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Design, synthesis, antimicrobial evaluation and molecular docking studies of some new thiophene, pyrazole and pyridone derivatives bearing sulfisoxazole moiety

Tamer Nasr [a, *], Samir Bondock [b, c], Sameh Eid [d]

[a] Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Helwan University, 11795 Helwan, Cairo, Egypt
[b] Department of Chemistry, Faculty of Science, Mansoura University, ET-35516 Mansoura, Egypt
[c] Department of Chemistry, Faculty of Science, King Khalid University, 9004 Abha, Saudi Arabia
[d] BioMed X Innovation Center, Im Neuenheimer Feld 583, 69120 Heidelberg, Germany

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ABSTRACT

Development of new antimicrobial agents is a good solution to overcome drug-resistance problems. In this context, new functionalized thiophene, acrylamide, arylhydrazone, pyrazole and pyridone derivatives bearing sulfisoxazole moiety were designed, synthesized and evaluated for their *in vitro* antibacterial and antifungal activities. Among the synthesized compounds, thiophene **4d** and 6-thioglucosylpyridone **17** displayed significant antibacterial activities against *Escherichia coli* (MIC, 0.007 μg/mL *vs* gentamycin 1.95 μg/mL) and *Bacillis subtilis* (MIC, 0.007 μg/mL *vs* ampicillin 0.24 μg/mL), respectively. Whereas, the pyrazole **6** showed the highest antifungal activity against *Aspergillus fumigates* (MIC, 0.03 μg/mL *vs* amphotericin B 0.12 μg/mL). In general, most of the synthesized compounds exhibited better antimicrobial activities than sulfisoxazole; this might be attributed to the synergistic effect of the sulfonamide and attached heterocyclic moieties as well as the increased lipophilic characters of the synthesized compounds. Molecular docking studies indicated that the synthesized compounds could occupy both *p*-amino benzoic acid (PABA) and pterin binding pockets of the dihydropteroate synthase (DHPS), suggesting that the target compounds could act by the inhibition of microbial DHPS enzyme. The results provide important information for the future design of more potent antimicrobial agents.

1. Introduction

Many drug-resistant human pathogenic microbes have been observed in the past few decades [1]; the reasons are the misuse and widespread use of antimicrobial agents as well as inaccurate diagnosis [2]. Among these drug-resistant microbes are methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant *Enterococci* and azole-resistant *Candida* species [3]. Treatment of these infections is a major impediment especially in immunocompromised patients [4]; to overcome this problem we need to search for new powerful antimicrobial agents [5]. The discovery of completely new antimicrobial pharmacophore and modifying the structure of a well known antimicrobial agent are the main two strategies to accomplish this [6]. In the second strategy; two or more different antimicrobial pharmacophores are often combined together in one molecule to get powerful synergistic effect [7].

Sulfonamides have diverse biological activities including antibacterial [8], carbonic anhydrase inhibitor [9], insulin release inducer [10], antiviral [11], antifungal [12], anticancer [13], and anti-inflammatory activities [14]. The antimicrobial sulfonamides act as competitive inhibitors to PABA substrate for the DHPS enzyme active site and thus inhibit the biosynthesis of dihydrofolic acid [15]. DHPS facilitate the biosynthesis of the folate intermediate, 7,8-dihydropteroic acid, from PABA and dihydropterin-6-hydroxymethyl pyrophosphate (DHPP). Despite the relative abundance of DHPS crystal structures in the Protein Data Bank (PDB), only two structures to-date were solved with a sulfa-related drug in the active site of the enzyme. Yun et al., reported the crystal structure of *Bacillus anthracis* dihydropteroate synthase (BaDHPS) bound to sulfathiazole-6-hydroxymethyl-7,8-dihydropterin-pyrophosphate (STZ-DHPP) adduct. They showed that STZ-DHPP adduct occupies both the PABA and pterin binding pockets of HDPS (Fig. I,

* Corresponding author.
E-mail address: tamerhefni@yahoo.com (T. Nasr).

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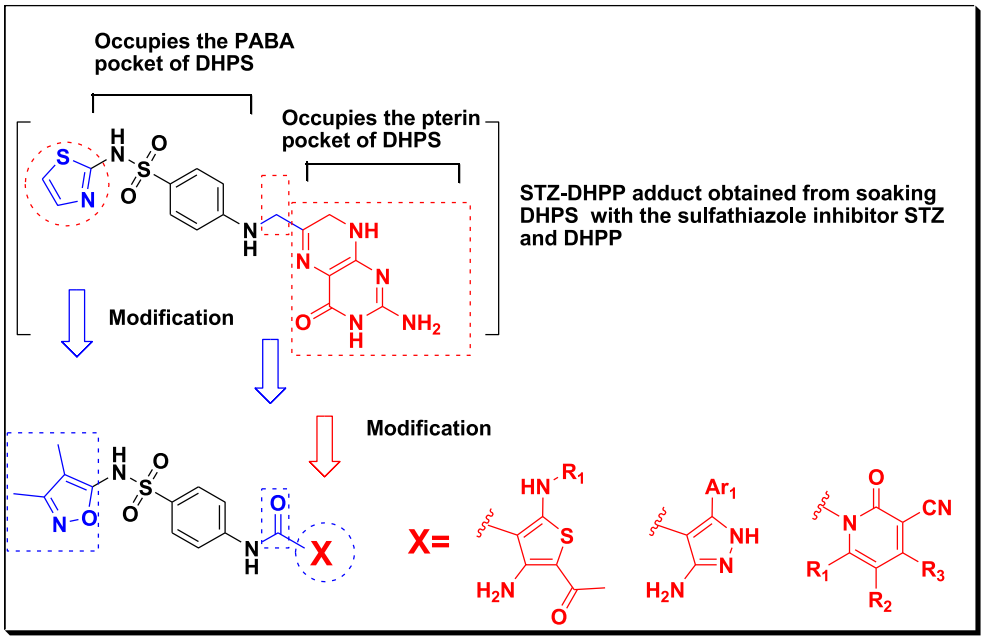

Fig. 1. Design of antimicrobial DHPS inhibitors.

supplementary data) [16]. The Co-administration of sulfonamides and the dihydrofolate reductase inhibitor, trimethoprim, increases the therapeutic efficacy [17].

Literature survey revealed that thiophene, acrylamide, arylhydrazone, pyrazole and 2-pyridone derivatives are important scaffolds in pharmacologically active compounds. Regarding thiophene ligands, their metal complexes possess antimicrobial activities [18]. For cyanothiophene scaffolds, they act as MurF ligase inhibitor which prevents the bacterial peptidoglycan biosynthesis [19]. Interestingly; several cyanoacrylamide [20], arylhydrazone [21], pyrazole [22], and 2-pyridone derivatives exhibit promising antimicrobial activities [23].

Sulfisoxazole is an available sulfa drug acting as PABA competitive inhibitor. Here we aimed to substitute its primary amino group by flexible antimicrobial pharmacophores to occupy both the PABA and pterin binding pockets for the DHPS enzyme (Fig. 1) to get new potent antimicrobial agents.

Based on the above considerations and as extension of our search for effective antimicrobial agents, we designed and synthesized new thiophene, acrylamide, arylhydrazone, pyrazole and pyridone compounds tagged with sulfisoxazole moiety. The synthesized compounds were evaluated *in vitro* for their antimicrobial activities against human pathogenic microbes. Molecular docking and lipophilicity studies were used to explain the obtained biological data.

2. Results and discussion

2.1. Chemistry

The synthetic strategies adopted for constructing the target molecules are illustrated in Schemes 1–3. The starting material, 2-cyano-*N*-(4-{[(3,4-dimethylisoxazole-5-yl)amino]sulfonyl}-phenyl)acetamide (**3**), was prepared in a quantitative yield by cyanoacetylation of sulfisoxazole **1** with 1-cyanoacetyl-3,5-dimethylpyrazole (**2**) in refluxing dry dioxan (Scheme 1). The reactivity of a CH_2 group of compound **3**, with various types of substituted isothiocyanates and each of chloroacetone and chloroacetonitrile, was evaluated. Thus, treatment of an ethanolic sodium ethoxide solution of compound **3** with a series of substituted isothiocyanates, namely, methyl-, ethyl-, allyl-, adamantly- and phenyl-isothiocyanates, at room temperature followed by addition of chloroacetone or chloroacetonitrile afforded, in each case, a single product, in moderate yields (55–65%). Elemental analyses and spectral data (IR, MS, ^{1}H and ^{13}C NMR spectra) confirmed the reaction products as 4-aminothiophene-3-carboxamides **4a**–**f**. The one-pot formation of the functionalized thiophenes **4a**–**f** starting from activated nitrile, isothiocyanates, and haloalkanes is in the line of the work reported earlier by Gewald et al. [24].

α,β-Unsaturated nitriles are versatile intermediates and were utilized for the synthesis of functionalized aminopyrazoles. In this context, the Knoevenagel condensation of compound **3** with aromatic and heteroaromatic aldehydes was investigated. Thus, treatment of **3** with various types of aldehydes in refluxing ethanol containing a catalytic amount of piperidine produced, in each case, a single stereoisomer, identified as (*E*)-2-cyano-3-aryl-acrylamides **5a**–**e** (Scheme 2). The *E*-configuration of compound **5a**, as representative example, was assigned based on its ^{1}H NMR spectrum which displayed a downfield singlet signal at δ 8.34 ppm due to the olefinic (CH=) proton that agrees with the chemical shift of the olefinic proton (8.36 ppm) of similar structure, (*E*)-*N*-(pyridin-2-yl)-2-cyano-3-phenylprop-2-enamide, confirmed by X-ray analysis [25].

Treatment of (*E*)-2-cyano-3-(4-methoxyphenyl)acrylamide **5b** with hydrazine hydrate in ethanol, under reflux, furnished the functionalized pyrazole derivative **6**. Formation of pyrazole **6** is believed to proceed through the Michael addition of hydrazine hydrate to α,β-unsaturated nitrile **5b** and *in situ* intramolecular 1,5-dipolar cyclization *via* the addition of amino group to a cyano function to give the non-isolable dihydropyrazole which underwent auto-oxidation to give the target pyrazole. The pyrazole formation is in the line with our previous report [26].

Treatment of **3** with dimethylformamide-dimethylacetal (DMF-DMA), in dry dioxan, at reflux temperature, afforded a yellow product identified as (*E*)-2-cyano-3-(*N*,*N*-dimethylamino)