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Short communication

Access to a new class of biologically active quinoline based 1,2,4-triazoles

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ABSTRACT

As an aspect of our ongoing research in search of new antimicrobial armamentarium, a series of 1,2,4-triazol-3-ylthio-acetamides was constructed and *in vitro* analyzed for their antimicrobial activity against several bacteria and fungi. Aiming to establish an increased potency, the bioassay results were matched to those of 1,3,4-oxadiazoles, utilized previously. Remarkably, 1,2,4-triazoles were found to possess a good spectrum of antifungal potency, which eventually suggested the azole template as an essential pharmacophore to diversify the biological occupations of the attendant molecules. However, it was noticed that the potency of final analogs against each strain placed reliance on the type of substituent present on benzothiazole ring. The structures of final compounds were confirmed with the aid of IR, ^{1}H NMR, ^{13}C NMR spectroscopy and CHN analysis.

1. Introduction

The resolute appearances of microbial infections followed by the expansion of several resistant bacterial and fungal strains against clinically used antimicrobial arsenal have urged medicinal communities to look for new incorporations into the current armamentarium. Severe chances of microbial infections among immunosuppressive individuals due to the HIV infection, cancer treatments and organ transplantations [1–3] actuated additional urgency to generate new antimicrobial agents. Availability of few classes of antifungal drugs restricts the choice of implementing doses to the patients, and a long term administration of these drugs is progressively associating with multi-drug resistant emergence [4]. Fluconazole, ketoconazole, itraconazole, posaconazole and some other azole class of drugs are currently used as antifungal management [5]. However, their treatment failures were witnessed by the medical communities [6]. Therefore, development of new chemical scaffolds with novel structural features will be the remarkable breakthroughs.

We have previously generated quinoline based 1,3,4-oxadiazole derivatives involving attachment of 6-substituted benzothiazole moieties through sulfur linkage [7]. These derivatives were perceived to demonstrate significant antibacterial potency against a wide range of microorganisms. In this context, 1,2,4-triazole derivatives with similar structural qualities would be projected to result in newer molecular systems with increased efficacy. Definitely, 1,2,4-triazole template has been known to express significant antimicrobial activity, particularly, antifungal potencies including the fact that existing antifungal drugs hold 1,2,4-triazole pharmacophore in their elemental structures [5]. In addition, benzothiazole motif has settled a fine proportion with various heterocyclic individuals manifesting admirable antimicrobial action [7], while quinoline ring is well corroborated for its consequential potency as antimicrobial, anticancer and antimalarial agents [8–10]. In a view of above mentioned prominence of quinoline and benzothiazole moieties and the surpassing results obtained in previous studies carrying 1,3,4-oxadiazoles, we aspired to derive similar systems with the 1,2,4-triazole template to confirm the preliminary hypothesis that new analogs will be having much better potencies. Additionally, the influence of C-6 substituent variation in benzothiazole ring on the anticipated biological activities was also an imperative task; hence, their coupling has been carried out to the sulfur atom of the 1,2,4-triazole ring.

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2. Results and discussion

2.1. Chemistry

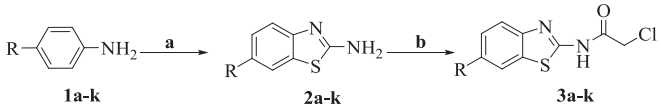
The reaction arrangements adapted to furnish intermediate and final derivatives **12a**–**k** are outlined in Schemes 1–3. Solvents and reagents were used as received or were dried prior to use as needed. *Para*-substituted aryl amines were reacted with potassium thiocyanate in the presence of bromine in acetic acid to yield the 2-amino-6-substituted benzothiazoles (**2a**–**k**) via known preparation methods [12,13]. The amino group of **2a**–**k** was subsequently utilized to construct *N*-(benzo[*d*]thiazol-2-yl)-2-chloroacetamides (**3a**–**k**) using chloroacetyl chloride in refluxing benzene (Scheme 1) as described throughout the literature [7,14,15].

In another sequence of reactions, ammonium thiocyanate and benzoyl chloride were reacted to generate *in situ* benzoyl isothiocyanate (**2**) which was then treated with 1-naphthylamine (**3**) to furnish *N*-(naphthalen-1-ylcarbamothioyl)benzamide (**4**). This Intermediate (**4**) was heated in 10% NaOH followed by acidification to generate α-naphthylthiourea (**5**) upon maintaining the basic pH [16,17]. α-Naphthylthiourea was refluxed in a redistilled chlorobenzene to yield the final intermediate derivative α-naphthyl isothiocyanate (**6**), extracted using hexane (Scheme 2) [18]. The synthesis of α-naphthyl isothiocyanate was accomplished using a reported method, and its structure was confirmed using FT-IR and ^{1}H NMR analysis, which were in conformity with the proposed one in the literature.

Quinoline-6-carboxylic acid (**7**) was treated with thionyl chloride in methanol to obtain the corresponding ester (**8**) derivative. This ester was then hydrazinolyzed with 99% hydrazine hydrate in ethanol to give the corresponding carbohydrazide precursor (**9**) in good yield, and the correct synthesis of these two intermediates was confirmed recording FT-IR and ^{1}H NMR spectra [19]. Reaction of α-naphthyl isothiocyanate with carbohydrazide in refluxing ethanol yielded *N′*-(naphthalene-1-carbonothioyl)quinoline-6-carbohydrazide (**10**) which was then refluxed in 2 N NaOH to afford the corresponding 1,2,4-triazole-3-thiol moiety (**11**) [20]. The formally structured *N*-(benzo[*d*]thiazol-2-yl)-2-chloroacetamides were coupled with 1,2,4-triazole-3-thiol intermediate in refluxing benzene to yield the final products **12a**–**k** (Scheme 3) [21]. The structures of the new compounds were fully supported through their spectroscopic data (FT-IR, ^{1}H NMR, ^{13}C NMR spectroscopy and CHN analysis).

2.2. Pharmacology

In vitro evaluation of antibacterial and antifungal productiveness was carried out for analogs **12a**–**k** and results are summarized in Table 1. From the bioassay results, it is clear that the sorts of analogs designed and built via efficient chemical transformations were of having interesting biological action towards each microorganism studied. The minimum inhibitory concentrations of **12a**–**k** against a range of bacterial and fungal strains were journeyed from 6.25 to 50 μg/mL, while for the control drugs; similar range of MICs was observed. We commenced the present study to furnish scaffolds with better antimicrobial potency than the similar partner analogs (1,3,4-oxadiazoles) we have studied recently [19]. Although, the current molecular structures appeared with interesting features, expressing altered biological profiles. For example, previously afforded 1,3,4-oxadiazoles had better efficacy against bacteria than fungi, whereas, 1,2,4-triazoles currently investigated reflected decreased antibacterial activity and increased potency against both the fungal strains. In case of the structural attributes of active analogs against the particular strain of bacteria or fungi, similar tendency was contemplated as noticed for oxadiazoles. However, the case of the activity of triazoles against *Pseudomonas aeruginosa* and *Klebsiella pneumoniae* was an exception. In addition, marked decrease in the potency of 1,2,4-triazoles was encountered against *K. pneumoniae*. The overall monitoring of shifting the particular pharmacophore in the molecular system of **12a**–**k** suggested that the azole ring (oxadiazole or triazole) was fundamental for the potency. Additionally, benzothiazole nucleus was appeared to retain the overall efficacy of the current molecules than those involving substitution of aromatic acetamide linkage studied formally; hence, bioassay results for final compounds with aromatic acetamide substituents were excluded in the present report. Basic core, quinoline ring instituted higher level of antimicrobial strength than aromatic systems at the corresponding place having moderate potencies.



Scheme 1. Synthetic protocol for **3a**–**k**. Reagents and conditions: (a) KCNS, Br_2, AcOH, R.T.; (b) $ClCH_2COCl$, anhyd. K_2CO_3, benzene, reflux.

Final analog (**12d**) with electron withdrawing fluorine substituents exposed potent action against Gram-positive bacteria *Staphylococcus aureus* at 25 μg/mL of MIC. Another halo-analog (**12c**) with a bromine substituent indicated 25 μg/mL of MIC against Gram-positive bacteria *Bacillus cereus*. These two derivatives demonstrated half fold potency against both Gram-positive strains when compared to the control drug ampicillin (MIC: 12.5 μg/mL). From these results, it can be determined that final scaffolds bearing electron withdrawing substituents were active against Gram-positive bacteria. Two analogs, one with a cyano (**12f**) and another with a nitro (**12g**) substituent manifested excellent inhibition of Gram-negative *Escherichia coli* and *K. pneumoniae* at 50 μg/mL of MIC. These derivatives were regarded as moderately active against *E. coli* and half fold potent against *K. pneumoniae* as compared to control drugs ampicillin and gentamicin (MICs: 6.25–25). Analog **12f** and **12g** exerted potential inhibitory efficiency against *Candida albicans* and *Aspergillus niger* fungi at 6.25 μg/mL of MIC, respectively, and were equipotent or more potent than standard drug fluconazole (MIC: 6.25–12.5 μg/mL). Presence of electron releasing substituents like ethoxy (**12j**) proved intrinsic to conduce noteworthy activity against Gram-negative *P. aeruginosa* at 25 μg/mL, as well as against the *C. albicans* fungi at 6.25 μg/mL of MIC. The compound was equipotent as ampicillin (MIC: 25 μg/mL) against *P. aeruginosa* while more potent against *C. albicans* than fluconazole (MIC: 12.5 μg/mL) standard. When equating the bioassay results with those of previously reported for quinoline base 1,3,4-oxadiazoles, it was observed that the 1,2,4-triazole analogs studied presently are having enhanced potencies against both the fungal species, whereas, decreased potency against bacteria. In case of activity against bacterial strains with the presence of either EWD or ED substituents, both the types of scaffolds were observed to follow similar pattern, except against *P. aeruginosa*. For example, alkoxy group took place of cyano, whereas, in case of *K. pneumoniae*, cyano and nitro functionalized scaffolds replaced the alkoxy functionalities. All the remaining analogs were sighted with good inhibitory effects at MIC level around 100 μg/mL, whereas some were devoid of potency with >100 μg/mL of MIC against the mentioned panel of microorganisms.