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Ultrasonic-assisted synthesis of 1,4-disubstituted 1,2,3-triazoles *via* various terminal acetylenes and azide and their quorum sensing inhibition

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ABSTRACT

An efficient synthesis of 1,4-disubstituted 1,2,3-triazole derivatives was studied. 1,4-Disubstituted 1,2,3-triazoles containing isoxazole and thymidine structures were synthesized in 84–96% yields starting from various terminal isoxazole ether alkynes and β-thymidine azide derivatives *via* a 1,3-dispolar cycloaddition using copper acetate, sodium ascorbate as the catalyst under ultrasonic assisted condition. All the target compounds were characterized by HRMS, FT-IR, ^{1}H NMR and ^{13}C NMR spectroscopy. Furthermore, the quorum sensing inhibitory activities of synthesized compounds were evaluated with *Chromobacterium violaceum* (*C. Violaceum* CV026) based on their inhibition of violacein production, with compound C_{10}-HSL as a positive control. The compounds **8a**, **8c** and **8f** exhibited considerable levels of inhibitory activity against violacein production, and IC_{50} values were 217 ± 19, 223 ± 20 and 42.8 ± 4.5 μM, respectively, which highlighted the potential of these compounds as lead structures for further research towards the development of novel QS inhibitors.

1. Introduction

Quorum sensing (QS) is one of cell communication mechanisms involving the generation, release and detection of small signaling molecules which can activate specific receptors associated with transcription signals that are responsible for controlling a variety of different biochemical processes [1–3]. QS can effectively regulate some important phenotypes that are mostly relevant to antibiotics resistance [4–6], such as the bioluminescence, virulence expression and formation of biofilm and so on. In recent years, much more bacterial strains showed resistance to antibiotics, and it is urgent to find an effective solution. QS inhibitors are new target agents, which can provide insights into bacterial signaling processes from fundamental and applied perspectives, conducive to the discovery of novel antibacterial strategy and antimicrobial agents [7–9]. It was reported that the amide structure of the pyrimidine ring has a potential quorum sensing inhibitory effect. β-Thymidine derivatives contain lactam structure are expected to possess good quorum sensing inhibitory effect to Gram negative bacteria [10,11].

Thymidine derivatives are more widely used in the world of organic heterocyclic compounds [12,13], in particular, the amide structure of the pyrimidine ring has a potential quorum sensing inhibitory effect. They are concerned by people because they exhibit good biological and pharmaceutical activity[14,15] *etc*.. Several 2′,3′-dideoxynucleosides, including 3′-azido-3′-deoxythymidine (AZT, zidovudine), have been used as antiretroviral drugs for the treatment of acquired immunodeficiency syndrome (AIDS) [16,17]. In addition, some nucleoside derivatives also have strong resistance to some tumour cells [18,19], bacteria [20,21] and so on. Isoxazoles and 1,2,3-triazoles with better anti-bacterial [22,23], anti-cancer [24,25], antiviral [26,27], analgesic and anti-inflammatory [28,29] are also important heterocyclic skeleton for synthesizing a drug molecule, and have been widely used in clinical practice [30,31]. Therefore, the study of the synthetical method and biological activity of heterocyclic compounds containing thymidine, isoxazole and 1,2,3-triazole has always been a search realm with vitality in the organic chemistry and medical chemistry. The structural features and physiochemical properties of their fragment are of great interest in drug design and discovery.

It is known that 1,3-dipolar cycloaddition reaction occurred between 1,3-dipole body and olefins, alkynes or corresponding derivatives. Nitrile oxides and azides as the most common 1,3-dipolar body were important precursor for synthesizing isoxazole

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and 1,2,3-triazole derivatives [32–35]. The most widely used method to build the 1,2,3-triazole system is the 1,3-dipolar cycloaddition of alkynes with azides, which is the famous Click reaction [36]. However, the major disadvantage of this method is the parallel formation of 1,4 and 1,5-regioisomers. Early as 2002, it was reported that Husigen-Click reaction, which copper(I)-catalyzed alkyne-azide independently conducted 1,3-dipolar cycloaddition reaction (CuAAC), was able to exclusively obtain 1,4-product with a good regioselectivity [37]. Successively, ruthenium-catalyzed method was reported for the regioselective synthesis of the 1,5-product [38]. However, the synthesis of isoxazole-thymidine derivatives has not been reported using copper(I) as a catalyst. With the development of technology, several improved methods including microwave and ultrasonic assisted method were reported to increase the yield of the cycloaddition [39,40]. Ultrasonic-assisted organic synthesis is a powerful technique that is widely being used in organic synthesis reaction. The notable features of the ultrasound approach are enhanced reaction rate, formation of pure product in high yield, and easier manipulation. In this work, we reported the cyclization between 3-aryl-5-((prop-2-yn-1-yloxy)methyl) isoxazoles and 1-(4-azido-5-(azido methyl)tetrahydrofuran-2-yl)-5-methylpyrimidine-2,4(1*H*,3*H*)-dione or 1-(4-azido-5-(hydroxymethyl)tetrahydrofuran-2-yl)-5-methyl pyrimidine-2,4(1*H*,3*H*)-dione using the CuAAC reaction under conventional heating and ultrasonic-assisted condition. The structures of the synthesized compounds were characterized by HRMS, FT-IR, ^{1}H and ^{13}C NMR spectroscopy. Herein, we combined 1,2,3-trizole and isoxazole into thymidine derivative structure get novel target molecules, further evaluated their QS to Gram negative bacteria. It suggested that 4-substituted group of phenyl on isoxazole had important effect on antibacterial and antimicrobial agents.

2. Results and discussion

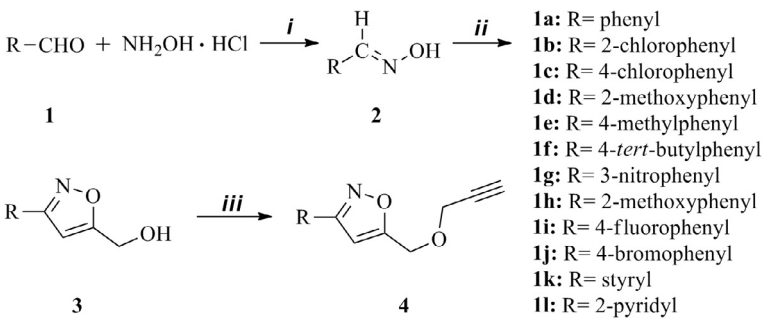
2.1. Synthesis

It is known that isoxazole is a versatile scaffold for the synthesis of varieties of complex natural products, and functionalized isoxazole derivatives are active pharmacophores in many pharmacologically important molecules [41,42]. In the present work, 3-substituted phenyl-5-((prop-2-yn-1-yloxy)methyl)isoxazoles (**4**) were synthesized in three steps starting form substituted benzaldehyde (Scheme 1, Table 1) according to the literature [43,44]. In the process for synthesizing 3-substituted phenylisoxazol-5-yl) methanols (**3**), 1,3-dipolar cycloaddition reaction was catalyzed using $ZnCl_2$ as a catalyst by one-pot method under ultrasound-assisted with 58–88% yields, which resulted in the yield of the synthesized desired products enhancing 12–29% compared with conventional method. A series of compounds **4** were prepared by employing intermediate **3** and propargyl bromide under NaH with 68–96% yields at room temperature condition, and the influence of different substituents on the yield was investigated.

Sequentially, the synthesis of 5-((4-(((3-(4-chlorophenyl)isoxazol-5-yl)methoxy)methyl)-1*H*-1,2,3-triazol-1-yl)methyl)-4-hydroxytetrahydrofuran-2-yl)-5-methylpyrimidine-2,4(1*H*,3*H*)-dione (**7c**) were explored by employing 3-(4-chlorophenyl)-5-((prop-2-yn-1-yloxy)methyl)isoxazole (**4c**) and *β*-thymidine azide derivatives (**5**) in the presence of copper(I) (Scheme 2). In order to optimize the reaction conditions, we screened the different heating mode and catalyst, a variety of H_2O-organic solvents and examined their influence on reaction time and yield of the obtained target product. The results are summarized in Table 2.

As shown in Table 2, the desired **7c** was successfully synthesized with 56–92% and 35–85% yields in the presence of organic solvents and catalyst under ultrasonic radiation and traditional heating, respectively. Exhilaratingly, ultrasonic radiation as an efficient and convenient process, could shorten reaction time (20 h→20 min; 10 h→10 min and 4 h→10 min). Also, the yields of the obtained target product were enhanced 6–21% compared with traditional heating. Under the other identical reaction conditions, no desired product was obtained in the absence of catalyst. When copper acetate was used as in situ generation of copper(I) ion with sodium ascorbate as a catalyst, the yield of the obtained **7c** was higher than that of copper sulfate, copper chloride and directly loading copper(I) iodide (Table 2, entries 2–5). However, when the reaction temperature was decreased to room temperature and 35 °C, respectively, the yield of the obtained **7c** respectively decreased to 35% and 70% (traditional heating) and 56% and 70% (ultrasonic radiation) (Table 2, entries 4, 6 and 7). Sequentially raising the reaction temperature to 55 °C, the yield of the obtained target product was remained (78% and 90% under the different heating mode) (Table 2, entry 8). Besides, the solvent played a significant role in progress of reaction. Among the examined solvents, when *i*-PrOH and water were used alone, the yields of 46% (conventional heating), 58% (ultrasonic heating) and trace for the model reaction were obtained after 24 h, respectively (Table 2, entries 11 and 12). The low yield obtained for the corresponding triazole derivatives using pure water as a solvent is attributed to lack of organic material solubility in water. The mixed solvents of *i*-PrOH–H_2O, DMF–H_2O and DMSO–H_2O (2:1, V/V) all afforded the better yield (Table 2, entries 4, 14 and 15). Considering economy and environment, the confirmed optimal synthesis condition was copper acetate, sodium ascorbate as the catalyst, *i*-PrOH–H_2O mixture (2:1, V/V), under ultrasound-assisted at 45 °C for 10 min.

Having been optimized the reaction conditions for the model system (Table 2, entry 4) was chosen to explore the scope and limitations of this protocol (Table 3). As shown in Table 3, all scanned reactants afforded the corresponding 1,2,3-triazole derivatives under conventional heating and ultrasonic heating in 66–85% and



Scheme 1. The route for synthesizing 3-substituted phenyl-5-((prop-2-yn-1-yloxy)methyl)isoxazoles **4a–l** from aromatic aldehyde **1a–l**. Reagents and conditions: (i) NaOH aq. (6 mol/L), EtOH, reflux. (ii) (a) NCS, DMF. (b) Propargyl alcohol, $ZnCl_2$, Et_3N, U.S. 0 °C–r.t.. (iii) NaH, propargyl bromide, THF, 0 °C–r.t..