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Synthesis, Biological Evaluation and Molecular Docking of Deferasirox and Substituted 1,2,4-Triazole Derivatives as Novel Potent Urease Inhibitors: Proposing Repositioning Candidate

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Abstract. A series of new deferasirox derivatives were synthesized through the reaction of monosubstituted hydrazides with 2-(2-hydroxyphenyl)-4*H*-benzo[*e*][1,3]oxazin-4-one. For the first time, deferasirox and some of its derivatives were evaluated for their *in vitro* inhibitory activity against Jack bean urease. The potencies of the members of this class of compounds are higher than that of acetohydroxamic acid. Compounds **7d** and **7e,** analogs bearing tetrazole and hydrazine derivatives (bioisoester of carboxylate group), represented the most potent urease inhibitory activity with IC_{50} values of 1.268 and 3.254 μM, respectively. *In silico* docking studies were performed to delineate possible binding modes of the compounds with the enzyme, urease. Docking analysis suggests that the synthesized compounds were anchored well in the catalytic site and extending to the entrance of binding pocket and thus restrict the mobility of the flap by interacting with its crucial amino acid residues, CME592 and His593. The overall results of urease inhibition have shown that these target compounds can be further optimized and developed as a lead skeleton for the discovery of novel urease inhibitors

Keywords: Heterocycles • Inhibitors • Deferasirox analogs • Cyclization • Repositioning candidate

Introduction

Urease (urea amidohydrolase: EC 3.5.1.5), is a nickel-dependent metalloenzyme. Followed by the spontaneous hydrolysis of the carbamate to ammonia and carbonic acid, it catalyzes the hydrolysis of urea to yield ammonia and carbamate.[1-4] Urease is broadly distributed in nature among prokaryotes, as well as in eukaryotes, including fungi and plants.[5]

Although there are differences in organization and number of whole enzyme subunits in nature, the structure of the active site around the nickel(II) ions is conserved and has a consequence of the similar catalytic activity.[6]

Ammonia production leads to an increase in the local pH. Thus urease activity plays an essential role in the pathogenesis of human and animal diseases, including urinary stones, peptic ulcers, hepatic encephalopathy, and, more importantly, gastric cancer, which is the second leading cause of cancer-related deaths worldwide.[7] The most substantial known risk factor for developing peptic ulcers and gastric cancer is the urease activity of *Helicobacter pylori* (*H. pylori*), which helps to neutralize the stomach acid, making a more hospitable environment for this pathogen.[8, 9] Consequently, besides other targets for controlling *H. pylori* infection,[10] urease inhibitors have recently drawn significant attention as potential drugs for gastric and urinary tract infections.[11, 12]

During current years, several structural classes of urease inhibitors have been reported including hydroxamic acids,[13-15] phosphoramidates,[16] urea and thiourea derivatives,[17, 18] oxoindoline and isoindolin-1-one derivatives,[19, 20] polyphenols, isoniazids,[21] thiosemicarbazones,[22-24] benzimidazoles,[25] benzophenone sulfonamides,[26] catechol-based inhibitors,[27] diflunisal derivatives,[28] aryl urea-triazole-based derivatives,[29] 1,3,4-oxadiazoles,[30] cinnamate-based phosphonic acids,[31] coumarin-hybrids,[32] and metal complexes.[33]

The mode of action of the above inhibitors is based on two main mechanisms. The first one is the non-competitive inhibition mechanism. These types of inhibition can be obtained by compounds containing groups that are reactive to thiol groups, which can interact with Cys592 forming an enzyme-inhibitor complex. It was hypothesized that the active site flap in these enzyme-inhibitors complex is unable to completely close, a position that is essential for the correct accommodation of the catalytic residues such as His593.[34]

The other mechanism is based on competitive inhibition. Most of these inhibitors, like hydroxamic acid and imidazole [35], are suitable metal chelators, and their mechanism of inhibition involves binding to the metal ions of the enzyme active site. Nevertheless, regardless of the chemical class of the compounds, it is reported [1, 36] that “only a few functional groups with electronegative atoms such as oxygen, nitrogen and sulfur act either as bidentate, tridentate or as ligand chelator to form octahedral complexes with two slightly distorted octahedral nickel atoms of the enzyme.” Deferasirox (DFX) is a new and essential oral tridentate chelator that binds to the metallic center with a ratio of 1:2. It is used to remove the toxic metals in the case of iron overload disease and was approved for treating iron overload diseases such as ß-thalassemia.[37] Farkas *et al.* showed that like Fe ion, iron chelators could coordinate with other metals such as Ni(II), Zn(II), and Cu(II) ions. Additionally, this study indicated that the formation of nickel and iron chelation starts above pH ca. 5.[38]

DFX has a 1,2,4-triazole ring and two phenolic groups that, as electron donor groups, are considered to be useful metal chelators with various affinity [37, 39] (Figure **1**). Furthermore, the heterocyclic 1,2,4-triazole moiety has attracted considerable attention in medicinal chemistry due to its wide range of pharmacological activities, low toxicity, and high bioavailability.[40, 41]

Among different classes of heterocyclic compounds, 1,3,4-oxadiazole, 1,3,4-thiadiazole, and 1,2,4-triazole have been found able to interact with the urease nickel metallocenter, which results in urease inhibitory activity.[42, 43] The high potency of these compounds over all other inhibitors of ureases can be attributed to the fact that Ni ions of urease have a higher affinity for nitrogen-based ligands, thereby stabilizing the binding of N substituents of the inhibitors’ pharmacophores.[44]

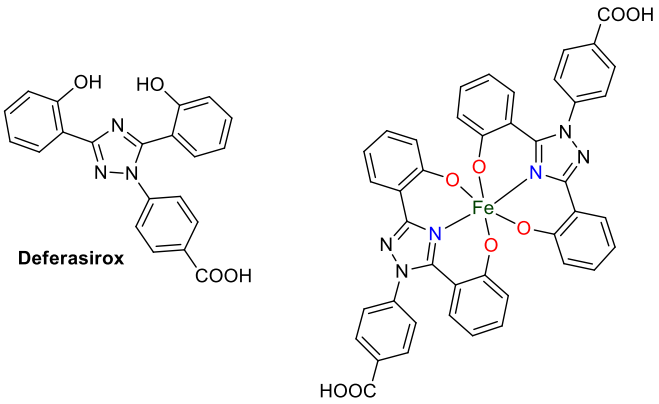
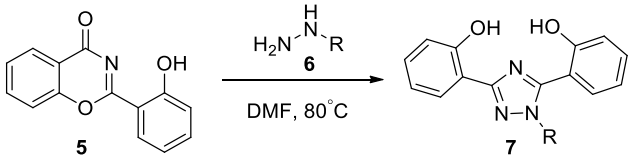


Figure 1. The structure of DFX and its complexation with iron.

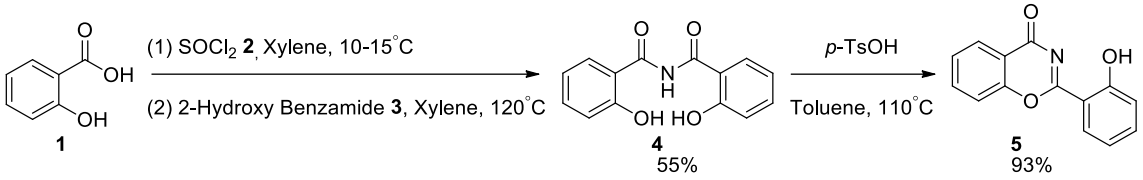
These observations stimulated our interest to study the urease inhibitory activity of the DFX and some of its new derivatives for the first time and investigate the role of –OH and various substituted 1,2,4-triazole groups in the inhibition of urease activity. In this regard and continuation of our research interest in the synthesis of heterocyclic skeletons [45-50], we report an efficient procedure for the synthesis of some DFX analogs, (*N*-substituted *bis*-hydroxyphenyl-1,2,4-triazoles), containing triazole backbone (Scheme **1**). The present article, therefore, describes urease inhibitory properties of newly synthesized compounds and investigates their mode of molecular interaction to reveal the probable mechanism class of these compounds, including complexation of nickel ions, blocking the active channel site, or the possibility of covalent interaction with a cysteine residue.



Scheme 1. Synthesis of deferasirox analogs containing triazole moiety.

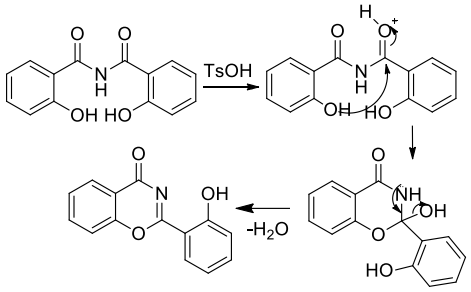
Results and Discussion

In the beginning, 2-hydroxybenzoic acid **1** was reacted with thionyl chloride **2** to obtain benzoyl chloride, which was then reacted with 2-hydroxy benzamide **3** to yield compound **4** in 55% yield. Spectroscopic data confirmed the structure of **4**. The IR spectrum of **4** showed a band of -NH stretching located at 3250 cm^{-1}, and the carbonyl C=O stretching band was observed at 1692 cm^{-1}. ^1H NMR spectrum of compound **4** exhibited a singlet at δ 10.98 ppm for –NH amide. Thus, these data confirm the successful synthesis of compound **4**. In the next step, the cyclization of compound **4** was investigated using *p*-toluenesufonic acid (*p*-PTSA) to access the benzoxazinone **5**. Spectroscopic data confirmed its structure, and its purity was established based on the pharmacopeia. The schematic representation of the acid-catalyzed cyclization reaction is shown in Scheme **2**.



Scheme 2. Synthesis of benzoxazinone **5.**

The proposed mechanism for the synthesis of benzoxazinone **5** through cyclization reaction is shown in Scheme **3**.

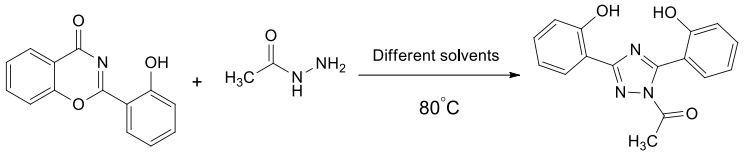


Scheme 3. Proposed mechanism for the acid-catalyzed synthesis of benzoxazinone **5.**

In the final step, the cyclization reaction of compound **5** was achieved using 4-hydrazinobenzoic acid in DMF at 80 ºC to afford the final DFX.

With the optimized reaction conditions in hand (Table 1), we next studied the scope and limitations of reaction by employing five types of hydrazines and hydrazides, which resulted in the formation of compounds **7a-e** in good to excellent yields in DMF at 80 ºC (Scheme **4**).

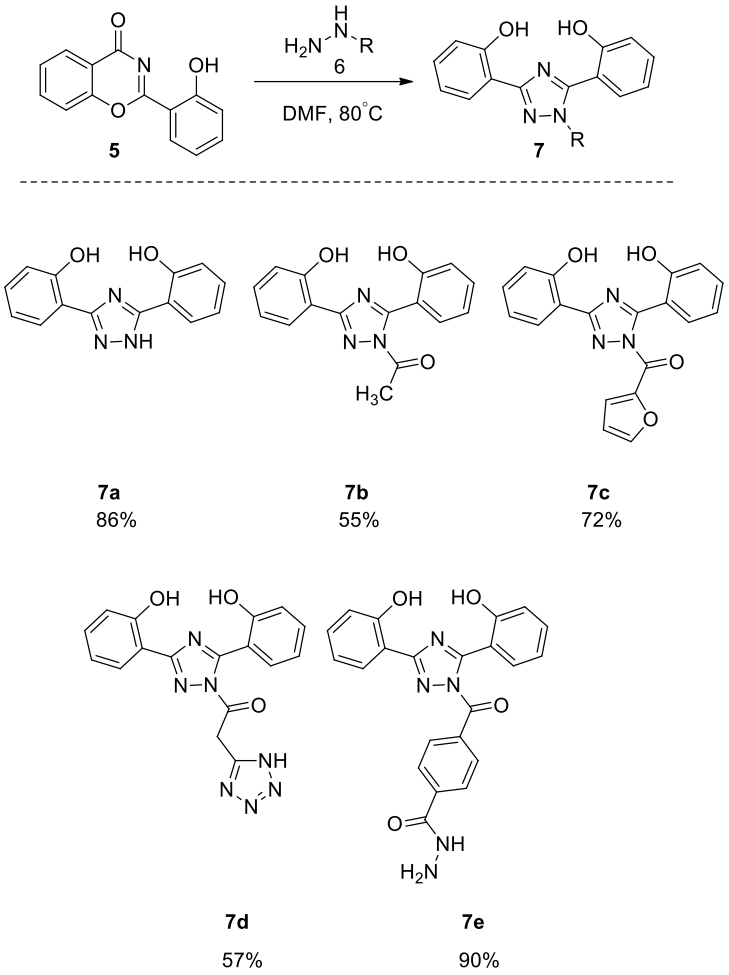
Table 1. The optimization of reaction condition in the synthesis of 1-(3,5-bis (2-hydroxyphenyl)-1H-1,2,4-triazol-yl) ethan-1-one **7b**.



5 **7b**

Entry	Solvent	Time (h)	Yield (%)[a]
1	EtOH	3.5	30
2	EtOH/H_2O (1:1)	4	35
3	CH_3CN	4.5	30
4	DMF	2	55

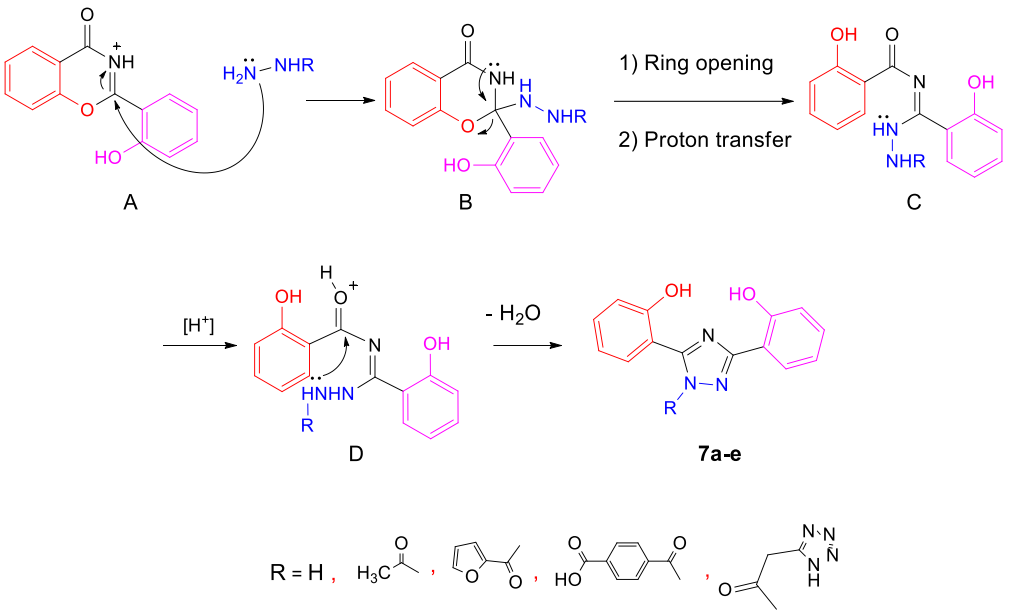
[a] Isolated yields.



Scheme 4. Synthesis of DFX derivatives.

The absence of the amidic hydrogen in all ^{1}H NMR spectra confirmed the cyclization reaction and access to the target products **7a-e**, which was further supported by the distinguished peak at 151.5-159.0 ppm in ^{13}C NMR spectra related to =CH in triazole ring. Furthermore, the HR-MS data confirmed the molecular formula of the synthesized compounds. 2-(1*H*-Tetrazol-5-yl) acetohydrazide as one of the starting materials in the cyclization reaction was synthesized from the reaction of ethyl cyanoacetate with sodium azide and then reaction with hydrazine hydrate. It was selected as one of the members of this library because of more nitrogen atoms in its structure that result in higher activity.

The most probable mechanism for the synthesis of compounds **7a-e** is shown in Scheme **5**. Benzoxazinone ring-opening occurred followed by protonation of benzoxazinone (formation of intermediate **A**), and the nucleophilic addition of hydrazine or hydrazide led to intermediate **B**. Then, after ring-opening and proton transfer, intermediate **C** is formed. Finally, in the acidic media, triazole ring formation was carried out through intermediate **D** (Scheme **5**).



Scheme 5. The proposed reaction mechanism for the synthesis of DFX and its analogs **7a-e.**

Urease inhibitory activity of the synthesized compounds was evaluated according to the Berthelot urease assay method[51, 52] and compared with acetohydroxamic acid (AHA) as the positive control (Table **2**). Interestingly, all compounds showed significantly higher urease inhibition (in a range of 48.35± 0.23 to 1.27± 2.03 µM) in comparison to AHA (IC_{50} = 100 ± 2.49 µM). Among the investigated compounds, compounds **7d** and **7e** having tetrazol-5-yl and benzohydrazide moieties in their structure were set up to be the most effective compounds with IC_{50} values of 3.25 ±1.80 and 1.27 ± 2.03 µM, respectively. On the other hand, compound **7a** with no substituent and **7c** with acetoxy substituent showed reduced activities (IC_{50} value of 48.35± 0.23 and 7.34± 2.19 µM), respectively. These findings reveal that 3,5-*bis*(2-hydroxyphenyl)-1*H*-1,2,4-triazol-1-yl) scaffold that has substituents present in the 1,2,4-triazol-1-yl part, can be considered as a potential lead for new *H. pylori* urease inhibitors.

Molecular modeling

The dependability of the applied docking protocol was measured using re-docking of acetohydroxamic acid (AHA) into the active site of the JBU. The essential characteristic of a good docking program is its ability to reproduce the experimental or crystallographic binding modes of ligands. Evaluating this issue, a ligand is taken out of the X-ray structure of its protein-ligand complex and re-docked into its binding site. The docked binding mode is then compared with the experimental binding mode, and the RMSD is calculated; a prediction of a binding mode is considered successful if the RMSD is below a specific value (usually<2.0 Å). The urease active site which located in $(\alpha\beta)_8$ TIM barrel domain and the surrounded residue composition is shown in Figure **2a**. Figure **2b** shows the superimposed structure between the docked and the experimental binding mode for AHA over JBU in which the RMSD value was within the cutoff limit of 1.02 Å. Therefore, the performed docking procedure was applied to evaluate the interaction between newly synthesized compounds **7a**-**e** and DFX over the JBU active site in comparison to the AHA reference urease inhibitor. The top-scoring pose of compounds was analyzed inside the binding site of JBU.

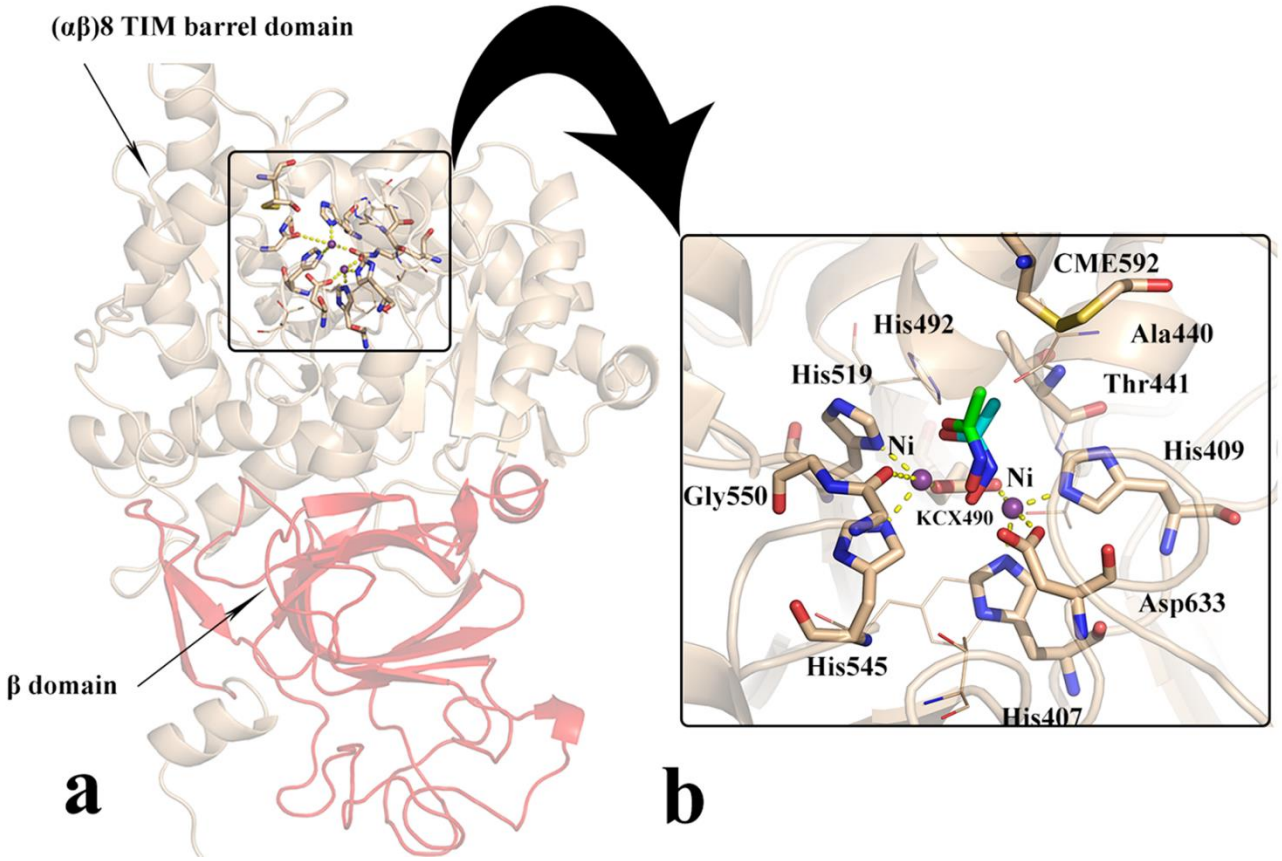
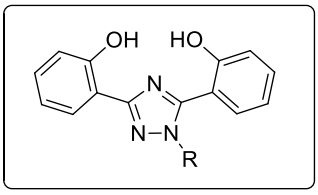


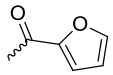
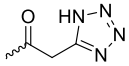
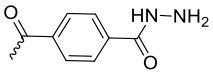
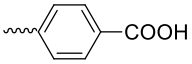
Figure 2. The location of JBU active site over C-terminal ($\alpha\beta$)$_8$ TIM barrel domain (a), Close-up representation of the active site, the AHA co-crystallized, and the corresponding re-docked form are represented in green and cyan color, respectively (b).

In the binding model, all compounds were successfully occupied in the bi-nickel active site cavity. The scores of the docking energy of the synthesized compounds varied from −4.28 to −7.78 Kcal mol^{-1}, proposing that the binding interaction differs as the functional group is varied (Table **2**).

Table 2. Docking energy and IC$_{50}$ values of compounds **7a-e** over JBU



Compound	R	IC$_{50}$ ± SD (µMol)	Docking energy (Kcal mol^{-1})
7a	H	48.35 ± 0.23	-4.28 (1*H*) -3.10 (4*H*)
7b		-	-5.25

7c		7.34± 2.19	-6.34
7d		1.27 ± 2.03	-7.78
7e		3.25 ±1.80	-7.66
DFX		16.64 ±1.13	-8.27
AHA	-	100 ± 2.1	-4.74

Based on docking results, the synthesized compounds oriented in two distinct poses relative to the bi-nickel center over the active site. Figure **3a** exhibits the first pose, including compounds **7d**, **7e**, and DFX, in which the (3,5-*bis* (2-hydroxyphenyl) moiety (shown in red color) adapts flexible conformation in the large hydrophobic opening of the active site pocket. In contrast, the N_1 substitution on the 1,2,4-triazole ring (shown in yellow color) tends to orient toward the two nickel atoms. The next pose includes compounds **7a**, **7b**, and **7c**, which adapted in a manner that one of the 2-hydroxyphenyl moieties pointed toward the metals at the center and the remaining part of the molecule occupied the surrounding hydrophobic pocket (Figure **3b**).

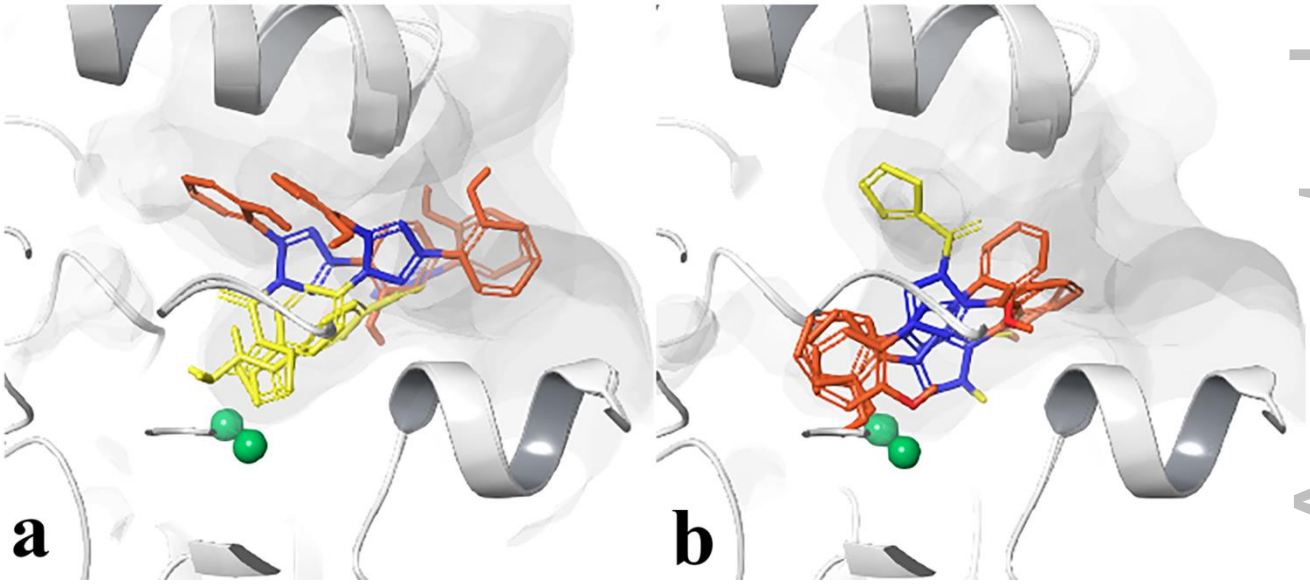


Figure 3. Representation of two different docking poses of compounds relative to bi-nickel center over JBU active site: Compounds with 1,2,4-triazole-N_1 substituted oriented toward the metal center (a), and compounds with 2-hydroxyphenyl pointed one (b) (3,5-*bis*(2-hydroxyphenyl) moiety, related N_1 substitution and 1,2,4-triazole ring are shown in red, yellow, and navy, respectively.

According to the docking binding energy calculations, compounds **7d** and **7e** have the lowest free energy of docking (−7.78 and -7.66 Kcal mol^{-1}, respectively), which is inconsistent with the result of the highest inhibitory activity over JBU active site.
Figure **4** gives an explanation and understanding of molecular interactions of AHA and DFX into the binding site of JBU. As shown in Figure **4a,** AHA forms one H-bond with Asp633 by donating hydrogen and two ionic bonds with two Ni^{2+} ions. Also, the binding

mode of DFX was depicted in Figure **4b**, which revealed that like AHA carboxylate group pointed to the bi-nickel ion center. Besides, DFX formed a π-π stacking with His593 and two H-bond interactions from its 2-hydroxyl group with Ala440 (C=O) and CME592 (-OH). The binding modes of DFX suggested that it positioned more stably into the urease binding pocket by interacting with Ni^{2+} ions (mimicked the binding mode of the reference drug AHA) and key residues His593 and CME 592. Thus, these interactions supported lower docking energy (-8.27 vs. -4.74 Kcal mol^{-1}) and higher anti-urease activity than the AHA (16.64 ±1.13 vs. 100 ± 2.1 µMol).

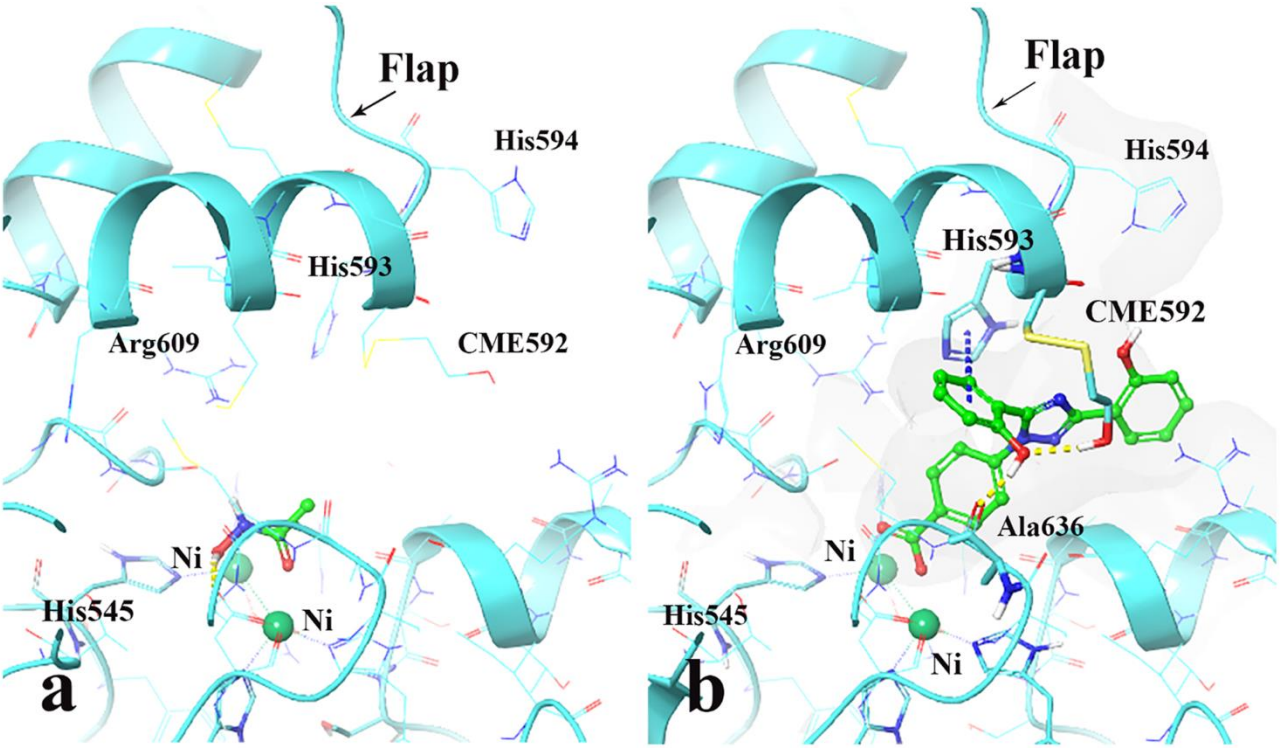


Figure 4. Molecular docking representation of AHA (a), and DFX (b) over JBU active site. H-bond and π – π staking are shown in yellow and navy, respectively**.**

Figure **5a** shows the 1-(1*H*-tetrazol-5-yl)propan-2-one moiety of compound **7d** oriented along the bi-nickel center through salt bridge interaction and formed π-π stacking with His492 and His519. The other part of compound **7d** consists of 3,5-*bis*(2-hydroxyphenyl)-1*H*-1,2,4-triazole moiety in which 2-hydroxyphenyl groups formed H-bond interaction with Asp494 and Ala636. Also, the phenol ring center interacted with His593 through π-π interaction. In the docked conformation of compound **7e** (Figure **5b**), the benzohydrazide moiety pointed to the Ni^{+2} ions center. In addition, the NH_2 group of hydrazide interacted with H-bonding to the backbone carbonyl (C=O) of Gly550 and carboxylate side chain of Asp633 (1.9 Å and 2.3 Å). The proximal 2-hydroxyphenyl ring interacted with Arg439 through H-bond and charge-cation interactions. Furthermore, the other 2-hydroxyphenyl group and the 1,2,4-triazole moiety contacted with H-bonding interaction Ala436 (C=O) and CME592, respectively.

As mentioned above, like the carboxylate group of DFX, the tetrazol-5-yl moiety of compound **7d** and benzohydrazide group of compound **7e** pointed toward the existed positive field around two Ni^{2+} ions. Both of these groups have the potential to produce ionized form as a result of weak acidic character. The resulting carbanion is stabilized to a considerable degree due to the additional aromatic delocalization of negative charge (Figure **6**). In other words, this resonance stabilized con base may mimic the behavior of the hydroxyl oxygen in AHA, which acts to stabilize the tetrazol-5-yl moiety and the benzohydrazide group with the surrounded positive field of the Ni^{2+} ions.

Moreover, based on the ability of hydrazide and tetrazole functional groups to bridge transition metals [53, 54], one of the nitrogen atoms in both of the mentioned groups may coordinate with the nickel ion, which is reminiscent of the behavior of the carbonyl oxygens in AHA.

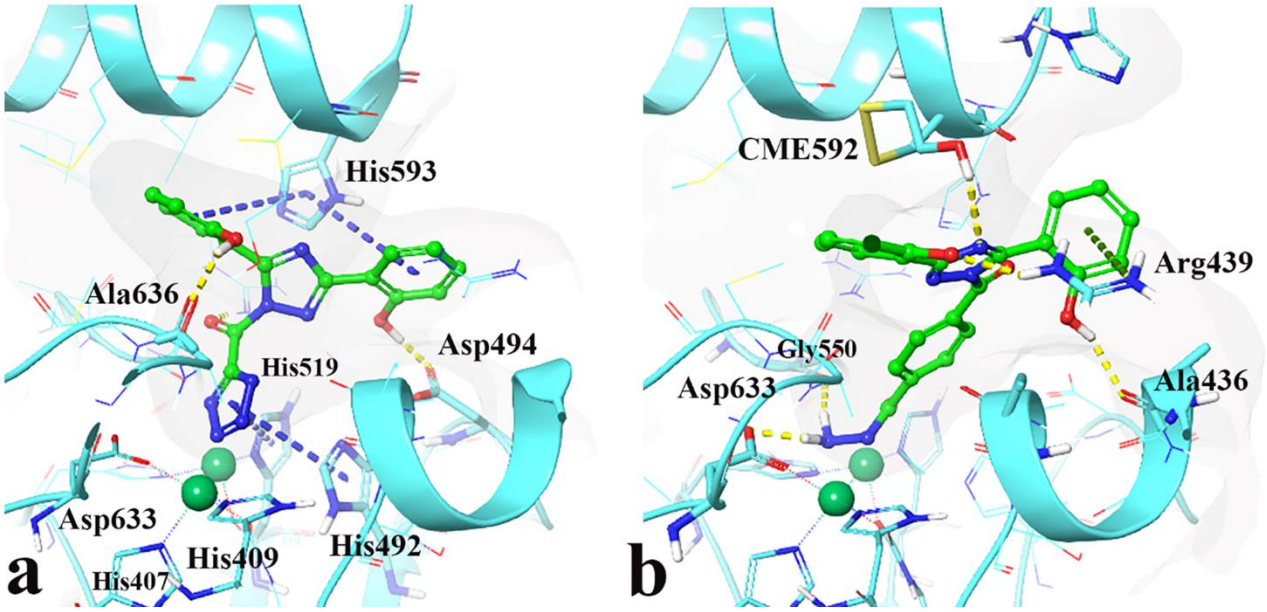


Figure 5. Molecular docking representation of tetrazol-5-yl derivative, **7d** (a), and benzohydrazide derivative, **7e** (b) over JBU active site. H-bond, π – π staking, and π –cation interactions are shown in yellow, navy, and green, respectively**.**

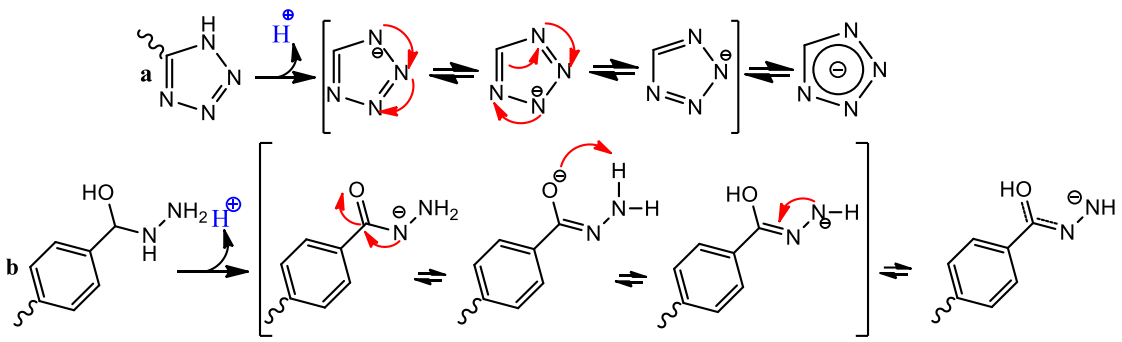


Figure 6. Representation of the aromatic stabilization and tautomerization of tetrazol-5-yl (a) and benzohydrazid (b)

Unlike the above structures, compound **7a** with no substitution on the 1,2,4-triazole ring, and compounds **7b** and **7c** with acetoxy and 1-(furan-2-yl)ethan-1-one moieties, respectively, which cannot be ionized or being metal coordinated, resulted in interacting with different manner over JBU active site pocket.

The interaction patterns shown in Figure **7** represent different poses rather than those of compounds **7d** and **7e**. In all compounds **7a-c**, beside chelation of the oxygen atom of one of the proximal 2-hydroxyphenyl groups with the bi-nickel center in the catalytic site, the related phenyl group forms π – π stacking with His545. Further stability was due to the formation of hydrophobic π–π stacking interactions of the distal 2-hydroxyphenyl group of compounds **7b** and **7c** with the active site flap His593, hence resulting in urease active site inhibition (Figures **7c** and **7d**).

Furthermore, as compound **7a** could be in two distinct tautomers (1*H* and 4*H*-1,2,4 triazol), it can lay in two slightly different poses over the active site. Docking result showed although they contributed to H-bonding and hydrophobic interactions with the active site residues, there are some differences in the way both tautomers coordinated with the center of bi-nickel. The alteration in the interaction pattern is shown in Figures **7a** and **7b**.

In the case of 4*H* tautomer, the 1,2,4-triazole ring was stabilized by charge-transfer interaction with Arg633 and contributed H-bond interaction through its –NH group to Ala636 (C=O). Consequently, it went closer to the helix-turn-helix motif over the active-site cavity so it could interact with His593, while the 1,2,4-triazolo ring of the 1*H* tautomer just contributed in π -π and H-bonding with His519 and Ala440, respectively and it could not interact with any of the flap residues at the entrance of the active site channel. The difference in interaction mode between **7a** 4*H* and 1*H* tautomers was reflected in different docking binding energies of -4.28 and -3.10 Kcal mol^{-1}, respectively.

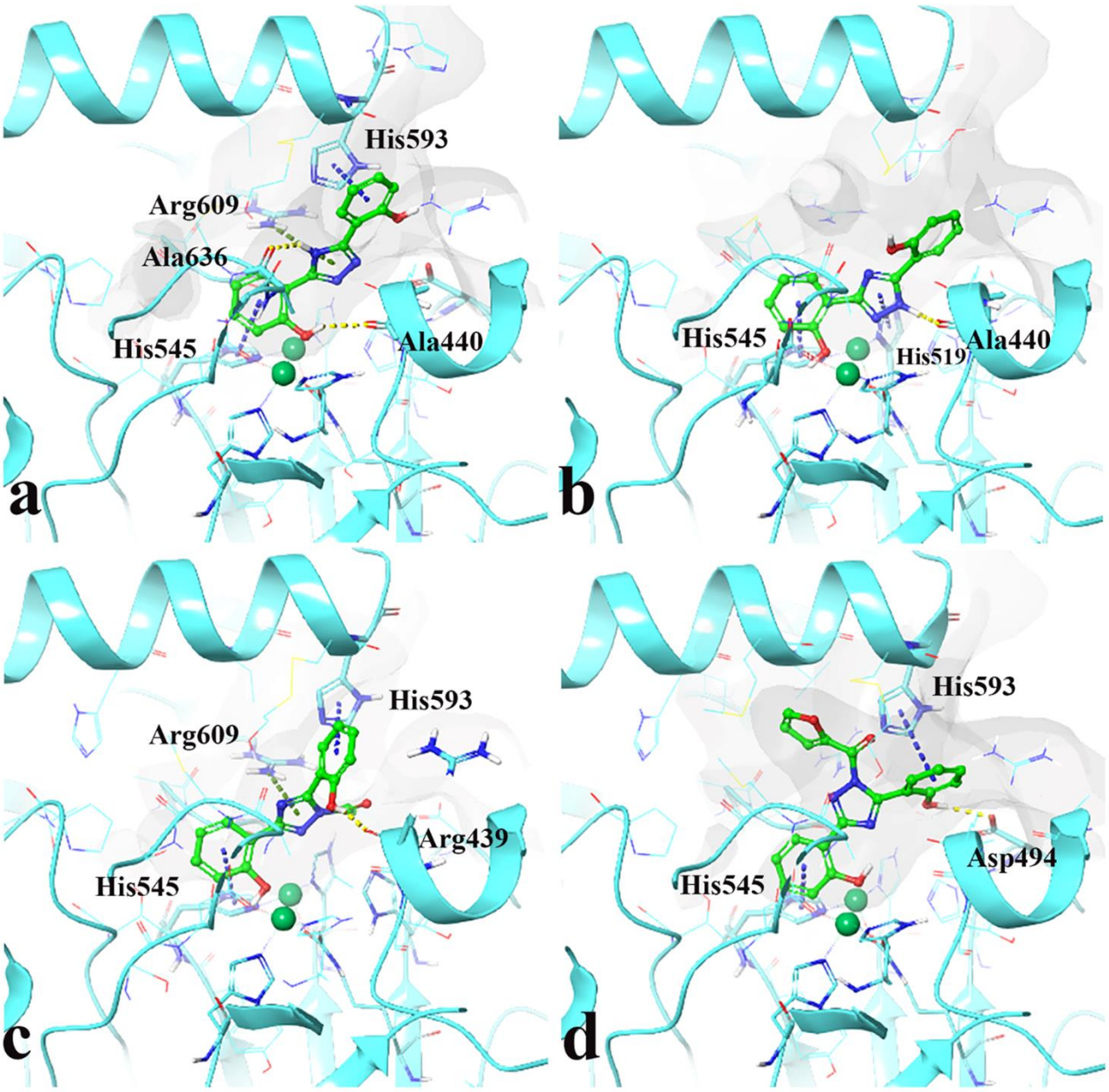


Figure 7. Docking mode of compounds **7a** (4*H* tautomer) (a), **7a** (1*H* tautomer) (b), **7b** (c), and **7c** (d) over JBU active site. H-bond, π – π stacking, and π –cation interactions are shown in yellow, navy and green, and cyan, respectively.

Conclusions

We have developed an efficient method for the synthesis of DFX derivatives using the reaction of benzoxazinone and hydrazide derivatives to obtain 1,2,4-triazoles through cyclization reaction with good to high yields efficiency.

Using this approach, a novel class of urease inhibitors was identified with significant biological activities. This is the first study to investigate the inhibition activity of deferasirox and some of its derivatives over jack bean urease. The potencies of this class of compounds are higher than those of acetohydroxamic acid. Among the series compounds **7d** and **7e,** the analogs bearing tetrazole and hydrazine derivatives (bioisoester of carboxylate group) provided the highest urease inhibition activity. These compounds can be in the form of conjugated base orienting toward the positive field around the bi-nickel center.

According to the docking analysis, DFX and the synthesized compounds were harbored well in the catalytic site. They interacted like ligand chelator (substrate-like inhibitor) and, at the same time, took advantage of interacting with the entry of active site channels, accordingly, limited the flexibility of the helix-turn-helix motif which known as flap by interacting with His593 or CME592 as the critical amino acid residues.

Generally, although the exact mechanism of urease inhibition of our test compounds is not known, deferasirox repositioning can be proposed by our investigation in which this structure can be further optimized and developed as the lead for urease inhibition activity, and it is intriguing to investigate detailed kinetics of such interaction.

Experimental Section

Urease inhibition assay

The enzyme assay was performed by the Berthelot alkaline phenol-hypochlorite method. This method is based on the release of ammonia (NH_3), which reacts with hypochlorite (OCl^-) to form a monochloramine.[51, 52] This product then reacts with phenol to form blue-colored indophenols that its absorbance is measured at 625 nm. In brief, 10 μl of enzyme solution was incubated with 140 μl of urea and 5 μl of inhibitor at a final concentration of 25 mM in phosphate buffer solution (pH 7.6, 100 mM) for 15 min at 37°C. The ammonia liberated was estimated using 500 μl of solution A (containing 5.0 g phenol and 25 mg of sodium nitroprusside) and 500 μl of solution B [containing 2.5 g sodium hydroxide and 4.2 ml of sodium hypochlorite (5% chlorine) in 500 ml of distilled water] at 37°C for 30 min. The absorbance was measured at 625 nm against the control. For all analyzed compounds, the values of IC_{50} were calculated using GraphPad Prism 5 software (GraphPad Software, Inc., San Diego, CA).

Molecular docking procedure

To find out the interactions mode of designed molecules over the urease enzyme, the flexible docking study was performed on Autodock 4.2.6 software.[55] The X-ray crystallographic structure of *Jack bean* urease (JBU) (in complex with acetohydroxamic acid, AHA) was downloaded from the Protein Data Bank (PDB ID; 4h9m) (www.rcsb.org). The urease are reported to be functionally active in a monomeric state, then all the docking studies were performed on a single monomer. Also, the prosthetic group and co-factors are not directly involved in urease inhibition, so they removed before docking investigation. Water molecules and co-crystallized ligands were removed from the enzyme's crystallographic structures. The pKa values of the residues in the enzyme were calculated to determine if any of them were likely to adopt nonstandard ionization states, using PROPKA 2.0.[56] The side chains of the lysine, arginine, and histidine residues were protonated, while the carboxylic groups of glutamic acid and aspartic acid were deprotonated. After adding polar hydrogens and partial atomic charges, the enzyme structures saved in PDBQT. A grid box of 60× 60× 60 Å (x, y, and z) created at the center of the enzyme's active pocket with the spacing of 0.375 nm in each dimension to evaluate the ligand-protein interactions. The center of the grid box set to the center average coordinates of the crystallographic AHA over JBU structure. The 2D structures of all synthesized compounds were drawn in Marvin 15.10.12.0 program (http://www.chemaxon.com)[57] and converted into PDB. Gasteiger charges assigned and saved in PDBQT file format. Of the three different search algorithms offered by AutoDock 4.2.6, the Lamarckian genetic algorithm (LGA) consisting of 100 runs, 25×10^6 energy evaluations, and 27,000 generations was applied. Other docking parameters were set to default. Cluster analysis was performed on the docked results by means of a root mean square (RMS) tolerance of 2.0 Å.

Description of the active site of JBU

The JBU consists of two domains; $(\alpha\beta)_8$ TIM barrel domain and β domain. The Ni^{2+}–Ni^{2+} distance is 3.4 Å. These two Ni^{2+} ions are bridged by a carbamylated lysine (KC490) through its O atoms. One of the Ni^{2+} ions is coordinated by His407 (NE2), His409 (ND1), Asp633 (NE2), and KCX490 (OQ1), and the other is coordinated by His519 (NE2), His545 (NE2), KCX490 (OQ2), and Gly550 (OD2). Also, Arg439, CME592, and His593 located at the mouth of the active site channel. CME592 (modified Cys592), located on the mobile flap, is an essential residue and highly conserved in many ureases. Other pocket residues are Ala440, CME592, Gly550, Ala636, Met637, His492, Thr441, and Arg609.[58]

Supplementary Material

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/MS-number, which contains the detailed procedure for synthesis and characterization of all compounds.

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Author Contribution Statement

RSA, NSA, VFV, and SB performed the experiments, analyzed the data, and wrote the paper. HA and MA contributed to docking, the analysis of the data, and the writing of the article. SM and NS contributed samples/reagents/materials/analysis tools analyzed the data. MA and MB conceived and designed the experiments. All authors read and approved the final manuscript.

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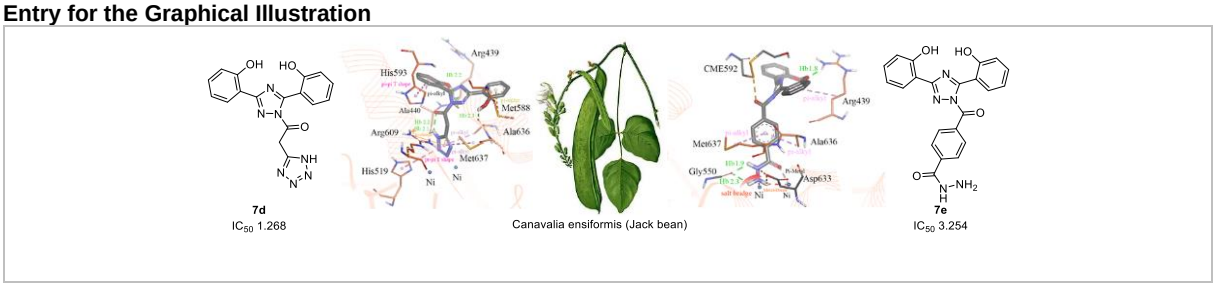
Entry for the Graphical Illustration



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For the first time, deferasirox and some of its derivatives were evaluated for their *in vitro* inhibitory activity against Jack bean urease.