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Research Article

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Synthesis of quinazolinone-1,3,4-oxadiazole conjugates and studies of their antibacterial and antioxidant activity

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ABSTRACT

Quinazolinone - 1,3,4-oxadiazole conjugates were obtained from the mixed hydrazides of (hetero)aromatic carboxylic acids and 3-[4-oxoquinazolin-3(4H)-yl]propanoic acid. The latter was synthesized from isatoic anhydride, β-alanine and formic acid. Antimicrobial and antioxidant activities of the synthesized compounds were studied. Although the newly obtained compounds did not demonstrate significant antimicrobial activity, several substances containing hydrazide moiety in the side chain at C-3 showed promising antiradical activity. Several of the observed antiradical activities against frequently used standards of free radicals 2,2-diphenyl-1-picrylhidrazyl and galvinoxyl were comparable with those of well known antioxidant butylated hydroxytoluene. Interestingly, transformation of hydrazides into oxadiazoles caused dramatic loss of antiradical activity. The obtained mixed hydrazides represent an unexplored class of antioxidants, in which the hydrazide moiety is crucial for the antiradical activity.

Key words: Quinazolinone, oxadiazole, mixed hydrazides, antimicrobial activity, antioxidant activity

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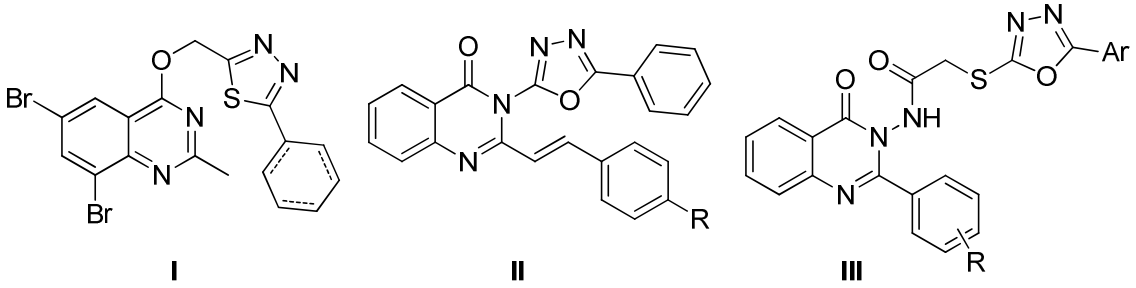
INTRODUCTION

Compounds containing quinazolinone moiety exhibit various biological activities. They are known as inhibitors of various enzymes and substances that posses antiviral, anticonvulsant and antimicrobial activities [1, 2]. Also derivatives of oxadiazole exhibit wide range of biological activities [3]. Compounds containing 1,3,4-oxadiazole fragment are active against a wide variety of Gram-positive and Gram-negative bacteria [4]. Besides that, oxadiazole moiety is used as pharmacophore and bioisostere of carboxylic acids, their esters and amides [5, 6].

We were interested into hybrid compounds, which would combine moiety of quinazolinone and oxadiazole into one molecule. It can be predicted that the new hybrid compounds would demonstrate stronger or different type of biological activity.

To the best of our knowledge only few examples of such kind of quinazolinole-azole conjugates are found in the literature. Antibacterial and antifungal activity is studied for quinazolinoles **I** containing various nitrogen heterocycles, including oxadiazoles in the side chain. Thiadiazole derivatives were obtained from ethyl ester or hydrazide of 4-(6,8-dibromo-2-phenyl-2-oxo-(4*H*)quinazolin-3-yl) benzoic acid [7]. Several 3-[5-(4-substituted)phenyl-1,3,4-oxadiazol-2-yl]-2-stiryl quinazolin-4(3*H*)ones **II** were obtained by condensation of 2-methylquinazolinone and 4-substituted benzaldehydes in glacial acetic acid. The stiryl derivatives demonstrated both antibacterial activity to *Staphylococcus aureus, Bacillus subtilis, Pseudomonas acruginosa* and *Escherichia coli* and antifungal activity to *Aspergillus niger* and *Fusariumoxysporum.* The above mentioned compounds exhibited also sedative and neuroleptic properties [8-10]. *N*-(4-Oxo-2-aryl-quinazolin-3(4*H*)-yl)-2-[(5-aryl-1,3,4-oxadiazol-2-yl)sulphanyl)acetamides **III** have demonstrated strong antibacterial and moderate antioxidant action. They were

obtained from 2-aryl-3-chloroacetamidoquinazolin-4(3*H*)-ones and various 5-phenyl or 5-(pyridine-4-yl)-1,3,4-oxadiazol-2-thioles [11].



I **II** **III**

EXPERIMENTAL SECTION

^{1}H NMR spectra were recorded on *Bruker 300* spectrometer at 300 MHz. The compounds **6** were dissolved in DMSO-d_6, the compounds **8** in $CDCl_3$. The proton signals for residual non-deutered solvent (δ 2.50 for DMSO-d_6 and δ 7.26 for $CDCl_3$) were used as an internal reference. Combustion analyses were carried out on *Carlo-Erba* element analyzer (model EA 1108). Melting point was detected on *Fisher Digital* melting point analyzer (model 335). UV-VIS absorption was measured on *Camspec* M501 single beam spectrophotometer. The progress of reaction was monitored by TLC. *Merc Silica gel 60F$_{254}$* plates were eluted with solvent mixture $CHCl_3$:MeOH:AcOH (95:5:3).

3-[4-Oxoquinazolin-3(4*H*)-yl] propionic acid (**4**) was synthesized according to known method [12].

Analytical data for compounds **6** and **8** are presented in Table 1, ^{1}H NMR spectra – in Table 2.

N`-[3-(4-Oxoquinazolin-3(4*H*)-yl)propanoyl]-aryl(heteroaryl) hydrazides **6a-j** (general procedure).
1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide EDCI (1.15 g, 6 mmol) was added by mixing to the solution of 3-(4-oxoquinazolin-3(4*H*)-yl) propionic acid (**4**) (1.10 g, 5 mmol) in dry dimethylformamide (12 mL). Hydrazide **5a-j** (5 mmol) was added to the resulting reaction mixture and it was continued to stir for 15 h at ambient temperature. DMF was evaporated under reduced pressure. The residue was dissolved in ethyl acetate and the organic layer was washed with ice-cold water, dried over anhydrous Na_2SO_4, filtered and evaporated. Compounds **6a-j** were used for the next step of the synthesis without further purification. For analytical purposes the compounds were purified by crystallization.

3-[2-(5-Aryl(heteroaryl)-1,3,4-oxadiazol-2-yl)ethyl]quinazolin-4(3*H*)-ones **8a-j** (general procedure).
p-Toluenesulfonic acid chloride (**7**) (1.0 mmol) and triethylamine (2.4 mmol) were added to the solution of compound **6** (1.0 mmol) in dichloromethane (15 mL). The resulting mixture was stirred at ambient temperature for 12-17 h. Dichloromethane (15 mL) and brine (15 mL) were added to the reaction mixture. The organic layer was separated, dried over anhydrous Na_2SO_4, filtered and evaporated. The solid residue was and crystallized from the solvent indicated in Table 1.

Evaluation of antimicrobial activity for compounds **6a-j** and **8a-j**.
MIC was determined according to the broth dilution method [13]. A series of solutions of compounds **6** and **8** with a range of 0.25 to 512 μg/ml were dissolved in *BBL Mueller Hinton* broth (for the *Lactobacillus reuteri* the solutions were prepared in *Difco Lactobacilli MRS*). In order to establish MIC logarithmical phase culture with density OD_{600} = 0.1 (corresponds to ~$1.2 \cdot 10^8$ CFU/ml) was used and diluted 100 times in 96-well plate (*Greiner Bio-One*). The plate was incubated at 37°C for 24 h and the bacterial growth was measured with microplate reader *Tecan* by monitoring the absorption at 600 nm. All experiments were done in triplicate.

Evaluation of antioxidant activity for compounds **6a-j** and **8a-j**.
All experiments were carried out at 18-20°C. DPPH test: 2 mL 400, 200 or 100 μM solution of compound **6** or **8** in ethanol was added to the solution of DPPH (2 mL, 200 μM) in ethanol; *UV-VIS* absorption was measured at 515 nm after 30 min [14]. GO test: 2 mL 160, 80 or 40 μM solution of compound **6** was added to the solution of GO (2 mL, 20 μM) in ethanol; *UV-VIS* absorption was measured at 428 nm after 4 h [15]. All experiments were carried out in triplicate.

Table 1 Physicochemical properties of compounds 6 and 8

Comp.	Chemical formula	Combustion analysis Found, % / Calculated, %			Melting point, ºC (solvent for crystallization)	Yield, %	Time, h
		C	H	N			
6a	$C_{18}H_{16}N_4O_3$	63.98 64.28	4.77 4.79	16.61 16.66	195-197 (ethanol)	88	15
6b	$C_{18}H_{15}ClN_4O_3$	58.22 58.31	4.14 4.08	15.12 15.11	246-247 (methanol)	81	
6c	$C_{18}H_{15}BrN_4O_3$	52.37 52.06	3.83 3.64	13.40 13.49	250-251 (ethanol)	68	
6d	$C_{18}H_{16}FN_4O_3$	60.91 61.01	4.31 4.27	15.76 15.81	219-220 (ethanol)	90	
6e	$C_{18}H_{16}N_4O_4$	61.28 61.36	4.63 4.58	15.73 15.90	260-262 (methanol)	85	
6f	$C_{18}H_{17}N_5O_3$	61.63 61.53	5.01 4.87	19.94 19.93	185-186 (methanol)	86	
6g	$C_{17}H_{15}N_5O_3$	60.46 60.53	4.53 4.48	20.68 20.76	225-226.5 (methanol)	90	
6h	$C_{17}H_{15}N_5O_3$	60.24 60.53	4.53 4.48	20.59 20.76	133-135 (methanol)	71	
6i	$C_{16}H_{14}SN_4O_3$	56.20 56.13	4.06 4.12	16.29 16.36	221-222 (methanol)	78	
6j	$C_{16}H_{14}N_4O_4$	59.20 58.89	4.52 4.32	16.92 17.17	129-131 (ethanol:water, 3:1)	70	
8a	$C_{18}H_{14}N_4O_2$	67.74 67.91	4.51 4.43	17.28 17.60	168-169 (ethanol)	52	12
8b	$C_{18}H_{13}ClN_4O_2$	61.50 61.28	3.96 3.71	15.65 15.88	158-159 (ethanol)	90	17
8c	$C_{18}H_{13}BrN_4O_2$	54.49 54.43	3.55 3.30	13.85 14.10	180-182 (ethanol)	65	16
8d	$C_{18}H_{13}FN_4O_2$	63.89 64.28	3.89 3,90	16.38 16.66	182-183 (methanol)	84	16
8e	$C_{18}H_{14}N_4O_3$	64.29 64.66	4.42 4.22	16.60 16.76	183-186 (ethanol)	66	14
8f	$C_{18}H_{15}N_5O_2$	64.48 64.86	4.51 4.54	20.72 21.01	192-193 (methanol)	51	15
8g	$C_{17}H_{13}N_5O_2$	63.86 63.94	4.32 4.10	21.74 21.93	188-190 (ethanol)	60	12
8h	$C_{17}H_{13}N_5O_2$	63.79 63.94	4.18 4.10	21.92 21.93	160-161 (ethanol)	50	12
8i	$C_{16}H_{12}SN_4O_2$	59.27 59.25	3.82 3.73	17.01 17.27	163-165 (ethanol)	63	15
8j	$C_{16}H_{12}N_4O_3$	62.13 62.33	3.87 3.92	18.11 18.17	164-165 (ethanol)	84	16

RESULTS AND DISCUSSION

Hence, we report here the synthesis of novel quinazolines with the oxadiazole moiety in the side chain (quinazolinone-oxadiazole conjugates) according to the following scheme: the starting material for the synthesis of the target compounds **6** and **8** is 3-[4-oxoquinazolin-3(4*H*)-yl]propionic acid (**4**) which was synthesized from isatoic anhydride (**1**), 3-aminopropanoic acid (*β*-alanine) (**2**) and formic acid [12]. The next step was formation of hydrazides between propanoic acid **4** and aromatic (**5a-f**) or heteroaromatic hydrazides (**5g-j**) in the presence of 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide EDCI. The obtained hydrazides **6** were further transformed into quinazolinone 1,3,4-oxadiazole conjugates **8a-j** in the presence of *p*-tosyl chloride [16].

Compounds **8a-j** were easily purified by crystallization. The spectroscopic and physical properties (^{1}H NMR spectra, LC-MS and CHN analysis) of all new compounds were fully consistent with the assigned structures. Typical chemical shifts of NH protons for hydrazide moiety appeared as two singlets in the range of 10.0 to 10.7 ppm.

The synthesized compounds **6** and **8** were studied for their antibacterial and antioxidant activity. Antibacterial activity was expressed as the minimal inhibitory concentration (MIC). It is the concentration of antimicrobial agent that completely inhibits cell growth during 24 h incubation at 37°C. The compounds **6** and **8** were tested as antimicrobial agents to Gram-positive *Staphylococcus aureus*, *Staphylococcus epidermidis* and *Lactobacillus reuteri* and Gram-negative *Escherichia coli* and *Pseudomonas acruginosa*. Unfortunately, the compounds **6** and **8** did not demonstrate significant inhibition when the concentration was smaller than 512 mg/ml under the test conditions.

In order to evaluate antioxidant activity of the synthesized compounds **6** and **8** two free radicals - 2,2-diphenyl-1-picrylhidrazyl (DPPH) and galvinoxyl (GO) – were employed. Antioxidant activity was expressed as inhibition of free radical (%), when the molar ratio of the test compound (**6** or **8**) and the free radical (DPPH or GO) was 1:1. Results are presented in Tables 3 and 4. Compound **6e** containing salicylic acid moiety demonstrates the highest antiradical activity. The GO test was carried out only for compounds **6** when the compound demonstrated at least negligible inhibition of DPPH. Due to the same reasons none of the compounds **8** was tested by the GO test. Compounds **6c**,**e** exhibited similar level of inhibition of DPPH and GO. Also hydrazides **6b**,**f**,**i** showed slight antiradical activity. Unexpectedly, 1,3,4-oxadiazoles **8** did not demonstrate considerable antiradical activity in comparison to the corresponding hydrazides **6**. Till now, only few compounds containing hydrazide moiety are known as antioxidants or antiradical agents [17, 18]. The above mentioned results demonstrate that the presence of NH in hydrazide moiety is crucial for antiradical activity. Thus we have established here a new type of antioxidants with hydrazide scaffold.

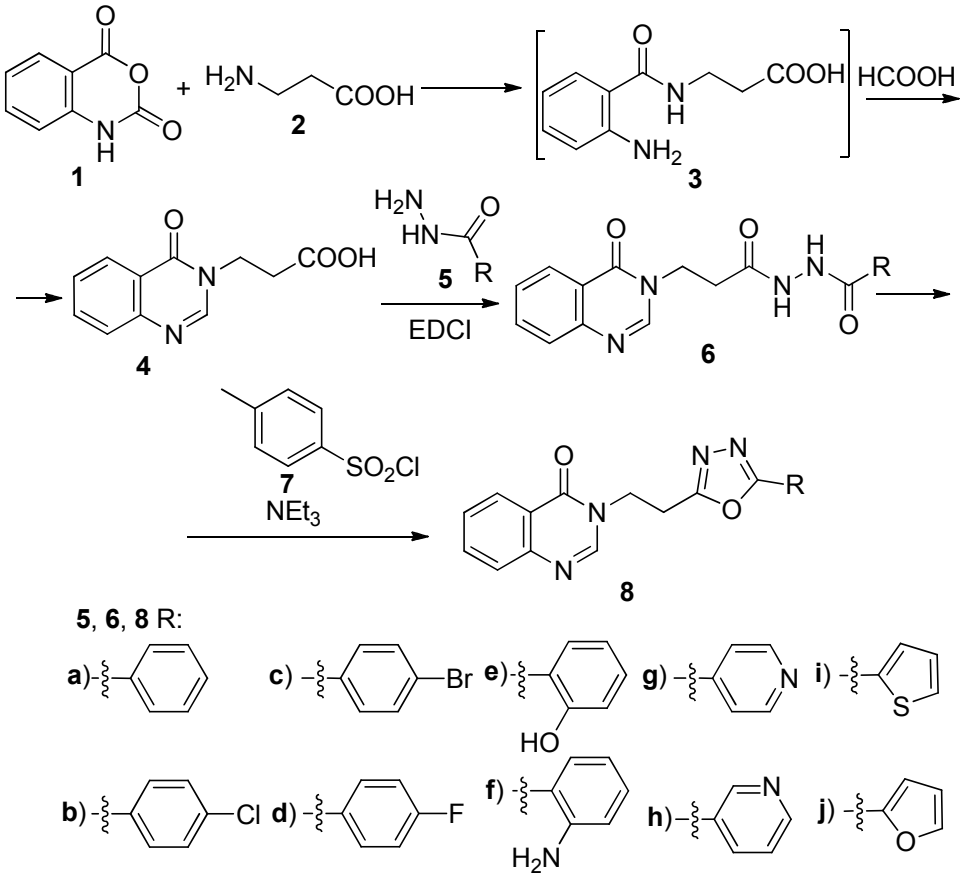


Table 2 ^{1}H NMR spectra (300 MHz) of the compounds 6a-j (DMSO-d_6) and 8a-j ($CDCl_3$)

Com-pound	Chemical shift, δ, ppm (spin-spin coupling constant, *J*, Hz)
6a	2.77 (2H, t, *J* = 6.6, NC$\underline{H}_2$CH$_2$); 4.23 (2H, t, *J* = 6.6, NCH$_2$C$\underline{H}_2$); 7.49 (2H, t, *J* = 7.5, arom.); 7.52-7.60 (2H, m, H-6/7, arom.); 7.68 (1H, d, *J* = 8.1, H-5/8); 7.80-7.88 (3H, m, H-6/7, arom.); 8.18 (1H, d, *J* = 8.1, H-5/8); 8.34 (1H, br. s, H-2); 10.04 (1H, s, NH); 10.34 (1H, s, NH)
6b	2.77 (2H, t, *J* = 6.2, NC$\underline{H}_2$CH$_2$); 4.23 (2H, t, *J* = 6.2, NCH$_2$C$\underline{H}_2$); 7.53-7.59 (3H, m, H-6/7, arom.); 7.67 (1H, d, *J* = 8.1, H-5/8); 7.77-7.89 (3H, m, H-6/7, arom.); 8.17 (1H, d, *J* = 8.1, H-5/8); 8.34 (1H, br. s, H-2); 10.08 (1H, s, NH); 10.43 (1H, s, NH)
6c	2.77 (2H, t, *J* = 6.5, NC$\underline{H}_2$CH$_2$); 4.24 (2H, t, *J* = 6.5, NCH$_2$C$\underline{H}_2$); 7.56 (1H, t, *J* = 8.1, H-6/7); 7.65-7.86 (6H, m, H-5/8, H-6/7, arom.); 8.21 (1H, d, *J* = 8.1, H-5/8); 8.34 (1H, s, H-2); 10.04 (1H, s, NH); 10.41 (1H, s, NH)
6d	2.75 (2H, t, *J* = 6.4, NC$\underline{H}_2$CH$_2$); 4.24 (2H, t, *J* = 6.4, NCH$_2$C$\underline{H}_2$); 7.28-7.37 (2H, m, arom.); 7.56 (1H, t, *J* = 8.3, H-6/7); 7.68 (1H, d, *J* = 8.3, H-5/8); 7.79-7.96 (3H, m, H-6/7, arom.); 8.18 (1H, d, *J* = 8.3, H-5/8), 8.34 (1H, br. s, H-2); 10.05 (1H, s, NH); 10.37 (1H, s, NH)
6e	2.79 (2H, t, *J* = 6.4, NC$\underline{H}_2$CH$_2$); 4.24 (2H, t, *J* = 6.4, NCH$_2$C$\underline{H}_2$); 6.89-6.98 (2H, m, arom.); 7.44 (1H, t, *J* = 7.2, arom.); 7.56 (1H, t, *J* = 8.1, H-6/7); 7.68 (1H, d, *J* = 8.1, H-5/8); 7.80-7.88 (2H, m, H-6/7, arom.); 8.18 (1H, d, *J* = 8.1, H-5/8); 8.33 (1H, br. s, H-2); 10.33 (1H, s, NH); 10.53 (1H, s, NH); 11.70 (1H, br. s, OH)
6f	2.75 (2H, t, *J* = 6.4, NC$\underline{H}_2$CH$_2$); 4.22 (2H, t, *J* = 6.4, NCH$_2$C$\underline{H}_2$); 6.39 (2H, br. s, NH$_2$); 6.50 (1H, t, *J* = 7.9, arom.); 6.71 (1H, d, *J* = 8.2, arom.); 7.17 (1H, t, *J* = 7.9, arom.); 7.50 (1H, д, *J* = 7.9, arom.); 7.56 (1H, t, *J* = 8.2, H-6/7); 7.67 (1H, d, *J* = 8.2, H-5/8); 7.84 (1H, t, *J* = 8.2, H-6/7); 8.18 (1H, d, *J* = 8.2, H-5/8); 8.33 (1H, s, H-2); 9.88 (1H, s, NH); 9.98 (1H, s, NH)
6g	2.78 (2H, t, *J* = 6.6, NC$\underline{H}_2$CH$_2$); 4.23 (2H, t, *J* = 6.6, NCH$_2$C$\underline{H}_2$); 7.56 (1H, t, *J* = 8.1 H-6/7); 7.67 (1H, d, *J* = 8.1, H-5/8); 7.71-7.76 (2H, m, arom.); 7.83 (1H, т, *J* = 8.1, H-6/7); 8.16 (1H, d, *J* = 8.1, H-5/8); 8.34 (1H, s, H-2); 8.75 (2H, d, *J* = 4.5, arom.); 10.18 (1H, s, NH); 10.67 (1H, s, NH)
6h	2.78 (2H, t, *J* = 6.4, NC$\underline{H}_2$CH$_2$); 4.23 (2H, t, *J* = 6.4, NCH$_2$C$\underline{H}_2$); 7.51-7.58 (2H, m, H-6/7, arom.); 7.68 (1H, d, *J* = 8.3, H-5/8); 7.84 (1H, t, *J* = 8.3, H-6/7); 8.16-8.21 (2H, m, H-5/8, arom.); 8.34 (1H, s, H-2); 8.73 (1H, d, *J* = 5.1, arom.); 9.99 (1H, m, arom.); 10.14 (1H, s, NH); 10.56 (1H, s, NH)
6i	2.76 (2H, t, *J* = 6.2, NC$\underline{H}_2$CH$_2$); 4.23 (2H, t, *J* = 6.2, NCH$_2$C$\underline{H}_2$); 7.18 (1H, t, *J* = 4.7, arom.); 7.57 (1H, t, *J* = 8.1, H-6/7); 7.69 (1H, d, *J* = 8.1, H-5/8); 7.78-7.88 (3H, m, H-6/7, arom.); 8.19 (1H, d, *J* = 8.1, H-5/8); 8.34 (1H, br. s, H-2); 10.04 (1H, s, NH); 10.35 (1H, s, NH)
6j	2.74 (2H, t, *J* = 6.4, NC$\underline{H}_2$CH$_2$); 4.21 (2H, t, *J* = 6.4, NCH$_2$C$\underline{H}_2$); 6.65 (1H, m, arom.); 7.20 (1H, d, *J* = 3.2, arom.); 7.55 (1H, t, *J* = 7.9, H-6/7); 7.67 (1H, d, *J* = 7.9, H-5/8); 7.81-7.91 (2H, m, H-6/7, arom.); 8.17 (1H, d, *J* = 7.9, H-5/8); 8.32 (1H, br. s, H-2); 9.99 (1H, s, NH); 10.24 (1H, s, NH)
8a	3.47 (2H, t, *J* = 6.6, NC$\underline{H}_2$CH$_2$); 4.45 (2H, t, *J* = 6.6, NCH$_2$C$\underline{H}_2$); 7.52-7.61 (4H, m, H-6/7, arom.); 7.69 (1H, d, *J* = 8.3, H-5/8); 7.80-7.91 (3H, m, H-6/7, arom.); 8.12 (1H, d, *J* = 8.3, H-5/8); 8.45 (1H, br. s, H-2)
8b	3.52 (2H, t, *J* = 6.4, NC$\underline{H}_2$CH$_2$); 4.59 (2H, t, *J* = 6.4, NCH$_2$C$\underline{H}_2$); 7.42-7.48 (2H, m, arom.); 7.54 (1H, td, *J* = 8.1, *J* = 1.7, H-6/7); 7.72-7.84 (2H, m, H-6/7, H-5/8); 7.85-7.93 (2H, m, arom.); 8.31 (1H, d, *J* = 8.1, H-5/8); 8.45 (1H, s, H-2)
8c	3.48 (2H, t, *J* = 6.5, NC$\underline{H}_2$CH$_2$); 4.44 (2H, t, *J* = 6.5, NCH$_2$C$\underline{H}_2$); 7.55 (1H, t, *J* = 8.1, H-6/7); 7.69 (1H, d, *J* = 8.1, H-5/8); 7.74-7.89 (5H, m, H-6/7, arom.); 8.14 (1H, d, *J* = 8.1, H-5/8); 8.45 (1H, s, H-2)
8d	3.52 (2H, t, *J* = 6.2, NC$\underline{H}_2$CH$_2$); 4.61 (2H, t, *J* = 6.2, NCH$_2$C$\underline{H}_2$); 7.15 (2H, t, $J_{H\text{-}H}$ = 8.8, $J_{H\text{-}F}$ = 8.8, arom.); 7.50-7.58 (1H, m, H-6/7); 7.78 (2H, m, H-6/7, H-5/8); 7.91-7.97 (2H, m, arom.); 8.34 (1H, d, *J* = 8.8, H-5/8); 8.55 (1H, s, H-2)
8e	2.78 (2H, t, *J* = 6.6, NC$\underline{H}_2$CH$_2$); 4.24 (2H, t, *J* = 6.6, NCH$_2$C$\underline{H}_2$); 6.87-6.98 (2H, m, arom.); 7.43 (1H, t, *J* = 8.4, H-6/7); 7.55 (2H, t, *J* = 7.7, arom.); 7.67 (1H, d, *J* = 8.4, H-5/8); 7.80-7.83 (2H, m, H-6/7, arom.); 8.16-8.22 (1H, m, H-5/8), 8.32 (1H, s, H-2); 10.31 (1H, s, OH)
8f	3.52 (2H, t, *J* = 6.4, NC$\underline{H}_2$CH$_2$); 4.61 (2H, t, *J* = 6.4, NCH$_2$C$\underline{H}_2$); 6.56 (1H, t, *J* = 6.9, arom.); 6.67 (2H, br. s, NH$_2$); 6.86 (1H, d, *J* = 8.2, arom.); 7.22 (1H, t, *J* = 6.9, H-6/7); 7.43 (1H, d, *J* = 8.2, arom.); 7.54 (1H, t, *J* = 7.5, arom.); 7.67 (1H, d, *J* = 6.9, H-5/8); 7.84 (1H, t, *J* = 6.9, H-6/7); 8.13 (1H, d, *J* = 6.9, H-5/8); 8.44 (1H, s, H-2)
8g	3.53 (2H, t, *J* = 6.4, NC$\underline{H}_2$CH$_2$); 4.54 (2H, t, *J* = 6.4, CH$_2$); 7.68 (1H, td, *J* = 8.1, *J* = 1.3, H-6/7); 7.69 (1H, d, *J* = 8.1, H-5/8); 7.76 (1H, td, *J* = 8.1, *J* = 1.3, H-6/7); 7.78-7.84 (2H, m, arom.); 8.23 (1H, s, H-2); 8.26 (1H, d, *J* = 8.1, H-5/8); 8.73-8.80 (2H, m, arom.)
8h	3.50 (2H, t, *J* = 6.4, NC$\underline{H}_2$CH$_2$); 4.46 (2H, t, *J* = 6.4, NCH$_2$C$\underline{H}_2$); 7.52 (2H, m, H-6/7, arom.); 7.68 (1H, d, *J* = 8.3, H-5/8); 7.84 (1H, t, *J* = 8.3, H-6/7); 8.13 (1H, d, *J* = 8.3, H-5/8); 8.24-8.29 (1H, m, arom.); 8.46 (1H, s, H-2); 8.78 (1H, d, *J* = 4.5, arom.); 9.07 (1H, br. s, arom.)
8i	3.49 (2H, t, *J* = 6.4, NC$\underline{H}_2$CH$_2$); 4.58 (2H, t, *J* = 6.4, NCH$_2$C$\underline{H}_2$); 7.11-7.15 (1H, m, arom.); 7.50-7.55 (2H, m, H-6/7, arom.); 7.63 (1H, d, *J* = 7.7, H-5/8); 7.74-7.79 (2H, m, H-6/7, arom.); 8.30 (1H, d, *J* = 7.7, H-5/8); 8.43 (1H, br. s, H-2)
8j	3.52 (2H, t, *J* = 6.4, NC$\underline{H}_2$CH$_2$); 4.64 (2H, t, *J* = 6.4, NCH$_2$C$\underline{H}_2$); 6.54-6.57 (1H, m, H-6/7); 7.07 (1H, d, *J* = 3.6, arom.); 7.52-7.62 (2H, m, H-6/7, H-5/8); 7.78-7.88 (2H, m, arom.); 8.31 (1H, d, *J* = 7.9, H-5/8); 8.68 (1H, s, H-2)

Table 3 Antioxidant activity of compounds 6 and 8 expressed as inhibition (%) of DPPH

Compound **6**	Inhibition, %[a]	Inhibition % of standard compound BHT[b] (37.8±2.6%)	Compound **8**	Inhibition, %[a]	Inhibition % of standard compound BHT[b] (37.8±2.6%)
a	-[c]	-	**a**	-[c]	-
b	8.2±0.0	22	**b**	-[c]	-
c	14.3±2.2	38	**c**	2.2±0.1	6
d	2.9±0.4	8	**d**	3.4±0.1	9
e	27.8±1.8	74	**e**	-[c]	-
f	7.4±0.2	20	**f**	3.6±0.0	10
g	2.2±0.4	6	**g**	4.5±0.1	12
h	3.7±0.1	10	**h**	2.9±0.1	8
i	7.7±0.1	20	**i**	2.3±0.6	6
j	2.0±0.4	5	**j**	-[c]	-

[a] The inhibition was determined according to the known method [14]. [b] BHT – Butylated hydroxytoluene. [c] The compound did not demonstrate any inhibition of DPPH.

Table 4 Antioxidant activity of compounds 6 expressed as inhibition (%) of GO

Compound **6**	Inhibition, %[a]	Inhibition % of standard compound BHT[b] (58.7±1.2%)
b	0.2±0.1	0.3
c	14.0±0.9	24
e	32.0±1.5	54
f	3.9±0.3	7
i	1.6±1.4	3

[a] The inhibition was determined according to the known method [15]. [b] BHT – Butylated hydroxytoluene.

CONCLUSION

In summary, novel conjugates between quinazolinone and 1,3,4-oxadiazole were synthesized by convenient method from isatoic anhydride, *β*-alanine and formic acid. Their antimicrobial and antioxidant activities were studied. The compounds did not demonstrate any significant antimicrobial activity. Several quinazolinone-derived hydrazides showed slight or moderate antiradical activity. Transformation of hydrazides into 1,3,4-oxadiazoles in the side chain caused the dramatic loss of antiradical activity.

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