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Synthesis and evaluation of *in vitro* antibacterial activity of novel 2,5-disubstituted-1,3,4-thiadiazoles from fatty acids

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Abstract

A series of new 1-(alkenoyl/hydroxyalkenoyl)-4-benzoyl-thiosemicarbazides **2a–d** and 2-benzamide-5-alkenyl/hydroxyalkenyl-1,3,4-thiadiazoles **3a–d** were synthesized from fatty acid hydrazides. Structure of all these compounds was confirmed by IR, ^{1}H NMR, ^{13}C NMR, mass spectra and elemental analysis. The bioassay results indicate that some compounds **2c**, **2d**, **3c** and **3d** have good antibacterial activity.

Keywords: Aroylthiosemicarbazide; 1,3,4-Thiadiazole; Antibacterial activity

The therapeutic effects of compounds containing 1,3,4-thiazole ring have been studied for many pathological conditions which include antibacterial [1], antifungal [2], antimicobacterial [3], antidepressant [4], inflammatory [5] and analgesic [6]. Antibacterial diseases are very common all over the world. Currently used antimicrobial agents are not effective due to resistance developed by microbes, and therefore it is an ongoing effort to synthesize new antimicrobial agents. Over and above there is no permanent structure and activity relationship. Recently the importance of –N=C=S linkage has been well stressed [7]. It has been found that this linkage is responsible for various biological activities in many compounds containing sulphur, such as dithiocarbamates, thiourea and thiosemicarbazides [8]. In continuation to this we have selected fatty acids as starting materials because they are known to possess antibacterial [9,10], antifungal [10,11], pesticidal [12], and anticancer activities [13].

Keeping in mind the practical application of 1,3,4-thiadiazoles, we considered the synthesis of hitherto new thiadiazoles bearing long alkenyl and hydroxyl-alkenyl chain and their in vitro antibacterial activity.

1. Experimental

The reaction sequences leading to the formation of different title compounds **3a–d** are outlined in Scheme 1. Benzoylisothiocynate a versatile reagent for synthesis of different thiosemicarbazides [14] was prepared according to literature method [15]. Fatty acid hydrazides **1a–d** were prepared according to method described in our previous paper [16]. Undec-10-enoyl-hydrazide **1a** was dissolved in minimum amount of ethyl acetate and added portion wise to

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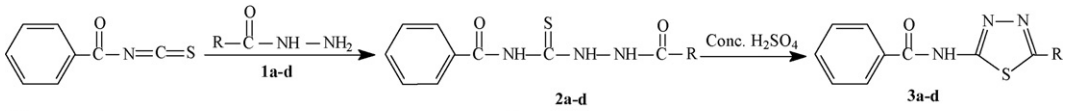

Compounds	R
1a-3a	$CH_2{=}CH(CH_2)_8$
1b-3b	$CH_3(CH_2)_7CH{=}CH(CH_2)_7$
1c-3c	$CH_3(CH_2)_5CH(OH)CH_2CH{=}CH(CH_2)_7$
1d-3d	$CH_3(CH_2)_4CH{=}CH(CH_2)_2CH(OH)(CH_2)_7$

Scheme 1. Synthesis of thiosemicarbazides and 2,5-disubstituted-1,3,4-thiadiazoles.

isothiocynate solution while stirring at reflux temperature for 3–4 h. Excess solvent was removed and the precipitated compound was filtered and crystallised from benzene–chloroform to give 1-(undec-10-enoyl)-4-benzoyl-thiosemicarbazides **2a**. Similarly compounds **2b–d** were prepared.

1-(Undec-10-enoyl)-4-benzoyl-thiosemicarbazides **2a** was treated with concentrated sulphuric acid at 0 °C in an ice bath with constant stirring for 1–2 h. The reaction mixture was poured into 50 mL ice water. The product was precipitated, filtered and washed with excess cold water to afford 2-benzamido-5-(dec-9-enyl)-1,3,4-thiadiazole **3a** in quantitative yield. It was also observed that sulphuric acid was a better dehydrating agent than acetic anhydride, which takes more reaction time and poor yields. Structures of all new synthesized compounds were elucidated by spectral data and elemental analysis [17].

2. Results and discussion

1-(Undec-10-enoyl)-4-benzoyl-thiosemicarbazides **2a** showed characteristic IR bands at 3226 (NH–NH, NH), 1667 (C=O) and 1300 cm^{-1} (C=S). ^1H NMR was more informative in assigning the structure showing peaks at δ 13.02 (s, 1H, NH) and 9.18 (br. s, 2H, NH–NH). In ^{13}C NMR peaks at δ 168.2 (C=S), 165.4 (C=O) and 160.8 (C=O) were observed. Elemental analysis and mass spectral data [m/z = 384 $(M+Na)^+$] established its molecular formula $C_{19}H_{27}N_3O_2S$.

2-Benzamido-5-(dec-9-enyl)-1,3,4-thiadiazole **3a** gave significant IR bands at 3181 (NH), 1664 (C=O), 1541 (C=N) and 707 cm^{-1} (C–S–C). ^1H NMR peak at δ 8.32 (s, 1H, NH) was observed in addition to peaks of normal fatty acid chain. In ^{13}C NMR peaks at δ 165.2 (C=S), and 153.2 (C=N) were observed. Elemental analysis and mass spectral data [m/z = 366 $(M+Na)^+$] established its molecular formula $C_{19}H_{25}N_3OS$.

These synthesized compounds were also screened for their antibacterial activity against *Escherichia coli*, *Salomonella typhi*, *Staphylococcus aureus* and *S. albus* by cup plate method [18]. From Table 1 it may be seen that compounds **2c** and **2d** showed good activity against *E. coli*. Compounds **2a** and **2b** showed moderate activity against all the bacteria while as compounds **2c**, **2d**, **3c** and **3d** showed good activity against all the bacteria. It may be noticed

Table 1
Antibacterial screening data for **2a–d** and **3a–d**.

Compound	Diameter of zone of inhibition (mm)			
	Gram-negative bacteria		Gram-positive bacteria	
	Escherichia coli	*Salmonella typhi*	*Staphylococcus aureus*	*S. albus*
2a	12	9	11	8
2b	10	11	12	10
2c	17	16	16	14
2d	18	14	16	17
3a	10	17	13	18
3b	10	7	11	8
3c	14	13	16	17
3d	15	16	14	13
Chloromycetin	22	20	23	20
(Control) DMF	–	–	–	–

Concentration used = 50 μg/mL of DMF.