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Synthesis, Antimicrobial Evaluation, Crystal Structure, Hirshfeld Surface Analysis and Docking Studies of 4-[2-(1-methyl-1H-imidazol-2-ylsulfanyl)-acetylamino]-benzenesulfonic acid

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Abstract

The synthesis of a new 4-[2-(1-methyl-1H-imidazol-2-ylsulfanyl)-acetylamino]-benzenesulfonic acid from available reagents using an efficient strategy was reported, and its antimicrobial ability against bacterial strains was investigated. This new compound was characterised using a single crystal technique, which showed that the compound crystallised with a monoclinic system in a P21/c space group. Its unit-cell parameters were $a = 17.0692$ (2) Å, $b = 5.0326$ (3) Å, $c = 17.2979$ (4) Å, $\beta = 106.596^\circ$ (2) and $Z = 4$. Crystal packing was stabilised by hydrogen bonds, pi- stacking, C-H...pi and van der Waals interactions. The intermolecular interaction analysis of the crystal structure was affected by Hirshfeld surface analysis, and associated two-dimensional fingerprint plots were utilised. In addition, docking investigations of the biological activity of the synthesised compound was also performed.

Keywords: synthesis, antimicrobial activity, docking, crystal structure, Hirshfeld surface analysis

Introduction

Heterocyclic chemistry is a vast field, considering that the number of heterocyclic compounds continues to increase. Among the different classes of heterocyclic compounds, nitrogenous structures are the most common and are present in many natural compounds of plant, animal and synthetic origin. Heterocyclic structures are sometimes associated with each other, but are, in most cases, linked to very diverse structural scaffolds. Some hybrid compounds, comprising mainly heterocycles containing nitrogen, sulphur and/or oxygen atoms, have shown remarkable pharmacological activity [1–4].

For example, the imidazole nucleus is responsible for the synthesis of a large number of active agents used in various fields. In the medical and therapeutic fields, it is crucial for anticancer treatments [5,6], antihistamines [7], anti-inflammatories [8], bactericides [9], fungicides [10,14] anti-hypertensives [11–14], anti-tuberculosis drugs [15], anti-parasitic agents [16,17], etc. It is also used in the agrochemical sector [18,19] and in the industry sector (e.g., catalysts, flame retardants, steel corrosion inhibitors, etc.) [20–23].

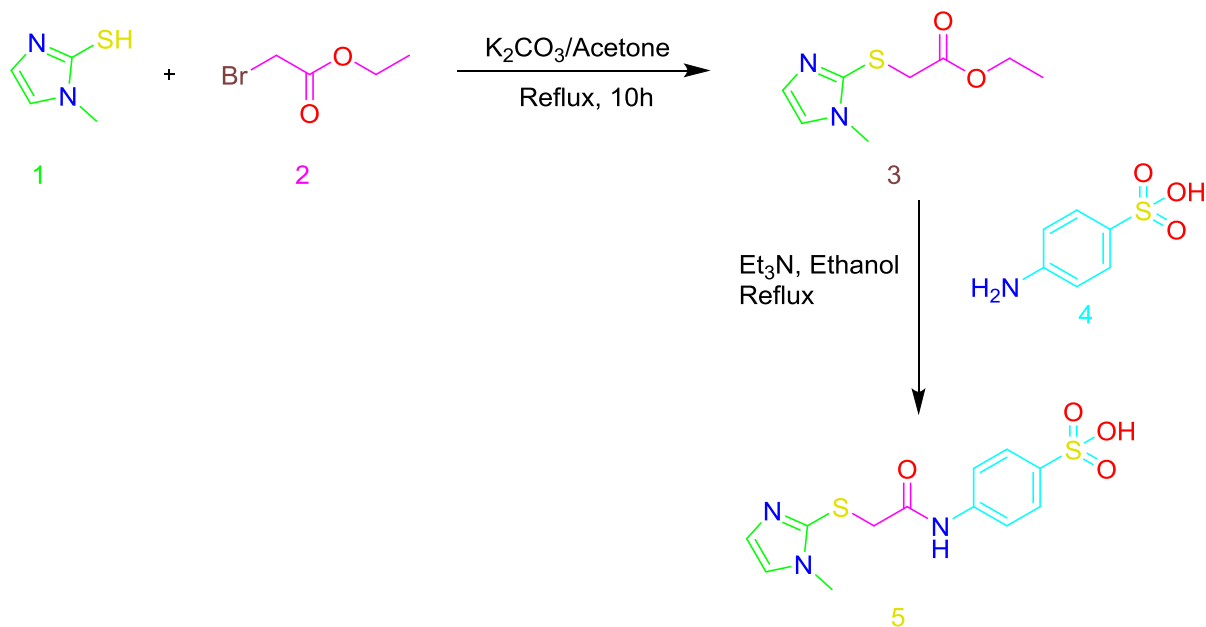
This research was performed because of our experience with the synthesis and characterisation of novel active heterocyclic compounds [24–31]. The main objective was the preparation, biological evaluation and crystal structural identification of a new, imidazole-containing molecule: 4-[2-(1-methyl-1H-imidazol-2-ylsulfanyl)-acetylamino]-benzenesulfonic acid (hereafter, “**5**”).

Methodology and Results

Synthesis

First, an intermediate compound (**3**) was prepared from the reaction of (**1**) 2-mercapto-1-methylimidazole (1 mmol) and (**2**) ethyl 2-bromoacetate (1 mmol) in the presence of potassium carbonate (0.5 mmol) under refluxed acetone for 10 h. The intermediate compound (**3**) was obtained after filtration and recrystallisation in ethanol. Then, 1 mmol of the intermediate

compound (**3**) and 1.1 mmol of benzenesulfonic acid were refluxed in the presence of 20 mg of trimethylamine and 10 mL of ethanol for 3 h. After the reaction's completion (monitored using TLC), the mixture was filtered and the resulting solid was recrystallised in a mixture of ethanol and water to achieve a pure compound (**5**) with an 83% yield (Scheme 1).



Scheme 1. Synthesis of 4-[2-(1-methyl-1H-imidazol-2-ylsulfanyl)-acetylamino]-benzenesulfonic (**5**)

Antimicrobial Performance

Herein, the minimum inhibitory concentration (MIC) is referred to as the concentration of **5**, for which bacterial growth was completely inhibited. MIC was determined by two-fold microdilution in sterile flat-bottom 96-well polystyrene plates, as detailed in [32].

Dimethyl sulfoxide (DMSO) was used as the negative control. The MIC was determined as follows: first, concentrations of **5** in DMSO were adjusted to 100, 75, 50, 38.5, 25, 18.75 and 12.5 $\mu\text{g/mL}$. Second, 200 μL of the former serially diluted test samples were dispensed to 96-well microtrays. Next, test bacteria were inoculated into the wells by adjusting the final volume to 400 μL , followed by the incubation of the plates at 37 $^\circ\text{C}$ for 24 h. The concentration, for which a clear reduction in turbidity was observed, was referred to as the MIC. All experiments were carried out in triplicate.

The prepared **5** was tested for antimicrobial efficiency against different microbial pathogens, such as methicillin-resistant *Staphylococcus aureus* (MRSA), *Klebsiella pneumoniae* (Kp), *Aspergillus niger* (An) and *Candida albicans* (Ca). As shown in Table 1, the synthesised derivative was found to be effective against all tested microbes.

Table 1. Antibacterial activity of synthesized derivative.

		Microbial Strains			
		MRSA	<i>Klebsiella pneumoniae</i>	<i>Aspergillus niger</i>	<i>Candida albicans</i>
Compound 5	MIC (µg/ml)	6.25	25	6.25	6.25
	MBC (µg/ml)	9.5	18.75	9.5	9.5
	Inhibition zone in mm (100 µg/ml)	25	17	24	26
	IC ₅₀ (µM)	19.11	76.45	19.11	19.11

^aMIC: Minimum inhibitory concentration in µg/mL. MBC: Minimum bactericidal concentration

^b: No inhibition zone, no activity.

X-ray Diffraction Analysis

Single-crystal data for C₁₂H₁₃N₃O₄S₂ were collected on a Bruker Apex II diffractometer equipped with a molybdenum anticathode and graphite monochromator. The colourless crystal compound had a plate form about 0.45 × 0.12 × 0.02 mm³ in size. Absorption corrections were empirical. The φ and ω scan modes were used and the crystal-detector distance was 35 mm. The DENZO-SMN programme was used to reduce the data. The SIR97 programme was used to determine a structural hypothesis [33]. The structure solution was solved by the SHELX97 programme, and refinement was performed on F² via the full-matrix least squares technique using the SHELXL programme [34]. Hydrogen atoms were theoretically located. The MERCURY programme for Windows was used for structural visualisation [35]. All programmes mentioned above were included in the WINGX package [36].

At the end of refinement, the reliability factors and goodness of fit were determined to have final values of $R_1 = 0.0570$ and $wR_2 = 0.1514$ and 1.001 , respectively. The residual electronic density ranged from -0.474 – 0.489 e. \AA^{-3} . These three values prove the good quality of this refinement. The Cambridge Crystallographic Data Centre (CCDC) now contains crystallographic data for **5** (CCDC2151896), which can be obtained via the following link: www.ccdc.cam.ac.uk/data_request/cif.

In addition, the structure refinement showed that **5** crystallises with a monoclinic system in a $P21/c$ space group and has the following unit-cell parameters: $a = 17.069$ (2) \AA , $b = 5.033$ (3) \AA , $c = 17.298$ (2) \AA , $\beta = 106.60^\circ$ (2) and $Z = 4$. The unit cell contained four molecules of $C_{12}H_{13}N_3O_4S_2$.

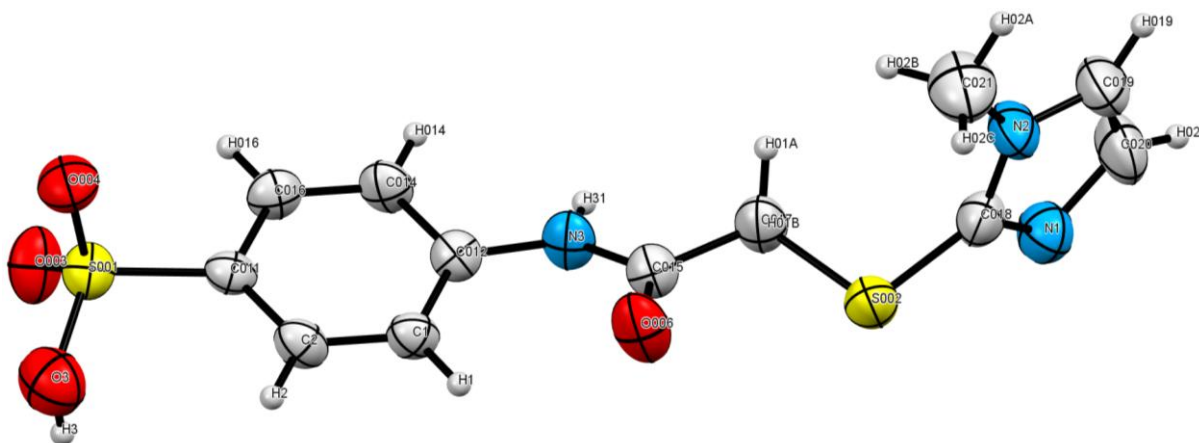


Figure 1. View of asymmetric unit of the titled compound $C_{12}H_{13}N_3O_4S_2$

A complex network of intermolecular hydrogen bonds, π -stacking and π - π stacking interactions ensured cohesion between molecules (see Figure 2). Indeed, a strong hydrogen-bond interaction exists between the acetamide moiety via $C=O \cdots H-N$ with a distance of 2.513 \AA , as well as between the sulfonic acid via $S=O \cdots OH=S$ with a distance of 2.882 \AA . Also, there exists a hydrogen-bond interaction in the methyl group of imidazole (CH_3) with a distance of 1.739 \AA . The distances of π - π stacking interactions around the aromatic ring are in the range of 3.387 – 3.392 \AA , and the distance of the π -stacking interaction in the imidazole ring is 2.882 \AA . The angle between the plane of the hydroxamic acid and the molecule itself is $\sim 86.80^\circ$.

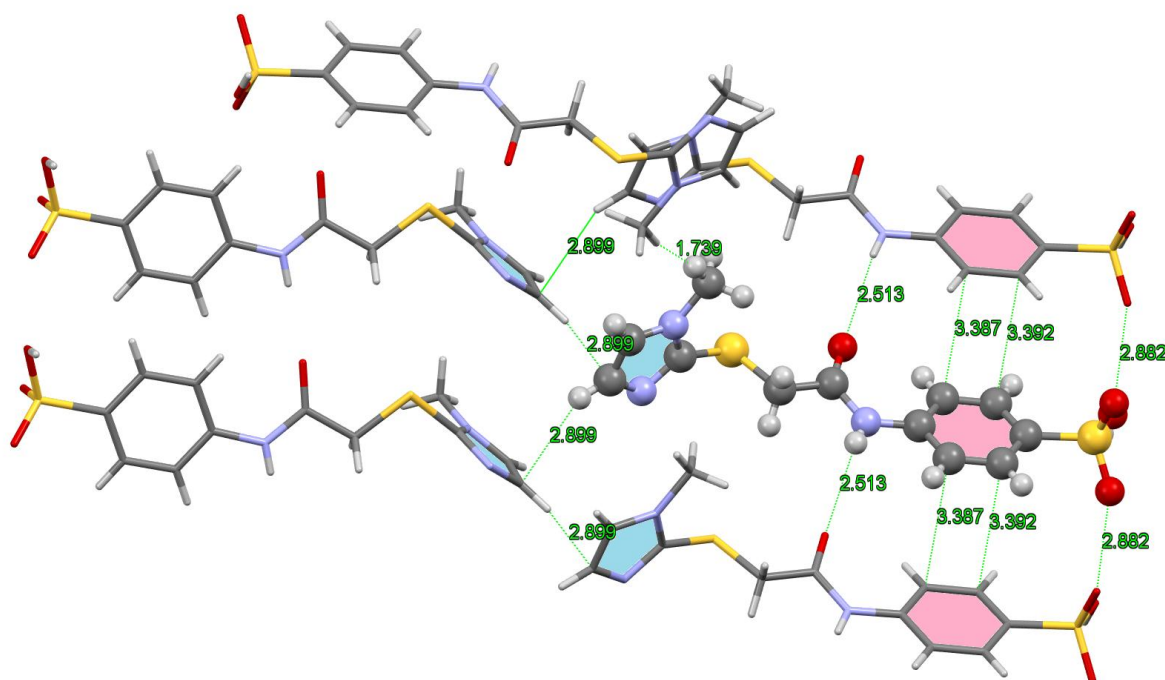


Figure 2. Visualisation of the hydrogen bonds, pi - stacking and C-H...pi and interactions between molecules (dashed lines).

The hydrogen bonds, pi-stacking and C-H...pi interactions between neighbouring molecules make crystal packing possible. Indeed, each molecule is connected to nine other neighbouring molecules with acetamide, sulfonic acid, imidazole and a methyl group (CH₃).

Via 5's Hirshfeld surface, which was generated using CrystalExplorer [37], we observed and analysed the behaviour of the intermolecular interactions in the crystal. The analysis of these intermolecular contacts around the asymmetric unit revealed different interactions computed by the Hirshfeld surface d_{norm} mapping (see Figure 5). Indeed, Figure 5a shows the contributor contacts on the Hirshfeld surface: the red spots represent the shorter hydrogen bonds of the H...H (2.059 Å), N-H...O=C (2.059 Å), S-O...H (2.430 Å) and -S-HO...O-S- (2.882 Å) interactions, whereas the blue and white areas represent the H...S, C...H, N...C, C...C, C...O,

N...O and C...S contacts. The red regions represent the numerous hydrogen bonds on the d_{norm} surface, which is consistent with the results obtained by X-ray diffraction.

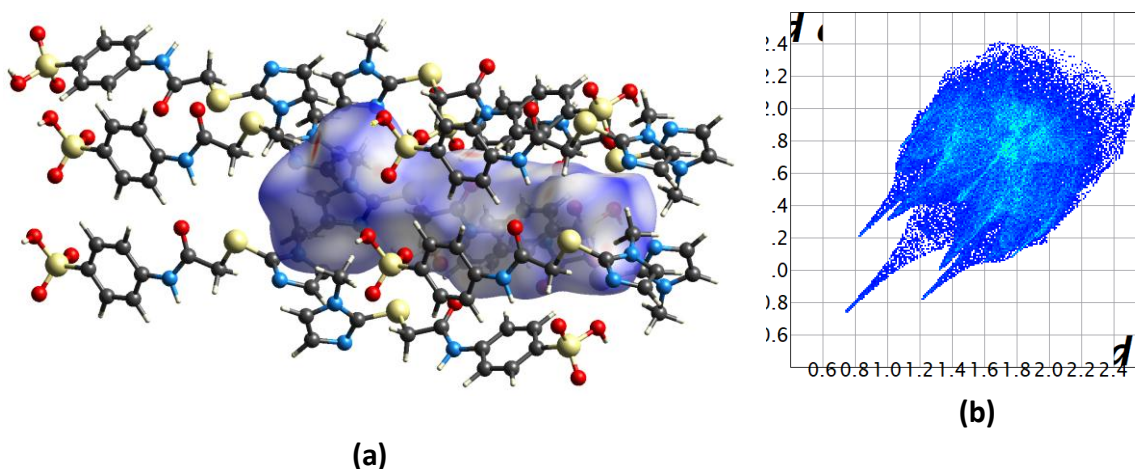


Figure 5. d_{norm} mapped on the Hirschfeld surface for visualizing intermolecular interactions of $C_{12}H_{13}N_3O_4S_2$.

Docking Studies

The binding interactions between **5** and the active residues of sterol 14-demethylase (CYP51) were emphasised using a molecular docking study. Sterol 14-demethylase was chosen as the target enzyme for *C. albicans* inhibition. The docking of **5** into the active sites of the sterol 14-demethylase was performed using the PDB code 6AYB [38]. Calculations were performed using the AutoDock package [39]. Validation of molecular docking was done by re-docking the original ligand ketoconazole into the active site of sterol 14-demethylase, which was reproduced with an RMSD value of 1.203 Å. Stepwise molecular docking studies were reported in our previous study [40].

As seen in Table 3, **5** showed relatively potent antifungal activity against *C. albicans*. In an attempt to determine the binding interactions between **5** and the original docked ligand ketoconazole into the sterol 14-demethylase binding site, the binding energies and number of conventional intermolecular hydrogen bonds established in the stable complexes **5**-sterol 14-demethylase and ketoconazole-sterol 14-demethylase were determined.

Table 2. Docking binding energies, conventional hydrogen bonds and the number of residues closest to the docked compounds (**5** and ketoconazole) into the active sites of sterol 14-demethylase.

	Free binding energy (kcal/mol)	Conventional H-Bonds (HBs)	Number of closest residues to the docked ligand in the active site
5	-7.57	0	MET A360, MET A362, LEU A358, TYR A120, ALA A39
ketoconazole	-13.14	0	MET A360, PHE A216, MET A362, LEU A467, LEU A358, THR A297, CYS A430, ALA A293, PHE A292, PHE A114, VAL A119, ALA A289, TYR A120

The different binding interactions of **5** and ketoconazole into the active binding site of sterol 14-demethylase are represented in Figure 6. The complexes **5**-sterol 14-demethylase and ketoconazole-sterol 14-demethylase display negative binding energies, which may explain their potent antifungal activity. Furthermore, by observing the molecular docking outputs (see Table 3 and Figure 6), the original docked ligand ketoconazole demonstrated a higher (almost double) enzymatic inhibition than **5**. This is mainly due to the high number of interactions established between ketoconazole and the active residues of sterol 14-demethylase. Indeed, ketoconazole interacts with 13 amino acids and the co-factor porphyrin (HEM A501), while **5** interacts with only five amino acids. Interestingly, **5** established strong π -cation and π - σ interactions with the co-factor porphyrin (see Figure 6): the π -cation interaction was established between porphyrin's ferrous ion (Fe^{2+}) and the π electrons of **5**'s imidazole.

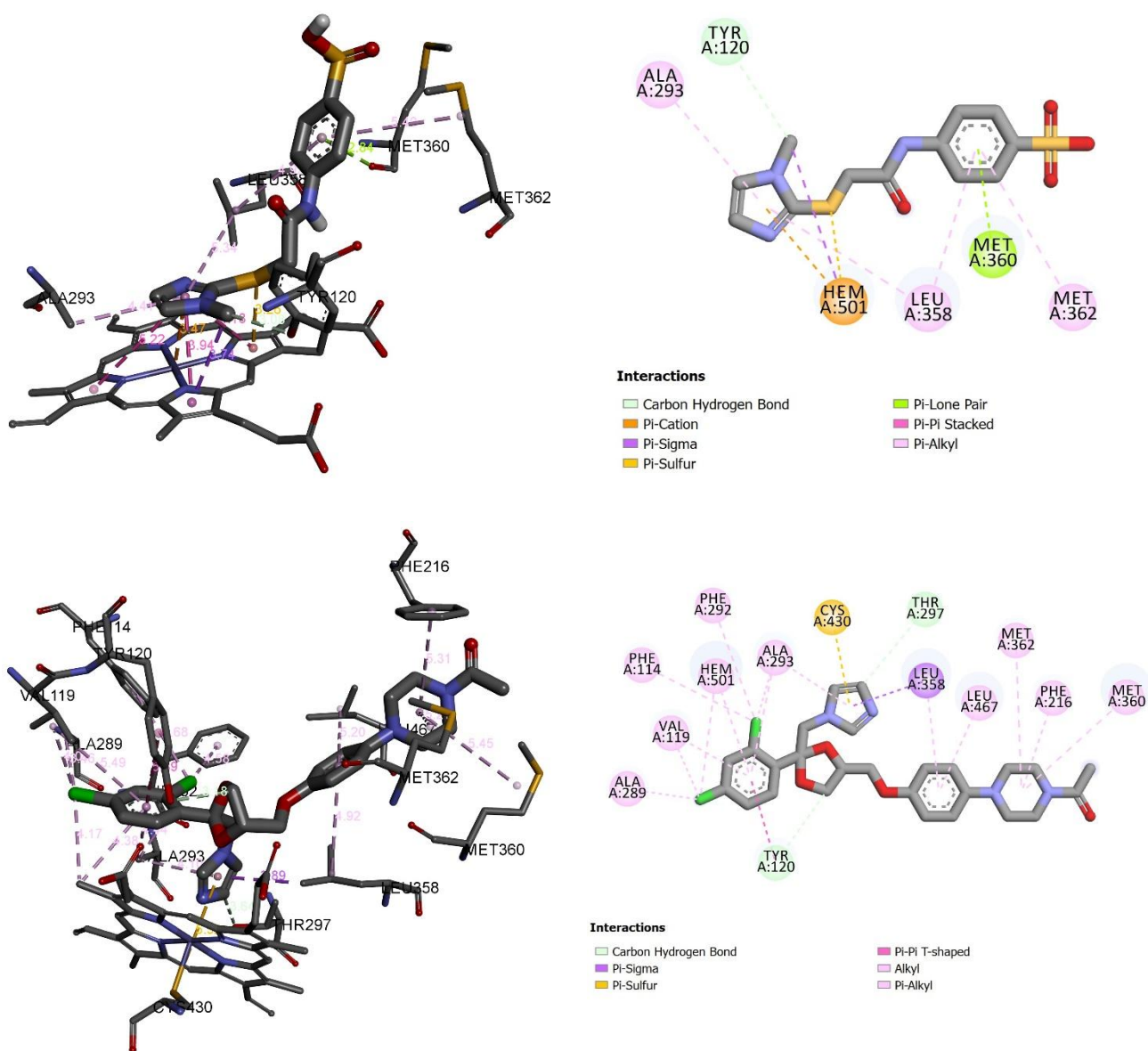


Figure 6. 3D (right) and 2D (left) closest interactions established **5-Sterol 14-**demethylase (up) and **5-Sterol 14-**demethylase (bottom) complexes.

Conclusion

We synthesised a new imidazole derivative 4-[2-(1-methyl-1H-imidazol-2-ylsulfanyl)-acetylamino]-benzenesulfonic acid—via a simple and efficient two-step process. The synthesised derivative was evaluated for its antimicrobial efficiency against four microbial pathogens. In

addition, the compound was characterised using a single crystal technique to confirm its geometric structure. Finally, the inhibitory mechanism was determined using docking studies.

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