ISSN 1070-3632, Russian Journal of General Chemistry, 2023, Vol. 93, No. 2, pp. 449–454. © Pleiades Publishing, Ltd., 2023.

Urease Inhibition Studies of New Benzimidazoles Containing Triazole Ring

G. Akyüz[a,*], E. Menteşe[a], and B. Kahveci[b]

[a] *Department of Chemistry, Faculty of Arts and Sciences, Recep Tayyip Erdogan University, Rize, 53950 Turkey*
[b] *Department of Nutrition and Dietetics, Faculty of Health Sciences, Karadeniz Technical University, Trabzon, 61000 Turkey*
**e-mail: gulay.candan@erdogan.edu.tr*

Received December 30, 2022; revised February 1, 2023; accepted February 2, 2023

Abstract—A new series of benzimidazoles including triazole and thiosemicarbazide moieties was synthesized and their urease inhibition studies were evaluated according to the method of Van Slyke and Archibald. Especially triazole derivatives have effective inhibition activities between 0.04±0.026 and 0.26±0.042 μM IC_{50} values. The best antiurease activities with IC_{50} 0.04±0.026 and 0.06±0.033 μM belongs to 5-[(5,6-dichloro-1*H*-benzimidazol-1-yl)methyl]-4-nitrophenyl-4*H*-1,2,4-triazole-3-thiol and 2-[(2-benzyl-5,6-dichloro-1*H*-benzimidazol-1-yl)acetyl]-*N*-(4-nitrophenyl)hydrazinecarbothioamide, respectively.

Keywords: benzimidazoles, triazoles, thiosemicarbazides, urease inhibition

DOI: 10.1134/S1070363223020287

INTRODUCTION

Urease is playing a significant role in the nitrogen mineralization process and so pH control on human health and agriculture. Urease accelerates the transformation of urea into carbon dioxide and ammonia [1, 2]. Due to ammonia formation, this reaction tends to increase the pH of the environment. Thereby the high urease content, resulting in a number of infections like hepatic coma, gastric ulcer, urolithiasis, pyelonephritis and cancer [3–5]. In recent years, urease inhibitors played prominent role at the infections treatment by urease producing bacteria Helicobacter pylori. Urease inhibitors are considered being potential antiulcer drugs [6–8]. Because of all inhibitors of urease have been recently reviewed and many of them taken their place in pharmaceutical and medicinal chemistry [9–11].

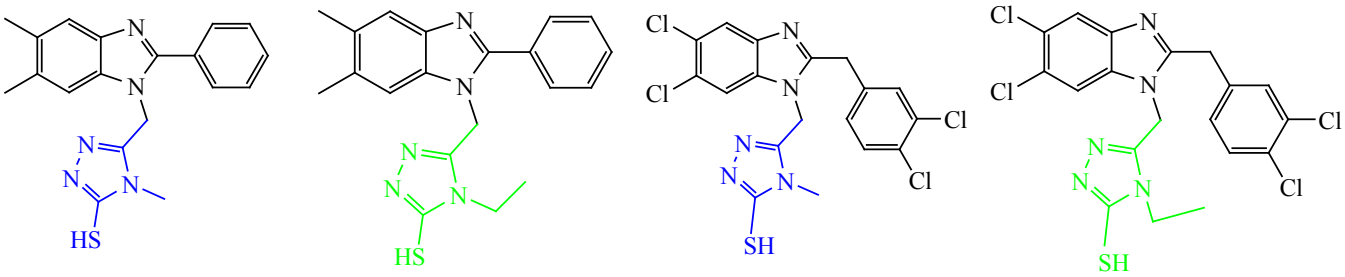
Benzimidazoles have a wide field in biological and medicinal applications. In recent years inhibition studies with benzimidazoles have been increased and some benzimidazole derivatives of thiosemicarbazides, triazoles, Schiff bases were reported as potential urease inhibitors [12–14]. Also, studies on urease inhibition of benzimidazole compounds containing triazole ring reported (Scheme 1) [15, 16].

Therefore, in our continuous attempt to introduce novel urease inhibitors, we have synthesized novel benzimidazoles containing triazole and thiosemicarbazide group at 1-position and then examined their antiurease activities. In this study, novel benzimidazoles especially triazole derivatives have more effective urease inhibition activity than the standard inhibitor.

RESULTS AND DISCUSSION

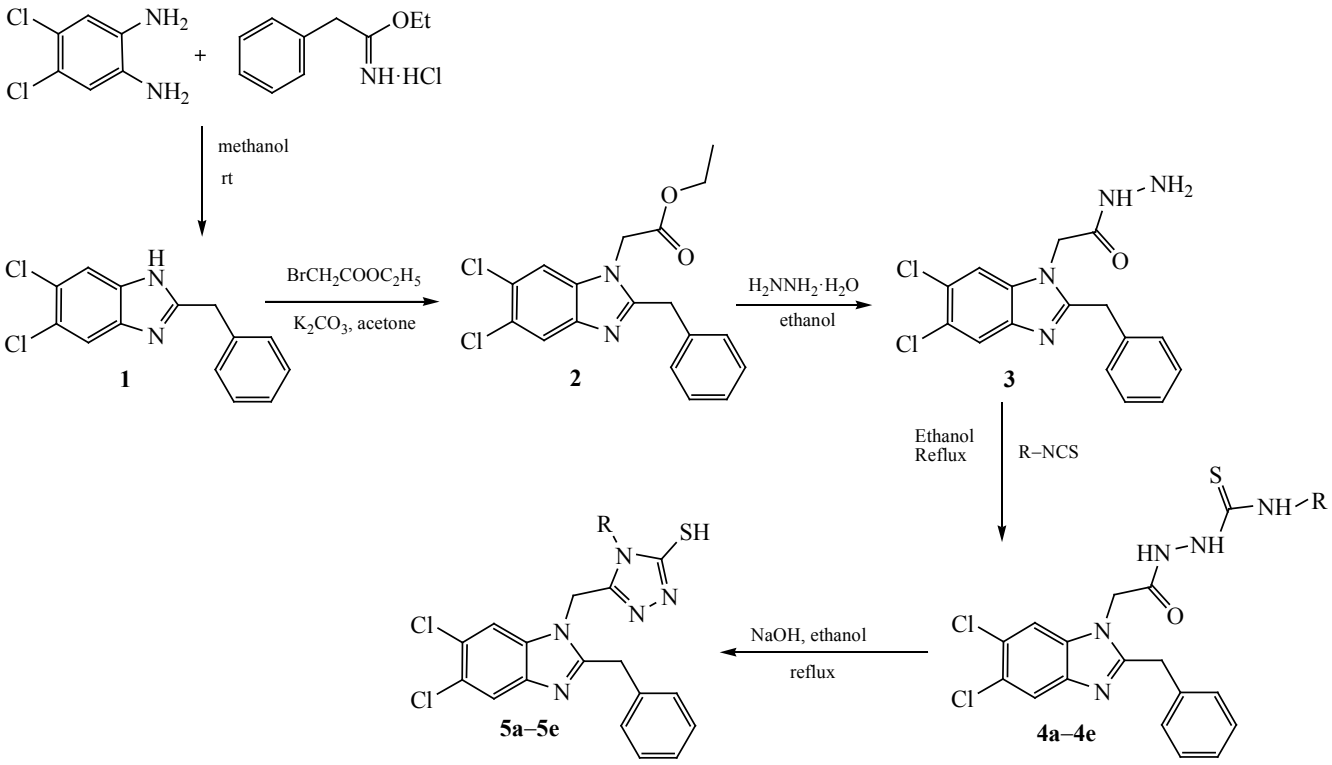
Chemistry. We have synthesized new 5,6-dichloro-benzimidazoles containing triazole ring at position 1 and benzyl ring at position 2. Synthesis of all target compounds is shown in Scheme 2. First, iminoester hydrochloride was prepared according to the procedure [17]. The solution of iminoester hydrochloride and 4,5-dicloro-1,2-phenylenediamine in dry methanol was stirred at room temperature for a day resulting to compound **1**. The starting compound **1** was reacted with ethyl bromoacetate in acetone with K_2CO_3 to synthesize ester form of benzimidazole and then it was converted by hydrazine hydrate in ethanol to compound **3**. Thiosemicarbazides **4a**–**4e** were synthesized by the nucleophilic addition of compound **3** with different isothiocyanates**.** Compounds **5a**–**5e** were obtained by

Scheme 1.



IC_{50} 24.03 μg/mL IC_{50} 25.60 μg/mL IC_{50} 46.79 μg/mL IC_{50} 14.37 μg/mL

Scheme 2.

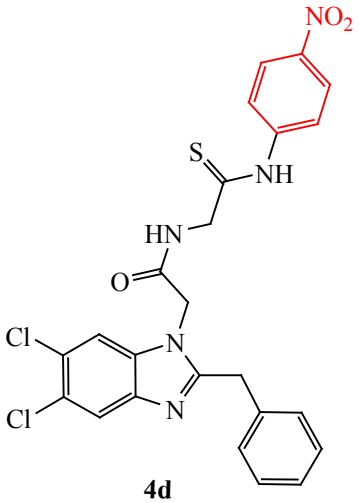


R = CH_3 (**a**), CH_2CH_3 (**b**), Ph (**c**), 4-NO_2Ph (**d**), 4-MePh (**e**).

intramolecular cyclization of compounds **4a**–**4e** in the presence of NaOH. The structures of all new synthesized compounds were confirmed by ^{1}H NMR, ^{13}C NMR spectroscopy. Spectroscopic results of all new synthesized molecules matched the proposed structure.

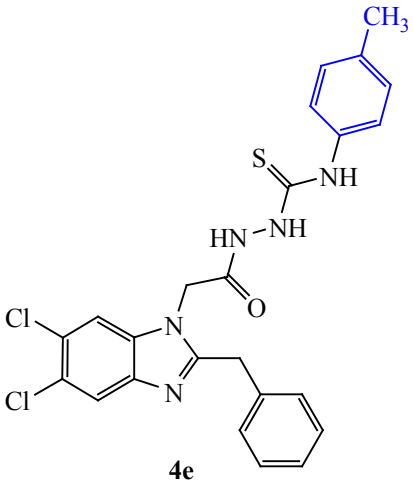
***In vitro* urease inhibition activities.** All of the thiosemicarbazides and triazoles showed effective urease inhibition activity when compared with the standard, thiourea (Table 1). Compounds **5a**–**5e** containing triazole ring have the best urease inhibition results in the range of IC_{50} from 0.04±0.026 to 0.26± 0.042 μg/mL, when compared with the standard (0.267±0.022 μg/mL). 5-[(5,6-Dichloro-1*H*-benzimidazol-1-yl)methyl]-4-nitrophenyl-4*H*-1,2,4-triazole-3-

Scheme 3.



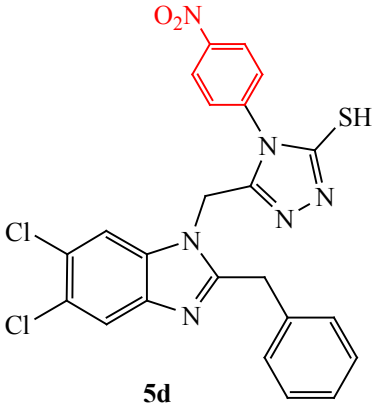
4d

IC_{50} 0.06±0.033 μM



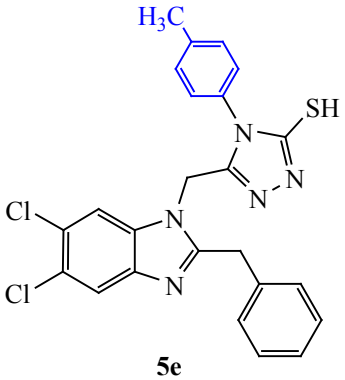
4e

IC_{50} 0.11±0.021 μM



5d

IC_{50} 0.04±0.026 μM



5e

IC_{50} 0.14±0.017 μM

thiol **5d**, having 4-nitrophenyl group on triazole ring at the positions N^1 of benzimidazole core, was found to be the most active inhibitor with the IC_{50} value of 0.04±0.026 μM.

The higher IC_{50} values of compounds **1**–**3** showed that the starting benzimidazole, its ester and hydrazide forms have low urease inhibition activities. The activity increases as it converts to thiosemicarbazides and triazole forms. The most active compounds are **4d** and **5d** containing 4-nitrophenyl moiety (Scheme 3).

After the compounds with nitro group on phenyl ring the most active group has methyl group on phenyl ring. In thiosemicarbazides and triazoles, compounds **4e** and **5e** have best results with IC_{50} values of 0.11±0.021 and 0.14±0.117 μM, respectively. The results showed that 4-nitrophenyl and 4-methylphenyl groups have positive impact on urease inhibition activity.

CONCLUSION

The aim of this work was to design, synthesize and evaluate urease inhibition activities of novel benzimidazole derivatives with benzyl ring at position 2 and containing ester, hydrazide, thiosemicarbazides or triazoles at position 1. Based on the tested activities of the compounds, it was found that the triazole derivatives exhibited the best urease inhibition activity among the tested compounds. Also, nitro group on phenyl ring and methyl molecule on phenyl ring showed the best

Table 1. Urease inhibition activity of compounds **1**–**5**

Compound	IC_{50}, μM
1	0.68±0.450
2	0.65±0.126
3	0.49±0.141
4a	0.26±0.049
4b	0.17±0.035
4c	0.14±0.029
4d	0.06±0.033
4e	0.11±0.021
5a	0.16±0.112
5b	0.15± 0.115
5c	0.26± 0.042
5d	0.04±0.026
5e	0.14±0.117
Thiourea	0.267± 0.022

inhibition activity with thiosemicarbazides and triazoles compared to other compounds.

EXPERIMENTAL

2-Benzyl-5,6-dichloro-1*H*-benzimidazole (1). 4,5-Dichloro-1,2-phenylenediamine (0.010 mol) and ethyl-2-phenylethanimidoate in dry methanol (15 mL) was stirred at room temperature for 12 h. The reaction progress was monitored by TLC. After the reaction copleted, the mixture was poured into water. The precipitate was filtered off and recrystallized from ethanol–water mixture (1 : 3). Yield 93%, mp 184–186°C. IR spectrum, ν, cm^{-1}: 3022 (NH), 1441 (C=N). ^{1}H NMR spectrum, δ, ppm: 4.16 s (2H, CH_2), 7.19–7.72 m (7H, ArH), 12.59 s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 35.25, 124.23, 127.11, 127.43, 128.97, 129.25, 137.47, 156.96.

Ethyl (2-benzyl-5,6-dichloro-1*H*-benzimidazol-1-yl)acetate (2). A solution of compound **1** (0.010 mol) and K_2CO_3 (0.025 mol) in 10 mL of acetone was stirred at room temperature for 1h. Then 0.01 mol of ethyl bromoacetate was added to the reaction mixture and stirred at room temperature for 8h. The reaction mixture was poured into water and precipitation was observed. The white product was filtered off, washed with water and recrystallized. Yield 92%, mp 145–147°C. IR spectrum, ν, cm^{-1}: 1700 (C=O), 1455 (C=N). ^{1}H NMR spectrum, δ, ppm: 1.19 t (3H, CH_3, J = 7.2 Hz), 3.95 m (2H, OCH_2), 4.24 s (2H, CH_2), 5.18 s (2H, NCH_2), 7.25 m (5H, ArH), 7.85 s (1H, ArH), 7.89 s (1H, ArH). ^{13}C NMR spectrum, δ_C, ppm: 14.31, 33.23, 45.21, 61.68, 109.98, 112.65, 120.23, 124.63, 124.96, 127.12, 128.87, 129.33, 129.35, 135.80, 136.21, 142.09, 156.98, 167.77.

2-(2-Benzyl-5,6-dichloro-1*H*-benzimidazol-1-yl) acetohydrazide (3). A solution of compound **2** (0.010 mol) and hydrazine monohydrate (0.035 mol) in ethanol (10 mL) was stirred for 4 h at room temperature. The reaction progress was monitored by TLC (ethanol–ethyl acetate, 3 : 1). When the reaction was completed, the mixture was filtered. The precipitate was dried and recrystallized from an ethanol–water (1 : 2) mixture. Yield 85%, mp 240–241°C. IR spectrum, ν, cm^{-1}: 3310–3299 (NH–NH_2), 1652 (C=O), 1461 (C=N). ^{1}H NMR spectrum, δ, ppm: 9.45 s (1H, NH), 7.82 d (2H, ArH, J = 8.0 Hz), 7.27 m (5H, ArH), 4.83 s (2H, NCH_2), 4.22 s (2H, NH_2), 3.30 s (2H, CH_2). ^{13}C NMR spectrum, δ_C, ppm: 33.32, 45.17, 112.45, 120.18, 124.44, 124.72, 125.86, 127.10, 128.89, 129.45, 135.78, 136.59, 142.17, 157.31, 165.94.

General procedure for synthesis of compounds 4a–4e. Benzimidazole hydrazide **3** (0.010 mol) was dissolved in 15 mL of ethanol. An appropriate isothiocyanate (0.011mol) was added to the hydrazide solution and the mixture was refluxed for 4 h. The solution was cooled and a white solid product was appeared. The white solids were filtered off and recrystallized from ethanol to obtain the desired pure thiosemicarbazide **4a**–**4e**.

2-[(2-Benzyl-5,6-dichloro-1*H*-benzimidazol-1-yl)-acetyl]-*N*–methylhydrazinecarbothioamide (4a). Yield 85%, mp 233–235°C. IR spectrum, ν, cm^{-1}: 3261 (NH), 1682 (C=O), 1554 (C=N), 1239 (C=S). ^{1}H NMR spectrum, δ, ppm: 10.24 s (1H, NH), 9.73 s (1H, NH), 9.31 s (1H, NH), 7.83 s (2H, ArH), 7.27 m (5H, ArH), 4.96 s (2H, NCH_2), 4.23 s (2H, CH_2), 1.04 t (3H, NCH_3). ^{13}C NMR spectrum, δ_C, ppm: 28.0, 31.38, 45.20, 112.57, 120.34, 124.68, 125.01, 125.86, 127.04, 127.31, 135.70, 138.09, 142.42, 156.46, 166.52.

2-[(2-Benzyl-5,6-dichloro-1*H*-benzimidazol-1-yl)-acetyl]-*N*-ethylhydrazinecarbothioamide (4b). Yield 87%, mp 222–224°C. IR spectrum, ν, cm^{-1}: 3266 (NH), 1685 (C=O), 1549 (CN), 1221 (C=S). ^{1}H NMR spectrum, δ, ppm: 10.22 s (1H, NH), 9.70 s (1H, NH), 9.23 s (1H, NH), 8.07 s (1H, ArH), 7.83 t (3H, ArH, J = 6.8 Hz), 7.26 m (3H, ArH), 4.96 s (2H, NCH_2), 4.22 s (2H, NCH_2), 3.46 s (2H, CH_2), 1.08 s (3H, NCH_3). ^{13}C NMR spectrum, δ_C, ppm: 14.87, 28.05, 38.72, 45.19, 112.53, 112.77,

120.34, 124.67, 125.01, 125.64, 127.01, 127.31, 135.73, 138.11, 142.03, 156.48, 166.38.

2-[(2-Benzyl-5,6-dichloro-1*H*-benzimidazol-1-yl)-acetyl]-*N*-phenylhydrazinecarbothioamide (4c). Yield 85%, mp 198–200°C. IR spectrum, ν, cm^{-1}: 3315 (NH), 1728 (C=O), 1544 (C=N), 1212 (C=S). ^{1}H NMR spectrum, δ, ppm: 10.49 s (1H, NH), 9.87 s (1H, NH), 9.67 s (1H, NH), 7.90 s (1H, ArH), 7.84 s (1H, ArH), 7.53 d (2H, ArH, *J* = 8 Hz), 7.43 d (2H, ArH, *J* = 8 Hz), 7.28 m (6H, ArH), 5.03 s (2H, NCH_2), 4.26 s (2H, CH_2). ^{13}C NMR spectrum, δ_C, ppm: 28.04 45.28, 112.64, 120.20, 124.55, 124.82, 125.86, 127.10, 127.16, 127.30, 128.95, 128.90, 129.44, 129.46, 135.74, 136.62, 139.32, 142.21, 157.41, 160.38.

2-[(2-Benzyl-5,6-dichloro-1*H*-benzimidazol-1-yl)-acetyl]-*N*-(4-nitrophenyl)hydrazinecarbothioamide (4d). Yield 78%, mp 196–198°C. IR spectrum, ν, cm^{-1}: 3300 (NH), 1737 (C=O), 1519 (C=N), 1203 (C=S). ^{1}H NMR spectrum, δ, ppm: 10.58 s (1H, NH), 10.13 s (1H, NH), 9.98 s (1H, NH), 8.27 s (1H, ArH), 8.21 d (2H, ArH, *J* = 8 Hz), 7.87 m (3H, ArH), 7.29 m (5H, ArH), 5.07 s (2H, NCH_2), 4.28 s (2H, CH_2). ^{13}C NMR spectrum, δ_C, ppm: 27.04, 45.46, 112.77, 112.91, 120.06, 121.50, 124.54, 124.79, 125.05, 127.19, 128.96, 135.57, 136.42, 139.99, 141.63, 142.04, 146.11, 157.35, 165.72.

2-[(2-Benzyl-5,6-dichloro-1*H*-benzimidazol-1-yl)-acetyl]-*N*-(4-methylphenyl)hydrazinecarbothioamide (4e). Yield 75%, mp 198–200°C. IR spectrum, ν, cm^{-1}: 3202 (NH), 1728 (C=O), 1542 (C=N). ^{1}H NMR spectrum, δ, ppm: 10.45 s (1H, NH), 10.27 s (1H, NH), 9.60 s (1H, NH), 7.88 s (1H, ArH), 7.81 s (1H, ArH), 7.28 m (3H, ArH), 7.15 m (6H, ArH), 5.02 s (2H, NCH_2), 4.26 s (2H, CH_2), 1.21 s (3H, CH_3). ^{13}C NMR spectrum, δ_C, ppm: 21.30, 33.27, 45.24, 112.65, 112.77, 120.20, 124.82, 124.55, 127.13, 128.94, 128.15, 129.45, 129.37, 129.18, 130.35, 135.76, 136.63, 136.72, 142.21, 157.41, 165.54.

General procedure for synthesis of compounds 5a–5e. A mixture of 2 N NaOH (10 mL) and 0.01 mol of thiosemicarbazide **4a**–**4e** in ethanol was refluxed for 12 h. The reaction progress was monitored by TLC. After the reaction completed, the mixture was cooled to room temperature, then acidified with 37% HCl to pH 5–6. The precipitate was filtered off, washed with water and recrystallized.

5-[(5,6-Dichloro-1*H*-benzimidazol-1-yl)methyl]-4-methyl-4*H*-1,2,4-triazole-3-thiol (5a). Yield 90%, mp 300°C (decomp.). IR spectrum, ν, cm^{-1}: 3031 (NH), 1502 (C=N), 1337 (C=S). ^{1}H NMR spectrum, δ, ppm: 7.97 s (1H, ArH), 7.84 s (1H, ArH), 7.23 m (5H, ArH), 5.67 s (2H, NCH_2), 4.26 s (2H, CH_2), 1.03 s (3H, CH_3). ^{13}C NMR spectrum, δ_C, ppm: 30.36, 40.55, 45.20, 112.79, 120.25, 124.75, 125.03, 127.03, 128.70, 129.34, 135.62, 136.46, 142.06, 148.46, 157.34, 167.90.

5-[(5,6-Dichloro-1*H*-benzimidazol-1-yl)methyl]-4-ethyl-4*H*-1,2,4-triazole-3-thiol (5b). Yield 85%, mp 315°C (decomp.). IR spectrum, ν, cm^{-1}: 2627 (SH), 1574 (C=N). ^{1}H NMR spectrum, δ, ppm: 7.94 s (1H, ArH), 7.86 s (1H, ArH), 7.19 m (5H, ArH), 5.65 s (2H, NCH_2), 4.52 s (2H, CH_2), 4.27 s (2H, CH_2), 1.14 s (3H, CH_3). ^{13}C NMR spectrum, δ_C, ppm: 13.51, 27.94, 40.54, 112.70, 112.75, 120.32, 124.80, 125.11, 127.32, 128.71, 129.26, 135.68, 136.15, 142.12, 147.61, 157.12, 167.47.

5-[(5,6-Dichloro-1*H*-benzimidazol-1-yl)methyl]-4-phenyl-4*H*-1,2,4-triazole-3-thiol (5c). Yield 80%, mp 150°C. IR spectrum, ν, cm^{-1}: 3030 (NH), 1496, 1454 (C=N), 1307 (C=S). ^{1}H NMR spectrum, δ, ppm: 13.77 s (1H, NH), 7.83 s (1H, ArH), 7.77 s (1H, ArH), 7.50 m (3H, ArH), 7.41 s (2H, ArH), 7.23 m (5H, ArH), 5.45 s (2H, NCH_2), 4.14 s (2H, CH_2). ^{13}C NMR spectrum, δ_C, ppm: 32.87, 45.83, 112.82, 120.22, 124.76, 125.12, 125.95, 126.97, 127.10, 127.22, 128.53, 128.57, 130.15, 133.30, 135.43, 137.84, 141.72, 147.35, 156.61, 169.07.

5-[(5,6-Dichloro-1*H*-benzimidazol-1-yl)methyl]-4-nitrophenyl-4*H*-1,2,4-triazole-3-thiol (5d). Yield 85%, mp 317°C (decomp.). IR spectrum, ν, cm^{-1}: 3228 (NH), 1630, 1516 (C=N), 1332 (C=S). ^{1}H NMR spectrum, δ, ppm: 8.23 s (1H, ArH), 8.03 d (1H, ArH, *J* = 8.0 Hz), 7.64 m (4H, ArH), 7.28 s (1H, ArH), 7.21 m (3H, ArH), 5.80 s (2H, NCH_2), 4.34 s (2H, CH_2). ^{13}C NMR spectrum, δ_C, ppm: 29.96, 49.42, 112.00, 120.35, 121.75, 125.12, 125.82, 125.49, 126,55, 127.10, 128.85, 130.39, 133.39, 135.78, 136.60, 137.18, 138.45, 140.40, 141.65, 157.09, 168.92.

5-[(5,6-Dichloro-1*H*-benzimidazol-1-yl)methyl]-4-methylphenyl-4*H*-1,2,4-triazole-3-thiol (5e). Yield 84%, mp 310°C (decomp.). IR spectrum, ν, cm^{-1}: 3336 (NH), 1515 (C=N), 1397 (C=S). ^{1}H NMR spectrum, δ, ppm: 8.67 s (1H, ArH), 7.91 s (1H, ArH), 7.87 m (4H, ArH), 7.52 s (1H, ArH), 7.10 m (3H, ArH), 5.54 s (2H, NCH_2), 4.08 s (2H, CH_2) 1.20 s (3H, CH_3). ^{13}C NMR spectrum, δ_C, ppm: 21.14, 33.17, 44.35, 112.58, 119.98, 120.35, 124.51, 124.79, 125.05, 125.84, 127.13, 127.32, 128.82, 129.15, 135.75, 136.74, 137.78, 138.12, 147.77, 156.58.

***In vitro* urease inhibition assay by Van Slyke and Archibald method.** The urease inhibition assay was

determined by spectrophotometrically according to the method of Van Slyke and Archibald [18]. Benzimidazole derivatives and standard thiourea dissolved in DMSO at 4 different concentrations (1.0×10^{-5}–1.0×10^{-2} μg/mL). Urea, the substrate solution and *Jack bean* urease were prepared in 100 mM phosphate buffer at pH 6.8. *Jack bean* urease solution concentration was 16 mg/mL.

In brief, 500 μL of *Jack bean* urease solution was added to 500 μL of the test compounds and standard. The mixture was incubated for 15 min at room temperature. After incubation, 400 μL phenol red solution which was prepared in urea-phosphate buffer (pH 6.8) was added to mixture. The absorbance value of the final mixtures was measured at 570 nm using a UV-Visible spectrophotometer (Perkin Elmer Lambda 35). Inhibition was calculated from the equation below. IC_{50} values (%) of the urease enzyme was calculated from the regression equation and calculated in micromolar unit.

$$\text{Inhibition} = \frac{A_0 - A_1}{A_0} \times 100,$$

where A_0 is absorbance of control, A_1 is absorbance of the sample.

AUTHOR INFORMATION

G. Akyüz, ORCID: https://orcid.org/0000-0002-4452-7387

E. Menteşe, ORCID: https://orcid.org/0000-0002-3408-8202

B. Kahveci, ORCID: https://orcid.org/0000-0001-7394-0552

CONFLICT OF INTEREST

No conflict of interest was declared by the authors.

REFERENCES

1. Kafarski, P. and Talma, M., *J. Adv. Res.*, 2018, vol. 13, p. 101. https://doi.org/10.1016/j.jare.2018.01.007
2. Devesa, S.S., Blot, W.J., and Fraumeni, J.F., *Cancer*, 1998, vol. 83, p. 2049. https://doi.org/10.1002/(SICI)1097-0142(19981115)83:10<2049::AID-CNCR1>3.0.CO;2-2
3. Golbabaei, S., Bazl, R., Golestanian, S., Nabati, F., Omrany, Z.B., Yousefi, B., and Amanlou, M., *DARU J. Pharm. Sci.*, 2013, vol. 21, p. 2. https://doi.org/10.1186/2008-2231-21-2
4. Menteşe, E., Akyüz, G., Emirik, M., and Baltaş, N., *Bioorg. Chem.*, 2019, vol. 83, p. 289. https://doi.org/10.1016/j.bioorg.2018.10.031
5. Kosikowska, P. and Berlicki, Ł., *Expert. Opin. Ther. Pat.,* 2011, vol. 21, p. 945. https://doi.org/10.1517/13543776.2011.574615
6. Valenzuela-Valderrama, M., Cerda-Opazo, P., Backert, S., González, M.F., Carrasco-Véliz, N., Jorquera-Cordero, C., Wehinger, S., Canales, J., Bravo, D., and Quest, A.F.G., *Cancers*, 2019, vol. 11, p. 799. https://doi.org/10.3390/cancers11060799
7. Mobley, H.L.T., Island, M.D., and Hausinger, R.P., *Microbiol. Rev.,* 1995, vol. 59, p. 451. https://doi.org/10.1128/mr.59.3.451-480.1995
8. Ricc, A., Coppo, E., Barbieri, R., Debbia, E.A., and Marchese, A., *J. Chemother.*, 2017, vol. 29, p. 67. https://doi.org/10.1080/1120009X.2016.1195069
9. Amtul, Z., Rahman, A.U., Siddiqui, R.A., and Choudhary, M., *Curr. Med. Chem.*, 2002, vol. 14, p. 1323. https://doi.org/10.2174/0929867023369853
10. Follmer, C., *J. Clin. Pathol.*, 2010, vol. 63, p. 424. https://doi.org/10.1136/jcp.2009.072595
11. Upadhyay, L.S.B., *Ind. J. Biotechnol.*, 2012, vol. 11, p. 381.
12. Mentese, E., Emirik, M., and Sökmen, B.B., *Bioorg. Chem,* 2019, vol. 86, p. 151. https://doi.org/10.1016/j.bioorg.2019.01.061
13. Mentese, E., Bektaş, H., Sökmen, B.B., Emirik, M., Çakır, D., and Kahveci, B., *Bioorg. Med. Chem. Lett.*, 2017, vol. 27, p. 3014. https://doi.org/10.1016/j.bmcl.2017.05.019
14. Salar, U., Nizamani, A., Arshad, F., Khan, K.M., Fakhri, M.I., Perveen, S., Ahmed, N., and Choudhary, M.I., *Bioorg. Chem.*, 2019, vol. 91, p. 103170. https://doi.org/10.1016/j.bioorg.2019.103170
15. Karaali, N., Aydın, S., Baltaş, N., and Mentese, E., *J. Heterocycl. Chem.*, 2020, vol. 57, p. 1806. https://doi.org/10.1002/jhet.3905
16. Baltaş, N., Yılmaz, F., and Mentese, E., *Hacettepe J. Biol Chem,* 2016, vol. 45, p. 293. https://doi.org/10.15671/HJBC.20164420572
17. Van Slyke, D.D. and Archibald, R.M., *J. Biol. Chem.,* 1944, vol. 154, p. 623.
18. Pinner, A., *Die Imidoäther und ihre Derivate,* Berlin: Oppenheim, 1892.