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New 1,3,4-thiadiazole compounds including pyrazine moiety: Synthesis, structural properties and antimicrobial features

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ABSTRACT

In the study, some new 1,3,4-thiadiazole compounds were synthesized and we have reported identification of the structures by using UV-Vis, FT-IR, ^{1}H NMR, ^{13}C NMR and Mass spectroscopic methods. Antimicrobial activities of the compounds against three microorganisms, namely, *Candida albicans* ATCC 26555, *Staphylococcus aureus* ATCC 9144, and *Escherichia coli* ATCC 25922 were investigated by using disk diffusion method. These thiadiazoles exhibited an antimicrobial activity against *Staphylococcus aureus* and *Candida albicans*. The experimental data was supported by the quantum chemical calculations. Density functional theory (DFT) calculations were carried out to obtain the ground state optimized geometries of the molecules using the B3LYP, M06 and PBE1PBE methods with 3–21 g, 4–31 g, 6–311++g(2d,2p), cc-pvtz and cc-pvqz basis sets in the different combinations. Frontier molecular orbitals (FMOs) energies, band gap energies and some chemical reactivity parameters were calculated by using the aforementioned methods and basis sets, and the results were also compared with the experimental UV-Vis data.

1. Introduction

Structures including heterocyclic systems exhibit biologic activities due to their molecular structures [1]. These systems are used in the design of new drugs owing to their physicochemical properties. Besides, heterocyclic systems including nitrogen and sulphur atom have been recently becoming very attractive [2]. The molecules including both pyrazine and 1,3,4-thiadiazole moieties are used in many applications because they include two heterocyclic aromatic moieties member of the heterocyclic aromatic compound. The pyrazine, which is also known as 1,4-diazine, is a six-membered heterocyclic aromatic compounds having the chemical formula $C_4H_4N_2$. The pyrazine has an essential function for perfumes, pharmaceuticals, agricultural chemicals and food spices as an intermediate material [3,4]. The 1,3,4-thiadiazoles are attractive structures owing to their applications in many pharmaceutical, biological and analytical field. The substituted thiadiazoles are important for a wide range of anti-microbial activity studies because it possess (S–C=N) toxophoric unit. Having the inductive impact of the sulphur atom and relatively high aromaticity, the 1,3,4-thiadiazole ring is rather weak base [1,2]. Substituted thiadiazoles might be easily metabolized by routine biochemical reactions, and increased the lipid solubility due to their hydrophilic effect. Additionally, the researchers have demonstrated that these substituted thiadiazoles have other interesting activities such as antimicrobial, analgesic, antitubercular, anticonvulsant and anti-hepatitis B viral activities [2]. Moreover, thiadiazoles show a widespread spectrum of biological efficiency such as antihistaminic, anti-parkinsonism and anti-asthmatic [5].

It was reported that pyrazine and related heterocyclic compounds possess positive effects against a large variety biologic activities such as antimicrobacterial, antibacterial, antifungal, oxidant, cytotoxic and antituberclosis in their review researches [6]. In a study on multiple biological activities of piperazine and pyrazine by Meher et al., they demonstrated that pyrazine moiety

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showed a wide range of biological activities and the various substituted pyrazine had significant antianginals, antidepressant, antipsychotic, antidiabetic, antihistamines, hypolipidemic agent [7]. It was stated that pyrazine substituted-1,3,4-thiadiazole derivatives were synthesized. They synthesized fifteen thiadiazole molecules and investigated their anticonvulsant effects. They also expressed that electron-withdrawing groups substituted thiadiazole derivatives caused an increase of anticonvulsant effects [8]. Microbiologic and tuberculostatic activity of pyrazine-containing 1,3,4-thiadiazole compounds are available in the literature [9].

It is well known that the density function theory (DFT) which is an advance quantum chemical approach and a computational technique has proved to be a very successful and effective approach to calculate the various electronic properties of matter, and also has come to the forefront with its accuracy and low calculation costs. The density function theory has been widely used in recent years to study the molecular structures, atomization energies, ionization energies, electric and magnetic properties, vibrational frequencies, reaction paths, and so on.

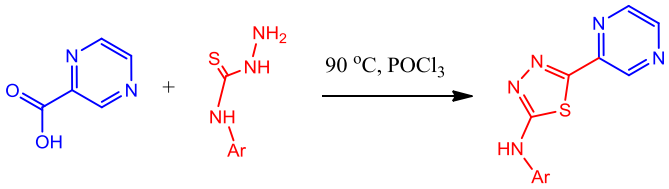
In this study, 1,3,4-thiadiazole derivatives including pyrazine moiety were obtained through the reaction of pyrazine carboxylic acid and thiosemicarbazide derivatives with $POCl_3$. The compounds were characterized with UV-Vis, IR, ^1H NMR spectroscopies. Furthermore, it has been reported their electronic properties and UV-Vis assignments by using the DFT-B3LYP/M06/PBE1PBE methods with 3–21 g, 4–31 g, 6–311++g(2d,2p), cc-pvtz and cc-pvqz basis sets level in the different combinations. After that, the data obtained from the quantum calculations were analyzed by comparing with experimental results, and so the theoretical results enabled us to make some comments on the experimental UV-Vis spectra of the molecules. Moreover, their antimicrobial activities were investigated against three microorganisms, namely, *Candida albicans* ATCC 26555, *Staphylococcus aureus* ATCC 9144, and *Escherichia coli* ATCC 25922 were investigated by using disk diffusion method.

2. Experimental

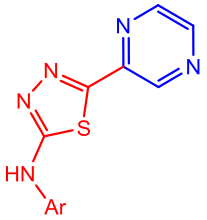
2.1. Synthesis of N-(2-methoxyphenyl)-5-(2-pyrazinyl)-1,3,4-thiadiazole-2-amine (compound I)

The general method of synthesis of 1,3,4-thiadiazole derivatives: Pyrazine carboxylic acid (n mol) and an equal amount of 2-methoxyphenyl thiosemicarbazide (n mol) are taken into a 250 ml flask. After $POCl_3$ compound (3n mol) slowly added to the flask by stirring, the last mixture was refluxed at 90 °C for 3 h. After the reaction was completed, the reaction flask was cooled to the room temperature, poured to stirred ice-cold water and neutralized with ammoniac solution. The precipitated product was filtered, washed with water and crystallized in DMSO/water mixture (2:1). Light brown product, Yield: (78%), mp: 205 °C; FT-IR (cm^{-1}) υ_{max}: 3263.58–3215.26 (–NH), 3063.46 (Aromatic C–H), 2981.72–2964.36–2904.26–2868.77 (Aliphatic C–H), 1578.63 (C=N thiadiazole), 1438.25 (C=N pyrazine), 699.10 (C–S–C), 1083.61 (C–O); ^1H NMR (400 MHz, DMSO-d_6, 25 °C) δ (ppm): 3.39 (s, 3H, $-OCH_3$), 6.97–8.33 (7H, aromatic C–H), 9,94 (1H, s, –NH); ^{13}C NMR (DMSO-d_6) δ: 56.19 (OCH_3, C-13), 111.53 (CH, C-2), 119.55 (CH, C-3), 121.10 (CH, C-5), 123.46 (CH, C-4), 128.64 (C, C-6), 128.96 (CH, C-10), 129.87 (CH, C-12), 133.12 (CH, C-11), 148.86 (C, C-9), 152.96 (C, C-7), 162.55 (C, C-8), 164.55 (C, C-1); HR-MS: 286.3305 [M+H], calc. 286.3307.

The designed compounds were synthesized by the method illustrated in Scheme 1 and they were demonstrated in Scheme 2.



Scheme 1. General Synthesis Route.



Ar: 2-, 3-, 4-methoxyphenyl-, benzyl-, 2-,4-methylphenyl-, 2-, 4-fluorophenyl-, 4-nitrophenyl-, 2-chlorophenyl-, 2,4-dichlorophenyl-, phenylethyl-

Scheme 2. General illustration of synthesized compounds.

2.2. Synthesis of N-(3-methoxyphenyl)-5-(2-pyrazinyl)-1,3,4-thiadiazole-2-amine (compound II)

Light yellow product, yield: (82%), mp: 211 °C; FT-IR (cm^{-1}) υ_{max}: 3218.91–3188.68 (–NH), 3066.42 (Aromatic C–H), 2995.58–2981.76–2964.92–2870.02 (Aliphatic C–H), 1599.73 (C=N thiadiazole), 1420.21 (C=N pyrazine), 700.80 (C–S–C), 1082.85 (C–O); ^1H NMR (400 MHz, DMSO-d_6, 25 °C) δ (ppm): 3.50 (s, 3H, $-OCH_3$), 6.61–7.75 (7H, aromatic C–H), 10.60 (1H, s, –NH); ^{13}C NMR (DMSO-d_6) δ: 54.80 (OCH_3, C-13), 102.86 (CH, C-3), 107.28 (CH, C-1), 109.49 (CH, C-5), 128.90 (CH, C-4), 130.50 (CH, C-10), 132.61 (CH, C-12), 141.20 (C, C-6), 151.86 (CH, C-11), 152.57 (C, C-9), 160.00 (C, C-7), 161.55 (C, C-8), 163.23 (C, C-2); HR-MS: 286.3308 [M+H], calc. 286.3307.

2.3. Synthesis of N-(4-methoxyphenyl)-5-(2-pyrazinyl)-1,3,4-thiadiazole-2-amine (compound III)

Light yellow product, yield: (75%), mp: 201 °C; FT-IR (cm^{-1}) υ_{max}: 3164.7–1508.7 (–NH), 3011.0 (Aromatic C–H), 2833.6–2927.2–2945.9 (Aliphatic C–H), 1571.0 (C=N thiadiazole), 1440.2 (C=N pyrazine), 700.6 (C–S–C), 1090.3 (C–O); ^1H NMR (400 MHz, DMSO-d_6, 25 °C) δ (ppm): 3.76 (s, 3H, $-OCH_3$), 6.95–7.73 (7H, aromatic C–H), 10.60 (1H, s, –NH). ^{13}C NMR (DMSO-d_6) δ: 55.05 (OCH_3, C-13), 114.40 (CH, C-2 and C-4), 118.63 (CH, C-5 and C-1), 128.46 (CH, C-6), 132.00 (C, C-10), 134.16 (CH, C-12), 134.87 (CH, C-11), 148.12 (CH, C-9), 150.69 (C, C-7), 154.15 (C, C-8), 163.91 (C, C-3); HR-MS: 286.3303 [M+H], calc. 286.3307.

2.4. Synthesis of N-benzyl-5-(2-pyrazinyl)-1,3,4-thiadiazole-2-amine (compound IV)

Black-violet product, yield: (72%), mp: 282 °C (decomposed); FT-IR (cm^{-1}) υ_{max}: 3195.9–1495.5 (–NH), 3063.3 (Aromatic C–H), 3009.3 (Aliphatic C–H), 1581.3 (C=N thiadiazole), 1420.6 (C=N pyrazine), 698.9 (C–S–C); ^1H NMR (400 MHz, DMSO-d_6, 25 °C) δ (ppm): 7.09–9.36 (7H, aromatic C–H), 10.59 (1H, s, –NH); ^{13}C NMR (DMSO-d_6) δ: 52.70 (CH_2, C-13), 127.79 (CH, C-3), 127.15 (CH, C-2 and C-4), 128.91 (CH, C-5 and C-1), 138.61 (CH, C-10), 141.81 (C, C-6), 145.65 (CH, C-12), 146.77 (CH, C-11), 147.54 (C, C-9), 156.25 (C,