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Novel 2-amino-1,3,4-thiadiazoles and their acyl derivatives: Synthesis, structural characterization, molecular docking studies and comparison of experimental and computational results

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ABSTRACT

This study aims to synthesize and characterize compounds containing 2-amino-1,3,4-thiadiazole and compare experimental results to theoretical results. For this purpose, firstly mono, di and tetra 2-amino-1,3,4-thiadiazole compounds **(2a–c, 14, 20 and 25)** were synthesized in relatively high yields (74–87%). The target compounds **(3–11**, **15–17**, **21–23** and **26–28)** were then synthesized in moderate to high yields (65–85%) from the reactions of 2-amino-1,3,4-thiadiazole compounds with various acyl chloride derivatives.

The structures of all synthesized compounds were elucidated by IR, ^{1}H NMR, ^{13}C NMR, elemental analyses and mass spectroscopy techniques. The structures of **2b** ($C_9H_8N_4O_2S$) and **2c** ($C_{11}H_{13}N_3O_2S$) were also elucidated by X-ray diffraction analysis.

Lastly, IR spectrum, ^{1}H NMR and ^{13}C NMR chemical shift values, frontier molecular orbital (FMO) values of these molecules containing heteroatoms were examined using the Becke-3- Lee-Yang-Parr (B3LYP) method with the 6-31G(d) basis set. Two different molecular structures containing 2-amino-1,3,4-thiadiazole **(2b, 2c)** were used in our study to examine these properties. Also, compounds **2b** and **2c** form a stable complex with beta-Lactamase as can be understood from the binding affinity values and the results show that the compound might inhibit the beta-Lactamase enzyme. It was found that theoretical and experimental results obtained in the experiment were compatible with each other and with the values found in the literature.

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1. Introduction

In recent years, despite significant increases in their discovery, the uses of compounds with biological activities were quite limited due to the development of resistance against these compounds and the presence of various side effects. For these reasons, chemists have been striving to develop compounds with biological activities for use in pharmaceutical chemistry.

Thiadiazole is a five-membered heterocyclic aromatic compound with the molecular formula of $C_2H_2N_2S$. 1,3,4-Thiadiazole and its derivatives have become the focus of attention in drug, agriculture and material chemistry due to their high activity in 2′ and 5′ positions against nucleophilic substitution reactions [1–8]. The –N=C–S group in the structure allows for great structural stability and is known to be the component responsible for biological activity [9,10]. 1,3,4-thiadiazole and its heterocyclic derivatives have been synthesized on a large scale for many years due to a variety of biological activities, including antifungal, antibacterial, antimicrobial, anti-inflammatory, anticonvulsant, anti-HIV, antituberculosis, and antiproliferative activities [11–27]. The synthesis of these compounds is particularly important due to the high anticancer activities of 2-amino-1,3,4-thiadiazole and derivatives, [28–31]. In addition, it has been reported in various studies conducted with 1,3,4-thiadiazole and its derivatives that these compounds were used in various areas such as polymer, dye, herbicide

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and insecticide production [32–35].

Today, beta-lactam antibiotics are the most widely used antibiotic derivatives. The most important source of resistance against beta-lactam antibiotic derivatives for members of *Enterobacteriaceae* are beta-lactamase enzymes secreted by bacteria. Beta-lactamase enzymes are mostly synthesized by Gram negative bacteria and cause resistance against antibiotics that carry beta-lactam ring [36]. Beta-lactam antibiotics inhibit transpeptidase and carboxypeptidase enzymes, which are responsible for peptidoglycan synthesis, and inhibit cell wall synthesis [37]. The most significant pathogen that synthesizes beta-lactamase among Gram-positive bacteria is *Staphylococcus aureus*.

In the light of the important data gathered through research of the literature, the primary purpose of this study was to synthesize a variety of substituted groups containing 1,3,4-thiadiazole ring with potential biological activity, acylate these compounds with various acyl groups, and to characterize them. The synthetic routes of all synthesized compounds are given in Schemes 1–4.

The secondary purpose of the study was to theoretically examine the following properties of the synthesized compounds to support experimental studies: IR, NMR spectra and frontier molecular orbital (FMO).

Also, structures of **2b** and **2c** compounds were compared with the ligands of prominent antibacterial targets in terms of similarity. Trial docking studies made for this enzyme showed that the crystal structure 1BLH of beta-Lactamase from *S. aureus* was the most appropriate target of the **2b** and **2c** compounds.

2. Experimental

2.1. Materials and methods

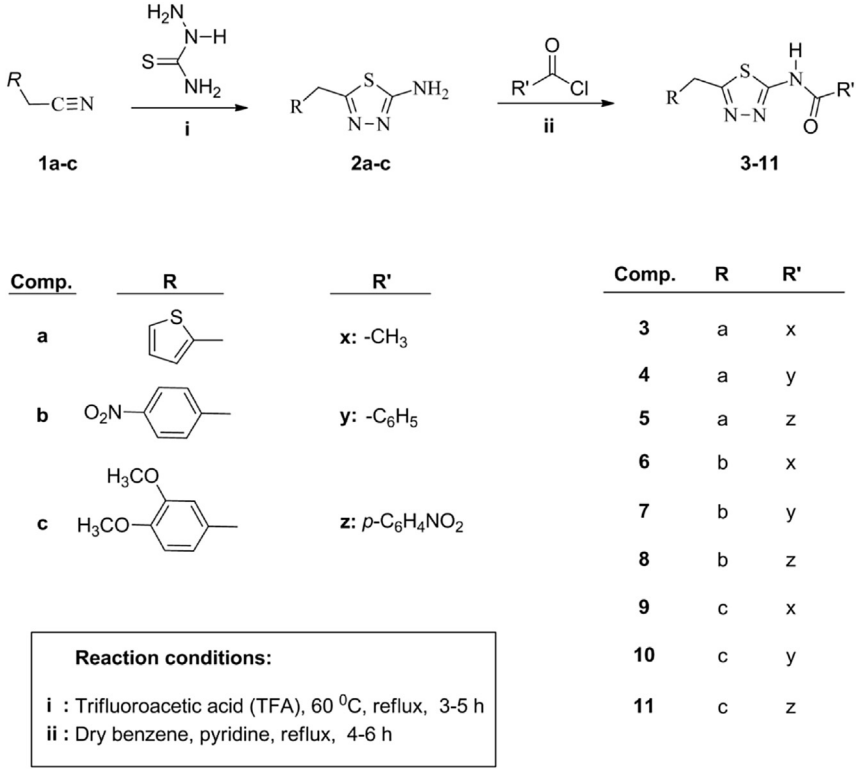
The reactions were carried out under a nitrogen atmosphere using standard Schlenk techniques. The ^{1}H NMR and ^{13}C NMR spectra of the compounds were recorded in DMSO-d_6 using an Agilent NMR VNMRS spectrometer at 400 MHz and 100 MHz, respectively. TMS was used as an internal standard. The IR spectra were measured in ATR using a Perkin Elmer FT-IR Spectrometer Frontier. The mass spectra were measured with a Thermo TSQ Quantum Access Max LC-MS/MS spectrometer. Elemental analyses were performed on a LECO 932 CHNS (Leco-932, St. Joseph, MI, USA) instrument and the results were within ±0.4% of the theoretical values. Melting points were recorded on a Thermo Scientific IA9000 series apparatus and were uncorrected. All of the chemicals were obtained from Merck Chemicals.

2.2. Synthesis

2.2.1. General method for the synthesis of mono 2-amino-1,3,4-thiadiazole derivatives (**2a–c**)

In a round-bottomed flask, compounds **(1a–c)** (0.002 mol) and thiosemicarbazide (0.003 mol) in trifluoroacetic acid (5 mL) at 60 °C were stirred for 3–5 h. The progress of the reaction was monitored by TLC at appropriate time intervals. After completion of the reaction, the mixture was poured into 200 mL of ice-cold water and neutralized with ammonia. The solution was filtered and the solid matter was obtained. It was washed with deionized water, ethanol and diethyl ether, respectively. The solid was recrystallized from the appropriate solvent. The physical properties and spectral data derived from the obtained products are listed below.

2.2.1.1. 5-(thiophen-2-ylmethyl)-1,3,4-thiadiazol-2-amine ***(2a)***. Yield: (74%); White solid, mp 183–184 °C (from DMF-EtOH, 1:3). IR (ATR, cm^{-1}): 3260–3100 ($-NH_2$), 3045 (Ar-CH), 2973 (Aliph. CH), 1517–1503 (C=N), 1159 (N–N), 622–578 (C–S). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 4.36 (s, 2H, $-CH_2$), Thiophene-H [6.93 (d,



Scheme 1. General synthesis of mono 2-amino-1,3,4-thiadiazole derivatives (**2a–c**), and their acyl derivatives (**3–11**).

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