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Crystal structure and molecular docking studies of 1,2,4,5-tetraaryl substituted imidazoles

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Abstract: 2-(4-Bromophenyl)-1-(3-chloro-2-methylphenyl)-4,5-diphenyl-1*H*-imidazole (**1**) and 1-(3-chloro-2-methylphenyl)-2-(4-chlorophenyl)-4,5-diphenyl-1*H*-imidazole (**2**) were synthesized by one-pot four-component reactions. These compounds crystallize in the monoclinic crystal system with the space group $P2_1/n$. The crystal structures were solved by direct methods and refined by a full matrix least squares procedure to a final R value of 0.0572 (**1**) and 0.0588 (**2**) for 2748 and 2278 observed reflections, respectively. Molecular docking studies were implemented to understand the inhibitory activity of related compounds against glucosamine 6-phosphate (GlcN-6-P) synthase, the target protein for the antimicrobial agents.

Keywords: molecular docking; multi-component; single crystal; X-ray diffraction.

Introduction

Development of new multi-component reactions (MCRs) [1], in particular for the synthesis of polysubstituted imidazoles is an important area of research in medicinal chemistry. The imidazoles exhibit a wide spectrum of biological activities [2–14]. The 1,2,4,5-tetrasubstituted imidazoles are present in many biological systems and drug molecules such as olmesartan, medoxomil, losartan, eprosartan and trifenagrel [15, 16]. Such imidazoles are generally synthesized by a four-component condensation of aldehyde, 1,2-diketone, amine and ammonium acetate. This paper describes the synthesis of two 1,2,4,5-tetrasubstituted imidazole derivatives, **1** and **2**, and their molecular docking with the binding pockets of glucosamine-6-phosphate synthase (GlcN-6-P). This enzyme is the target in antimicrobial chemotherapy, and several antimicrobial compounds related to **1** and **2** form a complex with GlcN-6-P [17, 18].

Results and discussion

The synthesis of compounds **1** and **2** by a one-pot four-component reaction is shown in Scheme 1. Under optimized conditions, equimolar amounts of benzil, aldehyde, amine and ammonium acetate were allowed to react in acetic acid at 60°C in the presence of 0.1 equivalent of ZnO nanoparticles to furnish compounds **1** and **2** in the yields of 89% and 92%, respectively. The reaction is highly inefficient in the absence of the nanocatalyst. As the catalyst is insoluble in hot ethanol, it can be recycled by simple filtration. No significant decrease in the percentage yields of the products was observed even after four catalytic cycles.

As shown by the X-ray crystallographic analysis (Figures 1 and 2), the molecular structures of compounds **1** and **2** are virtually identical excepting the substitution at the carbon atom C13. Both compounds crystallize in the monoclinic crystal system with the space group $P2_1/n$. Bond lengths and bond angles have normal values compared with the related structures [19–21]. In both compounds, all rings are twisted from coplanarity.

The C-CH_3 bond distances of 1.479(6) Å (**1**) and 1.486(4) Å (**2**) significantly differ from the standard value of 1.53 Å [22]. The four dihedral angles between the imidazole and four phenyl groups are 34.01(2)°, 41.26(2)°, 45.08(2)°, 70.49(2)° in **1** and 34.36(1)°, 41.03(1)°, 43.7(1)°, 69.56(1)° in **2** for the respective phenyl rings attached at the positions C7, C8, C9 and N1. Both chlorine atoms in **2** are slightly deviated from the planes of their respective

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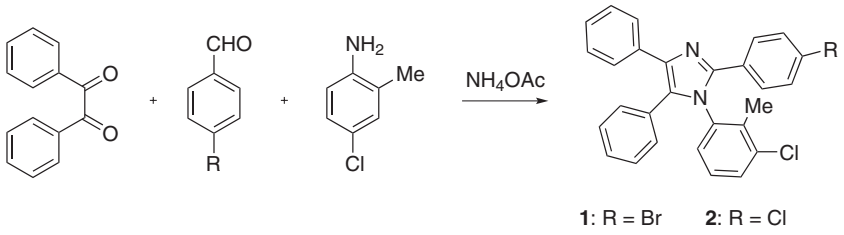

Scheme 1

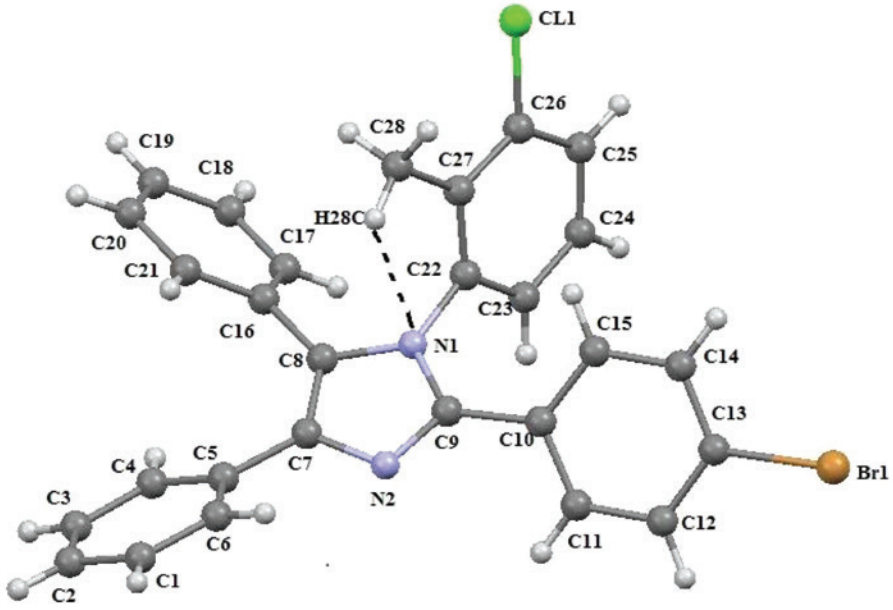

Figure 1 ORTEP plot of **1** with thermal ellipsoids drawn at 40% probability. The dotted line shows the intramolecular hydrogen bond.

rings, while the methyl group at C27 for both **1** and **2** lies slightly below the plane of the ring C22-C27. The exocyclic bond angles formed by the atoms of the imidazole ring at N1, C7, C8 and C9 are of similar values for **1** and **2**. The molecular packings of **1** and **2** in the crystal are virtually identical (Figures 3 and 4).

As already mentioned, compounds related to **1** and **2** are good antimicrobial agents [23]. Hence, the synthesized imidazole derivatives were docked into the active site of GlcN-6-P synthase (PDB ID: 1MOQ), the known target for antibacterial and antifungal agents, and the interactions were compared with those of the complexes of the standard drugs ciprofloxacin and fluconazole. For each docked complex, nine conformations were obtained, and based on the high docking energy score the best conformation was selected. Figure 5 shows the ligand-protein binding interactions of compound **1**, compound **2**, ciprofloxacin and fluconazole with the 1MOQ binding site. Table 1 shows the docking score and interactions of compound **1**, compound **2**, ciprofloxacin and fluconazole with the binding site of the target protein 1MOQ (GlcN-6-P).

The docking results show that the docking energies for the **1**-1MOQ complex (–7.8 kcal/mol) and for the **2**-1MOQ complex (–7.7 kcal/mol) are higher than those of fluconazole-1MOQ complex (–6.7 kcal/mol) and ciprofloxacin-1MOQ complex (–6.5 kcal/mol). The **1**-1MOQ complex is stabilized by one hydrogen bond and one π-sulfur interaction as shown in Figure 5A. The atom N of the residue GLY301 interacts with the atom N2 of the ligand through a hydrogen bond at the distance of 3.818 Å. Also, a sulfur-π interaction is observed between the SG atom of the residue CYS300 and the C1···C6 benzene ring of the ligand at a distance of 4.267 Å.

The **2**-1MOQ complex is stabilized by one hydrogen bond and one π-sulfur interaction as shown in Figure 5B. The atom N of the residue GLY301 interacts with the atom N2 of the ligand through hydrogen bond

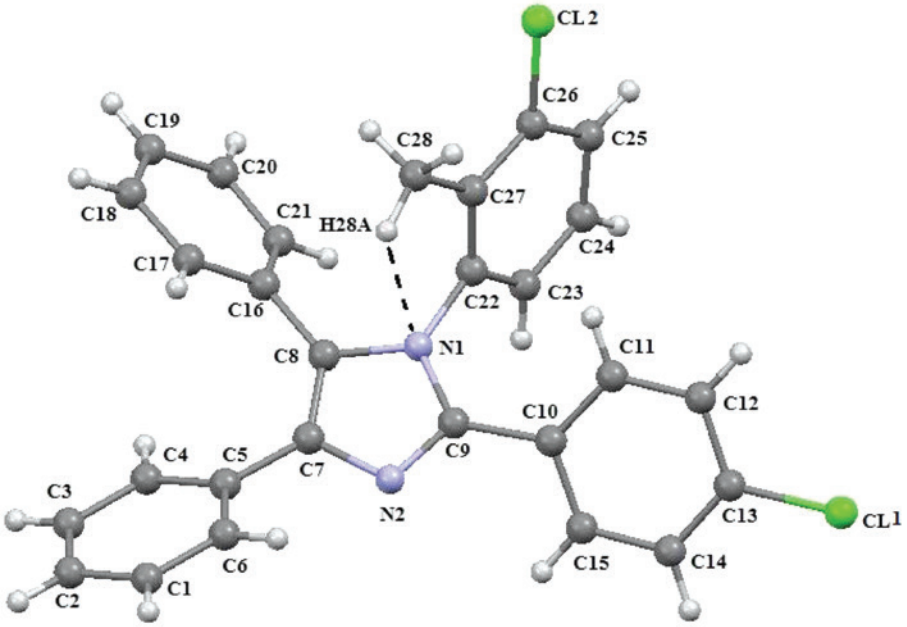

Figure 2 ORTEP plot of **2** with thermal ellipsoids drawn at 40% probability. The dotted line shows the intramolecular hydrogen bond.

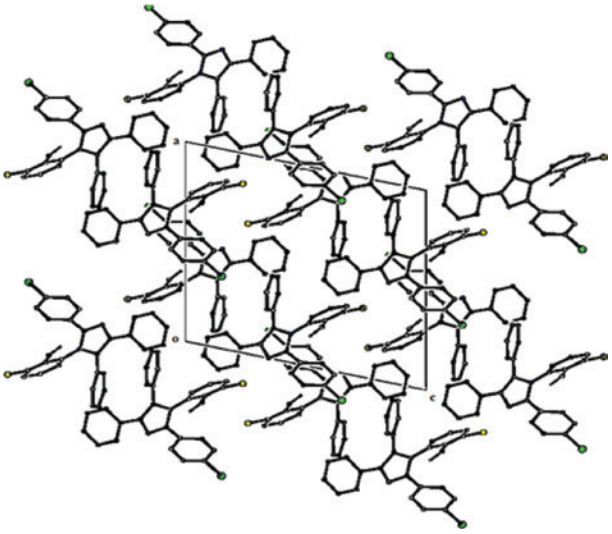

Figure 3 Packing view of **1** along the b-axis.

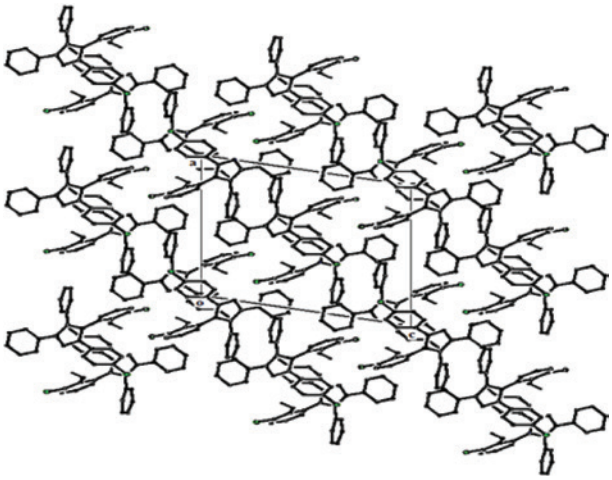

Figure 4 Packing view of **2** along the b-axis.

at the distance of 3.807 Å. Also, a sulfur-π interaction is observed between the SG atom of the residue CYS300 and the C10 · · · C15 benzene ring of the ligand at a distance of 4.207 Å. The fluconazole-1MOQ complex is stabilized by only one hydrogen bond with the residue GLY348 (Figure 5C), and ciprofloxacin-1MOQ complex is stabilized by only one hydrogen bond with the residue SER401 (Figure 5D).

The presence of a hydrogen bond and sulfur-π interaction in both complexes results in an increase in the binding affinity of the synthesized imidazole derivatives over the reference drugs. Also, the docked **1**-1MOQ and **2**-1MOQ complexes exhibit better binding energy over the standard drug complexes (Table 1). These docking results suggest that compounds **1** and **2** may act as inhibitors of GlcN-6-P synthase.

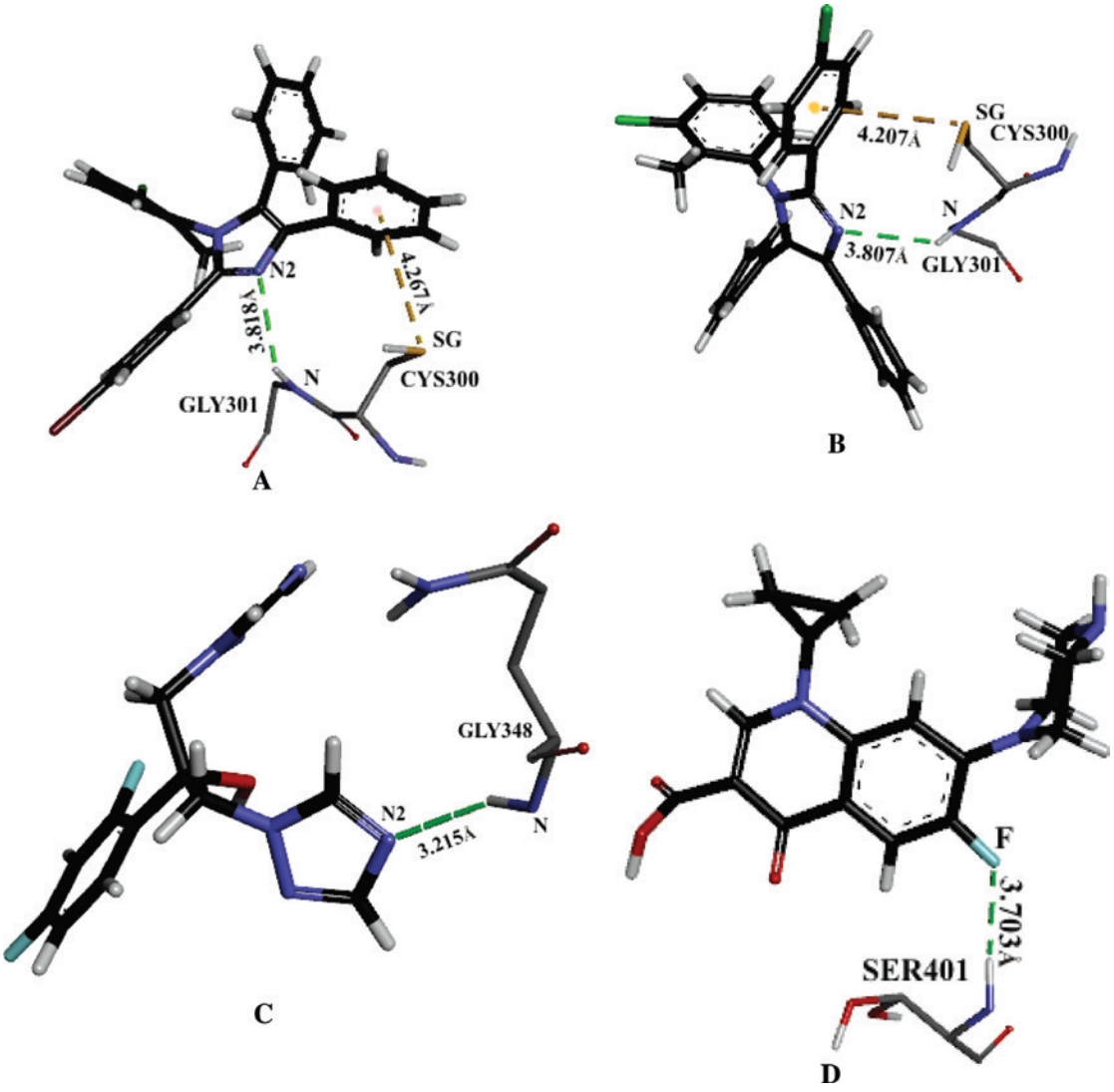

Figure 5 Ligand-protein binding interactions of (A) **1**-1MOQ complex, (B) **2**-1MOQ complex, (C) fluconazole-1MOQ complex and (D) ciprofloxacin-1MOQ complex.

Table 1 Docking energy and interactions of compounds **1**, **2**, fluconazole and ciprofloxacin with the target protein 1MOQ.

Target protein	Inhibitor	Docking energy (kcal/mol)	Interactions	Distance (Å)	Bonding	Bonding type
GlcN-6-P (PDB ID: 1MOQ)	Compound **1**	−7.8	(GLY301)N-H···N2	3.818	Hydrogen	H-bond
			(CYS300)SG···π (C1···C6 ring)	4.267	π-sulfur bond	s-π bond
	Compound **2**	−7.7	(GLY301)N-H···N2	3.807	Hydrogen	H-bond
			(CYS300)SG···π (C10···C15 ring)	4.207	π-sulfur bond	s-π bond
	Fluconazole	−6.7	(GLY348)N-H···N2	3.215	Hydrogen	H-bond
	Ciprofloxacin	−6.5	(SER401)N-H···F	3.703	Hydrogen	H-bond

Conclusions

Tetrasubstituted imidazole derivatives **1** and **2** were synthesized by a one-pot four-component reaction. The molecular structures were determined by using an X-ray diffraction technique. The molecular docking of **1** and **2** with protein GlcN-6-P, a known target of antimicrobial drugs, was conducted.

Experimental

Synthesis of compounds 1 and 2

A mixture of benzil (1 mmol), substituted amine (1 mmol), aryl aldehyde (1 mmol), ammonium acetate (1 mmol) and ZnO nanoparticles (0.1 mmol) in glacial acetic acid was heated at 60°C under stirring for 2 h. The progress of the reaction was monitored by thin-layer chromatography (TLC). After the completion of the reaction, the mixture was cooled to room temperature, poured into cold water and the resultant precipitate was filtered by suction. An analytically pure compound was obtained by crystallization from ethanol/water.

2-(4-Bromophenyl)-1-(3-chloro-2-methylphenyl)-4,5-diphenyl-1*H*-imidazole (1) Yield 89%; mp >350°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.08–7.60 (m, 17H), 1.90 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.7, 138.8, 137.4, 135.8, 135.0, 134.1, 131.5, 131.2, 130.7, 130.2, 130.1, 129.5, 129.3, 128.5, 128.4, 128.2, 127.9, 127.3, 127.0, 126.9, 122.9, 15.3; FT-IR: 3064, 1366, 742, 694 cm^{-1}.

1-(3-Chloro-2-methylphenyl)-2(4-chlorophenyl)-4,5-diphenyl-1*H*-imidazole (2) Yield 92%; mp >350°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.07–7.61 (m, 17H), 1.90 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.7, 138.7, 137.4, 135.8, 135.0, 134.6, 134.1, 131.1, 130.7, 130.2, 130.1, 129.3, 128.9, 128.6, 128.5, 128.3, 128.2, 127.9, 127.3, 127.0, 126.9, 15.3; FT-IR: 3061, 1363, 750 cm^{-1}.

X-ray intensity data collection and structure refinement

Crystals of **1** and **2** suitable for X-ray diffraction analysis were obtained by crystallization from acetone/water. X-ray intensity data of well-defined crystals were collected at 293(2) K on the X-calibur charge coupled device area detector of the single crystal X-ray diffractometer equipped with graphite monochromatic Mo$K\alpha$ radiation ($\lambda = 0.71073$ Å). The cell dimensions were determined by the least-squares fit of angular settings of 2013 (**1**) and 2359 (**2**) reflections in the θ range from 4.0 to 25.5 (**1**) and from 4.0 to 28.90 (**2**), respectively. The $I > 2\sigma$ criterion was employed to the unique data sets. Data were corrected for Lorentz and polarization factors. The structures were solved by direct methods using SHELXS97 [24]. All non-hydrogen atoms of the molecules were located from the best E-map, and a full-matrix least-squares refinement was carried out using SHELXL97 [24]. All hydrogen atoms were geometrically fixed and allowed to ride on the corresponding non-H atoms. Multi-scan absorption correction was employed ($T_{min} = 0.651$ for **1** and 0.895 for **2**, $T_{max} = 1.0$ for both structures) [25]. The crystallographic data are summarized in Table 2. The Oak Ridge Thermal Ellipsoid Plot (ORTEP) [26] views of the molecules with atomic labeling are shown in Figures 1 and 2. The geometrical calculations were performed using the PLATON [27] and PARST [28] software programs. CCDC-1479682 (**1**) and 1479683 (**2**) are the deposition numbers of the supplementary crystallographic data which can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.ac.uk/data request/cif.

Molecular docking studies

Molecular docking was carried out using Autodock Vina to find the binding energy and interactions of synthesized imidazole derivatives to the binding pocket of glucosamine 6-phosphate synthase (PDB ID: 1MOQ) which was downloaded from the Protein Data Bank (http://www.rcsb.org) [29]. After docking, the results were viewed using Discovery Studio [30].

Table 2 Crystal structures and refinement details for **1** and **2**.

Compound	1	2
Chemical formula	$C_{28}H_{20}BrClN_2$	$C_{28}H_{20}Cl_2N_2$
M_r	499.82	455.36
Crystal system, space group	Monoclinic, $P2_1/n$	Monoclinic, $P2_1/n$
Temperature (K)	293	293
a, b, c (Å)	14.2014 (11), 10.8335 (8), 15.6804 (7)(8)	14.2071 (10), 10.7790 (8) 15.4101 (8)
β (°)	102.767 (6)	101.492 (6)
V (Å^3)	2352.8 (3)	2312.6 (3)
Z	4	4
Radiation type	Mo $K\alpha$	Mo $K\alpha$
μ (mm^{-1})	1.88	0.30
Crystal size (mm)	0.30×0.20×0.10	0.30×0.20×0.10
Absorption correction	Multi-scan	Multi-scan
T_{min}, T_{max}	0.651, 1.0	0.895, 1.0
No. of measured, independent and observed [$I > 2\sigma(I)$] reflections	8779, 4125, 2748	8468, 4060, 2278
R_{int}	0.040	0.045
$(\sin\theta/\lambda)_{max}$ (Å^{-1})	0.595	0.595
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.057, 0.153, 1.05	0.059, 0.176, 1.01
No. of reflections	4125	4060
No. of parameters	291	291
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	0.74, −0.43	0.45, −0.33

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