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Synthesis of oxadiazole substituted new carbazole derivatives as antioxidant and antiurease agent

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ABSTRACT: Heterocyclic compounds containing nitrogen together with an oxygen atom in their structures are an important class of medicinal chemistry compounds due to their interesting diverse biological applications. Some compounds including carbazole ring, which are aromatic organic compounds in tricyclic structure, show biological activity in a wide spectrum. Oxadiazole compounds attract the attention of many chemists thanks to their antibacterial, antitumor, anticancer, anti-viral, antimicrobial, anti-HIV, antituberculosis and antioxidant properties. In this study, new oxadiazole substituted carbazole derivatives were synthesized and their antioxidant, antiurease activities were investigated. 9H-carbazole is a good starting material for the synthesis of carbazole derivatives. The antioxidant and antiurease activities of synthesized oxadiazole substituted new carbazole derivatives were investigated. Antioxidant activity methods such as DPPH (1,1'-diphenyl-2-picrylhydrazyl), ABTS (2,2'-azino-bis(3-ethylbenzothiazoline-6-sulphonic acid) diammonium salt) radical scavenging activities and iron reducing power capacities were used to determine antioxidant activity of the compounds. All synthesized carbazole compounds showed antioxidant and antiurease activity. While compound 4 shows the strongest enzyme inhibition activity, the least active compound was found 5. All tested compounds showed higher enzyme inhibition activity than thiourea. The highest and the lowest antioxidant activities were observed as compounds 3 and 6, respectively.

Keywords: Carbazole; Antioxidant activity; Radical scavenging activity; Antiurease activity.

1. INTRODUCTION

Oxadiazole drugs are the first effective chemotherapeutic reagents developed for the systematic treatment and prevention of bacterial diseases in human applications. Among these, 1,3,4-oxadiazoles have been found to have the strongest biological effects. In the past years, it was observed that 1,3,4-oxadiazoles have anti-inflammatory [1, 2], antimitotic [3], antimalarial [4], antitubercular [5], antihypoglycemic [6], anticancer [7], antiviral [8] and insecticidal [9] properties.

Carbazole is a compound with the general formula $C_{12}H_9N$, showing very weak basic properties. Carbazole and its derivatives are used in various electronic and photonic applications due to their natural electron donor structure, nonlinear optical properties and excellent photoconductivity properties [10]. In

addition, carbazole and its derivatives are also found in industrial applications. For example, they are used as flexible building blocks in the construction sector, as well as raw materials in the synthesis of paints due to their low cost and ease of use [11].

In addition, it has been observed that a large number of natural or synthetic carbazole derivatives exhibit various biological activities. A carbazole derivative called MHY407 has been noted to sensitize cancer cells to chemotherapeutic drugs such as doxorubicin and etoposide and radiation therapy through DNA damage [12]. In another study, it was determined that staurosporine, a protein kinase inhibitor is a potential agent for cancer treatment [13] and a strong apoptosis stimulant in many different cell types [14]. In a study conducted by Katz et al., the reducing effects of rimcazole on cocaine were revealed [15]. Rimcazole is a sigma receptor antagonist as well as a dopamine reuptake inhibitor. It is also known that carbazoles show antimicrobial [16], antitumor [17], antiviral [18], antiinflammatory [19], antimalarial antidiarrheal [20] properties. In addition, these carbazole derivatives have biological properties such as immunosuppression [21], neurological protection [22], and pancreatic lipase inhibition [23].

Many drugs with carbazole structures have been synthesized so far. Some of them were given examples here. Ellipticine (Figure 1) is a cancer prodrug that acts through DNA damage. It damages biological membranes and has hemolysis and cardiovascular side effects. It is suggested that the antitumor activity of ellipticine is caused by the insertion of the DNA double helix and inhibiting the activity of the DNA topoisomerase II enzyme [24].

Carprofen is one of the propanoic acid class of drugs (Figure 1). It is a non-steroidal anti-inflammatory (NSAID) drug. Like other NSAIDs, it is believed to act by inhibiting the cyclooxygenase (COX) enzyme. It synthesizes basic cyclooxygenase, COX-1, prostaglandins necessary for digestive and kidney function. Inducible cyclooxygenase, COX-2 generates prostaglandins related to inflammation. While COX-2 inhibition provides anti-inflammatory activity, COX-1 inhibition is thought to cause toxicity in the digestive system and kidneys. Studies on carprofen have shown that it selectively inhibits the COX-2 enzyme [25].

Carvedilol (Figure 1) is a non-selective β- and α-1 blocker used in high blood pressure. First-generation β-blockers such as propranolol and timolol are non-selective β1/β2 antagonists and have been used in the treatment of myocardial infarction without high blood pressure and heart failure. Second-generation β-blockers (β1 selective), including atenolol, metoprolol and bisoprolol, were developed to address the problems that developed when the first generation β-blocker was used, as α-adrenergic activity cannot be resisted. Carvedilol, on the other hand, is a third generation-blocker with vasodilator properties, affecting all three important adrenergic receptors (β1, β2, and α1). Ondansetron is a highly specific and selective serotonin (5HT-3) receptor antagonist and an antiemetic drug used in the treatment of chemotherapy irradiation and surgery-induced nausea and vomiting (Figure 1). It shows a low affinity for dopamine receptors.

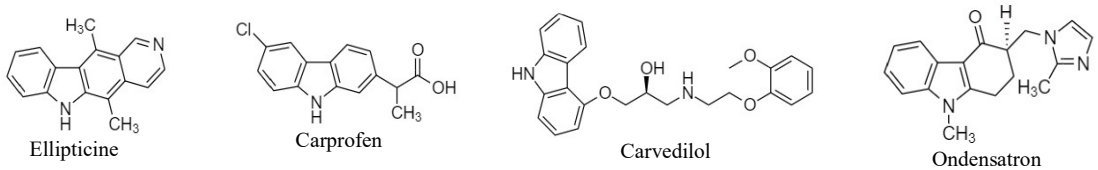

Figure 1. Carbazole-based drugs.

Free radicals are caused carcinogenesis, atherosclerosis, nephritis, and various diseases. Because lipid peroxidation is a free radical chain reaction [26] that causes the disrupt of cell membranes. In the other hand, antioxidants are the main defense mechanisms of the body [27]. Therefore, synthetic antioxidant compounds are needed from foreign sources. It is known that 1,3,4-oxadiazole seeds have potential antioxidant activity. During the research of antioxidant drugs, it was discovered that these substances have antioxidant activity [28].

Urease (Urea amidohydrolase EC 3.5.1.5) is a nickel-containing enzyme that catalyzes urea hydrolysis resulting in the production of ammonia and carbamic acid or carbon dioxide [29]. Urease enzyme is regarded as major factor many diseases such as kidney stones, pyelonephritis, urolithiasis, gastric cancer, gastric ulcer, chronic gastritis, duodenal ulcer in humans and animals [30]. One of the main methods used to solve these problems is to control the activity of urease using urease inhibitors. Some organic compounds can be extensively categorized as urease inhibitors such as 1,4-benzoquinone, imidazoles, Schiff bases, phosphorodiamidates, hydroxamic acid and humic acid [31-33].

Keeping in view the importance of Carbazole Shiff bases, our objective is to create hybrid molecules from a mixture of various pharmacophores in a single frame to be used as ligands and to study the ligands and their metal complexes from a structural point of view. Metal chelates of Carbazole Schiff bases hold exciting possibilities for the future concerning their wide applications viz in designing new catalytic systems, in formulating new synthetic route, in developing new analytical reagents and in metal-based antimicrobial agents etc., In addition, the synthesis of a compound can be used in a selective extraction of the metal is of great importance for the environment and the metal industry.

In our study, we obtained some new carbazole derivatives. Their antioxidant and antiurease activities were determined by *in vitro* assay and compared to the activity of standards.

2. MATERIALS AND METHODS

2.1. General

Compounds 9-butyl-9*H*-carbazole (1) and 9-butyl-9*H*-carbazole-3,6-dicarbaldehyde (2) have been reported earlier [34]. ^{1}H NMR and ^{13}C NMR spectra were obtained on Bruker Advance 400 MHz spectrometers. MS (EI) measurements were performed on SHIMADZU G-MS-QP2010 spectrometers. Antioxidant activities of compounds were measured spectrophotometrically (UV-1240, Shimadzu, Japan).

2.2. Synthesis of N',N'''-((1E,1'E)-(9-butyl-9H-carbazole-3,6-bis(methaneylylidene))-bis(4-chlorobenzohydrazide) (3)

In a 100 mL flask, compound 2 (1.40 g; 5.00 mmol), 4-chloro-benzoic acid hydrazide (2.05g; 12.02 mmol), ethanol (60 mL) and glacial acetic acid (4 mL) were added. Then it was boiled under reflux for 12 hours in oil bath. When the boiling process was completed, the solvent of the obtained product was removed in the evaporator, crystallized with methanol and powdery solid product was recovered. Yield: 2.27g (76%); m.p: 247ºC; Proton NMR: 0.90-1.10 (triplet, 3H), 1.26–1.37 (multiplet, 2H), 1.85–1.92 (multiplet, 2H), 4.22-4.35 (triplet, 2H), 7.60 (multiplet, 2H), 8.05-8.17 (multiplet, 4H), 8.22-8.41 (multiplet, 2H), 8.56-8.62 (multiplet, 4H), 8.51 (singlet, 2H, N=CH), 8.71 (singlet, 2H), 12.24 (singlet, 2H, NH); Carbon NMR:12.18, 19.42, 29.56, 41.50, 107.13, 111.48, 118.92, 121.45, 124.79, 127.13, 128.44, 129.63, 131.89, 142,35 161.30, 168.24; MS (EI): m/z: 598 $[M]^{+}$; E. A. calcd (%) for $C_{33}H_{29}Cl_2N_5O_2$ (598.53): C 66.22, H 4.88, N 11.70; found: C 66.31, H 4.72, N 11.78.

2.3. Synthesis of N',N'''-((1E,1'E)-(9-butyl-9H-carbazole-3,6-ethaneylylidene))bis(4-methylbenzohydrazid (4)

In a 100 mL flask, compound 2 (1.40 g; 5.00 mmol), p-toluic acid hydrazide (1.80 g; 12.02 mmol), ethanol (60 mL) and glacial acetic acid (4 mL) were added. Then it was boiled under reflux for 12 hours in oil bath. When the boiling process was completed, the solvent of the obtained product was removed in the evaporator, crystallized with methanol and powdery solid product was recovered. Yield: 2.18 g (78%); m.p: 263ºC; Proton NMR: 0.99-1.32 (triplet, 3H), 1.34–1.40 (multiplet, 2H), 1.80–1.90 (multiplet, 2H), 2.38 (singlet, 3H), 4.28-4.32 (triplet, 2H), 7.60-7.74 (multiplet, 2H), 7.90-8.06 (multiplet, 2H), 8.10-8.24 (multiplet, 4H), 8.27-8.40 (multiplet, 4H), 8.57 (singlet, 2H), 8,60 (singlet, 2H, N=CH), 11.86 (singlet, 2H, NH); Carbon NMR: 13.74, 18.87, 21,56, 27.39, 42.93, 108.67, 111.90, 119.12, 126.63, 127.32, 128.16, 129.65, 131.44, 132.08, 144.13, 160.81, 169.73; MS (EI): m/z: 557 $[M]^+$; E. A. calcd (%) for $C_{35}H_{35}N_5O_2$ (557.70): C 75.38, H 6.32, N 12.56; found: C 75.67, H 6.44, N 12.23.

2.4. 5,5'-(9-butyl-9H-carbazole-3,6-diyl)bis(2-(4-chlorophenyl)-1,3,4-oxadiazole) (5)

In a 50 mL flask, compound 3 (1.50 g; 2.51 mmol) and $KMnO_4$ (0.94 g; 5.90 mmol) were mixed in 25 mL of acetone for 6 hours in an oil bath at 50°C with the aid of a magnetic stirrer. Then acetone was removed in the evaporator. Saturated Na_2SO_3 (40 mL) solution was added to the residue and it was extracted first with dichloromethane and then with ethyl acetate twice. The obtained organic phase was dried with anhydrous $MgSO_4$ and filtered under vacuum. As a result of these processes, a powder product was obtained. Yield: 0.96 g (66%); e.n: 163ºC; Proton NMR: 0.98-1.20 (triplet, 3H), 1.35-1.45 (multiplet, 2H), 1.79-1.90 (multiplet, 2H), 4.30-4.36 (triplet, 2H), 7.55 (multiplet, 2H), 8.15 (multiplet, 2H), 8.27 (multiplet, 4H), 8.44 (multiplet, 4H), 8.76 (singlet, 2H); Carbon NMR: 10.68, 17.41, 26.99, 43.00, 109.56, 116.53, 118.71, 123.35, 125.80, 127.61, 129.14, 130.62, 133.80, 145.16, 152.35, 153.70; MS (EI): m/z: 581 $[M]^+$; E. A. Calcd (%) for $C_{32}H_{24}Cl_2N_5O_2$ (581.48): C 66.10, H 4.16, N 12.04; found: C 66.07, H 4.23, N 12.16.

2.5. 5,5'-(9-butyl-9H-carbazole-3,6-diyl)bis(2-(p-tolyl)-1,3,4-oxadiazole) (6)

In a 50 mL flask, compound N',N'''-((1E,1'E)-(9-butyl-9H-carbazole-3,6-diyl)-bis(methaneylylidene))-bis(4-methylbenzohydrazide) (4) (1.50 g; 2.69 mmol) and $KMnO_4$ (0.99 g; 6.32 mmol) were mixed in 25 mL of acetone for 6 hours in an oil bath at 50°C with the aid of a magnetic stirrer. Then acetone was removed in the evaporator. Saturated Na_2SO_3 (40 mL) solution was added to the residue and it was extracted first with dichloromethane and then with ethyl acetate twice. The obtained organic phase was dried with anhydrous $MgSO_4$ and filtered under vacuum. As a result of these processes, a powder product is obtained. Yield: 1.00 g (69%); e.n: 186ºC; Proton NMR: 0.95-1.20 (triplet, 3H) 1.30-1.40 (multiplet, 2H), 1.74-1.83 (multiplet, 2H), 2.43 (singlet, 3H), 4.34-4.40 (triplet, 2H), 7.64-7.70 (multiplet, 2H), 8.19-8.26 (multiplet, 2H), 8.33-8.40 (multiplet, 4H), 8.43-8.55 (multiplet, 4H), 8.59 (singlet, 2H); Carbon NMR: 11.42, 16.90, 20.97, 25.72, 46.95, 112.57, 117.45, 118.92, 120.33, 123.86, 125.14, 126.42, 131.62, 134.27, 146.08, 152.89, 153.36; MS (EI): m/z: 540 $[M]^+$; E. A. calcd (%) for $C_{34}H_{30}N_5O_2$ (540.64): C 75.53, H 5.59, N 12.95; found: C 75.62, H 5.46, N 12.86.

2.6. Antioxidant and urease inhibitory activity assays

Stock solutions (1 mg/mL) of all compounds and standards in dimethyl sulfoxide (DMSO) were prepared. Then, stock solutions were diluted to different concentrations. Antioxidant activity and urease inhibition assays were performed in the concentration ranges of 25-100 µg/mL and 0.0001-0.1 µg/mL,

respectively. The DPPH and ABTS radical scavenging activities of diluted compounds were measured according to the procedure described by Brand-Williams et al. [34] and Arnao et al. [35], respectively. The reducing power antioxidant capacities were determined according to the method described by Oyaizu [36].

Urease inhibitory activities of carbazole compounds were studied accoering to Van Slyke method [37]. All activity experiments were measured spectrophotometrically.

3. RESULTS AND DISCUSSION

In this study, new heteroaryl substituted carbazole derivatives were synthesized. For this reason, 1,3,4-oxadiazole-carbazole derivatives were synthesized from 9H-carbazole according to the synthesis plans. Firstly, 9H-carbazole compound was converted to 9-n-butylcarbazol (1) and the aldehyde group was attached to the 3 and 6 positions and compound 2 was obtained according to the literature [38].

As a result of the reaction of compound 2 in ethanol in the presence of p-chloro-benzoic acid hydrazide and p-toluic acid hydrazide, carbazole hydrazide compounds (3, 4) were obtained. Donor-acceptor (D-A) type carbazole-π-oxadiazole compounds 5, 6 were obtained by reacting these compounds separately with $KMnO_4$ in acetone.

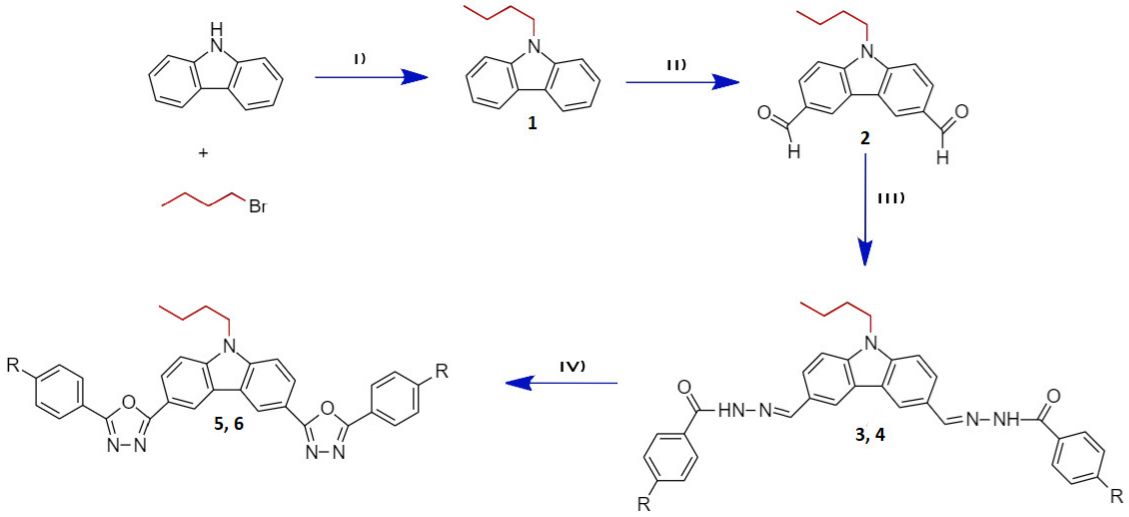

Figure 2. I) TBAI, NaOH; II) $POCl_3$, DMF; III) p-choloro/methylbenzohydrazide, C_2H_5OH; IV) $KMnO_4$, Na_2SO_3; R: Cl, CH_3.

All newly synthesized carbazole compounds (Figure 2) and standard (Thiourea) showed effective urease inhibitory activity (Table 1). Lower IC_{50} values indicate higher enzyme inhibitor activity. All of the compounds showed antiurease activity (0.025-0.759 µM). Compound 4 with an IC_{50}= 0.025 ± 0.0069 µM appeared to be the most potent enzyme inhibition activity. The lowest active compound 5 had an IC_{50}= 0.759±0.0584 µM. However, compounds 4 and 6 showed higher activity than thiourea (IC_{50}= 0.267 ± 0.022 µM), while compounds 3 and 5 showed lower inhibitory activity.

The DPPH free radical scavenging activities of synthesized carbazole compounds and standard (BHT, Butylated hydroxytoluene) were given in Table 1. Lower SC_{50} values suggest higher DPPH radical scavenging potential. All the tested carbazole derivatives demonsrated free radical scavenging activities. Among all tested carbazole derivatives the highest and the lowest DPPH free radical scavenging activities were found to be compounds 3 and 6, respectively. Compounds 3 and 5 showed higher activity than BHT (SC_{50}= 211.13 ± 12.02 µM).

Table 1. showed the ABTS radical scavenging behavior of carbazole derivatives relative to BHT. The radical scavenging activity of ABTS has increased with rising concentration. All of the compounds (96.64-292.74 µM) demonstrated ABTS radical scavenging The highest and lowest activities were found in compounds 3 and 6, respectively. However, compound 3 showed higher activity than BHT (SC_{50} = 174.70 ± 30.13 µM).

Table 1. Antiurease, DPPH and ABTS radical scavenging antioxidant activities of carbazole derivatives (3-6).

Compounds	Antiurease IC_{50} (µM)*	DPPH SC_{50} (µM)*	ABTS SC_{50} (µM)*
3	0.603±0.0836	58.35±08.398	96.64±07.764
4	0.025±0.0069	279.63±26.168	229.69±33.295
5	0.759±0.0584	200.89±21.272	183.85±20.079
6	0.252±0.0535	481.18±98.920	292.74±30.233
BHT	-	211.13±12.020	174.70±30.130
Thiourea	0.267± 0.022	-	-

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

DPPH is a free radical compound widely used to test the free radical scavenging ability of various materials. Since exposure to proton radical scavenger, DPPH decreases significantly [39]. Bilgin Sokmen et al. have synthesized newly imine derivatives and their DPPH SC_{50} values found between 4376.08-13337.95 µM [40]. In a previous study, we have synthesized some 2,5-disubstitue-1,3,4-oxadiazoles and their ABTS radical scavenging activity values (SC_{50}) were determined between 1348-16883 µM [41].

Table 2. Iron reducing power antioxidant activity of carbazole derivatives (3-6).

Compounds	Reducing Power Absorbance*
3	0.369±0.0771 0.507±0.0304 0.629±0.0347 0.763±0.0332
4	0.132±0.0092 0.155±0.0191 0.184±0.0120 0.229±0.0197
5	0.155±0.0106 0.179±0.0106 0.216±0.0177 0.272±0.0359
6	0.099±0.0092 0.122±0.0099 0.142±0.0099 0.177±0.0297
BHT	0.187±0.0151 0.275±0.0211 0.319±0.0217 0.405±0.0271

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

Reducing the potency of a compound can serve as a significant indicator of its antioxidant activity. The highest and lowest levels of activity were found in compounds 3 and 6, respectively (Table 2). Iron ions

(Fe^{3+}) reducing power of the carbazole derivatives and BHT at studied all concentrations exhibited the following order: 3 > BHT > 5 > 4 > 6 (25-100 μg/mL).

4. CONCLUSION

Within the scope of our study, four different codes carbazole-oxadiazole derivatives were synhesized. In this study, the findings revealed that the synthesized carbazole derivatives had antiurease and antioxidant activity. In addition, these synthesized derivatives contain the properties of oxadiazole and carbazole. For these reasons, they can be used as electronic materials. Especially in recent years, they can be used in the structure of organic and polymeric light-emitting diodes (OLED and PLED), which stand out due to their advantages over other lighting systems. By adding these derivatives to the structure of LEDs, the light quality of the LEDs can be increased by ensuring the balance of the load carriers.

Authors' Contributions: NG; studied synthesis of oxadiazole substituted new compounds, elucidated the structure of compounds, and edited the manuscript. BBS; studied antioxidant and antiurease activity of the synthesized compounds. Both authors read and approved the final manuscript.

Conflict of Interest: The authors declare no conflict of interest.

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