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Synthesis of Some New 1,2,4-Triazole-3-one Derivatives and Investigation of Biological Activity

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Abstract

Schiff bases have excellent characteristics, structural similarities with natural biological agents and synthetic flexibility. Schiff base-bimolecular condensation products with aldehydes of primary amines represent valuable intermediates in organic synthesis. Schiff bases derived from salicylaldehyde have been reported to have plant growth regulator, antimicrobial or antimycotic activity. In studies describing the relationship between quantitative structure-antitumor activity of a series of Schiff bases, Salicyldehydes have been shown to provide the best correlation in the ligands. In this study, 6 new Schiff bases were synthesized from the reaction of the substituted amino compounds with 5-bromosalicylaldehyde and their structures were illuminated spectroscopic data. The biological activities of this compound series were evaluated. The results show that the novel compounds synthesized have effective antioxidant and antiurease activities.

Keywords: 1 2 4-Triazole-3-one, 5-Bromosalicylaldehyde, Amino Compounds, Antioxidant Activity, Antiurease Activity

Bazı Yeni 1,2,4-Triazole-3-on Türevlerinin Sentezi ve Biyolojik Aktivitelerinin İncelenmesi

Öz

Schiff bazları mükemmel karakteristikliğe, doğal biyolojik maddelerle yapısal benzerliklere ve sentetik esnekliğe sahiptirler. Primer aminlerin aldehidler ile Schiff baz-bimoleküler kondenzasyon ürünleri, organik sentezde değerli ara maddeleri temsil eder. Salisilaldehitden türeyen Schiff bazlarının bitki büyüme düzenleyici, antimikrobiyen veya antimikotik aktivitesi olduğu bildirilmiştir. Bir dizi Schiff bazının kantitatif yapı-antitümör aktivite ilişkisini açıklayan çalışmalarda, salisilaldehitlerden elde edilen ligandlarda en iyi korelasyonun sağlandığı gösterilmiştir. Bu çalışmada substitue amino bileşiklerinin 5-Bromosalisilaldehit ile reaksiyonundan 6 yeni Schiff bazları sentezlendi ve yapıları, spektroskopik verilerle aydınlatıldı. Bu bileşik serisinin biyolojik aktiviteleri değerlendirildi. Sonuçlar, sentezlenen yeni bileşiklerin etkili antioksidan ve antiüreaz aktiviteye sahip olduğunu göstermektedir.

Anahtar Kelimeler: 1 2 4-Triazole-3-on, 5-Bromosalisilaldehit, Amino Bileşikleri, Antioksidan Aktivite, Antiüreaz Aktivite

1. Introduction

Schiff bases have a wide range of applications in many fields such as analytical, inorganic and biological chemistry. As with optical and electrochemical sensors, used to determine the selectivity and sensitivity in various selective chromatographic methods (Lawrence and Frei, 1976; Valcarcel and Laque de Castro, 1994; Spichiger-Keller, 1998). Among all organic reagents used, Schiff bases have unique characteristics, structural similarities with natural biological agents, relatively simple preparation procedures, and synthetic flexibility that makes it possible to design appropriate structural features (Jungreis and Thabet, 1969; Patai, 1970). Schiff bases are characterized by the N=CH- (imine) group which clarifies the transamination and racemation reaction mechanism in the biological system (Shawali et al., 1985; Lau, 1999). Schiff bases have been studied for their important properties in catalysis (Hernandes et al., 2002). Demonstrate catalytic activity in the hydrogenation of olefins (Olie and Olive, 1984). They find application in biomimetic catalytic reactions.

Many commercial inhibitors contain aldehydes or amines, but probably due to the C = N bond Schiff bases, more effectively in many cases. (Khalifa et al., 2010; Maliha et al., 2009; Naz and Igbal, 2009; Imran et al., 2009; Li et al.,1999). The main interaction between inhibitor and metal surface is chemisorption (Ashassi-Sorkhabi et al., 2006). The inhibitor molecule must have centers capable of bonding with the metal surface by electron transfer. The nucleophilic centers of the protective compound, such as oxygen and nitrogen atoms, have free pair of electrons ready to share. Together with atoms of benzene rings, they form multiple absorption sites for the inhibitor and thus provide stable monolayer formation (Quan et al., 2001).

Biological features Schiff bases, such as antibacterial and antifungal activities have been reported (Sari et al., 2003; Verma et al., 2004; Williams, 1972; Campos et al.,1999).

Recently performed synthesis and the biological activities of the 3-alkil(aril)-4-amino-4,5-dihidro-1H-1, 2, 4-triazole-5-on type compounds obtained from many derivatives were examined. Also, it was expressed antibacterial, antifungal, antituberculastatic, anticancer and anti-HIV effects (Chidananda et al., 2012; Li et al., 2013; Henen et al., 2012). In this study, the synthesis of new derivatives of 4 types of compounds has been planned.

Oxidative agents play a significant role in the pathogenesis of various diseases, such as carcinogenesis, atherosclerosis, diabetes, nefritisis, cardiovascular diseases and neurodegenerative diseases (Rice-Evans and Diplock, 1991; Griendling and FitzGerald, 2003). Because of this reason, new synthetic antioxidants are demanded from exterior sources (Sogawa et al., 1994).

Ureases (urea amidohydrolase EC 3.5.1.5) are a nickel-dependent enzyme which catalyzes the hydrolysis to ammonia and carbon dioxide of urea. This enzyme is the most widely found in various

plants, fungi, algae, bacteria and soil (Juszkiewicz et al., 2004; Modolo et al., 2015). Bacterial ureases are important deadliness factors, which are infected in the some pathogenesis such as kidney stone formation, pyelonephritis, etc. (Maroney and Ciurli, 2014). Urease inhibitors are used to prevent the formation of stone in the urinary tracts (Sheo, 2012).

In current study, synthesized new ligands containing salicyl moiety with high efficiency. Biological activities of new ligands were determined by *in vitro* assay and compared to the activity of standard compounds.

2. Material ve Metod

2.1. General

Specific melting points of the new compounds were examined in the Barnstead Electrothermal apparatus. ^{1}H-NMR and ^{13}C-NMR spectra (δ, ppm) were determined on a Varian Mercury 200 MHz spectrophotometer. The IR spectra (υ, cm^{-1}) were carried with a Perkin-Elmer 1600 FTIR spectrometer. The required chemicals were supplied from Merck and Fluka Ethylp-methylbenzimidate hydrochlorides **(1a-c)** were synthesized using a published method (Gumrukcuoglu, 2007). Biological activities of samples were assayed spectrophotometrically (UV-1240, Shimadzu, Japan).

2.2. Synthesis of Schiff Bases (4a–c, 5a-c)

Salicyl aldehyde derivative (10 mmol) was added to a solution of the compound **(3)** (10 mmol) in 20 ml of acetic acid and boiled for 1.5 hours under reflux. After cooling the balloon contents, it was precipitated by addition of purified water. The precipitated crude product was then filtered off, washed with distilled water and dried in vacuo. It was crystallized from DMSO-water (1: 3). The crystals recovered were further crystallized from the same mixture several times and dried in vacuo to give the compounds **(4a–c, 5a-c)**.

4-{[(3-methoxy-2-hydroxyphenyl)methylene]amino}-5-cyclopropyl-2,4-dihydro-3H-1,2,4-triazole-3-one (4a): (Yield 2.56 g, 81%), m.p. 232–233°C; IR (KBr)/cm: 3158 (NH), 1709 (C=O), 1630, 1603 (2 C=N), 1243 (C-O); ^{1}H-NMR (DMSO-d_6) δ (ppm) 2.63 (m, 4H, CH_2), 3.78 (m, 1H, CH), Ar–H [7.63 (d, 1H J=8.02 Hz), 7.72 (s, 1H), 7.88 (d, 1H, J=8.02 Hz), 9.36 (s, 1H, N=CH), 10.38 (s, 1H, OH), 12.19 (s, 1H, NH); ^{13}C-NMR (DMSO-d_6) δ (ppm) 171.09 (N=CH), 155.87 (C=O), 153.41 (C=N), Ar–C [142.12 (C), 137.40 (C), 134.55 (CH), 125.34 (CH), 121.33 (CH), 115.87 (C)], 40.12 (CH), 31.28 (2 CH_2).

4-{[(3-methoxy-2-hydroxyphenyl)methylene]amino}-5-4-methylphenyl-2,4-dihydro-3H-1,2,4-triazole-3-one (4b):(Yield 3.20 g, 85%), m.p. 228–229°C; IR (KBr)/cm: 3180 (NH), 1720 (C=O), 1623, 1592 (2 C=N), 1250 (C-O); ^{1}H-NMR (DMSO-d_6) δ (ppm) 2.36 (s, 3H, Ar-CH_3), Ar–H [7.16 (d, 2H, J=7.65 Hz), 7.45 (d, 2H, J=7.65 Hz), 7.60 (d, 1H J=8.20 Hz), 7.75 (s, 1H), 7.82 (d, 1H, J=8.20 Hz), 9.30 (s, 1H, N=CH), 10.36 (s, 1H, OH), 12.24 (s, 1H, NH); ^{13}C-NMR (DMSO-d6) δ (ppm) 170.22 (N=CH), 155.12 (C=O), 153.46 (C=N), Ar–C [147.56 (2CH), 140.39 (C), 138.13 (2 CH), 136.99 (C), 135.00 (C), 133.76 (CH), 129.34 (CH), 128.66 (C), 124.32 (CH), 117.21 (C)], 21.19 (Ar-CH_3).

4-{[(3-methoxy-2-hydroxyphenyl)methylene]amino}-5-4-chlorophenyl-2,4-dihydro-3H-1,2,4-triazole-3-one (4c): (Yield 3.23g, 82%), m.p. 235–236°C; IR (KBr)/cm: 3146 (NH), 1712 (C=O), 1629, 1598 (2 C=N), 1247 (C-O); ^{1}H-NMR (DMSO-d_6) δ (ppm) Ar–H [7.20 (d, 2H, J=7.80 Hz), 7.34 (d, 2H, J=7.80 Hz), 7.64 (d, 1H J=8.20 Hz), 7.78 (s, 1H), 7.85 (d, 1H, J=8.20 Hz), 9.35 (s, 1H, N=CH), 10.43 (s, 1H, OH), 12.07 (s, 1H, NH); ^{13}C-NMR (DMSO-d_6) δ (ppm) 168.11 (N=CH), 155.65 (C=O), 153.25 (C=N), Ar–C [148.87 (2CH), 147.44 (C), 141.18 (2 CH), 139.59 (C), 136.77 (C), 134.21 (CH), 131.85 (CH), 129.13 (C), 125.42 (CH), 114.36 (C)].

4-{[(5-Bromo-2-hydroxyphenyl)methylene]amino}-5-cyclopropyl-2,4-dihydro-3H-1,2,4-triazole-3-one (5a): (Yield 2.10 g, 77%), m.p. 251–252 °C; IR (KBr)/cm: 3143 (NH), 1714 (C=O), 1625, 1599 (2 C=N), 1245 (C-O); ^{1}H-NMR (DMSO-d_6) δ (ppm) 2.61 (m, 4H, CH_2), 3.99 (m, 1H, CH), 3.56 (s, 3H, OCH_3), Ar–H [7.60 (s, 1H), 7.74 (s, 1H), 7.90 (s, 1H), 9.35 (s, 1H, N=CH), 10.32 (s, 1H, OH), 12.21 (s, 1H, NH); ^{13}C-NMR (DMSO-d_6) δ (ppm) 173.20 (N=CH), 155.40 (C=O), 153.15 (C=N), Ar–C [146.34 (CH), 138.16 (C), 137.82 (C), 126.15 (CH), 123.18 (CH), 116.43 (C)], 59.45 (OCH_3), 43.07 (CH), 32.45 (2 CH_2).

4-{[(5-Bromo-2-hydroxyphenyl)methylene]amino}-5-4-methylphenyl-2,4-dihydro-3H-1,2,4-triazole-3-one (5b): (Yield 2.55 g, 79%), m.p. 216–217°C; IR (KBr)/cm: 3152 (NH), 1710 (C=O), 1625, 1594 (2 C=N), 1253 (C-O); ^{1}H-NMR (DMSO-d_6) δ (ppm) 2.32 (s, 3H, Ar-CH_3), 3.64 (s, 3H, OCH_3), Ar–H [7.38 (d, 2H, J=7.65 Hz), 7.56 (d, 2H, J=7.65 Hz), 7.62 (s, 1H), 7.70 (s, 1H), 7.85 (s, 1H), 9.38 (s, 1H, N=CH), 10.45 (s, 1H, OH), 12.34 (s, 1H, NH); ^{13}C-NMR (DMSO-d_6) δ (ppm) 168.18 (N=CH), 155.00 (C=O), 153.49 (C=N), Ar–C [149.00 (2CH), 143.76 (C), 141.13 (2 CH), 138.34 (C), 136.12 (C), 136.06 (CH), 131.98 (CH), 129.44 (C), 127.63 (CH), 118.66 (C)], 59.76 (OCH_3), 22.35 (Ar-CH_3).

4-{[(5-Bromo-2-hydroxyphenyl)methylene]amino}-5-4-chlorophenyl-2,4-dihydro-3H-1,2,4-triazole-3-one (5c): (Yield 2.82 g, 81%), m.p. 261–262°C; IR (KBr)/cm: 3170 (NH), 1718 (C=O), 1620, 1590 (2 C=N), 1251 (C-O); ^{1}H-NMR (DMSO-d_6) δ (ppm) 3.60 (s, 3H, OCH_3), Ar–H [7.18 (d, 2H, J=7.80 Hz), 7.26 (d, 2H, J=7.80 Hz), 7.54 (s, 1H), 7.60 (s, 1H), 7.78 (s, 1H), 9.30 (s, 1H, N=CH), 10.41 (s, 1H, OH), 12.18 (s, 1H, NH); ^{13}C-NMR (DMSO-d_6) δ (ppm) 171.35 (N=CH),

155.07 (C=O), 153.12 (C=N), Ar–C [149.31 (2CH), 148.16 (C), 144.66 (CH), 141.88 (C), 137.11 (C), 135.64 (2CH), 133.90 (CH), 131.16 (C), 124.48 (CH), 114.56 (C)], 59.22 (OCH_3).

2.3. Antioxidant and Antiurease Activities Assays

2.3.1. Reducing Power Assay

The reducing power capacities of the triazolee derivatives were examined according to the method described by Oyaizu (Oyaizu, 1986). Different amounts of samples (50-200 µg/mL) in 1 ml of DMSO were mixed with 2.5 mL of phosphate buffer (0.2 M, pH 6.6) and 2.5 mL potassium ferricyanide (1%) and then the mixture was incubated at 50 °C for 30 min. Afterwards, 2.5 mL of TCA (10%) was added to the mixture to stop the reaction, then the mixture was centrifuged at 3000 rpm for 10 min. The supernatant (2.5 mL) was mixed with 2.5 mL distilled water and 0.5 ml $FeCl_3$ (0.1%), and then absorbance values were measured at 700 nm in spectrophotometer. The reducing power of the tested compounds increased with the absorbance values.

2.3.2. DPPH Radical Scavenging Activity

DPPH activity of the Schiff base derivatives was determined according to by Brand Williams et al. (Brand Williams et al., 1995). 0.1 mL of sample at different concentrations (50-200 µg/mL) were added to 3.9 mL of a 6x10-5 M methanolic solution of DPPH. The absorbance was read at 517 nm after 30 min of reaction in the dark. The assays were carried out in triplicate (Brand-Williams et al., 1995).

2.3.3. ABTS Radical Scavenging Activity

The ABTS radical scavenging activity of the new compounds was measured according to the method of Arnao et al. (Arnao et al., 2001). 2850 µL ABTS solution was added with 150 µL test compound which was prepared different concentrations (50-200 µg/mL). The mixture was kept for 2h at dark. Then, the absorbance was read at 734 nm (Arnao et al., 2001). The assays were carried out in triplicate.

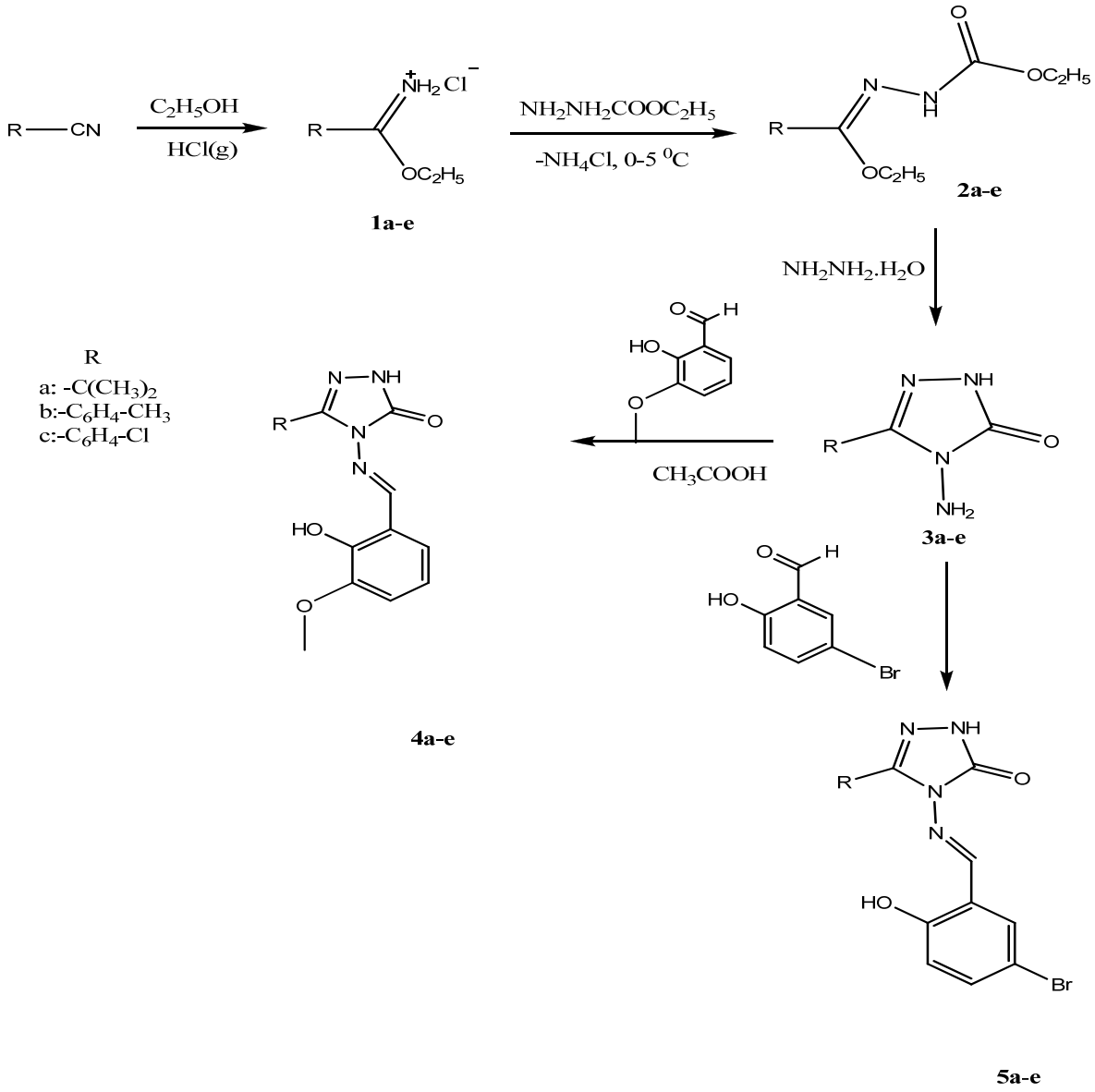
2.3.4. Anti-Urease Activity

Antiurease activity of compounds was assayed according to the method of Van Slyke and Archibald (Van Slyke and Archibald, 1944). Urease inhibitory activity of the samples at different concentrations ($1.0x10^{-5}$-$1.0x10^{-2}$ μg/mL) were determined spectrophotometrically according to the method of Van Slyke and Archibald. Briefly, 0.5 mL of urease (jack bean) solution was added to 0.5 mL of the sample. The mixture was incubated for 15 min at room temperature. After incubation, 0.4 mL phenol red solution which was prepared in urea-phosphate buffer (pH 6.8) was transferred to the mixture. The absorbance was read at 570 nm. Thiourea was utilized for standard urease inhibitor. The assays were done in triplicate (Van Slyke and Archibald, 1944).

3. Findings and Discussion

The reaction mechanism of the synthesized compounds is shown in Scheme 1. Starting compounds, iminoester hydrochlorides (**1a–c**) and hydrazones (**2a–c)** were prepared the reported procedure before (Pinner, 1892). Hydrazones **(2a–c)** were used in the intermediate step for 1, 2, 4-triazole-3-ones. Therefore, compounds **(3a–c)** were obtained by the reaction of hydrazones with hydrazine hydrate in acetic acid for 1.5 hours reflux. Compounds (**4a–c)** and (**5a–c)** were synthesized as a result of the reaction of 4-amino-2, 4-dihydro-3H-1, 2, 4-triazole-3-ones **(3a–c)** with 3-methoxy and 5-bromo-salicylic aldehydes in order.

The structures of the compounds were proved by IR, ^{1}H NMR, ^{13}C- NMR data. IR spectra of compounds **(4a–c)** and (**5a–c)** showed a sharp band between 3280-3110 cm^{-1} corresponding to νNH group, a carbonyl band between 1720-1650 cm^{-1}, two C=N bands (imine and triazolee) between 1630-1590 cm^{-1}, and a strong C=O band at about 1250 cm^{-1}. νOH signal was not shown for all compounds because of intra-molecular hydrogen bond. ^{1}H NMR spectra of compounds **4a–c** and **5a–c** showed a signal at about 12.20 NH, 10.30 OH, and 9.30 ppm imine CH, respectively. ^{13}C-NMR signals for the –N=CH group of compounds (**4a–c**) and **5a-c** were recorded at δ 168–173, C=O. Also C=N (triazolee) signals were observed at about 155, 153 ppm.



Scheme 1. Synthesized all ligands.

The reducing power antioxidant activities of the Schiff base compounds were studied at different concentration range (50-200 µg/mL), and results were compared with BHT (Table 1). In this study, the reducing power of novel synthesized six compounds rised with increasing concentration of samples. Compounds **4b** and **5c** were showed similar results. The highest and lowest activity values were observed at compounds **4c** and **5b**. Studied compound **4c** showed higher activity than BHT at 150 and 200 µg/mL at concentrations.

Table 1. The reducing power antioxidant activity of new ligands and standard (**4a–c**, **5a-c**).

Compounds	Reducing Power Absorbance*	Compounds	Reducing Power Absorbance*
	0.049±0.0042		0.046±0.0050
4a	0.081±0.0064	5a	0.071±0.0099
	0.102±0.0099		0.112±0.0085
	0.138±0.0106		0.158±0.0106
	0.027±0.0028		0.026±0.0071
4b	0.049±0.0071	5b	0.051±0.0021
	0.088±0.0184		0.074±0.0078
	0.117±0.0028		0.105±0.0099
	0.112±0.0134		0.028±0.0085
4c	0.201±0.0177	5c	0.041±0.0071
	0.408±0.0184		0.061±0.0127
	0.539±0.0177		0.111±0.0127
	0.162±0.012		
BHT	0.205±0.018	-	-
	0.274±0.021		
	0.311±0.025		

*Values were the means of three replicates ± Standard deviation (SD).

The DPPH radical scavenging activity of Schiff base derivatives are presented in Table 2. As standard substance was used antioxidant6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid (Trolox). All the tested compounds showed DPPH free radical scavenging activities. Their comparable scavenging activities were also expressed with SC_{50} (The effective concentration at which the free radicals were scavenged by 50%) value in Table 1. Compound **4c** had the highest DPPH scavenging activity among all the compounds tested (SC_{50}= 2476.62±29.89 μM). The lowest radical scavenging activity among all the compounds tested and standards showed.

Table 2 showed the ABTS radical scavenging activity of Schiff base compounds compared with Trolox. Radical scavenging activity values increased with increasing concentration. Lower SC_{50} values show higher ABTS radical scavenging ability. All of the synthesized compounds (322.52-4326.16 μM) showed lower ABTS radical scavenging activity than Trolox (SC_{50}=214.55 ± 24.56 μM). The highest and lowest activities were found at compounds **4c** and **5c**, respectively.

All newly synthesized Schiff base compounds showed effective urease inhibitory activity (Table 2). The antiurease activity was increased with increasing sample concentration. Lower IC_{50} values indicate higher enzyme inhibitor activity. Compounds **5c** and **5a** proved to be the most potent showing any enzyme inhibition activity with an IC_{50}= 0.17±0.011 and IC_{50}=0.17±0.072 μM, respectively. The least active compound **4b** had an IC_{50}=0.38±0.006 μM.

Table 2. The antioxidant and antiurease activities of new ligands and standards (**4a–c**, **5a–c**).

Compounds	DPPH SC_{50} (µM)*	ABTS SC_{50} (µM)*	Antiurease IC_{50} (µM)*
4a	13413.29±1050.46	3049.12±277.92	0.29±0.030
4b	10141.29±418.85	3160.52±245.85	0.38±0.006
4c	2476.62±29.89	322.52±51.43	0.22±0.089
5a	9652.42±417.09	1991.37±63.59	0.17±0.072
5b	13312.36±895.18	3348.75±142.74	0.28±0.083
5c	10237.43±366.62	4326.16±398.70	0.17±0.011
Trolox	133.25±11.42	214.55±24.56	-
Thiourea	-	-	0.48±0.012

*Values were the means of three replicates ± Standard deviation (SD).

4. Conclusions

We have investigated antioxidant and antiurease activities of synthesized several 1,2,4-triazolee-3-one derivatives. In current study, obtained results showed that the synthesized new Schiff base derivatives had antioxidant and highly effective urease inhibitor activities. Consequently, these compounds could be used as a source of antioxidant in cosmetic, pharmaceutical and agricultural industries.

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