **VIII** and **IX** were not found to be active against any tested microorganism. Only **X** and **XI** were found to be active against *Proteus*.

TABLE 1

The melting points, yields and elemental analysis of compounds **I-XI**

Comp.	M P. (°C)	Yield (%)	Mol. Formula (mol. weight)	El. Anal. (calc/found)			
				C	H	N	S
I	193	90.1	$C_{15}H_{15}N_3O_2S$	59.78	5.02	13.94	10.64
			301.37	60.47	4.65	13.81	9.82
II	203	87.2	$C_{20}H_{19}N_3O_2S$	65.73	5.24	11.50	8.77
			365.45	65.50	4.73	11.68	8.10
III*	195	97.8	$C_{18}H_{15}N_3O_2S$	64.08	4.48	12.45	9.50
			337.40	64.28	4.60	12.28	10.07
IV	209	96.2	$C_{18}H_{14}N_3BrO_2S$	51.94	3.39	10.09	7.70
			416.29	52.37	3.15	10.38	7.38
V	198	94.9	$C_{18}H_{14}N_3ClO_2S$	58.14	3.80	11.30	8.62
			371.84	57.27	3.38	11.33	8.10
VI	220-3	83.7	$C_{18}H_{14}N_3FO_2S$	60.84	3.97	11.82	9.02
			355.39	60.30	4.19	11.99	8.40
VII	196	85.6	$C_{18}H_{14}N_3FO_2S$	60.84	3.97	11.82	9.02
			355.39	60.19	3.67	12.06	8.47
VIII	191	74.4	$C_{19}H_{14}N_3F_3O_2S$	55.67	3.56	10.25	7.82
			$1/4H_2O$	55.21	3.52	10.31	7.47
			409.90				
IX	190	90.5	$C_{19}H_{17}N_3O_2S$	64.94	4.88	11.96	9.12
			351.43	64.41	4.75	12.04	8.41
X	197	96.0	$C_{19}H_{17}N_3O_3S$	61.08	4.99	10.96	8.36
			$1/4C_2H_5OH.1/4H_2O$	60.56	4.32	11.35	8.00
			383.44				
XI	199	91.7	$C_{18}H_{14}N_4O_4S$	55.24	3.86	14.31	8.19
			$1/2H_2O$	55.19	3.23	13.65	7.77
			391.41				

*: not novel compound.

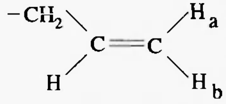
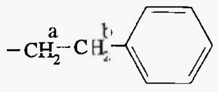
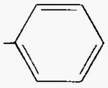
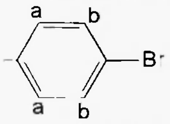
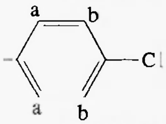
TABLE 2

UV spectral data of the compounds

Comp.	UV_{max}, ε(EtOH) (1 mg/100 ml)
I	241.0(87457), 285.6(18052)
II	239.6(110219), 285.6(22804)
III	238.6(111139)
IV	236.4(54742), 275.6(21106)
V	237.0(76227), 275.0(29301)
VI	238.4(103845), 284.8(34046)
VII	243.4(125346), 272.2(58390), 284.0(56365)
VIII	236.6(59148), 275.0(23027)
IX	236.6(49059)
X	237.0(65843)
XI	235.4(63517), 349.0(22638)

TABLE 3

^{1}H-NMR data of the compounds

Comp.	R	^{1}H-NMR, δ (ppm)
I		8.59-7.31 (m,6H: H_1,H_5,H_8,H_6,H_7,H_4), 6.00 (m, 1H, CH), 5.29 (dd,1H, H_a, J=17.28), 5.20 (dd, 1H, H_b, J=10.31), 4.28 (s, 2H, CH_2)
II		8.51(s,1H,H_1), 7.88(d,1H,$H_{5 or 8}$,J=8.10), 7.76(d,1H,$H_{5 or 8}$,J=8.23), 7.51(t, 1H,$H_{6 or 7}$,J=7.37), 7.40-7.18(m,7H: 5H,$H_{5 or 7}$, H_4), 3.68 (q, 2H, CH_2-a), 2.85 (t, 2H, CH_2-b)
III		8.53 (s,1H,H_1), 7.90(d,1H,$H_{5 or 8}$,J=8.09), 7.76(d,1H,$H_{5 or 8}$,J=8.18), 7.56-7.31(m,7H: 5H,$H_{5 or 7}$, H_4), 7.15 (t,1H,$H_{6 or 7}$,J=7.14)
IV		8.53 (s,1H,H_1), 7.90(d,1H,$H_{5 or 8}$,J=8.14), 7.75(d,1H,$H_{5 or 8}$,J=8.18), 7.52-7.35(m,6H: H_6, H_7, 2H_a,2H_b), 7.31(s,1H, H_4)
V		8.54 (s,1H,H_1), 7.90(d,1H,$H_{5 or 8}$,J=8.09), 7.76(d,1H,$H_{5 or 8}$,J=8.23), 7.59-7.32(m,7H: H_6, H_7, H_4,2H_a,2H_b)

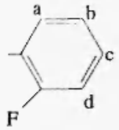
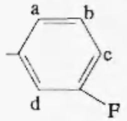
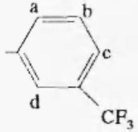
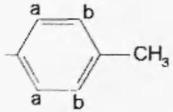
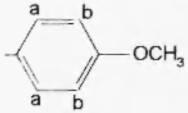
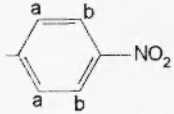
VI		8.55 (s,1H,H_1), 7.89(d,1H,$H_{5\text{ or }8}$,J=8.05), 7.75(d,1H,$H_{5\text{ or }8}$,J=8.21), 7.51(t,1H, $H_{6\text{ or }7}$,J=7.26), 7.39-7.16(m,6H: $H_{6\text{ or }7}$, H_4,H_a,H_b,H_c,H_d)
VII		8.53 (s,1H,H_1), 7.90(d,1H,$H_{5\text{ or }8}$,J=8.17), 7.75(d,1H,$H_{5\text{ or }8}$,J=8.26), 7.63-6.96(m,7H: H_6, H_7, H_4,H_a,H_b,H_c,H_d)
VIII		8.55 (s,1H,H_1), 8.00 (s, 1H, H_d), 7.91(d,1H,$H_{5\text{ or }8}$,J=8.23), 7.84(d,1H,H_c,J=8.05), 7.76(d,1H,$H_{5\text{ or }8}$,J=8.30), 7.62-7.48(m,3H: $H_{6\text{ or }7}$, H_a,H_b), 7.40-7.33(t,2H:$H_{6\text{ or }7}$,H_4)
IX		8.52 (s,1H,H_1), 7.89(d,1H,$H_{5\text{ or }8}$,J=8.10), 7.76(d,1H,$H_{5\text{ or }8}$,J=8.23), 7.51(t,1H,$H_{6\text{ or }7}$,J=7.43), 7.41-7.14(m,6H: H_4,$H_{6\text{ or }7}$, 2H_a,2H_b), 2.29 (s, 3H, CH_3)
X		8.52 (s,1H,H_1), 7.89(d,1H,$H_{5\text{ or }8}$,J=8.08), 7.75(d,1H,$H_{5\text{ or }8}$,J=8.24), 7.51(t,1H,$H_{6\text{ or }7}$,J=7.26), 7.34(t,4H:$H_{6\text{ or }7}$,H_4,2H_a), 6.91 (d, 2H, H_b, J=8.85), 3.75 (s, 3H, OCH_3)
XI		8.67 (s,1H,H_1), 8.34 (d, 2H, H_b, J=9.10), 8.07 (d, 3H: 2H_a,$H_{5\text{ or }8}$), 7.89(d,1H,$H_{5\text{ or }8}$, J=8.31), 7.64(t,1H,$H_{6\text{ or }7}$,J=7.48), 7.49(t,1H,$H_{6\text{ or }7}$, J=7.51), 7.45(s,1H,H_4)

TABLE 4

In vitro antibacterial activity data (MIC, µg/ml) of compounds **I-XI**

Comp.	***S. aureus* *ATCC 33862***	***E. coli* *ATCC 35218***	***Pseudomonas* *ATCC 10145***	***Klebsiella* *ATCC 33495***	***Proteus* *ATCC 7002***
I	-	-	-	-	-
II	-	-	-	-	-
III	50	-	-	100	-
IV	-	-	-	-	-
V	-	-	-	-	-
VI	50	-	-	100	-
VII	50	-	-	100	-
VIII	-	-	-	-	-
IX	-	-	-	-	-
X	25	-	-	-	100
XI	12.5	50	100	100	100
Cipro.	0.6	0.15	1.25	5	0.6

Cipro. = ciprofloxazine

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