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Research paper

Synthesis, characterization and interaction studies of 1,3,4-oxadiazole derivatives of fatty acid with human serum albumin (HSA): A combined multi-spectroscopic and molecular docking study

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ABSTRACT

An efficient synthesis of fatty acid derivatives of 1,3,4-oxadiazole has been reported and comparative study between conventional heating to that of microwave irradiation also described. The newly synthesized compounds **(2A-F)** were characterized by FT-IR, ^{1}H NMR, ^{13}C NMR and mass spectral analysis. The binding interaction of (Z)-2-(heptadec-8′-enyl)-5-methyl-1,3,4-oxadiazole **(2C)** with human serum albumin (HSA) has been evaluated by UV, fluorescence, circular dichroism (CD) and molecular docking studies. Fluorescence results showed that compound **2C** interacts with HSA through static quenching mechanism with binding affinity of 2×10^{3} M^{-1} and Gibbs free energy change (ΔG) was found to be -16.83 kJ mol^{-1}. Molecular docking studies have been performed to evaluate possible mode of interaction of compound **2C** with HSA.

1. Introduction

Heterocyclic compounds particularly 5-membered rings acquired importance because of their versatile pharmacological and biological activities [1]. In particular, 1,3,4-oxadiazoles have been used as 'privileged' scaffolds to produce substances of interest in numerous therapeutic areas. Differently substituted 1,3,4-oxadiazoles have been found to exhibit anti-inflammatory, antimicrobial, antitubercular, antidepressant, antimalarial, anti-HIV, and anticancer activities [2–7]. 1,3,4-Oxadiazoles are well known bioisosteres of amides and esters [8], that can contribute significant pharmacokinetic property due to presence of N=C–O linkage in oxadiazole nucleus which increases the lipophilicity that influence the ability of drug to reach the target by transmembrane diffusion and show remarkable biological activity. Often, these molecules are used as pharmacophores due to their ability to bind with target proteins through hydrogen bond formation [9].

Human serum albumin (HSA) is the most important and abundant extracellular protein among plasma proteins that act as an excellent carrier of drugs and other small molecules [10] due to availability of multiple binding sites, which helps in transporting drugs to the target site. The study of interactions between drugs and plasma protein is an emerging field in medicinal chemistry [11]. HSA has two important binding sites located in hydrophobic cavities in subdomain IIA and IIIA. Site I is formed as a pocket in subdomain IIA and having the lone tryptophan of HSA (Trp-214). It has been observed that most of the aromatic and heterocyclic moieties were bound within two hydrophobic pockets in sub domain IIA and IIIA, site I and site II respectively [12].

HSA plays an important role in the transport and deposition of a various endogenous and exogenous substances including fatty acids [13]. In addition, fatty acids and its derivatives have been found to possess promising biological activities such as antimicrobial, anti-HIV, antioxidant, antidepressant, anticancer and DNA binding studies [14,15]. Owing to this, it is important to investigate the interaction of 1,3,4-oxadiazole containing long alkyl chain with HSA. In viewing aforementioned facts, the present study is focus on the synthesis of 1,3,4-oxadiazole containing fatty acid chains via efficient and easy protocol as a part of drug development programme. The synthetic strategy involves formation of 2,5-disubstituted 1,3,4-oxadiazoles (**2A-F**) using fatty acid hydrazides and triethyl orthoacetate. A comparative study of conventional to

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that of microwave synthesis also outlined as recently, there has been growing interest in the application of microwave irradiation in chemical reaction enhancement, due to improved reaction rates and increased yields [16]. Further, we explore the binding study of a newly synthesized compound **2C** with HSA by various spectroscopic tools. To our knowledge, the interaction of oxadiazole derivatives with HSA has not been studied so far. Since, binding interaction of fatty acid with HSA have been studied [17], and oleic acid is most abundant fatty acid in plasma, so 1,3,4-oxadiazole containing oleic chain (**2C**) has been chosen to show different interactions with HSA.

2. Results and discussion

2.1. Chemistry

The synthesis of 2,5-disubstituted 1,3,4-oxadiazoles (**2A-F**) was carried out utilizing fatty acid hydrazides (**1A-F**) and triethyl orthoacetate. The long chain fatty acid hydrazides (**1A-F**) used as the starting materials were prepared from corresponding fatty acids by esterification followed by reaction with hydrazine hydrate [18]. The reaction of (**1A-F**) with excess triethyl orthoacetate in presence of glacial acetic acid under reflux resulted the formation of desired 2,5-disubstituted 1,3,4-oxadiazoles (**2A-F**) in good yields (70–79%, Table 1) (procedure A) (Scheme 1). However, the long reaction times (15–20 h, Table 1), made the conventional method less attractive. Thus, we decided to carry out same reactions under microwave irradiation (procedure B). The desired products (**2A-F**) obtained exclusively, upon a 10 min irradiation, in high yields, as depicted in (Table 1). The FT-IR spectrum of the compound (**2A**) revealed characteristic peaks at 2922 cm^{-1} and 2852 cm^{-1} for the asymmetrical and symmetrical bands of C–H of fatty acid respectively. The absorption peaks showed at 1588 cm^{-1} and 1243 cm^{-1} also observed for C=N and C–O–C of the oxadiazole ring. The ^{1}H NMR was more informative in assigning the structure. Appearance of singlet at δ 2.49 for CH_3 attached to oxadiazole ring (**2A**). Diagnostic peaks at δ 2.79 (t, 2H, J = 7.6 Hz, CH_2 α to ring), 1.57 (m, 2H, CH_2 β to ring), 1.27 (br. s, 28H, $(CH_2)_{14}$ chain) and 0.87 (dist. t, 3H, CH_2CH_3) were also observed. The ^{13}C NMR peaks at δ 167.2 and 163.5 were observed for two ring carbons which further confirm the structure. The mass spectra showed characteristic molecular ion peak in accord with the molecular formula. Similarly other compounds were characterized from their spectral data.

2.2. UV–vis measurements

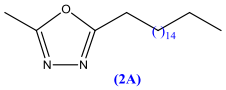
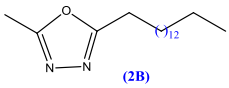
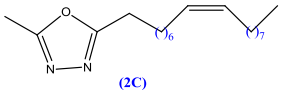
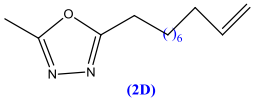
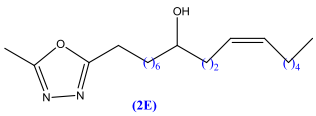
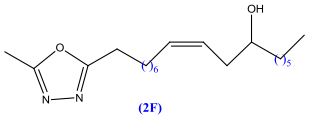
UV–Vis spectroscopy is used for monitoring structural changes in protein and to investigate formation of drug-protein complex [19]. HSA has main absorption band located in the range of 260–300 nm which is the absorption band of the aromatic amino acids (Trp, Tyr, and Phe) [20].

UV–Vis absorption spectra of HSA in the absence and presence of **2C** are shown in (Fig. 1). As can be seen in Fig. 1, HSA has strong absorbance with a peak at 280 nm and the absorbance of HSA increased with the addition of **2C**. In addition, the absorbance value at 280 nm of the **2C** at a concentration of 50 and 100 μM is very low (<0.03). Our results confirmed that the interaction between HSA and **2C** took place [21].

2.3. Steady state fluorescence measurements

Fluorescence spectroscopy is valuable tool for studying ligand-protein interaction [22]. HSA contains only one tryptophan (Trp 214) located in subdomain IIA. A fixed concentration of HSA (5 μM) was titrated with varying concentration of **2C** (0–200 μM). The maximum emission wavelength of HSA was found at 340 nm and the value decreases regularly upon increasing concentration of compound **2C**, indicating that interaction between compound **2C**

Table 1
Products of the reaction of fatty acid hydrazides **(1A-F)** with triethyl orthoacetate.

Products	Mol. formula	Mol. weight	Procedure A		Procedure B	
			Yield (%)	Time (h)	Yield (%)	Time (min)
 (2A)	$C_{20}H_{38}N_2O$	322.46	71	18	88	10
 (2B)	$C_{18}H_{34}N_2O$	294.42	77	17	91	10
 (2C)	$C_{20}H_{36}N_2O$	320.44	74	20	93	10
 (2D)	$C_{13}H_{22}N_2O$	222.28	79	15	94	10
 (2E)	$C_{20}H_{36}N_2O_2$	336.45	70	19	87	10
 (2F)	$C_{20}H_{36}N_2O_2$	336.45	72	20	89	10