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Original article

Synthetic transformation of 6-Fluoroimidazo[1,2-a]Pyridine-3-carbaldehyde into 6-Fluoroimidazo[1,2-a]Pyridine-Oxazole Derivatives: *In vitro* urease inhibition and *in silico* study

Rafaqat Hussain [a], Wajid Rehman [a,*], Fazal Rahim [a], Ayman M. Mahmoud [b], Mohammed M Alanazi [c], Shoaib Khan [a], Liaqat Rasheed [a], Imran Khan [a]

[a] Department of Chemistry, Hazara University, Mansehra 21120, Pakistan
[b] Department of Life Sciences, Faculty of Science and Engineering, Manchester Metropolitan University, Manchester, UK
[c] Department of Pharmaceutical Chemistry, College of Pharmacy, King Saud University, P. O. Box 2457, Riyadh 11451, Saudi Arabia

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ABSTRACT

Purpose: Ulcer is a serious disease that is caused due to different bacteria and over usage of various NSAIDs which caused to reduce the defensive system of stomach. Therefore, some novel series are needed to overcome these issues.
Methods: Oxazole-based imidazopyridine scaffolds (**4a-p**) were designed and synthesized by two step reaction protocol and then subjected to urease inhibition profile (in vitro). All the newly afforded analogs (**4a-p**) were found potent and demonstrated moderate to significant inhibition profile.
Results: Particularly, the analogs **4i** (IC_{50} = 5.68 ± 1.66 μM), **4o** (IC_{50} = 7.11 ± 1.24 μM), **4 g** (IC_{50} = 9.41 ± 1.19 μM) and **4 h** (IC_{50} = 10.45 ± 2.57 μM) were identified to be more potent than standard thiourea drug (IC_{50} = 21.37 ± 1.76 μM). Additionally, the variety of spectroscopic tools such as ^{1}H NMR, ^{13}C NMR and HREI-MS analysis were employed to confirm the precise structures of all the newly afforded analogs.
Discussion: The structure–activity relationship (SAR) studies showed that analogs possess the substitution either capable of furnishing strong HB like –OH or had strong EW nature such as -CF_3 & –NO_2 groups displayed superior inhibitory potentials than the standard thiourea drug. A good PLI (protein–ligand interaction) profile was shown by most active analogs when subjected to molecular study against corresponding target with key significant interactions such as pi-pi stacking, pi-pi T shaped and hydrogen bonding.

1. Introduction

Urea is the primary nitrogenous waste product of biological system and is easily metabolized by bacteria (Qin et al., 1994, Pervez et al., 2008, Smith et al., 2023). The urease enzyme (EC 3.5.1.5) is found in plants, bacteria and fungi. It is crucial to the nitrogen cycle because it catalyzes the hydrolysis of urea into carbon dioxide and ammonia at a rate that is around 1014 times faster than a non-catalyzed reaction (Ara et al., 2007, Arshad et al., 2017, Naz et al., 2020) and enhanced the microorganism growth by providing nitrogen. In the hydrolysis of urea, the urease plays an important role but excessive amounts of it can have negative effects on living things and harm the environment and the economy (Bremner 1996). Urease hyperactivity causes a variety of clinical issues in both humans and other animals, including infection-induced reactive arthritis, peptic ulcers, pyelonephritis and kidney stones (Ashraf et al., 2013). It is also necessary for Helicobacter pylori to colonize human stomach mucosa. The ammonia developed by the urea hydrolysis is hazardous for several stomach cell lines and serves as a favorable environment for the growth of *H. pylori*, which can cause ulcers and gastric cancer. Additionally, it has been noted that urease promotes the development of infectious kidney stones brought on by *Proteus mirabilis* and *Yersinia enterocolitica* (Bayerdörffer and Ottenjann 1988, Mobley et al., 1995). In

* Corresponding author at: Department of Chemistry, Hazara University-21120, Pakistan.
E-mail address: sono_waj@yahoo.com (W. Rehman).

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agricultural industry, high soil urease concentrations can quickly break down the fertilizer urea and cause phytopathic consequences. Furthermore, crop yields suffer due to the loss of volatilized ammonia (Gioacchini et al., 2002, Lodhi et al., 2013, Taha et al., 2016). Due to the role of urease in a variety of clinical disorders and for agricultural applications, the identification of effective and secure urease inhibitors is a crucial field in pharmaceutical and plant research (Taha et al., 2015, Al-Rooqi et al., 2023). The N-Containing heterocyclic compounds are also crucial for the research of biological activity and for use in pharmaceuticals (Orlemans et al., 1989). Particularly, imidazopyridine with both and imidazole pyridine moieties, which constitutes a typical, favored scaffold, exhibits antifungal activities and serves as an antagonist to the H1 receptor as well as kinase an and antilipases inhibitor (Fig. 1) (Belohlavek and Malfertheiner 1979).

Heterocyclic small molecules are essential for understanding cell biology and treating wide range of diseases because they control the function of protein–protein interactions, receptors and enzymes (Zhao et al., 2015, Wang et al., 2023). In this perspective, oxazoles are heterocyclic five-membered molecules with heteroatoms of nitrogen and oxygen that have established a significant class of therapeutic prospects in organic chemistry. Typically, substituted oxazoles containing heterocycles might bind many receptors and enzymes via non-covalent bond and in the biological system to demonstrate a wide range of biological activities (Delost et al., 2018, Warner et al., 2018, Zhang et al., 2018, Ke et al., 2019, Sun et al., 2019, Melfi et al., 2023). There are numerous oxazole-containing drugs have been reported and are widely used in market for the treatment of various kind of diseases, including such as ditazole (platelets aggregation inhibitor), oxaprozin, JTE-5229 COX-2 inhibitors (anti-inflammatory drug), (-)-muscoride **A** (peptide alkaloid), aleglitazar (antidiabetic), aristoxazole (anti-inflammatory drugs), and AD-5061 (antidiabetic agent) (Fig. 2) (Mukku et al., 2020).

Our research groups had reported various *N*-containing heterocyclic compounds such as benzimidazole, benzoxazole, triazole and thiazole scaffolds for their potentials cholinesterase, urease, *alpha*-amylase and *alpha*-glucosidase inhibitors (Hussain et al., 2022, Khan et al., 2022). It is noteworthy that oxazole moiety is structurally resemblance to thiazole ring. Further, imidazopyridine-based oxazole analogs have not been reported as urease inhibitors therefore, it is the need of time to incorporate both imidazopyridine and oxazole rings in same molecules to explore their urease activity. Considering the biological importance of oxazole (Georgiades and Rizeq 2015, Lechel et al., 2019, Rahim et al., 2019) and imidazopyridine (Park et al., 2017, Thakur et al., 2020, Mishra et al., 2021) rings, herein we have designed and synthesized hybrid scaffolds incorporating both imidazopyridine and oxazole rings in the same molecules to further explore urease inhibition profile (in vitro) and further correlated by in silico molecular docking studies (Fig. 3).

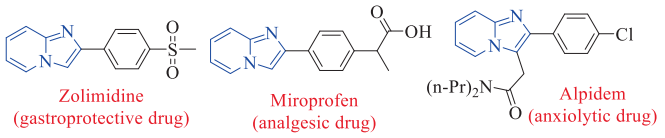


Fig. 1. Bioactive drugs bearing imidazopyridine skeleton.

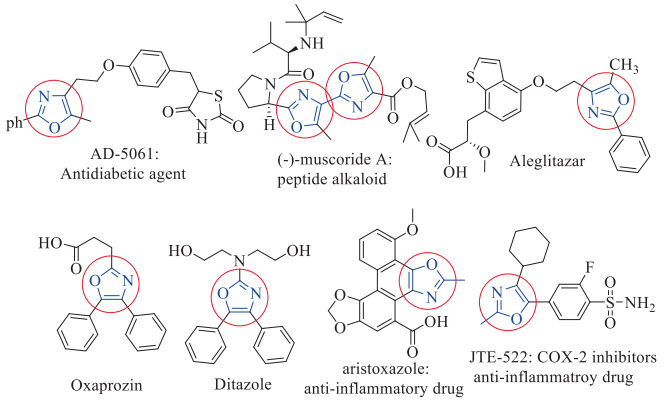


Fig. 2. Biologically potent drugs containing oxazole moiety in their core skeleton.

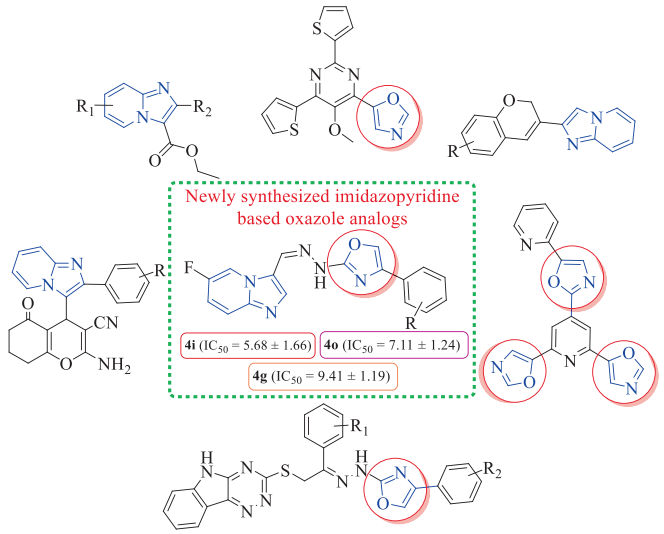


Fig. 3. Rational of the current study.

2. Methods

2.1. Materials and setting

All chemicals were bought from Sigma Aldrich and Merck (Germany) (USA). A Bruker AM spectrometer was used to record the NMR spectra (600 MHz). Mass spectra (EI-MS, HR-EI-MS, and FAB) were recorded on the mass spectrometers JEOL JMS-600H, MAT 312, and MAT 113D. TLC was carried out using precoated silica gel-254 from Merck, Germany. At 366 and 254 nm, dots were visible under UV light. Chemical shift values were measured in ppm, and coupling constants are displayed in Hz, with DMSO d_6 acting as the reference.

2.2. General procedure for the synthesis of imidazopyridine containing oxazole analogs (4a-l)

In two steps, the hybrid imidazopyridine-based oxazole scaffolds (4a-l) were afforded. Initially, flouro-substituted imidazopyridine-3-carbaldehyde (1 equivalent) in methanol (10 mL) was reacted with flouro-substituted semicarbazide (1) (1 equivalent) and glacial acetic acid (few drops). The reaction mixture was stirred under reflux at refluxing temperature to obtain semicarbazone substrate (2). After completion of reaction, the solvent was removed using a rotary evaporator to obtained the solid intermediate (2). This intermediate then underwent cyclization when it was refluxed and stirred for 16hrs over pre-heated sand bath with different substituted 2-bromoacetophenone (3) (1 equivalent) in ethanol (10 mL) along with few drops of triethylamine as a catalyst. The solid residue so obtained was washed

with n-hexane to give targeted imidazopyridine-based oxazole analogs (4a-l) in appropriate yield.

2.3. Spectral analysis (provided in supplementary information)

See Scheme 1 and Table 1.

2.4. Assay protocol for urease inhibition

The protocol was carried by following the previously published study (Mumtaz et al., 2022).

2.5. Assay protocol for molecular docking study

It has also been carried out according to our previously published work (Khan et al., 2022, Mumtaz et al., 2022).

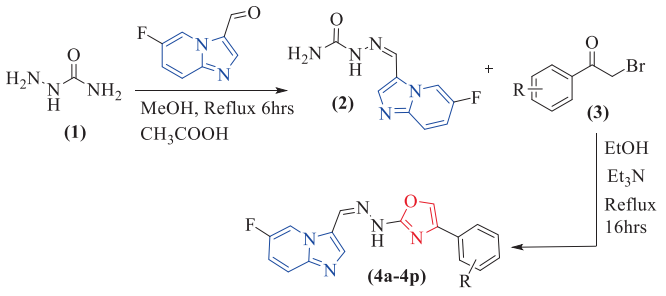
3. Results

3.1. Chemistry

The hybrid scaffolds (**4a-p**) based on imidazopyridine containing oxazole moiety were afforded in two steps. In the first step, semicarbazide (**1**) was treated with flouro-substituted imidazopyridine-3-carbaldehyde in methanol along with few drops of acetic acid (glacial) and resulting residue was refluxed and stirred at refluxing temperature to afford imidazopyridine-based semicarbazone substrate (**2**). As the reaction was completed, the solvent was evaporated via rotary evaporator to deliver the solid intermediate (**2**) which further undergoes cyclization on putting reflux with various substituted 2-bromoacetophenone (**3**) in ethanol followed by addition of few drops of triethylamine as catalyst. The reaction mixture was refluxed and stirred until the formation of targeted imidazopyridine-based oxazole analogs were complete (conversion were monitored by TLC, refluxed 16 hrs). After being cooled to room temperature, the solvent was removed by applying reduced pressure to give solid residue which was further washed and then recrystallized from ethyl acetate to afford purified targeted imidazopyridine-based oxazole analogs (**4a-p**). All the newly synthesized scaffolds (**4a-p**) were characterized structurally by employing variety of spectroscopic techniques including HREI-MS, ^{1}H NMR and ^{13}C NMR.

3.2. Biological analysis (4a-p)

Imidazopyridine-based oxazole scaffolds (4a-p) were subjected to possible urease inhibitory potentials for the first time. It is interesting to mention that the majority of synthesized analogs were found to be active against target urease enzyme with IC_{50} values ranging from 5.68 ± 1.66 μM to 81.48 ± 7.18 μM. The results obtained were compared to reference thiourea drug with IC_{50} value 21.37 ± 1.76 μM. Interestingly, the scaffolds 4i (IC_{50} = 5.68 ± 1.66 μM), 4o (IC_{50} = 7.11 ± 1.24 μM), 4 g (IC_{50} = 9.41 ± 1.19 μM) and 4 h (IC_{50} = 10.45 ± 2.57 μM) were found to be significantly active against urease enzyme as compared to standard thiourea drug. However, the rest of the analogs showed moderate to good urease inhibitory activity.



Scheme 1. Synthesis of imidazole-fused-pyridine containing oxazole derivatives.

3.3. Molecular docking study

To establish the correlation between in vitro and in silico studies of all the active synthesized **4i, 4o, 4 h** and **4 g** analogs, molecular docking study has been performed. Subsequently, all these active analogs bind well in the active cavity of target with different binding affinities and also correlate well with the in vitro studies in (Figs. 4-7).

4. Discussion

4.1. Urease inhibitory activity

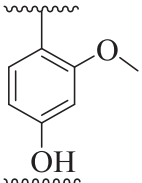
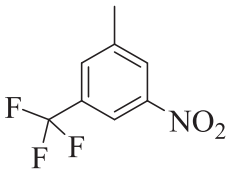
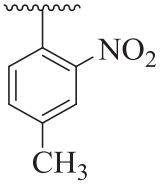
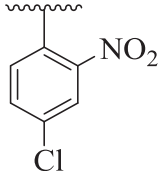
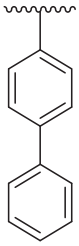
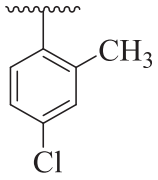
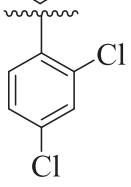
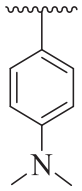
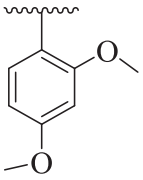
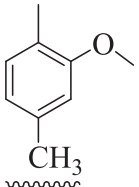
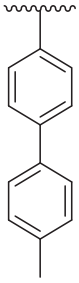
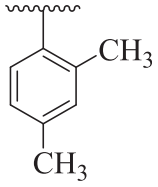
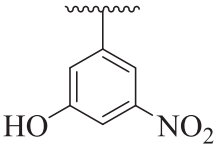
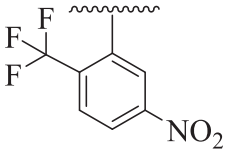
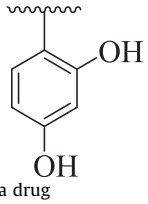
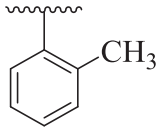
4.1.1. Structure-activity relationship (SAR)

For the sake of simplification of the SAR studies, it was explained based on variation in position, nature and number/s of attached substituent (s) on aryl ring. Electron withdrawing -CF_3 and –NO_2 groups bearing analogs **4i** (holds 3-CF_3 & 5-NO_2 groups at aryl ring) and **4o** (bearing 2-CF_3 & 5-NO_2 moieties at aryl ring) were identified as excellent inhibitors of urease enzyme. Analog **4i** was found to be the most active inhibitor of urease, even more potent than standard thiourea drug. Shifting the –CF_3 moiety from *meta*-position to *ortho*-position as in the case of analog **4o** demonstrates slightly decreased inhibitory potentials compared to scaffold **4i**. However, the activity was further declined by replacement of *meta*-CF_3 group with –OH group as in case of compound **4 g** (bearing *meta*-hydroxy and *meta*-nitro groups at aryl part). Further, the comparison of analog **4 g** with analog **4 h** (having *di*-hydroxy at 2,4-position of aryl ring) revealed that changing the nature (–NO_2 group was replaced with –OH group) of attached substituent (s) decreased the inhibitory potentials of analog **4 h** than its counterpart **4 g**. The analog **4 h** bearing *di*-hydroxy groups at 2,4-position of aryl part exhibited less inhibitory potentials than compound **4 g** but still found to be more potent than standard urease drug (Fig. 8).

The substituent(s) of electron donating nature such as –OCH_3 and –CH_3 groups were found to be encouraging for significant urease inhibitory potentials. The analog **4e** (bearing *di*-OCH3 substitution at 2,4-position of aryl part) was identified as an outstanding urease inhibitors, but found less potent when compared to standard thiourea drug. However, the urease inhibitory potential of analog **4e** was decreased sharply by replacing 4-OCH_3 group with –CH_3 group as in case of compound **4 m**. This shows that –OCH_3 group plays an effective role in inhibition of urease enzyme than –CH_3 group. The urease inhibitory potential of scaffold **4e** was further reduced by replacing both 2,4-dimethoxy substituents with 2,4-diCH_3 moieties as in case of scaffold **4n** indicating that –OCH_3 groups enhanced the urease inhibitory activity. The compound **4 k** (holds *ortho*-CH_3 and *para*-Cl moieties at aryl part) was interestingly found to be active than analog **4n**. This activity comparison confirmed that -Cl substitution at the *para*-position uplift the inhibitory strength to a good extent (Fig. 9).

Further, comparison of analog **4d** (that holds di-Cl moieties at 2,4-position of phenyl ring) with analog **4j** (bearing 2-NO_2 & 4-Cl group on phenyl ring) shows that analog **4j** was emerged as excellent urease inhibitor, even more active than standard thiourea drug. This activity comparison confirmed that –NO_2 substitution relative to –Cl substitution uplift the urease inhibitory potential. The scaffold **4b** (that holds 2-NO_2 & 4-CH_3 substitution at phenyl

Table 1
Different substituent (s) and in vitro urease inhibitory profile of synthesized imidazole-fused-pyridine containing oxazole analogs (**4a-p**).

S.NO	R	IC_{50} ± SEM[a] [μM]	S.NO	R	IC_{50} ± SEM[a] [μM]
4a		18.23 ± 2.05	**4i**		5.68 ± 1.66
4b		15.32 ± 2.46	**4j**		11.33 ± 2.01
4c		81.49 ± 7.18	**4 k**		21.56 ± 2.24
4d		16.13 ± 1.65	**4 l**		74.55 ± 7.18
4e		43.49 ± 4.20	**4 *m***		48.54 ± 4.18
4f		71.69 ± 6.13	**4*n***		58.05 ± 6.69
4 g		9.41 ± 1.19	**4o**		7.11 ± 1.24
4 h		10.45 ± 2.57	**4p**		63.57 ± 7.25
Standard Thiourea drug					21.37 ± 1.76 **µM**

ring) showed slightly decreased urease inhibitory potential than analog **4j**. This activity comparison indicates that changing the nature of substituent (*para*-Cl group is replaced with *para*-CH_3 group) at *para*-position slightly decreased the urease inhibitory potential. The compound **4a** (bearing *ortho*-methoxy & *para*-hydroxy substitution at aryl ring) displayed better urease inhibitory potential

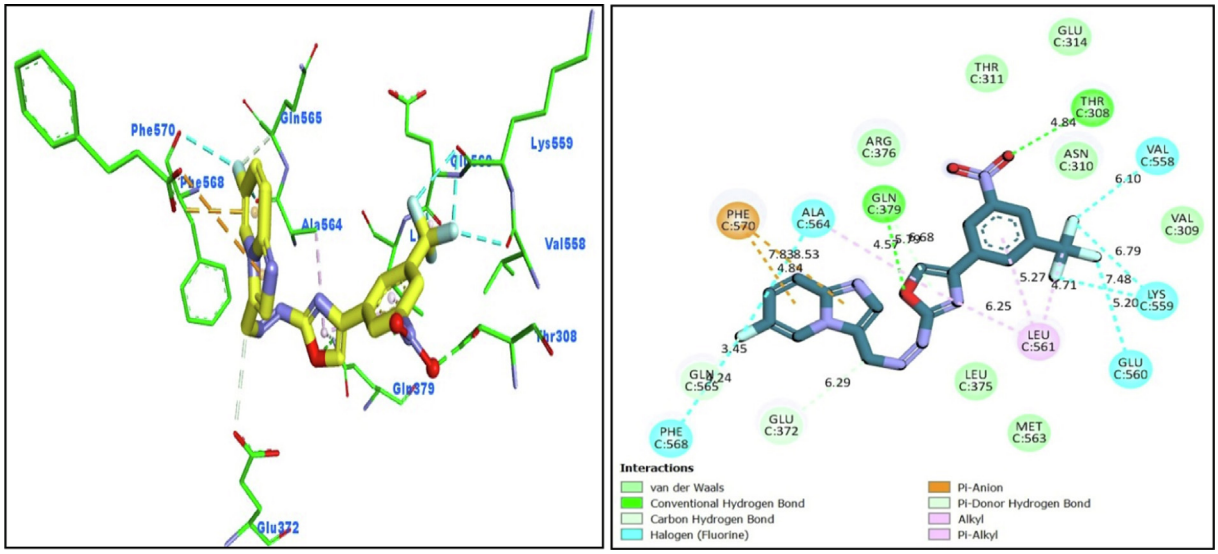


Fig. 4. The PLI (protein–ligand interaction) profile of analog-**4i** against urease target and its 3D (left) and 2D (right) diagram.

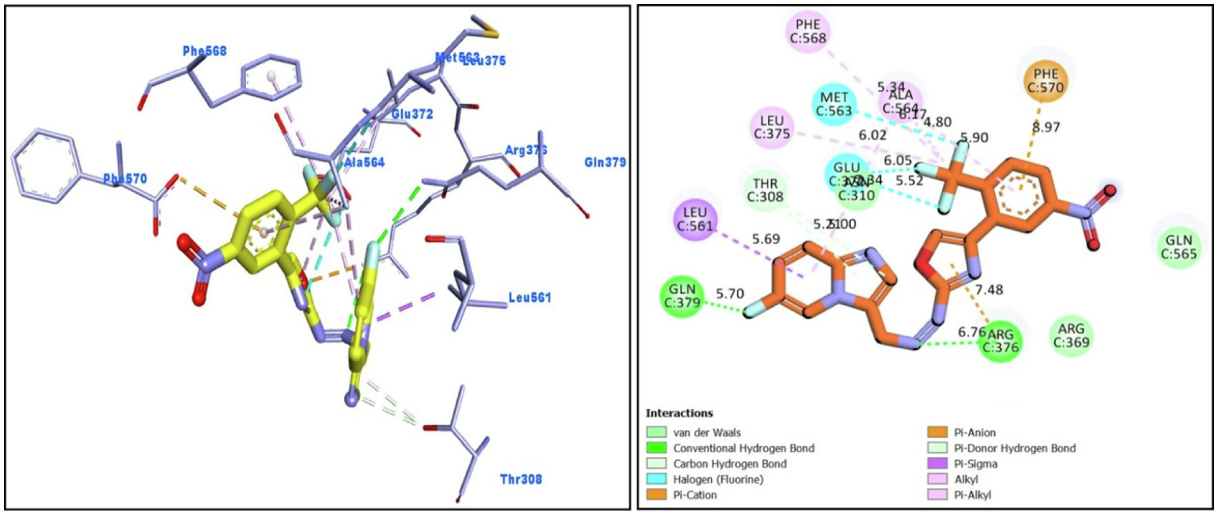


Fig. 5. The protein–ligand interaction (PLI) profile of analog-**4o** against urease target and its 3D (left) and 2D (right) diagram.

even more potent than standard thiourea drug. This uplift inhibitory potential of analog **4a** might be due to associating nature of –OH group which bind well with urease target active sites and hence enhanced the urease inhibitory potential (Fig. 10).

However, the analogues **4c** bearing phenyl group at *para*-position (IC_{50} = 81.49 ± 7.18 μM) and **4f** bearing toluene moiety on *para*-position (IC_{50} = 71.69 ± 6.13 μM) were found to be three-fold least potent of urease inhibitor as compared to the standard drug thiourea (IC_{50} = 21.37 ± 1.76 μM). Because the phenyl, toluene, -$N(CH_3)_2$ have bulky nature present at *para*-position of the aryl part of the oxazole (Gattu et al., 2023, Khan et al., 2023, Vanjare et al., 2023) resulted to reduced inhibitory potentials against urease inhibitor. The analogue **4c** bearing *para*-phenyl moiety at aryl part and analogue **4f** having *para*-toluene moiety at the same *para*-position were showing least potent competitor against urease inhibitor. Moreover, compound **4 l** has -$N(CH_3)_2$ at *para*-position and **4p** has methyl group on *ortho*-position of the aryl ring showing three-fold least potency as compared to the standard drug thiourea. Hence, the bulky groups are responsible for the least potency of molecules (**4c, 4f** and **4 l**) as compared to the standard drug (Fig. 11).

On the basis of aforementioned observation, it was summarized form SAR studies that either EW groups such as -CF_3, -Cl and –NO_2 or group with strong associating nature (–OH) play an important role in significant inhibitory potentials of synthesized analogs against targeted enzyme. However, other groups when placed at certain position and number/s also demonstrated better inhibitory activities.

4.2. Molecular docking study

Subsequently, all these active analogs bind well in the active cavity of target with different binding affinities and also correlate well with the in vitro studies. All these active analogs almost have similar chemistry with slight modification at varied position. These varied functional moieties at varied position of active analogs resulted to different interactions with target urease active sites. The compound **4i** was identified as the most active likewise in the vitro analysis. This active analog furnished maximum interactions with target active sites. The detailed PLI of most potent analog **4i** shows that this scaffold furnished several significant interactions target urease active

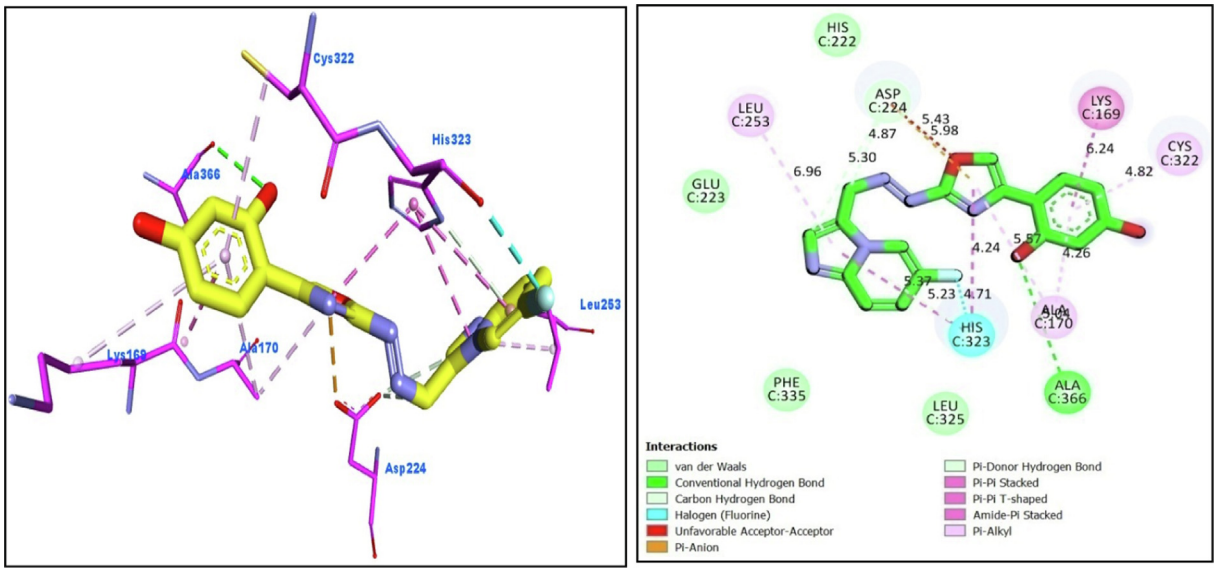


Fig. 6. The PLI (protein–ligand interaction) profile of analog-**4 h** against urease target and its 3D (left) and 2D (right) diagram.

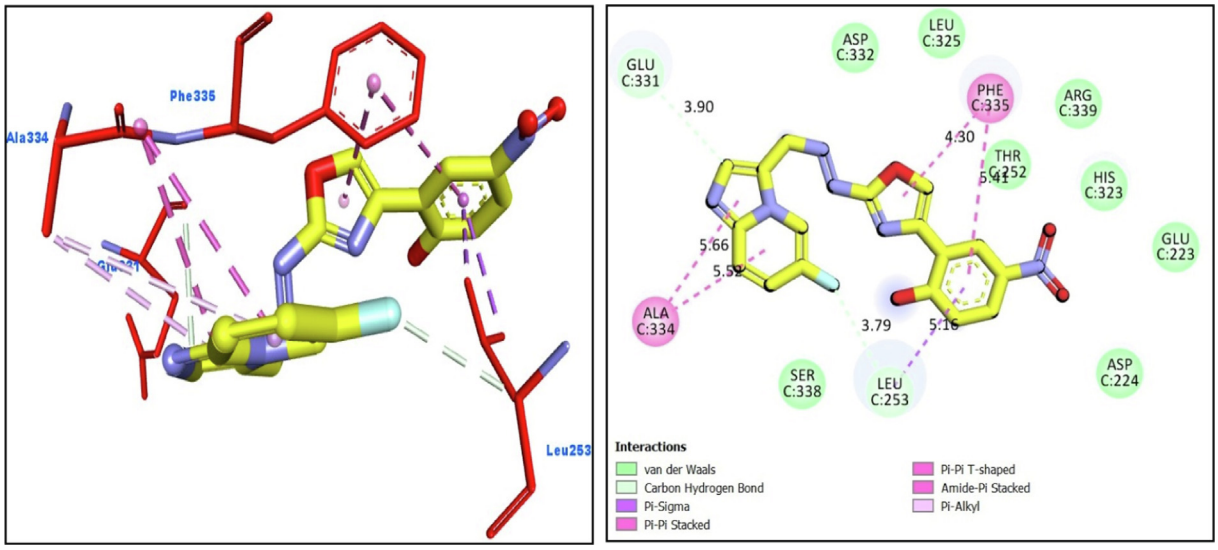


Fig. 7. The PLI (protein–ligand interaction) profile of analog-**4 g** against urease target and its 3D (left) and 2D (right) diagram.

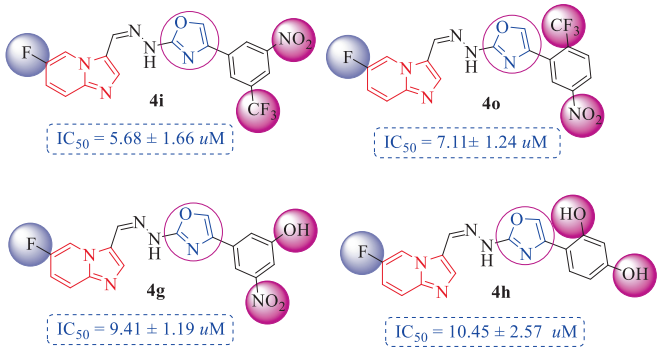


Fig. 8. SAR studies of 4 g, 4 h, 4o and 4i analogs.

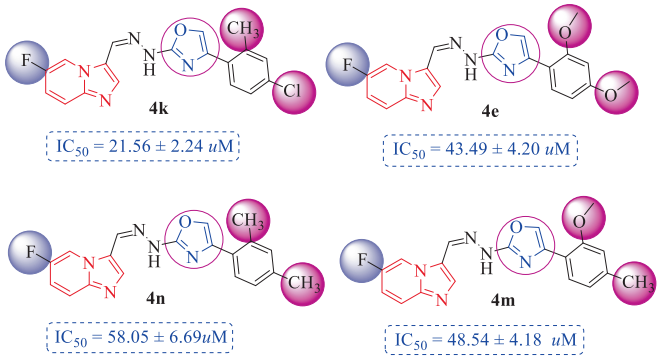


Fig. 9. SAR studies of 4e, 4 k, 4 m and 4n analogs.

sites such as Thr308 (CHB), Val558 (halogen (fluorine)), Lys559 (halogen (fluorine)), Glu560 (halogen (fluorine)), Leu561 (pi-alkyl & alkyl), Gln379 (CHB & carbon hydrogen bond), Ala564 (halogen (fluorine) & pi-alkyl), Phe570 (pi-anion), Phe568 (halogen (fluorine)) and Glu372 (carbon hydrogen bond) interactions (Fig. 4).

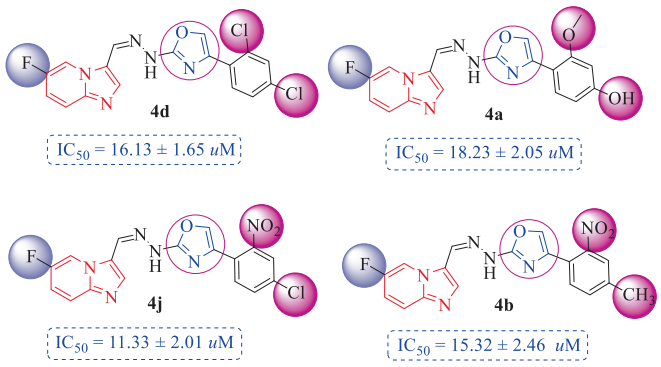


Fig. 10. SAR studies of 4a, 4b, 4d and 4j derivatives.

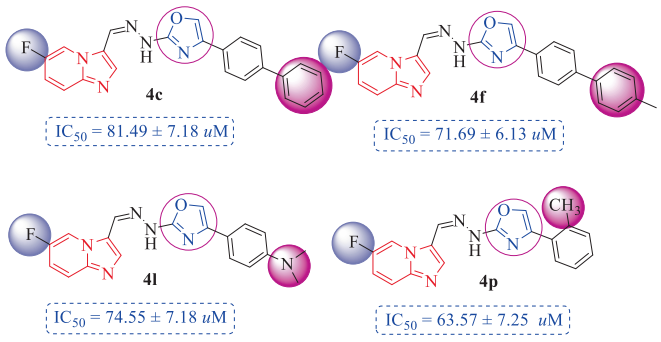


Fig. 11. SAR studies of 4c, 4f, 4 l and 4p analogs.

The PLI of second most potent scaffold **4o** demonstrated that although this analog is quite like most active analog **4i** in structure, the only difference is that analog **4o** holds $-CF_3$ moiety at *meta*-position of aryl ring; however, the analog **4i** have $-CF_3$ moiety attached at *ortho*-position of the aryl part of oxazole ring. The discrepancy in the enzymatic potential may perhaps owing to varied position of functional moiety $-CF_3$ around aryl part, which therefore causes both these active **4i & 4o** analogs to interacts in different way. This second most potent analog **4o** showed less interaction when compared to its structurally similar analog **4i**. The detail PLI of second most active scaffold **4o** demonstrated that this analog adopted number/s of significant interactions with target urease active sites such as Gln379 (CHB), Leu561 (pi-sigma), Thr308 (carbon hydrogen bond), Glu384 (halogen (fluorine)), Ala564 (pi-alkyl & alkyl), Phe568 (alkyl), Leu375 (alkyl), Met563 (halogen (fluorine)), Phe570 (pi-sigma) and Arg376 (pi-sigma & CHB) interactions (Fig. 5).

From docking analysis, it was also observed that not only the EW groups enhanced the enzymatic inhibition, but also the substituent that forms strong hydrogen bond with the active sites of target also elevate the inhibition profile; therefore, analog **4 h** (bearing di-hydroxy at 2,4-position of aryl part) established numerous key interactions target urease active sites including Leu253 (pi-alkyl), His323 ((halogen (fluorine), pi-pi stacked & amide-pi stacked), Ala366 (CHB), Ala170 (pi-alkyl), Cys322 (pi-alkyl), Lys169 (pi-pi T shaped) and Asp224 (pi-anion & carbon hydrogen bond) interactions (Fig. 6).

The analog **4 g** bearing 2-hydroxy and 5-NO_2 moieties at aryl part of oxazole ring was also emerged as the active inhibitor of urease enzyme and hence displayed several significant important interactions including Ala334 (pi-pi T shaped & amide-pi stacked), Glu331 (carbon hydrogen bond), Leu253 (pi-sigma & carbon hydrogen bond) and Phe335 (pi-pi T shaped & pi-pi stacked) interactions with urease target active sites (Fig. 7).

5. Conclusion

A library of imidazopyridine-based oxazole (**4a-l**) and synthesized and their chemical structures were elucidated by HREI-MS, ^{13}C NMR and ^{1}H NMR analysis. The anti-urease activity of newly afforded analogs was tested and obtained results were compared with standard thiourea drug. All imidazopyridine-based oxazole analogs, particularly **4i, 4o, 4 g** and **4 h** with IC_{50} values of 5.68 ± 1.66, 7.11 ± 1.24, 9.41 ± 1.19 and 10.45 ± 2.57 μM respectively, were identified to be significantly potent and amazing anti-urease agent with strong binding to enzyme that correlated well with the experimental data. While other analogs demonstrated relatively moderate activity. Additionally, the molecular docking studies were performed on the most promising compounds **4i, 4o, 4 g** and **4 h** in the active sites of urease and results obtained showed that these active scaffolds established several significant interactions with the active sites of targeted urease. There was a good association between in vitro and in silico studies. Moreover, a structure–activity relationship (SAR) study was performed out for all synthesized analogs based on varying substitution (s) around the aryl ring while keeping imidazopyridine and oxazole rings constant and docking results of the active analogs shown excellent urease inhibition profile and these analogs are found to be suitable for the treatment of Ulcer.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jsps.2023.05.026.

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