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FULL PAPER

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Synthesis, evaluation, and molecular docking studies of aryl urea-triazole-based derivatives as anti-urease agents

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Abstract

Considering the importance of urease inhibitors in the treatment of ureolytic bacterial infections, in this work, the synthesis of novel, aryl urea-triazole-based derivatives as effective urease inhibitors is described. Dichloro-substituted derivative **4o**, with IC_{50} = 22.81 ± 0.05 μM, is found to be the most potent urease inhibitor, determined by Berthelot colorimetric assay. Docking studies were also carried out for compound **4o** to confirm the effective interactions with the urease active site.

KEYWORDS
click reaction, docking study, triazole, urease

1 | INTRODUCTION

Urease (EC 3.5.1.5) is a large dinuclear metalloenzyme from the amidohydrolase family,[1–3] which is known as the first purified enzyme molecule in its crystalline form.[4] This enzyme, depending on its sources (soil,[5] bacteria, fungi,[6–9] and plants[10]), plays critical roles in plant growth, agriculture, human and animal health. Bacterial urease has been contributed as the prominent antigenic component in some infectious disease of humans.[11] For instance, the best condition for colonization and survival of *Helicobacter pylori* (*H. pylori*) in acidic medium of the stomach is provided by virtue of the ureolytic activity. The alkaline character of produced ammonia, which normally leads to elevated pH values generates the required environment for *H. pylori* survival.[12–14] In this regard, depending on colonization site, various types of diseases including peptic, duodenal, gastric ulcer, and urinary tract infection[15–17] have occurred, which affected approximately 3 billion people around the

world. These *H. pylori*-associated diseases prevalently occur in developing countries and increase the risk of third leading cause of death worldwide, meaning gastric cancer.

To reduce the risk of this disease, the development of urease inhibitors[18,19] triggers enticing attention of several research groups to introduce more efficient agents. The urease inhibitory activity has been observed in compounds with different structural motifs, including heavy metal complexes[20] and various organic scaffolds.[21–31] Meanwhile, the promising importance of aryl urea class of inhibitors has driven extensive efforts to consider homologues of this moiety as a leading pattern in designing novel inhibitors. This activity can be related to the capability of urea moiety in filling the distance between the catalytic site and the surrounding residue.

1,2,3-Triazole is one of the most potent nuclei in bioactive compounds,[32] widely studied for the beneficial biological effects. Apart from this medicinal value, a literature survey[33–36] reveals the substantial applicability of triazole containing molecules in drug delivery agents, tissue engineering, and organometallic ligands which will be served in light emitting devices, solar energy conversion and as a organocatalyst in organic transformations.

Traditionally, the main approach for the construction of 1, 4-disubstituted triazoles is the copper-catalyzed azide-alkyne cycloaddition reaction (CuAAC).[37] This reaction provides an experimentally simple and mild pathway for the formation of carbon-heteroatom bond, affording triazoles in a single step procedure. In terms of unique properties associated with this type of reaction, many triazole-containing molecules have been prepared through the simple and efficient click reaction.[38–40] Taking this into account and the importance of urea and triazole[41,42] moieties in urease inhibitors, we now report the synthesis and antiurease activity of novel 1-((1-substituted benzyl)-1*H*-1,2,3-triazol-4-yl)methyl)-3-phenyl urea derivatives.

2 | RESULTS AND DISCUSSION

2.1 | Chemistry

Treatment of phenyl isocyanate and 4-methoxy phenyl isocyanate with propargyl amine **2** in dichloromethane gave the propargylated product **3** (Scheme 1). The reaction was carried out according to the previously reported procedure.[43,44] Then, 1-(substituted phenyl)-3-(prop-2-ynyl) urea **3** undergo click reaction with commercially available benzyl halides (chloride and bromide), sodium azide, copper sulfate, and sodium ascorbate to generate 1-((1-substituted benzyl)-1*H*-1,2,3-triazol-4-yl) methyl)-3-phenyl urea derivatives. Regarding the critical role of copper catalyst in this transformation, it was found that 0.1 mol of copper sulfate in 10 mL of H_2O/*t*-BuOH yielded the desired products in good yields.

The generality of this protocol was subsequently examined, by employing a variety of benzyl halides. Electron-donating and electron withdrawing groups at different positions of phenyl ring underwent click reaction to furnish the desired products in good yields. Seventeen representative examples of this class were synthesized and confirmed by IR, ^{1}H and ^{13}C NMR spectroscopy.

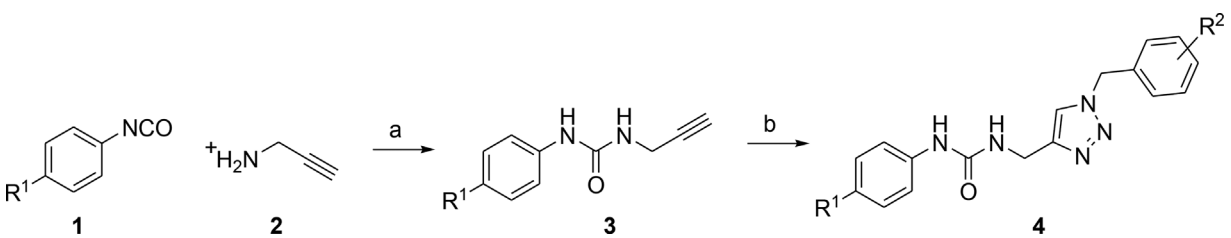
2.2 | Biological evaluation

The profile of antiurease activity of **4a–q** was established by Berthelot colorimetric method. The influence of different substituents at benzyl and phenyl ring on urease inhibitory activity can be observed in Table 1. The results revealed that good urease inhibitory activity is dependent upon the presence of methoxy at *para* position of phenyl ring. As summarized in Table 1, the presence of methoxy group has a positive effect on inhibitory activity (IC_{50}s ranged from 22 to 96 μM) compared to unsubstituted counterparts. The unsubstituted derivatives are three- to fivefold less potent than *p*-methoxy-substituted derivatives.

The observations suggested that the presence of substituents (fluoro and chloro) at the *para* position of the benzyl ring results in promising inhibitory activities. While moving these substituents to the *ortho* and *meta* positions leads to the reduced activities. The *p*-substituted fluorine group improves the antiurease activity compared to chloro and bromo bearing derivatives in both series. These observations suggested that more electron-withdrawing group could enhance the inhibitory activity. The presence of a large and lipophilic group at *para* position, meaning bromine, causes increased IC_{50} value. Dichloro-substituted derivatives are the most potent compounds in both series. Maintaining the *p*-chloro group, introduction of a second chloro group in *ortho* and *meta* positions led to the increased inhibitory potencies. It seems that the presence of two chlorine atoms provides appropriate spatial arrangement to fit in active site and subsequently enhanced the inhibitory activity against urease.

2.3 | Docking studies

The binding mode of compound **4o** illustrated that the NH and methoxy groups formed hydrogen bonds with Asp494 and Arg439,



SCHEME 1 Synthsis of compounds **4**. Reagents and conditions: (a) CH_2Cl_2, 20°C; (b) (i) $ArCH_2Br(Cl)$, NaN_3, H_2O/*t*-BuOH (1:1), Et_3N; (ii) **3**, $CuSO_4$, sodium ascorbate, r.t.

TABLE 1 Urease inhibitory activity of compounds **4a–q**

Entry	Compound	R^1	R^2	IC_{50} (μM)[a] ± SEM	Docking energy (kcal/mol)
1	**4a**	H	2-F	149.85 ± 0.12	−6.4
2	**4b**	H	3-F	173.01 ± 1.33	−5.7
3	**4c**	H	4-F	140.91 ± 0.29	−6.4
4	**4d**	H	2-Cl	169.15 ± 2.02	−6.1
5	**4e**	H	3-Cl	192.17 ± 1.20	−5.4
6	**4f**	H	4-Cl	161.21 ± 1.52	−6.2
7	**4g**	H	4-Br	184.43 ± 2.16	−5.5
8	**4h**	H	2,4-*di*Cl	127.68 ± 1.8	−6.4
9	**4i**	H	3,4-*di*Cl	118.73 ± 0.22	−6.5
10	**4j**	OMe	2-F	46.23 ± 0.08	−7.3
11	**4k**	OMe	3-F	54.26 ± 0.56	−6.9
12	**4l**	OMe	4-F	39.11 ± 1.06	−7.7
13	**4m**	OMe	3-Cl	73.02 ± 0.21	−6.7
14	**4n**	OMe	4-Cl	51.12 ± 1.14	−6.9
15	**4o**	OMe	2,4-*di*Cl	22.81 ± 0.05	−7.9
16	**4p**	OMe	3,4-*di*Cl	37.4 ± 1.20	−7.7
17	**4q**	OMe	4-Me	96.16 ± 0.37	−6.8
18	Hydroxyurea	–	–	100 ± 0.15	
19	Thiourea	–	–	23 ± 1.7	

[a]Values were the means of three replicates ± standard deviation (SD).

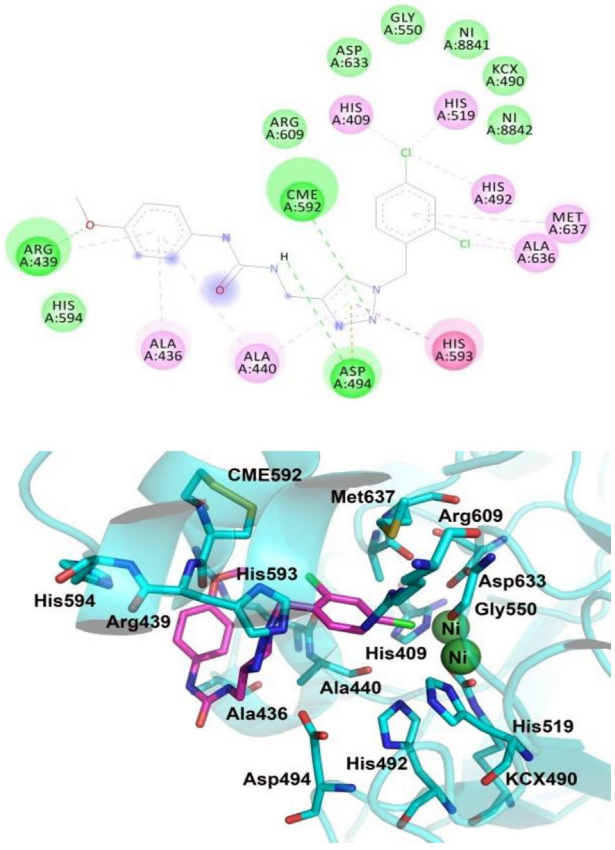


FIGURE 1 Docking pose of **4o**

respectively (Figure 1). The triazole ring exhibited hydrogen bonding interaction with CME 592. The notable π–alkyl interactions are observed with His409, His492, His593, His519, Met637, Ala636, Ala440, and Ala436. The appropriate interaction with nickel could be observed in the active site. In addition, the Van der Waals interaction is observed for **4o** with His594, CME-592, Arg609, Asp633, KCX490, and Gly550 for compound **4o**.

2.4 | Molecular properties prediction

The ADME properties of the synthesized compounds were evaluated by Molinspiration online toolkit and the Lipinski's molecular properties are shown in Table 2. This *in silico* study under Lipinski's "Rule of five" determined the drug-likeness of compounds in comparison to known drugs.[45] Good oral bioavailability of tested compounds depended on the <5 values of logP, MW (<500), HBA (≤10), and HBD (<5). The molecular flexibility is determined by the number of rotatable bonds (nROTB) values which should be <10. Furthermore, the topological polar surface area (TPSA) range of synthesized compounds indicated the good permeability of the evaluated compounds in the cellular plasma membrane. Finally, according to ADME findings, no violations were found for the synthesized compounds, affording positive drug-likeness values.

3 | CONCLUSION

In this paper, the synthesis and *in vitro* urease inhibition of 17 aryl urea-triazole-based compounds are presented. All prepared

TABLE 2 *In silico* molecular properties calculations of compounds **4a–q**[a,b]

Compound	miLog P	MW	nON	nOHNH	Violations	nROTB	TPSA	Volume
4a	2.71	325.35	6	2	0	5	71.84	286.24
4b	2.73	325.35	6	2	0	5	71.84	286.24
4c	2.76	325.35	6	2	0	5	71.84	286.24
4d	3.22	341.80	6	2	0	5	71.84	294.84
4e	3.25	341.80	6	2	0	5	71.84	294.84
4f	3.27	341.80	6	2	0	5	71.84	294.84
4g	3.40	386.25	6	2	0	5	71.84	299.19
4h	3.88	376.25	6	2	0	5	71.84	308.38
4i	3.88	376.25	6	2	0	5	71.84	308.38
4j	2.77	355.37	7	2	0	6	81.08	311.78
4k	2.79	355.37	7	2	0	6	81.08	311.78
4l	2.81	355.37	7	2	0	6	81.08	311.78
4m	3.30	371.83	7	2	0	6	81.08	320.39
4n	3.33	371.83	7	2	0	6	81.08	320.39
4o	3.93	406.27	7	2	0	6	81.08	333.92
4p	3.93	406.27	7	2	0	6	81.08	333.92
4q	3.10	351.41	7	2	0	6	81.08	323.41

[a]LogP, octanol/water partition coefficient; TPSA, topological polar surface area; MW, molecular weight; nON, number of hydrogen bond acceptors; nOHNH, number of hydrogen bond donors; nrotb, number of rotatable bonds.
[b]Data were obtained from http://www.molinspiration.com/cgi-bin/properties (accessed 04.23.18).

derivatives are characterized by spectral data. Among the synthesized compounds, 4-methoxy bearing derivatives are more potent urease inhibitors with acceptable ADME properties. It is concluded that dichloro-substituted derivatives are attractive candidates for further development to discover novel urease inhibitors.

4 | EXPERIMENTAL

4.1 | Chemistry

4.1.1 | General

Melting points were determined with a Kofler hot stage apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded with a Bruker FT-500, using TMS as an internal standard. IR spectra were recorded on a Nicolet Magna FTIR 550 spectrophotometer using KBr disks. Mass spectra were obtained with an Agilent Technology (HP) mass spectrometer operating at an ionization potential of 70 eV. Elemental analysis for C, H, and N was determined with an Elementar Analysen System GmbH VarioEL CHNS mode. Figure 2 shows the atom numbering of compounds **5a**,**e**,**o**, only used for NMR spectra interpretation.

The NMR spectra and the InChI codes of the investigated compounds together with some biological activity data are provided as Supporting Information.

4.1.2 | General procedure for the synthesis of compounds 4a–q

The corresponding benzyl halide (1 mmol), sodium azide (1 mmol), and triethyl amine (1 mmol) were stirred at room temperature in (H_2O/*t*-BuOH 1:1) (5 mL) for 2 h. Afterward, a solution of compound **3** (1 mmol), $CuSO_4$ (10 mol%) and sodium ascorbate (10–15 mol%) in (H_2O/*t*-BuOH 1:1) (5 mL) and stirred for 24 h. The crude mixture was purified by column chromatography (petroleum ether/ethyl acetate 4:1) to afford the desired compounds.

1-((1-(2-Fluorobenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)-3-phenylurea (4a)

Yellow solid; yield: 72%; mp: 232–234°C; IR (KBr): 3180, 1654 (C═O) cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): 4.32 (d, J = 5.5 Hz, CH_2NH), 5.63 (s, CH_2N), 6.55–6.57 (m, 1H triazole), 6.89 (t, J = 7.0 Hz,

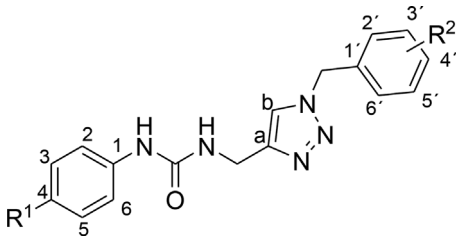


FIGURE 2 Atom numbering of compounds **4a–q** only used for NMR spectra interpretation

H_4), 7.20–7.22 (m, $H_{3,5,2',5',6'}$), 7.37–7.38 (m, $H_{2,6,4'}$), 7.96 (s, NH), 8.48 (s, NH). ^{13}C NMR (125 MHz, DMSO-d_6): 34.7 (CH_2NH), 46.7 (CH_2N), 115.6 (d, $C_{3'}$Ar, J = 20 Hz), 117.7 ($C_{2,6}$Ar), 121.0 (C_b triazole), 122.7 (C_4Ar), 123.7, 124.7, 128.5 ($C_{3,5}$Ar), 130.6 (C_1Ar), 133.5, 137.1, 139.2, 140.2 (C_a triazole), 145.7, 155.0 (CO), 161.0 (d, $C_{2'}$Ar, J = 225 Hz). Anal. calcd. for $C_{17}H_{16}FN_5O$: C, 62.76; H, 4.96; N, 21.53. Found C, 62.59; H, 5.10; N, 21.68.

1-((1-(3-Fluorobenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)-3-phenylurea (4b)

White solid; yield: 70%; mp: 216–218°C; IR (KBr): 3145, 1679 (C═O) cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): 4.34 (s, CH_2NH), 5.60 (s, CH_2N), 6.55–6.57 (m, 1H triazole), 6.89–6.90 (m, H_4), 7.15–7.18 (m, $H_{3,5,4'}$), 7.20–7.23 (m, $H_{2',6'}$), 7.37–7.39 (m, $H_{2,6,5'}$), 8.05 (s, NH), 8.49 (s, NH); ^{13}C NMR (125 MHz, DMSO-d_6): 34.8 (CH_2NH), 51.9 (CH_2N), 114.6 (d, $C_{4'}$Ar, J = 19 Hz), 117.7 ($C_{2,6}$Ar), 121.0 (C_b triazole), 122.5 (C_4Ar), 123.9, 124.8, 125.6, 127.3, 128.5 ($C_{3,5}$Ar), 130.6 (C_1Ar), 138.6, 140.2 (C_a triazole), 146.4, 155.0 (C═O), 162.4 (d, $C_{3'}$Ar, J = 205 Hz). Anal. calcd. for $C_{17}H_{16}FN_5O$: C, 62.76; H, 4.96; N, 21.53. Found C, 62.89; H, 4.80; N, 21.32.

1-((1-(4-Fluorobenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)-3-phenylurea (4c)

Orange solid; yield: 69%; mp: 189–191°C; IR (KBr): 3180, 1648 (CO) cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): 4.32 (d, J = 5.0 Hz, CH_2NH), 5.56 (s, CH_2N), 6.52–6.54 (m, 1H triazole), 6.89 (t, J = 7.0 Hz, H_4), 7.17–7.22 (m, $H_{3,5,3',5'}$), 7.37–7.38 (m, $H_{2,6,2',6'}$), 7.99 (s, NH), 8.48 (s, NH); ^{13}C NMR (125 MHz, DMSO-d_6): 34.8 (CH_2NH), 51.8 (CH_2N), 115.3 (d, $C_{3',5'}$Ar, J = 21 Hz), 117.7 ($C_{2,6}$Ar), 121.0 (C_b triazole), 122.7 (C_4Ar), 125.4, 128.5 ($C_{3,5}$Ar), 130.1 (C_1Ar), 132.3, 136.2, 140.2 (C_a triazole), 146.0, 155.0 (CO), 162.0 (d, $C_{4'}$Ar, J = 220 Hz). Anal. calcd. for $C_{17}H_{16}FN_5O$: C, 62.76; H, 4.96; N, 21.53. Found C, 62.91; H, 5.14; N, 21.70.

1-((1-(2-Chlorobenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)-3-phenylurea (4d)

Pale yellow solid; yield: 66%; mp: 180–182°C; IR (KBr): 3200, 1678 (C═O) cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): 4.34 (d, J = 5.5 Hz, CH_2NH), 5.68 (s, CH_2N), 6.55 (t, J = 5.5 Hz, 1H triazole), 6.89 (t, J = 7.0 Hz, H_4), 7.20–7.23 (m, $H_{3,5,6'}$), 7.30–7.33 (m, $H_{4'}$), 7.36–7.39 (m, $H_{2,6,5'}$), 7.50 (d, J = 7.0 Hz, $H_{3'}$), 7.97 (s, NH), 8.49 (s, NH); ^{13}C NMR (125 MHz, DMSO-d_6): 34.7 (CH_2NH), 50.4 (CH_2N), 117.7 ($C_{2,6}$Ar), 121.0 (C_b triazole), 123.0 (C_4Ar), 127.6, 128.5 ($C_{3,5}$Ar), 129.4, 129.9, 130.1 (C_1Ar), 130.3, 132.5 133.2, 140.2 (C_a triazole), 142.3, 145.6, 155.0 (C═O). Anal. calcd. for $C_{17}H_{16}ClN_5O$: C, 59.74; H, 4.72; N, 20.49. Found C, 59.91; H, 4.59; N, 20.22.

1-((1-(3-Chlorobenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)-3-phenylurea (4e)

Yellow solid; yield: 81%; mp: 151–153°C; IR (KBr): 3161, 1655 (C═O) cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): 4.34 (d, J = 5.0 Hz, CH_2NH), 5.59 (s, CH_2N), 6.54–6.56 (m, 1H triazole), 6.89 (t, J = 7.0 Hz, H_4), 7.21 (t, J = 7.5 Hz, $H_{3,5}$), 7.24–7.27 (m, $H_{2',6'}$), 7.38–7.39 (m, $H_{2,6,4',5'}$), 8.04 (s, NH), 8.50 (s, NH); ^{13}C NMR (125 MHz, DMSO-d_6): 34.8 (CH_2NH), 51.9 (CH_2N), 117.7 ($C_{2,6}$Ar), 121.0 (C_b triazole), 122.7 (C_4Ar), 123.8, 126.5, 127.6, 127.8, 128.0, 128.5 ($C_{3,5}$Ar), 130.5 (C_1Ar), 133.2, 138.4, 140.2 (C_a triazole), 145.9, 155.0 (CO). Anal. calcd. for $C_{17}H_{16}ClN_5O$: C, 59.74; H, 4.72; N, 20.49. Found C, 59.59; H, 4.95; N, 20.60.

1-((1-(4-Chlorobenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)-3-phenylurea (4f)

Pale yellow solid; yield: 63%; mp: 142–144°C; IR (KBr): 3139, 1692 (CO) cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): 4.32 (d, J = 5.0 Hz, CH_2NH), 5.57 (s, CH_2N), 6.53–6.55 (m, 1H triazole), 6.89 (t, J = 8.0 Hz, H_4), 7.21 (t, J = 7.5 Hz, $H_{3,5}$), 7.33 (d, J = 7.5 Hz, $H_{2',6'}$), 7.37 (d, J = 7.5 Hz, $H_{3',5'}$), 7.43 (d, J = 7.5 Hz, $H_{2,6}$), 8.00 (s, NH), 8.49 (s, NH); ^{13}C NMR (125 MHz, DMSO-d_6): 34.8 (CH_2NH), 51.8 (CH_2N), 117.7 ($C_{2,6}$Ar), 121.0 (C_b triazole), 122.7 (C_4Ar), 124.3, 128.5 ($C_{3,5}$Ar), 129.8, 130.6 (C_1Ar), 132.7, 135.0, 140.2 (C_a triazole), 142.2, 145.8, 155.0 (C═O). Anal. calcd. for $C_{17}H_{16}ClN_5O$: C, 59.74; H, 4.72; N, 20.49. Found C, 59.98; H, 4.59; N, 20.31.

1-((1-(4-Bromobenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)-3-phenylurea (4g)

Pale yellow solid; yield: 74%; mp: 176–178°C; IR (KBr): 3201, 1666 (C═O) cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): 4.32 (d, J = 5.0 Hz, CH_2NH), 5.56 (s, CH_2N), 6.54–6.57 (m, 1H triazole), 6.89 (t, J = 8.5 Hz, H_4), 7.21 (t, J = 7.5 Hz, $H_{3,5}$), 7.26 (d, J = 7.5 Hz, $H_{2',6'}$), 7.37 (d, J = 7.5 Hz, $H_{3',5'}$), 7.56 (d, J = 8.0 Hz, $H_{2,6}$), 8.00 (s, NH), 8.48 (s, NH); ^{13}C NMR (125 MHz, DMSO-d_6): 34.8 (CH_2NH), 51.9 (CH_2N), 117.7 ($C_{2,6}$Ar), 121.0 (C_b triazole), 121.2, 122.6 (C_4Ar), 128.5 ($C_{3,5}$Ar), 130.1 (C_1Ar), 131.4, 131.6, 134.2, 135.4, 140.2 (C_a triazole), 145.8, 154.9 (CO). Anal. calcd. for $C_{17}H_{16}BrN_5O$: C, 52.86; H, 4.18; N, 18.13. Found C, 53.06; H, 4.35; N, 18.02.

1-((1-(2,4-Dichlorobenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)-3-phenylurea (4h)

Yellow solid; yield: 70%; mp: 221–222°C; IR (KBr): 3177, 1645 (C═O) cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): 4.34 (d, J = 5.0 Hz, CH_2NH), 5.67 (s, CH_2N), 6.54–6.56 (m, 1H triazole), 6.89 (t, J = 7.0 Hz, H_4), 7.21 (t, J = 7.0 Hz, $H_{3,5}$), 7.26 (d, J = 8.5 Hz, $H_{6'}$), 7.38 (d, J = 7.5 Hz, $H_{2,6}$), 7.45 (d, J = 8.5 Hz, $H_{5'}$), 7.67 (s, $H_{3'}$), 7.98 (s, NH), 8.50 (s, NH); ^{13}C NMR (125 MHz, DMSO-d_6): 34.8 (CH_2NH), 49.8 (CH_2N), 117.7 ($C_{2,6}$Ar), 121.1 (C_b triazole), 123.0 (C_4Ar), 127.7, 128.5 ($C_{3,5}$Ar), 129.0, 130.8 (C_1Ar), 131.1, 133.4, 133.8, 134.0, 140.0 (C_a triazole), 145.7, 147.4, 154.9 (C═O). Anal. calcd. for $C_{17}H_{15}Cl_2N_5O$: C, 54.27; H, 4.02; N, 18.61. Found C, 54.40; H, 4.20; N, 18.48.

1-((1-(3,4-Dichlorobenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)-3-phenylurea (4i)

Pale yellow solid; yield: 71%; mp: 183–185°C; IR (KBr): 3098, 1679 (C═O) cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): 4.32 (d, J = 5.0 Hz, CH_2NH), 5.59 (s, CH_2N), 6.53–6.55 (m, 1H triazole), 6.89 (t, J = 7.0 Hz, H_4), 7.21 (t, J = 7.5 Hz, $H_{3,5}$), 7.28 (d, J = 8.0 Hz, $H_{6'}$), 7.37 (d, J = 7.5 Hz, $H_{2,6}$), 7.61 (s, $H_{2'}$), 7.62 (d, J = 8.0 Hz, $H_{5'}$), 8.04 (s, NH), 8.49 (s, NH);

^{13}C NMR (125 MHz, DMSO-d_6): 34.8 (CH_2NH), 51.2 (CH_2N), 117.7 ($C_{2,6}$Ar), 121.0 (C_b triazole), 122.9 (C_4Ar), 123.2, 128.3, 128.5 ($C_{3,5}$Ar), 129.9, 130.1, 130.8 (C_1Ar), 130.9, 131.2, 137.0, 140.2 (C_a triazole), 145.9, 155.0 (C═O). Anal. calcd. for $C_{17}H_{15}Cl_2N_5O$: C, 54.27; H, 4.02; N, 18.61. Found C, 54.09; H, 3.89; N, 18.89.

1-((1-(2-Fluorobenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)-3-(4-methoxyphenyl)urea (4j)

Pale yellow solid; yield: 68%; mp: 194–196°C; IR (KBr): 3180, 1660 (CO) cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): 3.70 (s, OMe), 4.32 (d, J = 5.5 Hz, CH_2NH), 5.64 (s, CH_2N), 6.47 (d, J = 8.0 Hz, $H_{3\ or\ 5}$), 6.52 (t, J = 5.0 Hz, 1H triazole), 6.85 (d, J = 8.0 Hz, $H_{3\ or\ 5}$), 7.10–7.13 (m, $H_{2,6}$), 7.20–7.26 (m, $H_{3',5'}$), 7.34 (t, J = 7.5 Hz, $H_{4'}$), 7.39–7.42 (m, $H_{6'}$), 8.04 (s, NH), 8.51 (s, NH); ^{13}C NMR (125 MHz, DMSO-d_6): 34.7 (CH_2NH), 46.7 (CH_2N), 54.7 (OMe), 103.5, 106.6 (d, $C_{3'Ar}$, J = 30 Hz), 110.0, 115.4, 115.6, 120.7, 122.7, 124.7, 129.2, 130.6, 133.2, 141.5 (C_a triazole), 154.7 (C_{4Ar}), 159.3 (CO), 161.0 (d, $C_{2'Ar}$, J = 249 Hz). Anal. calcd. for $C_{18}H_{18}FN_5O_2$: C, 60.84; H, 5.11; N, 19.71. Found C, 60.69; H, 4.97; N, 19.58.

1-((1-(3-Fluorobenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)-3-(4-methoxyphenyl)urea (4k)

Pale yellow solid; yield: 79%; mp: 185–186°C; IR (KBr): 3190, 1659 (C═O) cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): 3.69 (s, OMe), 4.32 (d, J = 5.0 Hz, CH_2NH), 5.60 (s, CH_2N), 6.47 (d, J = 7.5 Hz, $H_{3\ or\ 5}$), 6.53–6.55 (m, 1H triazole), 6.85 (d, J = 7.5 Hz, $H_{3\ or\ 5}$), 7.09–7.15 (m, $H_{2,6,2',4',6'}$), 7.40–7.42 (m, $H_{5'}$), 8.03 (s, NH), 8.52 (s, NH); ^{13}C NMR (125 MHz, DMSO-d_6): 34.8 (CH_2NH), 52.0 (CH_2N), 54.8 (OMe), 103.5, 106.6 (d, $C_{4'Ar}$, J = 30 Hz), 110.0, 114.6 (d, $C_{2'Ar}$, J = 25 Hz), 114.9, 122.7, 122.9, 123.9, 129.3, 130.7, 138.7, 141.5 (C_a triazole), 154.9 (C_{4Ar}), 159.8 (CO), 162.0 (d, $C_{3'Ar}$, J = 242 Hz). Anal. calcd. for $C_{18}H_{18}FN_5O_2$: C, 60.84; H, 5.11; N, 19.71. Found C, 60.68; H, 5.00; N, 19.91.

1-((1-(4-Fluorobenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)-3-(4-methoxyphenyl)urea (4l)

Pale yellow solid; yield: 64%; mp: 200–202°C; IR (KBr): 3145, 1633 (C═O) cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): 3.70 (s, OMe), 4.31 (d, J = 5.5 Hz, CH_2NH), 5.56 (s, CH_2N), 6.47 (d, J = 8.0 Hz, $H_{3\ or\ 5}$), 6.53 (t, J = 5.5 Hz, 1H triazole), 6.85 (d, J = 8.0 Hz, $H_{3\ or\ 5}$), 7.09–7.13 (m, $H_{2,6}$), 7.19 (t, J = 8.5 Hz, $H_{3',5'}$), 7.38 (t, J = 7.0 Hz, $H_{2',6'}$), 7.99 (s, NH), 8.51 (s, NH); ^{13}C NMR (125 MHz, DMSO-d_6): 34.7 (CH_2NH), 51.8 (CH_2N), 54.8 (OMe), 103.5, 106.6, 110.0, 115.4 (d, $C_{3',5'Ar}$, J = 21 Hz), 122.4 (d, $C_{2',6'Ar}$, J = 16 Hz), 129.3, 130.2, 132.3, 141.5 (C_a triazole), 145.8, 154.9 (C_{4Ar}), 159.6 (C═O), 161.0 (d, $C_{4'Ar}$, J = 242 Hz). Anal. calcd. for $C_{18}H_{18}FN_5O_2$: C, 60.84; H, 5.11; N, 19.71. Found C, 60.69; H, 5.24; N, 19.55.

1-((1-(3-Chlorobenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)-3-(4-methoxyphenyl)urea (4m)

Pale yellow solid; yield: 60%; mp: 166–168°C; IR (KBr): 3220, 1693 (CO) cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): 3.70 (s, OMe), 4.32 (d, J = 5.0 Hz, CH_2NH), 5.597 (s, CH_2N), 6.47 (d, J = 7.5 Hz, $H_{3\ or\ 5}$), 6.53–6.56 (m, 1H triazole), 6.85 (d, J = 7.5 Hz, $H_{3\ or\ 5}$), 7.09–7.14 (m, $H_{2,6}$), 7.26–7.29 (m, $H_{6'}$), 7.38–7.41 (m, $H_{2',4',5'}$), 8.04 (s, NH), 8.51 (s, NH); ^{13}C NMR (125 MHz, DMSO-d_6): 34.8 (CH_2NH), 51.9 (CH_2N), 54.8 (OMe), 103.5, 106.5, 110.0, 122.7, 126.5, 127.8, 127.9, 129.2, 130.5, 133.2, 138.4, 141.5 (C_a triazole), 145.9, 154.9 (C_{4Ar}), 159.6 (CO). Anal. calcd. for $C_{18}H_{18}ClN_5O_2$: C, 58.14; H, 4.88; N, 18.84. Found C, 58.29; H, 5.01; N, 18.65.

1-((1-(4-Chlorobenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)-3-(4-methoxyphenyl)urea (4n)

Pale yellow solid; yield: 65%; mp: 181–182°C; IR (KBr): 3222, 1696 (C═O) cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): 3.70 (s, OMe), 4.32 (d, J = 5.0 Hz, CH_2NH), 5.57 (s, CH_2N), 6.47 (d, J = 7.5 Hz, $H_{3\ or\ 5}$), 6.53–6.55 (m, 1H triazole), 6.85 (d, J = 7.5 Hz, $H_{3\ or\ 5}$), 7.09–7.14 (m, $H_{2,6}$), 7.33 (d, J = 7.5 Hz, $H_{2',6'}$), 7.42 (d, J = 7.5 Hz, $H_{3',5'}$), 8.00 (s, NH), 8.52 (s, NH); ^{13}C NMR (125 MHz, DMSO-d_6): 34.8 (CH_2NH), 51.8 (CH_2N), 54.7 (OMe), 103.5, 106.5, 110.0, 122.7, 128.7, 129.2, 129.8, 132.7, 135.0, 141.5 (C_a triazole), 145.8, 154.9 (C_{4Ar}), 159.6 (CO). Anal. calcd. for $C_{18}H_{18}ClN_5O_2$: C, 58.14; H, 4.88; N, 18.84. Found C, 57.96; H, 4.97; N, 18.99.

1-((1-(2,4-Dichlorobenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)-3-(4-methoxyphenyl)urea (4o)

Pale yellow solid; yield: 71%; mp: 172–174°C; IR (KBr): 3100, 1646 (C═O) cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): 3.70 (s, OMe), 4.32 (d, J = 5.0 Hz, CH_2NH), 5.67 (s, CH_2N), 6.47 (d, J = 7.5 Hz, $H_{3\ or\ 5}$), 6.52–6.54 (m, 1H triazole), 6.85 (d, J = 7.5 Hz, $H_{3\ or\ 5}$), 7.09–7.13 (m, $H_{2,6}$), 7.25 (d, J = 8.0 Hz, $H_{6'}$), 7.45 (d, J = 7.5 Hz, $H_{5'}$), 7.68 (s, $H_{3'}$), 7.98 (s, NH), 8.51 (s, NH); ^{13}C NMR (125 MHz, DMSO-d_6): 34.7 (CH_2NH), 49.8 (CH_2N), 54.8 (OMe), 103.5, 106.5, 110.0, 122.8, 127.7, 128.4, 129.2, 129.7, 132.4, 133.5, 135.0, 141.5 (C_a triazole), 145.6, 154.9 (C_{4Ar}), 159.6 (C═O). Anal. calcd. for $C_{18}H_{17}Cl_2N_5O_2$: C, 53.21; H, 4.22; N, 17.24. Found C, 53.06; H, 4.38; N, 17.41.

1-((1-(3,4-Dichlorobenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)-3-(4-methoxyphenyl)urea (4p)

Pale yellow solid; yield: 68%; mp: 152–153°C; IR (KBr): 3211, 1638 (C═O) cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): 3.70 (s, OMe), 4.32 (d, J = 6.0 Hz, CH_2NH), 5.59 (s, CH_2N), 6.47 (d, J = 8.0 Hz, $H_{3\ or\ 5}$), 6.54 (t, J = 5.5 Hz, 1H triazole), 6.85 (d, J = 8.0 Hz, $H_{3\ or\ 5}$), 7.09–7.14 (m, $H_{2,6}$), 7.28 (d, J = 8.5 Hz, $H_{6'}$), 7.61 (s, $H_{2'}$), 7.63 (d, J = 8.5 Hz, $H_{5'}$), 8.04 (s, NH), 8.51 (s, NH); ^{13}C NMR (125 MHz, DMSO-d_6): 34.7 (CH_2NH), 51.2 (CH_2N), 54.8 (OMe), 103.5, 106.6, 110.0, 122.7, 128.3, 129.2, 129.9, 130.1, 130.8, 133.4, 137.0, 141.5 (C_a triazole), 145.9, 154.9 (C_{4Ar}), 159.6 (C═O). Anal. calcd. for $C_{18}H_{17}Cl_2N_5O_2$: C, 53.21; H, 4.22; N, 17.24. Found: C, 53.00; H, 4.44; N, 17.06.

1-((1-(4-Methylbenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)-3-(4-methoxyphenyl)urea (4q)

Pale yellow solid; yield: 73%; mp: 141–142°C; IR (KBr): 3099, 1645 (C═O) cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): 2.27 (s, Me), 3.71 (s, OMe), 4.30 (d, J = 5.0 Hz, CH_2NH), 5.50 (s, CH_2N), 6.47 (d, J = 8.0 Hz, $H_{3'\ or\ 5'}$), 6.52–6.54 (m, 1H triazole), 6.85 (d, J = 8.0 Hz, $H_{3'\ or\ 5'}$),

7.09–7.13 (m, $H_{2',6'}$), 7.16 (d, J = 7.5 Hz, $H_{3',5'}$), 7.21 (d, J = 7.5 Hz, $H_{2',6'}$), 7.93 (s, NH), 8.49 (s, NH); ^{13}C NMR (125 MHz, DMSO-d_6): 20.5 (Me), 34.7 (CH_2NH), 52.5 (CH_2N), 54.8 (OMe), 103.5, 106.5, 110.0, 122.4, 127.9, 129.2, 129.9, 133.0, 137.3, 141.5, 145.7, 154.9 (C_{4Ar}), 159.6 (CO). Anal. calcd. for $C_{19}H_{21}N_5O_2$: C, 64.94; H, 6.02; N, 19.93. Found: C, 64.70; H, 5.84; N, 19.78.

4.2 | Biological evaluation

All chemicals and jack bean urease (EC 3.5.1.5) were purchased from Sigma–Aldrich (USA) and other commercial sources. Ultra-pure water (HPLC grade; Duksan, Korea) was utilized in all experiments. Potassium phosphate buffer solution (100 mM), pH 7.4, was prepared in distilled water. The absorbance spectra were recorded on a Synergy H1 Hybrid multi-mode microplate reader (BioTek, Winooski, VT, USA).

Urease inhibitory assays of the synthesized compounds were evaluated at the concentration of 0–10 mg/mL, using the modified Berthelot spectrophotometric method at 625 nm. The obtained results were compared with the standard compounds, hydroxyurea and thiourea.[46,47]

The enzymatic reactions were performed in phosphate buffer (100 mM, pH 7.4) solution which reach to the 985 µL by adding urea (850 µL) and the synthesized compound (100 µL, 0–10 mg/mL). Then, after the addition of the urease enzyme (15 µL), the concentration of liberated ammonia was measured after 60 min. The corresponding concentration of ammonia was obtained by addition of incubated solution (100 µL) to the mixture of solution A (500 µL, containing 5.0 g phenol and 25.0 mg sodium nitroprusside in 500 mL distilled water) and solution B (500 µL, containing 2.5 g sodium hydroxide and 4.2 mL sodium hypochlorite (5% chlorine) in 500 mL distilled water) which was incubated at 37°C for 30 min. The absorbance was determined by measuring indophenols at 625 nm. The activity of uninhibited urease was considered as the control activity of 100%. The inhibition studies were conducted according to this formula: I (%) = [1 − (T/C)] × 100; where I (%) is the inhibition of the enzyme, T (test) is the absorbance of the evaluated sample (analyzed compounds) in the presence of enzyme, and C (control) is the absorbance of the solvent in the presence of enzyme. Data were expressed as mean ± standard error (SD) and run in triplicate. The values of IC_{50} for all analyzed compounds were calculated using GraphPad Prism 5 software (GraphPad Software, Inc., San Diego, CA).

4.3 | Molecular docking study

The binding interaction of the most active compound was investigated using docking study. The AutoDock 4.2 package[48,49] (the parameters are based on the Amber force field) was used with Lamarckian genetic algorithm (LGA) on PDB structure (3LA4) http://www.pdb.org with resolution of 2.05 Å for these calculations. Marvin sketch applet v.5.7 (Marvin package, Chemaxon Company) was utilized to sketch the potent inhibitor. Each dimension around the active site was 0.375 nm and each grid map consisted of 60 × 60 × 60 Å points. The nickel and the non-standard residues (KCX and CME) were included in the binding site characterization. Afterwards, polar hydrogens and rotatable bonds were added by AutoDock Tools (1.5.6, ADT), respectively. In addition, the preparation of input files was performed by graphical user interface AutoDock Tools. 2D and 3D ligand–receptor interactions were evaluated by Ligplot$^+$ version v.1.1.0 program[50] and Discovery Studio v.3.5.[51] Docking studies were carried out by maximum number of 25×10^6 energy evaluations. After clustering analysis, the best conformation with the most sensible binding energy was obtained.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article. The spectra of synthesized compounds for each compound are provided as supporting file.

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