Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy 153 (2016) 510–516

Contents lists available at ScienceDirect

Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy

journal homepage: www.elsevier.com/locate/saa

Synthesis and multi-spectroscopic DNA binding study of 1,3,4-oxadiazole and 1,3,4-thiadiazole derivatives of fatty acid

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ARTICLE INFO

Article history:
Received 8 April 2015
Received in revised form 3 September 2015
Accepted 10 September 2015
Available online 12 September 2015

Keywords:
1,3,4-Oxadiazole
1,3,4-Thiadiazole
CT-DNA binding
Spectral studies

ABSTRACT

A facile and convenient synthesis of a series of fatty acid derivatives of 1,3,4-oxadiazole and 1,3,4-thiadiazole has been described. The key step of this protocol is the cyclization of acyl thiosemicarbazides via iodobenzene diacetate and methanesulfonic acid under mild conditions. The newly synthesized compounds were characterized by FT-IR, ^{1}HNMR, ^{13}CNMR and mass spectral study. The binding affinity of 5-(pentadecyl)-N-propenyl-1,3,4-oxadiazol-2-amine (**3a**) and 5-(heptadecyl)-2-amino-1,3,4-thiadiazole (**6a**) with CT-DNA has been evaluated by UV, fluorescence, Circular Dichroism (CD) and thermal denaturation studies. It has been found that these small and planer heteroaromatic compounds are capable of binding to the minor groove region of DNA.

1. Introduction

The interaction of small molecules with DNA is gaining interest in the area of medicinal chemistry for exploring the structural and functional features of macromolecules to design new and effective drugs against various diseases [1]. Synthetic indol alkaloids such as β-carboline alkaloid possessing large pharmaceutical activities, particularly as a potential antitumoral agent by way of intercalation into DNA and inhibition of topoisomerase I and II [2]. Certain bis-benzimidazoles act as minor groove binders and exhibited anticancer activity by blocking the DNA helicase activity at specific base sequences [3]. Similarly the bis-amidines such as pentamidine, berenil and furamidines bind to the minor groove of DNA and exert their biological activity through the inhibition of DNA associated enzymes topoisomerases [4]. In addition, the compounds containing 1,3,4-oxadiazole and 1,3,4-thiadiazole nucleus possess a vast spectrum of biological activities [5]. 1,3,4-Oxadiazoles are bioisosteres which increase the pharmaceutical activity by participating H-bonding with receptors [6] and toxophoric moiety N = C–S present in 1,3,4-thiadiazole determines their biological activity [7]. On the other hand, fatty acids and its derivatives itself have potential pharmacological activity and earlier study reveals the role of long chain alkyl groups in increasing the pharmaceutical activity [8]. So it is important to investigate the interaction of these 5-membered heterocyclic compounds containing long alkyl chain with DNA. To our knowledge, the interaction of oxadiazole and thiadiazole derivatives with DNA has not been studied so far. After viewing the aforementioned facts, and as a part of drug development programmes [9], in this study we synthesized 1,3,4-oxadiazole and 1,3,4-thiadiazole compounds containing fatty acid chains by an efficient and simple protocol. Our synthetic strategy was based on the formation of a heterocyclic moiety in the fatty acid chain by introducing a reactive thiosemicarbazide moiety followed by cyclization using iodobenzene diacetate (Scheme 1) and methanesulfonic acid (Scheme 2) under very mild conditions. We explore the interaction of two new compounds **3a** and **6a** with CT-DNA by various spectroscopic methods.

2. Results and discussion

2.1. Chemistry

The synthesis of 5-substituted-N-propenyl-1,3,4-oxadiazole-2-amine (**3a–d**) was carried out by the desulfurization of acyl thiosemicarbazide (**2a–d**) using iodobenzene diacetate [PhI $(OAc)_2$]. The long chain fatty acid hydrazides (**1a–d**) used as the starting material were prepared from corresponding fatty acids by esterification followed by reaction with hydrazine hydrate [10]. The reaction of (**1a–d**) with allylisothiocyanate ($CH_2 = CHCH_2NCS$) under reflux condition afforded (**2a–d**). Subsequent cyclo desulfurization of (**2a–d**) in tetrahydrofuran (THF) afforded the target compounds (**3a–d**) in good yields (Scheme 1). The IR spectrum of the compound (**3a**) showed a broad band at 3222 cm^{-1} which is the characteristic of the N–H group and the absorption bands at 2924 cm^{-1} and 2851 cm^{-1} are the symmetrical and unsymmetrical bands of C–H of fatty acid respectively. The ^{1}HNMR spectrum was more informative in assigning the structure. The disappearance of three singlet ^{1}HNMR peak of (**2a**) at δ 9.40, 8.75 (NH–NH) and 7.0 (CSNH) and appearance of broad singlet due to N–H proton at δ 10.74 confirmed the structure of **3a** (Supplementary file Fig. S1).

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http://dx.doi.org/10.1016/j.saa.2015.09.005
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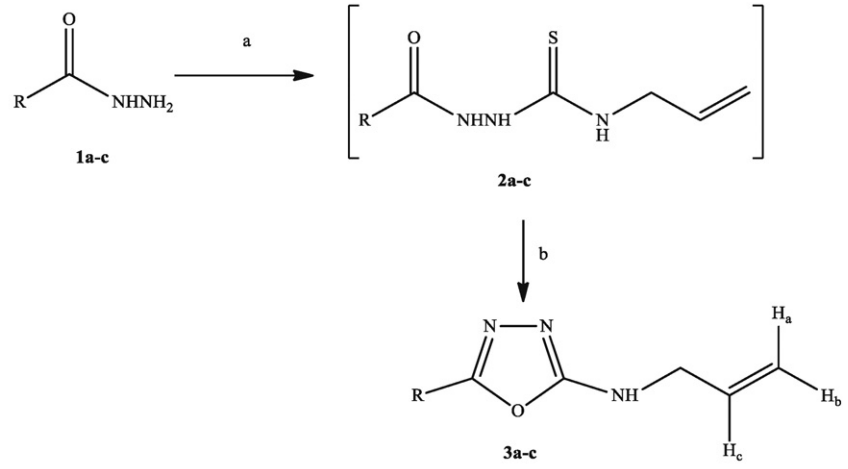
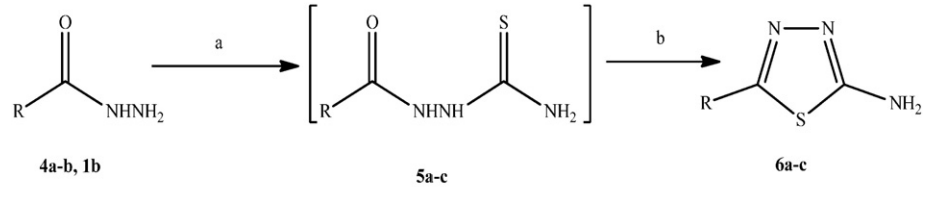


Compound	R
1a, 2a, 3a	$H_3C-(CH_2)_{11}-CH_2$
1b, 2b, 3b	$H_3C-(CH_2)_6-CH=CH-(CH_2)_5-CH_2$
1c, 2c, 3c	$H_3C-(CH_2)_3-CH(OH)-CH_2-CH=CH-(CH_2)_6-CH_2$

Scheme 1. Reagents and conditions : (a) $^1CH_2 = CHCH_2NCS$, absolute EtOH, Reflux, 8 h (b) $PhI(OAc)_2$, THF, stirr, RT, 6–8 h (^{1}Formation of **2a–c** was confirmed by FT-IR and ^{1}HNMR data of **2a**).

Diagnostic peaks at δ 2.59 (t, CH_2 α to ring), 5.88, 5.28 and 5.12 (m, unresolved dd, unresolved dd of three double bond protons (H_c, H_a and H_b of the allyl group respectively)) were also observed (Supplementary file Fig. S1). The ^{13}CNMR peaks at δ 169.0 and 154.3 were observed for two ring carbons which further confirm the structure. A series of compounds (**6a–c**) were synthesized via methanesulfonic acid (CH_3SO_3H) mediated cyclization of acylthiosemicarbazide (**5a–c**) (Scheme 2). The compounds (**5a–c**) were prepared by refluxing of fatty acid hydrazides (**1a–b**, **4a**) with potassium thiocyanate (KSCN) in a mixture of ethanol, water and concentrated hydrochloric acid. The structure elucidation of all new synthesized compounds (**5a–c**) was based on FT-IR, ^{1}HNMR, ^{13}CNMR and mass spectra. 5-Heptadecanyl-2-amino-1,3,4-thiadiazole (**6a**) showed that FT-IR bands at 3414 cm^{-1} correspond to NH_2 group and other bands at 2918 cm^{-1} and 2850 cm^{-1} (C–H, alkyl chain). The structure of **6a** is supported by the fact that, three singlet peaks at (δ 8.45, 8.30 and 8.11) of three N–H protons of **5a** disappeared and a broad singlet at δ 10.85 that corresponds to NH_2 protons was observed on the ^{1}HNMR spectrum (Supplementary file Fig. S2). In the ^{13}CNMR spectrum, two peaks at δ 167.6 and 153.0 were the characteristic peaks of two carbons of 1,3,4-thiadiazole ring. The mass spectral results



Compound	R
4a, 5a, 6a	$H_3C-(CH_2)_{13}-CH_2$
1b, 5b, 6b	$H_3C-(CH_2)_6-CH=CH-(CH_2)_5-CH_2$
4b, 5c, 6c	H_a, H_b, $-(CH_2)_6-CH_2$

Scheme 2. Reagents and conditions : (a) ^{1}KSCN, EtOH–H_2O, H_2SO_4, Reflux, 8 h (b) $MeSO_3H$, Toluene, Reflux, 5–6 h (^{1}Formation of **5a–c** was confirmed by FT-IR and ^{1}HNMR data of **5a**).