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ORIGINAL ARTICLE

Molecular docking studies of some new imidazole derivatives for antimicrobial properties

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Abstract In modern drug designing, molecular docking is routinely used for understanding drug-receptor interaction. In the present study six imidazole derivatives containing substituted pyrazole moiety (**2a,b** and **4a–d**) were synthesized. Structures of the newly synthesized compounds were characterized by spectral studies. Compounds were screened for their antibacterial activity. Compound **4c** was found to be potent antimicrobial against *Pseudomonas aeruginosa* at concentrations of 1 and 0.5 mg/mL compared to standard drug Streptomycin. All the compounds were subjected to molecular docking studies for the inhibition of the enzyme L-glutamine: D-fructose-6-phosphate amidotransferase [GlcN-6-P] (EC 2.6.1.16). The *in silico* molecular docking study results showed that, all the synthesized compounds having minimum binding energy and have good affinity toward the active pocket, thus, they may be considered as good inhibitor of GlcN-6-P synthase.

1. Introduction

Molecular docking may be defined as an optimization problem, which would describe the "best-fit" orientation of a ligand that binds to a particular protein of interest and is used to predict the structure of the intermolecular complex formed between two or more molecules. The most interesting case is the protein ligand interaction, because of its applications in medicines. Ligand is a small molecule, which interacts with protein's binding sites. There are several possible mutual conformations in which binding may occur. These are commonly called binding modes (Sharma et al., 2010). In modern drug

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designing, molecular docking is routinely used for understanding drug-receptor interaction. Molecular docking provides useful information about drug receptor interactions and is frequently used to predict the binding orientation of small molecule drug candidates to their protein targets in order to predict the affinity and activity of the small molecule.

Human beings have been in constant exposure to pathogens for many decades. Invasive microbial infections are major problems around the world, especially in immuno compromised patients. The recent expansion of antimicrobial drug research has occurred because there is a critical need for new antimicrobial agents to treat these life threatening invasive infections. The development of antimicrobial resistance has increased in this century and there is a need for developing new antimicrobial agents which will be more selective, potent and less toxic compared to the existing drugs in clinical treatment. Heterocycles containing an azole ring system are found to exhibit a wide spectrum of biological activities, including antibacterial and antifungal properties. Imidazole and its derivatives have gained remarkable importance due to their widespread biological activities and their use in synthetic chemistry. Imidazole derivatives possess a broad spectrum of pharmacological activities such as, anti-inflammatory (Suzuki et al., 1992), analgesic, anti-convulsant (Pinza et al., 1993), antitubercular (Pandey et al., 2009), antimicrobial, anticancer and anti-Parkinson (Miyachi et al., 1998) activities. Imidazole and its derivatives are of great significance due to their important roles in biological systems, particularly in, enzymes as proton donors and/or acceptors, coordination system ligands and the base of charge–transfer processes. The imidazole nucleus appears in a number of naturally occurring products like, amino acids histidine and purines, which comprise many of the most important bases in nucleic acids.

Similarly pyrazole derivatives have showed significant biological activities, such as anti-microbial (Isloor et al., 2009), analgesic (Isloor et al., 2000), anti-inflammatory (Bekhita and Abdel-Aziem, 2004) and anticancer (Dhanya et al., 2009) activities. This gave a great impetus to the search for potential pharmacologically active drugs carrying pyrazole substituents.

The enzyme, namely glucosamine-6-phosphate synthase (GlmS, GlcN-6-P synthase,L-glutamine:D-fructose-6P amidotransferase, EC 2.6.1.16) also known under the trivial name of glucosamine-6-phosphate synthase, is a new target for antifungals (Chmara et al., 1984). GlcN-6-P synthase catalyzes the first step in hexosamine metabolism, converting fructose 6-phosphate (Fru6P) into glucosamine 6-phosphate (GlcN6P) in the presence of glutamine. The reaction catalyzed by GlmS is irreversible, and is therefore considered as a committed step. The end product of the pathway, *N*-acetyl glucosamine, is an essential building block of bacterial and fungal cell walls. Structural differences between prokaryotic and human enzymes may be exploited to design specific inhibitors, which may serve as prototypes of anti-fungal and anti-bacterial drugs (Borowski, 2000).

It has been shown that even a short time inactivation of GlcN-6-P synthase is lethal for fungal cells, while in mammals depletion of the amino sugar pool for a short time is not lethal, because of the much longer lifespan of mammalian cells, long half lifetime of GlcN-6-P synthase, and rapid expression of the mammalian gene encoding the enzyme GlcN-6-P synthase (Milewski et al., 1986). It is well established that small modifications in the structure of the targets are altering their biological character as well as their physiochemical properties. A detailed literature survey on antimicrobial activity of various types of compounds indicated that, the presence of certain pharmacophore such as imidazole/pyrazole in any molecule plays an important role in enhancing activity. In our previous paper (Vijesh et al., 2011), we reported the synthesis and the antimicrobial activity of the imidazole derivatives containing pyrazole nucleus. In continuation of that, we have performed the molecular docking studies of the biologically active six compounds for better understanding of the drug-receptor interaction.

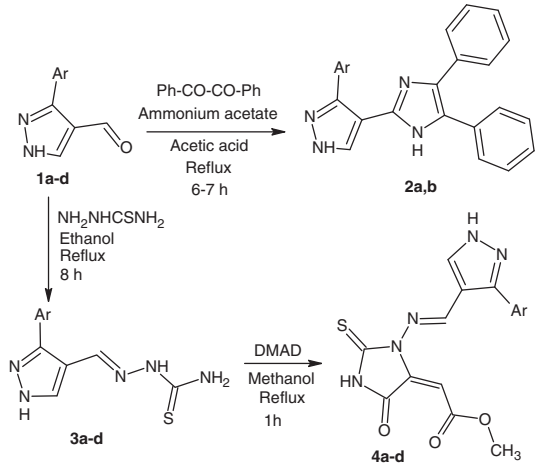
2. Experimental

2.1. Materials and methods

Melting points were determined by open capillary method and were uncorrected. The IR spectra (in KBr pellets) were recorded on a JASCO FT/IR-4100 spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded (DMSO-d_6) on a Bruker (400 MHz) using TMS as the internal standard. Chemical shift values are given in δ (ppm) scales. The mass spectra were recorded on a JEOL JMS-D 300 spectrometer operating at 70 eV. Elemental analyses were performed on a Flash EA 1112 series CHNS-O Analyzer. The completion of the reaction was checked by thin layer chromatography (TLC) on silica gel coated aluminum sheets (silica gel 60 F254) obtained from Merck. Commercial grade solvents and reagents were used without further purification (see Scheme 1).

2.2. General procedure for the synthesis of new derivatives of 2,4,5-trisubstituted imidazoles (**2a,b**)

A mixture of 3-aryl-1*H*-pyrazole-4-carbaldehyde **1a,b** (0.01 mol), benzil (0.01 mol) and ammonium acetate (0.05 mol) in acetic acid (50 mL) was refluxed for 6–7 h at 120 °C. After completion of the reaction, the reaction mixture was allowed to cool and filtered to remove any precipitate. 300 mL of ice-water was added to the filtrate and the precipitated product was collected by filtration. The crude product was recrystallized using ethanol–DMF mixture (Vijesh et al., 2011).



Ar = 4-Thioanisyl, 2,4-Dichlorophenyl, 2,5-Dichlorothiophene, 4-Tolyl

Scheme 1 Synthetic route for the compounds **2a**,**b** and **4a**–**d**.