Synthesis and Biological Evaluation of Some 1,3-Benzoxazol-2(*3H*)-one Hybrid Molecules as potential Antioxidant and Urease Inhibitors

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Abstract

A new series 1,3-benzoxazol-2(*3H*)-one hybrid compounds including coumarin, isatin 1,3,4-triazole and 1,3,4-thiadiazole moieties were synthesized and biologically evaluated for their antioxidant capacities and antiurease properties. The synthesized benzoxazole-coumarin (**6a-e**) and benzoxazole-isatin (**10a-c**) hybrids showed remarkable urease inhibitory activities with IC_{50} (μM) ranging from 0.0306 ± 0.0030 to 0.0402 ± 0.0030, while IC_{50} of standard thiourea is 0.5027 ± 0.0293. The synthesized benzoxazole-triazole (**8a-c**) and benzoxazole-thiadiazole (**9a-c**) hybrids showed similar urease inhibitory activities with IC_{50} (μM) ranging 0.3861 ± 0.0379 to 0.5126 ± 0.0345. The antioxidant activity of synthesized compounds were evaluated for their antioxidant activities such as reducing power and ABTS (2,2′-azino-bis(3-ethylbenzothiazoline-6-sulphonic acid) diammonium salt) radical scavenging. The results of ABTS radical scavenging activities of some of the synthesized molecules showed higher activities than standard trolox, SC_{50} (μM)= 213.04 ± 18.12. One benzoxazol-coumarin (**6f**), two benzoxazole-isothiocyanate (**7b, 7c**) and two benzoxazole-triazole (**8b, 8c**) derivatives showed higher activities (SC_{50} (μM) values, 82.07 ± 10.34, 120.19 ± 7.30, 104.58 ± 10.55, 153.26 ± 7.14 and 144.82 ± 10.68, repectively) than standard Trolox, (SC_{50} (μM)= 213.04 ± 18.12).

Keywords: Benzoxazole, Antioxidant activity, ABTS radical scavenging activity, Antiurease activity

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/jhet.4165

1. Introduction

Urease enzyme, (EC 3.5.1.5), is a nickel-dependent metalloenzyme that catalyses the hydrolysis of urea to carbon dioxide and ammonia [1]. Urease enzyme belongs to the family of amidohydrolases and phosphotriesterases. It is found in some bacteria, fungi, plants, and some invertebrate animals, and soils, as a soil enzyme. The increasing amount of ammonia causes rising of pH in the aqueous reaction medium that causes the survival of Helicobacter pylori [2]. It is known that *Helicobacter pylori* causes some gastroduodenal disorders such as peptic gastric, ulcer, gastric cancer [3,4].

Urease inhibitors are promising agents to prevent the effects of ureolytic bacterial infections [5]. The inhibition of these enzymes has leaded to organic chemists for designing new molecules which can be used as urease inhibitors. Urease enzyme can be inhibited by different kinds of compounds such as coumarins, thiadiazoles, triazoles, semicarbazones, isatins and Schiff bases[6–13]. Over the last years, many antiurease compounds have been reported and they have received special attentions due to their activities [10,14].

The use of antioxidants is known as the most effective way to protect the human organism against cellular damages caused by oxidative stress. Oxidative stress can be caused numerous diseases such as liver damage [15], cancer [16], myocardial infarction [17], Alzheimer's disease [18] and Parkinson's disease [19]. However, there is no certainty on whether oxidants trigger these diseases, or are produced as a secondary consequence of the diseases [20]. For these reasons, it is very important to design and synthesize new antioxidant drugs.

Nitrogen and oxygen containing five membered compounds are important bioactive compounds because of their wide range of pharmacological applications. Benzoxazole derivatives have attracted much attention in last years due to their wide use for the synthesis of new biological compounds. They have become important heterocycle in medicinal chemistry due to their wide range of biological properties [21–27]. A number of drugs which have benzoxazole moiety are found in market like nonsteroidal, Priaxim and Benoxaprofen (as anti-inflammatory drugs), Calcimycin and Boxazomycin B (as antibiotic) and Chloroxazone (as muscle relaxant).

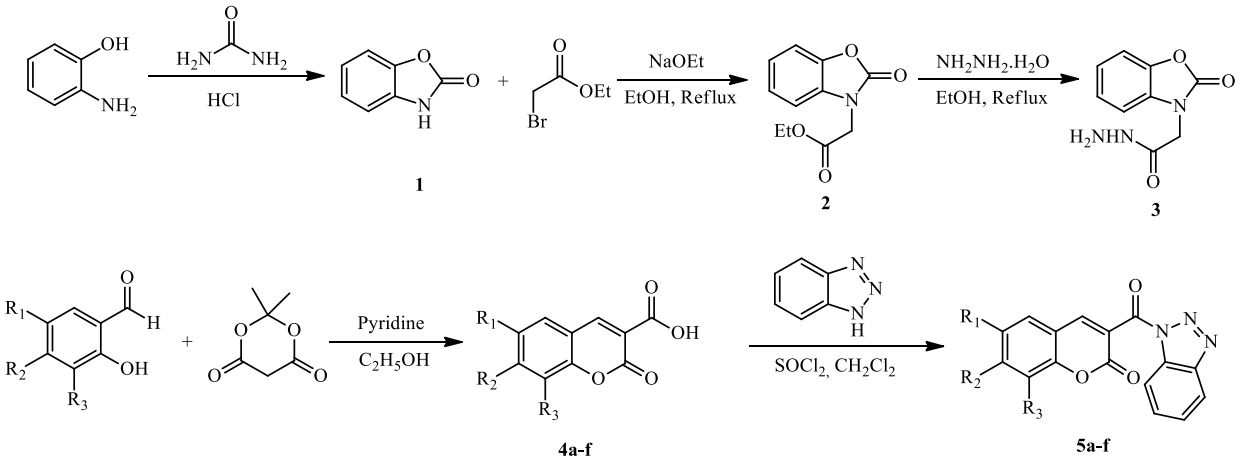
Previously, we have synthesized and evaluated some quinazolin-4(3*H*)-one-coumarin hybrid derivatives that showed strong urease activities [28–31]. Then, we have obtained biological activity results above average close to the target value. Also, in our literature survey, we have observed the role of benzoxazole moiety in drug design and development. So, in this work, we have worked on the benzoxazole compounds containing coumarin, 1,2,4-triazole, 1,2,4-thiadiazole and isatin groups. The aim of this work is to understand the effect of these moieties with benzoxazole on antioxidant and urease inhibition activities.

2. Result and Discussion

2.1.Chemistry

Initially, 1,3-benzoxazol-2-one (**1**) compound was synthesized from the reaction of 2-aminophenol and urea by using HCl as a catalyst.[32] Then, compound **1** was reacted with ethyl bromoacetate in ethanolic sodium ethoxide to obtain ester derivative (**2**). 2-(2-Oxo-1,3-benzoxazol-3(*2H*)-yl)acetohydrazide (**3**) was synthesized from the reaction of compound **2** and hydrazine hydrate.

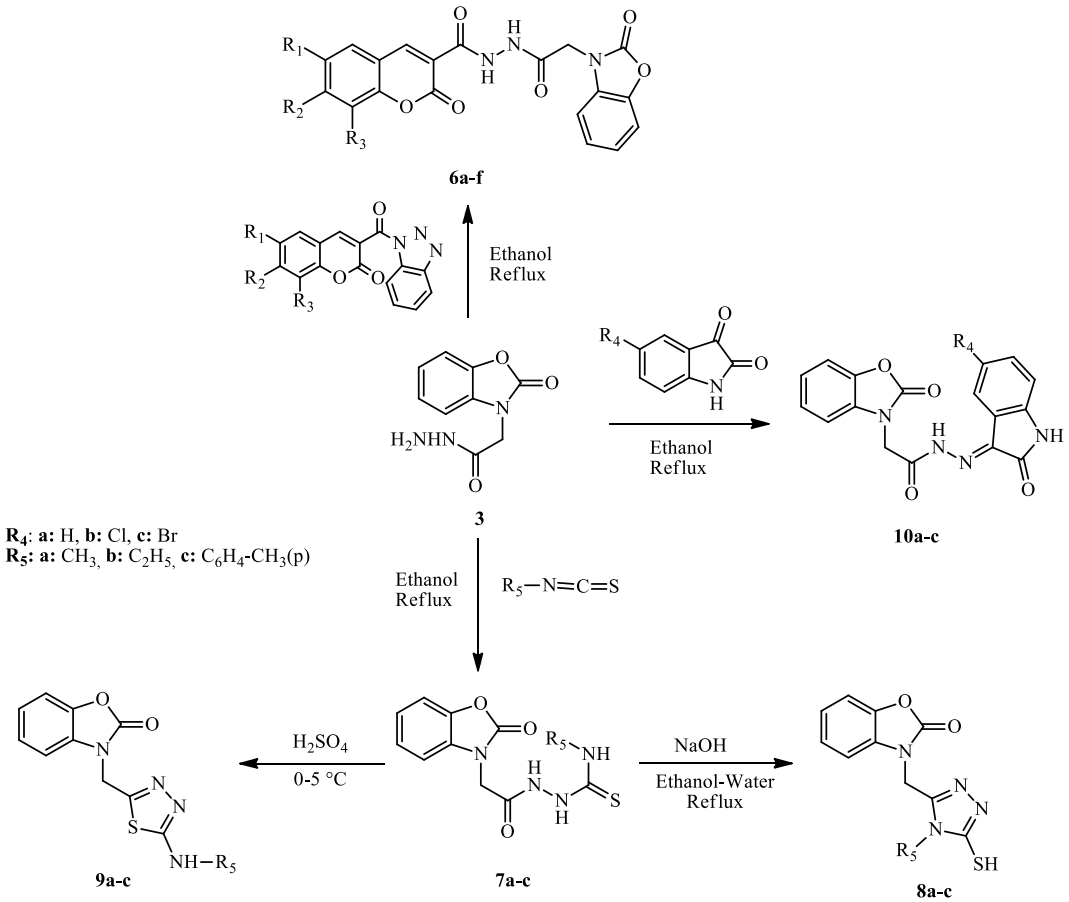
In the next step, 3-(1*H* -benzotriazol-1-ylcarbonyl)-2*H* -chromen-2-ones (**5a–f**) were obtained. Firstly, coumarin-3-carboxylic acids (**4a–f**) were synthesized from the reaction of Meldrum's acid and salicylaldehyde derivatives in ethanol (containing 1 mL of pyridine). Our literature search has shown that benzotriazole group is an easy leaving group and thus offers many advantages for synthetic applications [33]. Therefore, compounds **4a-f** were reacted with 1*H* -benzotriazole in dichloromethane to obtain compounds **5a-f** (Scheme 1.).



	a	**b**	**c**	**d**	**e**	**f**
R_1	H	Cl	Br	Cl	H	H
R_2	H	H	H	H	$N(Et)_2$	H
R_3	H	H	H	Cl	H	OCH_3

Scheme 1. Synthesis of compounds **1-5**

In the last step, the targeted molecules were prepared. To do this, benzoxazole derivatives were converted to coumarin derivatives (**6a-f**) from the reaction of compound **3** and compounds **5a-f** in absolute ethanol. Thiosemicarbazide derivatives (**7a-c**) were prepared by the nucleophilic addition of 2-(2-oxo-1,3-benzoxazol-3(*2H*)-yl)acetohydrazide (**3**) to corresponding isothiocyanate derivatives. Intramolecular cyclization of compounds **7a-c** in the presence of NaOH solution under reflux condition resulted in the formation of 1,2,4-triazole derivatives (**8a-c**). The cyclization of compounds **7a-c** with concentrated sulfuric acid resulted in the formation of thiadiazole derivatives (**9a-c**). We have also prepared benzoxazole-isatin hybrids (**10a–c**) with Schiff base formation reaction (Scheme 2.).



Scheme 2. Synthesis of benzoxazole hybrid molecules (**6-10**)

2.2. Biological Activity

2.2.1. Antioxidant Capacity

Table 1 showed the ABTS radical scavenging activity of synthesized compounds compared with Trolox. ABTS radical scavenging activity increased with increasing concentration. Lower SC_{50} values indicate higher ABTS radical scavenging ability. All of the compounds (82.07-1241.33 µM) and 6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid (Trolox) as standard antioxidant (SC_{50}= 213.04 ± 18.12 µM) showed ABTS radical scavenging activity. The lowest and highest activities were found at compounds **1** and **6f**, respectively.

Table 1. The ABTS antioxidant activities of synthesized compounds (1-10).

Compounds	ABTS SC_{50} (µM)*	Compounds	ABTS SC_{50} (µM)*
1	1241.33 ± 117.32	**8a**	159.21 ± 8.12
6a	503.07± 27.36	**8b**	153.26 ± 7.14
6b	472.35 ± 33.52	**8c**	144.82 ± 10.68
6c	435.35 ± 37.92	**9a**	726.59 ± 21.99
6d	439.90 ± 49.99	**9b**	690.41 ± 19.93
6e	427.19 ± 33.96	**9c**	558.01 ± 28.76
6f	82.07 ± 10.34	**10a**	630.92 ± 73.85
7a	131.13 ± 6.20	**10b**	549.38 ± 33.75
7b	120.19 ± 7.30	**10c**	499.91 ± 44.36
7c	104.58 ± 10.55	**Trolox**	213.04 ± 18.12

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

The reducing power capacities of the synthesized compounds were studied at different concentrations (25-100 µg/mL), and results were compared with butylated hydroxytoluene (BHT) (Table 2). The reducing power capacity of a compound may serve as a major indicator for its antioxidant activity [34]. In this study, the reducing ability of compounds synthesized raised with increasing concentration of samples. Compounds **6a, 6c, 6d, 9a, 9b, 9c, 10a, 10b** and **10c** showed similar results. The highest and lowest activity was observed at compounds **6f** and **1**. **6f** and **7b** compounds showed higher activity than BHT at all concentrations.

Table 2. The reducing power antioxidant activity of synthesized compounds (**1-10**).

Compounds	Reducing Power Absorbance*	Compounds	Reducing Power Absorbance*	Compounds	Reducing Power Absorbance*
	0.077 ± 0.011		0.156 ± 0.015		0.112 ± 0.010
	0.095 ± 0.010		0.185 ± 0.013		0.132 ± 0.010
1	0.120 ± 0.011	**7a**	0.220 ± 0.018	**9b**	0.153 ± 0.010
	0.130 ± 0.012		0.316 ± 0.027		0.174 ± 0.012
	0.088 ± 0.009		0.155 ± 0.018		0.103 ± 0.013
	0.114 ± 0.011		0.182 ± 0.010		0.130 ± 0.011
6a	0.133 ± 0.011	**7b**	0.223 ± 0.016	**9c**	0.150 ± 0.012
	0.159 ± 0.015		0.302 ± 0.023		0.172 ± 0.015
	0.090 ± 0.011		0.182 ± 0.023		0.106 ± 0.011
	0.114 ± 0.011		0.202 ± 0.018		0.119 ± 0.010
6b	0.133 ± 0.011	**7c**	0.240 ± 0.013	**10a**	0.132 ± 0.011
	0.159 ± 0.015		0.306 ± 0.013		0.150 ± 0.012
	0.090 ± 0.012		0.154 ± 0.015		0.098± 0.013
	0.108 ± 0.016		0.163 ± 0.004		0.116 ± 0.011
6c	0.130 ± 0.012		0.172 ± 0.016	**10b**	0.136 ± 0.010
	0.157 ± 0.018	**8a**	0.208 ± 0.022		0.153 ± 0.010
	0.093 ± 0.009		0.134 ± 0.01		0.108 ± 0.009
	0.109 ± 0.011		0.153 ± 0.006		0.125 ± 0.011
6e	0.121 ± 0.012	**8b**	0.171 ± 0.012	**10c**	0.138 ± 0.010
	0.131 ± 0.009		0.201 ± 0.021		0.161 ± 0.011
	0.099 ± 0.008		0.145 ± 0.009		0.121 ± 0.011
	0.116 ± 0.009		0.173 ± 0.016	**BHT**	0.162 ± 0.018
6d	0.135 ± 0.011	**8c**	0.199 ± 0.022		0.229 ± 0.021
	0.150 ± 0.013		0.227 ± 0.029		0.301 ± 0.028
	0.21 ± 0.013		0.089 ± 0.013		
	0.251 ± 0.023		0.103 ± 0.016		
6f	0.305 ± 0.028	**9a**	0.119 ± 0.011		
	0.351 ± 0.033		0.143 ± 0.010		

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

2.2.2. Urease Inhibitory Activity

All newly synthesized compounds showed effective urease inhibitory activities (Table 3). The inhibition was increased with increasing sample concentration. Lower IC_{50} values indicate higher enzyme inhibitor activity. All of the synthesized compounds showed urease inhibitory activity with IC_{50} value from 0.0306 ± 0.0030 to 1.1143 ± 0.2357 µM, while

thiourea,which is used as standard urease inhibitor, showed IC_{50} value of 0.5027 ± 0.0293 μM. Compounds **6c, 6d, 6e** and **10c** proved to be the most potent showing an enzyme inhibition activity with an IC_{50}= 0.0307 ± 0.039, IC_{50}= 0.0314 ± 0.0040; IC_{50}= 0.0306 ± 0.0030 and IC_{50}= 0.0316 ± 0.0012 μM, respectively. The least active compound **1** had an IC_{50}= 1.1143 ± 0.2357 μM.

Table 3. The urease activities of synthesized compounds (**1-10**).

Compounds	Urease IC_{50} (μM)*	Compounds	Urease IC_{50} (μM)*
1	1.1143 ± 0.2357	**8a**	0.5377 ± 0.0547
6a	0.0367± 0.0042	**8b**	0.5049 ± 0.0586
6b	0.0341± 0.0037	**8c**	0.3999 ± 0.0302
6c	0.0307 ± 0.0039	**9a**	0.5126 ± 0.0345
6d	0.0314± 0.0031	**9b**	0.5031 ± 0.0559
6e	0.0306 ± 0.0030	**9c**	0.4055 ± 0.0382
6f	0.0333 ± 0.0029	**10a**	0.0402 ± 0.0030
7a	0.4652 ± 0.0145	**10b**	0.0367 ± 0.0031
7b	0.4441 ± 0.0127	**10c**	0.0316 ± 0.0012
7c	0.3861 ± 0.0379	**Thiurea**	0.5027 ± 0.0293

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

3. Conclusion

In summary, we have described the design, synthesis, antioxidant and in vitro antiurease activity of benzoxazole hybrid molecules including coumarin, triazole, thiadiazole and isatin functionalities. Most of the synthesized compounds displayed significant activity of antioxidant and antiurease when compared with standard Trolox and thiourea. Among the synthesized compounds, while most of the benzoxazole-coumarin hybrids showed weak antioxidant activity, compound **6f**, which includes OCH_3 group on coumarin cycle, showed efficient antioxidant activity (SC_{50}= 82.07 ± 10.34 μM). Among the series, isothiocyanate derivatives showed the most potent antioxidant activity after compound **6f**, (SC_{50}= 120.19 ± 7.30 for **7b** and SC_{50}= 104.58 ± 10.55 for **7c**), while 1,2,4-triazole, 1,2,4-thiadiazole and isatin derivatives showed weak antioxidant activities. In Urease inhibition studies, most of the compounds showed more efficient activity than standard thiourea (IC_{50}= 0.5027 ± 0.0293 μM). Among the series, coumarin derivatives (**6a-f**) and isatin derivatives (**10a-c**) showed the most potent urease inhibition activities with IC_{50} value between 0.0306 ± 0.0030 (for **6f**) and 0.0402 ± 0.0030 (for **10a**). The results showed that the addition of coumarin and isatin functionalities to benzoxazole cycle has caused an increase in urease inhibition activities.

4. Experimental section

4.1.Chemistry

4.1.1. Synthesis of 1,3-benzoxazol-2-one (1):

This product was prepared by treating 2-amino phenol and urea in concentrated HCl for 4 hours as reported earlier [32].

Yield: 1.24 g, 92%; m.p.: 135-136 °C, (135 °C [32]).

4.1.2. Synthesis of Ethyl (2-oxo-1,3-benzoxazol-3(*2H*)-yl)acetate (2):

This product was synthesized according to the literature [32].

Yield: 1.90 g, 86%; m.p.: 90-91 °C, (89 °C [32]).

4.1.3. 2-(2-Oxo-1,3-benzoxazol-3(2*H*)-yl)acetohydrazide (3):

Yield: 1.50 g, %72; m.p.: 215-217 °C, (215 °C [32]).

4.1.4. Synthesis of compounds 4a-f

These products were synthesized according to the literature [35].

2-Oxo-2*H*-chromene-3-carboxylic acid (4a): Yield: 1.39 g, 73%; m.p. 189–190 °C, (188 °C [35]).

6-Chloro-2-oxo-2*H*-chromene-3-carboxylic acid (4b): Yield: 2.47 g, 76%; m.p. 194–195 °C; (mp 193 °C [36]).

6-Bromo-2-oxo-2*H*-chromene-3-carboxylic acid (4c): Yield: 1.80 g, 67%; m.p. 195–196 °C (194–196 °C [35]).

6,8-Dichloro-2-oxo-2*H*-chromene-3-carboxylic acid (4d): Yield: 1.78 g, 69%; m.p. 222–223°C (220–224 °C [37]).

7-Diethylamino-2-oxo-2*H*-chromene-3-carboxylic acid (4e): Yield: 1.95 g, 75%; m.p. 232–233 °C (230–232 °C [38]).

8-Methoxy-2-oxo-2*H*-chromene-3-carboxylic acid (4f): Yield: 1.95 g, 75%; m.p. 215–216 °C (214–216 °C [39]).

4.1.5. Synthesis of compounds 5a-f

This product was synthesized according to the literature [35].

3-(1*H*-Benzotriazol-1-ylcarbonyl)-2*H*-chromen-2-one (5a): Yield: 2.12 g, 73%; m.p. 179–180 °C (176–177 °C [35]).

3-(1*H*-Benzotriazol-1-ylcarbonyl)-6-chloro-2*H*-chromen-2-one (5b): Yield: 2.20 g, 63%; m.p. 248–249 °C (248–249 °C [40]).

3-(1*H*-Benzotriazol-1-ylcarbonyl)-6-bromo-2*H*-chromen-2-one (5c): Yield: 2.52 g, 68%; m.p. 250–251 °C (m.p. 250–251 °C [37]).

3-(1*H*-Benzotriazol-1-ylcarbonyl)-6,8-dichloro-2*H*-chromen-2-one (5d): Yield: 2.34 g, 65%; m.p. 263–264 °C (263–264 °C [38]).

3-(1*H*-Benzotriazol-1-ylcarbonyl)-7-diethylamino-2*H*-chromen-2-one (5e): Yield: 2.46 g, 68%; m.p. 210–211 °C (210–211 °C [38]).

3-(1*H*-Benzotriazol-1-ylcarbonyl)-8-methoxy-2*H*-chromen-2-one (5f): Yield 2.46 g, 68%; m.p. 236–237 °C (236–237 °C [41]).

4.1.6. Synthesis of compounds 6a-f

These products were synthesized according to the literature [35]. A solution of compound **5a**–**f** (0.01 mol) and 2-(2-oxo-1,3-benzoxazol-3(2*H*)-yl)acetohydrazide **(3)** (0.011 mol) in ethanol (15 ml) was placed in a round-bottomed flask. The mixture was refluxed for 8 h. After the completion of the reaction (monitored by TLC, ethyl acetate:hexane 3:1), the mixture was cooled to room temperature, and a solid formed. This crude product was filtered off and washed with ethanol.

2-Oxo-*N*'-[(2-oxo-1,3-benzoxazol-3(2*H*)-yl)acetyl]-2*H*-chromene-3-carbohydrazide (6a): Yield: 2.84 g, 75%; m.p.: 300-301 °C; ^{1}H-NMR (DMSO-d_6, 400 MHz): 4.76 (s, 2H, CH_2), 7.17-7.24 (m, 2H, Ar-H), 7.34 (t, *J*=7.6 Hz, 1H, Ar-H), 7.43 (t, *J*=7.6 Hz, 1H, Ar-H), 7.49 (d, *J*=8.4 Hz, 1H, Ar-H), 7.65 (d, *J*=7.6 Hz, 1H, Ar-H), 7.74 (t, *J*=7.2 Hz, 1H, Ar-H), 7.97 (d, *J*=7.2 Hz, 1H, Ar-H), 8.85 (s, 1H, coumarin C_4-H), 10.64 (s, 1H, NH), 11.23 (s, 1H, NH). ^{13}C-NMR (DMSO-d_6, 100 MHz): 43.45 (CH_2), 111.91, 116.68, 118.38, 118.67, 121.53, 123.27, 123.79, 125.69, 127.03, 130.79, 134.92, 137.49 (Ar-C), 148.49 (coumarin-c4), 154.36 (coumarin-c3), 159.34, 160.22, 164.18, 169.64 (C=O). Elemental Analysis: Found, %: C 60.12; H 3.37; N 11.01. $C_{19}H_{13}N_3O_6$. Calculated, %: C 60.16; H 3.45; N 11.08.

6-Chloro-2-oxo-*N*'-[(2-oxo-1,3-benzoxazol-3(2*H*)-yl)acetyl]-2*H*-chromene-3-carbohydrazide (6b): Yield: 2,56 g, 62%; m.p.: 322-323 °C; ^{1}H-NMR (DMSO-d_6, 400 MHz): 4.75 (s, 2H, CH_2), 7.19-7.24 (m, 2H, Ar-H), 7.34 (t, *J*=7.6 Hz, 1H, Ar-H), 7.45 (d,

J=8.8 Hz, 1H, Ar-H), 7.65 (d, *J*=7.6 Hz, 1H, Ar-H), 7.85 (d, *J*=8.8 Hz, 1H, Ar-H), 8.21 (s, 1H, Ar-H), 8.78 (s, 1H, coumarin C_4-H), 10.59 (s, 1H, NH), 11.19 (s, 1H, NH). ^{13}C-NMR (DMSO-d_6, 100 MHz): 43.43 (CH_2), 111.89, 117.18, 118.97, 119.64, 120.50, 121.52, 123.27, 123.87, 127.05, 132.54, 137.04, 137.44 (Ar-C), 147.08 (coumarin-c4), 153.37 (coumarin c3), 159.24, 160.68, 164.32, 169.69 (C=O). Elemental Analysis: Found, %: C 55.08; H 2.85; N 10.06. $C_{19}H_{12}ClN_3O_6$. Calculated, %: C 55.15; H 2.92; N 10.16.

6-Bromo-2-oxo-*N*'-[(2-oxo-1,3-benzoxazol-3(2*H*)-yl)acetyl]-2*H*-chromene-3-carbohydrazide (6c): Yield: 3.38 g, 74%; m.p.: 327-328 °C; ^{1}H-NMR (DMSO-d_6, 400 MHz): 4.81 (s, 2H, CH_2), 7.15-7.23 (m, 2H, Ar-H), 7.36 (t, *J*=7.6 Hz, 1H, Ar-H), 7.48 (d, *J*=8.4 Hz, 1H, Ar-H), 7.61 (d, *J*=7.6 Hz, 1H, Ar-H), 7.89 (d, *J*=8.4 Hz, 1H, Ar-H), 8.41 (s, 1H, Ar-H), 8.68 (s, 1H, coumarin C_4-H), 10.69 (s, 1H, NH), 11.13(s, 1H, NH). ^{13}C-NMR (DMSO-d_6, 100 MHz): 43.49 (CH_2), 110.81, 116.38, 118.94, 119.04, 120.34, 121.59, 123.64, 125.87, 126.95, 133.55, 137.74, 138.44 (Ar-C), 148.02 (coumarin-c4), 154.35, (coumarin c3), 158.26, 160.43, 166.21, 169.53 (C=O). Elemental Analysis: Found, %: C 49.71; H 2.55; N 9.07. $C_{19}H_{12}BrN_3O_6$. Calculated, %: C 49.80; H 2.64; N 9.17.

6,8-Dichloro-2-oxo-*N*'-[(2-oxo-1,3-benzoxazol-3(2*H*)-yl)acetyl]-2*H*-chromene-3-carbohydrazide (6d): Yield: 2.91 g, 65%; m.p.: 317-318 °C; ^{1}H-NMR (DMSO-d_6, 400 MHz): 4.77 (s, 2H, CH_2), 7.18-7.25 (m, 1H, Ar-H), 7.35 (t, *J*=8.0 Hz, 1H, Ar-H), 7.55 (d, *J*=8.8 Hz, 1H, Ar-H), 7.65 (d, *J*=8.8 Hz, 1H, Ar-H), 7.79 (d, *J*=8.8 Hz, 1H, Ar-H), 8.13 (d, *J*=1.6 Hz, 1H, Ar-H), 8.83 (s, 1H, coumarin C_4-H), 10.63 (s, 1H, NH), 11.24 (s, 1H, NH). ^{13}C-NMR (DMSO-d_6, 100 MHz): 43.48 (CH_2), 111.93, 118.75, 119.77, 120.11, 121.54, 123.28, 123.27, 123.77, 127.01, 129.32, 129.63, 134.23, 137.53 (Ar-C), 147.11 (coumarin-c4), 153.02 (coumarin c3), 159.74, 164.16, 169.59 (C=O). Elemental Analysis: Found, %: C 50.83; H 2.43; N 9.33. $C_{19}H_{11}Cl_2N_3O_6$. Calculated, %: C 50.91; H 2.47; N 9.38.

7-Diethylamino-2-oxo-*N*'-[(2-oxo-1,3-benzoxazol-3(2*H*)-yl)acetyl]-2*H*-chromene-3-carbohydrazide (6e): Yield: 3.37 g, 76%; m.p.: 283-284 °C; ^{1}H-NMR (DMSO-d_6, 400 MHz): 1.10 (t, J=7.2 Hz, 6H, 2xCH_3), 3.37 (m, 4H, 2xNCH_2), 4.75 (s, 2H, CH_2), 6.57 (s, 1H, Ar-H), 6.77 (d, *J*=8.8 Hz, 1H, Ar-H), 7.17-7.25 (m, 2H, Ar-H), 7.32 (t, *J*=7.2 Hz, 1H, Ar-H), 7.65 (t, *J*=6.4 Hz, 2H, Ar-H), 8.65 (s, 1H, coumarin C_4-H), 10.50 (s, 1H, NH), 11.14 (s, 1H, NH). ^{13}C-NMR (DMSO-d_6, 100 MHz): 12.72 (2xCH_3), 43.43 (CH_2), 44.87 (2xNCH_2), 96.31, 107.87, 108.06, 110.80, 111.90, 121.51, 123.24, 123.78, 123.03, 137.50 (Ar-C), 148.50

(coumarin-c4), 153.27 (coumarin c3), 157.82 (Ar-C), 160.45, 161.80, 163.96, 169.63 (C=O). Elemental Analysis: Found, %: C 61.26; H 4.88; N 12.39. $C_{23}H_{22}N_4O_6$. Calculated, %: C 61.33; H 4.92; N 12.44.

8-Methoxy-2-oxo-*N*'-[(2-oxo-1,3-benzoxazol-3(2*H*)-yl)acetyl]-2*H*-chromene-3-carbohydrazide (6f): Yield: 2.94 g, 72%; m.p.: 326-327 °C; ^{1}H-NMR (DMSO-d_6, 400 MHz): 4.01 (s, 3H, OCH_3), 4.72 (s, 2H, CH_2), 7.04 (s, 1H, Ar-H), 7.11(d, *J*=8.4 Hz, 1H, Ar-H), 7.16-7.24 (m, 2H, Ar-H), 7.35 (t, *J*=7.2 Hz, 1H, Ar-H), 7.67 (t, *J*=6.4 Hz, 2H, Ar-H), 8.71 (s, 1H, coumarin C_4-H), 10.44 (s, 1H, NH), 11.24 (s, 1H, NH). ^{13}C-NMR (DMSO-d_6, 100 MHz): 43.43 (CH_2), 44.87 (OCH_3), 96.36, 105.35, 107.17, 110.25, 112.45, 117.45, 121.24, 122.56, 123.98, 125.43, 138.46 (Ar-C), 147.54 (coumarin-c4), 154.35 (coumarin c3), 158.48 (Ar-C), 160.21, 162.35, 165.96, 169.47 (C=O). Elemental Analysis: Found, %: C 58.62; H 3.63; N 10.21. $C_{20}H_{15}N_3O_7$. Calculated, %: C 58.68; H 3.69; N 10.27.

4.1.7. Synthesis of compounds 7a-c

These compounds were synthesized according to the literature [28]. A mixture of 2-(2-oxo-1,3-benzoxazol-3(2*H*)-yl)acetohydrazide **(3)** (0.01 mol) and corresponding isothiocyanate (0.011 mol) was refluxed in ethanol (15 mL) for 3 h. The solution was cooled and a solid appeared. The precipitated product was filtrated and recrystallized from ethanol to obtain the desired pure product **7a-c**.

***N*-Methyl-2-[(2-oxo-1,3-benzoxazol-3(2*H*)-yl)acetyl]hydrazine carbothioamide (7a):** Yield: 2.66 g, 95%; m.p.: 232-233 °C; ^{1}H-NMR (DMSO-d_6, 400 MHz): 3.62 (s, 3H, CH_3), 4.68 (s, 2H, CH_2), 7.16-7.20 (m, 2H, Ar-H), 7.32 (t, *J*=7.6 Hz, 1H, Ar-H), 7.62 (d, *J*=7.6 Hz, 1H, Ar-H), 8.07 (s, 1H, NH), 9.30 (s, 1H, NH), 10.24 (s, 1H, NH). ^{13}C-NMR (DMSO-d_6, 100 MHz): 31.34 (CH_3), 43.60 (CH_2), 111.99, 121.44, 123.22, 123.84, 127.00, 137.47 (Ar-C), 166.47 (C=O), 169.77 (C=S). Elemental Analysis: Found, %: C 47.04; H 4.22; N 19.86. $C_{11}H_{12}N_4O_3S$. Calculated, %: C 47.13; H 4.32; N 19.99.

***N*-Ethyl-2-[(2-oxo-1,3-benzoxazol-3(2*H*)-yl)acetyl]hydrazine carbothioamide (7b):** Yield: 2.55 g, 87%; m.p.: 235-236 °C; ^{1}H-NMR (DMSO-d_6, 400 MHz): 1.04 (t, *J*=6.4 Hz, 3H, CH_3), 3.66 (m, 2H, CH_2), 4.68 (s, 2H, CH_2), 7.18-7.21 (m, 2H, Ar-H), 7.33 (t, *J*=8.0 Hz, 1H, Ar-H), 7.62 (d, *J*=8.0 Hz, 1H, Ar-H), 8.03 (s, 1H, NH), 9.22 (s, 1H, NH), 10.22 (s, 1H, NH). ^{13}C-NMR (DMSO-d_6, 100 MHz): 14.81 (CH_3), 43.61 ($2CH_2$), 112.00, 121.45, 123.23, 123.87,

127.00, 137.44 (Ar-C), 166.38 (C=O), 169.86 (C=S). Elemental Analysis: Found, %: C 48.88; H 4.68; N 18.96.$C_{12}H_{14}N_4O_3S$. Calculated, %: C 48.97; H 4.79; N 19.04.

***N*'-[(4-Methylphenyl)carbonothioyl]-2-(2-oxo-1,3-benzoxazol-3(2*H*)-yl)acetohydrazide (7c):** Yield: 2.69 g, 79%; m.p.: 245-246 °C; ^{1}H-NMR (DMSO-d_6, 400 MHz): 2.27 (s, 3H, CH_3), 4.74 (m, 2H, CH_2), 7.13-7.27 (m, 5H, Ar-H), 7.32 (t, *J*=6.4 Hz, 2H, Ar-H), 7.64 (d, *J*=7.6 Hz, 1H, Ar-H), 9.63 (s, 2H, NH), 10.44 (s, 1H, NH). ^{13}C-NMR (DMSO-d_6, 100 MHz): 31.00 (CH_3), 43.76 (CH_2), 112.06, 121.45,121.47, 123.27, 123.80, 126.96, 129.16, 136.75, 137.56 (Ar-C), 169.70 (C=O). Elemental Analysis: Found, %: C 57.21; H 4.47; N 15.63.$C_{17}H_{16}N_4O_3S$. Calculated, %: C 57.29; H 4.52; N 15.72.

4.1.8. Synthesis of compounds 8a-c

These compounds were synthesized according to the literature [30]. In a round-bottomed flask, 1 M NaOH (10 mL) solution and 0.01 mol of compounds **7a-c** in ethanol (10 mL) were refluxed for 5 hours. At the end of this time, the mixture was taken in a beaker with water and the product was precipitated by neutralization with diluted HCl. The product was filtered off, washed with water and recrystallized from ethanol.

3-[(5-Mercapto-4-methyl-4*H*-1,2,4-triazol-3-yl)methyl]-1,3-benzoxazol-2(3*H*)-one (8a): Yield: 2.25 g, 86%; m.p.: 128-129 °C; ^{1}H-NMR (DMSO-d_6, 400 MHz): 4.45 (s, 3H, CH_3), 5.30 (s, 2H, CH_2), 6.46 (t, *J*=7.6 Hz, 1H, Ar-H), 6.75 (d, *J*=8.0 Hz, 1H, Ar-H), 6.92 (d, *J*=8.0 Hz, 1H, Ar-H), 7.19 (d, *J*=8.0 Hz, 1H, Ar-H),13.61 (s, 1H, SH). ^{13}C-NMR (DMSO-d_6, 100 MHz): 30.42 (CH_3), 37.36 (CH_2), 112.25, 118.09,123.40, 124.06, 127.09, 132.42, 147.16 (Ar-C), 148.41, 150.42 (C=N), 167.67 (C=S). Elemental Analysis: Found, %: C 50.29; H 3.76; N 21.30. $C_{11}H_{10}N_4O_2S$. Calculated, %: C 50.37; H 3.84; N 21.36.

3-[(5-Mercapto-4-ethyl-4*H*-1,2,4-triazol-3-yl)methyl]-1,3-benzoxazol-2(3*H*)-one (8b): Yield: 2.45 g, 89%; m.p.: 178-199 °C; ^{1}H-NMR (DMSO-d_6, 400 MHz): 1.15 (t, *J*=7.2 Hz, 3H, CH_3), 4.04 (d, *J*=7.2 Hz, 2H, CH_2), 5.35 (s, 2H, NCH_2), 7.21-7.27 (m, 1H, Ar-H), 7.35 (d, *J*=8.0 Hz, 2H, Ar-H), 7.69 (d, *J*=8.0 Hz, 1H, Ar-H),13.71 (s, 1H, SH). ^{13}C-NMR (DMSO-d_6, 100 MHz): 13.58 (CH_3), 37.62, 39.09 (CH_2), 112.23, 121.57, 123.52, 124.11, 127.19, 136.84, 147.33 (Ar-C), 167.49 (C=N), 169.54 (C=S). Elemental Analysis: Found, %: C 52.09; H 4.31; N 20.20. $C_{12}H_{12}N_4O_2S$. Calculated, %: C 52.16; H 4.38; N 20.28.

3-{[5-Mercapto-4-(4-methylphenyl)-4*H*-1,2,4-triazol-3-yl]methyl}-1,3-benzoxazol-2(3*H*)-one (8c): Yield: 2.94 g, 87%; m.p.: 189-190 °C; ^{1}H-NMR (DMSO-d_6, 400 MHz): 2.26 (s, 3H, CH_3), 4.74 (s, 2H, NCH_2), 7.12-7.33 (m, 6H, Ar-H), 7.58-7.64 (m, 2H, Ar-H), 13.91 (s, 1H, SH). ^{13}C-NMR (DMSO-d_6, 100 MHz): 21.20 (CH_3), 38.10 (CH_2), 111.99, 121.54, 127.01, 127.87, 130.48, 130.58, 136.67, 139.94 (Ar-C), 147.51 (2C=N), 169.10 (C=S). Elemental Analysis: Found, %: C 60.28; H 4.11; N 16.48. $C_{17}H_{14}N_4O_2S$. Calculated, %: C 60.34; H 4.17; N 16.56.

4.1.9. Synthesis of compounds 9a-c

These products were synthesized according to the literature procedure [28]. The compound **7a-c** (0.01 mol) was dissolved with cold H_2SO_4 in the ice bath. The mixture was stirred in ice bath for nearly an hour and then at room temperature nearly an hour too. At the end of this time, the mixture was taken in a beaker filled with ice and the product was precipitated by neutralization with NH_3. The product was filtered off and recrystallized from ethanol.

3-{[5-(Methylamino)-1,3,4-thiadiazol-2-yl]methyl}-1,3-benzoxazol-2(3*H*)-one (9a): Yield: 2.25 g, 86%; m.p.[: 185-186 °C; ^{1}H-NMR (DMSO-d_6, 400 MHz): 2.25 (s, 3H, CH_3), 5.39 (s, 2H, NCH_2), 7.18 (d, J=8.0 Hz, 1H, Ar-H), 7.18-7.23 (m, 2H, Ar-H), 7.45 (d, J=8.0 Hz, 1H, Ar-H). ^{13}C-NMR (DMSO-d_6, 100 MHz): 38.75 (CH_3), 40.56 (CH_2), 112.07, 118.11, 129.92, 131.67, 136.50, 138.57 (Ar-C), 153.21 (C=N), 169.39 (C=O). Elemental Analysis: Found, %: C 50.31; H 3.75; N 21.32. $C_{11}H_{10}N_4O_2S$. Calculated, %: C 50.37; H 3.84; N 21.36.

3-{[5-(Ethylamino)-1,3,4-thiadiazol-2-yl]methyl}-1,3-benzoxazol-2(3*H*)-one (9b): Yield: 2.23 g, 81%; m.p.: 167-168 °C; ^{1}H-NMR (DMSO-d_6, 400 MHz): 1.15 (t, J=7.2 Hz, 3H, CH_3), 4.42 (q, J=7.2 Hz, 2H, CH_2), 5.42 (s, 2H, NCH_2), 7.21 (d, J=7.6 Hz, 1H, Ar-H), 7.25-7.39 (m, 2H, Ar-H), 7.55 (d, J=7.6 Hz, 1H, Ar-H). ^{13}C-NMR (DMSO-d_6, 100 MHz): 11.53 (CH_2), 39.75 (CH_2), 40.56 (CH_2), 112.55, 118.26, 130.94, 133.61, 135.52, 139.69 (Ar-C), 154.76 (C=N), 169.87 (C=O). Elemental Analysis: Found, %: C 52.05; H 4.30; N 20.16. $C_{12}H_{12}N_4O_2S$. Calculated, %: C 52.16; H 4.38; N 20.28.

3-({5-[(4-Methylphenyl)amino]-1,3,4-thiadiazol-2-yl}methyl)-1,3-benzoxazol-2(3*H*)-one (9c): Yield: 2.57 g, 76%; m.p.: 198-199 °C; ^{1}H-NMR (DMSO-d_6, 400 MHz): 2.20 (s, 3H, CH_3), 5.41 (s, 2H, NCH_2), 7.10 (d, J=8.0 Hz, 2H, Ar-H), 7.18-7.23 (m, 1H, Ar-H), 7.34-

7.42 (m, 4H, Ar-H), 7.65 (d, *J*=8.0 Hz, 1H, Ar-H). ^{13}C-NMR (DMSO-d_6, 100 MHz): 20.75 (CH_3), 40.98 (CH_2), 112.07, 118.11, 121.75, 123.53, 124.12, 127.51, 129.92, 131.67, 136.50, 138.57 (Ar-C), 153.21 (C=N), 169.39 (C=O). Elemental Analysis: Found, %: C 60.23; H 4.10; N 16.45. $C_{12}H_{12}N_4O_2S$. Calculated, %: C 60.34; H 4.17; N 16.56.

4.1.10. Synthesis of compounds 10a-c

These products were synthesized according to the literature procedure [42]**.** Equimolar quantities (0.01 mol) of isatin derivative and compound **3** were dissolved in warm ethanol (40 mL) containing glacial acetic acid (0.5 mL). The reaction mixture was refluxed for 5 h (monitored by TLC, ethylacetate:Hexane, 3:1) and then kept at room temperature overnight. The resulting solid was washed with ethanol, dried and recrystallised from ethanol to afford compounds **10a-c**.

2-(2-Oxo-1,3-benzoxazol-3(2*H*)-yl)-*N*'-[2-oxo-1,2-dihydro-3*H*-indol-3-ylidene] acetohydrazide (10a): Yield: 2.79 g, 83%, m.p.: 223-224 °C; ^{1}H-NMR (DMSO-d_6, 400 MHz): 5.23 (s, 2H, NCH_2), 6.91 (d, *J*=7.6 Hz, 1H, Ar-H), 7.04 (brs, 1H, Ar-H), 7.20 (t, *J*=8.4 Hz, 1H, Ar-H), 7.32-7.39 (m, 3H, Ar-H), 7.69 (d, *J*=8.0 Hz, 1H, Ar-H), 8.14 (d, *J*=8.4 Hz, 1H, Ar-H), 10.84 (s, 1H, NH), 11.64 (s, 1H, NH). ^{13}C-NMR (DMSO-d_6, 100 MHz): 44.36 (CH_2), 96.76, 110.41, 112.07, 118.11, 119.75, 122.59, 124.12, 128.41, 130.12, 132.51, 136.78, 139.65 (Ar-C), 147.71 (C=N), 163.34, 165.71, 169.39 (C=O). Elemental Analysis: Found, %: C 60.63; H 3.51; N 16.54. $C_{17}H_{12}N_4O_4$. Calculated, %: C 60.71; H 3.60; N 16.66.

***N*'-[5-Chloro-2-oxo-1,2-dihydro-3*H*-indol-3-ylidene]-2-(2-oxo-1,3-benzoxazol-3(2*H*)-yl)acetohydrazide (10b):** Yield: 2.66 g, 72%; m.p.: 239-240°C; ^{1}H-NMR (DMSO-d_6, 400 MHz): 5.22 (s, 2H, NCH_2), 6.92 (d, *J*=8.4 Hz, 1H, Ar-H), 7.18-7.23 m, 1H, Ar-H), 7.34 (brs, 2H, Ar-H), 7.32-7.39 (m, 3H, Ar-H), 7.43 (brs, 1H, Ar-H), 7.69 (d, *J*=8.0 Hz, 1H, Ar-H), 8.35 (s, 1H, Ar-H), 10.86 (s, 1H, NH), 11.87 (s, 1H, NH). ^{13}C-NMR (DMSO-d_6, 100 MHz): 44.67 (CH_2), 98.72, 110.22, 113.17, 116.17, 118.71, 120.36, 122.19, 125.44, 131.35, 135.41, 137.39, 140.47 (Ar-C), 148.27 (C=N), 163.24, 168.01, 169.49 (C=O). Elemental Analysis: Found, %: C 55.01; H 2.92; N 15.03. $C_{17}H_{11}ClN_4O_4$. Calculated, %: C 55.07; H 2.99; N 15.11.

***N*'-[5-Bromo-2-oxo-1,2-dihydro-3*H*-indol-3-ylidene]-2-(2-oxo-1,3-benzoxazol-3(2*H*)-yl)acetohydrazide (10c):** Yield: 3.27 g, 79%; m.p.: 256-257 °C; ^{1}H-NMR (DMSO-d_6,

400 MHz): 5.22 (s, 2H, NCH_2), 6.92 (d, *J*=8.4 Hz, 1H, Ar-H), 7.18-7.23 m, 1H, Ar-H), 7.34 (brs, 2H, Ar-H), 7.32-7.39 (m, 3H, Ar-H), 7.43 (brs, 1H, Ar-H), 7.69 (d, *J*=8.0 Hz, 1H, Ar-H), 8.35 (s, 1H, Ar-H), 10.96 (s, 1H, NH), 11.88 (s, 1H, NH). ^{13}C-NMR (DMSO-d_6, 100 MHz): 44.76 (CH_2), 99.70, 110.23, 114.57, 116.77, 118.31, 121.30, 123.69, 126.48, 132.36, 134.48, 138.30, 141.40 (Ar-C), 147.22 (C=N), 162.23, 165.55, 168.41 (C=O). Elemental Analysis: Found, %: C 49.07; H 2.62; N 13.43. $C_{17}H_{11}BrN_4O_4$. Calculated, %: C 49.18; H 2.67; N 13.49.

4.2.Biological Activity

4.2.1. $ABTS^+$ scavenging activity

The $ABTS^+$ scavenging activities of the synthesized compounds were measured according to the procedure described by Arnao et al. (2001) [43].

4.2.2. Reducing power

The reducing power capacities of the synthesized compounds were determined according to the method described by Oyaizu (1986) [44].

4.2.3. Urease inhibition assay

Urease inhibitory activities of the synthesized compounds were assayed according to the previously reported procedure [45].

Acknowledgements

This work was supported by Research Fund of Recep Tayyip Erdogan University under the Project Number of FBA-2018-858. Author thanks all the colleagues in the project unit for this support.

Conflict of Interest

The authors declare no conflict of interest.

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