Journal of Molecular Structure 1125 (2016) 470–480

Contents lists available at ScienceDirect

Journal of Molecular Structure

journal homepage: http://www.elsevier.com/locate/molstruc

# Novel aldehyde and thiosemicarbazone derivatives: Synthesis, spectroscopic characterization, structural studies and molecular docking studies

Tuncay Karakurt [a, *], Hakan Tahtaci [b], Nuriye Tuna Subasi [c], Mustafa Er [d], Erbil Ağar [e]

[a] Department of Chemical Engineering, Faculty of Engineering and Architecture, Ahi Evran University, 40100, Kırşehir, Turkey
[b] Department of Polymer Engineering, Faculty of Technology, Karabük University, 78050, Karabük, Turkey
[c] Department of Food Engineering, Faculty of Engineering and Architecture, Ahi Evran University, 40100, Kırşehir, Turkey
[d] Department of Chemical Engineering, Faculty of Engineering, Karabük University, 78050, Karabük, Turkey
[e] Department of Chemistry, Faculty of Arts and Sciences, Ondokuz Mayıs University, 55139, Samsun, Turkey

ARTICLE INFO

*Article history:*
Received 27 January 2016
Received in revised form
7 July 2016
Accepted 7 July 2016
Available online 11 July 2016

*Keywords:*
Aldehyde
Thiosemicarbazone
NMR
B3LYP
Beta-lactam

ABSTRACT

In this study our purpose is that, synthesis and characterization of compounds containing the aldehyde and thiosemicarbazone groups and comparison of the theoretical results with the experimental results. The structures of all synthesized compounds were elucidated by IR, $^{1}$H NMR, $^{13}$C NMR, elemental analyses techniques. The structure of compound (**4**) ($C_9H_8N_4O_2S$) was also elucidated by X-ray diffraction analysis. In addition, the theoretical IR spectrum, $^{1}$H NMR and $^{13}$C NMR chemical shift values, frontier molecular orbital values (FMO) of these molecules were analyzed by using Becke-3- Lee-Yang-Parr (B3LYP) method with LanL2DZ basis set. Finally, molecular docking studies were performed on synthesized compounds using the 4DKI beta-lactam protein structure to determine the potential binding mode of inhibitors.



## 1. Introduction

Although recently, there were significant increases in the number of compounds having various biological activities their use has been rather limited because of the emergence of drug resistance to these compounds and their various side effects. For these reasons, chemists have been made a great effort to the development of compounds with biological activity that will be used in pharmaceutical chemistry. Due to having wide-spectrum biological activity of thiosemicarbazone derivatives that synthesis studies made, interest on these compounds has been considerably increased in the pharmaceutical sector at the present time. Supraventricular or ventricular (cardiac arrhythmia) disorders in which the thiosemicarbazone derivative of 3-amino-2-pyridine carboxaldehyde (triapin) [1] that is used as among the rhythm regulators in the treatment is known to be a new third generation antiarrhythmic (rhythm regulators) [2].

Thiosemicarbazones and semicarbazones due to be a small molecule widely used in the treatment of antiviral, anticancer and antiparasital disease. More recently, it has been found that they are highly effective antiparasital compounds against trypanasoma cruzi parasites that cause especially Malaria and Cagas diseases. Generally, thiosemicarbazones show this effect by causing the inhibition of cysteine proteases in this type of parasites and derivatives [3–6]. In higher electroshock applications aryl semicarbazones are known to cause antiepileptic effects on the central nervous system [7–12].

In other study menthone derivatives of thiosemicarbazone and semicarbazones were determined to have anti-HIV activity in an interesting way [13].

In another study of the thiosemicarbazones it was determined that salicyaldehyde thiosemicarbazones act as a pharmacophore (play regulatory role against certain amino acid protein) by forming dicyclic chelates with binding metal ions [14]. A study made on hydroxy derivatives of thiosemicarbazone and semicarbazones lower toxic effects and higher anticancer effects of the hydroxy semicarbazone were drown attention and this type of compounds have been shown to act as a ribonucleotide reductase (RR)

* Corresponding author. Tel.: +90 3862803825.
*E-mail address:* tuncaykarakurt@gmail.com (T. Karakurt).

http://dx.doi.org/10.1016/j.molstruc.2016.07.013
0022-2860/

inhibitors [15,16].

The biological activity of thiosemicarbazones is due to the aldehyde and ketone functional groups in their structure [17]. It is emphasized with current research in recent years that complex structures of thiosemicarbazone derivatives have antibacterial, antifungal, antiviral and antitumoral [18,19]. Also the copper complex of thiosemicarbazones was determined to have quite high antimicrobial activity especially to a group Streptococcus which cause tonsillitis [20]. It is indicated in studies that acetylacetone thiosemicarbazone and their metal complexes are effective against to *Staphylococcus aureus, Staphylococcus epidermidis* from G(+) bacteria and *Escherichia coli* and *Pseudomonas aeruginosa* from G(−) bacteria [19]. Furthermore, such molecules are reported to be effective against to human cancer cells in the literature [21].

Nowadays, beta-lactam antibiotics are the most commonly used antibiotic derivatives. The most important source of resistance against to beta-lactam antibiotic derivatives of *Enterobacteriaceae* family is beta-lactamase enzymes secreted by the bacteria. Beta-lactamase enzymes are synthesized by mostly gram-negative bacteria, they are believed to be derived from penicillin binding protein due to having similar sequence analyzes and they cause resistance to antibiotics with beta-lactam ring. At the present time there are many identified beta-lactamase enzymes [22]. Beta-lactam antibiotics show their effects by inhibiting the transpeptidase and carboxypeptidases which are responsible for peptidoglycan synthesis and stopping the cell wall [23]. All beta-lactam antibiotics show their effects by binding to target protein which is called penicillin-binding protein (PBP), responsible for the peptidoglycan synthesis in bacterial cell walls on bacterial cytoplasmic membranes. Since peptidoglycan cannot be synthesized, cell wall structure is broken in bacteria whom penicillin binding proteins are inhibited by beta-lactam antibiotics. This situation caused to the loss of osmotic resistance of bacteria and death [24]. *Staphylococcus aureus* is the most important pathogen which synthesizes beta-lactamase in gram-positive bacteria. *Staphylococcus aureus* enzymes are under the control of plasmid and they can pass through the sensitive cells by means of bacteriophages. In case of gram-negative bacteria beta-lactamases are located in the periplasmic space between the outer membrane and cytoplasmic membrane. In gram-negative bacteria, beta-lactamase enzymes are synthesized under the chromosome or plasmid control [25].

In the light of this important data which have been achieved with the literature survey considering that the thiosemicarbazones are biologically active compounds, synthesis of the thiosemicarbazone derivatives expected to show positive activity was carried out (Scheme 1). All of the synthesized compounds are original and their structures were clarified by elemental analysis and spectroscopic methods (FT-IR, NMR). Besides this, the other aim is that; in order to support the experimental studies of the synthesized compound to examine theoretically IR, NMR, UV spectra, potential energy distribution of the vibration frequency (PED) and the frontier molecular orbital (FMO). Additionally, the structures of (**4**) and (**5**) compounds were compared with the ligands of well-known antibacterial targets. Trial docking studies with this enzyme suggested that the crystal structure 4DKI of beta-Lactamase from *S. aureus* as most appropriate target of the (**4**) and (**5**) 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. Chemical shift values are given in ppm ($\delta$) with tetramethylsilane (TMS) as internal standard. The IR spectra were measured in ATR using a Bruker Optics Alpha FT-IR. The mass spectra were measured with a Thermo TSQ Quantum Access Max LC-MS/MS spectrometer equipped with ethyl alcohol and chloroform as solvents. 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 Sigma Aldrich Chemicals. Theoretical calculations of this study were done by using Gaussian 09 [26] and Gaussview 5.0 [27] package programs. In this study Density Functional Theory (DFT) [28] method is chosen because theoretical calculations of test results which we have done for the analyzed molecules gave the closest value to the experimental results. B3LYP hybrid functional which is one of the most commonly used exchange-correlation functionals that contain Becke's three-parameter exchange function [29–31] and Lee, Yang and Parr's correlation functionals [32] was used in DFT calculation. The LanL2DZ [33–35] base set, which gave the closest value to our experimental results as well and is widely used for large molecules, was selected. Veda4 [36] software was used for PED analysis of the vibration frequency. Molecular docking studies were performed by using Autodock Vina [37] and Discover studio Visualizer 4.5 [38] programs.

### 2.2. General procedure for the synthesis of 4,4′-((2,3-bis((4-formyl-2,6-dimethoxyphenoxy)methyl)but-2-ene-1,4-diyl)bis(oxy))bis(3,5-dimethoxybenzaldehyde) (**4**)

In a two-necked flask, 4-hydroxybenzaldehyde (**3**) (0.02 mol) and KOH (0.02 mol) were dissolved in absolute ethanol (100 mL) and the solution was stirred for 30 min at room temperature. 1,4-dibromo-2,3-bis(bromomethyl)but-2-ene (**2**) (0.005 mol) was dissolved in absolute ethanol (50 mL) and added drop by drop to this solution at room temperature with the assistance of a dropping funnel. The mixture was then refluxed and stirred for 8–10 h. The progress of the reaction was monitored by TLC at appropriate time intervals. After completion of the reaction, the solution was filtered and the solid matter was obtained. It was washed with deionized water, ethanol and diethyl ether, respectively. The solid matter was recrystallized from DMF-EtOH, 1:2). The synthesized compound was dried with $P_2O_5$ in a vacuum oven. The physical properties and spectral data of the obtained product are listed below.

This compound was obtained as white crystals, yield 3.26 g (81%), mp 178–179 °C (from DMF-EtOH, 1:2; IR (ATR, cm$^{-1}$): 3062 (Ar-CH), 2976, 2939 (Aliph. CH), 2839–2737 (CHO), 1684 (C=O), 1583, 1495 (CH=CH), 1117 (−$OCH_3$), 1322, 1264, 1223 (=C−O−C); $^{1}$H NMR (400 MHz, DMSO-$d_6$, $\delta$ ppm): 3.73 (s, 24H, O−$CH_3$), 4.69 (s, 8H, O−$CH_2$), Ar−H [7.17 (s, 8H)], 9.85 (s, 4H, CHO); $^{13}$C NMR (100 MHz, DMSO-$d_6$, $\delta$ ppm): 56.39 (O−$CH_3$), 68.61 (O−$CH_2$), Ar−C [106.87 (CH), 132.27 (C), 141.63 (C), 153.83 (C)], 137.48 (-C=C-), 192.33 (C=O). MS: m/z 826.97 (M + Na, 100). Anal. Calcd. for $C_{42}H_{44}O_{16}$: C, 62.68; H, 5.51. Found: C, 62.59; H, 5.59.

### 2.3. General procedure for the synthesis of (2E,2′E)-2,2′-((((2,3-bis((4-((E)-(2-carbamothioylhydrazono)methyl)-2,6-dimethoxyphenoxy)methyl)but-2-ene-1,4-diyl)bis (oxy))bis(3,5-dimethoxy-4,1-phenylene))bis(methanylylidene))bis(hydrazine carbothioamide) (**5**)

Compound (**5**) was synthesized according to a method given in the literature [39]. In a round-bottomed flask, compound (**4**) (0.0025 mol) and thiosemicarbazide (0.015 mol) were heated to