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The Synthesis of (1,3,4-Oxadiazol-2-yl)Acrylic Acid Derivatives with Antibacterial and Protistocidal Activities

L. D. Popov[a, 1], A. A. Zubenko[b], L. N. Fetisov[b], Yu. D. Drobin[b], A. I. Klimenko[c], A. N. Bodryakov[b], S. A. Borodkin[a], and I. E. Melkozerova[d]

[a] *Department of Chemistry, Southern Federal University, Rostov-on-Don, 344090 Russia*
[b] *North-Caucasian Zonal Scientific Research Veterinary Institute, Novocherkassk, 346421 Russia*
[c] *Don State Agrarian University, Persianovskii, 346493 Russia*
[d] *Rostov-on-Don Basic Medical College, Rostov-on-Don, 344022 Russia*

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Abstract—A series of new 1,3,4-oxadiazol-2-yl-acrylic acids was synthesized by cyclization of 4-(2-*R*-hydrazino)-4-oxo-2-butenic acids, and their antibacterial and protistocidal activities were studied. The *p*-substituted benzyl derivatives in the *Z*-form were shown to exhibit a high protistocidal activity, which exceeded that of the reference drug Baycox (toltrazuril) by several times, whereas the 3-hydroxy-2-naphthyl derivative, in addition to a very high protistocidal activity, also exhibited a moderate antibacterial activity.

Keywords: acrylic acid, antibacterial activity, 1,3,4-oxadiazol, protistocidal activity
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INTRODUCTION

Currently, a large number of drugs displaying antibacterial and protistocidal (towards monocelled protozoa) activities are known. However, normally, compounds with antibacterial properties lack protistocidal activity. In addition, protozoa rapidly develop resistance to protistocidal drugs including anticoccidials, which makes it necessary to search for new agents. The compounds bearing an acrylic acid residue deserve attention as potential protistocidal agents. For example, cinnamic acid and its derivatives found in plants demonstrated low toxicity and noticeable antibacterial [1, 2] and antifungal [3, 4] properties and are used as biologically active compounds [5]. These compounds are active as antitumor [6, 7] and anticancer [8, 9] agents and can serve as tyrosinase [10], trypsin [11], lipoxygenase and cyclogenase [12] inhibitors. They can help in the treatment of oral moniliasis (*Candida albicans*) [13], herpes [14], and regulation of sex hormones [15]. Recently, the inhibitory properties of cinnamic acid and its derivatives towards the final products of protein glycosylation were found [16] and the compounds of this type were shown to effectively release insulin [17] and, therefore, can serve as a basis for the development of antidiabetic products [18].

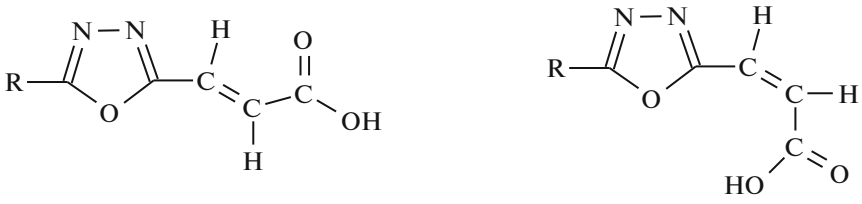
1,3,4-Oxadiazoles and their derivatives belong to one of the most important classes of five-membered nitrogen-containing heterocycles due to their synthetic availability and high structural variability as well as a wide spectrum of properties useful for practice. They display various biological activities [19, 20] and are widely used in different areas of medicinal chemistry [21] and pesticide chemistry [22, 23].

The presence of an acrylic acid residue and a heterocyclic fragment in one molecule may result in an increased biological activity. We prepared and studied some derivatives of (1,3,4-oxadiazol-2-yl)acrylic acid. The data about compounds of this type have been poor [24–29], their biological activity has not been studied.

RESULTS AND DISCUSSION

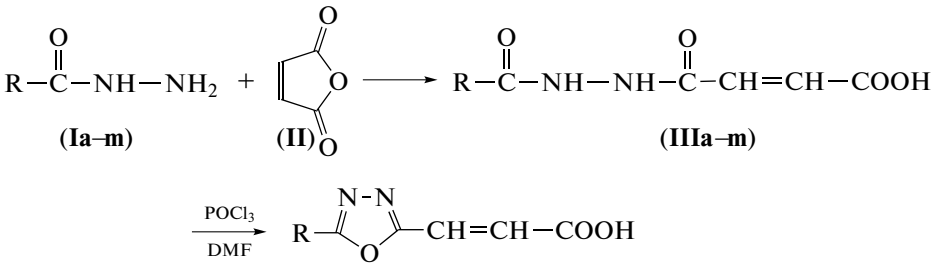
Derivatives of (1,3,4-oxadiazol-2-yl)acrylic acid were synthesized by the scheme shown below as described in [24]. The reaction of maleic anhydride **(II)** with hydrazides **(I)** resulted in hydrazides (**III**), which cyclized into 1,3,4-oxadiazoles **(IV)** in the presence of $POCl_3$.

[1] Corresponding author: e-mail: ldpopov@mail.ru.



E(*trans*) form *Z*(*cis*) form

Fig. 1. Isomeric forms of 1,3,4-oxadiazol-2-yl acrylic acids.



(Ia–m) **(II)** **(IIIa–m)**

(IVa–m)

Scheme 1. a: R = 2-furyl, **b**: R = 2,7a-dihydro-1,3-benzothiazol-2-ylsulfanylmethyl, **c**: R= 4-tolyl, **d**: R = 4-methoxyphenyl, **e**: R = 2-methoxyphenyl, **f**: R = 4-chlorophenyl, **g**: R = 4-bromophenyl, **h**: R = 4-nitrophenyl, **i**: R = 2*H*-thiophen-2-yl, **j**: R = 3-hydroxy-2-naphtyl, **k**: R = 2,6-dihydroxyphenyl, **l**: R = 2-hydroxyphenyl, **m**: R = phenoxymethyl.

Due to the presence of a double –CH=CH– bond, compounds (**IVa–m**) can exist in the form of either *trans*(*E*) and/or *cis*(*Z*) isomers (Fig. 1). The discrimination of these isomers is rather simple and is based on the coupling constant value (*J*) of ethylene protons.

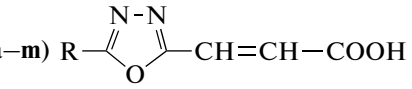
The larger constant ($J \sim 16$ Hz) corresponds to the *E*-isomer, and for the *Z*-isomer this constant is considerably lower. The difference in coupling constants for compounds of this type was first reported in [24]. In all cases the reactions yielded a mixture of *E*- and *Z*-isomers, an increase in the reaction time resulting in an increase in the content of the *E*-isomer. With the goal of obtaining one isomer, we used the maximal time described in [24]. However, according to the ^{1}H NMR data some of the compounds (**IVa**, **b**, **e**, **f**, **g**, **j**, **k**, **m**) were isolated as *Z*-isomers, others (**IVc**, **d**, **h**, **i**, **l**), as *E*-isomers. The *J* values for *E*-isomers were similar to those described in [24], in contrast to *Z*-isomers, whose *J* values were lower by two times ($J \sim 6$ Hz). In addition, in the ^{1}H NMR spectra of all the compounds synthesized we observed a proton resonance of a carboxyl group at 11.5–13.5 ppm, which disappeared after deuteration. The shape and position of resonances of all other protons completely coincided with the proposed structures.

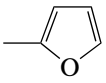
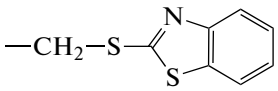
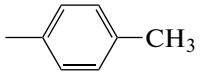
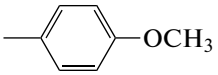
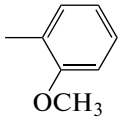
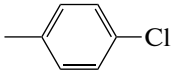
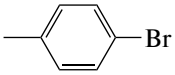
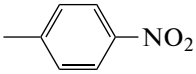
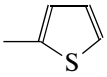
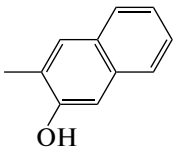
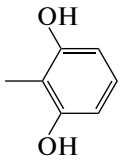
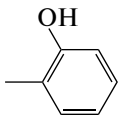
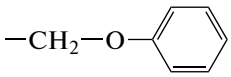
All the synthesized compounds (**IVa–m**) were tested for biological activity (Table 1).

As seen from the table, most of the compounds under study displayed a noticeable antiprotozoal activity against the *Colpoda steinii* model. A dramatic increase in the activity was observed after the introduction of halogen atoms into the benzene ring: the activity of compounds (**IVf**) and (**IVg**) was, by a hundred times and more, higher than that of the compounds with methyl and methoxy groups (compounds (**IVc–e**)). Probably, this difference can be associated with the isomer type (*Z*-isomers were more active) rather than with the nature of the substituent at the *para*-position of the benzene ring. The most active compound was the naphthyl derivative with a hydroxyl group (**IVj**), which was also isolated in the *Z* form. It could lyse protozoa cells at a concentration of 0.48 μg/mL, whereas the reference Baycox was only effective at a concentration of 62.5 μg/mL. Other *Z*-isomers obtained, for example, furyl derivative (**IVa**), did not manifest any antiprotozoal activity. This fact can be explained by the redistribution of electron density in the oxadiazole cycle, which, most probably, provides the high antibacterial activity of the compounds of this type. Thus, the search of antiprotozoal compounds within this class, especially *Z*-isomers, seems to be promising.

Also, the compounds under study manifested antibacterial properties, but the most effective compound (**IVj**) was 3–8 times less active than furazolidone.

Toxicity. We did not find the effect of acute toxicity for compounds (**IVf, g, j–l**) at a dose of 0.3 g/kg body weight when administered in the stomach of laboratory rats. The compounds can be preliminarily referred to as moderately toxic drugs.

Table 1. Biological activity of (1,3,4-oxadiazol-2-yl)acrylic acid derivatives (**IVa**–**m**) 

Code	R	Activity, μg/mL towards		
		St. aureus	*E. coli*	*C. steinii*
(IVa)		250.0	250.0	500.0
(IVb)		250.0	250.0	500.0
(IVc)		250.0	250.0	500.0
(IVd)		250.0	250.0	500.0
(IVe)		500.0	500.0	500.0
(IVf)		250.0	250.0	31.25
(IVg)		250.0	250.0	1.95
(IVh)		250.0	250.0	500.0
(IVi)		250.0	250.0	31.25
(IVj)		31.25	31.25	0.48
(IVk)		250.0	250.0	62.5
(IVl)		250.0	250.0	15.6
(IVm)		250.0	250.0	62.5
Reference compounds	Baycox	–	–	62.5
	Furazolidone	3.9	12.5	–
	Water	–	–	–

Definitions: (–) death (inhibition) of the test culture not found.

EXPERIMENTAL

^{1}H NMR spectra (δ, ppm, J, Hz) were recorded on a Bruker DPX-250 spectrometer (working frequency 250 MHz) in DMSO-d_6 using tetramethylsilane as a standard. Melting points were measured in an open capillary on a Chimlabpribor PTP device. Element analysis was carried out on an Elementar Vario Micro cube CHNS-analyzer. The reaction course and the product purity were monitored by TLC on Silufol UV-254 plates.

(*Z*)-3-[5-(2-Furyl)-1,3,4-oxadiazol-2-yl]acrylic acid (IVa). A solution of maleic anhydride (0.02 mol) in CH_3COOH (4 mL) was added to a solution of 2-furoic acid hydrazide (0.02 mol) in CH_3COOH (5 mL). Immediately, the mixture was warmed and a white precipitate was formed. The mixture was stirred for 1.5 h at room temperature. The precipitate was separated and washed twice with acetic acid and ethanol. Without additional purification, the resulting acylhydrazide was subjected to the reaction with a solution of $POCl_3$ (0.02 mol) in DMF (7 mL). The solution was stirred for 2 h at room temperature and poured into H_2O (50 mL). The precipitate was separated, washed twice with water and recrystallized from ethanol to give colorless crystals (72%); mp 205–206°C. ^{1}H NMR: 6.78 (s, 1H, fur.), 6.84 (d, 1H, CH=CH, *J* 5.5), 7.42 (s, 1 H, fur.), 7.48 (d, 1H, CH=CH, *J* 5.5), 8.11 (s, 1H, fur.), 13.24 (s, 1H, COOH). Found, %: C 52.10; H 3.00; N 13.40. $C_9H_6N_2O_4$. Calc., %: C 52.43; H 2.93; N 13.59.

Compounds (**IVb**)–(**IVm**) were prepared similarly to compound (**IVa**).

(*Z*)-3-[5-(2,7a-Dihydro-1,3-benzothiazol-2-ylsulfanylmethyl)-1,3,4-oxadiazol-2-yl]acrylic acid (IVb). Colorless crystals. The yield 68%. mp 197–198°C. ^{1}H NMR: 4.38 (s, 2H, CH_2), 6.92 (d, 1H, CH=CH, *J* 5.7), 7.35 (dd, 1H, arom., *J* 8.1, 8.1), 7.48 (dd, 1H, arom., *J* 8.1, 8.1), 7.84 (d, 1H, arom., *J* 8.1), 7.90 (d, 1H, CH=CH, *J* 5.7), 8.02 (d, 1H, arom., *J* 8.1), 11.88 (s, 1H, COOH). Found, %: C 48.90; H 2.50; N 12.40; S 14.60. $C_{13}H_9N_3O_3S_2$. Calc., %: C 48.89; H 2.84; N 13.16; S 20.08.

(*E*)-3-[5-(*p*-Tolyl)-1,3,4-oxadiazol-2-yl]acrylic acid (IVc). Colorless crystals. The yield 84%. mp 212–213°C. ^{1}H NMR: 2.40 (s, 3H, CH_3), 6.92 (d, 1H, CH=CH, *J* 15.9), 7.42 (d, 2H, arom., J 8.1), 7.43 (d, 1H, CH=CH, *J* 15.9), 8.01 (d, 2H, arom., *J* 8.1), 13.25 (s, 1H, COOH). Found, %: C 62.90; H 3.90; N 11.80. $C_{12}H_{10}N_2O_3$. Calc., %: C 62.63; H 4.35; N 12.17.

(*E*)-3-[5-(4-Methoxyphenyl)-1,3,4-oxadiazol-2-yl]acrylic acid (IVd). Colorless crystals. The yield 90%. mp 227–228°C. ^{1}H NMR: 3.85 (s, 3H, OCH_3), 6.90 (d, 1H, CH=CH, *J* 16.2), 7.15 (d, 2H, arom., *J* 9.0), 7.43 (d, 1H, CH=CH, *J* 16.2), 8.05 (d, 2H, arom., *J* 9.0), 13.20 (s, 1H, COOH). Found, %: C 58.90; H 3.60; N 11.60. $C_{12}H_{10}N_2O_4$. Calc., %: C 58.55; H 4.06; N 11.37.

(*Z*)-3-[5-(2-Methoxyphenyl)-1,3,4-oxadiazol-2-yl]-acrylic acid (IVe). Colorless crystals. The yield 55%. mp 195–196°C. ^{1}H NMR: 3.98 (s, 3H, OCH_3), 6.93 (d, 1H, arom., *J* 8.4), 7.13 (dd, 1H, arom., *J* 8.4, 8.4), 7.25 (d, 1H, CH=CH, *J* 5.7), 7.58 (dd, 1H, arom., *J* 8.4, 8.4), 7.89 (d, 1H, CH=CH, *J* 5.7), 7.95 (d, 1H, arom., *J* 8.4), 11.44 (s, 1H, COOH). Found, %: C 58.90; H 3.60; N 11.60. $C_{12}H_{10}N_2O_4$. Calc., %: C 58.55; H 4.06; N 11.37.

(*Z*)-3-[5-(4-Chlorophenyl)-1,3,4-oxadiazol-2-yl]-acrylic acid (IVf). Colorless crystals. The yield 48%. mp 179°C. ^{1}H NMR: 6.93 (d, 1H, CH=CH, *J* 5.7), 7.56 (d, 2H, arom., *J* 8.4), 7.88 (d, 2H, arom., *J* 8.4), 7.94 (d, 1H, CH=CH, *J* 5.7), 11.83 (s, 1H, COOH). Found, %: C 52.40; H 3.20; Cl 13.80; N 11.50. $C_{11}H_7ClN_2O_3$. Calc., %: C 52.72; H 2.79; Cl 14.17; N 11.17.

(*Z*)-3-[5-(4-Bromophenyl)-1,3,4-oxadiazol-2-yl]-acrylic acid (IVg). Colorless crystals. The yield 66%. mp 252°C. ^{1}H NMR: 6.93 (d, 1 H, CH=CH, *J* 5.7), 7.70 (d, 2H, arom., *J* 8.4), 7.80 (d, 2H, arom., *J* 8.4), 7.94 (d, 1H, CH=CH, *J* 5.7), 11.83 (s, 1H, COOH). Found, %: C 45.20; H 2.50; Br 26.50; N 10.00. $C_{11}H_7BrN_2O_3$. Calc., %: C 44.78; H 2.37; Br 27.08; N 9.49.

(*E*)-3-[5-(4-Nitrophenyl)-1,3,4-oxadiazol-2-yl]-acrylic acid (IVh). Colorless crystals. The yield 79%. mp 223–224°C. ^{1}H NMR: 6.73 (d, 1H, CH=CH, *J* 12.6), 6.96 (d, 1H, CH=CH, *J* 12.6), 8.21 (d, 2H, arom., *J* 9.0), 8.45 (d, 2H, arom., *J* 9.0), 13.45 (s, 1H, COOH). Found, %: C 50.80; H 2.20; N 16.50. $C_{11}H_7N_3O_5$. Calc., %: C 50.59; H 2.68; N 16.09.

(*E*)-3-[5-(2*H*-Thiophen-2-yl)-1,3,4-oxadiazol-2-yl]acrylic acid (IVi). Colorless crystals. The yield 80%. mp 234–235°C. ^{1}H NMR: 6.85 (d, 1H, CH=CH, *J* 15.9), 7.32 (dd, 1H, thioph., *J* 4.8, 3.6), 7.43 (d, 1H, CH=CH, *J* 15.9), 7.96 (dd, 1H, thioph., *J* 3.6, 1.2), 8.01 (dd, 1H, thioph., *J* 4.8, 1.2), 13.24 (s, 1H, COOH). Found, %: C 48.90; H 2.50; N 12.40; S 14.60. $C_9H_6N_2O_3S$. Calc., %: C 48.66; H 2.70; N 12.60; S 14.43.

(*Z*)-3-[5-(3-Hydroxy-2-naphtyl)-1,3,4-oxadiazol-2-yl]acrylic acid (IVj). Colorless crystals. The yield 71%. mp 192–195°C. ^{1}H NMR: 6.95 (d, 1H, CH=CH, *J* 5.7), 7.33 (s, 1H, arom.), 7.36 (dd, 1H, arom., *J* 7.5, 7.5), 7.52 (dd, 1H, arom., *J* 7.5, 7.5), 7.76 (d, 1H, arom., *J* 8.1), 7.99 (2H, arom. + CH=CH, *J* 5.7), 8.66 (s, 1H, arom.), 11.97 (s, 1H, OH), 12.05 (s, 1H, COOH). Found, %: C 63.40; H 3.90; N 10.30. $C_{15}H_{10}N_2O_4$. Calc., %: C 63.85; H 3.54; N 9.92.

(*Z*)-3-[5-(2,6-Dihydroxyphenyl)-1,3,4-oxadiazol-2-yl]acrylic acid (IVk). Colorless crystals. The yield 59%. mp 250–255°C. ^{1}H NMR: 6.43 (d, 2H, arom., *J* 8.4), 6.98 (d, 1H, CH=CH, *J* 5.7), 7.27 (dd, 1H, arom., *J* 8.4, 8.4), 7.99 (d, 1H, CH=CH, *J* 5.7), 12.16

(s, 1H, COOH), 12.64 (s, 2H, OH). Found, %: C 53.50; H 2.80; N 11.50. $C_{11}H_8N_2O_5$. Calc., %: C 53.25; H 3.22; N 11.29.

(*E*)-3-[5-(2-Hydroxymethyl)-1,3,4-oxadiazol-2-yl]-acrylic acid (IVl). Colorless crystals. The yield 72%. mp 197–198°C. ^{1}H NMR: 6.66 (d, 1H, CH=CH, *J* 12.6), 6.91 (d, 1H, CH=CH, *J* 12.6), 7.02 (dd, 1H, arom., *J* 7.8, 7.5), 7.08 (d, 1H, arom., *J* 8.1), 7.47 (dd, 1H, arom., *J* 8.1, 7.5), 7.71 (d, 1H, arom., *J* 7.8), 10.26 (s, 1H, OH), 13.30 (s, 1H, COOH). Found, %: C 57.30; H 3.80; N 11.60. $C_{11}H_8N_2O_4$. Calc., %: C 56.92; H 3.45; N 12.06.

(*Z*)-3-[5-(Phenoxymethyl)-1,3,4-oxadiazol-2-yl]-acrylic acid (IVm). Colorless crystals. The yield 64%. mp 210–211°C. ^{1}H NMR: 4.75 (s, 2H, CH_2), 6.85–6.90 (m, arom., 3H), 6.93 (d, 1H, CH=CH, *J* 6.3), 7.26 (dd, 2H, arom., *J* 8.1, 8.1), 7.87 (d, 1H, CH=CH, *J* 6.3), 11.62 (s, 1H, COOH). Found, %: C 60.10; H 4.00; N 11.10. $C_{12}H_{10}N_2O_4$. Calc., %: C 60.47; H 3.90; N 10.85.

The protistocidal activity was assessed as described in [30] using *C. steinii* protozoa (a field isolate from the collection of the laboratory of parasitology of the North Caucasus Zonal Research Veterinary Institute). The experiments were performed in microplates for immunoassays. As a medium for protozoa, a mixture of boiled tap water and sterile distilled water in equal volumes was used. Primary dilutions were carried out in distilled water in the presence of DMSO. Serial dilutions were prepared as follows.

Solution 1. The compound (5 mg) was dissolved under stirring in 70% DMSO (50 μL) and distilled water was added in portions (5 mL) to a concentration of 1000 μg/μL.

Solutions 2–12. A mixture of boiled tap water and sterile distilled water in equal volumes (150 μL) was added with an eight-channel automatic pipette to wells 2–12; then solution 1 (150 μL) was added to well 2 and the mixture was stirred. The resulting solution (150 μL) was transferred to well 3 and the procedure was repeated up to well 12. After stirring, the solution (150 μL) from well 12 was removed and a three-day *C. steinii* culture (30 μL) was added to each of the wells. Solution 1 (150 μL) and the protozoa suspension (30 μL) were added to well 1. The protozoa suspension was prepared in the way, so that 10 to 15 active individuals could be seen upon microscopy at low-power magnification. After the protozoa addition, the plate was covered with a cap and kept at room temperature (20–22°C) for 18–20 h.

The results were assessed as follows. An aliquot (30 μL) was taken from the last well after stirring using an automatic autopipette, transferred it to a clean slide and examined by low magnitude microscopy (10 × 15). The presence or absence of live organisms was recorded. Examination was performed from the right to the left. The first well, where no live microorganisms were found, was regarded as the one containing the compound under study at a minimal protistocidal concentration. The following solutions were taken as controls:

—Control medium (boiled tap water and sterile distilled water), 5 wells.

—Control solvent (70% DMSO (50 μL) and distilled water (5 mL); then, serial dilutions similarly to those for the tested compounds), 12 wells.

—Reference Baycox (toltrazuril).

The antibacterial (bacteriostatic) activity was evaluated by a twofold serial dilutions technique. As test cultures for the assessment of antimicrobial activity of chemotherapeutic drugs, two standard strains, *Staphylococcus aureus* P-209 and *Escherichia coli* 078 strain (a field strain), were used. The cultures were grown for a day at 37°C on an agar Luria–Bertani medium (LB). Solutions of the tested compounds at various concentrations (2 mL) prepared by twofold serial dilutions in the liquid nutrient medium [31–34] were added to the bacterial suspensions (2 mL) at a concentration of 500000 microorganisms/mL. The considered bioburden was 250000 microorganisms/mL. The resulting solutions were incubated for 18 h at 37°C. The medium containing 250000 microorganisms/mL served a positive control. The medium lacking bacteria served a negative control. The reference compound was furazolidone.

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