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Assessment of novel pyrazolopyridinone fused imidazopyridines as potential antimicrobial agents

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Abstract

The antimicrobial activity of pyrazolopyridinone fused imidazopyridines was investigated against various Gram-positive and Gram-negative bacteria as well as fungal strains using Ofloxacin and Fluconazole as positive controls, respectively. Interestingly, all the derivatives displayed good to excellent antibacterial activities against all bacterial strains with MIC values ranging from 25 to 0.39 μg/mL; compounds **3aA** and **4dA** displaying even better activity against *Staphylococcus epidermidis* than the positive control (MIC = 1.25 μg/mL). These derivatives also proved to be effective antifungal agents with MICs ranging from 12.5 to 0.39 μg/mL; compounds, **3aA** and **4dA** being most potent antifungal representatives against *Candida albicans* in comparison to the reference drug Fluconazole (MIC = 0.39 μg/mL). The SARs associated with different diversity points of these derivatives have also been discussed.

Keywords: Pyrazole; Imidazo[1,2-*a*]pyridines; Antimicrobial activity; MIC; Pyrazolopyridinone

1. Introduction

Pyrazole containing heterocyclic compounds are of immense significance as they represent an interesting template for the design, synthesis, and development of biologically active molecules and drug intermediates in medicinal chemistry [1]. The significance of pyrazole derivatives is also supported by the fact that several bioactive molecules and drugs have been reported in the literature holding this privileged nucleus in their molecular architecture. Moreover, some of these drugs have been approved by FDA during past years [2] while many are under clinical studies (Fig. 1) [3]. Interesting, these drugs have been commercialized successfully such as Sildenafil, Zometapin, Celebrex, Lonazolac, Fipronil and Rimonabant are enlisted among the most selling drugs albeit few have been retrieved from the market owing to side effects [4]. Pyrazole derivatives are also used as agrochemicals in the form of herbicides, fungicides, and insecticides for the protection of crops [5]. Therefore, pyrazole is a biologically rich nucleus and this motif is known to exhibit a broad spectrum of biological activities such as antibacterial, antifungal, anticancer, antitumor, anti-HIV, anti-inflammatory, antiviral, antipyretic, anticonvulsant and antidepressant [6]. Consequently, the

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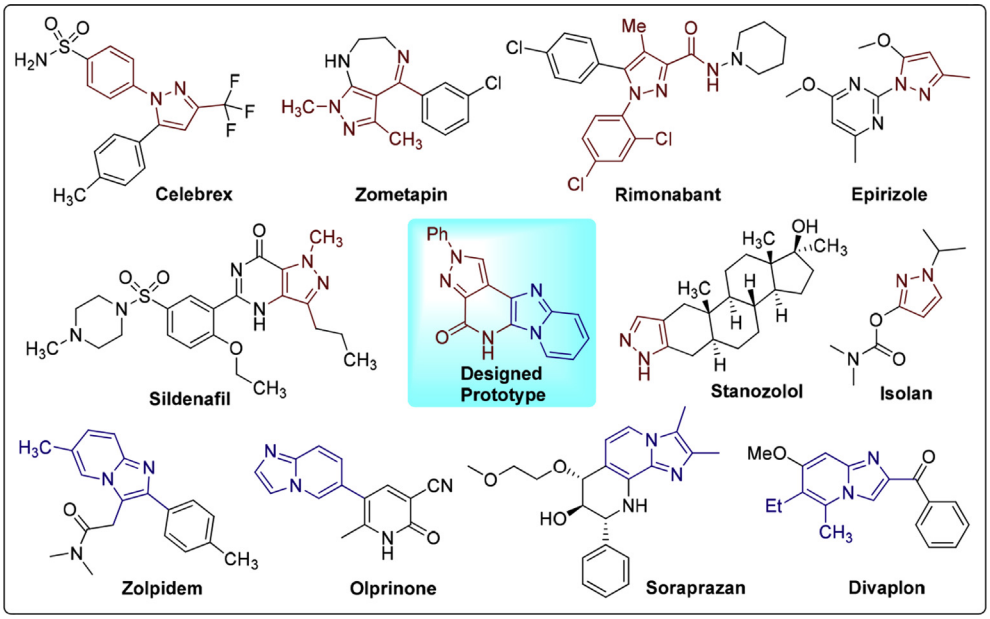

Fig. 1. Some examples of pyrazole and imidazo[1,2-*a*]pyridine based commercial drugs.

syntheses of pyrazole derivatives have gained considerable attention and synthetic chemists working in this area are interested in developing new methodologies which can produce new skeletons in a single operation in tandem manner and install the desired pattern of substitution to produce the desired activity with lesser side effects [7].

Similarly, imidazo[1,2-*a*]pyridine nucleus belonging to the family of *N*-fused heterocyclic compounds display broad spectrum of biological applications [8] and is prevalent in numerous drugs such as Zolpidem, Soraprazan, and Olprinone (Fig. 1) [9]. It is worthwhile to mention that recently we have comprehensively reviewed the synthetic developments and medicinal attributes of imidazo[1,2-*a*]pyridine derivatives throwing light on various applications of this biologically rich framework [10].

Taking into consideration the biological profile of these two pharmacophores (*i.e*. pyrazole and imidazo [1,2-*a*]pyridine nucleus), it was envisaged to combine these frameworks to construct a new molecular hybrid and successfully achieved the synthesis of pyrazolopyridinone fused imidazopyridines (**3**) from 4-formyl-1*H*-pyrazole-3-carboxylates (**1**), pyridin-2-amines (**A**−**F**) and *tert*-butyl isonitrile (**2**). These molecular architectures were prepared in tandem fashion *via* application of $In(OTf)_3$ assisted Groebke−Blackburn−Bienayme (GBB) multicomponent reaction to generate the *N*-fused imidazo[1,2-*a*]pyridine scaffolds which were further served *in-situ* HBF_4 mediated dealkylation and intramolecular amidation as described in our previous report [11]. In the present paper, we have reported the results of antimicrobial evaluation of pyrazolopyridinone fused imidazopyridine conjugates against various Gram-positive bacterial strains (*Staphylococcus aureus* and *Staphylococcus epidermidis*); Gram-negative bacterial strains (*Escherichia coli* and *Pseudomonas aeruginosa*) and fungal strains (*Aspergillus niger* and *Candida albicans*) using Ofloxacin and Fluconazole as reference drugs, respectively. The minimum inhibitory concentration (MIC, μg/mL) of the screened compounds has been measured and the structure−activity relationships (SARs) with various diversity points have also been discussed.

2. Results and discussion

2.1. Chemistry

The synthesis of pyrazolopyridinone fused imidazopyridines (**3**) was achieved from 4-formyl-1*H*-pyrazole-3-carboxylates (**1**), pyridin-2-amines (**A**−**F**) and *tert*-butyl isonitrile (**2**) which is outlined in Scheme 1. The desired conjugates were obtained *via* one-pot tandem strategy which included $In(OTf)_3$ assisted Groebke-Blackburn-Bienayme (GBB) multicomponent reaction to generate the *N*-fused imidazo[1,2-*a*]pyridine scaffolds which were further subjected to *in-situ* HBF_4-mediated dealkylation and tandem intramolecular condensation. All the products were

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