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Araştırma Makalesi / Research Article

Some New Bis-(1,2,4-Triazole) Compounds: Synthesis, Characterization and Urease Enzyme Inhibition

Nesrin ÜNAL KARAALİ[1*], Havva Nur CİHANGİR[2]

Abstract

In this study, thiosemicarbazide derivatives (**2a-c**) were obtained from the reaction of acetohydrazide derivative 1,2,4-triazole compound (**1**) with methyl isothiocyanate, phenyl isothiocyanate, and 4-methylphenyl isothiocyanate compounds, respectively. Then, by intramolecular cyclization of **2a-c** compounds, bis-(1,2,4-triazole) compounds (**3a-c**) were synthesized. The synthesized compounds' chemical structures were verified using FT-IR, ^{1}H-NMR, and ^{13}C-NMR spectroscopic methods. In addition, the urease enzyme inhibition of the synthesized compounds was evaluated using the Weatherburn method *in vitro*. All newly synthesized compounds showed urease enzyme inhibition in the range of 15.00 ± 0.10 to 16.00 ± 0.25 IC_{50} (µg/mL) compared to standard thiourea (IC_{50} = 15.75 ± 0.15 µg/mL).

Keywords: Bis-(1,2,4-triazole), Isothiocyanate, Thiosemicarbazide, Urease.

Bazı Yeni Bis-(1,2,4-Triazol) Bileşikleri: Sentez, Karakterizasyon ve Üreaz Enzim İnhibisyonu

Öz

Bu çalışmada, asetohidrazid türevi 1,2,4-triazol bileşiğinin (**1**) sırasıyla metil izotiyosiyanat, fenil izotiyosiyanat ve 4-metilfenil izotiyosiyanat bileşikleri ile reaksiyonundan tiyosemikarbazid türevleri (**2a-c**) elde edilmiştir. Daha sonra, **2a-c** bileşiklerinin intramoleküler siklizasyonu ile bis-(1,2,4-triazol) bileşikleri (**3a-c**) sentezlenmiştir. Sentezlenen bileşiklerin kimyasal yapıları FT-IR, ^{1}H-NMR ve ^{13}C-NMR spektroskopik yöntemleri kullanılarak doğrulandı. Ayrıca, sentezlenen bileşiklerin üreaz enzimi inhibisyonu *in vitro* Weatherburn yöntemi kullanılarak değerlendirildi. Yeni sentezlenen tüm bileşikler, standart tiyoüre (IC_{50} =15.75 ± 0.15 µg/mL) ile karşılaştırıldığında 15.00 ± 0.10 ila 16.00 ± 0.25 IC_{50} (µg/mL) aralığında üreaz enzim inhibisyonu göstermiştir.

Anahtar Kelimeler: Bis-(1,2,4-triazol), İzotiyosiyanat, Tiyosemikarbazid, Üreaz.

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1. Introduction

The synthesis of new compounds that can effectively treat infections and have as few side effects as possible is one of the important areas of organic synthesis chemistry today. Triazole moieties occupy an important place in this field. 1,2,4-Triazole and its heterocyclic derivatives are pharmacologically important compounds with a broad spectrum of activities, such as neuroprotectivet, antioxidant, antimalarial, antifreeze, anticancer, antimicrobial, anti-inflammatory, antifungal, anxiolytic, anticonvulsant, antimigraine, antiviral, antitumour, antituberculosis, antidepressant, analgesic and enzyme inhibitor. (Bekhit et al., 2004; Farghaly et al., 2000; Karaali and Mentese, 2016; Karaali et al., 2019). Triazole moieties are active ingredients of some commercially available drugs, such as Cefatrizine as an antibiotic, Tazobactum as an antibacterial agent, and Suvorexant for treating insomnia. In addition, the conazoles (itraconazole, fluconazole, posaconazole, triazolam, and alprazolam) are an important group of drugs in the azoleclass. (Gupta et al., 2007; Schiller and Fung, 2007). Ribavirin, which contains a 1,2,4-triazole ring, is a broad-spectrum antiviral agent. A combination of ribavirin and interferon is currently used to treat hepatitis C. The drugs anastrozole and letrozole, which are used to treat breast cancer by inhibiting aromatase, contain the 1,2,4-triazole nucleus (Figure 1).

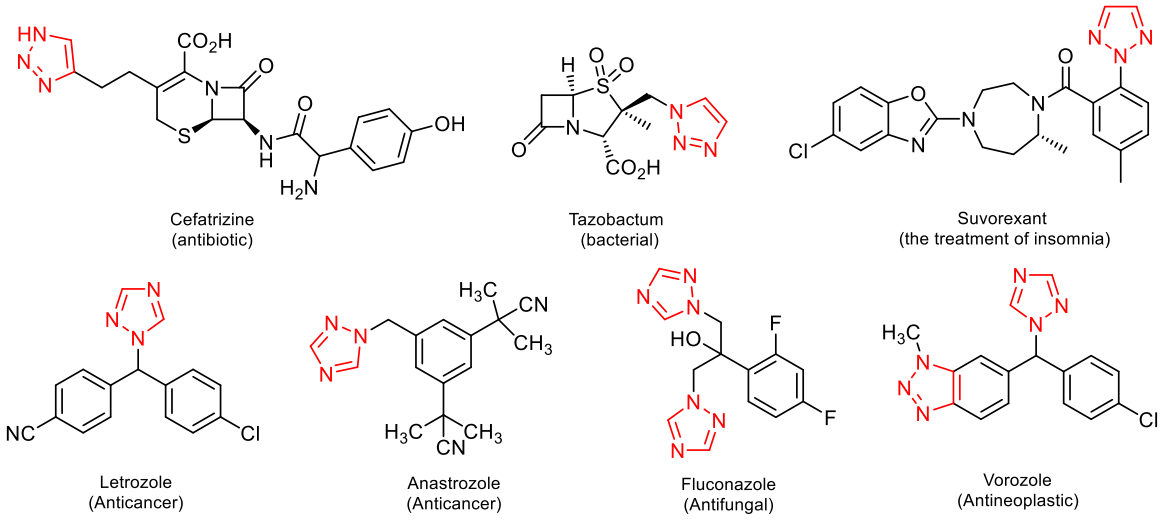


Figure 1. Biologically active drugs containing triazole units.

Triazoles are the most stable compounds of the azole class. Triazoles have characteristic properties such as amide esters and carboxylic acid isosteres. These heterocyclic derivatives with a five-membered ring have two isomeric forms, 1,2,4-triazole and 1,2,3-triazole (Bentley et al., 2002).

One of the most valuable methods for the formation of 1,2,4-triazoles is the interaction of carbothioamide derivatives with a base (El-Khawass et al., 1989; Ram et al., 1988; Amir and Shikha, 2004). In this study, some new bis-(1,2,4-triazole) compounds have been synthesized and their

structures elucidated, starting from the starting compound **1** (2-[4-amino-3-(4-bromobenzyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl] acetohydrazide). The synthesis of molecule **1** was carried out according to the method previously reported in the literature (Kahveci et al., 2015). Thiosemicarbazide derivatives (**2a-c**), which constitute the initial first part of the study, were obtained by boiling methyl isothiocyanate, phenyl isothiocyanate and 4-methylphenyl isothiocyanate compounds, respectively, with the compound **1** in ethanol under reflux. In the last step of the study, bis-(1,2,4-triazole) compounds (**3a-c**) were synthesized by intramolecular cyclization by boiling thiosemicarbazide derivatives (**2a-c**) in 2N NaOH solution under reflux.

2. Materials and Methods

2.1. Chemical

In this study, the chemicals used were obtained from Sigma-Aldrich, and the solvents were obtained from various local and foreign companies. The reaction times of the synthesized substances were determined using thin layer chromatography plate. The melting points of the synthesized compounds were determined using a Stuart mode SMP30 melting point determination apparatus. ^{1}H-NMR and ^{13}C-NMR (APT) spectra were obtained in DMSO-d_6 on a Varian Mercury 400 MHz, Bruker Avance III 400 MHz NMR instrument. IR spectra were obtained using the ATR technique on a Perkin Elmer 100 FT-IR spectrometer.

The general process for synthesizing compounds 2a–c

Compound **1** (1 mmol) and the corresponding isothiocyanate (1 mmol) were refluxed in 15 mL ethanol for 4 hours. The reaction time was determined by TLC. The mixture obtained was poured into water, the precipitate was filtered, and then washed with plenty of water. It was purified by crystallization in ethyl alcohol and dried over $CaCl_2$ in a desiccator.

2-[4-Amino-3-(4-bromobenzyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl]-*N*′-ethanthionylacetohydrazide (2a). IR spectrum (ATR, ν, cm-1): 1125 (C=S), 1696 (C=O), 3315, 3215 (NH_2, NH); ^{1}H-NMR spectrum (DMSO-d_6) δ (ppm): 2.85 (CH_3, 3H, s), 3.85 (CH_2, 2H, s), 4.99 (NCH_2, 2H, s,), 5.31 (NH_2, 2H, s), 7.19 (ArH, 2H, d, J = 8.0 Hz), 7.47 (ArH, 2H, d, J = 8.0 Hz,), 7.96 (NH, 1H, s), 9.29 (NH, 1H, s), 9.99 (NH, 1H, s).

2-[4-Amino-3-(4-bromobenzyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl]-*N'*-(phenylcarbonothionyl)acetohydrazide (2b). IR spectrum (ATR, ν, cm^{-1}): 1188 (C=S), 1679, 1704 (C=O), 3353, 3200, 3195 (NH_2, NH); ^{1}H-NMR spectrum (DMSO-d_6) δ (ppm): 3.85 (CH_2, 2H, s), 4.46 (NCH_2, 2H, s), 5.31 (NH_2, 2H, s), 7.14- 7.18 (ArH, 1H, m), 7.22 (ArH, 2H, d, J = 8.0 Hz), 7.32 (ArH, 2H, t, J = 8.0 Hz), 7.41 (ArH, 2H, d, J = 8.0 Hz), 7.48 (ArH, 2H, d, J = 8.0 Hz), 9.61 (NH, 1H, s), 9.70 (NH, 1H, s), 10.25 (NH, 1H, s); ^{13}C NMR spectrum (DMSO-d_6) δ (ppm): 30.27 (CH_2), 47.15 (NCH_2), 120.28, 125.72, 128.55, 131.56, 131.69, 135.61, 139.41 (ArC), 147.17 (C=N), 153.92 (C=O, triazole), 166.96 (C=O), 181.16 (C=S).

2-(4-Amino-3-(4-bromobenzyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)-*N'*-(4-methylphenylcarbonothionyl)acetohydrazide (2c). IR spectrum (ATR, ν, cm^{-1}): 1197 (C=S), 1678, 1694 (C=O), 3359, 3205 (NH_2), 3199 (NH); ^{1}H NMR spectrum (DMSO-d_6) δ (ppm): 2.27 (CH_3, 3H, s), 3.85 (CH_2, 2H, s), 4.45 (NCH_2, 2H, s), 5.30 (NH_2, 2H, s), 7.12 (ArH, 2H, d, J = 8.0 Hz), 7.21 (ArH, 2H, d, J = 8.0 Hz), 7.26 (ArH, 2H, d, J = 8.0 Hz), 7.47 (ArH, 2H, d, J = 8.0 Hz), 9.53 (NH, 1H, s), 9.62 (NH, 1H, s), 10.22 ve 10.94 (NH, 1H, s); ^{13}C NMR spectrum (DMSO-d_6) δ (ppm): 20.01 (CH_3), 30.26 (CH_2), 47.12 (NCH_2), 120.27, 122.17, 123.55, 129.01, 129.57, 131.55, 131.68, 134.91, 135.61, 136.83 (ArC), 147.14 (C=N), 153.91 (C=O, triazole), 166.72 (C=O), 181.07 (C=S).

The general process for synthesizing compounds 3a-c

A solution of 0.01 mol compound **2c** and 2N (15 mL) NaOH was refuxed for 7 hours. After cooling the reaction mixture to room temperature, the pH of the mixture was adjusted to 5-6 with 37% HCl. The precipitate was filtered, washed with plenty of water, purified by crystallization with ethanol, dried over $CaCl_2$ in a desiccator.

4-Amino-5-(4-bromobenzyl)-2-((5-mercapto-4-methyl-4*H*-1,2,4-triazol-3-yl)methyl)-2,4-dihydro-3*H*-1,2,4-triazol-3-one (3a). IR spectrum (ATR, ν, cm^{-1}): 1332 (C=S), 1580, 1572 (C=N), 1690 (C=O), 3114, 3434 (NH_2), 3217 (NH); 1H NMR spectrum (DMSO-d_6) δ (ppm): 3.37 (CH_3, 3H, s,), 3.85 (CH_2, 2H, s), 4.99 (NCH_2, 2H, s), 5.31 (NH_2, 2H, s), 7.19 (ArH, 2H, d, J = 8.0 Hz), 7.47 (ArH, 2H, d, J = 8.0 Hz), 13.66 (SH, 1H, s); ^{13}C NMR spectrum (DMSO-d_6) δ (ppm): 30.19 (CH_2), 30.52 (CH_3), 40.49 (NCH_2), 120.29, 131.37, 131.46, 131.70, 131.84, 135.54 (ArC), 148.02 (C=N, triazolone), 148.50 (C=N, triazolthiol), 153.39 (C=O, triazolone), 167.90 (C=N, triazolthiol).

4-Amino-5-{4-bromobenzyl)-2-[(5-mercapto-4-phenyl-4*H*-1,2,4-triazol-3-yl]methyl}-2,4-dihydro-3*H*-1 ,2,4-triazol-3-one (3b). IR spectrum (ATR, ν, cm^{-1}): 1356 (C=S), 1569 (C=N), 1694

(C=O), 3136 (NH), 3275, 3435 (NH_2); ^{1}H NMR spectrum (DMSO-d_6) δ (ppm): 3.75 (CH_2, 2H, s), 4.63 (NCH_2, 2H, s,), 5.04 (NH_2, 2H, s,), 7.08 (ArH, 1H, s,), 7.16 (ArH, 2H, d, J = 8.0 Hz), 7.28 (ArH, 3H, s), 7.48 (ArH, 2H, d, J = 8.0 Hz); ^{13}C NMR spectrum (DMSO-d_6) δ (ppm): 30.14 (CH_2), 41.16 (NCH_2), 120.22, 127.82, 128.33, 128.65, 131.51, 131.64, 135.70, 136.62 (ArC), 146.26 (C=N, triazolone), 146.63 (C=N, triazolthiol), 152.81 (C=O, triazolone), 168.51 (C=N, triazolthiol).

4-Amino-5-(4-bromobenzyl)-2-{[5-mercapto-4-(p-tolyl)-4*H*-1,2,4-triazol-3-yl]methyl}-2,4-dihydro-3*H*-1,2,4-triazol-3-one (3c). IR spectrum (ATR, ν, cm^{-1}): 1358 (C=S), 1572 (C=N), 1682 (C=O), 3275 (NH), 3314, 3440 (NH_2); ^{1}H NMR spectrum (DMSO-d_6) δ (ppm): 2.30 (CH_3, 3H, s,), 3.76 (CH_2, 2H, s,), 4.63 (NCH_2, 2H, s,), 5.09 (NH_2, 2H, s,), 6.99 (ArH, 2H, d, J = 8.0 Hz), 7.10 (ArH, 2H, d, J = 8.0 Hz), 7.17 (ArH, 2H, d, J = 8.0 Hz), 7.48 (ArH, 2H, d, J = 8.0 Hz); ^{13}C NMR spectrum (DMSO-d_6) δ (ppm): 21.20 (CH_3), 30.15 (CH_2), 41.10 (NCH_2), 120.26, 128.12, 129.38, 131.54, 131.66, 133.37, 135.66, 137.58 (ArC), 146.67 (C=N, triazolone), 146.80 (C=N, triazolthiol), 152.88 (C=O, triazolone), 168.67 (C=N, triazolthiol).

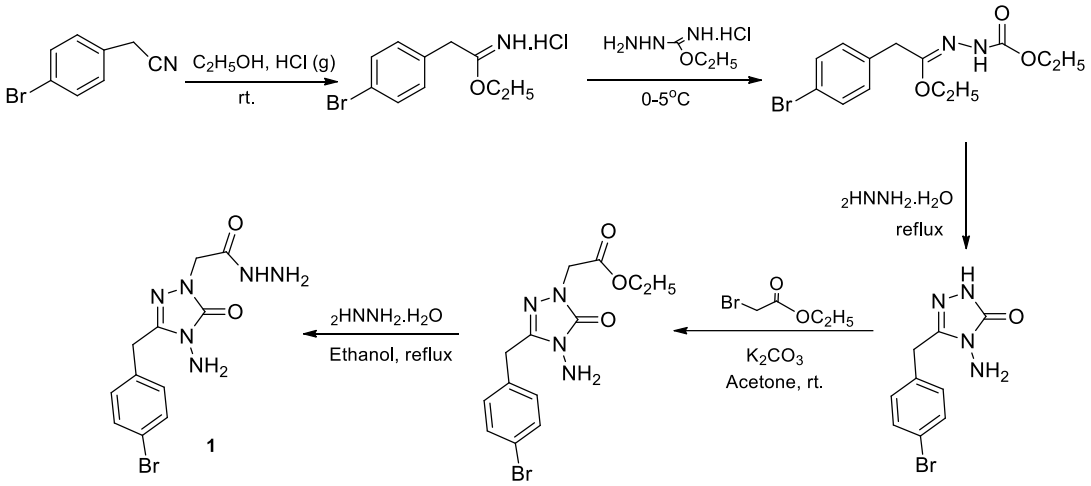
2.2. Urease inhibition assay

Urease inhibitory activities of the synthesized compounds were assayed according to the previously reported procedure (Akyüz and Menteşe, 2023).

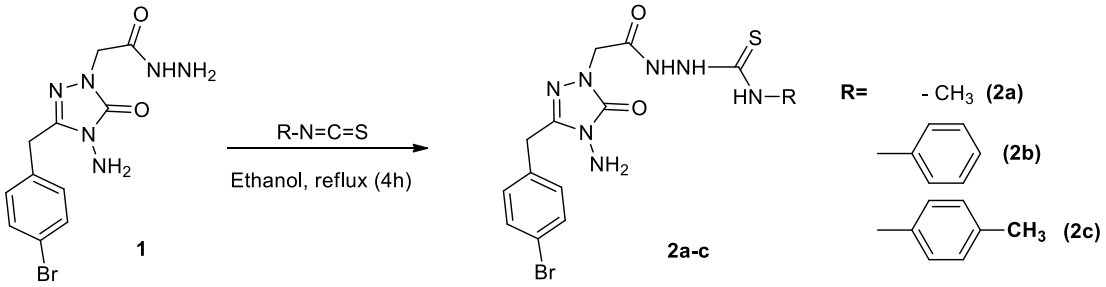
3. Findings and Discussion

In this study, thiosemicarbazide and bis-triazole derivatives of triazoles were synthesised, which have various biological properties reported in the literature and are in clinical use. Compound **1** was synthesized according to the previously reported method in the literature (Scheme 1) (Kahveci et al., 2015). The general reaction equation for the synthesis studies is shown in (Schemes 2, 3). The reaction of compound **1** with methyl isothiocyanate, phenyl isothiocyanate and 4-methylphenyl isocyanate separately afforded the compounds 2-[4-amino-3-(4-bromobenzyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl]-*N*′-ethanthionylacetohydrazide (**2a**), 2-[4-amino-3-(4-bromobenzyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl]-*N*′-(phenylcarbonothionyl)acetohydrazide (**2b**) and 2 -(4-amino-3-(4-bromobenzyl)-5-oxo-4,5-dihydro-1-*H*-1,2,4-triazol-1-yl)-*N*′-(4-methylphenylcarbonothionyl)acetohydrazide (**2c**) were obtained. When the IR spectra of type **2a-c** thiosemicarbazide derivatives were studied, it was observed that the NH_2 group in the triazole-3-one ring gave signals at 3359-3200 cm^{-1} and the C=O group at 1704-1667 cm^{-1}. NH signals from the thiosemicarbazide structure were observed at 3205-3195 cm^{-1} and the C=S signals at 1197-1188 cm^{-}

[1]. When the ^{1}H-NMR spectra of such compounds were examined, the NH signals originating from the thiosemicarbazide part added to the structure were observed in the range of 7.96, 9.29 and 9.99 ppm in the **2a** compound containing aliphatic side group and in the range of 9.53-9.61, 9.62-9.70 and 10.22-10.25 ppm in the **2b-c** compounds containing the aromatic side group. In the ^{13}C-NMR spectra of the **2a-c** compounds, the C=S peaks are in the range of 181.07-181.16 ppm.



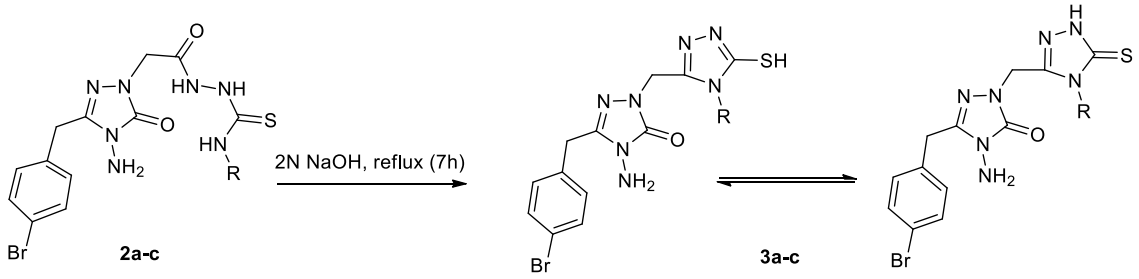
Scheme 1. The synthetic route for compound **1**



Scheme 2. The synthetic route for **2a-c** compounds.

In the second part of the study, bis-(1,2,4-triazole) derivatives (**3a-c**) were synthesized as a result of intramolecular cyclization reactions of **2a-c** compounds in basic medium. The signals belonging to the C=S group in the triazol-3-thion structure of these compounds were recorded in the range of 1330-1356 cm^{-1} in the IR spectrum. When the ^{1}H-NMR spectrum data of compounds **3a-c** were examined, it was found that the NH signals observed around 9-10 ppm in the thiosemicarbazide structure disappeared. Instead, the SH group in compound **3a** gave a signal at 13.66 ppm. When the ^{13}C-NMR spectrum data of the compounds were examined, it was observed that the C=N group in the triazole rings was at 146-148 ppm, and the C=O group in the triazol-3-one ring was at 152-153 ppm. In addition, the presence of C-3 carbons in the triazole-3-thiol ring in these molecules in the range of 167-168 ppm indicates that the structure is in the thiol form in DMSO-d_6. IR and NMR data

of the synthesized compounds confirm their molecular structures. The FT-IR(ATR), ^{1}H-NMR and ^{13}C-NMR (APT) spectras of compound **3a** is given as an example in Figure 2, 3, 4. Physical data of the synthesized compounds are given in Table 1.



Scheme 3. The synthetic route for **3a-c** compounds.

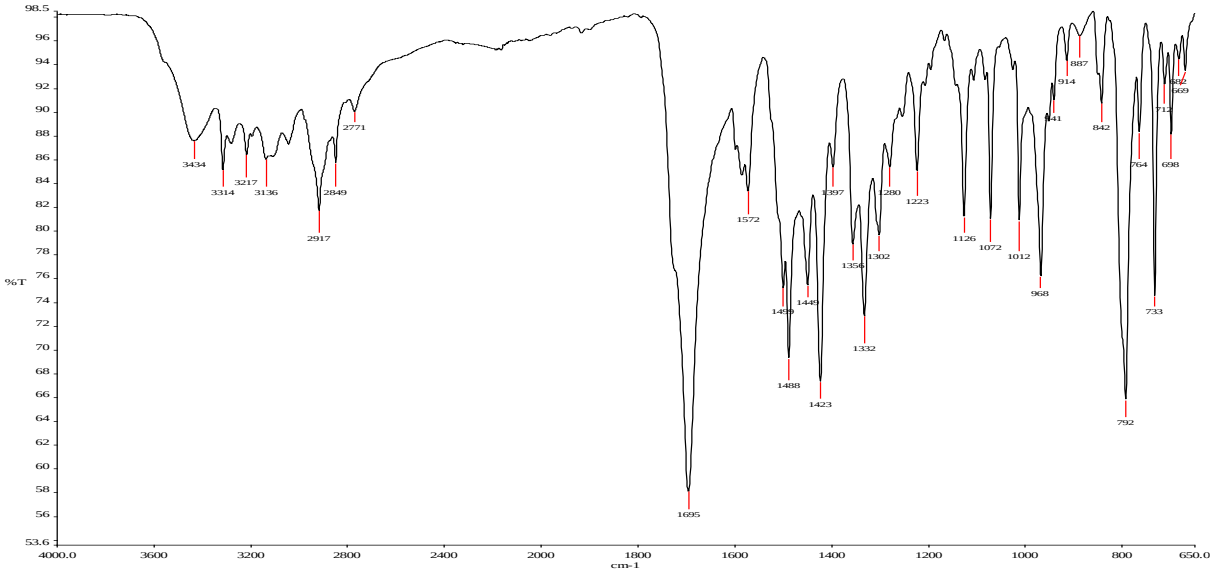


Figure 2. FT-IR(ATR) spectra of compound **3a**.

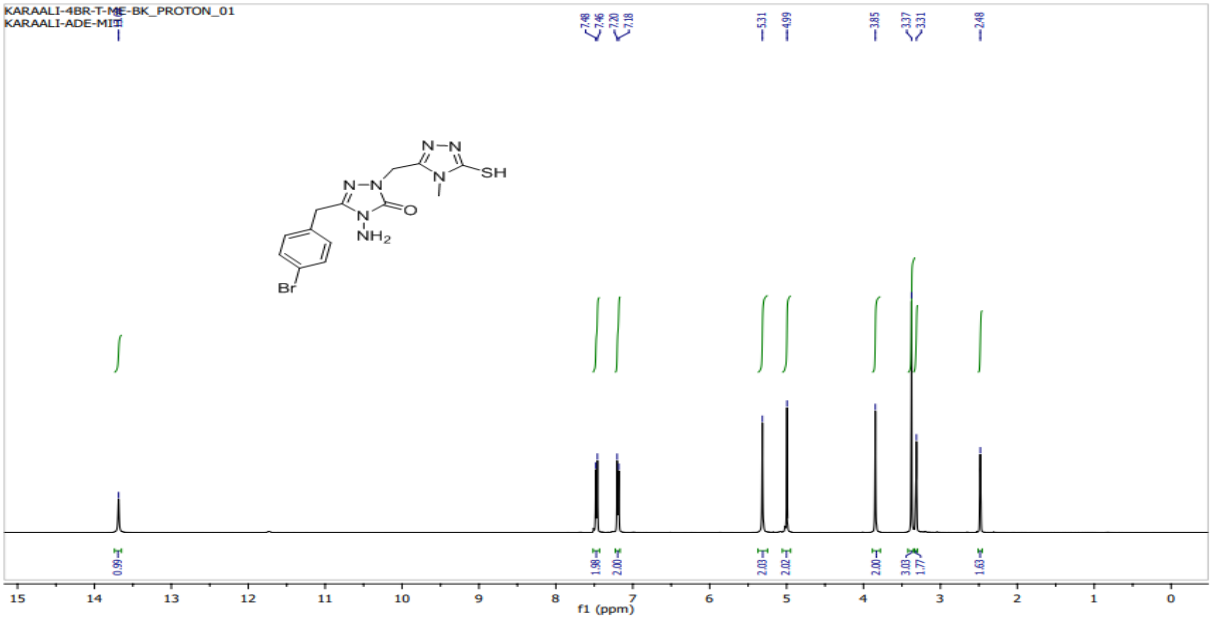


Figure 3. ^{1}H-NMR spectra of compound **3a** (400 MHz, DMSO-d_6).

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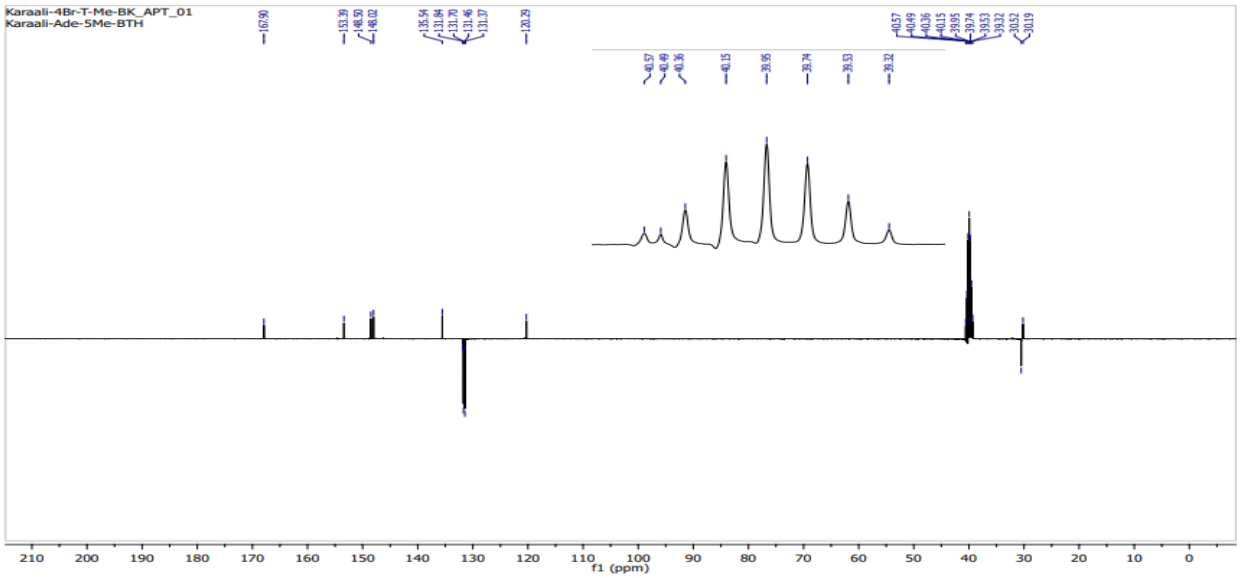

Figure 4. ^{13}C-NMR (APT) spectra of compound **3a** (100 MHz, DMSO-d_6).

Tablo 1. Physical data for **2a–c** and **3a-c.**

Compound	R	Chemical Formula	InChI	M.p. (°C)	Yield (%)
2a	CH_3	$C_{13}H_{16}BrN_7O_2S$	1S/C13H16BrN7O2S/c1-16-2(24)18-17-11(22)7-20-13(23)21(15)10(19-20)6-8-2-4-9(14)5-3-8/h2-5H,6-7,15H2,1H3,(H,17,22)(H2,16,18,24)	162-3	93
2b	C_6H_5	$C_{18}H_{18}BrN_7O_2S$	1S/C18H18BrN7O2S/c19-13-8-6-12(7-9-13)10-15-24-25(18(28)26(15)20)11-16(27)22-23-17(29)21-14-4-2-1-3-5-14/h1-9H,10-11,20H2,(H,22,27)(H2,21,23,29)	109-10	92
2c	$C_6H_4CH_3(4)$	$C_{19}H_{20}BrN_7O_2S$	1S/C19H20BrN7O2S/c1-12-2-8-15(9-3-12)22-18(30)24-23-17(28)11-26-19(29)27(21)16(25-26)10-13-4-6-14(20)7-5-13/h2-9H,10-11,21H2,1H3,(H,23,28)(H2,22,24,30)	190-1	90
3a	CH_3	$C_{13}H_{14}BrN_7OS$	1S/C13H14BrN7OS/c1-19-11(16-17-12(19)23)7-20-13(22)21(15)10(18-20)6-8-2-4-9(14)5-3-8/h2-5H,6-7,15H2,1H3,(H,17,23)	240-1	95
3b	C_6H_5	$C_{18}H_{16}BrN_7OS$	1S/C18H16BrN7OS/c19-13-8-6-12(7-9-13)10-15-23-24(18(27)26(15)20)11-16-21-22-17(28)25(16)14-4-2-1-3-5-14/h1-9H,10-11,20H2,(H,22,28)	202-3	93
3c	$C_6H_4CH_3(4)$	$C_{19}H_{18}BrN_7OS$	1S/C19H18BrN7OS/c1-12-2-8-15(9-3-12)26-17(22-23-18(26)29)11-25-19(28)27(21)16(24-25)10-13-4-6-14(20)7-5-13/h2-9H,10-11,21H2,1H3,(H,23,29)	200-1	90

In this study, the urease inhibition potentials of the synthesized compounds were invesigated. IC_{50} values for the urease inhibitory activity of the synthesized compounds and thiourea were determined (Table 2). Lower IC_{50} values indicate greater inhibition. All synthesized compounds showed urease enzyme inhibition in the range of 15.00 ± 0.10 to 16.00 ± 0.25 IC_{50} (µg/mL) compared to standard thiourea (IC_{50} (µg/mL): 15.75 ± 0.15). Compound **3a** (15.00 ± 0.10 µg/mL) has the highest potency among the compounds tested. Similar studies in the literature, have reported effective urease inhibition properties of compounds containing a triazole ring and having a thiosemicarbazide structure (Menteşe et al., 2019; Akyüz et al., 2022).

Table 2. Urease enzyme inhibition activity of synthesized compounds Compound (**2a-c**, **3a-c**).

Compound	**IC_{50} (µg/mL)**
2a	16.00 ± 0.25
2b	15.90 ± 0.55
2c	15.00 ± 0.05
3a	15.00 ± 0.10
3b	15.55 ± 0.15
3c	15.85 ± 0.10
Thiourea	15.75 ± 0.15

4. Conclusions and Recommendations

Triazole derivatives are widely used in synthesis chemistry in studies to discover new bioactive compounds because of their broad biological activity.In this study, new thiosemicarbazide derivatives containing 1,2,4-triazole moiety (2a-c) and bis-(1,2,4-triazole) compounds (**3a-c**) were synthesized and their urease enzyme inhibition properties were evaluated by *in vitro* Weatherburn method. With IC_{50} values ranging from 15.00 ± 0.10 to 16.00 ± 0.25 µg/mL, all the synthesized compounds showed good activities when compared with thiourea (IC_{50} = 15.75 ± 0.15 µg/mL) as a reference inhibitor. Among the thiosemicarbazide derivatives, compound **2c** (IC_{50}= 15.00 ± 0.05 µg/mL) containing 4-methyl phenyl group and compound **3a** (IC_{50} = 15.00 ± 0.10 µg/mL) containing methyl group among bis-(1,2,4-triazole) derivatives showed the highest inhibition potential against urease enzyme. These results will help in design of novel enzyme inhibitors with bis-(1,2,4-triazole) structures.

Authors' Contributions

Nesrin Ünal Karaali: Contributed to manuscript preparation, and carried out Synthesis and biological experimental studies. Havva Nur Cihangir: Contributed to Synthesis studies.

Statement of Conflicts of Interest

There is no conflict of interest between the authors.

Statement of Research and Publication Ethics

The author declares that this study complies with Research and Publication Ethics.

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