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Synthesis, X-ray crystal structure studies and molecular docking analysis of 2-(3,4-dimethoxyphenyl)-4,5-diphenyl-1H-imidazole

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ABSTRACT

The X-ray structure of 2-(3,4-dimethoxyphenyl)-4,5-diphenyl-1*H*-imidazole, has been determined. It crystallizes in orthorhombic space group $Pna2_1$, with $a = 9.5018(6)$ Å, $b = 21.636(2)$ Å, $c = 19.040(1)$ Å and $Z = 8$. The structure has been solved by direct methods and refined by full matrix least squares procedures to a final R value of 0.0675 for 2733 observed reflections. The asymmetric unit contains two crystallographic independent molecules. C–H…O and C–H…N intermolecular interactions were observed and these interactions are of paramount importance in assembling the molecules leading to packing stability. To understand pharmacological importance of the title compound, molecular docking was performed against two anti-inflammatory drug targets; Myeloperoxidase (MPO) and Cyclooxygenase (COX-2). Docking studies show binding mode of the titled molecule to be similar to the known inhibitor in their respective active site of anti-inflammatory drug targets. Thus, the title molecule also has similar mode of drug action.

Specification Table

Subject area	Organic chemistry, crystallography
Compound	2-(3,4-dimethoxyphenyl)-4,5-diphenyl-1*H*-imidazole
Data category	Crystallography, computational simulations
Data acquisition format	Single crystal X-ray diffraction method
Data type	Process and analysis
Procedure	The compound was synthesized and confirmed by X-ray diffraction method and molecular docking studies
Data accessibility	CCDC – 1556053

1. Rationale

Imidazole derivatives are one of the most interesting classes of heterocyclic compounds because they exhibit wide pharmacological and biological activities [1]. They shows analgesic [2], anti-inflammatory [3], antibacterial [4], antitumor [5], anti-allergy [6], antimycotic, antibiotic, antiulcerative and antibacterial activities [7]. Many 2,4,5 Trisubstituted imidazoles are known as fungicides, herbicides [8] and plant growth regulators [9]. In addition, they act as inhibitors of p38 MAP kinase

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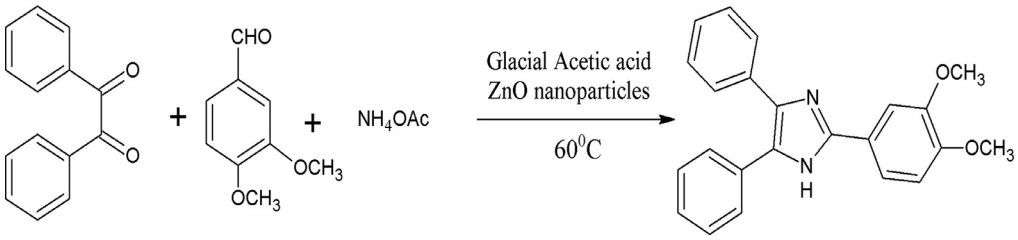

Fig. 1. Synthetic scheme of 2-(3,4-Dimethoxyphenyl)-4,5-diphenyl-1*H*-imidazole.

[8], B-Raf kinase [10] transforming growth factor b1 (TGF-b1) type 1 activin receptor-like kinase (ALK5) [11], cyclooxygenase-2 (COX-2) [12] and biosynthesis of interleukin-1 (IL-1) [13]. Cyclocondensation of a 1,2-diketone with an aldehyde using ammonium acetate as the ammonia source is one of the synthetic strategy for the synthesis of 2,4,5-trisubstituted imidazoles. In view of the importance of applications of 2,4,5-trisubstituted imidazoles in synthetic chemistry, we report the crystal structure of the title compound (**I**). For understanding the biological importance of 2,4,5-trisubstituted imidazoles, the chemical similarity of the titled compound with known drug-target containing database "Binding DB" was performed [14]. The results of molecular docking analysis exhibit inhibitory activity against top two anti-inflammatory drug targets. The known inhibitors of Myeloperoxidase (MPO) and Cyclooxygenase (COX-2) have more than 70% chemical identity with the title compound. Thus for prediction of binding mode of the title compound with these drug targets, molecular docking was performed to suggest the mode of action.

2. Procedure

2.1. Synthesis of the title compound

A mixture of benzil (0.210 g, 1 mmol), 3,4-dimethoxy benzaldehyde (0.166 g, 1 mmol), ammonium acetate (0.77 g, 1 mmol) and ZnO nanoparticles (0.008 g, 0.1 mmol) in 25 ml glacial acetic acid was heated at 60 °C under stirring for around 2 hr. The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was cooled to room temperature and then poured into cold water with constant stirring. The solid separated was filtered by suction to afford crude product. The pure product was obtained by further recrystallization from ethanol. Single crystal of the purified product was developed from acetone/DMF by slow evaporation method (M.P.: 475–477 K). Reaction scheme of the title compound is shown in Fig. 1.

2.2. X-ray crystal structure analysis and refinement

A suitable single crystal of approximate dimension $0.30 \times 0.20 \times 0.20$ mm was used for structural analysis using X-ray diffraction technique. X-ray intensity data was collected at room temperature (293 K) on *X'calibur* CCD area-detector single crystal X-ray diffractometer operating at 50 kV and 30 mA, using graphite monochromated Mo$K\alpha$ radiation of wavelength $\lambda = 0.71073$ Å [15]. A total number of 8425 reflections were collected and out of these reflections 4428 were found to be unique. The intensities were measured by ω–scan mode for θ ranging between 3.55° and 24.00°. A total number of 2733 reflections were treated as observed [$I > 2\sigma(I)$]. Data were corrected for Lorentz-polarization and absorption factors. The structure was solved by direct methods using SHELXS-97 [16]. All non-hydrogen atoms of the molecule were located in the best E-map. A full matrix least squares refinement was carried out using SHELXL-2016 [17]. All the hydrogen atoms were geometrically fixed and allowed to ride on the corresponding non-H atoms with C–H = 0.93–0.96 Å, N–H = 0.86 Å and $U_{iso} = 1.2\ U_{eq}$(C), except for the methyl groups where U_{iso}(H) = $1.5U_{eq}$(C). The final refinement cycles converged to an R- = 0.0675 and $wR(F^2) = 0.0877$ for 2733 observed reflections. Residual electron density ranges from −0.180 to 0.192 eÅ^{-3}.

2.3. Molecular docking analysis

Crystal structure of two anti-inflammatory drug targets such as Myeloperoxidase (MPO) and Cyclooxygenase (COX2) were retrieved from RCSB databank (PDB ID:4C1M and 5KIR) [18,19]. Proteins were prepared using Protein Preparation Wizard of Schrodinger suite 2014, where addition of hydrogen atoms, proper bond order and energy minimization were carried out [20]. Title compound was prepared using conjugate gradient energy optimization technique with 5000 step cycles in Macro Model module of Schrodinger suite 2014. Finally**,** Induced fit docking was performed for the title compound against MPO and COX2 in Schrodinger suite 2014 [21,22]. Based on binding free energy (Docking Score and Glide Energy), top 80 poses were shortlisted and best binding conformation was predicted which have minimum binding free energy. Structural visualization in binding complex was performed in Chimera software [23].