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Original article

Synthesis and evaluation of novel 4-nitropyrrole-based 1,3,4-oxadiazole derivatives as antimicrobial and anti-tubercular agents

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ABSTRACT

We report synthesis and antimicrobial evaluation of 42 novel 4-nitropyrrole-based 1,3,4-oxadiazoles. The synthesized molecules were evaluated for anti-bacterial, anti-fungal and anti-tubercular activities. Promisingly, most of the compounds showed equal or more potency than standard ciprofloxacin against *Staphylococcus aureus*, *Bacillus subtilis* and *Escherichia coli*. Compound **5e** exhibited highest anti-tubercular activity (0.46 μg/mL) close to that of standard Isoniazid (0.40 μg/mL). Equal antifungal activity (1.56 μg/mL) compared to standard Amphotericin-B was shown by most of the compounds. All the N-methylated compounds showed more potent to equal activity against MSSA (MIC 0.39–1.56 μg/mL) and MRSA (MIC 0.78–1.56 μg/mL). All compounds were tested for mammalian cell toxicity using VERO cell line and were found to be non-toxic.

1. Introduction

1,3,4-Oxadiazole is an important class of heterocyclic bioactive compounds [1]. The widespread use of them as a scaffold in medicinal chemistry establishes this moiety as a member of the privileged structures. Differently substituted 1,3,4-oxadiazoles have been found to exhibit anti-inflammatory [2], hypoglycemic [3], anti-anxiety [4], antidepressant [5], anti-proliferative [6], anti-fungal [7,8], antibacterial [9] and anti-tubercular activities [10,11]. Moreover, 1,3,4-oxadiazole heterocycles are very good bioisosteres of amides and esters, which contribute substantially to increasing pharmacological activity by participating in hydrogen bonding interactions with the receptors.

Natural nitropyrroles are the metabolites of bacterium *Actinosporangium vitaminophilium*, [12] and *Streptomyces* sp. [13]. Recently nitropyrrole-based natural products and their derivatives are reported for having potential antimicrobial activities [13–16]. For instance, N-substituted pyrrolomycin, a compound with 4-nitropyrrole moiety have shown antifungal activity better than clotrimazole [17], while anti-tubercular activity was reported for pyrrolonitrins [18]. Anti-malarial and antimicrobial properties were reported for 4-nitropyrrol-2-carboxaldehyde derivatives by Colwell et al. [19]. Krajewska and Midura-Nowaczek [20] synthesized and tested 4-nitropyrrole based-chloramphenicol derivative for their antibacterial properties, where MIC of 0.8 μg/mL was reported against *Staphylococcus aureus* (ATCC 12600). Etoposide analogs of 4-nitropyrrole are reported to have potent anti-tumor activity inhibiting DNA Topoisomerase II [21]. The antifungal and antibacterial properties of 1,2,4-triazoles substituted with 4-nitropyrrole scaffold was reported by Pourmorad and Shafiee [22] (Fig. 1). Based on the observations, an attempt to design a series of novel antimicrobial molecules by coupling 1,3,4-oxadiazole with 4-nitropyrrole moiety using molecular hybridization approach has been put forward. We synthesized 4-nitropyrrole based 1,3,4-oxadiazoles containing diverse set of aromatic and hetero-aromatic substitutions and evaluated them for their anti-bacterial, antifungal and anti-tubercular activities. Further we also evaluated effect of N-methylation on antimicrobial and anti-tubercular activity (Fig. 2).

2. Results and discussions

2.1. Chemistry

In the present work, the proposed molecules were synthesized as shown in Scheme 1. Acetylation of pyrrole was done using calculated amounts of trichloroacetyl chloride in diethyl ether as

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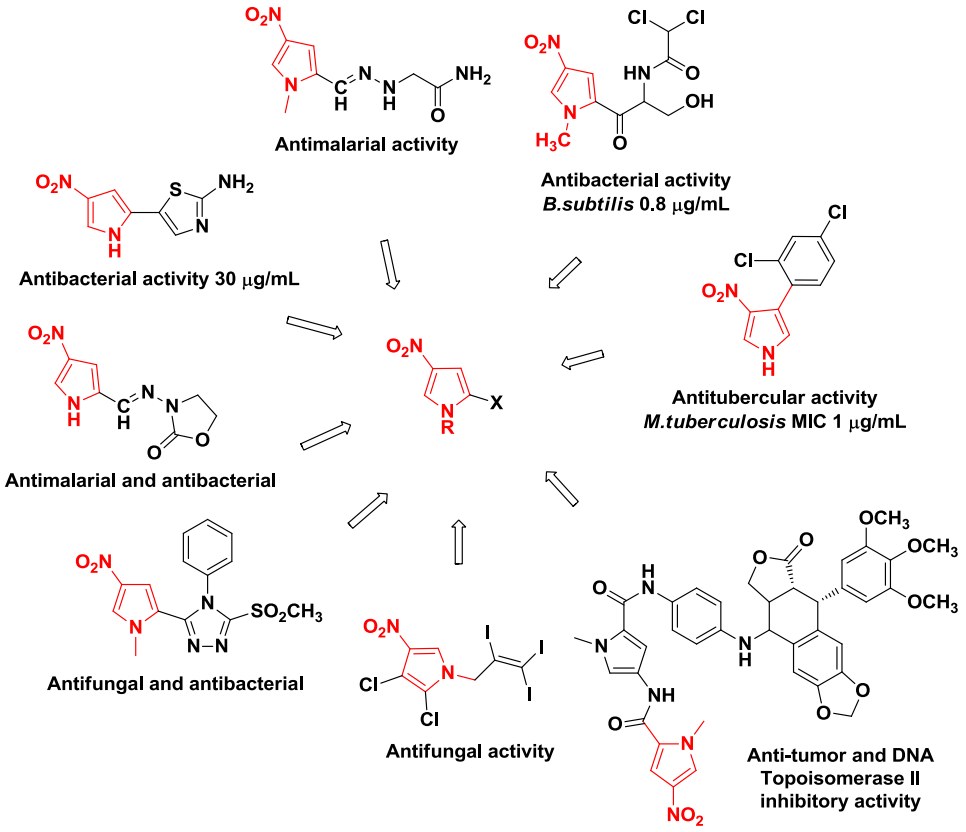

Fig. 1. Literature reports on nitropyrrole containing molecules [12–22].

solvent. Addition of pyrrole to trichloroacetyl chloride was done slowly over a period of 1–2 h using a dropping funnel. After the complete addition of pyrrole, the solvent was evaporated using rotary evaporator and the product was dried [11,23,24]. The formed acetylated pyrrole was nitrated using fuming nitric acid in acetic anhydride at ice-cold temperatures to give good yield of 4-nitro-2-trichloroacetyl-1*H*-pyrrole [25–27]. The nitrated product was converted to its hydrazide by treating with excess hydrazine hydrate in absolute alcohol and stirred for an hour to give 4-nitro-1*H*-pyrrole-2-carbohydrazide [11,24]. The obtained carbohydrazide when reacted with aromatic or heteroaromatic acids, in the presence of phosphorous oxychloride under reflux conditions, gave the final required compound 2-(4-nitro-1*H*-pyrrol-2-yl)-5-aryl-1,3,4-oxadiazole [11]. Using N-methylpyrrole the same reaction procedure was carried out to give 2-(4-nitro-1-methyl-pyrrole-2-yl)-5-aryl-1,3,4-oxadizoles.

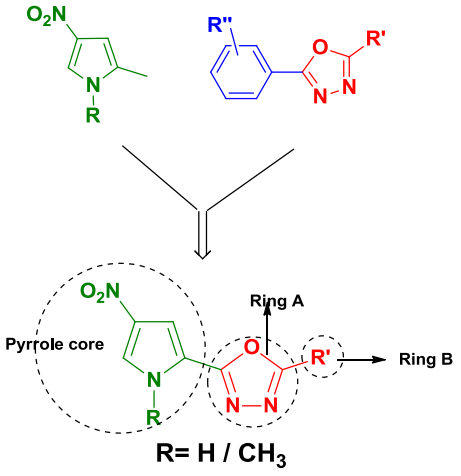

Fig. 2. Design of 4-nitropyrrole-based 1,3,4-oxadiazoles using molecular hybridization approach.

The synthesized compounds were characterized by ^{1}H NMR, MS, ^{13}C NMR and IR whose results confirmed the proposed structures of the synthesized molecules. The (M + H)+ molecular ion peak of all the compounds confirmed the respective molecular weights. In ^{1}H NMR spectra, the NH proton of pyrrole showed peak in the range of δ 13.6–13.3 ppm, while the N–CH_3 protons resonated between δ 4.2–4.0 ppm. The aryl protons of the ring B resonated between δ 9-6 ppm. IR spectroscopy showed a peak ranging between 3130 and 3142 cm^{-1} confirming the NH stretch and nitro group gave two sharp peaks at around 1498–1541 cm^{-1} and 1393–1414 cm^{-1}. The C=N stretch of oxadiazole ring was observed between 1620 and 1635 cm^{-1}.

2.2. Biological activity result

The synthesized molecules exhibited promising and encouraging antibacterial, antifungal and anti-tubercular activities (Table 1). Most of the compounds showed a broad spectrum of activity against both gram-positive and gram-negative bacterial strains. All the tested molecules showed moderate to high potency compared to standard ciprofloxacin against gram-positive bacterium *S. aureus* except **5c** and **5s**. Compounds **5p**, **5r** and **5u** exhibited two-fold activity (0.78 μg/mL) more than the standard ciprofloxacin. This indicated that presence of substituted phenyl ring and heterocyclic ring at ring B position is favorable and increasing the distance between ring A and ring B is unfavorable for activity against *S. aureus*. All the N-methylated compounds showed two to three fold potent